Confidence Interval Criteria for Assessment of Dose Proportionality

Brian P. Smith,[1,7] Francois R. Vandenhende,[2] Karl A. DeSante,[1,4] Nagy A. Farid,[3] Pamela A. Welch,[1,5] John T. Callaghan,[1,4,6] and S. Thomas Forgue[1]

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Purpose. The aim of this work was a pragmatic, statistically sound and clinically relevant approach to dose-proportionality analyses that is compatible with common study designs.

Methods. Statistical estimation is used to derive a (1-α)% confidence interval (CI) for the ratio of dose-normalized, geometric mean values (R_{dnm}) of a pharmacokinetic variable (PK). An acceptance interval for R_{dnm} defining the clinically relevant, dose-proportional region is established a priori. Proportionality is declared if the CI for R_{dnm} is completely contained within the critical region. The approach is illustrated with mixed-effects models based on a power function of the form $PK = \beta_0 \bullet Dose^{\beta 1}$; however, the logic holds for other functional forms.

Results. It was observed that the dose-proportional region delineated by a power model depends only on the dose ratio. Furthermore, a dose ratio (ρ_1) can be calculated such that the CI lies entirely within the pre-specified critical region. A larger ratio (ρ_2) may exist such that the CI lies completely outside that region. The approach supports inferences about the PK response that are not constrained to the exact dose levels studied.

Conclusion. The proposed method enhances the information from a clinical dose-proportionality study and helps to standardize decision rules.

KEY WORDS: bioequivalence; dose proportionality; mixed effects model; pharmacokinetics; power model.

INTRODUCTION

Dose proportionality assessment is a fundamental pharmacokinetic analysis conducted during clinical development of a new molecular entity. The term "dose proportionality" indicates that doubling the dose doubles the pharmacokinetic measure of maximal (C_{max}) or total (AUC) systemic exposure to the drug. Evaluation of the pharmacokinetic variable (PK) as a function of dose should be pragmatic, statistically sound and must support clinically meaningful inferences. The approach should be compatible with common study designs in drug development in order to foster standardization of decision rules. Conclusions about proportionality should identify the relevant dose range, since every drug can have nonlinear pharmacokinetics at extreme doses.

Numerous hypothesis testing approaches to dose-proportionality have been proposed. Haynes and Weiss (1) explored a multiplicative statistical model in order to describe a disproportionate PK response in terms of two straight lines. Yuh, Eller and Ruberg (2) outlined a step-down trend test in which an ANOVA evaluation of a dose-normalized PK parameter was followed with a family of linear contrasts. Patel (3) described a stepwise, "backward elimination" polynomial regression in the context of a within-subject design. If the coefficient of the highest order term in the polynomial model of degree q was not significantly different from 0, then the reduced model of order q-1 was considered, and so forth. Gough, et al. (4) reasoned that dose proportionality assessment is a problem of estimation rather than hypothesis testing. It is not helpful to perform hypothesis tests only to dismiss significant differences as being clinically inconsequential. Estimation of the magnitude of deviations from dose-proportionality and the precision of the estimates provide the essential information. Both estimation of a treatment difference and comparison of the corresponding confidence interval (CI) to an equivalence region have been applied in numerous studies (e.g. 5–8). Typically, log-transformed, dose-normalized AUC values are evaluated by ANOVA and ratios of geometric means and their corresponding 90% CI's are reported. Dose proportionality is concluded if the CI for the difference between two treatments lies entirely within the range defined for bioequivalence testing. Treating dose as a continuous, rather than a categorical variable requires a mathematical model.

The merits of a power model of the form $PK = \beta_0 \bullet Dose^{\beta 1}$ were recognized by Klamerus, et al. (9). General applicability of the power model to proportionality assessment was clearly outlined by Gough, et al. The power model is well suited to detect a nonlinear pharmacokinetic response and to estimate the magnitude of the deviation. Such an empirical model facilitates standardization of metrics and decision rules across studies and drugs. A theoretically correct mechanistic model, perhaps based on a Michaelis-Menton equation, can be pursued subsequently to investigate the nonlinear process. In the present paper, we extend the estimation approach to derive confidence intervals and decision rules for dose-proportional assessment of drug exposure. Although the approach is best illustrated in conjunction with the power model, the logic can be generally applied to empiric and mechanistic models.

METHODS

Proportionality as an Equivalence Problem

The logic for application of confidence intervals to the dose-proportionality problem is analogous to that for testing

[1] Lilly Laboratory for Clinical Research, 550 North University Boulevard, Indianapolis, Indiana 46202-5250.
[2] Lilly Development Centre, 11 rue Granbonpre, B-1348, Mont-Saint-Guibert, Belgium.
[3] Drug Disposition Department, Lilly Research Laboratories, Indianapolis, Indiana 46285.
[4] Department of Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana 46202.
[5] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana 46202.
[6] Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana 46202.
[7] To whom correspondence should be addressed. (e-mail: B.Smith@Lilly.com)

ABBREVIATIONS: PK, pharmacokinetic response variable; r, ratio of doses; R_{dnm}, dose-normalized ratio of pharmacokinetic mean values; CI, confidence interval; (Θ_L, Θ_H), acceptance interval (critical region) for R_{dnm}; (L, U), confidence interval for the estimate of β_1 from the power model; ρ_1, maximal dose ratio for proportionality; ρ_2, minimal dose ratio to exclude proportionality.

average bioequivalence in the United States. Bioequivalence is declared if the (1-α)% CI for the ratio of geometric mean values for C_{max} and AUC are contained completely in the acceptance interval (Θ_L, Θ_H), where $\Theta_L < 1 < \Theta_H$. The current FDA guidance (10) defines $\alpha = 0.1$, $\Theta_L = 0.80$ and $\Theta_H = 1/\Theta_L = 1.25$. Bioequivalence testing leads to a dichotomous outcome—the drug products are bioequivalent or they are not. There are three possible outcomes of the proposed CI approach for the actual dose range studied: 1) the PK variable is definitely proportional to dose; 2) PK is definitely not proportional to dose; and 3) statistical results are inconclusive. Furthermore, inferences from the CI approach are not limited to the actual dose levels used. Irrespective of outcome, the method delineates the maximal dose ratio that is compatible with a dose-proportional PK response, as well as a threshold dose ratio above which PK is definitely not proportional according to the pre-specified CI criterion.

Linking the CI Criterion to a Statistical Model

There are five steps in linking the desired acceptance interval (critical region) for the exposure ratio to the parameters of a preferred statistical model. Let h be the highest dose studied, let ℓ be the lowest dose, and let $r = h/\ell$ be the maximal dose ratio. Then: 1) Specify that proportionality exists if the ratio of geometric mean PK values equals r; 2) Divide both sides of the equation by r; thereby specifying that proportionality exists when the ratio of dose-normalized geometric mean values (R_{dnm}) is equal to unity; 3) Specify a lower limit (Θ_L) and an upper limit (Θ_H) for R_{dnm} as an inequality based on safety, efficacy or drug registration considerations; 4) Estimate the expected value of R_{dnm} and the corresponding confidence interval with a statistical model; 5) Solve the inequality for the model parameter(s) of interest.

Case 1: Two-dose Case (Analysis of Variance)

The values of PK would be measured at two dose levels, according to a parallel-group design, a 2-period crossover design or a dose-escalation design. It would be assumed that PK was log-normally distributed with equal variances (on the log scale) at the two dose levels, as is common for bioequivalence testing. Homogeneity of variance on the log scale is equivalent to a constant coefficient of variation for untransformed data. Let μ_h and μ_ℓ be the geometric means of the PK parameter at h and ℓ respectively. Dose proportionality holds when: $\mu_h/\mu_\ell = h/\ell$ or $(\ell \cdot \mu_h)/(h \cdot \mu_\ell) = 1$. Lower and upper limits for this dose-normalized ratio would be defined by the inequality: $\Theta_L < (\ell \cdot \mu_h)/(h \cdot \mu_\ell) < \Theta_H$. Solving for the model parameter of interest (μ_h/μ_ℓ) gives:

$$\frac{h}{\ell}\theta_L < \frac{\mu_h}{\mu_\ell} < \frac{h}{\ell}\theta_H \qquad (1)$$

Proportionality would be declared when the (1-α) • 100% CI for the ratio of geometric means, as estimated with an ANOVA model appropriate for the study design, is contained completely in the interval $(r \cdot \Theta_L, r \cdot \Theta_H)$, where r is the dose ratio.

Case 2: More than 2 Doses (Simple Linear Regression)

The untransformed PK parameter, measured at two or more dose levels, is modeled as: $PK = \beta_0 + \beta_1 \bullet DOSE$. The mean value of PK at the lowest dose is $\beta_0 + \beta_1 \cdot \ell$ and that at the highest dose is $\beta_0 + \beta_1 \cdot h$. Dose proportionality is defined as: $(\beta_0 + \beta_1 \cdot h)/(\beta_0 + \beta_1 \cdot \ell) = h/\ell$ which upon rearrangement gives: $(\ell/h)(\beta_0 + \beta_1 \cdot h)/(\beta_0 + \beta_1 \cdot \ell) = 1$. Lower and upper limits for this ratio are given by $\Theta_L < (\ell/h)(\beta_0 + \beta_1 \cdot h)/(\beta_0 + \beta_1 \cdot \ell) < \Theta_H$, which is algebraically equivalent to: $(h/\ell) \cdot \Theta_L \cdot (\beta_0 + \beta_1 \cdot \ell) < \beta_0 + \beta_1 \cdot h < (h/\ell) \cdot \Theta_H \cdot (\beta_0 + \beta_1 \cdot \ell)$. The left-hand side of the inequality may be rearranged to: $h \cdot \Theta_L \cdot \beta_1 - \beta_1 \cdot h < \beta_0 - (h/\ell) \cdot \Theta_L \cdot \beta_0$. Dividing both sides by β_1 and $1 - (h/\ell) \cdot \Theta_L$, and noticing that $1 - (h/\ell) \cdot \Theta_L$ is negative (for any dose range of clinical interest), gives $\beta_0/\beta_1 < h\ell(\Theta_L - 1)/(\ell - h\Theta_L)$. Similar algebra for the right hand side yields the desired inequality for the model parameters:

$$\frac{h\ell(\theta_H - 1)}{\ell - h\theta_H} < \frac{\beta_0}{\beta_1} < \frac{h\ell(\theta_L - 1)}{\ell - h\theta_L} \qquad (2)$$

To find the $(1 - \alpha) \times 100\%$ CI for this intercept/slope ratio requires either bootstrapping or use of Fieller's theorem (11). Equation (2) indicates that the magnitude of the intercept β_0 relative to the slope β_1, rather than β_0 alone, is the important determinant of proportionality in this case. This fact represents one reason that a hypothesis test of β_0 against 0 is inappropriate.

Case 3: Power Model (Regression of Log-transformed Data)

Here, the key modeling assumption is that the logarithm of the PK variable is linearly related to logarithm of dose:

$$\ln(PK) = \beta_0 + \beta_1 \cdot \ln(dose) \qquad (3)$$

The predicted geometric mean of the high dose is $e^{\beta_0}h^{\beta_1}$ and that of the low dose is $e^{\beta_0}\ell^{\beta_1}$. Dose proportionality corresponds to $e^{\beta_0}h^{\beta_1}/e^{\beta_0}\ell^{\beta_1} = h/\ell$ which can be rewritten as: $(h/\ell)^{\beta_1 - 1} = r^{\beta_1 - 1} = 1$. Lower and upper limits are defined as: $\Theta_L < r^{\beta_1 - 1} < \Theta_H$. Taking the natural log, it is seen that $\ln(\Theta_L) < (\beta_1 - 1)\ln(r) < \ln(\Theta_H)$. Solved for the model parameters of interest gives:

$$1 + \frac{\ln(\theta_L)}{\ln(r)} < \beta_1 < 1 + \frac{\ln(\theta_H)}{\ln(r)} \qquad (4)$$

Dose proportionality would be declared when the (1-α) • 100% CI for β_1 lies entirely within the critical region $(1 + \ln(\Theta_L)/\ln(r), 1 + \ln(\Theta_H)/\ln(r))$. This criterion is equivalent to having R_{dnm} contained completely within the interval (Θ_L, Θ_H). Notably, this interval has the attractive feature of being characterized completely by r and the protocol-specified Θ_L and Θ_H values. This means that only dose ratio (r), and not the actual doses given on any occasion, needs to be specified in order to support inferences about proportionality or lack thereof. It is also true that if $r_2 > r_1$ then:

$$\frac{\ln(r_1 \cdot \theta_L)}{\ln(r_1)} < \frac{\ln(r_2 \cdot \theta_L)}{\ln(r_2)} < 1 < \frac{\ln(r_2 \cdot \theta_H)}{\ln(r_2)} < \frac{\ln(r_1 \cdot \theta_H)}{\ln(r_1)} \qquad (5)$$

Thus, as the dose ratio increases, the critical region for β_1 narrows. It is intuitive that the criterion for proportionality should be more stringent for a large dose range than that for a narrow range. This property has two important consequences. First, a maximal dose ratio ρ_1 can be calculated such that the CI for β_1, denoted (L, U), is included entirely within the interval defined by Eq. (4). Second, a dose ratio ρ_2 can sometimes be calculated such that (L, U) lies completely outside the acceptance interval. The value of ρ_1 or ρ_2 may be larger or may be smaller than the actual dose range studied. Thus, the proposed approach supports inferences about how the PK response changes with dose that are not constrained to the doses studied. Extrapolation beyond the studied dose range should obviously be done cautiously.

The values of ρ_1 and ρ_2 may be calculated as follows. If 1-L > U-1 then solve the following equation for ρ_1: $1 + \ln(\Theta_L)/\ln(\rho_1) = L$. This gives $\rho_1 = \Theta_L \text{^}[1/(L-1)]$. If 1-L < U-1 then solving $1 + \ln(\Theta_H)/\ln(\rho_1) = U$ for ρ_1 gives $\rho_1 = \Theta_H \text{^}[1/(U-1)]$. This procedure ensures that if $r < \rho_1$ then (L, U) is completely contained in $(1 + \ln(\Theta_L)/\ln(r), 1 + \ln(\Theta_H)/\ln(r))$. If $\Theta_H = 1/\Theta_L$ then the analytical solution for ρ_1 is:

$$\rho_1 = \theta_H \text{^} \left[\frac{1}{\max(1-L, U-1)} \right] \quad (6)$$

A similar set of logic leads to the analytical solution for ρ_2 which is

$$\rho_2 = \theta_H \text{^} \left[\frac{1}{\max(L-1, 1-U)} \right] \quad (7)$$

When L < 1 and U > 1, ρ_2 cannot be solved. This is logical for this circumstance, since it implies strict dose proportionality is tenable.

Dose-proportionality data are commonly obtained following drug administration to healthy subjects or patients on two or more occasions. If the power model is appropriate, then a mixed-effects statistical model based on Eq. (3) can be used to account for correlation between repeated measurements in a given subjects. The following general form was considered:

$$\ln(PK_{ij}) = (\beta_0 + \eta_{1i}) + (\beta_1 + \eta_{2i}) \cdot \ln(DOSE_{ij}) + \varepsilon_{ij} \quad (8)$$

for the *j*th observation of PK in the *i*th subject. The model denotes random between-subject variability $\eta_{1i} \sim N(0, \xi_1^2)$ in the intercept parameter, random between-subject variability $\eta_{2i} \sim N(0, \xi_2^2)$ in the slope, as well as random error $\varepsilon_{ij} \sim N(0, \sigma^2)$. The data may not support inclusion of η_{2i} in the model. The random effects, as well as the fixed effects (β_0 and β_1) and their 90% confidence intervals, can be estimated with the MIXED procedure of SAS and other statistical packages.

Modeling of Clearance

When AUC is dose proportional, then the apparent oral clearance (CL/F = Dose/AUC; F ≤ 1.0) or the clearance after intravenous dosing (F = 1.0) is dose-independent. For any assessment to be congruous, an inference about whether or not AUC is dose proportional should be exactly the same as an inference about whether or not clearance is dose independent. If AUC at each dose level is log-normally distributed (an assumption of the power model), then CL/F is also log-normal since it is the inverse of AUC (times a constant). Substituting CL/F ● Dose as the PK parameter in Eq. (3) reveals that the coefficient of ln(dose) is $1-\beta_1$. Thus, the inference that $\beta_1 = 1$ for the AUC model is equivalent to the inference that $\beta_1 = 0$ for regression of ln(CL/F) on ln(Dose). The $(1-\alpha)$ confidence interval for the ratio of geometric mean CL/F values can be compared to a acceptance interval in a manner analogous to that described above.

Case 4: Saturable Elimination Model (Quadratic Regression with no Intercept)

This case applies the confidence interval logic to a common mechanistic model of pharmacokinetic non-linearity. Consider a single bolus intravenous dose of a drug that distributes to one volume (V) and that is eliminated by a saturable process characterized by a hyperbolic (Michaelis-Menton) function with parameters V_{max} and K_m. Here K_m is the drug concentration at which the elimination rate is half-maximal ($V_{max}/2$). Wagner (12) showed that drug exposure (AUC) is:

$$AUC = \frac{K_m}{V_{max}} Dose + \frac{1}{2V_{max} V} Dose^2 \quad (9)$$

where his equation has been reparameterized to relate it to quadratic regression through the origin. If V_{max} is large (elimination is not readily saturable), $1/(2V_{max}V) \rightarrow 0$ and AUC is given by dose times intrinsic clearance (V_{max}/K_m), a fundamental pharmacokinetic property. Chau (13) derived equations for AUC as a function of dose for more complex pharmacokinetic models of Michaelis-Menton elimination. Sheppard, et al. (14) showed that the dose-normalized AUC ratio is:

$$\left(\frac{1}{r}\right) \frac{AUC_h}{AUC_\ell} = \frac{2V \cdot K_m + h}{2V \cdot K_m + \ell}$$

The values of V and K_m are usually unknown; therefore, the statistical model would be based on an empirical form of Eq. (9) such as:

$$AUC = \beta_1 \cdot dose + \beta_2 \cdot dose^2$$

Table 1. Noncompartmental Parameters from a Phase 1, Dose-escalation Study

Subject Number	LY333013 Dose	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng · hr/mL)
1, 2	25 mg	64.82, 67.35	326.4, 437.82
4, 5, 6	50 mg	104.15, 143.12, 243.63	557.47, 764.85, 943.59
	250 mg	451.44, 393.45, 796.57	2040.84, 2989.29, 4107.58
7, 8, 9	75 mg	145.13, 166.77, 296.9	1562.42, 982.02, 1359.68
	250 mg	313, 387, 843	3848.86, 4333.1, 3685.55

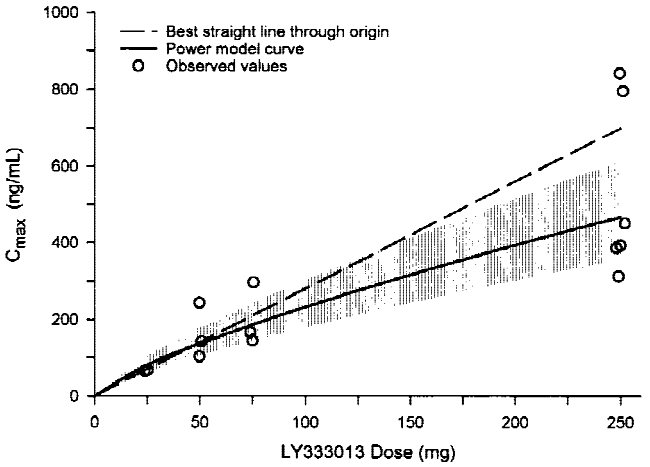

Fig. 1. Power model for example 1. The solid line denotes tile expected geometric mean value and the shading denotes the 90% prediction limits.

where $\beta_1 = K_m/V_{max}$ and $\beta_2 = 1/(2V_{max}V)$. Linking the CI criterion to the model and solving for the model parameters gives:

$$\frac{h - \ell\theta_L}{\theta_L - 1} < \frac{\beta_2}{\beta_1} < \frac{h - \ell\theta_H}{\theta_H - 1} \quad (10)$$

Calculation of a confidence interval for β_2/β_1 requires bootstrapping or use of Fieller's theorem (11) since it is a ratio of two normally distributed values.

Decision Rules

The acceptance interval (Θ_L, Θ_H) for R_{dnm} and the statistical model for estimation are not alone sufficient to support clinically meaningful conclusions. If (L, U) lay completely outside the acceptance interval, then one would conclude lack of proportionality. A 90% CI lying entirely within the critical region would confirm a proportionate increase in exposure. If the dose ratio of interest falls between ρ_1 and ρ_2, then (L, U) would span the critical region and no clear-cut statistic would be obtained. Here, β_1 as the best estimate of deviation from ideal proportionality, and (L, U) indicating the maximal possible deviations, could be interpreted in the context of drug safety and efficacy or pharmacological effect data. This is, understanding the association between systemic exposure and dose is more difficult that accepting a dichotomous outcome of a statistical test.

RESULTS AND DISCUSSION

Estimation of the expected PK value by means of a statistical power model, coupled with confidence interval criteria to define proportionate and disproportionate ranges is a pragmatic approach to obtaining clinically relevant information on variation in drug exposure with dose. An essential model assumption is that doubling the dose will increase PK by a constant proportion. For instance, if increasing -the dose from 100 to 200 causes a 90% increase in the PK parameter of interest, then a dose increment from 200 to 400 will also increase PK by 90%. The first example illustrates analysis of limited data typical of a dose-escalation study in early clinical development, and the second example represents a "definitive" dose proportionality study.

Example 1 (Secretory Phospholipase Inhibitor LY333013)

LY333013 is the methyl ester of [[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]ocy]acetate, which is a potent inhibitor of human non-pancreatic secretary phospholipase A_2 ($sPLA_2$). When orally administered, LY333013 is rapidly hydrolyzed to the active acid, which is measured in plasma. LY333013 is being developed for use in patients with chronic inflammatory conditions associated with elevated serum levels of $sPLA_2$. Evaluation of exposure (AUC and C_{max}) as a function of dose was an objective of the first clinical study, in which single doses of an oral suspension were administered to healthy subjects (Table I).

The PK values were evaluated with the following mixed effects statistical model:

$$\ln(PK_{ij}) = (\beta_0 + \eta_i) + \beta_1 \cdot \ln(dose_{ij}) + \varepsilon_{ij}$$

All η_i's and ε_{ij}'s were assumed to be mutually independent. Estimates of β_0 and β_1 and their 90% CI's were obtained with the MIXED procedure (ML method) of SAS. Results revealed a disproportionately low increase in C_{max} over the dose range (Figure 1). The estimate of the "intercept" parameter β_0 [1.94 with a 90% CI of (1.54, 2.35)] and its between-subject variability $\xi^2 = 0.097$ are not of interest here. The

Table 2. Dose Proportionality Assessment of a Phase 1, Dose-escalation Study

Dose range studied	Predicted geometric mean PK parameter values	R_{dnm} 90% confidence interval[a]	Conclusion for dose range studied[b]	Maximal proportional dose range[c] (ρ_1)	Threshold dose ratio to reject proportionality[d] (ρ_2)
C_{max} (ng/mL)		0.577			
25 to 250 mg	80.9 to 467	(0.477, 0.698)	not proportional	2.0	4.2
$AUC_{0-\infty}$ (ng · hr/mL)		0.808			
25 to 250 mg	415 to 3353	(0.653, 1.001)	inconclusive	3.3	no value[e]

[a] Ratio of model-predicted mean values for high and low dose, normalized for dose.
[b] Proportionality was concluded if the 90% confidence interval for R_{dnm} was contained completely within (0.8, 1.25).
[c] Proportionality would be concluded for any dose ratio less than this value.
[d] Lack of proportionality would be concluded for any dose ratio greater than this value.
[e] See qualification in text.

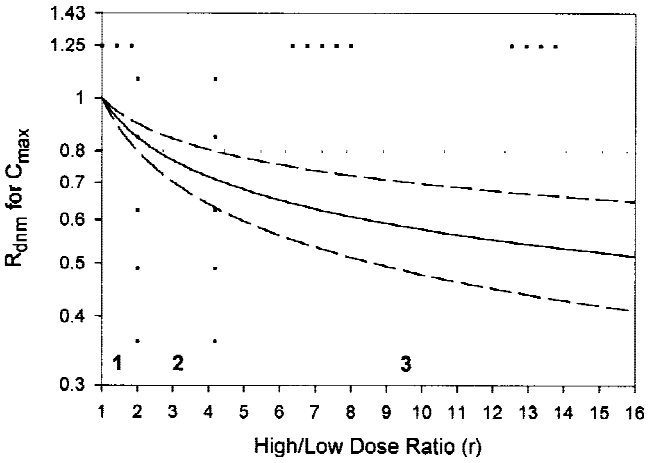

Fig. 2. The ratio of geometric mean C_{max} values normalized for dose (—) and its 90% CI (– – –) as predicted by the power model for example 1. Region 1 corresponds to a conclusion of proportionality, while C_{max} values in region 3 are definitely not proportional to dose. Region 2 corresponds to an inconclusive result.

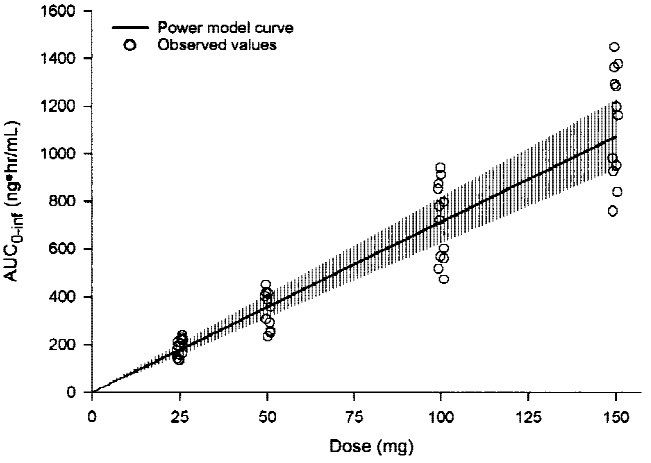

Fig. 3. Power model for Example 2. The solid line denotes the expected geometric mean value and the shaded region denotes the 90% prediction limits.

estimate of the slope parameter β_1 was 0.7615. The corresponding 90% CI (0.679, 0.844) fell outside the reference interval (0.903, 1.097) defined by Eq. (4) for r = 10 and $\Theta_H = 1/\Theta_L = 1.25$, indicating a disproportionate change in C_{max} across the dose range studied.

The modeling results were also expressed in terms of the actual pharmacokinetic parameter. The ratio of dose-normalized geometric means (R_{dnm}) was calculated, where each mean (Table II) was obtained as exp[1.942 + 0.7615 • ln(dose)]. An R_{dnm} value of 1.00 would denote ideal dose-proportionality. The 90% CI for the difference in log-transformed means was calculated within the MIXED procedure. Exponentiation of each limit and division by r gave the 90% CI for R_{dnm}. This CI lay completely outside (0.80, 1.25), indicating a disproportionate increase in C_{max}.

Setting the lower confidence limit for β_1 equal to 1 + ln(0.8)/In(r) and solving for r gave $r = \rho_1 = 2.0$. That is, if the dose ratio is ≤2.0, then the 90% CI for R_{dnm} will lie entirely within the critical region (Table II and Fig. 2). Setting U equal to 1 + ln(0.8)/In(r) gave $r = \rho_2 = 4.2$. If r ≥ 4.2, then the 90% CI for the ratio of C_{max} values will lie completely outside the critical region (Fig. 2; Region 3).

The 90% CI for R_{dnm} based on log-transformed $AUC_{0-\infty}$ values (Table II) intersects the acceptance interval (0.80, 1.25). This CI alone does not support any definitive conclusion for the 10-fold range, since the true R_{dnm} value may lie within or may lie outside of the acceptance interval. The 90% CI for β_1 was (0.8147, 1.0005). Setting these limits equal to ln(0.8r)/ln(r) yielded $r = \rho_1 = 3.3$ and no real value for ρ_2. Since (U, L) contains 1.0, no real value of r will yield a confidence interval for R_{dnm} in region 3.

Example 2 (AUC data from H. Patel)

Patel (3) reported $AUC_{0-\infty}$ data from a 4 × 4 replicated Latin square design with single 25, 50, 100 and 150 mg doses of an unidentified drug. Three subjects were randomly assigned to each of four treatment sequences. Lack of any carryover effect was evidenced by pre-dose plasma concentrations of "zero." In the reanalysis of these data, it was assumed that there was no period or sequence effect. The following power model with a mixed-effects statistical structure was used:

$$\ln(PK_{ij}) = \beta_0 + \eta_{1i} + (\beta_1 + \eta_{2i}) \bullet \ln(dose_{ij}) + \varepsilon_{ij},$$

for the *j*th observation in the *i*th subject. The random intercept (η_1), slope (η_2), and error (ε) effects, as well as all individuals η_{1i}, η_{2i}, and ε_{ij} values, were assumed to be mutually independent. This example demonstrates that the proposed approach does not restrict the variance model structure. The power model mirrored the obvious proportionate trend in the observed data (Fig. 3). It was possible to definitively conclude that $AUC_{0-\infty}$ increased proportionally with dose over the 6-fold range, since the 90% CI for R_{dnm} was completely contained within the acceptance interval (Table III).

The 90% CI for β_1 was (0.980, 1.019). The lower limit corresponds to $\rho_1 \cong 70{,}000$ indicating there was negligible evidence from this study alone to declare any deviation from

Table 3. Dose Proportionality Assessment of $AUC_{0-\infty}$ Data from Patel (3)*

Dose range studied	Predicted geometric mean $AUC_{0-\infty}$ values (ng · hr/mL)	R_{dnm} and 90% confidence interval	Conclusion for dose range studied	Maximal proportional dose range (ρ_1)	Threshold dose ratio to reject proportionality (ρ_2)
25 to 150 mg	179 to 1072	0.9996 (0.97, 1.04)	Proportional	~70,000[a]	no value[a]

* Column headers are described in Table II.
[a] See qualifications in text.

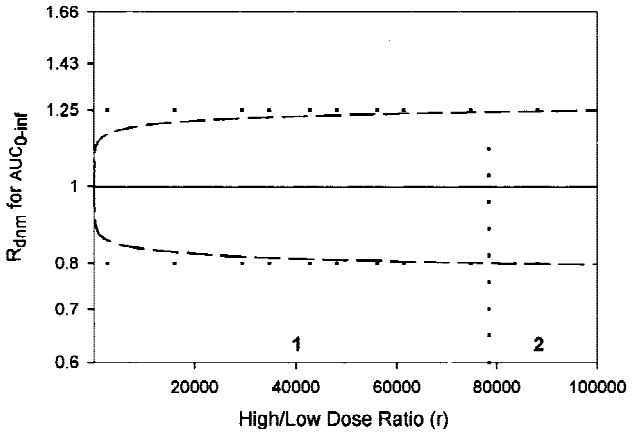

Fig. 4. The ratio of geometric mean values normalized for dose (—) and its 90% CI (– – –) as predicted by the power model for Example 2. Region 1 corresponds to a definitive conclusion of proportionality. Region 2 is inconclusive on dose proportionality.

ideal dose proportionality. This is not to condone extrapolation far beyond the dose levels studied, since any drug would be expected to display nonlinear pharmacokinetics at inordinately high or low doses. The 90% CI for β_1 contained 1.0; thus, a hypothesis that $AUC_{0-\infty}$ was truly proportional to dose could not be rejected based on this study alone. This is represented by the entry of "no value" in Table III.

Estimation of Deviations from Proportionality

The examples indicate that conclusions are not constrained to a dichotomous outcome of "proportional" or "not proportional" over an arbitrary dose range, since a maximal dose ratio consistent with proportionality and a threshold ratio above which exposure is definitely not proportional are defined. The need to link any conclusion on dose proportionality with a specific dose range has been well stated by Gough, et al. (4) and Sheppard et al. (14). Conclusions from the power model relate to a dose ratio rather than to specific dose levels. If there is evidence that this modeling assumption is inappropriate, then the CI criteria can be used with another function.

For a given subject sample size, a study design can be chosen in order to minimize the standard error for β_1 and thereby narrow its confidence interval (minimize region 2). The standard error is minimized (estimation is most efficient) when one-half of the observations are collected at the lowest dose at which precise PK measurements are possible and one-half at the maximum tolerated dose. From a statistical point of view, the optimal design is thus a 2-period, 2-treatment crossover. A desire to collect data at other levels and to verify the applicability of the power model could be persuasive for inclusion of additional treatments.

Decision rules based on a confidence interval for the statistical model of choice can be detached from the power model, as was noted above for the saturable elimination model. Irrespective of the mathematical relationship between PK and dose, the 90% CI for the ratio of expected mean (arithmetic, least squares, geometric, predicted geometric, etc.) values of the PK metric can be compared to a prespecified acceptance interval (Θ_L, Θ_H). This approach is straightforward and based on the logic used in bioequivalence testing. The method can be applied to common dose-escalation and crossover designs and supports standardization of decision rules and comparisons across studies and drugs.

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