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Including information on the therapeutic window in bioequivalence acceptance limits

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Summary

Pharmaceutical companies use pharmacokinetic measurements in bioequivalence (BE) trials as surrogate to prove that a new drug formulation or manufacturing procedure does not alter the safety and efficacy profile of the drug. In general, Health Authorities require that the 90% confidence intervals about the geometric mean test/reference ratios for both $C_{\max}$ and AUC fall between 80-125% to accept bioequivalence. For highly variable drugs and drug products, a high number of subjects is required in clinical trials to meet the current BE standards. Boddy (1995) and Karalis (2004, 2005) published approaches to correct or to widen, respectively, the acceptance ranges accounting for the degree of within-subject variability.

In 2006, Health Canada released a guidance on bioequivalence requirements for critical dose drugs and proposed more stringent acceptance limits of 90-112% for AUC. In that guidance, critical dose drugs are defined as those where small differences in dose or concentration lead to serious therapeutic failures and/or serious adverse drug reactions.

In this work, the approach of Karalis is extended to adapt the BE acceptance ranges to the therapeutic window of the drug, quantified as the ratio of the Maximum Tolerated Dose/Therapeutic Dose (MTD/D) and the Therapeutic Dose/Least Effective Dose (D/LED). A series of simulations was carried out to assess the performance of the adapted acceptance range in a two-treatment, two-period cross-over study, with different sample sizes (12, 24 or 36 subjects), within-subject variabilities (15, 35 and 55%CV) and various ratios of MTD/D and D/LED. In addition, the method was retrospectively applied to the phenytoin data of Meyer (2001), theophylline data of Mistry (1999), and digoxin data of Martin (1997).

The results show that the approach has the desirable property of resulting in a more narrow acceptance range for doses near the boundaries of the therapeutic window and a wider acceptance range for products with a broad therapeutic window.

Keywords: average bioequivalence; bioavailability; individual bioequivalence; therapeutic window.

1 Introduction

Bioequivalence studies are important in drug development to prove that two drug products give similar exposure in a subject, and therefore that the safety and efficacy profile is not altered and therapeutic equivalence can be claimed. Bioavailability and bioequivalence studies are performed to evaluate differences in drug products, for example research versus market tablets, various batches, or production sites. At the same time, those techniques are also used for evaluating food effects, drug-drug interactions, and comparing administration routes.

Schuirmann (1987) laid the foundations of modern bioequivalence testing. He proposed to perform two one-sided tests, to test the hypothesis that the ratio of the key pharmacokinetic parameters AUC and $C_{\max}$ is contained within a prespecified range, which usually is 80–125%. At the end of the twentieth century, average bioequivalence as proposed by Schuirmann was questioned because it only focusses on whether the average exposure of the study population is equivalent (Anderson and Hauck, 1990, Scheiner 1992). In the typical situation where drugs are on the market, each patient should maintain the same exposure independent of his choice. This led to the concept of individual bioequivalence (Anderson and Hauck, 1990), also known as switchability. Owing to the complexity of the technique and its favoring of highly variable drug products (Hsuan 2000), individual bioequivalence has not been used extensively to date.

There are two situations in which the traditional approach with a fixed acceptance range is not optimal: first the one of highly variable drug products, and secondly narrow index drugs, i.e., drugs where comparatively small differences in dose or concentration lead to dose-and concentration-dependent, serious therapeutic failures and/or serious adverse drug

reactions.

An area of discussion is the bioequivalence assessment of highly variable drug products, i.e., products with a within-subject variability of more than 30%. Authorities acknowledge that the large sample sizes for trials with such drug products cannot always be ethically justified (FDA 2003, CPMP EMEA 2006). The simplest correction for highly variable drug products, is by extending the acceptance limits from 80–125% to 75–133% (CPMP EMEA 2001). Boddy (1995) proposed to modify the limits for highly variable drug products according to a predefined estimate of the within-subject variability of the reference drug product. The disadvantage of the 30% threshold is a discontinuity at that threshold: For example, it is possible that in a given study, a within-subject variability of 29% is observed and no modification of the limits is applied, while if the variability was slightly more than 30%, adaptation of the acceptance limits could have yielded to a different conclusion.

Karalis et al. (2004, 2005) modified the idea of extending the bioequivalence limits. Whereas Boddy et al. (1995) categorize drug substances according to a within-subject variability of less versus more than 30%, Karalis expands the bioequivalence limits in a continuous fashion as a function of the within-subject variability. However, expanding the acceptance limits increases the risk of false positives, i.e., falsely concluding two drug products to be bioequivalent. Therefore, Karalis proposed to incorporate the observed geometric mean ratio of the pharmacokinetic parameters AUC and $C_{\max}$ in the acceptance limits: the further the geometric mean ratio deviates from equality, the more conservative the acceptance range becomes.

As suggested by the FDA guidance, the therapeutic window should be taken into account instead of performing an automatic extension of the acceptance ranges:

> "Where the test product generates plasma concentrations that are substantially above those of the reference product, the regulatory concern is not therapeutic failure, but the adequacy of the safety database from the test product. Where the test product has plasma concentrations that are substantially below those of the

reference product, the regulatory concern becomes therapeutic efficacy. When the variability of the test product rises, the regulatory concern relates to both safety and efficacy, because it may suggest that the test product does not perform as well as the reference product, and the test product may be too variable to be clinically useful." (FDA 2003)

The aim of the research in this paper is to present further approaches in bioequivalence acceptance taking into account the therapeutic window as suggested by the guidelines (FDA 2003). The proposed bioequivalence limits in this paper consider the position of the therapeutic dose with respect to the least effective dose (LED) and the maximum tolerated dose (MTD). A dose close to the LED and/or the MTD may require more stringent limits ensuring exposure remains within the therapeutic window.

The paper is organized as follows. First, the methodology for expanding the bioequivalence limits is described in Section 2. The performance of the method as evaluated through simulations is described in Section 3. Finally the method is applied to three known examples of narrow index drugs (theophylline, digoxin, and phenytoin) in Section 4.

2 Methodology

Let us first introduce some notation: U and L are the upper and lower acceptance limit, α the traditional limit (125%), β the extended limit (143%), Ψ the geometric mean ratio, σ_w the within-subject standard deviation, γ, δ, and θ are rate constants. D is the therapeutic dose, which usually corresponds more or less to the administered dose, however, the phenytoin example is an example where the administered dose is lower than the therapeutic dose.

A first approach to adapt the bioequivalence limits for studies with highly variable drug substances was introduced by Boddy (1995). His method maintains the original method and acceptance ranges proposed by Schuirmann (1987) for drug substances with a low variability, i.e., $\%CV < 30\%$. For drug substances with a higher variability, the acceptance ranges are rescaled using the within-subject variability, with the 90% confidence interval of

the difference on the logarithmic scale satisfying the criterion:

$$\mid \mu_T - \mu_R \mid \leq \vartheta \sigma_w, \tag{2.1}$$

where the left side of the expression is the treatment difference on the logarithmic scale, σ_w the within-subject standard deviation, and usually $\vartheta = 1$. This means there is a discontinuation in the acceptance ranges at a within-subject variability of 30%.

Karalis *et. al.* (2005) tried to overcome the discontinuity and proposed three types of bioequivalence limits depending on the geometric mean ratio and at the same time rescaling according to the within-subject variability in a continuous manner. In this paper Weibull type limits will be used to further refine the proposed approach of Karalis:

$$U = \alpha + (5 - 4\Psi)(\beta - \alpha)\{1 - e^{-(\gamma\sigma_w)^2}\}, \tag{2.2}$$

with γ a constant to regulate the expansion of the acceptance limit, the lower acceptance limit L is $1/U$. For low within-subject variability and $\Psi = 1$, the upper limit remains approximatively α, whereas for large variability and $\Psi = 1$, the upper limit approximates β. With $\Psi = \alpha$, the upper limit is fixed to α, regardless of the variability. Its sigmoid behavior ensures that the acceptance ranges remain almost unaffected under small variability, in contrast to the exponential and Michaelis-Menten type corrections (Karalis 2005). The continuity of the technique makes it also more appealing than the proposal of Boddy (1995).

A more general formulation is

$$U = \alpha + 5\left(1 - \frac{1}{\alpha}\Psi\right)(\beta - \alpha)\left\{1 - e^{-(\gamma\sigma_w)^2}\right\} 1_{\Psi \leq \alpha}, \tag{2.3}$$

with $L = 1/U$ as before. Using $\alpha = 125\%$ in the above equation simplifies to (2.2). $1_{\Psi \leq \alpha}$ is added to indicate explicitly that Ψ should fall within the acceptance range. As the focus is not on the choice of γ, it will be fixed in the rest of the paper to a value of 3. This restricts by no means the results of the paper and is mainly chosen based on the simulations from Karalis (2005) to ensure that the acceptance ranges remain close to the standard 80–125% for small variabilities.

In this paper, the expansion of the acceptance range will not only depend on the within-subject variability, but will also depend on the therapeutic window. Therefore, a

second correction factor, which represents a similar sigmoidal function of the therapeutic window is added.

$$\begin{aligned} U &= \alpha + 5\left(1 - \frac{1}{\alpha}\Psi\right)(\beta - \alpha)\left\{1 - e^{-(\gamma\sigma_w)^2}\right\}\left\{1 - e^{-\left(\delta\frac{MTD}{D}\right)^2}\right\} 1_{\Psi \leq \alpha}, \\ L &= \frac{1}{\alpha + 5\left(1 - \frac{1}{\alpha}\Psi\right)(\beta - \alpha)\left\{1 - e^{-(\gamma\sigma_w)^2}\right\}\left\{1 - e^{-\left(\delta\frac{D}{LED}\right)^2}\right\} 1_{\Psi \geq \alpha}}. \end{aligned} \tag{2.4}$$

The therapeutic window is defined as the ratio D/LED and the ratio MTD/D. Note the asymmetric character of the acceptance limits: the lower limit depends on the distance between the dose and the LED, whereas the upper limit depends on the distance between the dose and the MTD.

A more conservative approach can be applied for narrow-index drugs. The concern has been introduced in the Canadian guideline (Ministry of Health Canada, 2006) that for certain drugs the 80–125% acceptance range would be too liberal. Therefore, the standard 125% limit, which is used as a starting point in the current approach, can be modified in a similar way. This renders the resulting acceptance ranges even more narrow in case of narrow-index drugs. As a result, the following type of bioequivalence acceptance range is introduced:

$$\begin{aligned} U &= \alpha\text{"} + 5\left(1 - \frac{1}{\alpha\text{"}}\Psi\right)(\beta - \alpha\text{"})\left\{1 - e^{-(\gamma\sigma_w)^2}\right\}\left\{1 - e^{-\left(\delta\frac{MTD}{D}\right)^2}\right\} 1_{\Psi \leq \alpha\text{"}}, \\ L &= \frac{1}{\alpha' + 5\left(1 - \frac{1}{\alpha'}\Psi\right)(\beta - \alpha')\left\{1 - e^{-(\gamma\sigma_w)^2}\right\}\left\{1 - e^{-\left(\delta\frac{D}{LED}\right)^2}\right\} 1_{\Psi \leq \alpha'}}, \\ \alpha' &= 1 + (\alpha - 1)\left\{1 - e^{-\left(\theta\left(1 + \frac{D}{LED}\right)\right)^2}\right\}, \\ \alpha\text{"} &= 1 + (\alpha - 1)\left\{1 - e^{-\left(\theta\left(1 + \frac{MTD}{D}\right)\right)^2}\right\}, \end{aligned} \tag{2.5}$$

where, as before, δ, γ, and θ are rate constants.

3 Simulation Study

The proposed bioequivalence acceptance ranges (2.5) depend on the therapeutic window as well as on the within-subject variability. These parameters, as well as the influence of the choice of the parameters δ, θ, and γ, are explored through simulations.

In the first simulation run, the acceptance ranges are calculated using (2.5) to explore their behavior for different values of θ, δ, the ratios MTD/D and D/LED, and the within-subject variability with $\Psi = 1$. The within-subject variability is presented as a coefficient of variation ($\%CV$) in line with pharmacokinetics practice. It is linked to the within-subject variability, as follows:

$$\sigma_w = \sqrt{\ln(1 + \%CV^2)}. \tag{3.1}$$

Figure 1 shows the new acceptance range for different choices of δ and θ as a function of the ratio MTD/D for the upper limit and D/LED for the lower limit. It shows that, for each choice of δ and θ, the upper or the lower acceptance limit is reduced when the tested dose approaches the boundary of the therapeutic window, i.e., when MTD/D or D/LED approach unity. For doses far from the boundary of the therapeutic window, the ratios MTD/D and D/LED are larger and the acceptance ranges broaden (righthand side of the graphs). This is a conservative approach to ensure patients maintain a safe and efficacious exposure. With θ increasing from 0.1 to 1, the slopes of the acceptance ranges become steeper near the therapeutic borders. A value of 0.3 for θ seems reasonable: the resulting shallow slope protects patients by imposing strict acceptance limits close to the borders of the therapeutic window. For a higher value of θ, the influence of the ratios MTD/D and D/LED vanishes and they may not be sufficiently conservative.

Whereas the parameter θ regulates the shrinkage of the acceptance range with respect to the therapeutic window, the parameter δ determines the expansion of the limits as a function of the therapeutic window and the within-subject variability. It basically means that for a highly variable drug product with a dose near the boundaries of the therapeutic window, the expansion of the acceptance limits is smaller than the ones proposed by Karalis

et al. (2005). For a dose far from the therapeutic boundary, the acceptance ranges behave similar to the ones in the aforementioned article.

A small value for δ, e.g. 0.1, penalizes the acceptance ranges in a very conservative way, whereas values ranging over 0.7–1 are too liberal and impose little restriction (Figure 1). Therefore, an intermediate value of 0.4 for δ seems reasonable.

Although not demonstrated in the figures, the approach of Karalis et al. (2005) is maintained and extended: the acceptance ranges depend on the within-subject variability of the drug products and gradually expand from 80–125% to 70–143%, as a function of the within-subject variability.

Whereas the previous calculations mainly illustrated the general concepts of the new approach to acceptance limits, the ensuing set of simulations was performed to compare it to existing methods (Figure 2). Thousand two-treatment, two-period cross-over studies with 36 subjects where simulated per condition, defined by the within-subject variability ($\%CV$ of 15%, 35%, and 55%), and the true geometric mean ratio Ψ (100% to 150%). θ was fixed at 0.3, and δ set to 0.4. The simulation was simplified in a first step by setting MTD/D equal to D/LED. These ratios varied from 1 to 10 in the simulation, to cover a broad spectrum of therapeutic windows. Simulations were performed using SAS 9.1 and analyzed with procedure MIXED.

Our acceptance limits and those obtained by the method of Karalis et al. coincided for 35%CV for a MTD/D ratio from 7 onwards. For a narrow-index drug, e.g., a MTD/D of 3 or less, the acceptance rate is strongly decreased due to desired shrinkage of the acceptance limits. For low-variable drugs (15% CV), the methods are essentially equivalent to the Schuirmann method, but for highly variable drug products (55%CV), the methods give clear differences. The proposed method behaves as liberal as the Karalis' method for drugs with a broad therapeutic window, and more conservative than Schuirmann for narrow-index drugs. The simulations also indicate that only a very small amount of the studies with Ψ superior to 125% conclude bioequivalence as would be expected based on (2.5). For any Ψ, the acceptance rate increases with the therapeutic window. Further exploration of the effect of

the sample size and changes of the within-subject variability in Figures 3 and 4 confirmed the previous conclusions.

Table 1 contains a summary of the above simulations for the specific case of $\Psi = 125\%$, i.e. the point from where onwards bioequivalence is rejected in classic bioequivalence testing. It represents the proportion of simulated trials where bioequivalence is concluded, whereas in fact the two products are bio-inequivalent. This corresponds to the type-1 error for the Schuirmann method. These values are larger than for Schuirmann, but correspond to the method of Karalis for MTD/D large, but they decrease well below the Schuirmann error rate when the dose approaches the MTD. Therefore the new acceptance limits are conservative when it is in the patients interest. This illustrates well the strength of the method.

Figures 5 – 7 represent the same simulations as before, but now for a situation where the dose is closer to the LED than the MTD, where D/LED varies from 1 to 10 and MTD/D is fixed to 10. When the dose is close to the LED, i.e. less than 3, the number of accepted trials when $\Psi = 100\%$ was lower than when $\Psi = 105\%$. Here, the conservative nature of the acceptance limits clearly distinguishes our method from Schuirmann's and Karalis' methods: The asymmetry of the limits render many trials inconclusive for a true Ψ of 100%, whereas this is not the case for $\Psi = 105\%$. This ensures patients will maintain an efficacious exposure.

4 Application

The Canadian health authorities recently published a guideline for critical dose drugs (Ministry of Health Canada, 2006). In the appendix of the guideline, a list can be found with a number of drug substances for which a small difference in dose or concentration lead to dose- and concentration-dependent, therapeutic failure and/or serious adverse drug reactions: cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tracolimus, theophylline, and warfarin. For these drug substances, the more stringent 90–112% acceptance limits for AUC in case of single dose administration are proposed. The three examples below illustrate well

the conservative behavior of the new acceptance limits for narrow index drugs.

4.1 Theophylline

Also theophylline belongs to the list of critical-dose drugs (Ministry of Health Canada, 2006). The data of Mistry et al (1999) is reanalyzed with the different techniques. Note that the study was not fully powered to demonstrate a drug interaction of indinavir on a single dose of 250 mg theophylline immediate release.

Again, the MTD and LED of theophylline can be derived from the literature. Theophylline therapeutic plasma concentrations range from 10 to 20 μg/mL, seizures and cardiac problems can occur at the upper limit (Ministry of Health Canada, 2006). Estimates of the first-order compartmental model (k_e, k_a rate constants, CL clearance) were obtained from Pinheiro and Bates (2000): $\log(k_e) = -2.4327$, $\log(k_a) = -0.45146$, and $\log(CL) = -3.2145$, where dose was denoted in mg/kg. The accumulation factor for multiple dosing is $1/(1 - \exp(-k_e\tau))$, τ corresponding to 8 hours. Solving the equations for a $C_{\max}$ set equal to the above range limits yields an LED of 220 mg and a MTD of 450 mg for a subject of 70 kg. Estimates for the variability are derived from Steinijans et al (1995): $\%CV$ for AUC is 12%, 20% for $C_{\max}$.

The conclusion based on the traditional analysis was an absence of a drug interaction effect: 1.18 (1.13, 1.23) for AUC, and 0.99 (0.92, 1.07) for $C_{\max}$ fall both within the 80–125% Schuirmann acceptance ranges. As the Karalis acceptance limits are always broader or equal to Schuirmann, this method also brings us to concluding that a drug interaction is absent. Our new acceptance limits, taking the variability as well as the therapeutic window into account, were (0.94, 1.12) for AUC, and (0.88, 1.15) for $C_{\max}$. Therefore, the confidence interval for AUC falls entirely outside the acceptance range and a drug interaction would be concluded for AUC.

4.2 Digoxin

As a last example, digoxin is another critical dose drug (Ministry of Health Canada, 2006). Martin et al (1997) evaluated the drug interaction of eprosartan on 0.6 mg digoxin. We reevaluate these study results with the new method.

Serum digoxin levels ranging from 0.8 to 2.0 ng/mL are generally considered as therapeutic. Levels greater than 2.0 ng/mL are often associated with toxicity (Ministry of Health Canada, 2006). The IV compartmental model as well as parameter estimates of digoxin for healthy volunteers are found in Wagner (1975). The bioavailability for tablets is 80% (Bochner et al 1977). Estimates for the variability of digoxin are derived from Steinijans et al (1995): $\%CV$ for AUC is 8%, 19% for $C_{\max}$. Using these estimates, the MTD and LED of digoxin can be derived: 0.4 mg as LED, and 1 mg as MTD.

The geometric mean ratio in the original analysis was 1.01 (0.81, 1.26) for AUC, and 1.00 (0.86, 1.17) for $C_{\max}$. Our new acceptance limits were (0.90, 1.12) for AUC, and (0.90, 1.13) for $C_{\max}$. Therefore the trial was inconclusive for both parameters.

4.3 Phenytoin

In this section, we will reanalyse a bioequivalence study using one of these critical-dose drugs (phenytoin) comparing the method of Karalis to our newly proposed acceptance limit. In Meyer (2001), three different lots of 100 mg phenytoin sodium capsules were compared. In this study, the observed %CV was low, i.e., 14% and 11% for $C_{\max}$ and AUC respectively. The conclusion based on the traditional analysis was that all 3 lots were bioequivalent.

To apply our method, the MTD and LED of phenytoin were deduced from the literature. Phenytoin exhibits Michaelis-Menten kinetics, which is described by the following equation (Gibaldi and Perrier 1982) for the steady state plasma concentrations c_{ss}:

$$c_{ss} = \frac{FD}{\tau CL_s}, \tag{4.1}$$

where

$$CL_s = \frac{V_m V}{K_m + c_{ss}}, \tag{4.2}$$

and τ represents the dosing interval. CL_s is the clearance parameter, V_m is the theoretical maximum rate of the process, K_m the Michaelis constant, V is the volume of distribution, and F is the bioavailability. Estimates of the Michaelis-Menten constants V_m and K_m for phenytoin are reported as 17.87 mg/h and 4.29 mg/L, respectively (Santos Buelga 2002). In the same study, an average steady state concentration c_{ss} of 12.5 mg/L was observed after multiple dosing of 155 mg. Given the fact that phenytoin is traditionally prescribed as b.i.d., i.e., τ is set to 12 hours, solving (4.1) and (4.2) for the unknown apparent volume of distribution, leads to an estimate of

$$V/F = \frac{D}{\tau}\frac{K_m + c_{ss}}{V_m c_{ss}} = 0.97. \tag{4.3}$$

Phenytoin is associated with severe neurological toxicity from 160 μmol/L onwards, whereas therapeutic plasma concentrations range from 40 to 80 μmol/L (Ministry of Health Canada, 2006). Therefore, a dose associated with 160 μmol/L steady state plasma concentrations will be considered the MTD. Based on the above estimations and equations, one can now calculate the MTD associated with $c_{ss} = 160$ μmol/L, or $c_{ss} = 43.9$ mg/L, given the molecular weight of phenytoin sodium (274.3 g/mol). Solving again (4.1) and (4.2) for D gives an MTD of 190 mg b.i.d., or a total daily dose of 380 mg. Analogue, the lower limit of the therapeutic window is associated with $c_{ss} = 40$ μmol/L, or $c_{ss} = 10.975$ mg/L. This leads to an LED of 150 mg b.i.d. This means that the dose tested in the study was lower than the LED. However, drug-monitoring is required for phenytoin to ensure patients remain on an optimal exposure. Therefore, the dose corresponding to 60 μmol/L in an average patient will be considered as the therapeutic dose, i.e. 165 mg.

Table 2 contains the geometric mean ratio, its 90% confidence interval, the equivalence limits using Karalis' equation, and our newly proposed acceptance ranges. The conclusions do not change for the Karalis method and it is inconclusive for all but three cases with novel method because the lower limit of the confidence interval falls below the acceptance limit. This example illustrates that the technique of Karalis only expands the acceptance limits,

whereas in our approach, the acceptance limits reduce if the dose is close or outside the edge of the therapeutic window.

5 Discussion and Conclusions

Bioequivalence testing is an important topic in drug development. In this kind of trials, the pharmacokinetic parameters AUC and $C_{\max}$ serve as surrogate markers for safety and efficacy in the sense that the equivalence of the pharmacokinetic parameters between test and reference implicitly implies that test and reference products have equivalent efficacy and safety. To claim bioequivalence of the parameters, an acceptance range of 80–125% is predefined, which implicitly leads to the conclusion that the observed differences have no efficacy or safety repercussions.

However, the assumption that changes within the 80–125% range have no clinical implications ought to be verified. For narrow-index drugs, even an exposure change of 10% might affect safety and/or efficacy, whereas doubling the exposure for certain other drug products would not affect the safety at all. It is interesting to see that this idea was already reflected in the conclusion of Sheiner (1992):

> "... The main point is that the logical basis for current bioequivalence measurement and regulation is seriously inadequate: only with an appropriate model for dose effect, and a clear delineation of clinical context and values, can one devise, estimate and test bioequivalence measures that make clinical and scientific sense. We should judge future contributions to the bioequivalence literature by how well they meet this requirement."

Since then, to our knowledge, no paper has addressed bioequivalence testing in this respect.

One might question the regulatory imposed acceptance ranges, since this approach treats all drug products in the same way. One of the concerns is that highly variable drug

products, i.e., a within-subject variability of more than 30%, are treated the same way as the rest. This results in studies with unpractical large sample sizes. Boddy (1995) and Karalis (2004, 2005) proposed, respectively, scaled average bioequivalence and bioequivalence with levelling-off properties. Both of these correct the acceptance ranges with respect to the within-subject variability, but do not answer the clinical relevance of the acceptance limits, and rather limits to the logistics and ethics of the method.

The newly proposed acceptance ranges take besides the within-subject variability also the therapeutic window into account. More specifically, the proposed approach is highly conservative for doses near the boundaries of the therapeutic window, defined by the ratios MTD/D and D/LED, and more liberal for doses far from the maximum tolerated dose and least effective dose.

A simulation study shows that for doses near the MTD, lower acceptance limits are imposed for the upper limit of the 90% confidence interval: this should ensure that patients will not experience toxic exposures for compounds with a narrow therapeutic window. The same recommended for doses close to the least effictive dose: the lower acceptance limit will approach 100% to ensure patients remain on active doses. On the other hand, for doses far from the boundaries of the therapeutic window, the acceptance limits approach the ones of Karalis et al. (2005).

Based on the simulations, it has been demonstrated that the newly proposed bioequivalence limits differentiate between narrow index drugs and drug products with a wide therapeutic window. They are very strict when it is of interest for the patient, and more flexible when the therapeutic effect remains unaffected. Traditional methods, on the contrary, apply a uniform method, regardless as to where the marketed dose is positioned in the therapeutic window.

Since the newly proposed bioequivalence limits depend on the MTD and the LED, these quantities need to be determined as accurately as possible in an early stage of drug development. This emphasizes the need for adequate dose finding trials using stochastic methods such as most prominently, the continuous reassessment method (O'Quigley et al.

1990, Patterson et al. 1999). However, also literature can be a good source for estimates of the MTD and the LED as illustrated in the application.

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Table 1: The proportion of simulated trials for which bioequivalence was concluded erroneously at $\Psi = 125\%$, as a function of %CV and sample size, in the case of $MTD/D = D/LED = \mathcal{R}$, $\theta = 0.3$, $\delta = 0.4$, and $\gamma = 3$.

	Sample size 12			Sample size 24			Sample size 36		
%CV	15	35	55	15	35	55	15	35	55
Schuirman	0.0512	0.0190	0.0023	0.0475	0.0485	0.0066	0.0493	0.0529	0.0324
Karalis	0.0515	0.0227	0.0028	0.0478	0.0636	0.0601	0.0497	0.0641	0.0976
$\mathcal{R} = 10$	0.0515	0.0227	0.0028	0.0478	0.0636	0.0601	0.0497	0.0641	0.0976
$\mathcal{R} = 7$	0.0503	0.0225	0.0028	0.0468	0.0624	0.0591	0.0474	0.0637	0.0970
$\mathcal{R} = 5$	0.0394	0.0177	0.0021	0.0327	0.0539	0.0458	0.0308	0.0545	0.0876
$\mathcal{R} = 3$	0.0083	0.0037	0.0001	0.0027	0.0171	0.0020	0.0013	0.0184	0.0324
$\mathcal{R} = 2$	0.0007	0.0002	0	0	0.0005	0	0	0.0022	0
$\mathcal{R} = 1$	0	0	0	0	0	0	0	0	0

Table 2: Reconsidering the bioequivalence testing of Phenytoin using the data from Meyer (2001) .

	test vs reference	Ψ	90% confidence interval	Karalis limit	New limit
C_{max}	2 vs 1	0.986	(0.90; 1.04)	(0.781; 1.280)	(0.921; 1.090)
	3 vs 1	0.993	(0.92; 1.05)	(0.781; 1.280)	(0.921; 1.090)
	4 vs 1	0.979	(0.89; 1.02)	(0.780; 1.281)	(0.920; 1.090)
	3 vs 2	0.995	(0.92; 1.06)	(0.782; 1.279)	(0.921; 1.090)
	4 vs 2	0.993	(0.92; 1.05)	(0.781; 1.280)	(0.921; 1.090)
	4 vs 3	0.988	(0.91; 1.04)	(0.781; 1.280)	(0.921; 1.090)
AUC	2 vs 1	0.975	(0.90; 0.99)	(0.787; 1.270)	(0.922; 1.089)
	3 vs 1	0.997	(0.95; 1.04)	(0.788; 1.269)	(0.922; 1.088)
	4 vs 1	0.984	(0.92; 1.01)	(0.788; 1.270)	(0.922; 1.088)
	3 vs 2	0.980	(0.91; 1.00)	(0.787; 1.270)	(0.922; 1.088)
	4 vs 2	0.991	(0.93; 1.03)	(0.788; 1.269)	(0.922; 1.088)
	4 vs 3	0.989	(0.93; 1.02)	(0.788; 1.269)	(0.922; 1.088)

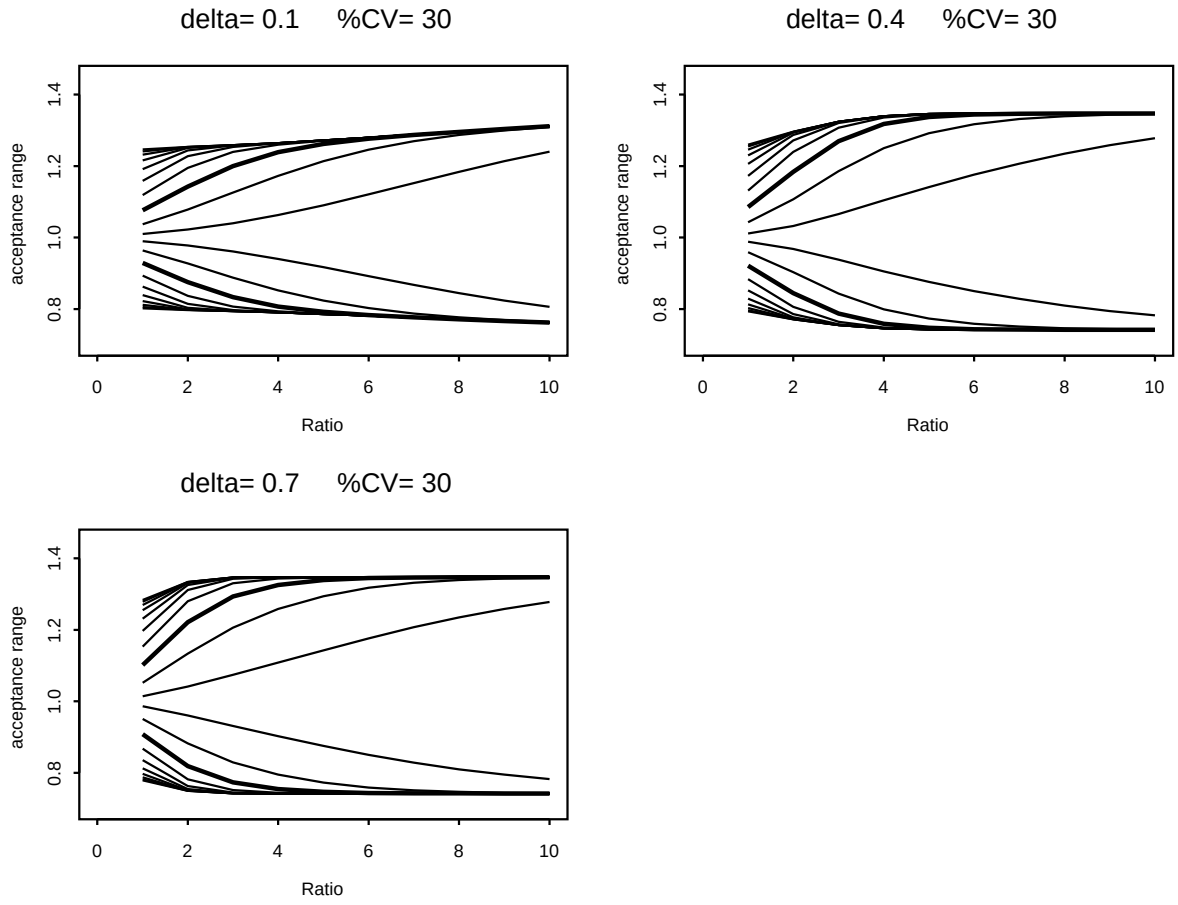

Figure 1: Illustration of the influence of therapeutic window by varying θ from 0.1 (middle) to 1 (outside) on the newly proposed bioequivalence acceptance range for different δ. The tick line represents the case $\theta = 0.3$. For the upper limit, the ratio in the x-axis represents MTD/D whereas D/LED for the lower limit. A %CV of 30% was assumed.

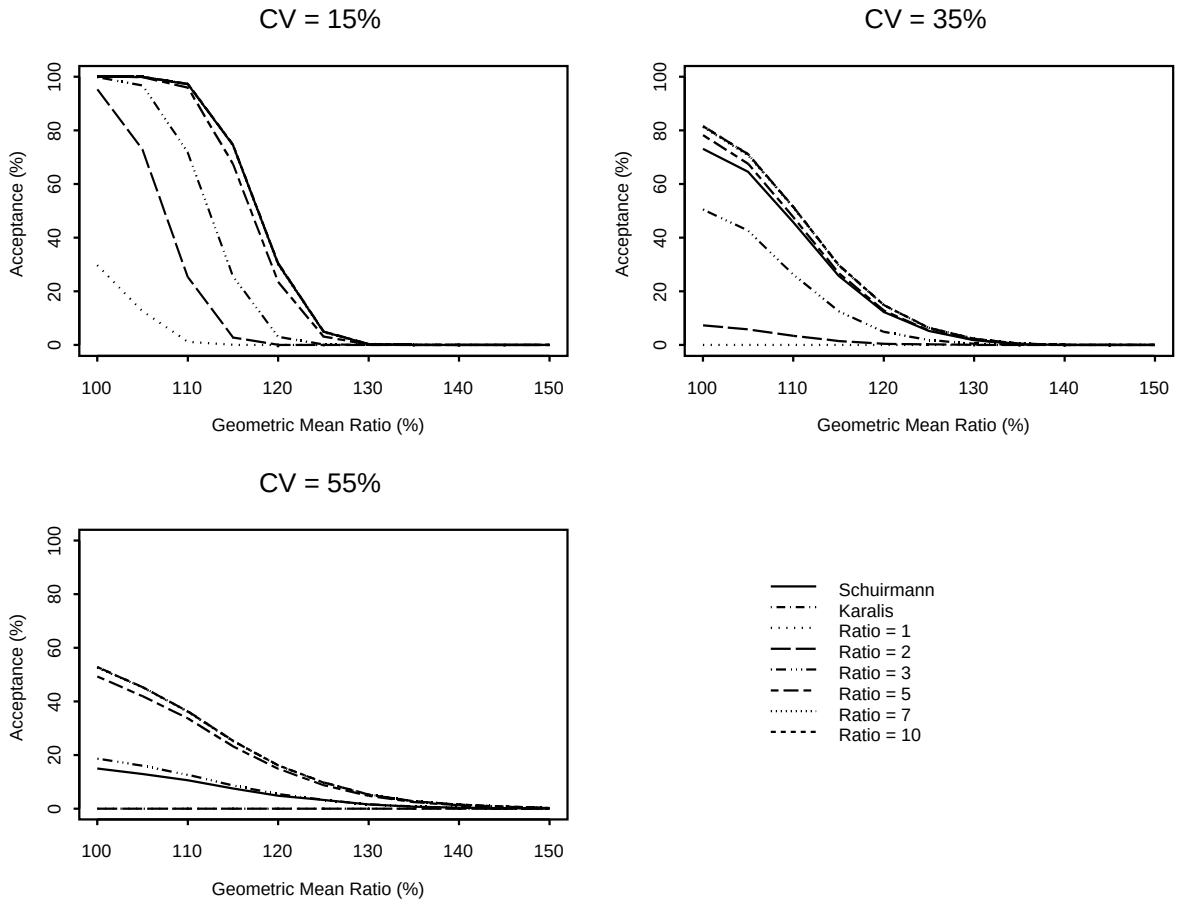

Figure 2: Influence of the within-subject variability on the acceptance (%) of bioequivalence trials using Schuirmann's method, Karalis and our new proposal with $MTD/D = D/LED$ from 1 to 10. The sample size is fixed to 36 subjects.

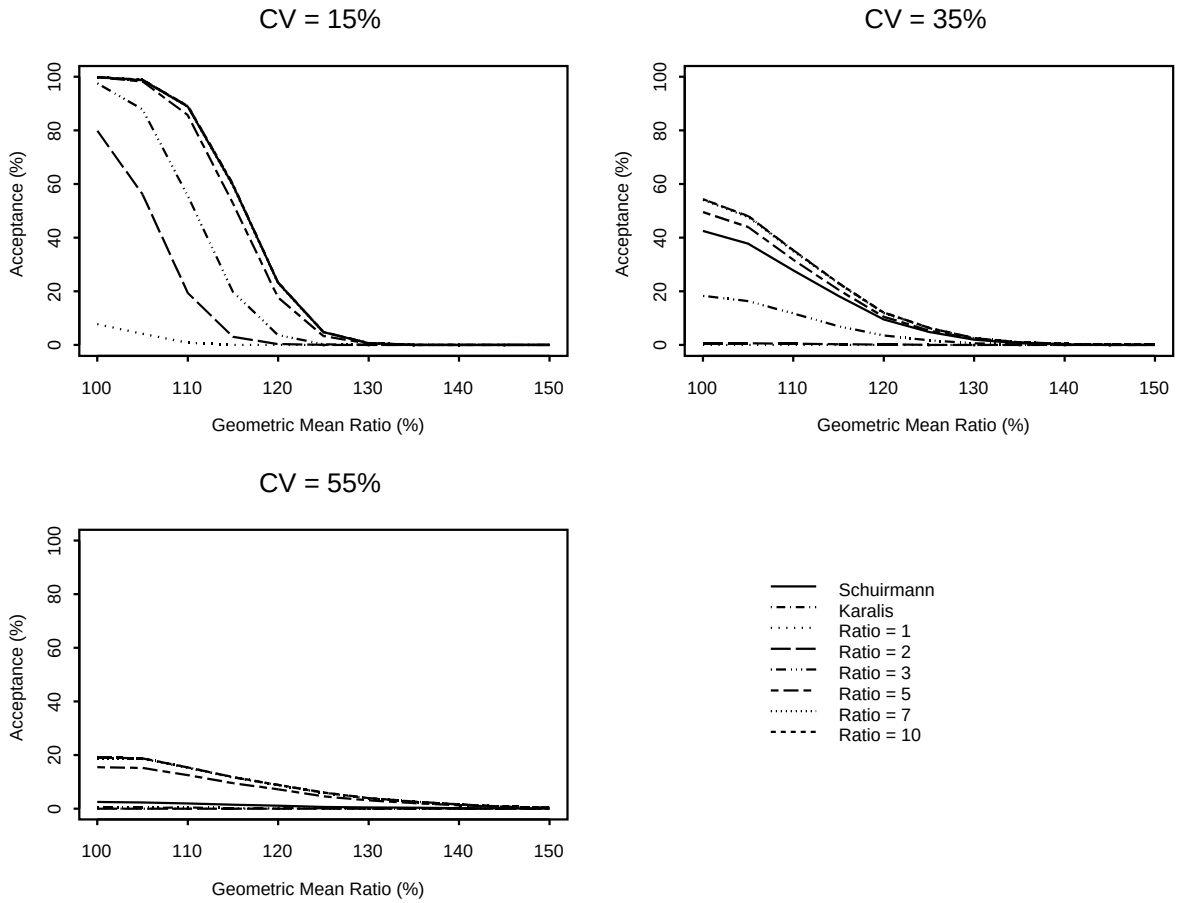

Figure 3: Influence of the within-subject variability on the acceptance (%) of bioequivalence trials using Schuirmann's method, Karalis and our new proposal with $MTD/D = D/LED$ from 1 to 10. The sample size is fixed to 24 subjects.

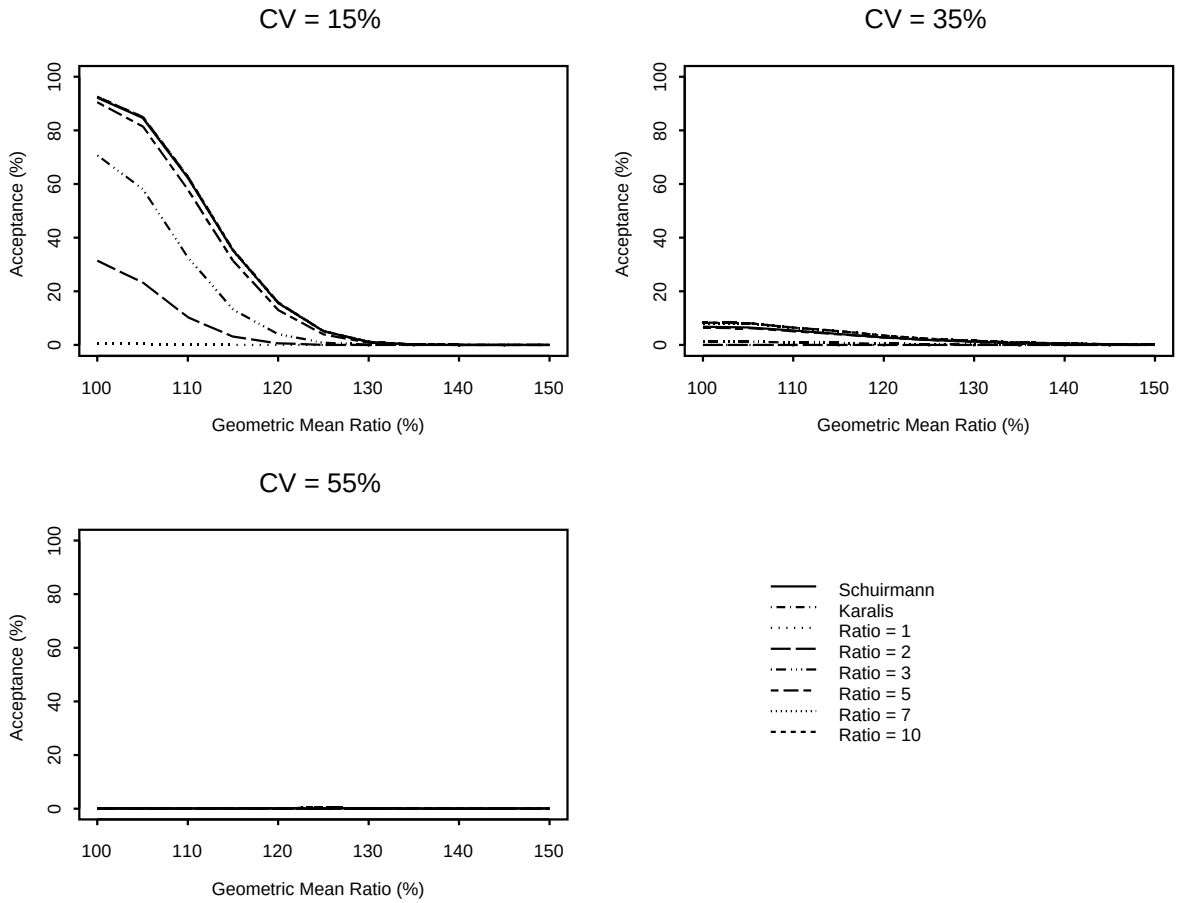

Figure 4: Influence of the within-subject variability on the acceptance (%) of bioequivalence trials using Schuirmann's method, Karalis and our new proposal with $MTD/D = D/LED$ from 1 to 10. The sample size is fixed to 12 subjects..

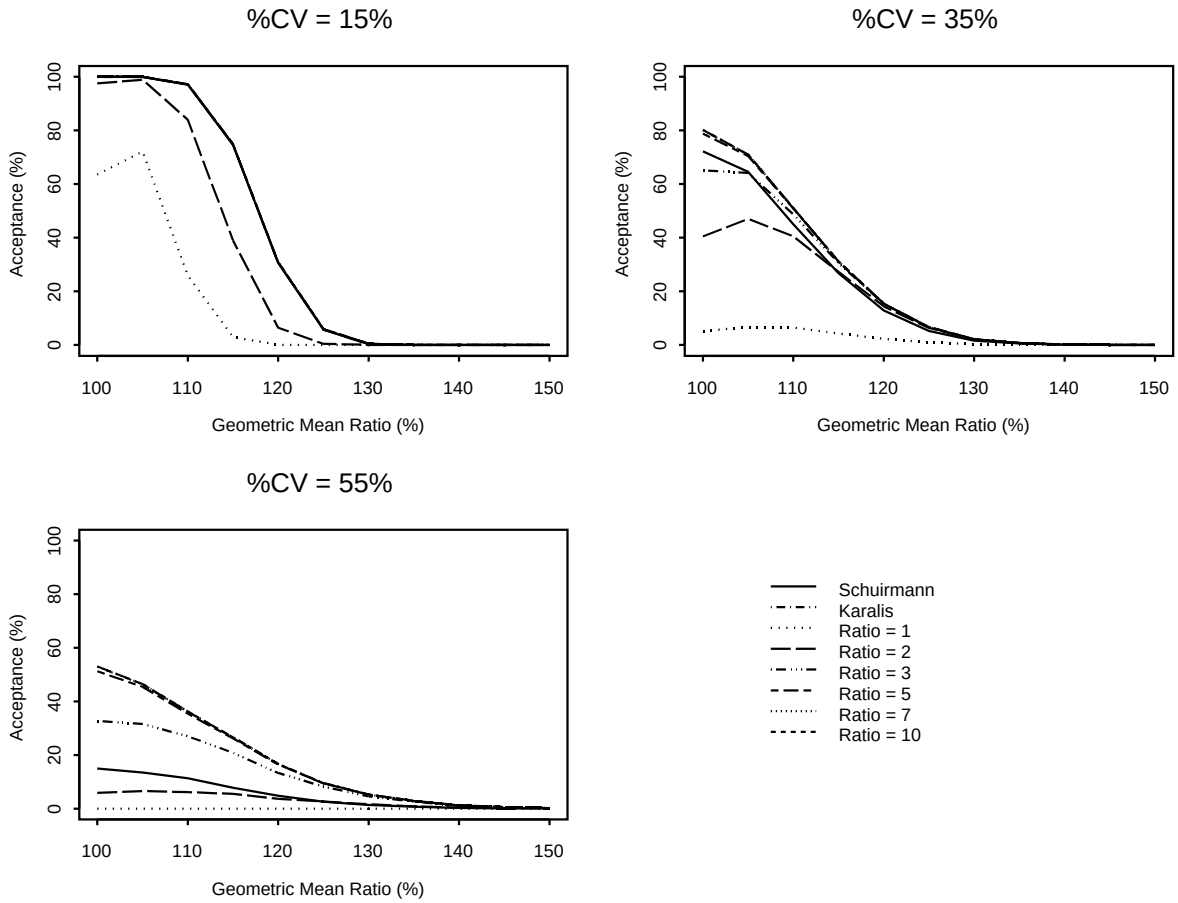

Figure 5: Influence of the within-subject variability on the acceptance (%) of bioequivalence trials using Schuirmann's method, Karalis and our new proposal with only D/LED from 1 to 10 and MTD considered large. The sample size is fixed to 36 subjects.

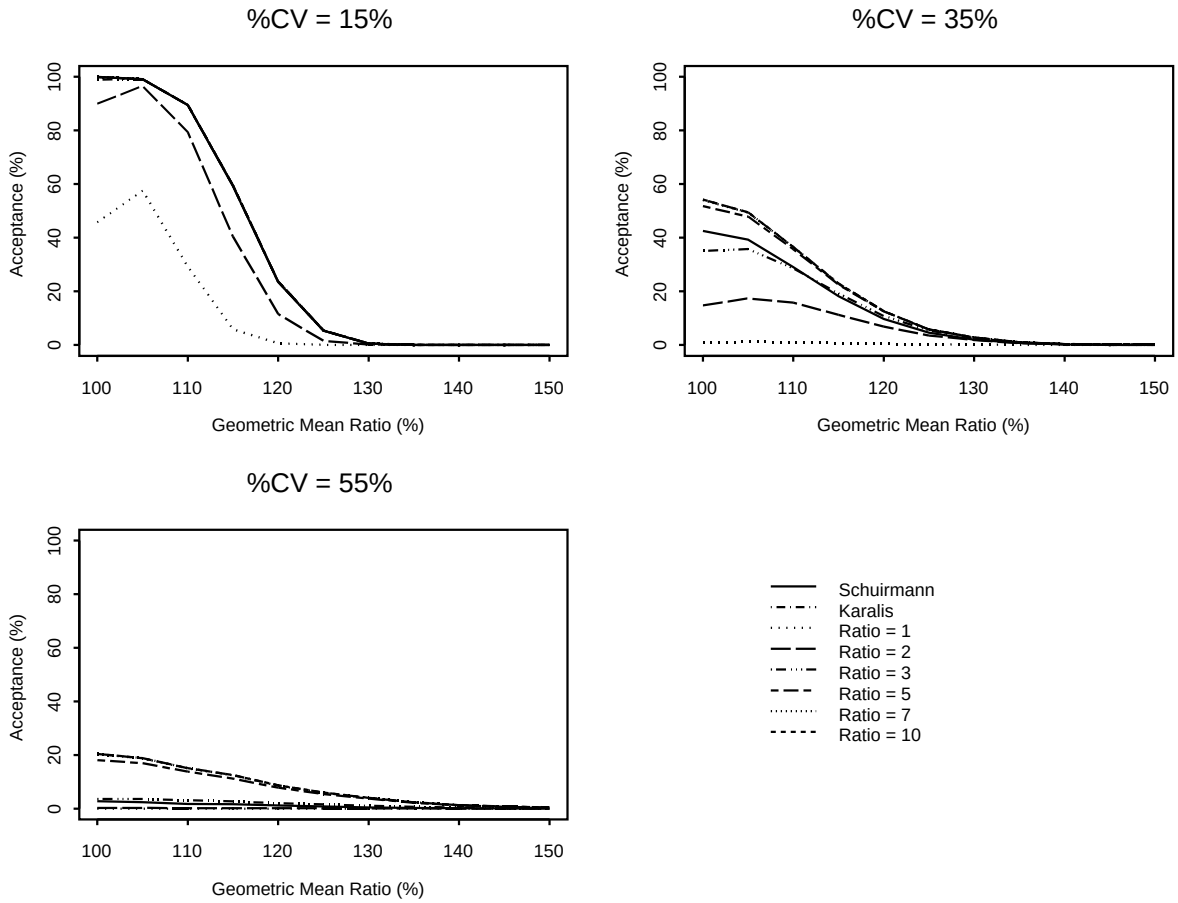

Figure 6: Influence of the within-subject variability on the acceptance (%) of bioequivalence trials using Schuirmann's method, Karalis and our new proposal with only D/LED from 1 to 10 and MTD considered large. The sample size is fixed to 24 subjects.

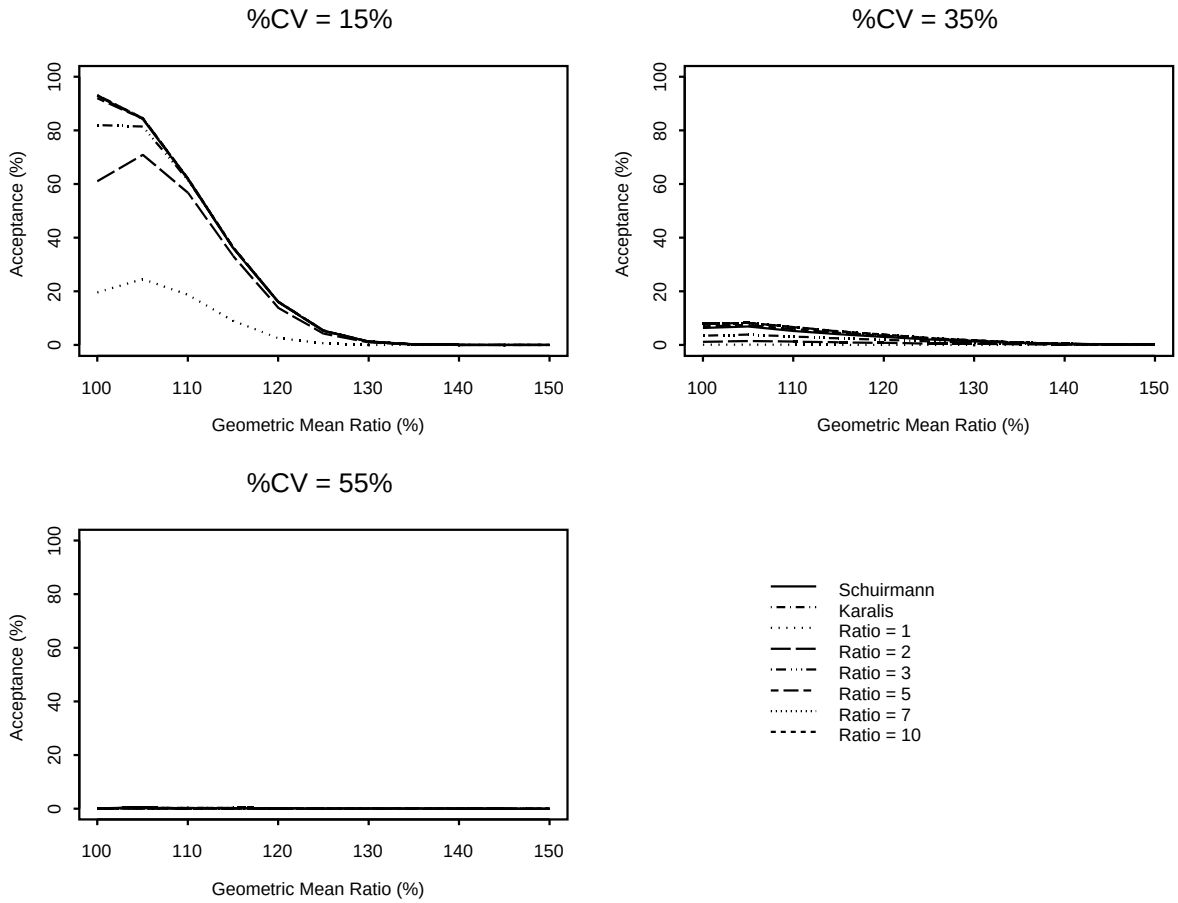

Figure 7: Influence of the within-subject variability on the acceptance (%) of bioequivalence trials using Schuirmann's method, Karalis and our new proposal with only D/LED from 1 to 10 and MTD considered large. The sample size is fixed to 12 subjects.