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Geometric mean ratio-dependent scaled bioequivalence limits with leveling-off properties

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Abstract

In this study, novel approaches for the design of bioequivalence (BE) limits are developed. The new BE limits scale with intrasubject variability but only until a geometric mean ratio (GMR)-dependent plateau value and combine the classic (0.80–1.25) and expanded (0.70–1.43) BE limits into a single criterion. Plots of the extreme GMR values accepted as a function of coefficient of variation (CV) have a convex shape, similar to the classic unscaled 0.80–1.25 limits. The performance of the novel approaches in comparison to the classic unscaled 0.80–1.25 limits as well as the two expanded BE limits, i.e., 0.70–1.43 and 0.75–1.33 was assessed using simulated data. Two-period crossover BE investigations with 12, 24 or 36 subjects were simulated with assumptions of CV 10%, 20%, 30% or 40%. At low CV values, the performance of the novel BE limits is almost identical to the 0.80–1.25 criterion. On the contrary, the expanded BE limits are very permissive even at high GMR values. For high CV% values (30% and 40%), the new BE limits show a much greater probability of declaring BE when GMR = 1 in comparison to the classic 0.80–1.25 limits. In addition, when the drug products differ more than 25%, the new BE limits show much lower percentage of acceptance than the expanded 0.70–1.43 limits. One of the major advantages of the new BE limits is their gradual expansion with variability until a GMR-dependent plateau value. Finally, the continuity and leveling-off properties of the new BE limits make them suitable for the assessment of BE studies, irrespective of the level of variability encountered.

Keywords: Bioequivalence; Highly variable drugs; Scaled bioequivalence limits; Regulatory criteria; GMR

1. Introduction

The current approach of average bioequivalence (BE) is based on constant BE limits at a level set by the regulatory agencies (Food and Drug Administration, 2000). In this context, BE is declared if the calculated 90% confidence interval (90% CI) for the ratio of the product averages (AUC, C_{max}) falls within the predefined BE limits of 0.80–1.25. This definition ensures the consumer safety since the probability of an erroneous acceptance of BE does not exceed the preset level of significance (Food and Drug Administration, 2000). However, the 0.80–1.25 BE limits, termed hereafter BEL, seem to be too restrictive leading to high producer risks for highly variable (HV) drugs. Consequently, establishing BE with these constant values of BE limits is problematic for HV drugs (Blume and Midha, 1993; Blume et al., 1995; Shah et al., 1996).

A method proposed to face this problem is the widening of BE limits to predefined constant values (e.g. 0.70–1.43, 0.75–1.33) (Blume et al., 1995; Diletti et al., 1992; European Agency for the Evaluation of Medicinal Products, 2001; Hauck et al., 2001; Tothfalusi et al., 2003). Thus, the broader limits have been proposed for HV drugs with wide therapeutic range. The use of this extended region of acceptance reduces the producer risk at high coefficient of variation (CV) values but at the same time the consumer risk rises.

Another approach for the expansion of the BE limits, suggested as an alternative for the reduction of producer risk, is the use of scaled BE limits, which widen with intrasubject

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variability (Boddy et al., 1995). However, a common drawback of the reported scaled BE limits (Boddy et al., 1995; Midha et al., 1998; Tothfalusi and Endrenyi, 2003) is their continuous increase with variability. This leads to very broad acceptance limits of bioequivalence, which are associated with very high consumer risk.

In order to overcome this drawback, novel scaled BE limits based on an effective constraint criterion were proposed recently (Karalis et al., 2004). These limits, termed BELscG1 and BELscG2, scale with intrasubject variability but include also a geometric mean ratio (GMR)-dependent criterion, which makes them less permissive at high GMR values. In simulated BE studies, both BELscG1 and BELscG2 showed a nice ability to declare BE even at high CV values. In addition, these BE limits exhibited the best performance, regarding consumer risk, among the scaled methods. BELscG1 and BELscG2 limits increase with CV, albeit to a lesser degree than all other scaled BE limits.

The aim of this study is to develop a new rationale for the design of scaled BE limits in order to improve the too restrictive behavior of the classic BEL when truly bioequivalent HV products are compared and concomitantly, reduce the percentage of accepted BE studies observed for expanded (0.70–1.43) and scaled BE limits when GMR is higher than 1.25. To this end, the BE limits developed in this study scale with intrasubject variability but only until a "plateau" value and combine the classic (0.80–1.25) and expanded (0.70–1.43) BE limits into a single criterion. In addition, in order to reduce the consumer risk at high GMR values, a GMR-dependent constraint factor (Karalis et al., 2004) is also incorporated in the new BE limits. The performance of the resulting new scaled procedures is evaluated and compared with the performance of the classic and expanded BE limits.

2. Methods

2.1. Average bioequivalence: classic BE limits

Average bioequivalence of two drug formulations is based on the comparison of the arithmetic means of a logarithmically transformed metric such as ln(AUC), ln(C_{max}). Two drug products are considered bioequivalent if the 90% confidence interval referring to the difference of the log means lies within preset bioequivalence limits (Food and Drug Administration, 2001). In case of two-treatment, two-period, crossover balanced design, the upper limit of the 90% CI is given by Eq. (1):

$$\text{Upper limit of the 90\% CI} = \exp\left(\text{Diff} + t_{0.05,N-2}\sqrt{s^2\frac{2}{N}}\right) \quad (1)$$

where Diff represents the difference between the test and reference means of the logarithmically transformed metric m_T and m_R, respectively, s^2 the intrasubject variability (calculated as the mean square error of ANOVA) and N is the number of subjects participating in the BE study.

In the case where the upper limit of the 90% CI falls exactly on the upper preset BE limit, Diff becomes equal to the maximum acceptable difference between the means, Diff_{max} (Midha et al., 1998):

$$\text{Diff}_{max} = \ln(\text{upper BE limit}) - \left(t_{0.05,N-2}\sqrt{\frac{2}{N}}\right)s \quad (2)$$

where the upper BE limit can be either constant (e.g. 1.25 according to the classic BEL) or take variable values (as in scaled BE limits). Therefore, the maximum acceptable ratio of geometric means, GMR_{max}, of the two formulations becomes equal to $\exp(\text{Diff}_{max})$.

According to Eq. (2), when the upper BE limit is preset to a constant value, Diff_{max} (or equivalently GMR_{max}) diminishes with variability. If the preset value of the upper BE limit is 1.25, as for the classic BEL, bioequivalence of HV drugs becomes difficult to be proven. However, as expected, if the preset value of the BE limit is high, e.g. 1.43, much larger values of GMR_{max} are accepted.

2.2. Average bioequivalence: scaled BE limits

The upper BE limit of scaled methods is most commonly defined as a fixed multiple, k, of intrasubject variability, i.e., upper BE limit = $\exp(ks)$ (Boddy et al., 1995; Midha et al., 1998). In this case, the value of GMR_{max} increases continuously with variability. Therefore, the GMR acceptance region of a GMR versus CV plot has a non-convex shape (Karalis et al., 2004), similar to that for the Hauck and Anderson's procedure as pointed out by Schuirmann (1987, see Fig. 12 of this reference). Thus, at high level of variation, GMR_{max} risks to attain a value exceeding the "goal post" of 1.25.

The recently proposed BE limits, BELscG1 and BELscG2 (Karalis et al., 2004), scale with intrasubject variability but also include a GMR-dependent constraint criterion. This makes the BE limits to be less permissive than other scaled methods at high GMR values. Consequently, in contrast to other scaled methods, GMR_{max} for BELscG1 and BELscG2 diminishes as variability increases. Although, this is a desired property, the decline is less pronounced compared to classic BEL (Karalis et al., 2004). A problem of theoretical interest, related to the use of BELscG1 and BELscG2, emerges when HV drugs are evaluated with a large number of subjects. In this case, the decrease of GMR_{max} as a function of CV is very small; thus, BE studies with GMR deviating from unity even at very high CVs, could be accepted. Obviously, this is only of theoretical concern because for high CV levels the extreme GMR accepted values imply practically an overlap of the intrasubject pharmacokinetic parameters (e.g. C_{max}) distributions for the Test and Reference formulations (Boddy et al., 1995). The abovementioned behavior of BELscG1 and BELscG2 is related to the fact

that the BE limits become continuously wider as variability increases.

2.3. Rationale for the development of the new BE limits

The use of constant upper and lower values for BE limits (i.e., the BE limits which are classically used today in BE studies) implies a reduction of GMR_{max} as CV increases. Thus, the first aim of our study was to design BE limits with this desired property but also leading to a lower producer risk than the classic unscaled BEL. A way to achieve this feature is the design of BE limits that scale with intrasubject variability but only until a "plateau" value.

On the other hand, the current use of expanded BE limits (e.g. 0.70–1.43) decreases the producer risk, but enhances the consumer risk. One can argue, however, that the BE limits should be less strict for a study with GMR around unity in comparison to a study exhibiting GMR close to the marginal value of 1.25. Therefore, our second aim was to design BE limits, which ensure a lower consumer risk as the GMR of the study becomes higher. A way to attain this characteristic is to include a GMR-dependent constraint factor (Karalis et al., 2004) in the design of the new scaled BE limits.

In order to combine the abovementioned desired properties into a single criterion, the upper BE limit can be expressed as a function of intrasubject variability which levels off at a GMR-dependent plateau value. Accordingly, this function should have three preset parameters that control:

(i) the minimum (or "starting") value of the upper BE limit;
(ii) the maximum (or "plateau") value of the upper BE limit;
(iii) the "rate" of the gradual change of the upper BE limit value.

The upper limit function must also include a GMR-dependent constraint factor that affects the plateau level.

A variety of different mathematical expressions possess the aforementioned characteristics. Obviously, the specific form of the mathematical expression affects the "rate" of gradual change of the BE limit. In this study, three different functions are considered: a Michaelis–Menten type Eq. (3), a simple exponential Eq. (4) and a Weibull type expression Eq. (5),

$$\text{Upper BELscM} = \alpha + (5 - 4\text{GMR})(\beta - \alpha)\left(\frac{s}{\gamma + s}\right) \quad (3)$$

$$\text{Upper BELscE} = \alpha + (5 - 4\text{GMR})(\beta - \alpha)(1 - e^{-\gamma s}) \quad (4)$$

$$\text{Upper BELscW} = \alpha + (5 - 4\text{GMR})(\beta - \alpha)(1 - e^{-(\gamma s)^2}) \quad (5)$$

where α is the parameter controlling the minimum value, β the parameter that affects the maximum value and γ is the parameter that controls the "rate" of gradual change of the upper BE limit value. The factor $(5 - 4\text{GMR})$ is the GMR-dependent constraint that affects the plateau level (Karalis et al., 2004). As variability increases, the maximum value is attained only when GMR = 1; however, the plateau value is reduced when GMR deviates from unity.

The simplest choice for the value of the parameter α, is the value of the classic upper BEL, $\alpha = 1.25$. A possible choice for the value of the plateau level is $\beta = 1.43$, which corresponds to the most commonly used upper expanded BE limit called hereafter BELw1. Different values of the parameter γ can be considered depending on the specific mathematical expression used for the upper BE limit. The choice of a value for γ may be based upon specific criteria; for example, one can assign a specific value to the upper BE limit (e.g. 95% of the plateau value = 0.95β) at CV = 30% and then calculate from Eqs. (3)–(5), using GMR = 1, $\alpha = 1.25$, $\beta = 1.43$, the value of γ. Obviously, alternative criteria may be also considered.

According to Eqs. (3)–(5) when $\alpha = 1.25$ and $\beta = 1.43$, the upper BE limit values range from 1.25 to 1.43. The specific value can be estimated only if the values of GMR and s are known. In a qualitative manner, when s is high and GMR close to 1, then the upper BE limit reaches a value near 1.43. On the contrary, when GMR is close to 1.25 the more strict BE limit of 1.25 is reached regardless of the s value.

It should be noted that Eqs. (3)–(5) apply for GMR ≥ 1; when GMR < 1, the reciprocal of GMR is used to calculate the upper BE limit. Due to symmetry of the BE limits with respect to unity, the lower BE limit is always equal to the reciprocal of the upper limit.

2.4. Simulation framework

Two-treatment, two-period, crossover bioequivalence studies, with equal number of subjects in each sequence, were simulated and evaluated using the classic BEL (0.80–1.25), the extended BELw1 (0.70–1.43) and BELw2 (0.75–1.33) BE limits, as well as the three novel methods: BELscM, BELscE and BELscW with $\alpha = 1.25$, $\beta = 1.43$ and various values for γ (Eqs. (3)–(5)). In each simulated crossover study, bioequivalence was declared if the 90% CI around the ratio of the estimated geometric means (GMR) for the two drug products was between preset BE limits. A number of 12, 24 or 36 subjects was assumed to participate in the simulated trials. Pharmacokinetic parameters were assumed to follow log-normal distribution. The true CV values considered for the simulations, ranged from 10 to 40%. The standard deviations (σ) of the logarithmically transformed parameters were calculated from the preset CV using the following expression: $\sigma = \sqrt{\ln(1 + \text{CV}^2)}$. The average parameter value for the reference formulation was arbitrary set to 100 units. The true ratio of geometric means was gradually changed, from 1.00 to 1.50. Twenty thousand simulated BE trials were performed under each condition and the percentage of simulated studies, in which BE is accepted, was recorded. Power curves

were constructed by plotting the percentage of accepted studies versus the true GMR value. The whole programming work was implemented by developing a computer program in Fortran.

3. Results and discussion

Fig. 1 illustrates the three new BE limits as a function of intrasubject variability (in terms of ANOVA–CV%) for various values of the parameter γ. The upper and lower family of curves for each one of the three plots, which correspond to the upper and lower BE limits, have been generated from Eqs. (3)–(5) using GMR = 1. For GMR values equal to 1.25 and 0.80 the BE limits are always equal to 1.25 and 0.80, respectively. Thereafter, the discussion will focus on the upper limits since similar comments can be also made for the lower limits. In all cases, the upper BE limits become higher as variability increases. The increase of γ values for BELscM or the reduction of γ values for BELscE and BELscW leads the upper BE limit to smaller values, i.e., the criterion becomes more strict. The widening of BE limits in case of BELscW, is less pronounced at smaller ANOVA–CV% values, but the slope of the curve is becoming more steep after a point forward. Due to the flexibility and continuity of the proposed BE limits (Fig. 1), regulatory agencies can select the most appropriate function in conjunction with the γ value to construct criteria with clinical relevance.

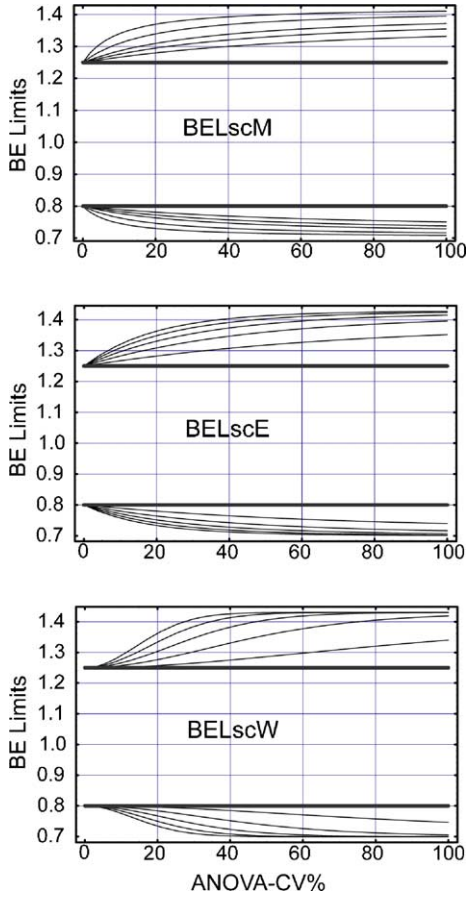

Fig. 1. Upper and lower BE limits as a function of intrasubject variability (ANOVA–CV%) for the three novel methods (BELscM, BELscE and BELscW) using various values of the parameter γ and GMR = 1. For GMR values equal to 1.25 and 0.80 the BE limits are always equal to 1.25 and 0.80, respectively (thick lines). The γ values used to construct the upper family of curves of each graph are (from top to bottom): 0.1, 0.2, 0.4, 0.6, 1.0 for BELscM; 5.0, 4.0, 3.0, 2.0, 1.0 for BELscE and BELscW. For the lower family of curves, the same γ values were used in a reverse order.

Fig. 2 shows the maximum and minimum GMR accepted values as a function of ANOVA–CV% using various γ values for two-period crossover BE studies with 24 subjects, by the three novel scaled BE approaches. Bioequivalence, between the two drug products, is declared when the GMR value of the study lies between the minimum (GMR_{min}) and the maximum (GMR_{max}) lines. In all cases, GMR_{max} declines (or equivalently GMR_{min} increases) with ANOVA–CV%. As the value of γ increases for BELscM or decreases for BELscE and BELscW, the curves become more steep and the value of GMR = 1 is reached for lower CV values. It should be also noted that the use of a larger number of subjects leads to

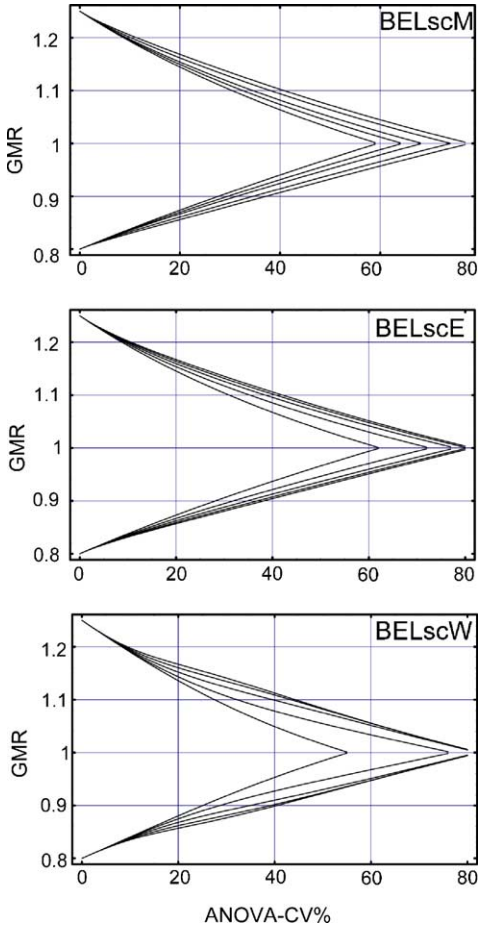

Fig. 2. Extreme GMR values accepted by the three novel methods as a function of ANOVA–CV% assuming $N = 24$. Each line corresponds to a different value of γ. Key (from left to right): $\gamma = 1.0, 0.6, 0.4, 0.2, 0.1$ for BELscM; $\gamma = 1.0, 2.0, 3.0, 4.0, 5.0$ for BELscE and BELscW.

a more permissive behavior (data not shown), i.e., the corresponding curves exhibit less steep slopes. A more strict performance is observed when a smaller number of subjects are used (data not shown). In all cases, the new scaled limits become more permissive than the classic unscaled BEL (Karalis et al., 2004; Fig. 2) as variability increases. Compared to the recently proposed scaled approaches, BELscG1 and BELscG2 (Karalis et al., 2004), the three novel BE limits present the advantage to be clearly less permissive at high CV values. GMR_{max} curves of the three new BE limits do not show the very smooth decline observed for BELscG1 and BELscG2, which allowed GMR values deviating from unity even at very high CVs. Obviously, this finding is a consequence of the new structure of the BE limits with leveling-off properties. Overall, the GMR acceptance region of the graph of Fig. 2 has a convex shape which is similar to that of the classic unscaled 0.80–1.25 limits (Karalis et al., 2004; Schuirmann, 1987). Undoubtedly, this is not only a desired property but also a unique characteristic for a scaled method.

Fig. 3 presents the percentage of studies in which BE is declared as a function of GMR by applying the three novel BE limits, as well as the classic unscaled BEL and the two extended BE limits, BELw1 and BELw2. Two-period crossover simulated studies were performed assuming 24 subjects and ANOVA–CV% equal to 35%. For each one of the new BE limits, three different values for the parameter γ were used. BELscM, BELscE and BELscW appear to be more permissive at the top graph and become stricter moving downwards, depending on the γ value used. These findings are in accordance with the theoretical expectations shown in Fig. 2. In all cases, the power curves of the new BE limits in Fig. 3 lie between the classic BEL and BELw1. For the set of the γ values used in Fig. 3A, the performance of all new BE limits is almost identical to BELw2. This interesting finding prompted us to further examine, using simulated studies, this specific set of γ values, i.e., 0.1, 5.0 and 5.0 for BELscM, BELscE and BELscW, respectively.

In this context, all procedures were evaluated using simulated data assuming 12, 24 and 36 subjects and CV values of 10, 20, 30 and 40%. The results shown in Fig. 4 correspond to simulation studies with $N = 24$. At low CV values (CV = 10%), the three novel BE limits are almost identical to the 0.80–1.25 criterion, while the expanded 0.70–1.43 (BELw1) seems to be extremely permissive even at high GMR values (e.g. 94.2% of accepted studies at GMR = 1.30). Even the less expanded BELw2 exhibits at this low CV value (10%), a very permissive performance, e.g. 67.0% of accepted studies at GMR = 1.25. As variability increases, BELscM, BELscE and BELscW exhibit similar performance and become more permissive. For high ANOVA–CV% values (30% and 40%), the new BE limits show a much greater probability of declaring bioequivalence when GMR = 1 in comparison to the classic BEL. The power curves of BELscM, BELscE and BELscW always lie between the curves corresponding to BEL and BELw1 and for high CV values (30% and 40%) are very close to BELw2. It is important to mention

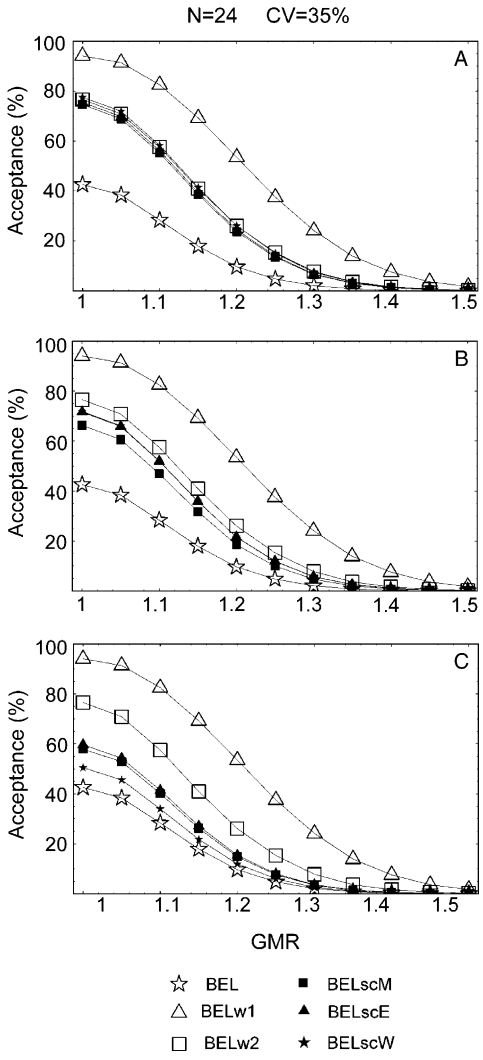

Fig. 3. Acceptance (%) of bioequivalence studies by the 0.80–1.25 (BEL), 0.70–1.43 (BELw1), 0.75–1.33 (BELw2), and BELscM, BELscE and BELscW procedures at various ratios of the geometric means (GMR). Under each condition, a number of 20,000 two-period crossover studies with 24 subjects were simulated at CV = 35%. Key (γ values for BELscM, BELscE and BELscW): A (0.1, 5.0, 5.0), B (0.4, 3.0, 3.0) and C (1.0, 1.0, 1.0).

that for GMR values higher than 1.25, the novel BE limits demonstrate much lower percentages of acceptance than the BELw1.

In Fig. 5, the power curves for two extreme scenarios are presented. A high variable drug, CV = 30% or 40%, is evaluated using $N = 12$ or 36, respectively. For both scenarios, the new BE limits have almost identical behaviour with BELw2. The new BE limits exhibit much higher statistical power than the classic BEL when the two drug products are truly bioequivalent. Furthermore, the percentage of accepted studies for the new BE limits is much lower than the expanded 0.70–1.43 limits at high GMR values.

The new BE limits posses several advantages in comparison to the classic BEL as well as the expanded BE limits. Thus, the new BE limits exhibit higher percentages

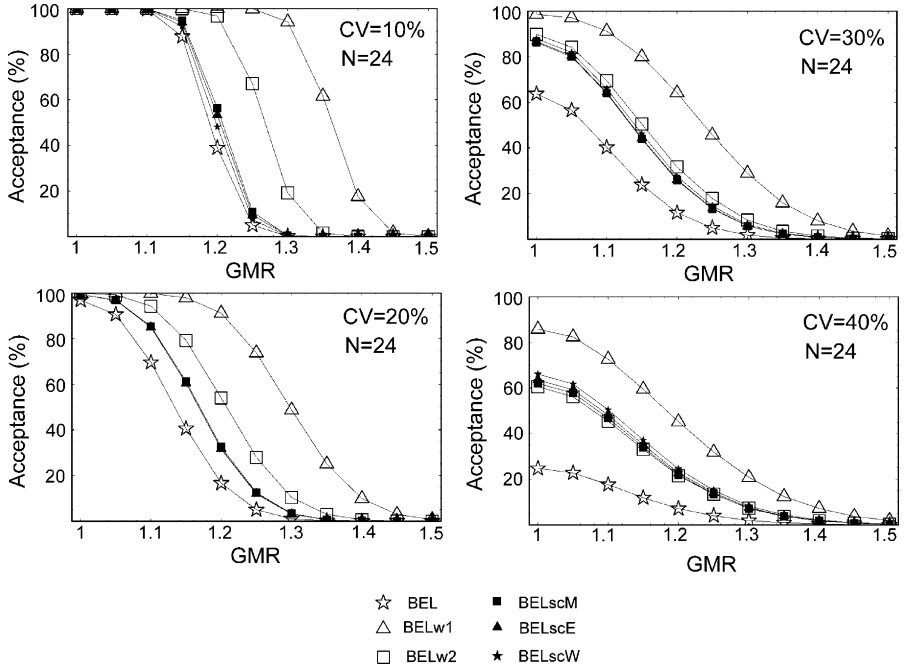

Fig. 4. Acceptance (%) of bioequivalence studies by the 0.80–1.25 (BEL), 0.70–1.43 (BELw1), 0.75–1.33 (BELw2), and BELscM, BELscE and BELscW procedures at various ratios of the geometric means (GMR). Under each condition, a number of 20,000 two-period crossover studies with 24 subjects were simulated at four levels of variation (CV values equal to 10, 20, 30 and 40%). The γ values for BELscM, BELscE and BELscW were 0.1, 5.0 and 5.0, respectively.

of acceptance than the classic BEL when truly bioequivalent high variable drug products are compared. In addition, for GMR values larger than 1.25 and high CV levels, the BELw1 is more permissive than the novel limits. Similarly, at low CV levels both BELw1 and BELw2 exhibit much higher percentage of accepted BE studies when the drug products differ more than 25%.

Compared to the recently proposed BELscG1 and BELscG2 approaches (Karalis et al., 2004; Figs. 3 and 4), at low and moderate variability values (CV = 10% and 20%) the three novel scaled BE limits show similar performance with BELscG1, while BELscG2 (as expected from its design) appear to be less permissive. At CV = 30%, all scaled methods present almost identical behavior. At high variability levels (CV = 40%) the new BE limits show a slight reduction of statistical power when compared to BELscG1 and BELscG2, i.e., about 3.8–7.6% less BE studies are accepted at GMR = 1; on the other hand, lower percentages of acceptance are recorded for GMR values larger than 1.25. Therefore, even though the leveling-off properties of the new functions used for the design of the three novel BE limits result in convex extreme GMR–CV plots, Fig. 2 (in contrast to the shallow extreme GMR–CV plots of BELscG1 and BELscG2 at high CVs; Karalis et al., 2004), it should be noted that the statistical power of the new approaches remains practically unaffected when truly bioequivalent drug products are compared (GMR = 1), at least for the range of variability values encountered in BE studies.

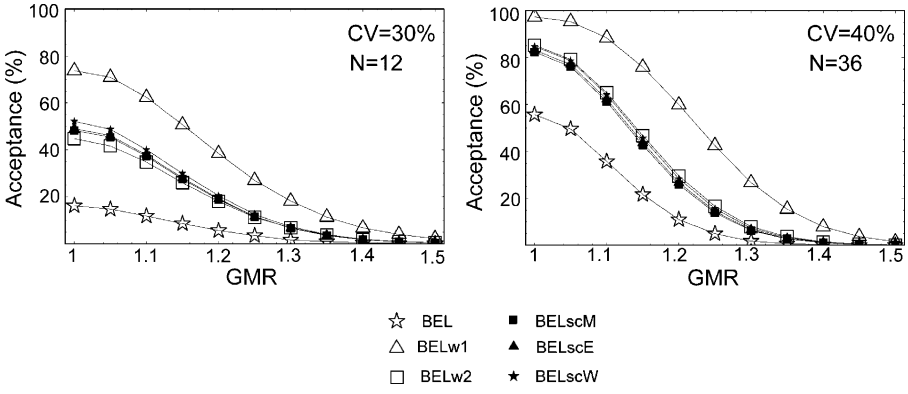

Fig. 5. Acceptance (%) of bioequivalence studies by the 0.80–1.25 (BEL), 0.70–1.43 (BELw1), 0.75–1.33 (BELw2), and BELscM, BELscE and BELscW procedures at various ratios of the geometric means (GMR). Under each condition, a number of 20,000 two-period crossover studies were simulated with 12 subjects and CV = 30% or 36 subjects and CV = 40%. The γ values for BELscM, BELscE and BELscW were 0.1, 5.0 and 5.0, respectively.

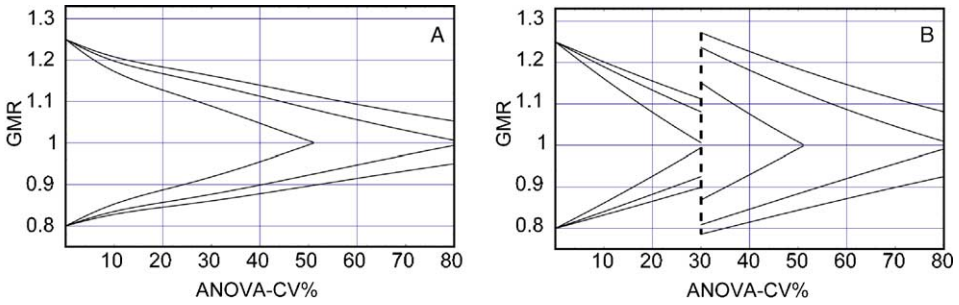

Fig. 6. Extreme GMR values accepted as a function of ANOVA–CV% by (A) BELscW with $\gamma = 5.0$ and (B) the combination of BEL (for CV < 30%) and BELw1 (for CV ≥ 30%) assuming a switching variability of CV = 30% (dashed line). Each line corresponds to a different level of sample size N considered: from top to bottom $N = 36$, 24 and 12 for the upper family of curves, while for the lower family of curves the same N values were used in a reverse order.

One of the major advantages of BELscM, BELscE and BELscW is their gradual expansion with variability until a plateau value. Thus, the new BE limits combine the properties of classic and the expanded BE limits into a single criterion. The gradual expansion of the BE limits is by far preferable than the use of expanded criteria only beyond an arbitrarily chosen, critical "switching" variability value. This is shown schematically in Fig. 6 using a GMR versus CV plot for BEL (0.80–1.25) and BELw1 (0.70–1.43) in contrast to BELscW. This discontinuity of the BE limits may lead to unfair treatment of different formulations of the same drug evaluated in separate BE studies and presenting only minor differences in variability. For example, assuming a "switching" variability of CV = 30%, it seems rather unfair, that a drug with broad therapeutic index and CV = 29.9% has to be evaluated using the classic BEL, which allows a $GMR_{max} = 1.08$, while the same drug could be evaluated in a different BE study with CV = 30%, using the expanded BELw1, which allows a $GMR_{max} = 1.24$ (Fig. 6B).

The gradual expansion from a "strict" to a "permissive" criterion, apart from avoiding the discontinuity around a "switching" variability, makes the new BE limits also suitable for use at low CV levels without the need of a secondary criterion (Tothfalusi and Endrenyi, 2003) of constrained GMR value. This becomes obvious even if one considers the use of the less expanded BELw2. In this case, the expanded limits must be used either only beyond a "switching" variability or with all CV levels but only concomitantly with a secondary criterion of constrained GMR value. Otherwise, BELw2 will be very "permissive" and consequently, unsuitable for low variability drugs, allowing large deviations of GMR from unity. On the other hand, at low CV levels, BELscM, BELscE and BELscW exhibit similar percentage of accepted BE studies as the classic BEL. Therefore, the new BE limits would be implemented in practice, for example, in the case of C_{max} ratio, in lieu of a wider acceptance interval, as quoted in the EMEA 2001 guideline.

It is also worthy to mention that the new BE limits present a quite flexible structure and therefore a variety of "starting" and "plateau" values for the upper BE limit can be considered. For example, values for the parameter α lower than 1.25 may be used if a more "strict" criterion is preferred for toxic drugs of low variability. Besides, values for the parameter β lower than 1.43 will result in a less expanded limit at high CVs.

Overall, the flexibility, continuity and leveling-off properties of the proposed BE limits in conjunction with their performance in the simulation studies make them suitable for the assessment of BE studies, irrespective of the level of variability encountered.

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