NOTE

Exploring the Relationships Between Scaled Bioequivalence Limits and Within-Subject Variability

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Received 2 July 2012; revised 20 September 2012; accepted 19 October 2012

Published online 15 November 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23365

ABSTRACT: Assessment of bioequivalence (BE) for highly variable drugs is challenging. As within-subject variability increases, it becomes more difficult to prove BE, unless a large number of subjects is recruited. In order to face this problem, several approaches have been proposed. Among them, scaled BE limits (BEL) have recently attracted special attention because the European Medicines Agency and the US Food and Drug Administration adopted scaled approaches. Scaled BELs expand with variability using specific mathematical functions while include additional regulatory criteria in some cases. The aim of this study is twofold: (1) to provide a deeper insight into the dependence of scaled BELs on variability and (2) to unveil the underlying mathematical relationships. The comparative analysis of these BELs is implemented through algebraic manipulations and graphic illustrations. Special emphasis is placed on the "absolute change" of each BEL and the "relative change," reflecting the portion of the relative to the maximum expansion of a BEL. This analysis reveals the causal differences between the different BELs on the mode of "absolute" and "relative" change. The results derived from this study are in agreement with the observed different performances of the various scaled BE approaches. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:296–301, 2013

Keywords: bioequivalence; bioavailability; scaled limits; highly variable drugs; European Medicines Agency; Food and Drug Administration; mathematical models; regulatory science; pharmacokinetics; relative change

INTRODUCTION

The assessment of bioequivalence (BE) relies on the concept of average BE.[1–3] Two drug products are considered bioequivalent if the calculated 90% confidence interval for the difference of their log-transformed mean measures of bioavailability lies between preset limits. However, this classic BE approach becomes problematic in case of highly variable drugs (HVDs), namely, drugs that are characterized by a within-subject coefficient of variation (CV_w) value greater than 30%.[4] In case of HVDs, the risk of erroneously rejecting BE between two drug products (producer risk) becomes relatively high. In order to alleviate this problem, several methods for expanding the BE limits (BELs), based on an estimate of within-subject variability, were proposed.[5–10] Recently, regulatory authorities[1,11] proposed scaled procedures for the assessment of BE of HVDs.

The purpose of the present work is to provide (1) a deeper insight into the dependence of the scaled BELs on the within-subject variability and (2) an explicit mathematical relationship connecting the different scaled BELs.

THEORY

The Classic BE Approach

Determination of average BE of two drug products (test vs. reference) is based on the comparison of the means of logarithmically transformed pharmacokinetic parameters, namely, area under the concentration-time curve (AUC) and peak plasma concentration (C_{max}). BE is accepted if the difference of the log-transformed means falls between specific predefined values for the upper and lower BELs.[1,3] The current approach of average BE is based on

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Journal of Pharmaceutical Sciences, Vol. 102, 297–301 (2013)

constant BELs ($BELs_0$) at a level set by the regulatory agencies[1,3]:

$$\text{Upper BE constant limit} = BEL_0 \quad (1)$$

where BEL_0 is usually set equal to 1.25. The lower BEL is simply the reciprocal of the upper limit, namely, 0.80. This classic approach is still widely used in BE studies. Nevertheless, the determination of BE becomes problematic for HVDs.

Scaled BE Approaches

Approaches based on scaled BELs, which incorporate the magnitude of within-subject variability, have been developed[5–10] to reduce the producer risk as variability increases.

Simple Scaled BELs

A method for expanding the BELs for HVDs was proposed. According to this method, BELs are scaled as a fixed multiple of within-subject standard deviation, σ_w, on the log scale.[5] Thus, simple scaled BELs ($BELs_{sc}$) can be constructed using Eq. 2, which actually describes the "absolute change" of the upper BEL as a function of σ_w:

$$\text{Upper simple scaled BE limit} = BEL_{sc} = \exp(k\sigma_w) \quad (2)$$

where k is a multiplying factor.

In practice σ_w can be replaced by s_{wR}, that is, the calculated sample within-subject standard deviation of the reference formulation, on the log-scale.[1,11] Scaled BELs are recommended to be used only beyond a switching criterion, that is, when the CV_w of the reference formulation (CV_{wR}) is greater than 30%. It is worth mentioning that CV_{wR} and s_{wR} are linked by the relationship: $CV_{wR} = \sqrt{e^{s_{wR}^2} - 1}$. The major drawback of the $BELs_{sc}$ is their continuous widening with variability, which appears to lead to very broad acceptance limits of BE.

Scaled BELs with Leveling-Off Properties

In order to combine the classic and expanded BELs into a single criterion, the so-called "leveling-off" (LO) scaled BELs have been proposed.[9,10] The advantage of the LO limits is their continuous scaling between a basal and an extreme plateau value. Consequently, no switching criteria are required. The LO limits are based on appropriate functions that provide a smooth widening of the BELs with the increase of variability.

The "absolute change" of the upper LO limit, in case of a sigmoid function, is given by Eq. 3:[10,12]

$$\text{Upper leveling} - \text{off BE limit} = LO = \alpha + \frac{\beta - \alpha}{1 + e^{-(s_{wR} - s_{w0})/\gamma}} \quad (3)$$

where γ is a parameter controlling the "rate" of gradual expansion, s_{w0} is the inflection point of the curve, and α, β refer to the basal and maximum values of the upper BEL, respectively.

Current View of the Regulatory Authorities

Recently, scaled procedures for the assessment of BE of HVDs have been proposed by the US Food and Drug Administration (FDA) working group on HVDs[11] and by the latest guideline of the European Medicines Agency (EMA).[1] The newly proposed EMA guideline recommends a mixed scaled approach in case of HVDs: The acceptance limits can gradually be expanded as a function of within-subject variability but only for CV_{wR} values between 30% and 50%, that is, two switching criteria are imposed. Therefore, regarding the upper BEL, fixed values (BEL_0) are assigned, namely 1.25 and 1.4319 for the lower and upper boundary values, respectively. It should be underlined that the increasing part of the scaled limits follows an exponential rise, as in Eq. 2, with a scaling factor k set equal to 0.760. These BELs actually exhibit leveling-off properties[12] because they are not allowed to scale continuously, but only up to $CV_{wR} = 50\%$. The scaled procedure proposed by the FDA working group on HVDs[11] recommends a scaling factor equal to ln(1.25)/0.25, corresponding to a higher k value, that is, 0.893. Scaling is also used for $CV_{wR} \geq 30\%$ but no upper boundary value is imposed. Therefore, this procedure results in broader BELs than EMA's.[13] Finally, it is worth mentioning that both FDA and EMA approaches[1,11,14] include a secondary constraint criterion, that is, the point estimate of test/reference geometric mean ratio of the study must fall within 0.80–1.25.

METHODS

The comparative analysis of the BELs is implemented through algebraic manipulations and graphic illustrations. Special emphasis is placed on (1) the "absolute change" of each BEL, which quantifies the expansion of BELs beyond the 0.80–1.25 range and (2) the "relative change", namely the ratio of complementary portions of the relative to the maximum expansion of a BEL.

RESULTS AND DISCUSSION

The major advantage of the $BELs_{sc}$, as originally proposed by Boddy et al.[5] in 1995, is the simple function used for the construction of BELs (Eq. 2). In fact, a log-linear function relates the BELs to the variability. Thus, for the upper limit, Eq. 2 can be written as

$$\ln(BEL_{sc}) = ks_{wR} \tag{4}$$

Therefore, in the case of the $BELs_{sc}$, the "absolute change", that is, the so-called "scaling" of the BEL, is log linearly related to s_{wR}. As mentioned earlier, BEL_{sc} cannot be applied effectively for the entire range of variability values encountered in BE studies, but should be combined with additional criteria, for example, with $BELs_0$. These discontinuity characteristics prompted us to propose a continuous, but more complicated sigmoid function, for the construction of BELs, the so-called LO limits.[10,12]

Starting from the original function of the LO BEL, Eq. 3 can be written as

$$\frac{LO - \alpha}{\beta - \alpha} = \frac{1}{1 + e^{-f(s_{wR})}} \tag{5}$$

where $f(s_{wR}) = (s_{wR} - s_{w0}) / \gamma$. By defining as, "expansion": $LO - \alpha = \varepsilon$, "maximum expansion": $\beta - \alpha = \varepsilon_{max}$, and "relative expansion": $\varepsilon/\varepsilon_{max} = \varepsilon_r$, Eq. 5 is expressed as

$$\varepsilon_r = \frac{1}{1 + e^{-f(s_{wR})}} \tag{6}$$

or

$$\ln\left(\frac{\varepsilon_r}{1 - \varepsilon_r}\right) = f(s_{wR}) \tag{7}$$

The left-hand side of Eq. 7 equals to

$$\ln\left(\frac{\varepsilon_r}{1 - \varepsilon_r}\right) = \ln\left(\frac{LO - \alpha}{\beta - LO}\right) \tag{8}$$

The ratio on the right-hand side of Eq. 8 can be defined as $\frac{LO-\alpha}{\beta-LO}$, the "relative change" of the BEL. The "relative change" becomes equal to 1 when $LO = (\alpha + \beta)/2$, that is, when LO attains its half expansion. A schematic representation of the LO BEL along with the parameters involved in the definition of the "relative change" of the limit is shown in Figure 1.

Substituting back the original parameters and variables from Eq. 3, into Eq. 7, one obtains:

$$\ln\left(\frac{LO - \alpha}{\beta - LO}\right) = \frac{1}{\gamma}s_{wR} - \frac{s_{w0}}{\gamma} \tag{9}$$

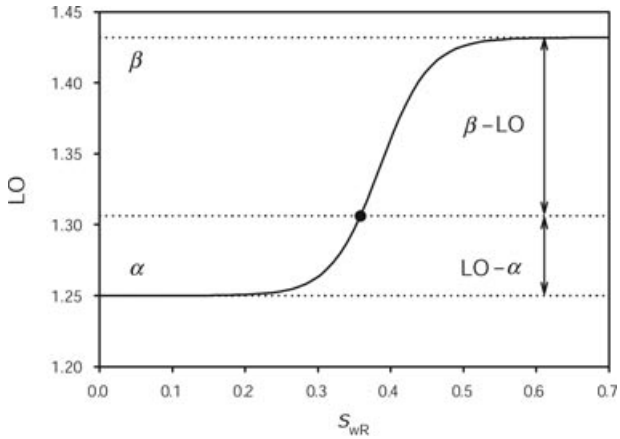

Figure 1. Schematic representation of the upper leveling-off (LO) bioequivalence limit along with the parameters involved in the definition of the "relative change" of the limit. As an example, the black dot corresponds to $s_{wR} = 0.36$ and $LO = 1.31$.

Therefore, as can be seen from Eq. 9, in the case of the continuous sigmoid LO limits, the "relative change" of the BEL is log linearly related to s_{wR}. For the $BELs_{sc}$, the "relative change" is equal to $(BEL_{sc} - \alpha)/(\beta - BEL_{sc})$.

Furthermore, inspection of Eqs. 4 and 9 reveals that a simple linear relationship is connecting the "relative change" of LO limits to the "absolute change" of BEL_{sc} on the log scale:

$$\ln\left(\frac{LO - \alpha}{\beta - LO}\right) = \frac{1}{k\gamma}\ln(BEL_{sc}) - \frac{s_{w0}}{\gamma} \tag{10}$$

Figure 2 presents the "absolute change" (Fig. 2a) and the "relative change" (Fig. 2b) of the BELs versus s_{wR}. For reasons of clarity, only the upper limits are shown. In addition, a second x-axis, depicting the corresponding CV_{wR} values, is shown in the graph. BEL_{sc}(EMA) were constructed by setting $k = 0.760$ in Eq. 4 (for $0.29356 < s_{wR} < 0.47238$ corresponding to $30\% < CV_{wR} < 50\%$), as suggested in the latest EMA guideline.[1] $BELs_0$ of 1.25 and 1.4319 for $CV_{wR} < 30\%$ and $CV_{wR} > 50\%$, respectively, are also depicted in the graph. LO limits were constructed by setting the appropriate values to the parameters[12] in Eq. 3, that is, $\alpha = 1.25$, $\beta = 1.4319$, $s_{w0} = 0.3853$, and $\gamma = 0.0336$. Scaled BELs corresponding to the FDA approach,[11] BEL_{sc}(FDA), with $k = 0.893$ are also shown. For comparative reasons, the "relative change" for these limits has been also calculated in respect to α and β boundary values.

Visual inspection of Figure 2a reveals the great similarity of the "absolute change" of the BEL_{sc}(EMA) and LO limits with s_{wR}. Obviously, the "absolute change" of BEL_{sc}(FDA) is steeper, leading to broader scaled limits.[13] In this case, the secondary constraint

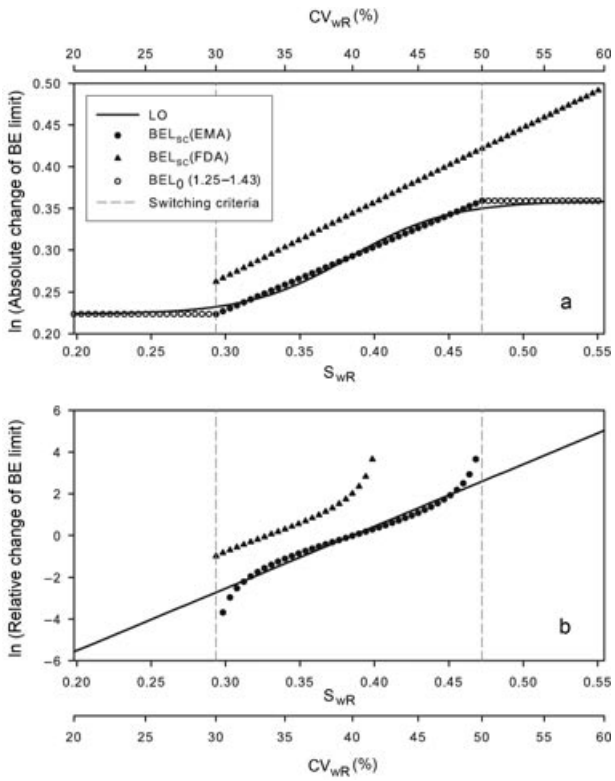

Figure 2. "Absolute change" (a) and "relative change" (b) of the BE limits (BELs) as a function of within-subject variability. LO,[12] leveling-off continuous limits based on a sigmoid function; BEL_{sc}(EMA),[1] simple scaled limits used for $30\% < CV_{wR} < 50\%$; BEL_{sc}(FDA),[11] simple scaled limits used for $CV_{wR} \geq 30\%$ and corresponding to the FDA approach; and BEL_0, constant BELs. The "relative change" of all limits has been calculated in respect to 1.25 and 1.4319 boundary values.

criterion on the parameters' geometric mean ratio value of the study would play an important role on the BE acceptance.[13] As it is expected, the LO limits show a smoother change because they are based on a single equation that changes gradually with $s_{wR,}$. On the contrary, the mixed scaled EMA approach, consisting of the combination of BEL_0 and BEL_{sc}(EMA), results in BELs that are piecewise continuous. In this case, the BEL presents a log-linear rising segment, corresponding to BEL_{sc}(EMA).

Figure 2b depicts the "relative change" of the BELs as a function of variability. It is worth mentioning that the "relative change" on the log scale can be evaluated only in the interval $30\% < CV_{wR} < 50\%$ for BEL_{sc}(EMA) and in the interval $30\% \leq CV_{wR} < 42\%$ for BEL_{sc}(FDA). As shown in Figure 2b, the "relative change" of the LO limit exhibits a log-linear relationship with variability (Eq. 9), whereas BEL_{sc} limits present a different, more complex pattern. As expected, the "relative change", on the log scale, is equal to zero when the BELs attain their half expansion, in respect to 1.25 and 1.4319 boundary values.

The mathematical analysis presented in this work provides a deeper insight into the properties of the different scaled BELs and unveils their interrelation. The "relative change" of the BELs is useful for exploring the dependence of the scaled BELs on variability. It is more convenient to describe the self-limiting change of a nonlinear BEL as the LO limit. Its linear dependence on variability (on the log scale) reflects the smooth change of the limit from a basal to a plateau value, and especially around the critical CV values of 30% and 50%. Furthermore, the "relative change" of the BELs reveals in a more clear way than the "absolute change," the discontinuity of a mixed approach, as, for example, the one adopted by EMA.

CONCLUSIONS

This study contributes to a better understanding of the properties of the currently used scaled BELs and their relationship with variability.

For the $BELs_{sc}$, the "absolute change" is related log linearly with variability. For the LO scaled BELs, the "relative change" is related log linearly with variability. A simple linear relationship connects the "relative change" of LO limits to the "absolute change" of BEL_{sc} on the log scale.

This analysis revealed the differences on the mode of "absolute" and "relative" change between the different BELs. The results derived from this study are in agreement with the observed differences in the performances of the various scaled BE approaches.

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