Supplementary material to Ocaña, J., Sánchez, M.P., Sánchez, A. and Carrasco, J.L. "On equivalence and bioequivalence testing", *SORT*, 32(2), 2008[1]

Scaling the bioequivalence limits

In its more general form (Tothfalusi and Endrenyi, 2003), the method of linearly scaling the bioequivalence limits combines the usual model to establish ABE, based on fixed bioequivalence limits (*BEL*):

$$-\theta < \phi < \theta,$$

with a scaled model:

$$-k\sigma_{SC} < \phi < k\sigma_{SC}$$

where σ^2_{SC} is a variance used as a scaling factor. In crossover two-period studies the scaling factor is the residual variance, $\sigma^2_{SC} = \sigma^2$. According to a preset regulatory variability limit, σ^2_0, ABE is evaluated using fixed bioequivalence limits if its variance is not greater than σ^2_0 and using scaled bioequivalence limits otherwise. That is, the scaled limits (*BELsc*) in the original scale are:

$$BELsc = \begin{cases} \mp\theta & \text{if } \sigma^2_{SC} \le \sigma^2_0 \\ \mp k\sigma_{SC} & \text{if } \sigma^2_{SC} > \sigma^2_0. \end{cases} \quad (1)$$

In order to avoid discontinuities in the ABE limits when taken as a function of σ^2_{SC}, the regulatory variability limit σ_0 and the proportionality constant *k*, which should have the form $k = \theta/\sigma_0$, must be adequately chosen. A possible choice is $\sigma_0 = 0.2$, recommended in the case of individual BE by the FDA guidance CDER(2001). Then the proportionality constant becomes $k = \ln(1.25)/0.2 = 1.116$. Other possibilities are $\sigma_0 = 0.22314$, recommended by Boddy et al. (1995) with $k = 1$, or $\sigma_0 = 0.294$ (Shah et al., 1996) with $k = 0.759$. This last possibility corresponds to an ANOVA-CV threshold of 30%, that defines the condition for a high variability drug.
In addition to the arbitrary choice of the "switching" variability, σ_0, the scaling variance must be estimated. As a consequence, different bioequivalence limits will be calculated for each individual study. The decision as to whether using constant or scaled limits is taken on the basis of a (random) variability estimate. And obviously, for a sufficiently large estimated variance, bioequivalence will be declared for $\bar{D}$ values far from the usual bioequivalence limits, a similar criticism to that one made to Berger and Hsu (1996) method.
To alleviate the arbitrariness of these criteria, Karalis et al. (2004) developed scaled BE limits incorporating variability and the constraint that the estimated formulation effect should not greatly exceed ±223. The general form of these limits is:

$$\mp\left(k_1\hat{\sigma}_{SC} + k_2 \log(1.25)\right) \quad (2)$$

where k_1 is a proportionality factor and k_2 is a "constraint" factor taking into account the maximum point estimate permitting ABE declaration. Different choices of k_1 and k_2

[1] All numeric references to formulae correspond to this paper

define different methods for specifying the limits, including fixed limits and scaling like the *BELsc* introduced previously.
Among the possible choices for k_1 and k_2 two possibilities defining the methods labelled as *BELscG*1 and *BELscG*2 in Karalis et al. (2004) are:

Method	k_1	k_2
*BELscG*1	$(5-4\exp(\bar{D}))\ 0.496$	1
*BELscG*2	$(3-2\ \exp(\bar{D}))\ 0.496$	$(3-2\ \exp(\bar{D}))$

More precisely:

$$\begin{aligned} BELscG1 &= \mp\left[\left(5-4\exp\left(\bar{D}\right)\right)\ 0.496\,\hat{\sigma}_{SC}\right]+\log(1.25) \\ BELscG2 &= \mp\left(3-2\exp\left(\bar{D}\right)\right)\left[0.496\,\hat{\sigma}_{SC}+\log(1.25)\right]. \end{aligned} \tag{3}$$

These equations are applied when $\bar{D}\geq 0$, otherwise $-\bar{D}$ is used to calculate the limits.
Additionally, Karalis et al. (2005) proposed limits scaling with variability but only up to a $\bar{D}$-dependent plateau value, combining the classic (0.80-1.25) with the FDA expanded (0.70-1.43) limits into a single criterion. The authors proposed three different functions, based on Michaelis-Menten, Exponential and Weibull type expressions:

$$\begin{aligned} UpperBELscM &= \pm\log\left[\alpha+\left(5-4\exp\left(\bar{D}\right)\right)+(\beta-\alpha)\left(\frac{\hat{\sigma}_{SC}}{\gamma+\hat{\sigma}_{SC}}\right)\right] \\ UpperBELscE &= \pm\log\left[\alpha+\left(5-4\exp\left(\bar{D}\right)\right)+(\beta-\alpha)\left(1-\exp\{-\gamma\hat{\sigma}_{SC}\}\right)\right] \\ UpperBELscW &= \pm\log\left[\alpha+\left(5-4\exp\left(\bar{D}\right)\right)+(\beta-\alpha)\left(1-\exp\left\{-\left(\gamma\hat{\sigma}_{SC}\right)^2\right\}\right)\right] \end{aligned} \tag{4}$$

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 BE limit. A recommended choice of parameter values is α= 1.25, β= 1.33 and γ= 4.
A possible disadvantage of these limits is precisely its over-parameterization. They are based on the need for the limits to be less strict for a study with $\bar{D}$ around zero in comparison to a study in which $\bar{D}$ is close to the bioequivalence limit. Kytariolos et al. (2006) developed limits based only on variability considerations. They considered that the failure of the classic unscaled limits was due to the high producer risk as variability increases. Thus, scaled BE limits should incorporate the magnitude of intrasubject variability, levelling off as a function of this magnitude. In the original scale, the upper bioequivalence limit has the general form:

$$basal\ BEL + BE_{ef}\left(s, u_{\lim}\right)$$

where, BE_{ef}, is known as the *bioequivalence limit expansion function.* The BE_{ef} is a function of intrasubject variability $\hat{\sigma}_{SC}$, and a predefined maximum value for the upper limit, u_{lim}. It affects the rate of gradual change of the limits. The basal limit is a minimum basal value, e.g. 1.20 or 1.25. Two model functions, the Sigmoid and the Weibull, were considered by the authors, giving rise to the following expressions for the upper limits:

$$BEL_{ef}scS = \pm\log\left\{\alpha + \frac{\beta-\alpha}{1+\exp\left[-\left(\frac{CV-CV_0}{\gamma}\right)\right]}\right\}$$
$$BEL_{ef}scW = \pm\log\left\{\alpha + (\beta-\alpha)\left(1-\exp\left[-(\gamma\hat{\sigma}_{SC})^2\right]\right)\right\} \quad (5)$$

where α is the minimum or basal value of the upper limits in the original scale (1.25 or 1.20), β is the maximum or *plateau* value of the upper limit (1.43 or 1.33), and γ is a constant controlling the *rate* of gradual change of the upper limit (1 to 8 in the Sigmoid Model and 1 to 5 in the Weibull model). The terms CV and CV_0 represent the estimated coefficient of variation and at the inflection point, respectively, both in the original scale. They are related to the corresponding variances in the logarithmic scale by means of (19) in Ocaña et al. (2008).

An example of HV drug study

Sánchez et al. (2008) illustrate the use of the preceding methods in Furosemide data (Furosemide 40 mg tablets, generic, as the test formulation vs. LASIX 40 mg, Aventis® as the reference formulation) coming from a randomized 2×2 crossover trial performed with $N = 16$ healthy individuals. The ANOVA estimated coefficient of variation for C_{max} was 36.67%, which seems to confirm that this diuretic is a HV drug with respect to this pharmacokinetic measure. The direct drug effect estimate for log C_{max} was $\bar{D} = -0.1599$ with $\widehat{\text{se}}_{\bar{D}} = 0.1256$. According to these values, the Schuirmann's TOST procedure lower and upper *p*-values were 0.0043 and 0.3112, respectively. Bioequivalence can't be declared due to the lack of rejection of one of the one-sided null hypotheses associated to the TOST procedure. Equivalently, the shortest 90% confidence interval is [68.3, 106.3], not included in the bioequivalence limits [80, 125]. A similar conclusion is reached using the 95% confidence intervals (13), (15) or (16), with values [68.3, 106.3], [68.3, 146.5] and [68.3, 106.3], respectively. Note also that there will be a similar conclusion if the widened (up to fixed values) bioequivalence limits [70, 143] (FDA proposal) or [75, 133] (EMEA proposal) were used.
The arbitrariness in the choice of the proportionality constant k in the scaled limits (20) is illustrated by the fact that for $k = 1.116$, the resulting equivalence limits are [67.3, 148.6] and bioequivalence should be declared, no matter the confidence interval type, while the opposite conclusion should be drawn under other possibilities ($k = 1$ or 0.759). The results with the scaled bioequivalence approach (21) are more coherent. The noncentral Student's t confidence interval (23) is [−3.24, 0.39]. For $k = 1.116$, 1 and 0.759 the corresponding bioequivalence limits are [−3.16, 3.16], [−2.83, 2.83] and [−2.15, 2.15]. Then, it is not possible to declare bioequivalence, irrespective of the choice of k.

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