Statistical Methods for Narrow Therapeutic Index and Highly Variable Drug Products

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Our approach for bioequivalence (BE) assessment for both Highly Variable Drugs and Narrow Therapeutic Index Drugs involves the use of ***Reference Scaled Average Bioequivalence*** (RSABE)

RSABE

Under RSABE, a Test Product (T) and a Reference Product (R) are considered BE if

$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} < \theta = \frac{(\ln \Delta)^2}{\sigma_{W0}^2}$$

where μ_T, μ_R are the population means for the log-transformed PK endpoint for the Test and Reference products

σ_{WR} is the within-subject standard deviation in the population for the log-transformed PK endpoint for the Reference product

RSABE

Under this criterion, the *implied* BE limits on μ_T-μ_R (i.e. on the ln(GMR)) are

$$|\mu_T - \mu_R| < (\ln \Delta) \frac{\sigma_{WR}}{\sigma_{W0}}$$

As σ_{WR} increases, the limits get wider.

This differs from regular *unscaled* average bioequivalence (ABE), for which the BE limits are $|\mu_T - \mu_R| < (\ln \Delta)$ (typically with Δ=1.25), regardless of σ_{WR}.

RSABE

For highly variable drugs, CDER uses

$$\Delta = 1.25$$

and

$$\sigma_{W0} = 0.25$$

Justification for RSABE for Highly Variable Drugs

- The Reference product, R, having gone through human clinical trials as the basis for its approval, is assumed to be safe and effective.
- If R has high within-subject variability, meaning that resulting blood levels may vary widely from one occasion to another within the same individual, then R must have a *Wide Therapeutic Window*. This argument has been made by, e.g., Prof. Leslie Z. Benet (e.g. Benet 2006.)
- Therefore, there is a scientific justification for defining wider BE limits for Highly Variable Drugs.

Replicated Crossover Designs for Highly Variable Drugs

In order to estimate σ_{WR}, we need a design where subjects receive the Reference product more than once. One design we recommend is the "partial replicate" design:

	period		
	1	2	3
sequence 1	T	R	R
sequence 2	R	T	R
sequence 3	R	R	T

Replicated Crossover Designs for Highly Variable Drugs

Another possible design for Highly Variable Drugs is a four-period ("full replicate") design:

	period			
	1	2	3	4
sequence 1	T	R	T	R
sequence 2	R	T	R	T

Replicated Crossover Designs for Highly Variable Drugs

Why don't we recommend a standard two-period crossover design, and scale by the residual mean square?

Three factors can make the residual mean square from a two-period crossover large:

1. If σ_{WR} is large.
2. If σ_{WT} is large.
3. If there is *Subject-by-Formulation Interaction*.

Of these three factors, only σ_{WR} being large implies a wide therapeutic window, as studied in the original human clinical trials. So we want to scale by σ_{WR}, and so we must be able to estimate σ_{WR}.

Statistical Approach for RSABE

We want to establish that $\frac{(\mu_T-\mu_R)^2}{\sigma_{WR}^2} < \theta$. This implies that

$$(\mu_T - \mu_R)^2 - \theta\ \sigma_{WR}^2 < 0$$

(this is called "the linearized criterion"), since $\sigma_{WR} > 0$.

We conclude that T and R are BE if a 95% *upper confidence bound* for $(\mu_T - \mu_R)^2 - \theta\ \sigma_{WR}^2$ is less than 0.

The 95% upper confidence bound is calculated using *Howe's Approximation I* (Howe, 1974).

Highly Variable Drugs – Mixed Scaling

When RSABE was being considered for use with BE studies of Highly Variable Drugs, we realized:

While we wanted the implied BE limits to get wider for high σ_{WR}, we did not want the limits to get *narrower* (than the standard

[ln(0.80), ln(1.25)] limits) for low σ_{WR}.

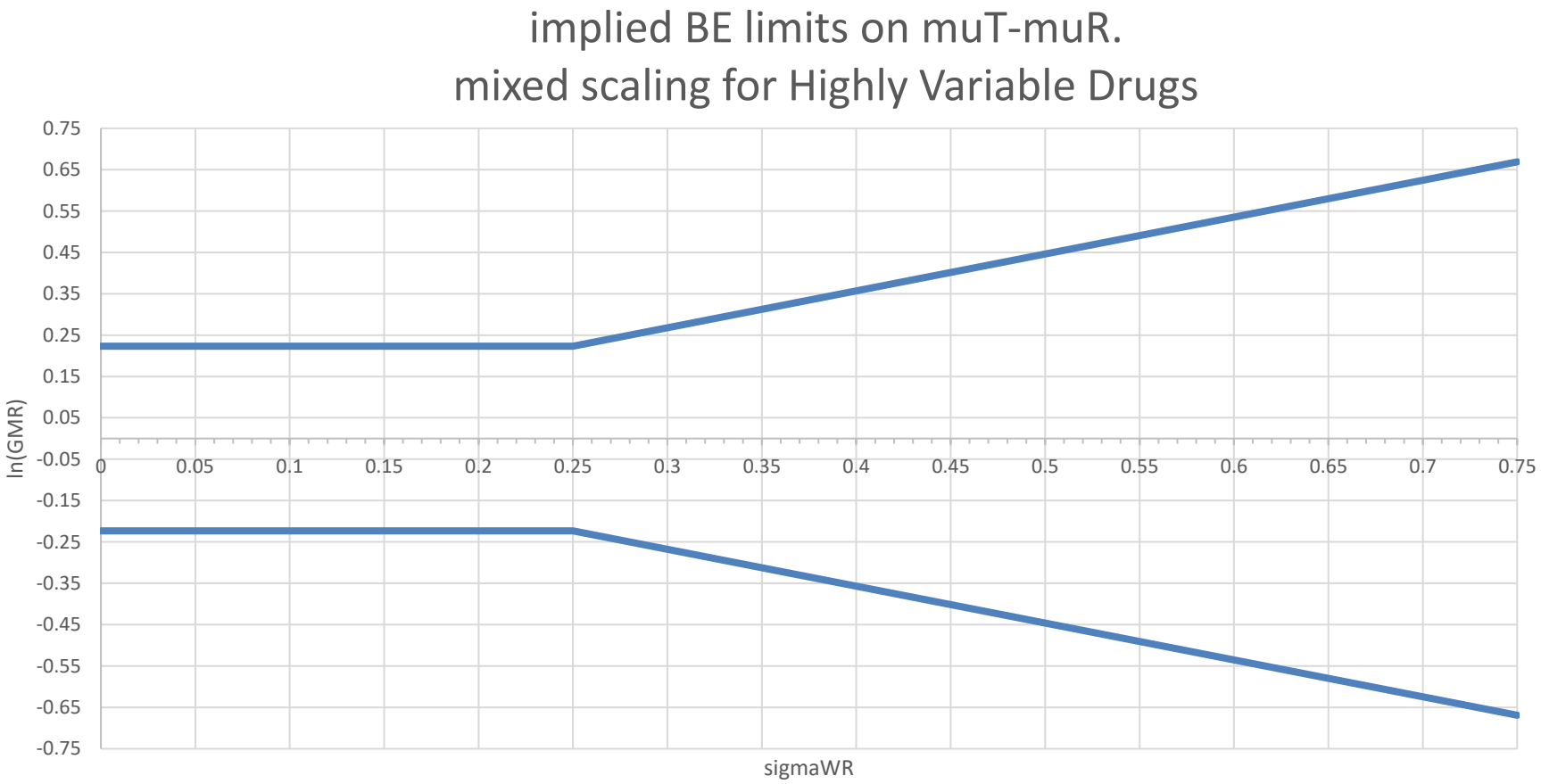
Highly Variable Drugs – Mixed Scaling

Under the *Mixed Scaling* criterion, T and R are considered BE if

$$(\mu_T - \mu_R)^2 < (\ln \Delta)^2 \qquad \text{if } \sigma_{WR} \leq \sigma_{W0}$$

$$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} < \theta = \frac{(\ln \Delta)^2}{\sigma_{W0}^2} \qquad \text{if } \sigma_{WR} > \sigma_{W0}$$

Highly Variable Drugs – Mixed Scaling



Highly Variable Drugs – Mixed Scaling

Note that there is ***no discontinuity*** in these implied BE limits on μ_T-μ_R under the Mixed Scaling criterion.

Highly Variable Drugs – Mixed Scaling

How can we implement the Mixed Scaling criterion? σ_{WR} is unknown, so we don't know whether it is greater than or less than σ_{W0}.

We have decided to base the choice of statistical analysis on s_{WR}, the *estimate* of σ_{WR}. If s_{WR} < cutoff, we use regular unscaled ABE. If $s_{WR} \geq$ cutoff, we use RSABE.

We have set the cutoff as 0.294. Note that the cutoff is not equal to $\sigma_{W0} = 0.25$.

Highly Variable Drugs – Mixed Scaling

A cutoff of 0.294 for s_{WR} corresponds, to three decimal places, to an estimated *within-subject CV* for R of 30%, based on the formula

$$\widehat{CV}_{WR} = \sqrt{e^{s_{WR}^2} - 1}$$

Highly Variable Drugs – Point Estimate Constraint

In addition to the RSABE/ABE Mixed Scaling analysis already described, there is an additional requirement for BE studies of Highly Variable Drugs – the *point estimate* for μ_T-μ_R must fall within the usual limits of [ln(0.80), ln(1.25)].

Highly Variable Drugs

Our recommended statistical analysis method for BE studies of Highly Variable Drugs is described in the *Draft Guidance on Progesterone* (2012).

Narrow Therapeutic Index Drugs

- It was noted (e.g. Benet 2006) that Narrow Therapeutic Index (NTI) Drugs usually have *low* within-subject variability.
- The use of RSABE for NTI Drugs was proposed in order to narrow the implied BE limits for these drugs.

Narrow Therapeutic Index Drugs

The same RSABE criterion was adopted for NTI Drugs

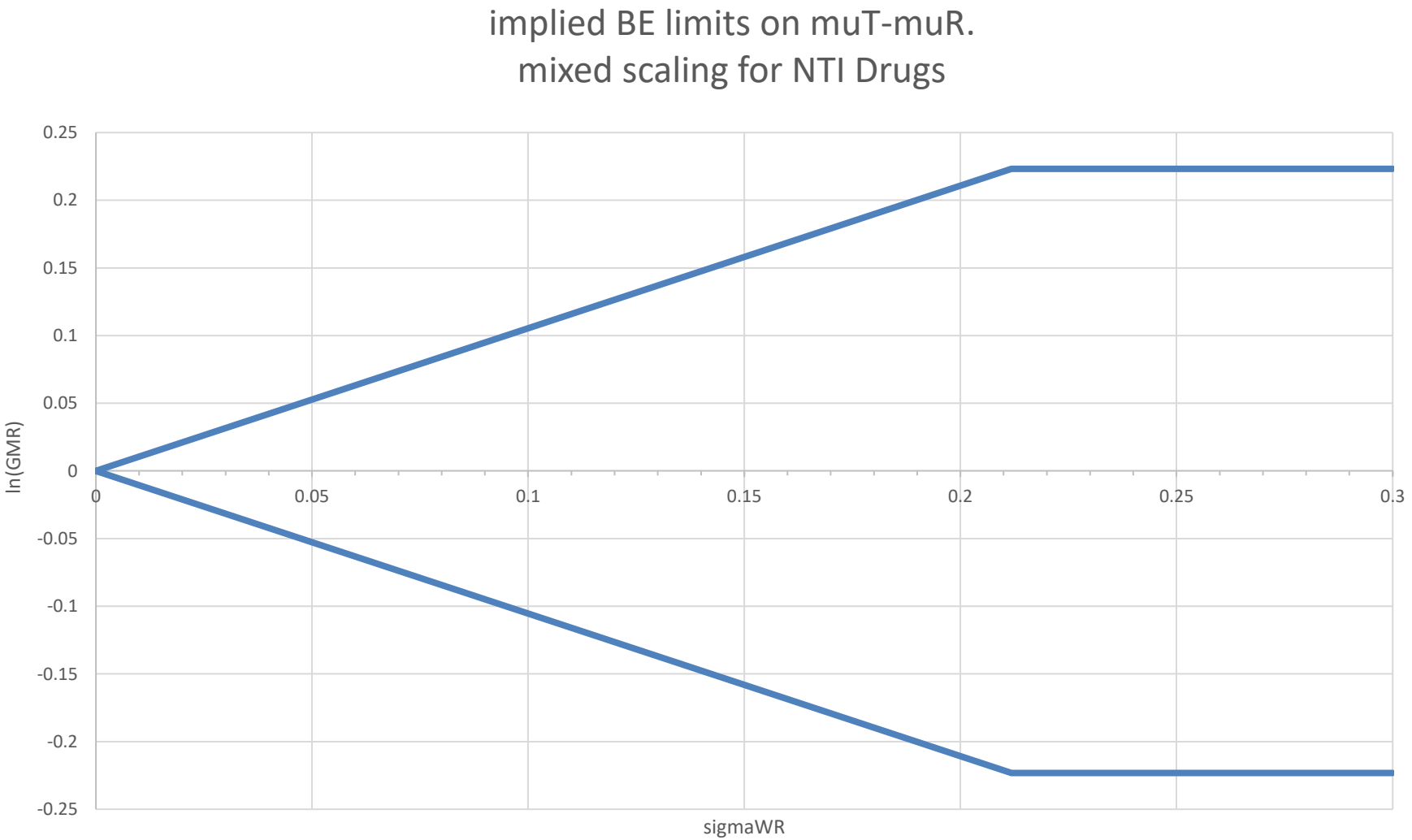
$$\frac{(\mu_T-\mu_R)^2}{\sigma_{WR}^2} < \theta = \frac{(\ln \Delta)^2}{\sigma_{W0}^2}$$

but with σ_{W0} = 0.10 and $\Delta = 1/0.9 \approx 1.11111$

Narrow Therapeutic Index Drugs – Mixed Scaling

- We noted that for Highly Variable Drugs we did not want the BE limits to get *narrower* (than the standard [ln(0.80), ln(1.25)] limits) for low σ_{WR}.
- For NTI Drugs, we do not want the BE limits to get *wider* (than the standard [ln(0.80), ln(1.25)] limits) for high σ_{WR}.
- For this reason, in addition to the RSABE analysis, a NTI Drug BE study *must also pass* standard ABE with [ln(0.80), ln(1.25)] limits.

Narrow Therapeutic Index Drugs – Mixed Scaling



Narrow Therapeutic Index Drugs

In addition to the RSABE analysis, the BE study for a NTI Drug must also establish that

$$\frac{\sigma_{WT}}{\sigma_{WR}} < 2.5$$

where σ_{WT} is the within-subject standard deviation in the population for the log-transformed PK endpoint for the *Test* product.

Since we must be able to estimate both σ_{WT} *and* σ_{WR}, we cannot use the "partial replicate" design for NTI Drugs.

Narrow Therapeutic Index Drugs

Our recommended statistical analysis method for BE studies of NTI Drugs is described in the *Draft Guidance on Warfarin Sodium* (2012).

References

- Benet, L. Z. (2006). Why Highly Variable Drugs are Safer. Meeting of FDA Advisory Committee for Pharmaceutical Science, October 6, 2006.
- Draft Guidance on Progesterone (Sep. 2012)
- Draft Guidance on Warfarin Sodium (Dec. 2012)
- Howe, W. G. (1974) Approximate Confidence Limits on the Mean of X + Y Where X and Y are Two Tabled Independent Random Variables. *J. Amer. Stat. Assoc*. 69(347): 789-794.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