

Statistical Test for Population Bioequivalence

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Outline



- ☐ Background
- ☐ PBE criterion
- ☐ The choice of PBE limit
- ☐ Statistical test for PBE

- ❑ Major changes:
 - Remove individual bioequivalence
 - Crossover design -> Parallel design
- ❑ PBE: mainly used as the key statistical approach for in vitro BE
 - Nasal drug products
 - Oral inhalation drug products

PBE Criterion

❑ Hypotheses:

$$H_0: \theta \geq \theta_P \quad \text{vs.} \quad H_a: \theta < \theta_P$$

$$\text{where } \theta = \begin{cases} \frac{(\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2}{\sigma_R^2} & \text{if } \hat{\sigma}_R > \sigma_0 \\ \frac{(\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2}{\sigma_0^2} & \text{if } \hat{\sigma}_R \leq \sigma_0 \end{cases}$$

❑ More notation:

- θ_P is the PBE limit
- σ_0^2 is a regulatory constant for variance (recommended as $\sigma_0^2 = 0.01$)

❑ Aggregate & mixed scaling approach

PBE Limit θ_P

- ❑ PBE measure can be expressed as follows:

$$\frac{(\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2}{\max\{\sigma_0^2, \sigma_R^2\}} = \frac{\text{Average BE limit} + \text{Variance term}}{\text{Scaled variance term}}$$

- ❑ An upper BE limit of 1.11 is recommended for the average BE limit.
- ❑ Allowance of 0.01 is recommended for the variance term. Note this value may be adjusted depending on the average BE limit for in vitro data.
- ❑ Accordingly, the PBE limit θ_P is recommended as

$$\theta_P = \frac{(\ln 1.11)^2 + 0.01}{0.01} = 2.089$$

Statistical Test of PBE

- ❑ A linearized form: $H_0: \gamma \geq 0$ ($\equiv H_0: \theta \geq \theta_P$), where

$$\gamma = \begin{cases} (\mu_T - \mu_R)^2 + \sigma_T^2 - (\sigma_R^2 + \theta_P \sigma_R^2) & \text{if } \hat{\sigma}_R > \sigma_0 \\ (\mu_T - \mu_R)^2 + \sigma_T^2 - (\sigma_R^2 + \theta_P \sigma_0^2) & \text{if } \hat{\sigma}_R \leq \sigma_0 \end{cases}$$

- ❑ PBE can be claimed $\Leftrightarrow \hat{\gamma}_U \leq 0$, where $\hat{\gamma}_U$ is a 95% upper confidence bound for γ .
- ❑ Approximated 95% upper confidence bound for γ is given in the FDA's draft guidance.

Thank you!

Questions?