U.S. FOOD & DRUG ADMINISTRATION

Statistical Test for Population Bioequivalence

Sungwoo Choi, Ph.D.
Mathematical Statistician
Division of Biometrics VIII
Office of Biostatistics
CDER, US FDA

FDA SBIA Webinar: March 14, 2023

Outline

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

Background

- 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:

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

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

- 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- Approximated 95% upper confidence bound for γ is given in the FDA's draft guidance.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?