# Impact of the predetermined biosimilarity margin on interchangeability

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## INTRODUCTION

Biological drug products are therapeutic moieties manufactured by a living system or organisms. Generic versions of biological products (or reference) have been produced, referred to as follow-on biologics (or biosimilar) drug products and it is expected that they produce the same clinical results as the reference product in any given patient.

The fundamental bioequivalence assumption is that the pharmacokinetic similarity between the reference and biosimilar product characteristics is extrapolated to the similarity in efficacy and safety endpoints. In the process of evaluating the similarity with the reference biological product, the biosimilarity margin in product characteristic is predetermined. However, depending on the predetermined margin, the interchangeability may be no longer valid.

## GOAL

We propose an unbiased test procedure to evaluate the extrapolation of the similarity in product characteristics to similarity in efficacy/safety endpoints in any given patient.

Assume that average bioequivalence holds:

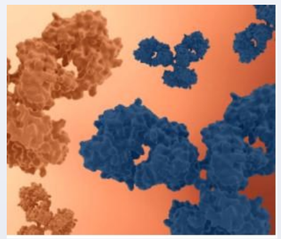
$$H_o : \mu_T - \mu_R \le -\delta \text{ or } \mu_T - \mu_R \ge \delta$$
$$H_A : -\delta < \mu_T - \mu_R < \delta$$

$\delta$: pre-specified margin (biosimilarity limits)
$\mu_T$: population mean of a biological product
$\mu_R$: population mean of a reference product

## STATISTICAL FRAMEWORK

Relationship between Y and X (reference)

$$\begin{aligned} Y_{ij} &= \beta_0 + \beta_1 X_{ij} + \beta_2^T \mathbf{Z}_{ij}^T + \varepsilon_{ij}, \quad j = 1, \cdots, n_i, \; i = 1, \cdots, k \\ X_{ij} &\sim N(\mu_{Ri}, \sigma_x^2) \text{ and } \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2) \text{ with means ordered as} \\ & \quad \mu_{R1} \le \cdots \le \mu_{Rk} \text{ (with at least one strict inequality)} \end{aligned}$$



Relationship between X (reference) and W (biosimilar)

$$W_{ij} = X_{ij} + \tau_{ij}, \quad \tau_{ij} \sim N(0, \sigma_\tau^2)$$

If taking W (biosimilar) instead of X (reference),

$$\begin{aligned} Y_{ij} | w_{ij}, \mathbf{z}_{ij} &\sim N(m(w_{ij}, \mathbf{z}_{ij}; \beta^T, \mu_{Ri}, \sigma_x^2, \sigma_\tau^2), v(\beta_1, \sigma_\varepsilon^2, \sigma_x^2, \sigma_\tau^2)) \\ m(w_{ij}, \mathbf{z}_{ij}; \beta^T, \mu_{Ri}, \sigma_x^2, \sigma_\tau^2) &= \beta_0 + \beta_1 \left(1 - \frac{\sigma_x^2}{\sigma_x^2 + \sigma_\tau^2}\right) \mu_{Ri} + \frac{\beta_1 \sigma_x^2}{\sigma_x^2 + \sigma_\tau^2} w_{ij} + \beta_2^T \mathbf{z}_{ij}^T \\ v(\beta_1, \sigma_\varepsilon^2, \sigma_x^2, \sigma_\tau^2) &= \sigma_\varepsilon^2 + \left(\frac{\sigma_\tau^2}{\sigma_x^2 + \sigma_\tau^2}\right) \beta_1^2 \sigma_x^2 \end{aligned}$$

Look !!

$$\begin{aligned} \gamma_{0i} &= \beta_0 + \beta_1 \left(1 - \frac{\sigma_x^2}{\sigma_x^2 + \sigma_\tau^2}\right) \mu_{Ri}, \; i = 1, \cdots, k \\ \gamma_1 &= \frac{\beta_1 \sigma_x^2}{\sigma_x^2 + \sigma_\tau^2} \text{ and } \boldsymbol{\gamma}_2 = \beta_2 \end{aligned}$$

Test on the pre-specified margin?

$$H_0 : \sigma_\tau^2 = 0 \quad \text{versus} \quad H_1 : \sigma_\tau^2 > 0.$$

Alternatively,
If $\sigma_\tau^2 = 0$, $\gamma_{01} = \cdots = \gamma_{0k}$
If $\sigma_\tau^2 > 0$, $\gamma_{01} \le \cdots \le \gamma_{0k}$

Unbiased Test for the intercepts!!

- $H_0^* : \gamma_{01} = \cdots = \gamma_{0k}$ and $H_1^* : \gamma_{01} \le \cdots \le \gamma_{0k}$
- Likelihood ratio statistic :

$$T = \frac{||\hat{\gamma} - \bar{\gamma}||_V^2 - ||\hat{\gamma} - \gamma^*||_V^2}{||\hat{\gamma} - \bar{\gamma}||_V^2 + ||y - U\hat{\gamma}||^2}$$

- $p$-value: $P[T > t] = \sum_{i=0}^{k-1} q_i P[B_{\frac{i}{2}, \frac{n-p-i-1}{2}} > t], \; 0 < t < 1$

$B_{\frac{a}{2}, \frac{b}{2}}$: Beta variable;

$q_i \equiv q_i(k-1, R_1[V_{11} - V_{12}V_{22}^{-1}V_{21}]^{-1}R_1^T, C_{k-1})$

| Parameter $\gamma$ | Unconstrained $\hat{\gamma}$ | Constrained ($H_0^*$) $\bar{\gamma}$ | Constrained ($H_1^*$) $\gamma^*$ |
|---|---|---|---|
| $\gamma_{01}$ | 4.021(0.065) | 3.924 | 4.027 |
| $\gamma_{02}$ | 3.985(0.063) | 3.924 | 4.014 |
| $\gamma_{03}$ | 4.053(0.075) | 3.924 | 4.014 |
| $\gamma_{04}$ | 3.878(0.060) | 3.924 | 3.910 |
| $\gamma_{05}$ | 3.896(0.068) | 3.924 | 3.910 |
| $\gamma_{06}$ | 3.930(0.063) | 3.924 | 3.910 |
| $\gamma_{07}$ | 3.927(0.062) | 3.924 | 3.910 |
| $\gamma_{08}$ | 3.712(0.108) | 3.924 | 3.715 |
| $\gamma_1$ | -0.028(0.019) | -0.041 | -0.025 |

Note: Standard errors are given in ( ).

$T = 0.00797$ with its p-value 0.00555.

Info on the predetermined margin:

$$\begin{aligned} \hat{\sigma}_\tau^2 &= \hat{\sigma}_W^2 - \hat{\sigma}_x^2 \approx \delta \text{ (the pre-specified margin)} \\ \text{where } \hat{\sigma}_x^2 &: \text{information from clinical trial on reference} \end{aligned}$$

## RESULTS

- When the predetermined margin for biosimilarity is small, the linear relationship between the biosimilar product and the clinical endpoint gets attenuated slightly in the slope estimation.
- If the predetermined margin is large, the relationship may not be the same as the relationship between reference product and the endpoint.
- The proposed unbiased test can detect the distortion of the relationship.

## DISCUSSION

- Unlike small-molecular drug products, the conclusion of therapeutic equivalence and interchangeability based on a statement of bioequivalence does not apply to biosimilar drug products.
- Under a condition that the variability in a biosimilar product is larger than that in reference product the bioequivalence may not be valid.
- Detecting the lack of the bioequivalence property would be a useful tool in biosimilarity studies.

## REFERENCE

Kim H and Park CG. A test for the presence of measurement error in a covariate in a regression model. 2015 under revision

## CONTACT INFORMATION

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