

Modified Wald Test for Reference Scaled Equivalence Assessment of Analytical Biosimilarity



Yu-Ting Weng & Yi Tsong & Meiyu Shen & Chao Wang

FDA/CDER/OB



This poster reflects the views of the author and should not be construed to represent FDA's views or policies

Abstract

For the reference scaled equivalence hypothesis, Chen et al. (2017)¹ proposed to use the Wald test with Constrained Maximum Likelihood Estimate (CMLE) of the standard error to improve the efficiency when the number of lots for both test and reference products is small and variances are unequal. However, by using the Wald test with CMLE standard error (Chen et al., 2017)¹, simulations show that the type I error rate is below the nominal significance level. Weng et al. (2017)² proposed the Modified Wald test with CMLE standard error by replacing the maximum likelihood estimate of reference standard deviation with the sample estimate (MWCMLE), resulting in further improvement of type I error rate and power over the tests proposed in Chen et al. (2017)¹. In this presentation, we further compare the proposed method to the exact-test-based method (Dong et al., 2017a)³ and the Generalized Pivotal Quantity (GPQ) method with equal or unequal variance ratios or equal or unequal number of lots for both products. The simulations show that the proposed MWCMLE method outperforms the other two methods in type I error rate control and power improvement.

Hypothesis Testing and Proposed Estimator

- Two one-sided hypothesis:

$$H_{01}: \mu_T - \mu_R \leq -f\sigma_R \text{ vs. } H_{a1}: \mu_T - \mu_R > -f\sigma_R$$

$$H_{02}: \mu_T - \mu_R \geq f\sigma_R \text{ vs. } H_{a2}: \mu_T - \mu_R < f\sigma_R$$

- MWCMLE (proposed estimator)²:

$$W_L = \frac{\tilde{\mu}_T - \tilde{\mu}_R + f\tilde{\sigma}_R}{\sqrt{\frac{\tilde{\sigma}_T^2}{n_T} + \left(\frac{1}{n_T} + \frac{f^2 n_R}{n_R - 1}\right)\tilde{\sigma}_R^2}} \text{ and } W_U = \frac{\tilde{\mu}_T - \tilde{\mu}_R - f\tilde{\sigma}_R}{\sqrt{\frac{\tilde{\sigma}_T^2}{n_T} + \left(\frac{1}{n_T} + \frac{f^2 n_R}{n_R - 1}\right)\tilde{\sigma}_R^2}}, \text{ which}$$

has sample mean and variance $(\tilde{\mu}_T, \tilde{\mu}_R, \tilde{\sigma}_R^2)$ and

CMLE $(\tilde{\sigma}_T^2, \tilde{\sigma}_R^2)$ plugged in;

- EB³:

$$T_L = \frac{\bar{X}_T - \bar{X}_R + fkS_R - (\mu_T - \mu_R + f\sigma_R)}{\sqrt{\frac{S_T^2}{n_T} + \left(\frac{1}{n_T} + f^2(k^2 - 1)\right)S_R^2}}, T_U = \frac{\bar{X}_T - \bar{X}_R - fkS_R - (\mu_T - \mu_R - f\sigma_R)}{\sqrt{\frac{S_T^2}{n_T} + \left(\frac{1}{n_T} + f^2(k^2 - 1)\right)S_R^2}}$$

which has sample mean and variance

$(\bar{X}_T, \bar{X}_R, S_T^2, S_R^2)$ and bias is corrected by k^4 .

- GPQ³:

$$G(\bar{X}_T, \bar{X}_R, S_T^2, S_R^2; \bar{x}_T, \bar{x}_R, S_T^2, S_R^2, \theta, \sigma_T, \sigma_R)$$

$$\bar{x}_T - \bar{x}_R - Z \sqrt{\frac{S_T^2}{n_T} \frac{1}{U^2} + \frac{S_R^2}{n_R} \frac{1}{W^2}}$$

$$= \frac{\sqrt{S_R^2}}{\sqrt{W^2}}$$

Proposed Estimator with Sample Size Adjustment⁵

AMWCMLME:

$$W_L = \frac{\tilde{\mu}_T - \tilde{\mu}_R + f\tilde{\sigma}_R}{\sqrt{\frac{\tilde{\sigma}_T^2}{n_T} + \left(\frac{1}{n_T} + \frac{f^2 V n_R}{n_R - 1}\right)\tilde{\sigma}_R^2}} \text{ and } W_U = \frac{\tilde{\mu}_T - \tilde{\mu}_R - f\tilde{\sigma}_R}{\sqrt{\frac{\tilde{\sigma}_T^2}{n_T} + \left(\frac{1}{n_T} + \frac{f^2 V n_R}{n_R - 1}\right)\tilde{\sigma}_R^2}}$$

$$n_T' = \min(n_T, 1.5n_R), n_R' = \min(n_R, 1.5n_T)$$

Notations and simulation setups

Notations:

- n_T and n_R : number of lots for test product and reference product, respectively
- μ_T and μ_R : population means of test product and reference product, respectively
- σ_T^2 and σ_R^2 : variances of test product and reference product, respectively
- f : pre-specified constant
- k : unbiased correction factor⁴

$= \sqrt{\frac{n_R - 1}{2}} e^{lnT(\frac{n_R - 1}{2}) - lnT(\frac{n_R}{2})}$ where $\Gamma(y)$ is the gamma function defined as $\Gamma(y) = \int_0^\infty x^{y-1} e^{-x} dx$, y is a positive number

- V_{n_R} : variance factor $(= 2 \left(\frac{n_R - 1}{2} - \frac{T^2(\frac{n_R}{2})}{T^2(\frac{n_R - 1}{2})} \right))$
- $nSim$: the number of simulation replicates
- alpha level: significance level.
- $Z = \frac{(\bar{X}_T - \bar{X}_R - \bar{x}_T - \bar{x}_R)}{\sqrt{\frac{\tilde{\sigma}_T^2}{n_T} + \frac{\tilde{\sigma}_R^2}{n_R}}} \sim N(0, 1)$, $U^2 = \frac{S_T^2}{\sigma_T^2} \sim \chi_{n_T-1}^2$, $W^2 = \frac{S_R^2}{\sigma_R^2} \sim \chi_{n_R-1}^2$.

Setups:

- $\mu_R = 0$ and μ_T is derived under the constraint of the null hypothesis given μ_R , σ_R , and f
- σ_R^2 is 1
- σ_T^2 is $k * \sigma_R^2$, $k = 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2$.
- alpha level = 0.05
- $nSim = 1,000,000$ (MWCMLE); 100,000 (EB and GPQ)

Simulation scenarios:

$f = 1.7$:

- Scenario 1: Compare the type I error of the proposed estimator (MWCMLE) to the type I errors of EB and GPQ with equal and unequal number of lots for both products.
- Scenario 2: Compare the type I error of MWCMLE to the type I error of AMWCMLE, after adjusting the degree of freedom, for unequal samples with different variances of test product.
- Scenario 3: Generate the type I error and power of MWCMLE and GPQ for small samples with different variances of test product.

Simulation results

Scenario 1: Type I Error with equal sample size

n_T	n_R	σ_T^2	Estimated type I error rate		
			MWCMLE	EB	GPQ
10	10	0.5	4.7844	5.175*	4.985
		1.0	4.8921	5.372*	4.95
		2.0	4.9968	5.506*	4.898
15	15	0.5	4.7584	5.17*	5.046*
		1.0	4.8348	5.297*	5.056*
		2.0	4.908	5.357*	5.105*
25	25	0.5	4.7771	5.102*	5.082*
		1.0	4.83	5.184*	5.096*
		2.0	4.8903	5.259*	5.165*

Scenario 1: Type I Error with unequal sample size

n_T	n_R	σ_T^2	Estimated type I error rate		
			MWCMLE	EB	GPQ
10	6	0.5	4.7593	5.236*	4.873
		1.0	4.8273	5.424*	4.881
		2.0	4.8729	5.556*	4.928
10	25	0.5	4.988	5.334*	4.855
		1.0	5.0936*	5.423*	4.899
		2.0	5.1456*	5.456*	4.934
6	10	0.5	5.0461*	5.511*	4.599
		1.0	5.2032*	5.699*	4.626
		2.0	5.2534*	5.8*	4.667
25	10	0.5	4.6836	5.154*	5.033*
		1.0	4.7191	5.223*	5.033*
		2.0	4.7568	5.343*	5.096*

Scenario 2: Type I Error with unequal sample size after adjusting the degree of freedom

n_T	n_R	σ_T^2	Estimated type I error rate	
			MWCMLE	AMWCMLE
10	6	0.5	4.7593	4.6684
		1.0	4.8273	4.6547
		2.0	4.8729	4.5935
10	25	0.5	4.988	3.6948
		1.0	5.0936*	4.0235
		2.0	5.1456*	4.3586
6	10	0.5	5.0461*	4.7738
		1.0	5.2032*	4.9710
		2.0	5.2534*	5.0602*
25	10	0.5	4.6836	4.3074
		1.0	4.7191	4.0370
		2.0	4.7568	3.6138

*: Type I error is inflated

Scenario 3: Type I Error for MWCMLE

$f = 1.7$	(n_T, n_R)					
	σ_T^2	(10, 10)	(10, 11)	(10, 12)	(10, 13)	(10, 14)
0.5	4.7844	4.8098	4.8137	4.8091	4.8562	4.8744
0.75	4.8409	4.8728	4.8823	4.8749	4.9228	4.9378
1	4.8921	4.9149	4.91	4.9066	4.9715	4.9763