Evaluation of biosimilarity between two biological products using alternative approaches

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Abstract
Biosimilar products have received more attention recently because many innovative biological products are losing their patent protection. The biosimilar should be highly similar, not identical, to the innovative biological product from the European Medicines Agency's guidance and the U.S. Food and Drug Administration's guideline. In this research, we focus on establishing posterior criterion to assess the biosimilarity between the biosimilar product and the innovator product. More specifically, we consider the prior information of the reference product and a non-informative prior to build the mixture empirical prior information of the biosimilar product. Then, we construct a posterior criterion to check the biosimilarity between the reference product and the biosimilar product. If the posterior probability of the similarity criterion is higher or equal to a pre-specified level, the biosimilarity between the reference product and the biosimilar product will be concluded. Numerical examples illustrate applications of the proposed approach in practice.

Key Words: Biosimilar, biosimilarity, mixture prior, empirical Bayes, posterior criterion

1. Introduction

The development of follow-on biologics products has received much attention from both sponsors and regulatory authorities while more biologic innovator products are losing their patent protection. Unlike the chemically synthesized drugs, biological drugs are much more complicated. Their size is much larger, their structure is more complicated, they can be sensitive to environmental conditions such as temperature or pressure, and they may expose patients to immunogen reactions. The European Medicines Agency (EMA) of the European Union (EU) has published a guideline on similar biological medicinal products for approval of these products since 2005. On February 9, 2012, the US Food and Drug

Administration (FDA) issued three draft guidance documents on biosimilar product development to assist industry in developing such products in the United States. In these guidance, however, no specific statistical methods for assessment of biosimilarity were mentioned. The bioequivalence trial design, which is used in the generic paradigm for the evaluation of bioavailability of generic chemical drugs, may be not appropriate for assessment of biosimilarity of the follow-on biology. Other statistical methodologies for evaluation of biosimilarity from different approaches are recommended.

In this research, we established a similarity criterion based on an empirical Bayes method to assess the similarity between the follow-on products and the reference products for continuous endpoint. The posterior distributions of treatment effect of the innovator biological product and the biosimilar were derived, respectively. The sample size required for the biosimilar clinical trial was determined based on the posterior probability of the proposed similarity criterion. We provided numerical examples to illustrate applications of the proposed approach in different scenarios.

2. Empirical Bayes Approach

Let R_i and B_j be the efficacy responses for the i^{th} subject and j^{th} subject receiving the innovator biological product and the biosimilar, respectively, $i=1,\ldots, N_R$, $j=1,\ldots, N_B$. Assume that $R_i \sim N(\mu_R, \sigma_R^2)$ and $B_j \sim N(\mu_B, \sigma_B^2)$, where $N(\mu, \xi^2)$ represents a normal distribution with mean μ and variance ξ^2. Here we assume that the unobservable real valued efficacy response μ_R of the innovator biological product have a prior distribution of $N(\theta, \tau^2)$, that is, $\mu_R \sim N(\theta, \tau^2)$. On the other hand, for the prior information of μ_B for the biosimilar, we consider a mixture model which is a weighted average of two priors as given below

$$\pi(\mu_B)=\gamma\pi_1(\mu_B)+(1-\gamma)\pi_2(\mu_B) \qquad (1)$$

where $0<\gamma<1$. In above mixture prior, $\pi_2(.)$ is a normal prior with mean θ and variance τ^2, whereas $\pi_1(.)$ is a normal prior with mean 0 and variance τ^2.

The proposed mixture model of the prior information for the biosimilar indicates that a γ value of 0 indicates that the prior π is equivalent to the prior used in the innovator biological product, while γ being 1 indicates that no strength of the evidence for the efficacy provided by the innovator biological product.

Let $\hat{\mu}_R = \sum_{i=1}^{n_R} R_i / n_R$ and $\hat{\mu}_B = \sum_{j=1}^{n_B} B_j / n_B$ be an estimator of μ_R and μ_B, respectively. It follows that $\hat{\mu}_R \mid \mu_R \sim N(\mu_R, \sigma_R^2/n_R)$ and $\hat{\mu}_B \mid \mu_B \sim N(\mu_B, \sigma_B^2/n_B)$. The marginal sampling density of $\hat{\mu}_R$ is $N(\theta, \tau^2 + \sigma_R^2/n_R)$. Given the data of the innovator biological product and prior information**,** the posterior distribution of μ_R is

$$\pi(\mu_R \mid \hat{\mu}_R) = \frac{1}{\sqrt{2\pi \dfrac{\tau^2 \sigma_R^2/n_R}{\tau^2 + \sigma_R^2/n_R}}} \exp\left[- \frac{\left(\mu_R - \dfrac{\hat{\mu}_R \tau^2 + \theta \sigma_R^2/n_R}{\tau^2 + \sigma_R^2/n_R} \right)^2}{2 \dfrac{\tau^2 \sigma_R^2/n_R}{\tau^2 + \sigma_R^2/n_R}} \right]. \qquad (2)$$

For the choice of above mixture prior, the marginal density of $\hat{\mu}_B$ is $N(\theta, \tau^2 + \sigma_B^2/n_B)$. Given the data of the biosimilar and mixture prior information**,** the posterior distribution of μ_B is

$$\pi(\mu_B \mid \hat{\mu}_B) = \gamma \frac{1}{\sqrt{2\pi \frac{\tau^2 \sigma_B^2/n_B}{\tau^2 + \sigma_B^2/n_B}}} \exp\left[- \frac{\left(\mu_B - \frac{\tau^2 \hat{\mu}_B}{\tau^2 + \sigma_B^2/n_B} \right)^2}{2 \frac{\tau^2 \sigma_B^2/n_B}{\tau^2 + \sigma_B^2/n_B}} \right] + (1-\gamma) \frac{1}{\sqrt{2\pi \frac{\tau^2 \sigma_B^2/n_B}{\tau^2 + \sigma_B^2/n_B}}} \exp\left[- \frac{\left(\mu_B - \frac{\tau^2 \hat{\mu}_B + \theta \sigma_B^2/n_B}{\tau^2 + \sigma_B^2/n_B} \right)^2}{2 \frac{\tau^2 \sigma_B^2/n_B}{\tau^2 + \sigma_B^2/n_B}} \right]. \quad (3)$$

The joint posterior distribution of (μ_B, μ_R) would be

$$\pi(\mu_B, \mu_R \mid \hat{\mu}_B, \hat{\mu}_R) = \pi(\mu_B \mid \hat{\mu}_B) \times \pi(\mu_R \mid \hat{\mu}_R). \quad (4)$$

3. Similarity Criterion

Similarity on efficacy for the biosimilar can be concluded if the following posterior probability of $\rho\mu_R < \mu_B < \mu_R/\rho$ large than a pre-specified limit λ, say 80% or 90%, where ρ is defined as a limit for allowing the similarity.

$$P_{sp} = \Pr(\rho\mu_R < \mu_B < \mu_R/\rho \mid \text{data}) > \lambda. \quad (5)$$

4. Maximum Likelihood estimators

In order to obtain the MLEs of (θ, τ^2), we consider a historical information of the innovator drug, say R_H. When γ=0, the joint marginal sampling distribution of $\hat{\mu}_R$ and $\hat{\mu}_{R_H}$ is

$$m(\hat{\mu}_{R_H}, \hat{\mu}_R) = N\left(\theta, \tau^2 + \frac{\sigma_{R_H}^2}{n_{R_H}} \right) N\left(\theta, \tau^2 + \frac{\sigma_R^2}{n_R} \right). \quad (6)$$

The maximum likelihood estimates of (θ, τ^2) are the simultaneous solutions of the following two equations:

$$\frac{\partial}{\partial \theta} \ell_{\theta,\tau^2}(\hat{\mu}_{R_H}, \hat{\mu}_R) = 0 \quad (7)$$

and

$$\frac{\partial}{\partial \tau^2} \ell_{\theta,\tau^2}(\hat{\mu}_{R_H}, \hat{\mu}_R) = 0. \quad (8)$$

The Newton's method is used to determine the MLE. By a familiar empirical Bayes approach, we replace θ and τ^2 with the MLEs.

5. Numerical Examples

The following numerical examples are used to illustrate applications of the proposed approach in practice and discover the pattern between the P_{sp} and the parameters corresponding to the mixture prior and the similarity criterion. First, we need to find the MLEs of the parameters (θ, τ^2) of the normal prior. According to the result of the trial and a historical result of the reference product, the MLEs can be obtained by Eq. (7) and (8). Here, we assume that $\hat{\mu}_R$=6.9, $\hat{\sigma}_R$=2.6, n_R=44 and $\hat{\mu}_{R_H}$=5.9, $\hat{\sigma}_{R_H}$=2.6, n_{R_H}=44 and the MLEs of the normal prior is ($\hat{\theta}$, $\hat{\tau}^2$)=(6.4, 0.0964). The mixure prior information can be adjusted by the weights of $\pi_1(\mu_B)$ and $\pi_2(\mu_B)$, respectively. However, the priors of the biosimilar and the innovator could be similar because of the similar manufacturing process of them. The selection of the weight in the mixture prior should be a small value, we choose γ=(0, 0.1, 0.2). When γ=0, the mixure prior information is the prior information of the reference biological product. On the otherhand, for the high similarity between the biosimilar and the innovator, the determination of limit, ρ should be large enough to claim the biosimilarity. We suggest that the determination of limit, ρ $\geqq$0.8. In this study, we select ρ=(0.8, 0.9). Let Δ be the difference of treatment effect of the biosimilar and the prior mean of the innovator product, where $\Delta=\mu_B-\hat{\theta}$. We consider that Δ=(-2, -1.5, -1, -0.5, 0, 0.5, 1, 1.5, 2). For each combination of parameters (γ, ρ, Δ), the posterior probability of $\rho\mu_R < \mu_B < \mu_R/\rho$ is calculated by Eq. (5) through the numerical integration.

Table 1 exhibit the posterior probability of $\rho\mu_R < \mu_B < \mu_R/\rho$ for the combinations of the parameters with $\hat{\sigma}_R = \hat{\sigma}_B = 2.6$ and n_B = 44. For instance, the first line in Table 1 corresponds to the posterior probability of $\rho\mu_R < \mu_B < \mu_R/\rho$ with $\hat{\mu}_R$=6.9, Δ=-2 (i.e., $\hat{\mu}_B = 4.9$), $\hat{\sigma}_R = \hat{\sigma}_B = 2.6$ and $n_R = n_B = 44$. Given ρ = 0.8, the posterior probability of $\rho\mu_R < \mu_B < \mu_R/\rho$ for γ equal to 0, 0.1, and 0.2, are, respectively, 0.9488, 0.8539, and 0.7590. If we choose λ=0.2, we would claim biosimilarity on efficacy for the biosimilar when $\Pr(\rho\mu_R < \mu_B < \mu_R/\rho) \geq 80\%$. For example, when Δ=0.5, ρ=0.9 and γ=0.1, the P_{sp} is equal to 0.8257 and lager than 0.8, the biosimilarity would be concluded.

Figure 1 is the plot of P_{sp} versus Δ with each various values of γ and ρ. The plot shows that the P_{sp} decreases as the absolute value of Δ increases if ρ and γ are fixed, espicially ρ=0.9. That indicates that the biosimilarity would be difficult to claimed if the copy version is much different to the innovator product; otherwise, the biosimilarity would be easier to claimed if the biosimilar is much similar to the innovator. The result also demonstrates that the P_{sp} decreases as the determination of limit, ρ increases. This makes intuitive sense, since the width of the similarity criterion of $\rho\mu_R<\mu_B<\mu_R/\rho$ is narrower as higher ρ (more stringent). Here, we also discover that the phenomenon of P_{sp} decreasing as the absolute value of Δ increasing is clear when ρ=0.9. The narrow width of $\rho\mu_R<\mu_B<\mu_R/\rho$ will be helpful to distinguish that the biosimilarity between the biosimilar and the reference product is exist or not. This evidence supports that ρ should be large to check the high similarity between the biosimilar and the innovator.

Table 1: The results of posterior probability for $\rho\mu_R < \mu_B < \mu_R/\rho$ for different combinations of (γ, ρ, Δ) with $\hat{\sigma}_B = 2.6$ and n_B = 44.

	ρ=0.8			ρ=0.9		
$\Delta=\mu_B-\hat{\theta}$	γ=0	γ=0.1	γ=0.2	γ=0	γ=0.1	γ=0.2
-2	0.9488	0.8539	0.7590	0.3444	0.3100	0.2755
-1.5	0.9878	0.8890	0.7903	0.5745	0.5171	0.4596
-1	0.9980	0.8982	0.7984	0.7802	0.7022	0.6241
-0.5	0.9998	0.8998	0.7998	0.9075	0.8168	0.7260
0	1.0000	0.9000	0.8000	0.9494	0.8544	0.7595
0.5	0.9999	0.8999	0.7999	0.9174	0.8257	0.7339
1	0.9991	0.8992	0.7993	0.8137	0.7323	0.6510
1.5	0.9956	0.8961	0.7965	0.6424	0.5781	0.5139
2	0.9833	0.8850	0.7867	0.4345	0.3911	0.3476

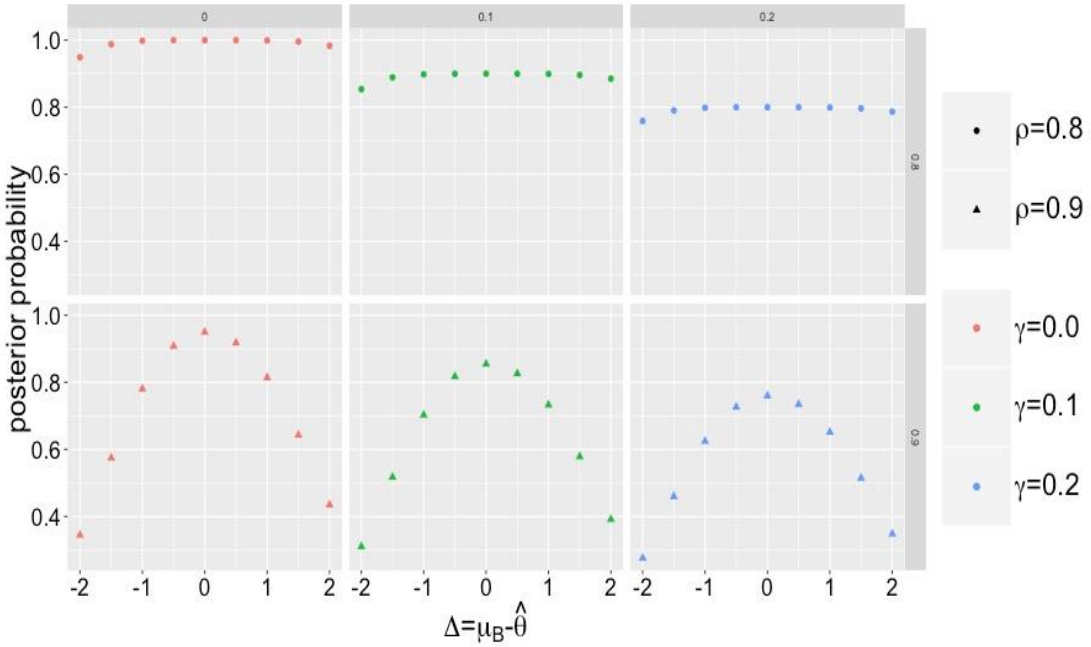

Figure 1: P_{sp} versus Δ with various values of γ and ρ.

6. Conclusion

In this research, we establish a posterior criterion to assess the biosimilarity of the biological products according to a mixture empirical prior information. The biosimilarity will be concluded if the posterior probability of the similarity criterion is higher than a pre-specified level, say 80 or 90%.

With an appropriate choice of γ, ρ and λ, our procedure can reach a conclusion that the biosimilar is highly similar to the reference product. However, selection of γ, ρ and λ may be rather crucial and critical. The sponsor should discuss the determination of (γ, ρ, λ) with the regulatory agency.

We expect that the priors of the biosimilar and the innovator could be similar because of the similar manufacturing process of them. The weight of the mixture prior, γ, should be a small value but keeps the flexibility of prior determination. In this study, we set that $\gamma \leqq 0.2$. Another point of view, the determination of limits, ρ decides the accuracy of the biosimilarity and should be large enough to confirm the accuracy. Here, we set that $\rho \geqq 0.8$. Finally, in order to claim high similarity between the biosimilar and the innovator, pre-specified limit λ should be equal to or higher than 80%.

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