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ASSESSING POPULATION BIOEQUIVALENCE IN A 2×2 CROSSOVER DESIGN WITH CARRYOVER EFFECT IN A BAYESIAN PERSPECTIVE

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ABSTRACT

A 2×2 crossover design including carryover effect is considered for assessment of population bioequivalence of two drug formulations in a Bayesian framework. In classical analysis, it is complex to deal with the carryover effect since the estimate of the drug effect is biased in the presence of a carryover effect. The proposed method in this article uses uninformative priors and vague proper priors for objectiveness of priors and the posterior probability distribution of the parameters of interest is derived with given priors. The posterior probabilities of the hypotheses for assessing population bioequivalence are evaluated based on a Markov chain Monte Carlo simulation method. An example with real data set is given for illustration.

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1. INTRODUCTION

When a brand-name drug is issued, generic copies of the brand-name drug are developed. Under current Food and Drug Administration (FDA) regulation, a patient may switch from the brand-name drug to its generic copy provided the generic copy has been shown to be bioequivalent in average to the brand-name drug. However, as indicated in Chen (1997) and the FDA draft guidance (1997), the average bioequivalence focuses only on the comparison in population averages between the test and reference formulations and so average bioequivalence fails to take into account the intra- or inter-subject variation between the test and reference formulation.

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As a results, the draft FDA guidence (1997) and Patnaik *et al.* (1997) asserted that average bioequivalence can be used neither for evaluation of prescribability for new patients or for switchability for patients already receiving long-term administration of medications. That is, average bioequivalence can guarantee neither prescribability nor switchability. Population and individual bioequivalence take these two concepts into consideration, respectively. Population bioequivalence compares overall distributions of bioavailability, therefore, it is prescribability for the new patient, while individual bioequivalence compares bioavailabilities within individuals (Anderson and Hauck, 1990; Schall, 1995), therefore, it is switchability within the same subject.

Individual bioequivalence is more ideal because it compares individually. However, in general, more complicated models such as 2×3 or 2×4 crossover design which may cause ethical or practical problem are needed for assessing individual bioequivalence. On the otherhand, population bioequivalence can be assessed based on the 2×2 crossover design which is the most commonly used for comparing two drug formulations.

Under the normality assumption, population bioequivalence can be established by demonstrating equivalence in both average and variability since a normal distribution is uniquely determined by its mean and variance.

For assessment of bioequivalence in variance only, two testing procedures have been proposed by Liu and Chow (1992) and Wang (1997). Also, Chen *et al.* (1996) derived an exact confidence region approach for the assessment of bioequivalence in variance only when the intersubject variance is known, and considered a large sample approximation when the intersubject variance is unknown. Hauck *et al.* (1997) proposed a method for assessing population bioequivalence in a reduced 2×2 crossover design in a classical approach. Oh *et al.* (2003) proposed a Bayesian anaysis for assessing population bioequivalence in a full 2×2 crossover design. However all these are based on the assumption of no carryover effect.

In this article, the 2×2 crossover design including carryover effect is considered for assessing population bioequivalence in a Bayesian approach. The procedure provided by Oh *et al.* (2003) is modified in this research.

In Section 2, we present a 2×2 crossover design including carryover effect with some assumptions. In Section 3, the posterior distribution of the parameters is derived with choice of priors. To get around the complexity of the posterior distribution, a Markov chain Monte Carlo algorithm is proposed for estimating the posterior probabilities of the hypotheses in Section 4. We apply the proposed

algorithm in an example data set in Section 5. Summary and discussion are given in Section 6.

2. THE MODEL

For comparison of two drug formulations, a reference drug (R) and a test drug (T), consider the following model accounting for carryover effect on a 2×2 crossover design,

$$y_{ijk} = \mu + S_{ik} + P_j + F_{(j,k)} + C_{(j-1,k)} + e_{ijk}, \quad i = 1, \ldots, n_k,\ j = 1, 2,\ k = 1, 2, \tag{2.1}$$

where

(a) y_{ijk} is the response of the i^{th} subject in the k^{th} sequence for the j^{th} period,

(b) μ is the overall mean,

(c) S_{ik} is the random subject effect of the i^{th} subject in the k^{th} sequence,

(d) P_j is the effect of the j^{th} period with $P_1 + P_2 = 0$,

(e) $F_{(j,k)}$ is the direct effect of the formulation in the k^{th} sequence which is administered at the j^{th} period such that

$$F_{(j,k)} = \begin{cases} F_R \text{ for } (j,k) = (1,1), (2,2) \\ F_T \text{ for } (j,k) = (1,2), (2,1) \end{cases}$$

with $F_R + F_T = 0$,

(f) $C_{(j-1,k)}$ is the carryover effect of the formulation in the k^{th} sequence which is administered at the $(j-1)^{th}$ period where $C_{(0,k)} = 0$ for $k = 1, 2$, $C_{(1,1)} = C_R$ and $C_{(1,2)} = C_T$ with $C_R + C_T = 0$,

(g) e_{ijk} is the intra subject random error in observing y_{ijk}.

It is assumed that S_{ik} are independent and identically distributed as $N(0, \sigma_s^2)$ and e_{ijk} are independently distributed as

$$e_{ijk} \sim \begin{cases} N(0, \sigma_R^2), \text{ if } j = k \\ N(0, \sigma_T^2), \text{ if } j \neq k. \end{cases}$$

Also, $\{S_{ik}\}$ and $\{e_{ijk}\}$ are assumed to be mutually independent.

Population bioequivalence of two drug bioavailabilities can be established by demonstrating equivalence in both average and variability since y_{ijk}'s are normally distributed in the above model. Thus, population bioequivalence can be

assessed by testing the following interval hypotheses;

$$\begin{aligned} &H_0 : [\ |\ F_T - F_R\ | \leq \delta_1 \ \text{ or } \ |\ F_T - F_R\ | \geq \delta_2] \ \text{ or } \ [\tfrac{\sigma_T^2}{\sigma_R^2} \leq \epsilon_1 \ \text{ or } \ \tfrac{\sigma_T^2}{\sigma_R^2} \geq \epsilon_2] \\ &\textit{versus} \\ &H_1 : \delta_1 \leq |\ F_T - F_R\ | \leq \delta_2 \ \text{ or } \ \epsilon_1 \leq \tfrac{\sigma_T^2}{\sigma_R^2} \leq \epsilon_2, \end{aligned} \tag{2.2}$$

where the constants δ_1, δ_2, ϵ_1 and ϵ_2 are chosen to define clinically significant differences. With these hypotheses, population bioequivalence between two formulations is confirmed if H_0 is rejected.

In general, the rejection criterion of Bayes test rejects H_0 if the posterior probability of H_1 is greater than the posterior probability of H_0. However, a stronger rejetion creterion is needed in bioequivalence test. Because it is common to use the 90% confidence interval for assessment of bioequivalence in classical analysis and thus the 90% highest probability density (HPD) interval (Berger, 1985) is used instead in Bayesian analysis. This implies that the posterior probability of H_1 should be greater than η for assessing bioequivalence of two drug formulations, where $\eta > 0.5$ chosen appropriately.

3. Posterior Distribution

The unknown parameters in the model (2.1) are μ, $P\ (= P_1)$, $F\ (= F_R)$ and $C\ (= C_R)$ for location parameters and σ_S^2, σ_R^2 and σ_T^2 for scale parameters. The joint posterior distribution of the unknown parameters can be devided into two parts, the conditional posterior distribution of location parameters given scale parameters and the posterior distribution of scale parameters;

$$P(\mu, P, F, C, \sigma_S^2, \sigma_T^2, \sigma_R^2 \mid y) = P(\mu, P, F, C | y, \sigma_S^2, \sigma_R^2, \sigma_T^2) P(\sigma_S^2, \sigma_R^2, \sigma_T^2 \mid y).$$

Let us first consider the conditional posterior distribution of location parameters given scale parameters. For the prior distribution, uniform prior distribution of $\pi(\mu, P, F, C) = 1$ is assumed, which is a well-known uninformative prior distribution. The likelihood function of (μ, P, F, C) can be represented easily by following independent sufficient statistics of each parameter.

$$\begin{aligned} \hat{\mu} &= \tfrac{1}{4}(\bar{y}_{.11} + \bar{y}_{.12} + \bar{y}_{.21} + \bar{y}_{.22}) \sim N(\mu, m\sigma_A^2/16), \\ \hat{P} &= \tfrac{1}{4}(\bar{y}_{.11} + \bar{y}_{.12} - \bar{y}_{.21} - \bar{y}_{.22}) \sim N(P, m\sigma_e^2/16), \\ \hat{F} &= \tfrac{1}{4}(\bar{y}_{.11} - \bar{y}_{.12} - \bar{y}_{.21} + \bar{y}_{.22}) \sim N(F - C/2, m\sigma_e^2/16), \\ \hat{C} &= \tfrac{1}{2}(\bar{y}_{.11} - \bar{y}_{.12} + \bar{y}_{.21} - \bar{y}_{.22}) \sim N(C, m\sigma_A^2/4), \end{aligned} \tag{3.1}$$

where $\sigma_e^2 = \sigma_R^2 + \sigma_T^2$, $\sigma_A^2 = 4\sigma_s^2 + \sigma_e^2$ and $m = 1/n_1 + 1/n_2$. Since the posterior density function is proportional to the product of the likelihood function and the prior density function,

$$\begin{aligned}
&P(\mu, P, F, C \mid y, \sigma_S^2, \sigma_R^2, \sigma_T^2) \\
&\propto f(\hat{\mu}, \hat{P}, \hat{F}, \hat{C} \mid \mu, P, F, C, \sigma_S^2, \sigma_R^2, \sigma_T^2) \cdot 1 \\
&\propto N(\hat{\mu}|\mu, m\sigma_A^2/16) N(\hat{P}|P, m\sigma_e^2/16) N(\hat{F}|F - C/2, m\sigma_e^2/16) N(\hat{C}|C, m\sigma_A^2/4),
\end{aligned}$$

where $N(X|\theta, \tau^2)$ denotes the density function of X from normal distribution with mean θ and variance τ^2. Integrating out μ and P gives

$$\begin{aligned}
&P(F, C \mid y, \sigma_S^2, \sigma_R^2, \sigma_T^2) \\
&\propto \frac{1}{\sigma_e} \exp\left\{-\frac{16}{2m\sigma_e^2}(\hat{F} - F + C/2)^2\right\} \frac{1}{\sigma_A} \exp\left\{-\frac{4}{2m\sigma_A^2}(C - \hat{C})^2\right\}. \quad (3.2)
\end{aligned}$$

Therefore

$$F \mid (y, \sigma_S^2, \sigma_R^2, \sigma_T^2) \sim N\Big(\hat{F} + \hat{C}/2,\ \frac{m}{8}(2\sigma_S^2 + \sigma_R^2 + \sigma_T^2)\Big). \quad (3.3)$$

If it is assumed that the carryover effect does not exist (*i.e.*, $C = 0$),

$$F \mid (y, \sigma_S^2, \sigma_R^2, \sigma_T^2) \sim N\Big(\hat{F},\ \frac{m}{16}(\sigma_R^2 + \sigma_T^2)\Big).$$

Hence the direct effect of the formulation does not depend on inter-subject variability when there is no carryover effect but it depends on inter-subject variability when there exists carryover effect. The conditional posterior distribution of the carryover effect given scale parameters is

$$C \mid (y, \sigma_S^2, \sigma_R^2, \sigma_T^2) \sim N\Big(\hat{C},\ \frac{m}{4}(4\sigma_S^2 + \sigma_R^2 + \sigma_T^2)\Big). \quad (3.4)$$

It can be seen that the carryover effect has more variability than the drug effect and its variability depends on the inter-subject variability more than the intra-subject variability.

Now, let us consider the posterior distribution of scale parameters. Orthogonal transformation by Liu (1991) is applied here to derive the posterior distribution of scale parameters. The orthogonal transformation is as follows; Let $Y_{jk} = (Y_{1jk}, \ldots, Y_{n_k jk})^t$ and let c_{gk} be $n_k \times 1$ vector of coefficients of normalized linear orthogonal contrasts of degree n_k such that $1^t c_{gk} = 0$, $c_{gk}^t \cdot c_{gk} = 1$, $c_{gk}^t \cdot c_{g'k} = 0$ for $g \neq g'$, where $g = 1, \ldots, n_k - 1$, $j = 1, 2$, $k = 1, 2$. Let $Z_{gjk} =$

$c_{gk}^t y_{jk} = c_{1gk}y_{1jk} + \cdots + c_{n_kgk}y_{n_kjk}$. Then $E(Z_{gjk}) = 0$, $\mathrm{Var}(Z_{gjk}) = \sigma_s^2 + \sigma_{F(j,k)}^2$ and $\mathrm{Cov}(Z_{gjk}, Z_{gj'k}) = \sigma_s^2(c_{gk}^t \cdot c_{gk}) = \sigma_s^2$ for all g, j and k. Hence,

$$\begin{aligned} Z = \ & (Z_{111}, \ldots, Z_{(n_1-1)11}, Z_{122}, \ldots, Z_{(n_2-1)22}, \\ & Z_{121}, \ldots, Z_{(n_1-1)21}, Z_{112}, \ldots, Z_{(n_2-1)12})^t \end{aligned}$$

is distributed as the multivariate normal distribution with mean 0 and covariance matrix Σ, where

$$\Sigma = \begin{pmatrix} (\sigma_s^2 + \sigma_R^2)I_{n_1+n_2-2} & \sigma_s^2 I_{n_1+n_2-2} \\ \sigma_s^2 I_{n_1+n_2-2} & (\sigma_s^2 + \sigma_T^2)I_{n_1+n_2-2} \end{pmatrix}.$$

Since the orthogonal transformation is linear, the units of the original data are maintained in the transformed data. Thus the likelihood function of $(\sigma_S^2, \sigma_R^2, \sigma_T^2)$ is derived as follows;

$$f(z \mid \sigma_S^2, \sigma_R^2, \sigma_T^2) \propto \exp\left\{-\frac{u(y)}{2(\sigma_R^2 + \sigma_T^2)}\right\} \rho^{-1/2} \exp\left\{-\frac{w(y, \sigma_R^2, \sigma_T^2)}{2\rho(\sigma_R^2 + \sigma_T^2)}\right\}, \quad (3.5)$$

where $\rho = \sigma_s^2\sigma_e^2 + \sigma_e^2$, $\rho > \sigma_R^2\sigma_T^2$, $u(y) = \sum(z_{i11} - z_{i21})^2 + \sum(z_{i22} - z_{i12})^2$ and $w(y, \sigma_R^2, \sigma_T^2) = \sum(\sigma_T^2 z_{i11} + \sigma_R^2 z_{i21})^2 + \sum(\sigma_T^2 z_{i22} + \sigma_R^2 z_{i12})^2$.

For prior distribution of scale parameters, vague proper priors are considered to avoid impropriety of the posterior distribution. Since $\pi(\rho, \sigma_R^2, \sigma_e^2) = \pi(\rho \mid \sigma_R^2, \sigma_e^2)\pi(\sigma_R^2 \mid \sigma_e^2)\pi(\sigma_e^2)$, priors are assumed as

$$\begin{aligned} \rho \mid (\sigma_R^2, \sigma_e^2) &\sim IG(\alpha_1, \beta_1)I_{(\rho > \sigma_R^2\sigma_T^2)}, \\ \sigma_R^2 \mid \sigma_e^2 &\sim \mathrm{Uniform}(0, \sigma_e^2), \\ \sigma_e^2 &\sim IG(\alpha_2, \beta_2), \end{aligned}$$

where $IG(\alpha, \beta)$ denotes the inverse gamma distribution with two hyperparamers α and β. Note that α and β near 0 yields a vague prior.

Hence the posterior density function of scale parameters $(\rho, \sigma_R^2, \sigma_e^2)$ is obtained by the likelihood function of $(\rho, \sigma_R^2, \sigma_e^2)$ from (3.5) with the priors given above as follows;

$$\begin{aligned} & P(\sigma_R^2, \sigma_e^2, \rho|y) \\ & \propto h(\rho, \sigma_R^2, \sigma_e^2, y)I_{(\rho > \sigma_R^2\sigma_T^2)} \left(\frac{1}{\sigma_e^2}\right)^{\alpha_2+1} e^{-\frac{1}{\sigma_e^2}(\frac{1}{\beta_2} + \frac{u(y)}{2})} \frac{1}{\sigma_e^2} I_{(\sigma_R^2 < \sigma_e^2)}, \end{aligned} \quad (3.6)$$

where $h(\rho, \sigma_R^2, \sigma_e^2, y) = \rho^{-(\alpha_1+3/2)} \exp(-\rho^{-1}\{w(y, \sigma_R^2, \sigma_e^2)/(2\sigma_e^2) + 1/\beta_1\})$. From (3.3) and (3.6), the joint posterior density function of the parameters of interest, $(F, \sigma_R^2, \sigma_T^2)$, for testing of population bioequivalence is given as

$$P(F, \sigma_R^2, \sigma_T^2 \mid y) \propto \int_{\sigma_R^2\sigma_T^2}^{\infty} \frac{1}{\sqrt{\sigma_A^2+\sigma_e^2}} \exp\Big\{-\frac{16}{m(\sigma_A^2+\sigma_e^2)}(F-\hat{F}-\hat{C}/2)^2\Big\} h(\rho, \sigma_R^2, \sigma_e^2, y)d\rho$$
$$\times (\tfrac{1}{\sigma_e^2})^{\alpha_2+1} \exp\big[-\tfrac{1}{\sigma_e^2}(1/\beta_2 + u(y)/2)\big] \tfrac{1}{\sigma_e^2} I_{(\sigma_e^2>\sigma_R^2)}.$$

However, it is very hard to compute the posterior probabilities of the hypotheses given in (2.2) from the above posterior density function because it is highly complicated. In the following section, a Markov chain Monte Carlo (MCMC) algorithm for estimating the poterior probabilities of the hypotheses is proposed.

4. MCMC ALGORITHM

From (3.6), the conditional posterior distribution of ρ given (σ_R^2, σ_e^2) follows the inverse gamma distribution, $IG(\alpha_1 + 1/2, w(y, \sigma_R^2, \sigma_e^2)/(2\sigma_e^2) + 1/\beta_1)$, $\rho > \sigma_R^2\sigma_T^2$ and the posterior density function of (σ_R^2, σ_e^2) is given as

$$P(\sigma_R^2, \sigma_e^2|y) \propto \int_{\sigma_R^2\sigma_T^2}^{\infty} h(\rho, \sigma_R^2, \sigma_e^2, y)d\rho \Big(\frac{1}{\sigma_e^2}\Big)^{\alpha_2+1} \exp\Big\{-\frac{1}{\sigma_e^2}\Big(\frac{1}{\beta_2} + \frac{u(y)}{2}\Big)\Big\} \frac{1}{\sigma_e^2} I_{(\sigma_e^2>\sigma_R^2)}.$$

However, since the conditional posterior density function of F depends on $(\rho, \sigma_R^2, \sigma_e^2)$, let us consider generating random samples of $(F, \rho, \sigma_R^2, \sigma_e^2)$.

We suggest generating samples of (σ_R^2, σ_e^2) by using a Metropolis-Hastings (M-H) algorithm of Hastings (1970) and then generate ρ from its conditional posterior distribution given (σ_R^2, σ_e^2), and then generate F from the conditional posterior distribution of F given $(\rho, \sigma_R^2, \sigma_e^2)$. For the proposal density in the M-H algorithm, we propose to use $g_1(\sigma_e^2)g_2(\sigma_R^2|\sigma_e^2)$, where $g_1(\sigma_e^2)$ is the density function of $IG(\alpha_2, \{u(y)/2 + 1/\beta\}^{-1})$ and $g_2(\sigma_R^2|\sigma_e^2)$ is the density function of Uniform$(0, \sigma_e^2)$. Details of the algorithm are as follows.

(i) Choose a starting point $(F^{(0)}, \rho^0, \sigma_R^{2(0)}, \sigma_e^{2(0)})$ and set $i = 0$.

(ii) Draw σ_e^2 from $IG(\alpha_2, \{u(y)/2 + 1/\beta\}^{-1})$, σ_R^2 from Uniform$(0, \sigma_e^2)$, and γ from Uniform$(0, 1)$. Let

$$\lambda = \min\left\{1, \frac{\int_{\sigma_R^2\sigma_T^2}^{\infty} h(\rho, \sigma_R^2, \sigma_e^2, y)d\rho}{\int_{\sigma_R^{2(i-1)}\sigma_T^{2(i-1)}}^{\infty} h(\rho, \sigma_R^{2(i-1)}, \sigma_e^{2(i-1)}, y)d\rho}\right\}.$$

Let

$$\begin{cases} (\sigma_R^{2(i)}, \sigma_e^{2(i)}) = (\sigma_R^2, \sigma_e^2), & \text{if } \gamma \leq \lambda, \\ (\sigma_R^{2(i)}, \sigma_e^{2(i)}) = (\sigma_R^{2(i-1)}, \sigma_e^{2(i-1)}), & \text{otherwise.} \end{cases}$$

(iii) Draw u from Uniform(0,1). Compute $G(1/(\sigma_R^2\sigma_T^2))$ and then let $p = 1 - (1-u)G(1/(\sigma_R^2\sigma_T^2))$ and let $\rho = 1/q_{1-p}$, where G denotes the cumulative distribution function and q_{1-p} denotes the $100(1-p)$ percentile of the inverse gamma distribution of ρ, $IG(\alpha_1 + 1/2, w(y, \sigma_R^2, \sigma_e^2)/(2\sigma_e^2) + 1/\beta_1)$.

(iv) Draw F from $N(\hat{F} + \hat{C}/2,\ m(2\sigma_S^2 + \sigma_R^2 + \sigma_T^2)/8)$, here σ_S^2 can be expressed by ρ, σ_R^2 and σ_e^2.

(v) Repeat steps (ii) to (iv).

Note that the step (iii) in the above algorithm, is a procedure for drawing random samples of ρ with the restriction of $\rho > \sigma_R^2\sigma_T^2$. From these random samples of $(F, \rho, \sigma_R^2, \sigma_e^2)$, samples from a burn-in phase of the Marcov chain are discarded and samples from every l^{th} iteration after burn-in, where l is the lag size where the autocorrelation between samples vanishes, can be taken and used for posterior inference. From these samples, the posterior probability of the hypotheses for assessing population bioequivalence in (2.2) can be evaluated.

Above all, from these random samples of $(F, \rho, \sigma_R^2, \sigma_e^2)$, average bioequivalence and variance bioequivalence are able to be testified by using the marginal random samples of F and the marginal random samples of (σ_R^2, σ_e^2), respectively. For the carryover effect, random samples of C from the posterior distribution given in (3.4) can be easily obtained by a slight modification of the MCMC algorithm above.

5. AN EXAMPLE

Let us consider an example of a 2×2 crossover design experiment concerning bioavailability between two formulations introduced by Liu and Chow (1992). It was shown that two drug formulations in the example were bioequivalent in average but not in variability under the assumption of no-carryover effect (Chow and Liu, 1992; Liu and Chow, 1992; Chen *et al.*, 1996). Oh *et al.* (2003) analysed the data by a Bayesian procedure and showed that the same conclusion was derived with the classical analysis.

However, from the data, the maximum likelihood estimate of the carryover effect is $\hat{C} = 4.7958$, which is bigger than the maximum likelihood estimate of the

drug effect, $\hat{F} = 1.1437$. Obviously, the carryover effect seems not to be ignorable in this case.

To perform the MCMC algorithm proposed in the previous section, we need to choose the hyperparameters of inverse gamma prior distributions. For the prior distribution of ρ, $IG(\alpha_1, \beta_1)$, we choose $\alpha_1 = 5$ and $\beta_1 = 0.0000003$ for vagueness of the prior distribution and for adjusting the prior mean to be larger than $\hat{\sigma}_R^2 \hat{\sigma}_T^2$ to satisfy the restriction of $\rho > \sigma_R^2 \sigma_T^2$, where $\hat{\sigma}_R^2$ and $\hat{\sigma}_T^2$ are sample variances of each drug formulation. For the prior distribution of σ_e^2, $IG(\alpha_2, \beta_2)$, we choose $\alpha_2 = 3$ and $\beta_2 = 0.001$ for vagueness of the prior distribution and for adjusting the prior mean to be equal to the sample variance $\hat{\sigma}_e^2$, where $\hat{\sigma}_e^2 = \hat{\sigma}_R^2 + \hat{\sigma}_T^2$.

From MCMC iterations, 110,000 random samples are generated and then first 10,000 samples are discarded. Finally 10,000 random samples are taken from every 10^{th} iteration from 100,000 samples. From these samples, the proportion of satisfying H_1 is 7.91%, which indicates obviously rejecting the null hypothesis and so assessing the population bioequivalence of two drug formulations is failed. Separate tests for bioequivalence in mean and variance yield 61.07% and 12.49% as the estimated posterior probabilities of H_1, respectively. Here 61.07% is bigger than 50%, that is, the estimated posterior probability of H_1 is greater than the estimated posterior probability of H_0, however, the 90% highest probability density (HPD) interval of F is estimated as $(-11.87, 18.66)$ which is not within the bioequivalence interval $(-8.2559, 8.2559)$. To satisfy the HPD interval criterion, the posterior probability of H_1 should be greater than 0.9. In that sense, two drugs in the example are not bioequivalent in mean as well as in variance by separate tests.

For sensitivity of the results on the choice of hyperparameters of the inverse gamma distributions, the results are hardly affected by reasonably vague specifications of the inverse gamma priors, for example, for $\beta_1' = 10^{-7}$ and $\beta_2' = 0.0001$, which are smaller than β_1 and β_2, it shows that the estimated posterior probability of H_1 is 54.89% in average bioequivalence test, 12.1% in variance bioequivalence test and 7.09% in population bioequivalence test.

Next, let us consider the case when the carryover effect is ignored in the same data which was considered in Chow and Liu (1992), Liu and Chow (1992), Chen *et al.* (1996) and Oh *et al.* (2003). Similar MCMC iterations are performed without carryover effect, showing that the estimated posterior probability of H_1 is 98.31% in average bioequivalence test, 11.73% in variance bioequivalence test and 11.56% in population bioequivalence test. Hence two drugs are bioequivalent in average only under the assumption of no-carryover effect, which coincides with

the results of those of the above articles.

Figure 5.1 shows the posterior probability density functions of F with and without carryover effect. Two vertical lines in the figure represent the bioequivalence limits, ± 8.2559. It can be seen that the variance of the drug effect F with the carryover effect is much larger than with no carryover effect.

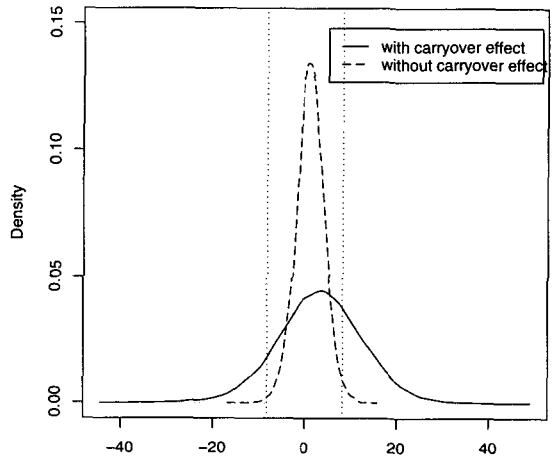

FIGURE 5.1 *The posterior density function of F.*

6. SUMMARY AND DISCUSSION

We have proposed a Bayesian method for assessing population bioequivalence in a 2×2 crossover design experiment including carryover effect. For objectiveness of priors, we have suggested using uniform priors for location parameters and vague proper priors for scale parameters. The likelihood functions of location parameters have derived by using independent sufficient statistics and the likelihood functions of scale parameters have derived by an orthogonal transformation of data. With given priors and the likelihood functions the posterior distribution of the parameters of interest has obtained. To get around the complexity of the posterior distribution, a Markov chain Monte Carlo algorithm has been proposed for estimating the posterior probabilities of the hypotheses.

In classical analysis, it is complex to deal with the carryover effect since the estimate of the drug effect is biased in the presence of a carryover effect. Thus it is assumed that there is no carryover effect by a long time of washout period

or data from the first period alone are used for anaysis if the carryover effect is believed to be exist by testing the null hypothesis of no carryover effect. However, it has been argued that the carryover effect is non-ignorable even for a sufficiently long washout period or by testing the point-null hypothesis of no carryover effect (Hills and Armitage, 1979; Grieve, 1985). Also, if we use data from the first period alone, we will lose much information that the crossover design experiment gives.

The proposed Bayesian method provides a tool for assessing population bioequivalence based on the full model including the carryover effect. It provides simpler way to estimate the drug effect with estimation error and it is not necessary to give up a part of the data from the experiment in the presence of a carryover effect. In addition, average bioequivalence, variance bioequivalence and population bioequivalence are able to be testified all at once by the proposed method.

Note that the carryover effect is completely confounded with the sequence effect in (3.1). This means that the randomization of allocation of subjects affects the carryover effect. Thus it should be careful for randomization in crossover design experiment.

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