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# A Bayesian Meta Analysis for Assessing Bioequivalence among Two Generic Copies of the Same Brand-Name Drug

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Abstract

As more generic drugs become available, the quality, safety, and efficacy of generic drugs have become a public concern. Specifically, drug interchangeability among generic copies of the same brand-name drug is a safety concern. This research proposes a Bayesian method for assessing bioequivalence between two generic copies of the same brand-name drug from two independent $2 \times 2$ crossover design experiments. Uninformative priors are considered for general use and the posterior distribution of the difference of two generic drug effects is derived from which the highest probability density interval can be evaluated. Examples are presented for illustration.

*Keywords* : $2 \times 2$ crossover design; HPD interval; Generic copies.

## 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 to the brand-name drug. However, approving bioequivalence between generic copies is not required in current FDA regulation.

Recently, as more generic drugs become available, the quality, safty, and efficacy of generic drugs have become a public concern because it is very likely that a patient may switch from one generic drug to another. Therefore it is necessary to consider assessing bioequivalence among generic copies of the same brand-name drug for safety consideration.

For assessing bioequivalence of the approved generic drugs of the same

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brand-name drug, meta analyses combining different bioequivalence trials of which each compares a generic drug with the same brand-name drug have been considered by Chow and Liu (1997) and Chow and Shao (1999).

Chow and Liu (1997) proposed the idea of a meta analysis to provide an overview of bioequivalence among generic drugs based on data from independent bioequivalence trials. In Chow and Liu's approach, a rather restricted, yet strong assumption of intersubject and intrasubject variances is made. Chow and Shao (1999) propose an alternative method for meta analysis that relaxes the assumption.

This paper proposes a Bayesian meta analysis for assessing bioequivalence among two generic copies of the same brand-name drug from two independent bioequivalence trials. Uninformative priors are assumed and the posterior distribution of the difference of two generic drugs is derived.

The statistical model of the meta analysis and the highest probability density(HPD) interval for assessing bioequivalence are proposed in Section 2. Derivation of the posterior distribution of the parameters with uninformative priors is described in Section 3. Examples given in Chow and Liu (1997) and Chow and Shao (1999) are considered to illustrate the method and the results are compared with Chow and Liu's and Chow and Shao's, respectively in Section 4. A brief summary and discussion is given in Section 5.

## 2. Statistical model

Suppose there are two different bioequivalence trials and each trial compares a generic drug with the same brand-name drug on a standard $2\times2$ crossover design. It is assumed that two trials are performed independently and each used the same statistical model as follows;

$$Y_{ijk} = \mu + G_k + S_{ik} + P_j + F_l + e_{ijk}, \quad i = 1,\cdots,n_k; j = 1,2; k = 1,2, \tag{1}$$

where $y_{ijk}$ is the pharmacokinetic response of interest for $i$th subject in the $k$th sequence for the $j$th period; $\mu$ is the overall mean; $G_k$ is the effect of the $k$th sequence with $\sum_k G_k = 0$; $S_{ik}$ is the inter-subject random effect of the $i$th subject in the $k$th sequence; $P_j$ is the effect of the $j$th sequence with $\sum_j P_j = 0$; $F_l$ is the effect of the $l$th drug formulation (when $j = k$, $l = T(F_l = F_T)$, test formulation; when $j \neq k$, $l = R(F_l = F_R)$, the reference(brand-name) formulation) with

$F_T + F_R = 0$; and $e_{ijk}$ is the intra-subject random error in observing $y_{ijk}$. It is assumed $S_{ik}$ are independent and identically distributed as $N(0, \sigma_S^2)$ and $e_{ijk}$ are independent and identically distributed as $N(0, \sigma_e^2)$, and $S_{ik}$ and $e_{ijk}$ are mutually independent.

To perform a meta analysis by combining two independent trials, we assume that inter- and intra-subject variabilities are the same across two independent trials. Also we assume the homogeneity of the reference formulations among two studies. The testing procedure for the homogeneity of the reference formulations is proposed in Chow and Liu (1997). With these assumption, an additional subscript $h$ which denotes $h$th trial is added to the equation (1) as follows;

$$Y_{ijkh} = \mu + G_{kh} + S_{ikh} + P_{jh} + F_{lh} + e_{ijkh}, \quad i = 1, \cdots, n_{kh}; j = 1,2; k = 1,2; h = 1,2, \qquad (2)$$

where $\sum_j P_{jh} = 0$, $\sum_k G_{kh} = 0$, $\begin{cases} F_{lh} = F_{R_h} = F_R, & j = k \\ F_{lh} = F_{Th}, & j \neq k \end{cases}$ with $F_{R_h} + F_{Th} = 0$;

$S_{ikh} \sim iid\ N(0, \sigma_S^2)$ and $e_{ijkh} \sim iid\ N(0, \sigma_e^2)$ for $h = 1,2$.

The average bioequivalence between two test drugs, $T_1$ and $T_2$, can be assessed to claim bioequivalence with $100(1-\alpha)\%$ assurance if the $100(1-\alpha)\%$ highest probability density(HPD) interval of $F_{T_1} - F_{T_2}$ falls in $(\epsilon_L, \epsilon_U)$ where $\epsilon_L$ and $\epsilon_U$ are some clinically meaningful limits.

The Division of Bioequivalence, U.S. FDA suggested use of an equivalence criterion of 80% to 120% for assessment of bioequivalence on the difference of average bioavailability and 80% to 125% for assessment of bioequivalence on the ratio of average bioavailability. Since $\log(0.8) = -0.2231 = -\log(1.25)$ on the logarithmic scale, $(\epsilon_L, \epsilon_U) = (-0.2231, 0.2231)$ if the logarithmic transformation has been used (Chow and Liu (2000)).

In the next section, we derive the posterior distribution of $F_{T_2} - F_{T_1}$ which is required to compute the $100(1-\alpha)\%$ HPD interval of $F_{T_2} - F_{T_1}$.

## 3. Posterior distribution

The unknown parameters in the model (2) are $\mu$, $G_{1h} = -G_{1h}$, $P_{1h} = -P_{2h}$, $F_{R_h} = -F_{T_h}$ for $h = 1,2$, $\sigma_S^2$ and $\sigma_e^2$. For simplicity, we denote $G_{1h} = G_h$ and $P_{1h} = P_h$. Thus the unknown parameters are $\mu$, $G_1$, $G_2$, $P_1$, $P_2$, $F_{T_1}$, $F_{T_2}$, $\sigma_S^2$ and $\sigma_e^2$.

To compute the joint posterior distribution of the unknown parameters given

$\{y_{ijkh}\}$, it is very useful to use the sufficient statistics for parameters which are independent each other(Berger (1985)). But since it is assumed that $F_{R_h} = F_R$ for $h = 1,2$ and both of $F_{T_1}$ and $F_{T_2}$ are assumed to be equal to $-F_R$ in the model, it is not possible to get two sufficient statistics which are orthogonal to the sufficient statistics for the rest of the parameters. However, by taking their difference, $F_{T_2} - F_{T_1}$ which is of our interest, it is easy to find its sufficient statistic which is orthogonal to sufficient statistics of the other parameters.

Orthogonal sufficient statistics of the parameters and their distributions are as follows (Grieve (1985) and Oh et al. (2003));

$$\hat{\mu} = \frac{1}{8}\sum_{j,k,h} \bar{y}_{.jkh} \sim N(\mu, \frac{m_1 + m_2}{32}\sigma_A^2)$$

$$\hat{P}_h = \frac{1}{4}(\bar{y}_{.11h} + \bar{y}_{.12h} - \bar{y}_{.21h} - \bar{y}_{.22h}) \sim N(P_h, \frac{m_h}{8}\sigma_e^2)$$

$$\hat{G}_h = \frac{1}{4}(\bar{y}_{.11h} - \bar{y}_{.12h} + \bar{y}_{.21h} - \bar{y}_{.22h}) \sim N(G_h, \frac{m_h}{8}\sigma_A^2)$$

$$\widehat{F_{T_2} - F_{T_1}} = \frac{1}{2}(\bar{y}_{.111} - \bar{y}_{.121} - \bar{y}_{.211} + \bar{y}_{.112} - \bar{y}_{.112} + \bar{y}_{.122} + \bar{y}_{.212} - \bar{y}_{.222})$$

$$\sim N(F_{T_2} - F_{T_1}, \frac{m_1 + m_2}{2}\sigma_e^2)$$

$$SSP = SSP_1 + SSP_2 \sim \sigma_A^2 \chi^2_{N_1 + N_2 - 4}$$

$$SSE = SSE_1 + SSE_2 \sim \sigma_e^2 \chi^2_{N_1 + N_2 - 4},$$

where $\bar{y}_{.jkh} = \sum_{i=1}^{n_{kh}} y_{ijkh}/(n_{kh})$, $m_h = (n_{1h} + n_{2h})/(n_{1h}n_{2h})$, $N_h = n_{1h} + n_{2h}$ for $j = k = h = 1,2$ and $\sigma_A^2 = 2\sigma_S^2 + \sigma_e^2$. For each $h = 1,2$, $SSP_h = 2(\sum_{i,k} \bar{y}^2_{i.kh} - \sum_k n_k \bar{y}^2_{..kh})$ and $SSE_h = \sum_{i,j,k} y^2_{ijkh} - SSP_h - \sum_k n_k \sum_j \bar{y}^2_{jkh}$ which represent the sums of squares between subjects and within subject in $h$th trial, respectively, where $\bar{y}_{i.kh} = \sum_j y_{ijkh}/2$, $\bar{y}_{..kh} = \sum_{i,j} y_{ijkh}/(2n_{kh})$, $\bar{y}_{.jkh} = \sum_i y_{ijkh}/(n_{kh})$.

Note that $P_h$ and $G_h$, $h = 1,2$ are estimated in each $h$th trial separately but $\mu$ and $\widehat{F_{T_2} - F_{T_1}}$ are estimated in combined data sets. Also, $SSP$ and $SSE$ are pooled estimates of inter-subject variability and intra-subject variability, respectively.

For notational convenience, let $F_{TD} = F_{T_2} - F_{T_1}$ since now. By reparametrization of the parameters the joint posterior distribution of $\Theta = \{\mu, G_1, G_2, P_1, T P_2, F_{TD}, \sigma_A^2, \sigma_e^2\}$ given $\{y_{ijkh}\}$ can be denoted as $P(\Theta | \{y_{ijkh}\}) = P(\Theta | \hat{\Theta})$, where $\hat{\Theta} = \{\hat{\mu}, \hat{G}_1, \hat{G}_2, \hat{P}_1, \hat{P}_2, \hat{F}_{TD}, SSP, SSE\}$ is the sufficient statistic of $\Theta$ in which

each component is defined as above.

Now let us consider the prior distribution of $\Theta$. A commonly used uninformative prior is Jeffreys prior along with the uniform prior;

$$\pi(\Theta)=\pi(\mu, G_1, G_2, P_1, P_2, F_{TD}, \sigma_A^2, \sigma_e^2)\propto \frac{1}{\sigma_A^2\sigma_e^2}, \quad \sigma_A^2>\sigma_e^2. \tag{3}$$

That is, the uniform priors for location parameters are given and Jeffereys priors for scale parameters with the restriction are considered independently with location parameters.

Since sufficient statistics in $\hat{\Theta}$ are all independent, the joint posterior distribution of $\Theta$ with the prior distribution of $\Theta$ given in (3) is

$$\begin{aligned}
&P(\Theta|\hat{\Theta})\propto f(\hat{\Theta}|\Theta)\pi(\Theta)\\
&\propto N(\hat{\mu}|\mu, \frac{m_1+m_2}{32}\sigma_A^2)\prod_{h=1}^{2}N(\hat{P}_h|P_h, \frac{m_h}{8}\sigma_e^2)N(\hat{G}_h|G_h, \frac{m_h}{8}\sigma_A^2)\\
&\times N(\hat{F_{TD}}|F_{TD}, \frac{m_1+m_2}{2}\sigma_e^2)\sigma_A^2 X^2_{N_1+N_2-4}\sigma_e^2 X^2_{N_1+N_2-4}\frac{1}{\sigma_A^2\sigma_e^2}, \quad \sigma_A^2>\sigma_e^2.
\end{aligned}$$

By integrating out $\mu$, $G_1$, $G_2$, $P_1$ and $P_2$ we get

$$\begin{aligned}
&P(F_{TD}, \sigma_A^2, \sigma_e^2|\{y_{ijkh}\})\propto (\frac{1}{\sigma_A^2})^{N/2-1}\exp(-\frac{SSP}{2\sigma_A^2})\\
&\times(\frac{1}{\sigma_e^2})^{N/2-1/2}\exp(-\frac{1}{\sigma_e^2}(SSE+\frac{2(F_{TD}-\hat{F}_{TD})^2}{m_1+m_2})), \quad \sigma_A^2>\sigma_e^2,
\end{aligned} \tag{4}$$

where $N=N_1+N_2$. Thus the posterior density of $F_{TD}$ with the restriction $\sigma_A^2>\sigma_e^2$ is given as

$$\begin{aligned}
&P(F_{TD}|\{y_{ijkh}\}, \sigma_A^2>\sigma_e^2)\propto \int_0^\infty\int_{\sigma_e^2}^\infty (\frac{1}{\sigma_A^2})^{N/2-1}\exp(-\frac{SSP}{2\sigma_A^2})\\
&\times(\frac{1}{\sigma_e^2})^{N/2-1/2}\exp(-\frac{1}{\sigma_e^2}(SSE+\frac{2(F_{TD}-\hat{F}_{TD})^2}{m_1+m_2}))d\sigma_A^2 d\sigma_e^2,
\end{aligned} \tag{5}$$

which is integrable if $N>4$. However, note that the condition of $N>4$ is satisfied without loss of generality in our model given in (2).

Now, the property of the posterior density of $F_{TD}$ is verified in the following lemma.

Lemma 1. The posterior density function of $F_{TD}$ given in (5) is proper if $N>4$.

*proof*: From the equation (5),

$$\int_{-\infty}^{\infty} P(F_{TD}|\{y_{ijkh}\},\sigma_A^2 > \sigma_e^2)dF_{TD}$$
$$\propto \int_0^{\infty}\int_{\sigma_e^2}^{\infty}(\frac{1}{\sigma_A^2})^{N/2-1}\exp(-\frac{SSP}{2\sigma_A^2})d\sigma_A^2$$
$$\times \int_{-\infty}^{\infty}(\frac{1}{\sigma_e^2})^{N/2-1/2}\exp(-\frac{1}{\sigma_e^2}(SSE+\frac{2(F_{TD}-\hat{F}_{TD})^2}{m_1+m_2}))dF_{TD}d\sigma_e^2$$
$$\propto \int_0^{\infty}\int_{\sigma_e^2}^{\infty}(\frac{1}{\sigma_A^2})^{N/2-1}\exp(-\frac{SSP}{2\sigma_A^2})(\frac{1}{\sigma_e^2})^{N/2-1}\exp(-\frac{SSE}{\sigma_e^2})d\sigma_A^2 d\sigma_e^2,$$

which is integrations of the product of two inverse-gamma density functions if $N>4$.

However, the direct integration of the formula (5) is not easy because of the restriction of $\sigma_A^2 > \sigma_e^2$. Let us consider the procedure for deriving the posterior distribution of $F_{TD}$ proposed in Box and Tiao (1992) in that the posterior distribution of $F_{TD}$ with the restriction $\sigma_A^2 > \sigma_e^2$ is derived by using the posterior distribution of $F_{TD}$ without the restriction.

By the definition of conditional probability,

$$P(F_{TD}|\{y_{ijkh}\},\sigma_A^2 > \sigma_e^2) = \frac{P(F_{TD}|\{y_{ijkh}\})P(\sigma_A^2 > \sigma_e^2|F_{TD},\{y_{ijkh}\})}{P(\sigma_A^2 > \sigma_e^2|\{y_{ijkh}\})}.$$

From the formula (4),

$$P(F_{TD}|\{y_{ijkh}\}) \propto Q^{-\frac{N-3}{2}},$$

where $Q = SSE(1+(2(F_{TD}-\hat{F}_{TD})^2)/((m_1+m_2)SSE))$. Hence the posterior distribution of $F_{TD}$ without the restriction follows the generalized $t$-distribution with $\nu$ degrees of freedom, location parameter $\hat{F}_{TD}$ and scale parameter $\tau^2$, where $\nu = N-4$ and $\tau^2 = ((m_1+m_2)SSE)/(2(N-4))$.

Now since $P(\sigma_A^2 > \sigma_e^2|F_{TD},\{y_{ijkh}\})$ is proportional to $P(F_{TD},\sigma_A^2,\sigma_e^2|\{y_{ijkh}\})$,

$$P(\sigma_A^2 > \sigma_e^2|F_{TD},\{y_{ijkh}\}) = P(F_{N-4,N-3} < \frac{N-3}{N-4}\frac{SSP}{Q}),$$

where $F_{\nu 1,\nu 2}$ denotes a random variable following $F$-distribution with the corresponding degrees of freedom. Similarly,

$$P(\sigma_A^2 > \sigma_e^2|\{y_{ijkh}\}) = P(F_{N-4,N-4} < \frac{SSP}{SSE}).$$

Thus

$$P(F_{TD}|\{y_{ijkh}\},\sigma_A^2 > \sigma_e^2) = \frac{t(F_{TD}|\nu,\widehat{F_{TD}},\tau^2)P(F_{N-4,N-3} < \frac{N-3}{N-4}\frac{SSP}{Q})}{P(F_{N-4,N-4} < \frac{SSP}{SSE})}, \quad (6)$$

where $t(F_{TD}|\nu, \hat{F}_{TD}, \tau^2)$ denotes the density function of $F_{TD}$ for the generalized $t$ -distribution, $t(\nu, \hat{F}_{TD}, \tau^2)$.

It is easy to derive the $100(1-\alpha)\%$ HPD interval of $F_{TD}$ from (6) by simple numerical method. Note that $(P(F_{N-4,N-3} < \frac{N-3}{N-4}\frac{SSP}{Q}))/(P(F_{N-4,N-4} < \frac{SSP}{SSE}))$ is monotonically decreasing in $(F_{TD}-\hat{F}_{TD})^2$. Thus $P(F_{TD}|\{y_{ijkh}\}, \sigma_A^2 > \sigma_e^2)$ is uniformly more concentrated about $\hat{F}_{TD}$ than $P(F_{TD}|\{y_{ijkh}\})$ which follows the generalized $t$-distribution, $t(\nu, \hat{F}_{TD}, \tau^2)$. That is, the $100(1-\alpha)\%$ HPD interval of $F_{TD}$ given $\sigma_A^2 > \sigma_c^2$ is shorter than the $100(1-\alpha)\%$ HPD interval of the generalized $t$-distribution $t(\nu, \hat{F}_{TD}, \tau^2)$.

## 4. Examples

To illustrate implementation of the proposed Bayesian meta analysis for assessing bioequivalence two generic copies from two studies, let us consider examples introduced in Chow and Liu (1997) and Chow and Shao (1999). There were three independent data sets of hypothetical log-transformed AUC(Area Under the plasma or blood concentration time-Curve) in both examples. In each example, a standard $2\times2$ crossover experiment was conducted in each trial with 24 healthy male subjects to assess bioequivalence between a test product and the same reference product. Bioequivalence between a test product and the reference product were verified in each trial.

From the three combined data, all pairwise combinations of three test drugs were compared simultaneously for assessing bioequivalence in each example. Based on the corresponding meta-analysis for generic copies in each paper, test drugs 1 and 2 and test drugs 2 and 3 could be claimed to be bioequivalent to each other, however test drugs 1 and 3 could not be claimed to be bioequivalent in the example given in Chow and Liu (1997). For the example given in Chow and Shao (1999), test drugs 1 and 3 and test drugs 2 and 3 could be claimed to be bioequivalent to each other, but test drugs 1 and 2 could not be claimed to be bioequivalent. The 90% confidence intervals are presented in the last column of each table in <Table 1>.

Now, since the proposed methodology in this paper consider assessing bioequivalence for two generic copies from two studies only, each two combinatorial data sets are selected and compared separately.

Statistical results of each comparison of two test drugs based on the Bayesian meta analysis proposed in this paper are summarized in <Table 1> for each

example of Chow and Liu (1997) and Chow and Shao (1999), respectively. For Chow and Liu's example, only test drugs 1 and 3 cannot be claimed to be bioequivalent since the 90% HPD interval for their difference doesn't fall in the interval $(-0.223, 0.223)$. Similarly, only test drugs 1 and 2 for Chow and Shao's example cannot be claimed to be bioequivalent. These coincide with the conclusions of the classical meta analysis proposed by Chow and Liu (1997) and Chow and Shao (1999).

Comparing the 90% HPD intervals with the 90% confidence intervals, the 90% HPD intervals are almost same as in Chow and Liu's example and a little wider in Chow and Shao's example. The model assumptions in our analysis are the same as in Chow and Liu's paper which assumes all equal inter-subject variabilities and all equal intra-subject variabilities. Thus under the same model with Chow and Liu (1997), the Bayesian method proposed in this paper gives similar information. On the other hand, Chow and Shao (1999) assumes inter-subject variabilities are different according to implemented drugs and so do intra-subject variabilities. It is natural that more precise assumptions give more accurate results(shorter interval).

Also, it can be notified that within-subject variabilities are much smaller than between-subject variabilities in Chow and Liu's example. So the posterior probability of $\sigma_A^2 > \sigma_e^2$ is near 1 which means the restriction of $\sigma_A^2 > \sigma_e^2$ is negligible, therefore $P(F_{TD}|\{y_{ijkh}\}, \sigma_A^2 > \sigma_e^2) \approx t(F_{TD}|\nu, \hat{F}_{TD}, \tau^2)$. Moreover, since within-subject variabilities(SSE) are very small with high degree of freedom $\nu = N - 4 = 44$, distributions of the difference of two test drugs are very concentrated on $\hat{F}_{TD}$. On the contrary, in Chow and Shao's example, since within-subject variabilities are similar to or even bigger than between-subject variabilities the restriction of $\sigma_A^2 > \sigma_e^2$ is sensible for the posterior distribution of $F_{TD}$.

<Figure 1> shows the posterior density functions for the difference of two test drugs. The vertical lines in the figure represent the bioequivalence limits, $-0.223$ and 0.223. In Chow and Liu's example, the values of the difference between test drugs 1 and 3 are obviously away from the limits and the values of the difference between the others are safely in the limits. In Chow and Shao's example, however, only test drugs 2 and 3 are seemed to be bioequivalent in the figure. Therefore even though the 90% HPD interval of the distribution of the difference between test drugs 1 and 3 is within the limits, it has to be careful to be claimed to be bioequivalent since the distribution is located at the side of the interval for assessing bioequivalence.

<Table 1> Statistical results of each comparison of two test drugs

(a) Chow and Liu's example

| | $\hat{F}_{TD}$ | SSP | SSE | 90% HPD Interval | 90% CI(Chow&Liu) |
|---|---|---|---|---|---|
| $T_1$ *vs* $T_2$ | 0.2004 | 0.275632 | 0.0151303 | (0.18769, 0.21314) | (0.18662, 0.21328) |
| $T_2$ *vs* $T_3$ | 0.1515 | 0.236972 | 0.0186222 | (0.13739, 0.16561) | (0.13896, 0.16562) |
| $T_1$ *vs* $T_3$ | 0.3519 | 0.262107 | 0.0172531 | (0.33833, 0.36550) | (0.33885, 0.36581) |

(b) Chow and Shao's example

| | $\hat{F}_{TD}$ | SSP | SSE | 90% HPD Interval | 90% CI(Chow&Shao) |
|---|---|---|---|---|---|
| $T_1$ *vs* $T_2$ | 0.1872 | 0.864547 | 0.84074 | ( 0.09793, 0.27648) | ( 0.0701, 0.2468) |
| $T_2$ *vs* $T_3$ | 0.0720 | 0.784189 | 1.13979 | (-0.02566, 0.16958) | (-0.0110, 0.1790) |
| $T_1$ *vs* $T_3$ | -0.1152 | 0.851010 | 1.23207 | (-0.21680,-0.01368) | (-0.1605, 0.0117) |

## 5. Summary and Discussion

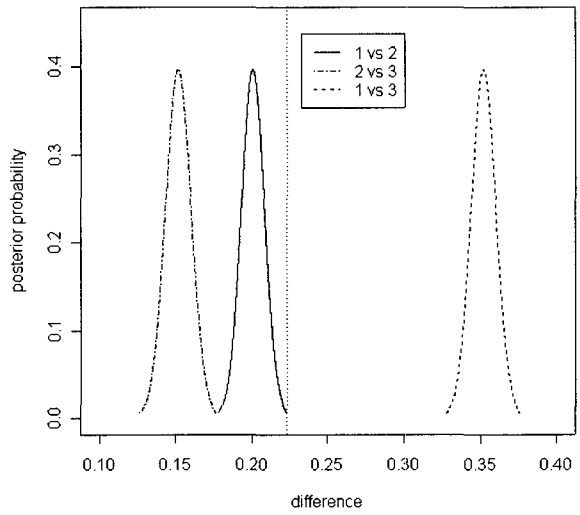
We have proposed a Bayesian method for assessing bioequivalence between two generic copies of the same brand-name drug from two independent $2\times2$ crossover design experiments. For the unknown parameters in the combined model uninformative priors have been considered and the posterior distribution of the difference between two generic drugs has been derived. For assessing bioequivalence between two generic drugs the 90% HPD interval would be evaluated from the derived posterior distribution by simple numerical method. Examples have been considered for illustration of our method along with comparison of the results with those by Chow and Liu (1997) and Chow and Shao (1999).

As more generic drugs become available recently it is very likely that a patient may switch from one generic drug to another. The proposed method provides a tool to evaluate bioequivalence among two generic copies of the same brand-name drug. If the result indicates that these two generic copies are not bioequivalent each other, the FDA may issue a warning to prohibit the substitution of these generic copy for safety consideration.

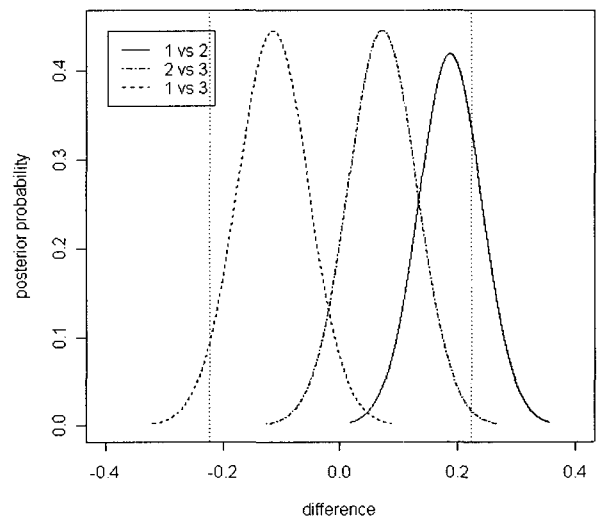
The proposed method assumes that inter- and intrasubject variabilities are the same across two independent trials. The proposed method can be applied to the case of different inter- and intrasubject variabilities with some modification.

Uninformative priors are considered so that the proposed method can be used in general. However, when there is useful prior information, one may use informative priors and the proposed method can be used with slight modification.

Assessing bioequivalence for only two generic copies of the same brand-name drug is considered in this paper. For more than two generic copies, a different combining data modelling would be considered such as hierarchical model(Gelmen et al.(1997)) which is our future research interest.




(a) Chow and Liu's example




(b) Chow and Shao's example

<Figure 1> posterior density functions for differences

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