

A Semiparametric Bayesian Approach to Average Bioequivalence

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May 25, 2005

Summary

Bioequivalence assessment is an issue of great interest. Development of statistical methods for assessing bioequivalence is an important area of research for statisticians. Bioequivalence is usually determined based on the normal distribution. We relax this assumption and develop a semiparametric mixed model for bioequivalence data. The proposed method is quite flexible and practically meaningful. Our proposed method is based on a mixture normal distribution and a nonparametric Bayesian approach using mixture of Dirichlet process prior. A numerical example illustrates the use of our procedure.

Key words: Average bioequivalence; Crossover design; Gibbs sampling; Mixture of Dirichlet Process prior; mixture of Normal; Markov Chain Monte Carlo;

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[‡]This research was partially supported by grant number CA075981 from the U.S. National Cancer Institute.

1 Introduction

Bioequivalence assessment has become an issue of great interest to the biopharmaceutical industry during the last few decades, especially after it became evident that the marketed products having the same amounts of the drug may exhibit marked differences in their therapeutic responses (Westlake, 1972, 1974 1979, 1981; Metzler, 1974). Nowadays, on the basis of simple pharmacokinetic concepts and parameters, bioavailability and bioequivalence studies have been established as acceptable surrogates for expensive, complicated and lengthy clinical trials. Such trials are used worldwide to establish and ensure consistent product quality, as well as reliable and therapeutically effective performance of marketed dosage form. Three situations have thus been defined (Chow and Liu, 2000) in which bioequivalence studies are required (i) when the proposed marketed dosage form is different from that used in pivotal clinical trials, (ii) when significant changes are made in the manufacture of the marketed formulation, and (iii) when a new generic formulation is tested against the innovator's marketed product.

A bioequivalence study is an experiment to compare a test product (T) to a reference product (R). Bioequivalence studies compare both the rate and extent of absorption of various drug formulations with the innovator (reference) product on the basis that if two formulations exhibit similar drug concentration-time profiles in the blood/plasma, they should exhibit similar therapeutic effects. For an unapproved generic dosage form to be marketed and accepted as therapeutically effective in relation to the innovator product, it must have established bioequivalence with the innovator product, *in vivo*. The determination of bioequivalence is, thus, very important in the pharmaceutical industry because regulatory agencies like the U.S. Food and Drug Administration (FDA) allow a generic drug to be marketed only if its manufacturer can demonstrate that the generic product is bioequivalent to the innovator product. According to FDA regulations (1999, 2001, 2002), a valid statistical evaluation of bioequivalence trial is essential in order to guarantee the safety and efficacy of the generic drug products.

Bioequivalence studies usually proceed by administering dosages to subjects and measuring the concentration of the drug in the blood just before and at set times after its administration. These concentration-by-time measurements are often connected with a polygonal curve and measurements of the drug's pharmacokinetics, like AUC (area under curve), C_{\max} (maximum concentration) and T_{\max} (time to maximum concentration) are calculated. For statistical analysis, these measures are taken as the response variables. Until recently, regulatory guidelines have suggested the consideration of average bioequivalence (ABE) (Mandallaz et. al., 1981; Berger et. al., 1996). ABE requires equivalence between the population means of the pharmacokinetic measurements for the reference and test formulations. Over the past few years, the FDA (1999, 2002) supplemented ABE with two more criteria, viz., population bioequivalence (PBE) and individual bioequivalence (IBE). These new criteria have also been the subject of dispute, however, and ABE still remains the main criterion for assessing bioequivalence between two formulations. The main advantage of ABE is its easier interpretation for the intended audiences, including regulators, prescribing physicians, pharmacists, and patients. The criterion of ABE has also found potential applications in several other areas such as, psychology (Rogers et. al., 1993), chemistry (Roy, 1997), and environmental statistics (McBride, 1998).

In this paper, we take a Bayesian approach to assessing ABE. The key advantage of using a Bayesian approach for bioequivalence trials is the ability of the Bayesian inferential paradigm to incorporate background information thought pertinent to the clinical question being asked (Ghosh and Khattree, 2003). Breslow (1990) argued that bioequivalence is a perfectly natural concept to be subjected to Bayesian analysis. Several authors have also advocated a Bayesian approach to average bioequivalence inference (Rodda and Davis, 1980; Mandallaz and Mau, 1981; Selwyn et. al., 1981; Grieve, 1985; Racine-Poon et. al., 1987). The main idea of all the above methods is to find the posterior distribution of the parameter of interest based on non-informative prior distributions for the parameters. Recently, Ghosh and Khattree (2003) used an intrinsic Bayes factor approach to test ABE.

All of the existing literature on ABE, however, relies heavily on a normality assumption. The normality assumption in a bioequivalence trial may not always be true, however, and the inference can be misleading. Chow and Tse (1990) and Bolton (1991) discussed that the normality assumption in a bioequivalence trial may lack robustness against outliers and skewness. Usually a bioequivalence trial is conducted with a small number of healthy subjects, and it is not always possible to validate the normality assumption. Instead of following a normal distribution, the data from a bioequivalence trial may have a mixture of normal distributions (e.g., diverse populations, such as from pharmacogenetic variation), a distribution with heavier tails, or some other distribution which can not be easily specified. Thus, it is of practical interest to develop statistical models in ABE that move beyond the traditional parametric model.

This paper addresses robust inference in bioequivalence studies by developing a robust Bayesian analysis to assess ABE. We show how a robust Bayesian model can lead to better insights in a bioequivalence study. Our method extends existing methods by allowing for possible heterogeneity of the subjects who are participating in the study. In our analysis, we use two different approaches to model the random subject effect. First we suggest modeling random subject effects using a mixture of two normal distribution. Mixture distributions can characterize different distributional shapes and can describe different features of the bioequivalence data. We also propose a Bayesian nonparametric methods using a Dirichlet process (DP) mixture (Ferguson, 1973; Antoniak, 1974; Escobar, 1994; MacEachern, 1994; Escobar and West, 1995) to relax the distributional assumption and to accommodate possible population heterogeneity. DP mixture models are, by far, the most widely used nonparametric Bayesian model, mainly because one can easily obtain posterior estimates using standard MCMC approaches, such as Gibbs sampling (Gilks et al., 1996; MacEachern and Müller, 1998).

The plan of the paper is as follows. Section 2 introduces a parametric random effects model for average bioequivalence (ABE) trial which assumes a normal distribution for the random effects. In section 3 we present the semiparametric extension of the model which allows for a

wide range of distributions for the random effects. In section 4, we describe the data and the results of the empirical analysis are presented. Section 5 draws conclusions and provides an outlook on future research.

2 Model

In most bioequivalence trials, a test formulation is compared with the innovator reference formulation in a group of normal, healthy subjects, as recommended by the US FDA (2001, 2002). Each participant receives the treatments alternatively in a crossover study. The most commonly used statistical design for comparing average bioequivalence between a test formulation (T) and a reference formulation (R) of a drug is a two-sequence, two-period, crossover design (Chow and Liu, 2000). We refer to this design as a standard 2×2 crossover design. The following statistical model is usually considered for a 2×2 crossover design.

$$y_{ijk} = \mu_{i,k} + S_i + P_k + \delta_{ij} + e_{ijk} \quad (1)$$

In this model, we consider y_{ijk} to be the logarithm of response in the i^{th} sequence from the k^{th} period for the j^{th} subject, ($i = 1, 2; j = 1, 2, \dots, n_i; k = 1, 2$). We use the logarithm, because often the response measures in a bioequivalence study follow a lognormal distribution, due to skewness. Furthermore, $\mu_{i,k}$ is the direct effect of the formulation in the i^{th} sequence that is administered at the k^{th} period, S_i is the fixed effect of the i th sequence ($S_1 + S_2 = 0$), P_k is the fixed effect of period k ($P_1 + P_2 = 0$), δ_{ij} is the random effect of the j^{th} subject in the i^{th} sequence, and e_{ijk} is the within subject random error in observing y_{ijk} .

If we assume, without loss of generality, that the first period in the first sequence is the

reference formulation (R), then

$$\mu_{i,k} = \begin{cases} \mu_R & \text{if } k = i \\ \mu_T & \text{if } k \neq i. \end{cases}; \mu_R + \mu_T = 0.$$

The random variables δ_{ij} are assumed to be *i.i.d* normal with mean 0 and variance σ^2 . The e_{ijk} are *i.i.d* normal with mean 0 and variance σ_l^2 , where $l = R$ if $k = i$ and $l = T$ otherwise. We assume that δ_{ij} and e_{ijk} are mutually independent.

2.1 Average Bioequivalence Criteria

Two drugs are called *average bioequivalent* if the population means of the drug-specific AUCs are sufficiently close. In statistical terms, the problem of ABE is to decide if the difference of two parameters $\Delta = \mu_T - \mu_R$ is close to zero. Formally, the hypothesis of average bioequivalence is formulated as:

$$H_0 : \Delta \leq \theta_L \quad \text{or} \quad \Delta \geq \theta_U \quad \text{vs.} \quad H_a : \theta_L < \Delta < \theta_U, \quad (2)$$

where the lower and upper tolerance limits θ_L and θ_U are known constants specified by the FDA. The limits $\theta_L = \log(0.8)$ and $\theta_U = \log(1.25)$ are widely accepted by drug authorities for testing bioequivalence in terms of AUCs.

The hypothesis testing set up in (2) is the reverse of the ordinary view of testing. Whereas a null hypothesis is usually a hypothesis of *equivalence*, we now consider the lack of equivalence the null hypothesis that we seek to disprove. This formulation makes a great deal of sense for bioequivalence trials. Here the type I error is the probability of declaring the drugs to be bioequivalent when they are not. Therefore, by setting up the hypothesis as in (2), the consumer's risk is protected. Once the consumer's risk is restricted to, say, a level 5% error, the agency leaves the pharmaceutical industry to determine the extent of manufacturer's risk via the type II error.

In a Bayesian hypothesis test, the construction might be based on the posterior probabilities of the hypothesis. In general, the hypothesis with higher posterior probability is accepted. Thus, in our case, if the posterior probability of H_1 is greater than 0.5 then ABE will be established. One could also incorporate utilities or losses and apply decision-theoretic criteria to make decisions about ABE. We do not follow that extension in this paper.

3 Robust Distribution of the Random Effect

The most common choice for the distribution of the random effect δ_{ij} in the model for a crossover design in (1) is the normal distribution. Almost all of the inferential procedures currently used for assessing ABE are based on this assumption. The choice of the normal distribution for the random effect, however, is quite arbitrary. It may well happen that the normal distribution does not correctly fit the data at hand, for example if the data are skewed, contain outliers, or consist of diverse populations. This section considers a model for the random effects that generalizes the normality assumption of δ_{ij} to include an entire class of distributions. The aim of this generalization is to protect the inference from bias resulting from incorrect specification of the random effect distribution. This generalization has the potential to make the inference robust to departures from a normal distribution while still having good performance if the actual distribution is normal. The motivation is to model the random effects by fitting a mixture of parametric distributions or by considering flexible non-parametric distributions. We consider these two possibilities in the following two subsections.

3.1 Normal Mixture Distribution

A viable alternative to a single normal distribution for the random effect is a mixture structure with several normal components for the δ_{ij} . See West (1992) and Robert (1996) for details

on mixture modeling. Verbeke and Lesaffre (1996) discussed the advantage of using a mixture model in linear mixed effects models. We follow Verbeke and Lesaffre (1996) and assume a two-component mixture. The mixture model proposed in equations (3-6) takes place at a latent observation level, since we only observe the data y_{ijk} . Formally we assume the following prior model specification:

$$\delta_{ij} \sim \pi N(\mu_1, \sigma_1^2) + (1 - \pi)N(\mu_2, \sigma_2^2) \quad (3)$$

$$\mu_f \sim N(0, \sigma_\mu^2); \quad f = 1, 2 \quad (4)$$

$$\sigma_f^2 \sim \text{IG}(a, b) \quad (5)$$

$$\pi \sim \text{Beta}(a_\pi, b_\pi) \quad (6)$$

The hyperparameters $(\sigma_\mu^2, a, b, a_\pi, b_\pi)$ are assumed to be known. We impose an ordering constraint on the means $(\mu_{j1} < \mu_{j2})$ (Roeder and Wasserman, 1996) to avoid well-recognized identifiability problems. Observe that in the formulation (3-6), the number of mixture components is assumed to be known, yielding a parametric mixture model. We carry out posterior inference using Markov chain Monte Carlo (MCMC) methods, which have appeared recently in the literature for analyzing data with mixture models (see for example. Diebolt and Robert, 1994; Roeder and Wasserman, 1997). The flexibility of a prior mixture model is its ability to accommodate a large number of true distributional forms. Unless the information feeding up from the data is incredibly strong and the true distributional form of the random effects is such that it cannot be represented by a mixture of two normals (e.g., if it is tri-modal), it is unlikely that this random effect distribution would be deemed inappropriate. Because of the flexibility allowed by the Bayesian approach and the easy Gibbs sampling simulation techniques, inference on this extension is possible using WinBUGS (2003) (<http://www.mrc-bsu.cam.ac.uk/bugs>). We provide some of the WinBUGS program in an appendix.

3.2 Mixture of Dirichlet Process

A further and more flexible extension for specifying the random effects distribution, one that goes beyond a finite mixture, is a Bayesian nonparametrics approach (Ferguson, 1973; Dey, Müller, & Sinha, 1997; Ghosh & Ramamoorthi, 2003). In this section, we model δ_{ij} using a Dirichlet process mixture prior that is given by:

$$\delta_{ij} \sim N(\mu_j, \sigma_\delta^2) \quad (7)$$

$$\mu_j \sim G \quad (8)$$

$$G \sim \text{DP}(\alpha G_0) \quad (9)$$

$$G_0 \sim N(0, \sigma_G^2) \quad (10)$$

$$\sigma_\delta^2 \sim \text{IG}(c, d) \quad (11)$$

The above prior is a mixture of normals with respect to a mixing measure G . The mixing measure, G is a Dirichlet process. The parameters of a Dirichlet process are G_0 a probability measure, and α , a positive scalar assigning mass to the real line. The parameter G_0 is often called the base measure and is a distribution that approximates the true nonparametric shape of G . The concentration parameter α reflects our prior belief about how similar G is to G_0 . Large values of α lead to a G that is very close to G_0 . Small values of α allow G to deviate more from G_0 and put most of its probability mass on just a few atoms. The prior for α is discussed in the next section. The hyperparameters (σ_G^2, c, d) are assumed to be known.

3.2.1 A Finite Approximation

The above representation provides a formal definition of the Dirichlet process mixture prior. There are several ways to implement a DP mixture prior. Recent research has focussed on using the constructive definition of the Dirichlet process to produce MCMC algorithms (Ishwaran and James, 2002; Ishwaran and Zarepour, 2000, 2002; Ishwaran and James, 2001). Following Sethu-

raman (1994), one way to generate the DP mixture prior is to regard the infinite dimensional parameter G as an infinite mixture. Thus, the Dirichlet process $DP(\alpha G_0)$ can be written as,

$$G = \sum_{l=1}^{\infty} v_l \delta_{Z_l} = V_1 \delta_{Z_1} + \sum_{l=2}^{\infty} (1 - V_1)(1 - V_2) \cdots (1 - V_{l-1}) V_l \delta_{Z_l}, \quad (12)$$

where V_1, V_2, \dots are i.i.d. Beta(1, α) random variables. Since the infinite series (12) is almost surely convergent, as l increases the random vectors (V_l, Z_l) will have diminishing effect on the prior distribution and thus on the posterior distribution of δ_{ij} . Thus, an approximation to the Dirichlet process can be obtained by truncating the higher order terms in the stick-breaking representations (12). This results in an approximating random probability measure (Choudhuri, Ghosal and Roy, 2004; Ohlssen, 2005) of the form

$$G = \sum_{l=1}^L v_l \delta_{Z_l} = V_1 \delta_{Z_1} + \sum_{l=2}^L (1 - V_1)(1 - V_2) \cdots (1 - V_{l-1}) V_l \delta_{Z_l} \quad (13)$$

where V_1, V_2, \dots, V_{L-1} are i.i.d. Beta(1, α) random variables, and V_L is set to one to ensure that the random weights sum to unity.

The finite approximation (13) for DP can be used in WinBUGS to implement the Gibbs sampling for fitting a DP mixture model. This can be done by introducing latent variables $\mathbf{J} = (J_1, J_2, \dots, J_n)$ that indicate group membership for the unobserved variables μ_j , along with a probability vector $\mathbf{w} = (w_1, w_2, \dots, w_L)^T$. Thus, model (7-11) can be written as:

$$\delta_{ij} \sim N(\mu_{J_j}, \sigma_\delta^2) \quad (14)$$

$$J_j | \mathbf{w} \sim \text{Multinomial}(\{1, 2, \dots, L\}, \mathbf{w}) \quad (15)$$

$$\mu_l \sim G, \quad l = 1, 2, \dots, L \quad (16)$$

$$G \sim \text{DP}(\alpha G_0) \quad (17)$$

$$G_0 \sim N(0, \sigma_G^2) \quad (18)$$

$$\mathbf{w} \sim \text{Dirichlet}\left(\frac{\alpha}{L}, \frac{\alpha}{L}, \dots, \frac{\alpha}{L}\right) \quad (19)$$

$$\sigma_\delta^2 \sim \text{IG}(c, d) \quad (20)$$

Note that the value of L in (13) is chosen to control the size of the tail probability

$$\sum_{k=L+1}^{\infty} v_k$$

The truncation point L needs to be chosen appropriately. The effect of truncation on the distribution of functionals of a Dirichlet process has been studied by Muliere and Tardella (1998), Ishwaran and Zarepour (2002), and Ohlssen, 2005. Ishwaran and Zarepour (2002) suggested $L = \sqrt{n}$ for large n and $L = n$ for small n . Since there is a linear relationship between α and L , we adopt a uniform prior for α .

3.3 Prior Distribution

Parameters in model (1) are μ , $S_1 = -S_2$, $P_1 = -P_2$, $F_R = -F_T$, σ_T^2 , σ_R^2 , and α . For simplicity we assume $S = S_1$, $P = -P_1$, $F = F_R$. To complete the Bayesian specification of the model, we assign weakly informative priors to the unknown fixed effect parameters. Specifically, we use conjugate prior for overall mean, $\mu \sim N(\mu_0, \sigma_\mu^2)$, sequence effect $S \sim N(S_0, \sigma_s^2)$, and period effect, $P \sim N(P_0, \sigma_p^2)$. For the error variance, we specify, $\sigma_l^2 \sim \text{IG}(a_l, b_l)$, $l = R, T$, where

$IG(a_l, b_l)$ denotes the inverse gamma distribution with shape parameter a_l and scale parameter b_l . The hyperparameters $(\sigma_\mu^2, c, d, \mu_0, S_0, \sigma_s^2, P_0, \sigma_P^2, a_R, a_T, b_R, b_T)$ are assumed to be known.

3.4 Gibbs Sampling

The posterior distributions are analytically intractable and thus computations are done via Monte Carlo approximations with the help of the MCMC method. The Gibbs sampler is probably the most widely used MCMC method and is implemented in the software package `WinBUGS` (2003). In general, MCMC works by drawing samples from distributions that converge to the correct posterior distribution of the parameters. In Gibbs sampling, one draws samples from the conditional posterior distributions of univariate parameters given the most recent draws of the other parameters. Thus, what is required for the Gibbs sampler to work is the ability to sample from the full conditional posterior distribution of the parameters. The conditional distribution of all the parameters are obtained from the joint distribution of all the parameters. We skip the explicit expression of the conditional distribution as `Bugs` calculates the conditional distribution automatically. The method proposed in section (3.2) can also be implemented in `WinBUGS`, since it is based on a finite mixture model. The main code is available from the authors on request.

4 Data analysis

We illustrate the usefulness of the above methods by analyzing a real data set (Bradstreet, 1994) in this section.

4.1 Illustration

A two-by-two crossover study randomized twenty-six healthy male subjects to one of two treatment sequences. The objective of the trial was to determine if the pharmacokinetic characteristics of one 40 mg capsule of a drug made by Company A are the same as the concurrent administration of two 20 mg capsules of the same drug made by Company B. The two treatment sequences were either treatment *A* in the first period followed by treatment *B* in the second period or vice versa. A five-day or seven-day washout period separated the treatment periods. The pharmacokinetic parameter AUC was calculated for each subject in each treatment period from drug levels assayed from plasma samples taken at 0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours post dose. The data is skewed and include a few outliers. See the histogram plots (Fig 1). The first row of panels in figure 1 shows histograms of the period differences in the first sequence of the log transformed data. There is an outlier in both sequences. The second and third row of figure 1 gives the exploratory plots for the treatment effects, assuming no period differences. The histograms indicates strong skewness in the data.

For the Bayesian analysis, we choose relatively diffuse priors. Specifically, throughout we assume independent diffuse prior distribution $N(0, 10^3)$ for the parameters μ , S , P and assume a weakly informative gamma prior distribution $\Gamma(0.01, 0.01)$ for the σ_l^{-2} .

For the mixture model (6), we assume $N(0, 10^2)$ for μ_1 and μ_2 . In the case of higher components of mixtures, a lower limit is set by the previous component of the mixture to avoid identifiability problems. A $Beta(1, 1)$ prior is assumed for the mixing probability π and a inverse-gamma (0.01, 0.01) prior is assumed for σ_1^2 , σ_2^2 .

For the DP model (11), we assume $G_0 \sim N(0, 1000)$. A $Uniform(0.5, 4)$ covers a sufficiently wide range of values of α . The upper bound 4 is essentially arbitrary and some sensitivity analysis on this may be useful. We tried various values of L and found that $L = 30$ works very well. With 26 subjects in this data set, a truncation point 30 is sufficiently high.

The initial values for the fixed parameters were selected by starting with the prior mean and covering ± 3 standard deviations. The initial values for the precision were arbitrarily selected. In the analysis, we used 5000 burn-in iterations and 10,000 updates. The posterior estimates of the parameters are presented in Table 1.

The estimates of the parameters across models agree broadly. In Table 1 we present the posterior means. The treatment effect is quite high in all the models, and it is significant, in the sense that the 95% credible interval does not contain zero. The negative estimates for the sequence shows that the AUC at the second sequence seems larger than that at the first sequence. Negative estimates for the period effect bear a similar interpretation. The variance estimates for formulation B are greater than the corresponding estimates for formulation A in all the models.

The Bayesian hypothesis test requires calculating the posterior probability of the hypotheses described in (2). Thus, the posterior probability of average bioequivalence is computed using the following equation:

$$\begin{aligned} P[ABE|data] &= \Pr[\log(0.8) < \mu_T - \mu_R < \log(1.25)|Data] \\ &\cong \frac{1}{m} \sum_{p=1}^m I[\log(0.8) < \mu_{Tp} - \mu_{Rp} < \log(1.25)] \end{aligned}$$

where $(\mu_{Tp} - \mu_{Rp} : p = 1, \dots, m)$ is a sample from the observed posterior density of $(\mu_T - \mu_R)$, $I(\cdot)$ denotes the indicator function, and $m = 10,000$ is the number of iterations. If the posterior probability defined by the above equation is greater than 0.5, then average bioequivalence is accepted. In Table 1, PABE is the posterior probability of ABE. ABE got rejected in all the models since the posterior probability of ABE is less than 0.5. We note that the frequentist threshold of 0.05 plays no role in interpreting posterior probabilities and we think the relevant threshold is 0.5, suggesting that one should retain the hypothesis with the higher posterior probability.

Rejection of ABE can be described by the high difference between the two treatments. Note,

however, that the treatment difference reduces from the normal model to the Dirichlet model. This happens because the effect of outliers and skewness of the data reduces in the Dirichlet model. Thus, the posterior probability of ABE also increases in the Dirichlet model and in the mixture model compared with the normal model. This example thus clearly indicates the usefulness of the mixture model, especially when the bioequivalence data are skewed and contain outliers. The advantage of MDP model can also be justified from the residual plot in figure 2. Residual plots from MDP model has a better behavior.

We compare the three models informally by computing the effective number of parameters p_D and the deviance information criterion (DIC) as presented by Spiegelhalter et. al. (2002). DIC can be implemented in WinBUGS and can be used to compare complex models. Large differences in the criterion can be attributed to real predictive differences in the models. The smaller the DIC the better the fit, and a difference larger than 10 is overwhelming evidence in favor of the better model (Burnham and Anderson, 2002).

Using DIC values in Table 2, we see that the MDP model gives improved model fit over the other two models. Spiegelhalter et. al. (2002) mention that p_D roughly indicates the number of parameters in the model. We see that DP model has maximum p_D .

5 Conclusion

We have provided an easily implemented robust Bayesian model for studying the effect of an assumption of normality for the random effects' distribution in bioequivalence trials. Our model affords the flexible use of informative priors. The flexibility stems from the fact that it allows for accommodation of the uncertainty in the distribution. The method yields flexible data-driven inference for bioequivalence. We have discussed how such inference can be obtained and illustrated our method with an example. We found that the models with normal and two-component mixture-of-normal distributions give quite similar results and, as expected, differ

from the results of the DP model.

We have illustrated our method of analysis in the context of a single parameter in the 2×2 crossover design with an equal number of subjects in each sequence and no dropouts. In practice, our Bayesian method could be extended to more parameters and to other criteria, such as individual bioequivalence. Such extensions are an area of ongoing research.

APPENDIX: Implementation Using WinBUGS

We describe the MDP prior WinBUGS code to implement the methods described in this paper. The full code is available from the authors upon request.

- * T denotes the treatment effect
- * S denotes the sequence effect
- * P denotes the period effect
- * `delta[g[i]]` denotes random subject effect
- * `g[i]` is a variable that assigns a common subject number to each set of two observations taken from the same subject

Model

```
{  
  
                2 x 2 crossover design  
  
  for ( i in 1:N)  
  {  
    y[i]~ dnorm(mu[i],tau)  
    mu[i]<-T*x[i,1]+S*x[i,2]+P*x[i,3]+delta[g[i]]  
  }  
tau~dgamma(0.001,0.001)
```

MDP model distribution of random effect

```
for (j in 1:K)  
{
```

```

    delta[j]~ dnorm(beta[group[i]],tau1)
    group[i]~ dcat(p[])
}
* Constructive DPP
p[1]<-r[1]
for (j in 2:L)
{
  p[j]<-r[j]*(1-r[j-1])*p[j-1]/r[j-1]
}
p.sum<-sum(p[])
for (j in 1:L)
{
  beta[j]~dnorm (0,tau2)
  r[j]~dbeta(1,alpha)
* scaling to ensure sum to 1
pi[j]<-p[j]/p.sum
}
alpha~dunif(0.5,4)
a~ dnorm(0,0.001)
tau1 ~ dgamma(0.001,0.001)
tau2 ~ dgamma (0.001,0.001)
}

```

ACKNOWLEDGEMENTS

We thank Prof. Peter Müller for many useful discussion and helpful comments. We also thank Dr. Thomas E. Bradstreet for providing the bioequivalence data.

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Table 1: Posterior Mean of the Parameters.

Parameter	Normal Model	Mixture Model	Dirichlet Model
Sequence	-0.1919	-0.1293	-0.2251
Period	-0.08439	-0.1512	-0.03874
Treatment	1.942	1.3	1.07
σ_{eA}^2	0.2575	0.2561	0.339
σ_{eB}^2	0.6515	0.6526	0.6858
PABE	0.131	0.3375	0.435

Table 2: Effective number of parameters, p_D and DIC for the three fitted models for the first data.

	p_D	DIC
Normal Model	9.393	58.410
Mixture Normal Model	11.261	50.790
DP Model	12.811	45.063

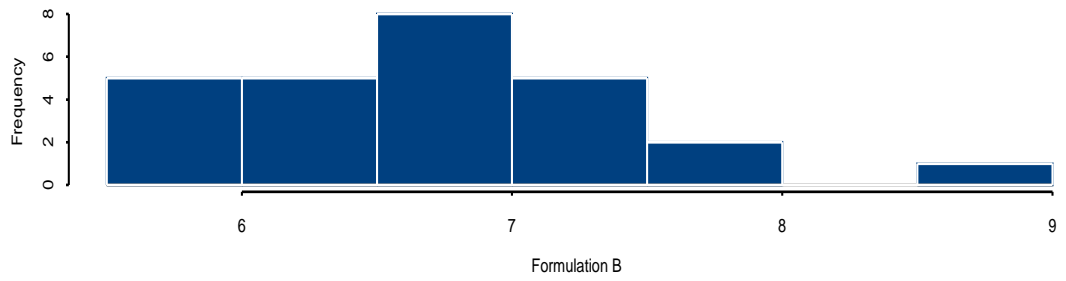
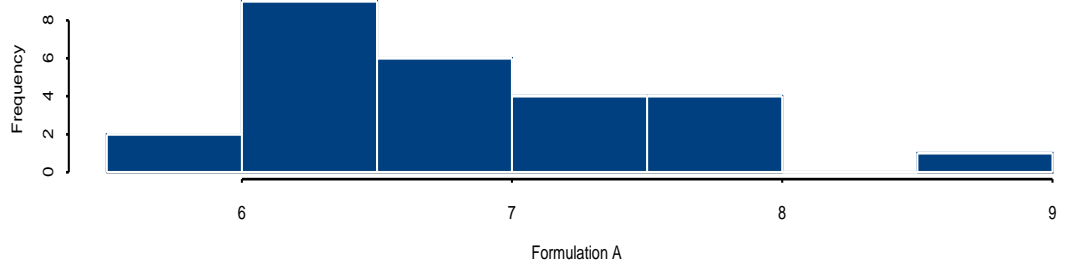
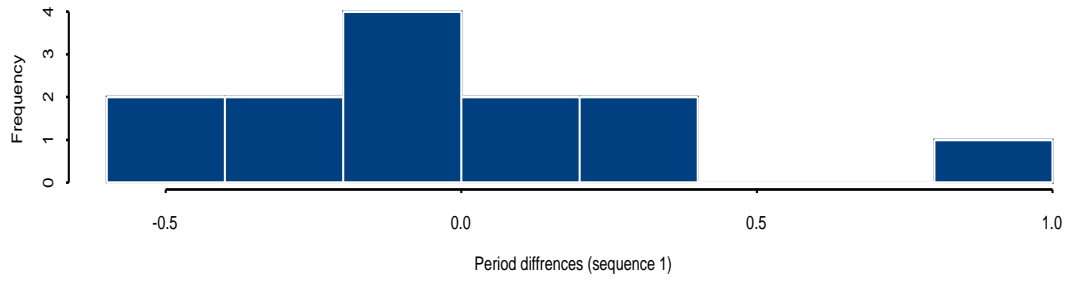


Figure 1: Histogram of Period differences and treatment formulation

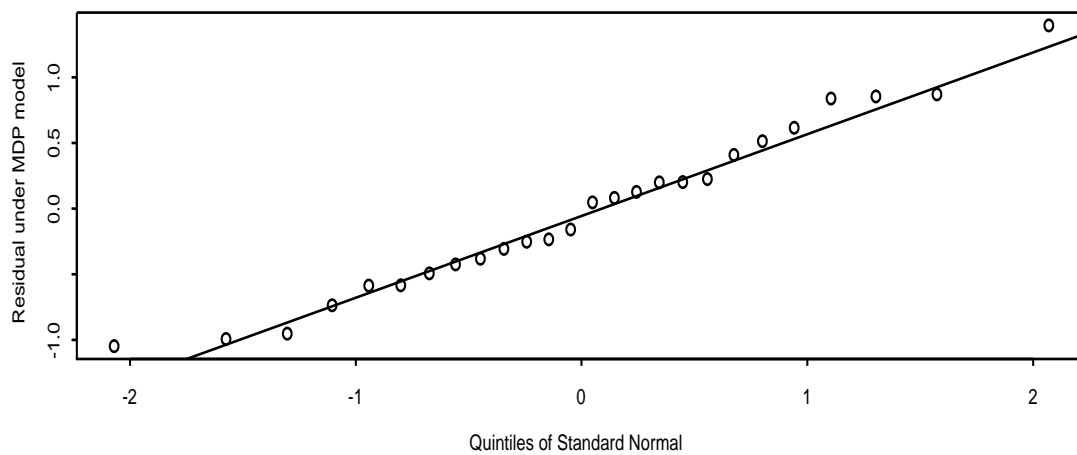
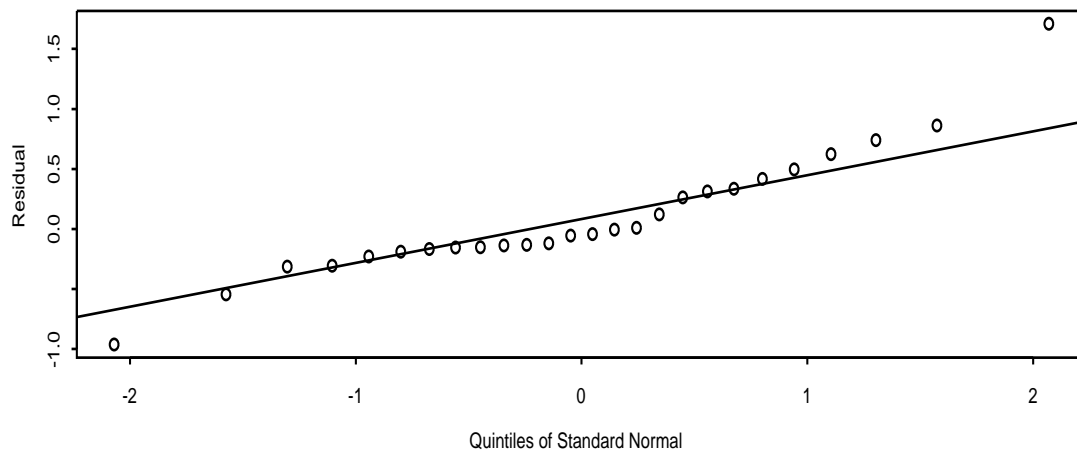


Figure 2: Residual plots