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**ASSESSING THE EFFECT OF PRIOR DISTRIBUTION ASSUMPTION ON THE VARIANCE PARAMETERS IN EVALUATING BIOEQUIVALENCE TRIALS**

by

Dawud A. Ujamaa

**Under the direction of Pulak Ghosh**

**ABSTRACT**

Bioequivalence determines if two drugs are alike. The three kinds of bioequivalence are Average, Population, and Individual Bioequivalence. These Bioequivalence criteria can be evaluated using aggregate and disaggregate methods. Considerable work assessing bioequivalence in a frequentist method exists, but the advantages of Bayesian methods for Bioequivalence have been recently explored. Variance parameters are essential to any of theses existing Bayesian Bioequivalence metrics. Usually, the prior distributions for model parameters use either informative priors or vague priors. The Bioequivalence inference may be sensitive to the prior distribution on the variances. Recently, there have been questions about the routine use of inverse gamma priors for variance parameters. In this paper we examine the effect that changing the prior distribution of the variance parameters has on Bayesian models for assessing Bioequivalence and the carry-over effect. We explore our method with some real data sets from the FDA.

INDEX WORDS: Average Bioequivalence, Bayesian methods, Carry-Over Effect, Crossover design, DIC, Individual Bioequivalence, Inter-subject variance, Intra-subject variance, Markov Chain Monte Carlo, Population Bioequivalence, Prior Distributions, WinBUGS

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by

Dawud A. Ujamaa

Thesis submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

In the College of Arts and Sciences

Georgia State University

**2006**

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Dawud A. Ujamaa
2006

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by

Dawud A. Ujamaa

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# LIST OF ABBREVIATIONS

| ABBREVIATION | DESCRIPTION |
|---|---|
| ABE | Average Bioequivalence |
| AIC | Akaike's Information Criterion |
| BUGS | Bayesian inference Using Gibbs Sampling |
| C.I. | Credible Interval |
| DIC | Deviance Information Criteria |
| FDA | Food and Drug Administration |
| IBE | Individual Bioequivalence |
| MCMC | Markov Chain Monte Carlo |
| PAB | Probability of Average Bioequivalence |
| PBE | Population Bioequivalence |
| PJT | Probability of Joint Average and Population Bioequivalence |
| PRV | Probability of Ratio of Variances |

## 1. INTRODUCTION

Bioavailability is defined as the amount or the rate at which a drug is absorbed into the circulatory system or becomes available at the site of physiological activity after administration (Merriam-Webster's Medical Dictionary, 2002). Two drug formulations are considered bioequivalent if the bioavailability for each drug formulation is similar in terms of effectiveness and safety. Bioequivalence can be assessed using the methods of Average Bioequivalence (ABE), Population Bioequivalence (PBE), and/or Individual Bioequivalence (IBE). Establishing Average Bioequivalence statistically involves comparing the average bioavailability of each population that receives the two drug formulations. Establishing Population Bioequivalence statistically involves ascertaining the population averages of the two drug formulations and also comparing the variability of the bioavailability of each population that receives the two drug formulations. Having statistical knowledge of the Population Bioequivalence of two drug formulations assists physicians in deciding which drug formulation to prescribe pharmaceutically (Chow and Liu, 1995). Not only can bioavailability vary between populations, but it can also vary from person to person and within each person of the population. The variability of the bioavailability from person to person is called "Between-subject "or "Inter-subject" variability. The variability of the bioavailability within an individual person is called "Within-subject" or "Intra-subject" variability. Assuming that each subject of each population receives both drug formulations, then bioavailability can also vary due to the subject-by-formulation interaction. Establishing Individual Bioequivalence statistically involves ascertaining the population averages of the two drug formulations and also

comparing the intra-subject variability and/or the subject-by-formulation interaction of the two drug formulations. Having statistical knowledge of the Individual Bioequivalence of two drug formulations assists physicians in making the pharmaceutical decision of whether or not a patient can switch from one drug formulation to another and still maintain the same efficacy (Chow and Liu, 1995). Population and Individual Bioequivalence can be evaluated by aggregate and disaggregate methods. Aggregate methods combine the main characteristics into one null hypothesis with a single criterion, while disaggregate methods have separate hypotheses for the main characteristics (Erickson, Seaman, Stamey, 2005).

The United States Food and Drug Administration's (FDA) 2001 Guidance recommends using an aggregate statistical test procedure for assessing IBE. The FDA uses a method proposed by Hyslop, Hsuan, & Holder (2000) under a replicated crossover design when examining population bioequivalence and individual bioequivalence. The FDA draft guidance (1999) suggests using a standard two-period crossover design when assessing population bioequivalence and using a replicated two-period crossover designs for assessing individual bioequivalence (Ghosh and Ntzoufras, 2005). Crossover (or Latin Squares) designs are the best experimental designs for bioequivalence studies because they enable estimation of the subject, formulation, period, and random effects; allow the separation of the inter- and intra-subject variations; and, if replicated, facilitate a way to estimate the subject-by-formulation interaction (Ghosh and Khattree 2005). Since the use of crossover designs in bioequivalence studies enable accountability for a number of the sources of variance, and since population bioequivalence and individual bioequivalence are both functions of variance, then it is apparent why the FDA

recommends the use of crossover designs for assessing population and individual bioequivalence.

Advantages of Bayesian methods for assessing bioequivalence assume that the unknown formulation effect is a random variable and follows a prior distribution (Ghosh and Khattree, 2005). A major advantage of the Bayesian approach is that it accounts for a variety of sources of parameter uncertainty for variance components as well as the other parameter estimates (Gill 2002; Gelman et al., 2004). Inferring whether two drug formulations are bioequivalent in the Bayesian approach is based upon the entire posterior distribution of the model parameters. The posterior distribution of the model parameters can be accurately assessed by generating samples using Markov chain Monte Carlo (MCMC) methods (Bernardo and Smith, 1994, p. 353). With the computation capabilities of computers increasing over the past several decades, and the development of Markov chain Monte Carlo methods and Gibbs sampling, powerful software applications such as WinBUGS have been created which enable sophisticated models to be produced based upon the Bayesian approach.

Erickson, Seaman, and Stamey (2005) developed a Bayesian model to be implemented in the WinBUGS application using disaggregate methods for assessing ABE and PBE. Ghosh and Ntzoufras (2005) developed a Bayesian model to be implemented in the WinBUGS application using aggregate methods for assessing PBE and IBE. The freely available WinBUGS software is used for fitting both models, so vague prior distributions are used for the scale parameters of the random effects. A paper by Lambert et al (2005) shows that the use of vague prior distributions in MCMC using WinBUGS may have an influence on any inference made. The paper also states “in a

random effects model, there is especially concern about the influence of the prior distributions on scale parameters." In addition to the influence that the prior distribution may have on scale parameters one must decide on "the distributional form of the prior distribution, and whether to put the prior on the variance, standard deviation or precision." Gelman *et al* (2004) have also recently questioned the routine use of the inverse gamma prior distribution for variance parameters. In this paper we assess the performance of the various prior distributions on the scale parameters for assessing Bioequivalence. We also address the issue of carryover effect on IBE. To our knowledge, this is the first attempt to incorporate carryover in Bioequivalence.

In chapter 2 we specify the model and the disaggregate criteria for assessing ABE and PBE. In chapter 3 we specify the model with and without carry-over effect and the aggregate criteria for assessing IBE. In chapter 4 we present the various prior distributions to be used for the variance parameters. In chapter 5 we present the results, and a final discussion about the results is presented in chapter 6. All of the WinBUGS codes and data sets used are available in the Appendix.

## 2. AVERAGE AND POPULATION BIOEQUIVALENCE

The FDA recommends the use of a 2×2 or higher-order crossover design for assessing bioequivalence. The higher-order crossover designs occur when the experiment is replicated. Replicated crossover designs are recommended for assessing Individual Bioequivalence; however, the simple crossover design can be used to assess average bioequivalence and population bioequivalence. In crossover designs for bioequivalence, there are generally two "treatments." One treatment is the reference drug formulation denoted by "*R,*" and one treatment is the test drug formulation denoted by "*T*." A replicated crossover design occurs when each subject receives more than one treatment of each drug formulation. Let $t = 2$ denote the total number of treatments. Let $r$ denote the total number of replications. For a standard 2×2 crossover design, $r = 1$. Each time a subject receives a drug treatment, it is called a "period." Let $p = tr = 2r$ denote the total number of periods. The order in which the subjects receive the drug formulation treatments are termed "sequences," and the total number of sequences is denoted by $s$, where $s \geq 2$.

### 2.1. Model Specification

Let $y_{ijk}$ denote the logarithm of the bioavailability for subject $j$ in formulation $k$ of sequence $i$. The normal model for the data is given by

$$y_{ijk} = \mu + \alpha_i + \gamma_{ij} + \tau_k + \pi_{ik} + e_{ijk} \tag{1}$$

where $\mu$ is the overall mean, $\alpha_i$ is the fixed effect of sequence $i$, $\tau_k$ is the fixed effect of formulation $k$, $\pi_{ik}$ is the fixed effect of period at which the $k$th formulation in the $i$th sequence is administered, $\gamma_{ij}$ is the random effect of subject $j$ in sequence $i$, and $e_{ijk}$ is the random effect of subject $j$ in formulation $k$ of sequence $i$ (Vuorinen and Turunen, 1996). This model can be written as $\mathbf{y} = \boldsymbol{\beta}\mathbf{x} + \boldsymbol{\gamma}\mathbf{z} + \mathbf{e}$, where $\mathbf{y}$ is the observed data vector, $\boldsymbol{\beta}$ is a vector of unknown fixed effects (sequence, formulation, and period), $\mathbf{x}$ is a known design matrix that links $\boldsymbol{\beta}$ to $\mathbf{y}$, $\boldsymbol{\gamma}$ is a vector of unknown random effects of subjects, $\mathbf{z}$ is a known design matrix linking $\boldsymbol{\gamma}$ to $\mathbf{y}$, and $\mathbf{e}$ is an unknown random error vector. This model assumes i) homogeneity of covariance structures in the two sequences; ii) linearity of the statistical model; iii) $\gamma_{ij}$ are independent and identically distributed normal random variables with mean 0 and inter-subject variance $\sigma_\gamma^2$; iv) $e_{ijk}$ are independent and identically distributed normal random variables with mean 0 and intra-subject variances $\sigma_{eR}^2$ and $\sigma_{eT}^2$ for the two formulations respectively.

The Bayesian model that uses disaggregate methodology for assessing Average and Population bioequivalence presented by Erickson, Seaman, and Stamey (2005) is based on the model presented above, and assumes the following:

$y_{ijk}$ ~ $N(\mu_{ijk}, \sigma_{\varepsilon\, ijk}^2)$, is the logarithm of the bioavailability of subject *j,* in sequence *i,* taking drug formulation *k*, where

$$\mu_{ijk} = \alpha + \beta_m x_{i,m} + \gamma_{ij}$$

$$= \alpha + \beta_1 x_{i,1} + \ldots + \beta_{s\text{-}1} x_{i,s-1} + \beta_s x_{i,s} + \ldots + \beta_{s+p-1} x_{s+p-1} + \beta_{s+p} x_{i,x+p} + \gamma_{ik}$$

$m$ = 1,…, $s$+$p$, where,

- For $m$ = 1,…,($s$-1), $\beta_m$ is the fixed sequence effect, and $x_{i,m}$ is the sequence indicator
- For $m$ = $s$,…,($s$+$p$-1), $\beta_m$ is the fixed period effect, and $x_{i,m}$ is the period

indicator

- For $m = s+p$, $\beta_m$ is the fixed treatment effect, and $x_{i,m}$ is the treatment indicator

$\alpha$ ~ $N(\alpha_0, \sigma_\alpha^2)$, where $\alpha_0 = 0$, and $\sigma_\alpha^2 = 10^4$

$\beta_m$ ~ $N(\eta_P, \sigma_\beta^2)$, is a fixed effect, where $\eta_P = 0$, and $\sigma_\beta^2 = 10^4$

$\gamma_{ij}$ ~ $N(\alpha, \sigma_\gamma^2)$, is the subject random effect for subject $j$ within sequence $i$

$e_{ijk}$ ~ $N(0, \sigma_{ek}^2)$, denotes the random error for subject $j$ within sequence $i$ taking treatment $k$

$\sigma_\gamma^2$ : is the between-subject (inter-subject) variance

$\sigma_{ek}^2$ : is the within-subject (intra-subject) variance for drug formulation $k$

We use weakly informative conditionally conjugate priors on the parameters to let the inference be dominated by the data. The prior distributions for $\sigma_\gamma^2$ and $\sigma_{ek}^2$ are discussed in Chapter 4. The prior distributions for the scale parameters of the random effects in this Bayesian model may or may not influence the inferences drawn from the model. The prior distributions for the scale parameters of the random effects can be put on the inter-subject variances ($\sigma_{eR}^2$ and $\sigma_{eT}^2$) and intra-subject variance ($\sigma_\gamma^2$); or on the inter-subject precisions ($\tau_{eR}$ and $\tau_{eT}$) and intra-subject precision ($\tau_\gamma$); or on the inter-subject standard deviations ($\sigma_{eR}$ and $\sigma_{eT}$) and intra-subject standard deviation ($\sigma_\gamma$). Thirteen different prior distributions were used for the scale parameters of the random effects for this mixed-effects Bayesian model to assess the influence that the priors have on the inferences drawn from the model.

## 2.2. Disaggregate Criteria for Assessing ABE and PBE

To describe the criterion used in the disaggregate methodology for assessing Average and Population Bioequivalence, the following notation is used:

$\mu_T$ = $\mu + \tau_T$, mean for test drug formulation, where $\mu$ is the overall mean and $\tau_T$ is the fixed effect of test drug formulation

$\mu_R$ = $\mu + \tau_R$, mean for reference drug formulation, where $\mu$ is the overall mean and $\tau_R$ is the fixed effect of reference drug formulation

$\sigma_T^2$ = $\sigma_\gamma^2 + \sigma_{eT}^2$, total variance (population variance) for the test drug formulation, where $\sigma_\gamma^2$ and $\sigma_{eT}^2$ are as previously defined

$\sigma_R^2$ = $\sigma_\gamma^2 + \sigma_{eR}^2$, total variance (population variance) for the reference drug, where $\sigma_\gamma^2$ and $\sigma_{eR}^2$ are as previously defined

Average bioequivalence (*ABE*) can be determined by testing the following two one-sided hypotheses proposed by Schuirmann (1987):

$$H_{01}: \ \mu_T - \mu_R \geq \theta_U \quad \text{versus} \quad H_{11}: \ \mu_T - \mu_R < \theta_U$$

and

$$H_{02}: \ \mu_T - \mu_R \leq \theta_L \quad \text{versus} \quad H_{12}: \ \mu_T - \mu_R > \theta_L$$

where $\theta_L = \ln(0.8)$ and $\theta_U = \ln(1.25)$ is the range of acceptable relative bioavailability for the formulation means as recommended by the FDA. Average bioequivalence is declared if and only if $H_{01}$ and $H_{02}$ are rejected simultaneously at significance level $\alpha$ for a *t*-distribution with $n_1+n_2-2$ degrees of freedom. In the Bayesian model, if we let **Y** denote the data, then computing the following posterior probability tests this hypothesis:

$$PAB \equiv P(\theta_L < \mu_T - \mu_R < \theta_U \mid \mathbf{Y})$$

If $PAB \geq 0.90$, then average bioequivalence is declared.

According to Liu and Chow (1995), equivalence in variability of bioavailability can be determined by testing the following two one-sided hypotheses:

$$H_{01}: \ \sigma_T^2 / \sigma_R^2 \le \lambda_L \qquad \text{versus} \qquad H_{11}: \ \sigma_T^2 / \sigma_R^2 > \lambda_L$$

and

$$H_{02}: \ \sigma_T^2 / \sigma_R^2 \ge \lambda_U \qquad \text{versus} \qquad H_{12}: \ \sigma_T^2 / \sigma_R^2 < \lambda_U$$

where $\lambda_L = 0.70$ and $\lambda_U = 1.43$ is the range of acceptable relative bioavailability for the test drug formulation and reference drug formulation variance components as suggested by Chow and Liu (1995). Equivalence in the variability of bioavailability is declared if and only if $H_{01}$ and $H_{02}$ are rejected simultaneously at significance level $\alpha$ for a *t*-distribution with $n_1+n_2-3$ degrees of freedom. This is a disaggregate method for assessing population bioequivalence. In the Bayesian model, computing the following posterior probability tests this hypothesis:

$$PRV \equiv P(\lambda_L < \sigma_T^2 / \sigma_R^2 < \lambda_U \mid \mathbf{Y})$$

After average bioequivalence is declared, if $PRV \ge 0.90$, then population bioequivalence is declared.

Average Bioequivalence and Population Bioequivalence can be tested simultaneously. If we let $A = \{\theta_L < \mu_T - \mu_R < \theta_U \mid \mathbf{Y}\}$ and $B = \{\lambda_L < \sigma_T^2 / \sigma_R^2 < \lambda_U \mid \mathbf{Y}\}$, then computing the following joint posterior probability of $A$ and $B$ will allow for simultaneous testing of Average and Population Bioequivalence:

$$PJT \equiv P(A \cap B \mid \mathbf{Y}) = PAB \times PRV$$

If $PJT \ge 0.90$, then two drug formulations are declared average bioequivalent and population bioequivalent.

## 3. INDIVIDUAL BIOEQUIVALENCE

The United States Food and Drug Administration's draft guidance (1999) recommends using two-period replicated crossover designs for assessing Individual Bioequivalence because replicated crossover designs enable a way to estimate the subject-by-formulation interaction. A two-period replicated crossover design for two treatments will yield a four-period design with two replications for each treatment. In addition to sequence, period, treatment, and subject effects, another nuisance parameter to be considered in crossover designs for bioequivalence is the carry-over effect. We consider two models for assessing individual bioequivalence with and without the assumption of carry-over effects.

### 3.1. Model Specification without Carry-Over Effect

Let $y_{ijkl}$ denote the logarithm of the bioavailability response for replicate $l$ on treatment $k$ for subject $j$ in sequence $i$. The linear mixed-effects model for the data is given by

$$y_{ijkl} = \mu_k + \gamma_{ikl} + \delta_{ijk} + e_{ijkl} \tag{2}$$

where $i = 1, \ldots, s$ indicates the sequence, $j = 1, \ldots, n_i$ indicates the subject within sequence $i$, $k = R, T$ indicates the drug treatment, $l = 1, \ldots, p_{ik}$ indicates the replicate number, $p_{ik}$ indicates the number of replicates for the $k$th treatment in the $i$th sequence, $\mu_k$ is the population average response for the $k$th formulation, $\gamma_{ikl}$ is the fixed effect (period and sequence effects) for replicate $l$ on treatment $k$ in sequence $i$, $\delta_{ijk}$ is the random

subject effect for subject $j$ in sequence $i$ on treatment $k$, and $e_{ijkl}$ is the random error for subject $j$ within sequence i on replicate $l$ of formulation $k$ (Chinchilli and Esinhart, 1996; Hyslop *et al*., 2000). We assume for our model $p_{iT} = p_{iR} = 2$.

The assumptions for this model are: i) the 2×1 vectors of random subject effects $\boldsymbol{\delta}_{ij} = (\delta_{ijR}, \delta_{ijT})^T$ are mutually independent bivariate normal with zero means and variance-covariance matrix $\boldsymbol{\Omega} = \begin{bmatrix} \sigma_{BR}^2 & \rho\sigma_{BT}\sigma_{BR} \\ \rho\sigma_{BT}\sigma_{BR} & \sigma_{BT}^2 \end{bmatrix}$, where $\sigma_{BT}^2$ and $\sigma_{BR}^2$ are the inter-subject variance components for the test and reference drug formulations respectively, and $\rho$ is the correlation between the responses on the same subject corresponding to the two drug formulations; ii) errors $e_{ijkl}$ are mutually independent and normally distributed with mean 0 and intra-subject variances $\sigma_{WR}^2$ and $\sigma_{WT}^2$ for the two formulations respectively; iii) $\delta_{ijk}$ and $e_{ijkl}$ are assumed to be mutually independent; iv) zero carryover effect; and v) the constraint $\sum_{i=1}^{s}\sum_{l=1}^{p_{ik}} \gamma_{ikl} = 0$ is applied to the nuisance parameters to avoid overparametrization of the model.

The Bayesian model that uses the FDA's aggregate methodology for assessing Individual bioequivalence presented by Ghosh and Ntzoufras (2005) is based on the model presented above, and assumes the following:

$y_{ijkl}$ ~ $N(\mu_{ijkl}, \sigma_{e\,k}^2)$, where,

$\mu_{ijkl}$ = $\mu_k + \gamma_{ikl} + \delta_{ijk}$

$\mu_k$ ~ $N(\mu_{0k}, \sigma_{0k}^2)$, is the population average response for the *kth* formulation

$\mu_{0k}$ ~ $N(\mu_{00}, \sigma_{00}^2)$, is a second stage hyper parameter of $\mu_k$, where $\mu_{00} = 0.0$ and $\sigma_{00}^2 = 10^4$

$\sigma_{0k}^2$ ~ Gamma ($a$, $b$), is a second stage hyper parameter of $\mu_k$, where $a = 10^4$ and

$b = 10^4$

$\gamma_{ikl}$ ~ $N(\mu_\gamma, \sigma^2_{\gamma k})$, denotes the fixed period and sequence effects for replicate *l* on treatment *k* in sequence *i,* where $\mu_\gamma = 0$ and $\sigma^2_{\gamma k} = 10^4$

$\boldsymbol{\delta_{ij}}$ ~ $N_2(\mathbf{0}, \mathbf{\Omega})$, denotes the random subject effect for subject *j* in sequence *i* on treatment *k*, where $\mathbf{\Omega} = \begin{bmatrix} \sigma^2_{BR} & \rho\sigma_{BT}\sigma_{BR} \\ \rho\sigma_{BT}\sigma_{BR} & \sigma^2_{BT} \end{bmatrix}$

$e_{ijk}$ ~ $N(0, \sigma^2_{Wk})$, denotes the random error for subject *j* within sequence *i* on replicate *l* of treatment *k*

$\rho$ ~ Uniform (-1, 1), is the correlation between the response of the same subject corresponding to the two drug formulations

$\sigma^2_{BR}$ : denotes the between-subject (inter-subject) variance for the reference drug formulation

$\sigma^2_{BT}$ : denotes the between-subject (inter-subject) variance for the test drug formulation

$\sigma^2_{Wk}$ : denotes the within-subject (intra-subject) variance for formulation *k*

The prior distributions for the scale parameters of the random effects in this Bayesian model may or may not influence the inferences drawn from the model. The prior distributions for the scale parameters of the random effects can be put on the inter-subject variances ($\sigma^2_{BR}$ and $\sigma^2_{BT}$) and intra-subject variances ($\sigma^2_{WR}$ and $\sigma^2_{WT}$); or on the inter-subject precisions ($\tau_{BR}$ and $\tau_{BT}$) and intra-subject precisions ($\tau_{WR}$ and $\tau_{WT}$); or on the inter-subject standard deviations ($\sigma_{BR}$ and $\sigma_{BT}$) and intra-subject standard deviations ($\sigma_{WR}$ and $\sigma_{WT}$). Thirteen different prior distributions discussed in Chapter 4 are used for $\sigma^2_{BR}$, $\sigma^2_{BT}$ and $\sigma^2_{Wk}$ to assess the influence that the priors have on the inferences drawn from the model.

### 3.2. Model Specification with Carry-Over Effect

A first-order carry-over effect is defined as the lingering effect of the treatment administered from the immediately preceding period on the measurement of the response in the current period (Chinchilli and Esinhart, 1996). A crossover design is balanced with respect to first-order carry-over effects if each treatment immediately precedes every other treatment the same number of times (Chinchilli and Esinhart, 1996). In a balanced crossover design, one nuisance parameter can be modeled as a common carry-over effect. The model for a balanced crossover design, which is a modification of the model in (2), allowing for a common carry-over effect denoted as $\lambda$ is given by

$$y_{ijkl} = \mu_k + r_{ikl}\lambda + \gamma_{ikl} + \delta_{ijk} + e_{ijkl} \tag{3}$$

where

$$r_{ikl} = \begin{cases} 1, & \text{if replicate } l \text{ of treatment } k \text{ in sequence } i \text{ occurs after period } 1 \\ 0, & \text{otherwise.} \end{cases}$$

This model has the additional constraint $\sum_{(i,k,l)\in J} \gamma_{ikl} = 0$, where $J = \{(i, k, l): r_{ikl} = 1,$ for each $i = 1, \ldots, s$, $k = 1, \ldots, t,$ and $l = 1, \ldots, p_{ik}\}$. The Bayesian model for (3) assumes that the common carry-over effect $\lambda$ follows a normal distribution with a zero mean and variance parameter of $10^4$ ($\lambda \sim$ Normal $(0, 10^4)$).

### 3.3. Aggregate Criteria for assessing IBE

The following notation is used to describe the criterion used in the aggregate methodology for assessing Individual Bioequivalence as recommended by the United States Food and Drug Administration (FDA):

$\mu_T$ = mean for test drug formulation

$\mu_R$ = mean for reference drug formulation

$\sigma_{TT}^2$ = $\sigma_{WT}^2 + \sigma_{BT}^2$, total variance (population variance) for the test drug formulation, where $\sigma_{WT}^2$ and $\sigma_{BT}^2$ are as previously defined

$\sigma_{TR}^2$ = $\sigma_{WR}^2 + \sigma_{BR}^2$, total variance (population variance) for the reference drug formulation, where $\sigma_{WR}^2$ and $\sigma_{BR}^2$ are as previously defined

$\rho$ = correlation coefficient between test and reference drug formulation

$\sigma_D^2$ = $(\sigma_{BT} - \sigma_{BR})^2 + 2(1-\rho)\sigma_{BT}\sigma_{BR}$, variance due to subject-by-formulation interaction

The FDA 2001 Guidance recommends using the following parameter to test for Individual Bioequivalence:

$$\Theta_{IBE} = \begin{cases} \dfrac{(\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2}{\sigma_{WR}^2} & \text{when } \sigma_{\mathrm{WR}}^2 > \sigma_{\mathrm{W0}}^2 \text{ (Reference scaled criterion)} \\ \dfrac{(\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2}{\sigma_{W0}^2} & \text{when } \sigma_{\mathrm{WR}}^2 \le \sigma_{\mathrm{W0}}^2 \text{ (Constant scaled criterion)} \end{cases}$$

Here $\sigma_{W0}^2$ is a constant with an FDA recommended value of 0.04. Testing the following hypothesis identifies individual Bioequivalence:

$$H_0\text{:}\ \Theta_{IBE} \ge \theta_I \qquad \text{versus} \qquad H_1\ \Theta_{IBE} < \theta_I$$

The FDA recommends a value of 2.4948 for $\theta_I$, and Individual Bioequivalence is declared if $H_0$ is rejected at significance level $\alpha$. In the Bayesian model, computing the following posterior probability tests this hypothesis:

$$IBEH0 \equiv P(\Theta_{IBE} < \theta_I \mid \mathbf{Y})$$

If $IBEH0 \ge 0.90$, then individual bioequivalence is declared.

## 4. PRIOR DISTRIBUTIONS FOR SCALE PARAMETERS

The paper by Lambert *et al* (2005) presents several prior distributions that can be used for the scale parameters of random effects in Bayesian models fit using WinBUGS software. Some of the prior distributions presented the paper are weakly informative versions of the other prior distributions presented in that they give zero density to implausibly large values and do not allow unrealistically large values to be sampled. These weakly informative prior distributions are presented to show how estimates can change when unrealistically large values cannot be sampled. We consider some of the prior distributions presented by Lambert *et al* (2005) for the scale parameters of the random effects in the mixed effects Bayesian models for bioequivalence presented earlier.

Since $standard\ deviation = \sqrt{variance} = \sqrt{1/\ precision}$, the prior distribution for the scale parameters of the random effects in the Bayesian models can be put on the variance, standard deviation, or precision. The parameter that receives the prior distribution is found stochastically while the other two parameters are found deterministically. For example, if the prior distribution is put on the variance parameter, then the standard deviation and precision parameters are found deterministically and the variance parameter is found stochastically. Thirteen different prior distributions were used for the scale parameters of the random effects in the two Bayesian models presented above. If we let $\sigma$ represent the inter-subject and intra-subject standard deviation from

the two Bayesian models for bioequivalence presented above, then the thirteen prior distributions are as follows:

*Prior 1*: $\frac{1}{\sigma^2} \sim Gamma(0.001, 0.001)$

Gamma (0.001, 0.001) on the Precision parameters is approximately uniform for most of its range, with a "spike" of probability mass close to zero.

*Prior 2*: $\frac{1}{\sigma^2} \sim Gamma(0.1, 0.1)$

Gamma (0.1, 0.1) on the Precision parameters has the same distributional form of Prior 1, but with the two parameters set to 0.1 to assess the sensitivity to the choice of parameter values.

*Prior 3*: $\log(\sigma^2) \sim Uniform(-10, 10)$

This prior distribution is uniform between –10 and 10 on the log variance scale of the variance parameters.

*Prior 4*: $\log(\sigma^2) \sim Uniform(-10, 1.386)$

This prior distribution is a weakly informative version of Prior 3, but only goes to a maximum of log(4.0) = 1.386. Although the choice for this upper bound is subjective and depends upon the particular analysis being considered, the rationale for the value of this upper bound is that it would seem doubtful that the inter-subject and intra-subject variances could have a value greater than four.

*Prior 5*: $\sigma^2 \sim Uniform(0.001, 1000)$

This prior distribution is uniform from 0.001 to 1000 on the variance parameters.

*Prior 6*: $\sigma^2 \sim Uniform(0.001, 4)$

This prior distribution is a weakly informative version of Prior 5. The choice for the upper bound value of 4 for this prior follows the same rationale given for the choice of the upper bound in Prior 4.

*Prior 7*: $\frac{1}{\sigma^2} \sim Pareto(1, 0.001)$

This Pareto prior distribution from 1 to 0.001 on the precision parameters is equivalent to a uniform distribution from 0 to 1000 on the variance parameters.

*Prior 8*: $\frac{1}{\sigma^2} \sim Pareto(1, 0.25)$

This prior distribution is a weakly informative version of Prior 7. This prior distribution is equivalent to a uniform prior distribution from 0 to 4 on the variance parameters, or from 0 to 2 on the standard deviation parameters.

*Prior 9*: $\sigma \sim Uniform(0, 100)$

This prior distribution is uniform from 0 to 100 on the standard deviation parameters.

*Prior 10*: $\sigma \sim Uniform(0, 2)$

This prior distribution is a weakly informative version of Prior 9.

*Prior 11*: $\sigma \sim Normal(0, 100)$

This prior places a half-normal distribution from 0 to 100 on the standard deviation parameters.

*Prior 12*: $\sigma \sim Normal(0, 1)$

This prior distribution is a weakly informative version of Prior 11.

*Prior 13*: Diffuse Priors Presented in Original Papers

For the Bayesian model for ABE and PBE presented in the paper by Erickson, Seaman, and Stamey, Gamma (0.01, 0.01) prior distributions were placed on the inter-subject and intra-subject precision parameters. For the Bayesian model for IBE presented by Ghosh and Ntzoufras, Gamma (0.0001, 0.0001) prior distributions were placed on the inter-subject and intra-subject precision parameters.

# 5. RESULTS

## 5.1. Average and Population Bioequivalence

The scale parameters of the random effects in the Bayesian Model for assessing average and population bioequivalence are tested on the prior distributions presented by Lambert *et al* (2005). We consider three different data sets to test this model. The first data set described by Chow and Liu (2000), is a 2×2 un-replicated crossover experiment with 24 subjects. The second data set is drug 8 from the FDA's website (http://www.fda.gov/cder/bioequivdata.), and is a 4×4 (two-period replicated) crossover experiment. The third data set is drug 14c from the FDA's website, and is a 2×4 crossover design. To analyze these data sets we use five parallel chains with 10,000 burn-in iterations and 20,000 updates as suggested by the paper by Erickson, Seaman, and Stamey.

For the 2×2 crossover data described by Chow and Liu (2000), Figure 1 shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance for each prior distribution and Table 1.A shows the results. We see in Table 1.A that the two drugs described in the Chow and Liu data would be declared Average Bioequivalent under all thirteen prior distributions, and would not be declared population or Joint-Average-and-Population Bioequivalent under all thirteen prior distributions. We see that Priors 2, 3, and 4 have the largest deviation from the original diffuse priors for Population Bioequivalence and Joint-Average-and-

Population Bioequivalence. For the variance parameters, Priors 2, 5, 6, 7, and 8 have the largest deviation from the original diffuse priors.

For the 4×4 crossover data of drug 8, Figure 2 shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance for each prior distribution and Table 2.A shows the results. We see in Table 2.A that these two drugs would be declared Average Bioequivalent but not Population or Joint-Average-and-Population Bioequivalent. Prior 2 gives the largest deviation from the original diffuse priors for Population and Joint-Average-and-Population Bioequivalence.

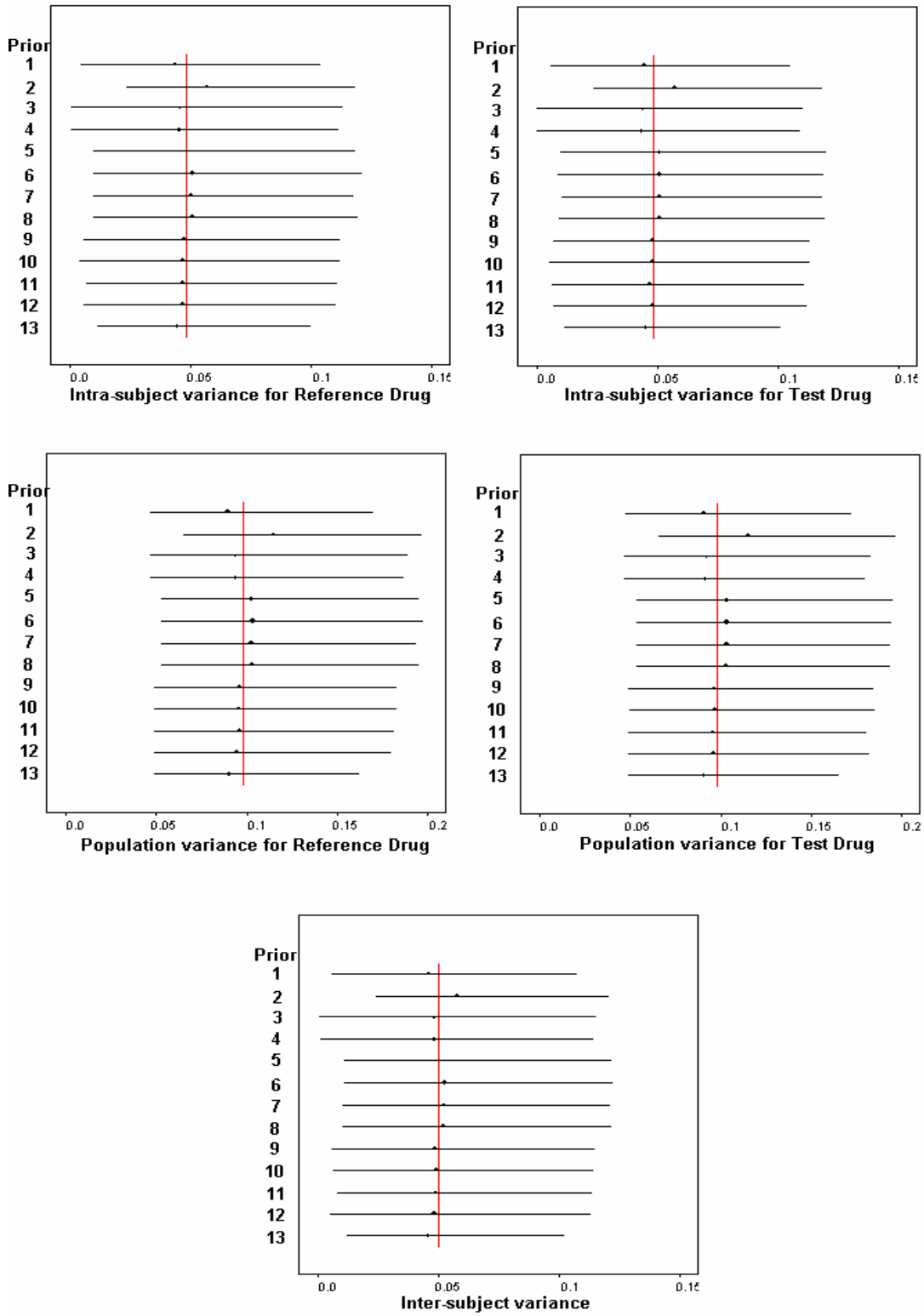
For the 2×4 crossover data of drug 14c, Figure 3 shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance for each prior distribution and Table 3.A shows the results. We see that the drugs described by this data would be declared Average, Population and Joint-Average-and-Population Bioequivalent.

Figures 1, 2, and 3 all show how the credible intervals differ for each prior distribution on the scale parameters. The differing credible intervals could influence the inference. Table 1.B, Table 2.B, and Table 3.B show the Percent Deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13). These tables show how the population bioequivalence (PRV) and "joint-average-and-population" bioequivalence (PJT) inference is changing for each prior distribution on the scale parameters. We see from these tables that the percent deviation on the average bioequivalence (PAB) inference is relatively small because average bioequivalence is not a function of variance. The bioequivalence inference drawn from the data of drug 14c

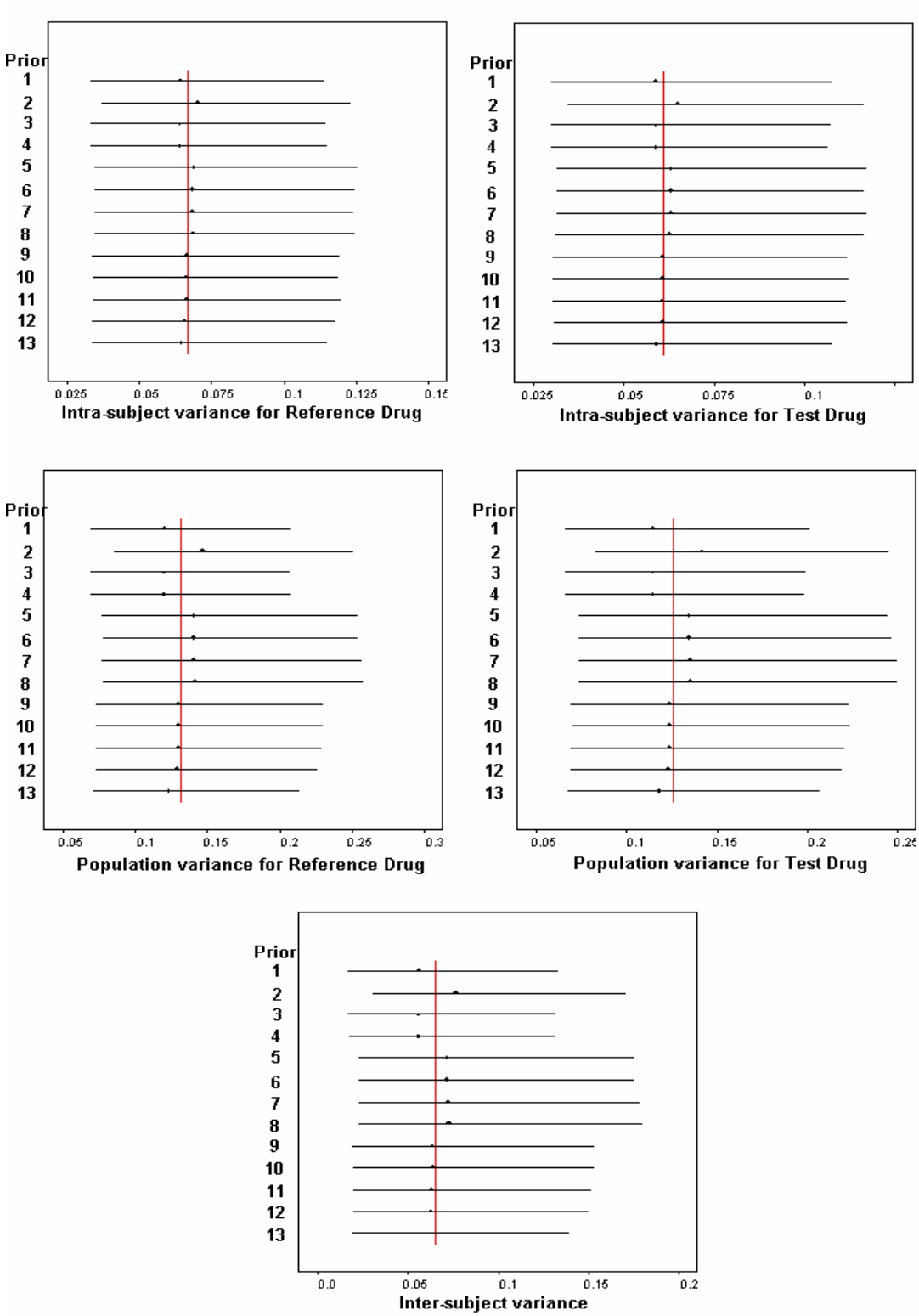
was the least affected, and the bioequivalence inference drawn from the Chow and Liu data was most affected by changing the prior distribution on the scale parameters.

Figure 4, Figure 5, and Figure 6 show the posterior densities of the variance parameters for prior distributions 1, 3, 5, 9, and 11 for the Chow and Liu data, FDA drug 8 data, and FDA drug 14c data respectively. These figures show the various prior distributions on the scale parameters can change the shape of the posterior distribution.

Table 4, Table 5, and Table 6 shows the Deviance Information Criterion (DIC) for the model in (1) on the Chow and Liu data, FDA drug 8 data, and FDA drug 14c data respectively.




**<u>FIGURE 1:</u> Figure 1 above shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance obtained using the model in (1) on the data described by Chow and Liu for each prior distribution on the scale parameters.**




**<u>FIGURE 2:</u> Figure 2 above shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance obtained using the model in (1) on the FDA drug 8 data for each prior distribution on the scale parameters.**

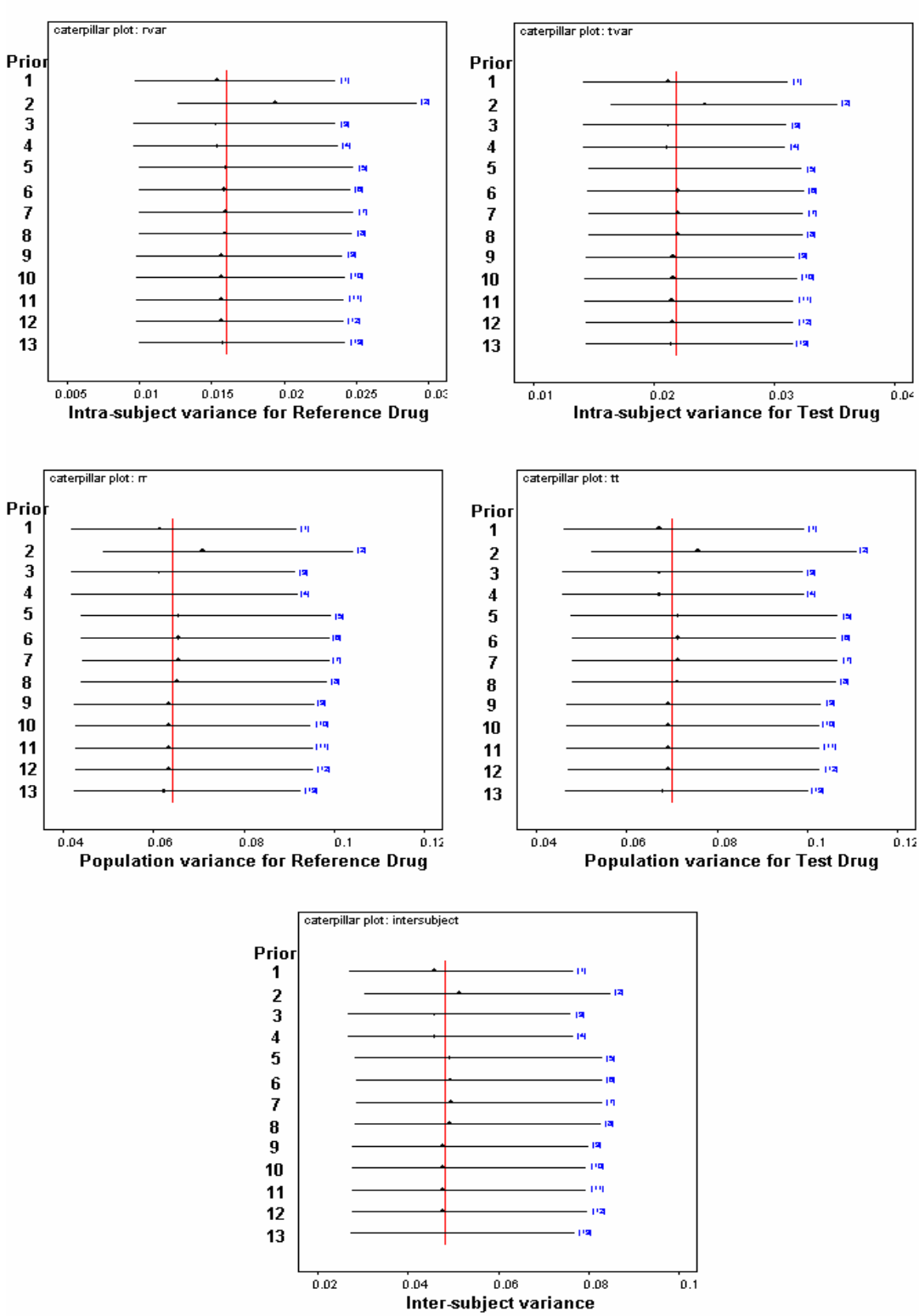



**FIGURE 3:** **Figure 3 above shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance obtained using the model in (1) on the FDA drug 14c data for each prior distribution on the scale parameters.**

**<u>TABLE 1.A:</u> Table 1.A below shows the estimated values using the disaggregate methodology for assessing average bioequivalence, population bioequivalence, joint average and population bioequivalence, population means, inter-subject variance, intra-subject variances, and population variances for the Chow and Liu data for each prior distribution on the scale parameters.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| PAB | 0.9984 | 0.9963 | 0.9982 | 0.9981 | 0.9968 | 0.9967 | 0.997 |
| PJT | 0.6122 | 0.7764 | 0.5478 | 0.5504 | 0.6387 | 0.6341 | 0.6406 |
| PRV | 0.6129 | 0.7788 | 0.5486 | 0.5514 | 0.6402 | 0.6357 | 0.642 |
| $\mu_R$ | 4.38 | 4.38 | 4.38 | 4.38 | 4.38 | 4.38 | 4.38 |
| $\mu_T$ | 4.351 | 4.351 | 4.351 | 4.351 | 4.351 | 4.351 | 4.351 |
| $\sigma^2_\gamma$ | 0.04607 | 0.0578 | 0.04819 | 0.04836 | 0.05241 | 0.05254 | 0.05242 |
| $\sigma^2_R$ | 0.08979 | 0.1146 | 0.09385 | 0.09366 | 0.1029 | 0.1035 | 0.1027 |
| $\sigma^2_{eR}$ | 0.04372 | 0.05681 | 0.04566 | 0.0453 | 0.05046 | 0.05094 | 0.0503 |
| $\sigma^2_T$ | 0.0906 | 0.1148 | 0.09217 | 0.09184 | 0.1034 | 0.1031 | 0.1034 |
| $\sigma^2_{eT}$ | 0.04453 | 0.057 | 0.04398 | 0.04348 | 0.051 | 0.05057 | 0.05097 |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| PAB | 0.9967 | 0.9976 | 0.998 | 0.9981 | 0.9979 | 0.9985 |
| PJT | 0.6366 | 0.624 | 0.6117 | 0.6187 | 0.6203 | 0.672 |
| PRV | 0.638 | 0.6251 | 0.6127 | 0.6196 | 0.6214 | 0.6727 |
| $\mu_R$ | 4.379 | 4.38 | 4.379 | 4.38 | 4.38 | 4.38 |
| $\mu_T$ | 4.351 | 4.351 | 4.351 | 4.351 | 4.351 | 4.351 |
| $\sigma^2_\gamma$ | 0.05216 | 0.04879 | 0.04909 | 0.04902 | 0.04825 | 0.04595 |
| $\sigma^2_R$ | 0.103 | 0.09593 | 0.09581 | 0.09594 | 0.09495 | 0.09019 |
| $\sigma^2_{eR}$ | 0.05085 | 0.04714 | 0.04672 | 0.04692 | 0.04671 | 0.04424 |
| $\sigma^2_T$ | 0.103 | 0.0965 | 0.09693 | 0.09591 | 0.09594 | 0.09109 |
| $\sigma^2_{eT}$ | 0.05085 | 0.04772 | 0.04784 | 0.04689 | 0.04769 | 0.04514 |

In Table 1.A we see that since PAB $\geq$ 0.90 for all prior distributions, then ABE inference is not affected by changing the prior distribution on the scale parameters. In Table 1.B we see that changing the prior distribution on the scale parameters does cause large percent deviation from the original diffuse priors for PJT and PRV, however, since PJT < 0.90 and PRV < 0.90 for all thirteen prior distributions, then PBE and joint ABE and PBE inference is not affected.

**TABLE 1.B: Table 1.B below shows the percent deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13) for the results in Table 1.A.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| PAB | 0.01% | 0.22% | 0.03% | 0.04% | 0.17% | 0.18% | 0.15% |
| PJT | 8.90% | 15.54% | 18.48% | 18.10% | 4.96% | 5.64% | 4.67% |
| PRV | 8.89% | 15.77% | 18.45% | 18.03% | 4.83% | 5.50% | 4.56% |
| $\mu_R$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| $\mu_T$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| $\sigma_\gamma^2$ | 0.26% | 25.79% | 4.87% | 5.24% | 14.06% | 14.34% | 14.08% |
| $\sigma_R^2$ | 0.44% | 27.07% | 4.06% | 3.85% | 14.09% | 14.76% | 13.87% |
| $\sigma_{eR}^2$ | 1.18% | 28.41% | 3.21% | 2.40% | 14.06% | 15.14% | 13.70% |
| $\sigma_T^2$ | 0.54% | 26.03% | 1.19% | 0.82% | 13.51% | 13.18% | 13.51% |
| $\sigma_{eT}^2$ | 1.35% | 26.27% | 2.57% | 3.68% | 12.98% | 12.03% | 12.92% |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| PAB | 0.18% | 0.09% | 0.05% | 0.04% | 0.06% | - |
| PJT | 5.27% | 7.14% | 8.97% | 7.93% | 7.69% | - |
| PRV | 5.16% | 7.08% | 8.92% | 7.89% | 7.63% | - |
| $\mu_R$ | 0.02% | 0.00% | 0.02% | 0.00% | 0.00% | - |
| $\mu_T$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | - |
| $\sigma_\gamma^2$ | 13.51% | 6.18% | 6.83% | 6.68% | 5.01% | - |
| $\sigma_R^2$ | 14.20% | 6.36% | 6.23% | 6.38% | 5.28% | - |
| $\sigma_{eR}^2$ | 14.94% | 6.56% | 5.61% | 6.06% | 5.58% | - |
| $\sigma_T^2$ | 13.07% | 5.94% | 6.41% | 5.29% | 5.32% | - |
| $\sigma_{eT}^2$ | 12.65% | 5.72% | 5.98% | 3.88% | 5.65% | - |

**TABLE 2.A: Table 2.A below shows the estimated values using the disaggregate methodology for assessing average bioequivalence, population bioequivalence, joint average and population bioequivalence, population means, inter-subject variance, intra-subject variances, and population variances for the FDA drug 8 data for each prior distribution on the scale parameters.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| PAB | 0.9998 | 0.9995 | 0.9997 | 0.9998 | 0.9996 | 0.9996 | 0.9996 |
| PJT | 0.8127 | 0.8691 | 0.8131 | 0.8135 | 0.8266 | 0.8273 | 0.8308 |
| PRV | 0.8128 | 0.8694 | 0.8133 | 0.8137 | 0.8269 | 0.8275 | 0.831 |
| $\mu_R$ | 7.598 | 7.598 | 7.598 | 7.598 | 7.598 | 7.598 | 7.598 |
| $\mu_T$ | 7.605 | 7.605 | 7.605 | 7.606 | 7.605 | 7.606 | 7.605 |
| $\sigma^2_\gamma$ | 0.05631 | 0.0769 | 0.05586 | 0.05597 | 0.07146 | 0.07173 | 0.07208 |
| $\sigma^2_R$ | 0.1206 | 0.1469 | 0.12 | 0.1201 | 0.1403 | 0.1403 | 0.1404 |
| $\sigma^2_{eR}$ | 0.06427 | 0.06995 | 0.06412 | 0.06417 | 0.06888 | 0.0686 | 0.06835 |
| $\sigma^2_T$ | 0.1151 | 0.1419 | 0.1147 | 0.1148 | 0.1344 | 0.1347 | 0.1353 |
| $\sigma^2_{eT}$ | 0.05877 | 0.06503 | 0.0588 | 0.05879 | 0.06292 | 0.06293 | 0.06321 |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| PAB | 0.9996 | 0.9997 | 0.9997 | 0.9997 | 0.9998 | 0.9998 |
| PJT | 0.8301 | 0.8187 | 0.8226 | 0.8206 | 0.8228 | 0.8217 |
| PRV | 0.8304 | 0.8189 | 0.8228 | 0.8208 | 0.823 | 0.8218 |
| $\mu_R$ | 7.598 | 7.598 | 7.598 | 7.598 | 7.598 | 7.598 |
| $\mu_T$ | 7.605 | 7.605 | 7.605 | 7.605 | 7.606 | 7.605 |
| $\sigma^2_\gamma$ | 0.07264 | 0.06345 | 0.06361 | 0.06326 | 0.06271 | 0.05883 |
| $\sigma^2_R$ | 0.1414 | 0.1298 | 0.1299 | 0.1296 | 0.1286 | 0.1234 |
| $\sigma^2_{eR}$ | 0.06873 | 0.06635 | 0.06629 | 0.06637 | 0.06588 | 0.06456 |
| $\sigma^2_T$ | 0.1354 | 0.1243 | 0.1244 | 0.1239 | 0.1235 | 0.1181 |
| $\sigma^2_{eT}$ | 0.06272 | 0.06081 | 0.06076 | 0.06063 | 0.06084 | 0.05922 |

In Table 2.A we see that PAB $\geq$ 0.90 for all prior distributions, thus the ABE inference is not affected by changing the prior distribution on the scale parameters. Since PJT < 0.90 and PRV < 0.90 for all thirteen prior distributions, then PBE and joint ABE and PBE inference is not affected here either. The two drugs described by this data would be declared Average Bioequivalent, but would not be declared Population Bioequivalent or Joint-Average-and-Population Bioequivalent for all thirteen prior distributions on the scale parameters.

**<u>TABLE 2.B</u>: Table 2.B below shows the percent deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13) for the results in Table 2.A.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| PAB | 0.00% | 0.03% | 0.01% | 0.00% | 0.02% | 0.02% | 0.02% |
| PJT | 1.10% | 5.77% | 1.05% | 1.00% | 0.60% | 0.68% | 1.11% |
| PRV | 1.10% | 5.79% | 1.03% | 0.99% | 0.62% | 0.69% | 1.12% |
| $\mu_R$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| $\mu_T$ | 0.00% | 0.00% | 0.00% | 0.01% | 0.00% | 0.01% | 0.00% |
| $\sigma_\gamma^2$ | 4.28% | 30.72% | 5.05% | 4.86% | 21.47% | 21.93% | 22.52% |
| $\sigma_R^2$ | 2.27% | 19.04% | 2.76% | 2.67% | 13.70% | 13.70% | 13.78% |
| $\sigma_{eR}^2$ | 0.45% | 8.35% | 0.68% | 0.60% | 6.69% | 6.26% | 5.87% |
| $\sigma_T^2$ | 2.54% | 20.15% | 2.88% | 2.79% | 13.80% | 14.06% | 14.56% |
| $\sigma_{eT}^2$ | 0.76% | 9.81% | 0.71% | 0.73% | 6.25% | 6.26% | 6.74% |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| PAB | 0.02% | 0.01% | 0.01% | 0.01% | 0.00% | - |
| PJT | 1.02% | 0.37% | 0.11% | 0.13% | 0.13% | - |
| PRV | 1.05% | 0.35% | 0.12% | 0.12% | 0.15% | - |
| $\mu_R$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | - |
| $\mu_T$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.01% | - |
| $\sigma_\gamma^2$ | 23.47% | 7.85% | 8.13% | 7.53% | 6.60% | - |
| $\sigma_R^2$ | 14.59% | 5.19% | 5.27% | 5.02% | 4.21% | - |
| $\sigma_{eR}^2$ | 6.46% | 2.77% | 2.68% | 2.80% | 2.04% | - |
| $\sigma_T^2$ | 14.65% | 5.25% | 5.33% | 4.91% | 4.57% | - |
| $\sigma_{eT}^2$ | 5.91% | 2.68% | 2.60% | 2.38% | 2.74% | - |

**TABLE 3.A: Table 3.A below shows the estimated values using the disaggregate methodology for assessing average bioequivalence, population bioequivalence, joint average and population bioequivalence, population means, inter-subject variance, intra-subject variances, and population variances for the FDA drug 14c data for each prior distribution on the scale parameters.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| PAB | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PJT | 0.9945 | 0.9973 | 0.9942 | 0.9942 | 0.9948 | 0.9942 | 0.9948 |
| PRV | 0.9945 | 0.9973 | 0.9942 | 0.9942 | 0.9948 | 0.9942 | 0.9948 |
| $\mu_R$ | 5.613 | 5.613 | 5.613 | 5.613 | 5.613 | 5.613 | 5.613 |
| $\mu_T$ | 5.599 | 5.599 | 5.599 | 5.599 | 5.599 | 5.6 | 5.6 |
| $\sigma^2_\gamma$ | 0.04611 | 0.05154 | 0.04606 | 0.04609 | 0.04948 | 0.04953 | 0.04957 |
| $\sigma^2_R$ | 0.06148 | 0.07096 | 0.06141 | 0.06148 | 0.06544 | 0.06545 | 0.06552 |
| $\sigma^2_{eR}$ | 0.01537 | 0.01942 | 0.01535 | 0.01539 | 0.01597 | 0.01592 | 0.01595 |
| $\sigma^2_T$ | 0.06734 | 0.07582 | 0.06724 | 0.06722 | 0.07143 | 0.07154 | 0.07154 |
| $\sigma^2_{eT}$ | 0.02123 | 0.02428 | 0.02119 | 0.02113 | 0.02195 | 0.02201 | 0.02197 |

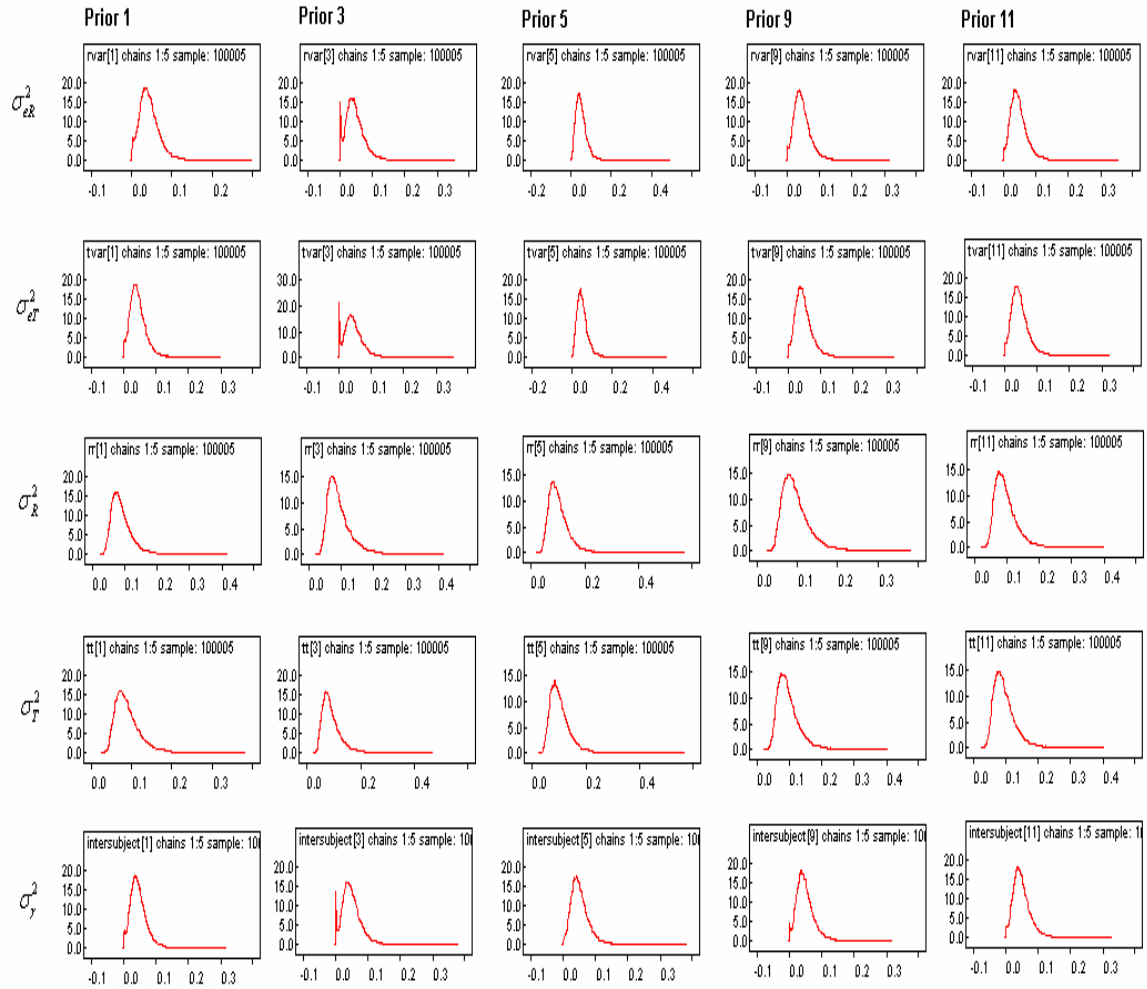
| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| PAB | 1 | 1 | 1 | 1 | 1 | 1 |
| PJT | 0.9946 | 0.9944 | 0.9943 | 0.9945 | 0.9947 | 0.9949 |
| PRV | 0.9946 | 0.9944 | 0.9943 | 0.9945 | 0.9947 | 0.9949 |
| $\mu_R$ | 5.613 | 5.613 | 5.613 | 5.613 | 5.613 | 5.613 |
| $\mu_T$ | 5.599 | 5.599 | 5.599 | 5.599 | 5.599 | 5.6 |
| $\sigma^2_\gamma$ | 0.04936 | 0.04776 | 0.04775 | 0.04779 | 0.04773 | 0.04665 |
| $\sigma^2_R$ | 0.0653 | 0.0634 | 0.06342 | 0.06342 | 0.06336 | 0.06245 |
| $\sigma^2_{eR}$ | 0.01593 | 0.01564 | 0.01567 | 0.01564 | 0.01564 | 0.0158 |
| $\sigma^2_T$ | 0.07133 | 0.06934 | 0.06934 | 0.06933 | 0.06927 | 0.06811 |
| $\sigma^2_{eT}$ | 0.02197 | 0.02157 | 0.02159 | 0.02154 | 0.02155 | 0.02146 |

In Table 3.A we see that PAB ≥ 0.90, PJT ≥ 0.90, and PRV ≥ 0.90 for all prior distributions, thus the ABE, PBE, and Joint-ABE-and-PBE inference is not affected by changing the prior distribution on the scale parameters.

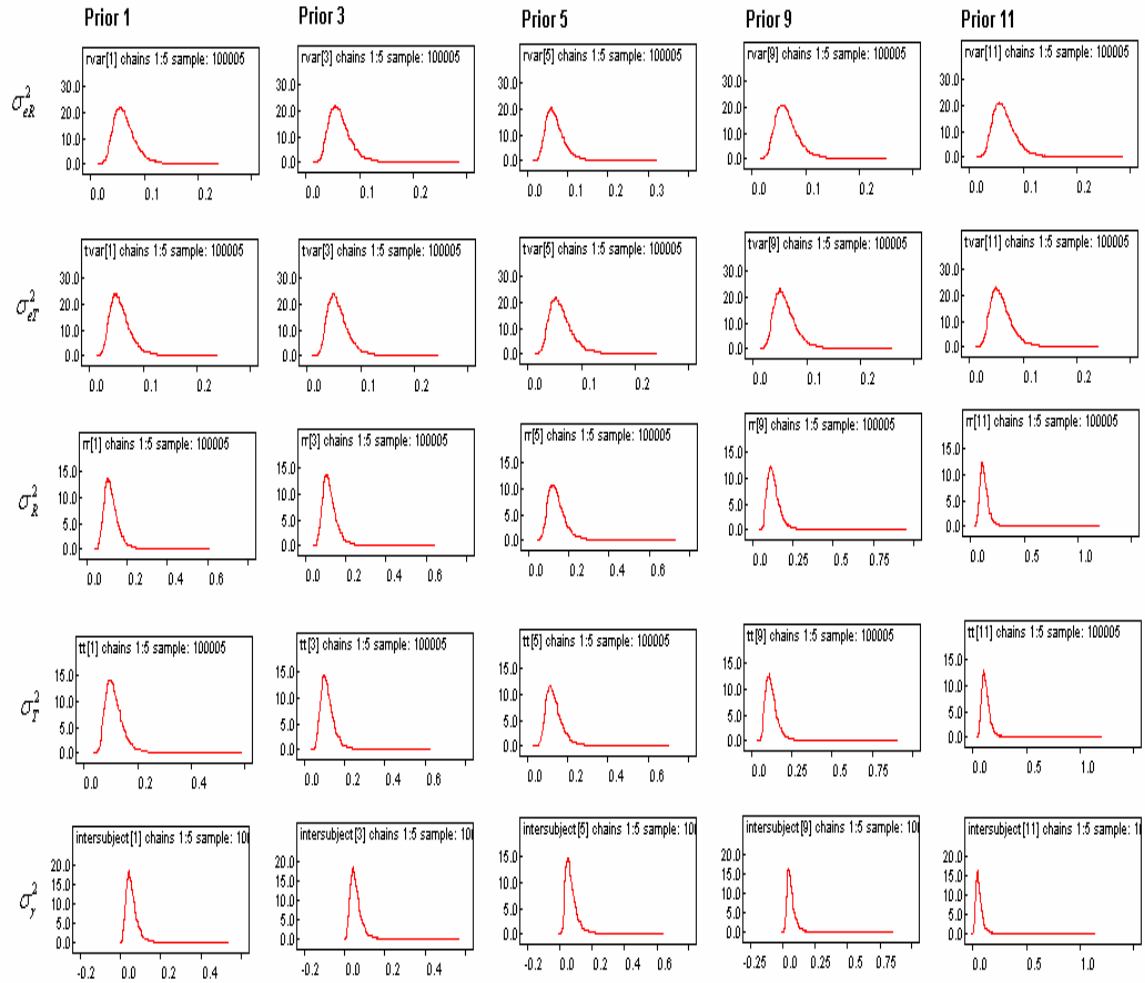
**TABLE 3.B: Table 3.B below shows the percent deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13) for the results in Table 3.A.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| PAB | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| PJT | 0.04% | 0.24% | 0.07% | 0.07% | 0.01% | 0.07% | 0.01% |
| PRV | 0.04% | 0.24% | 0.07% | 0.07% | 0.01% | 0.07% | 0.01% |
| $\mu_R$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| $\mu_T$ | 0.02% | 0.02% | 0.02% | 0.02% | 0.02% | 0.00% | 0.00% |
| $\sigma_\gamma^2$ | 1.16% | 10.48% | 1.26% | 1.20% | 6.07% | 6.17% | 6.26% |
| $\sigma_R^2$ | 1.55% | 13.63% | 1.67% | 1.55% | 4.79% | 4.80% | 4.92% |
| $\sigma_{eR}^2$ | 2.72% | 22.91% | 2.85% | 2.59% | 1.08% | 0.76% | 0.95% |
| $\sigma_T^2$ | 1.13% | 11.32% | 1.28% | 1.31% | 4.87% | 5.04% | 5.04% |
| $\sigma_{eT}^2$ | 1.07% | 13.14% | 1.26% | 1.54% | 2.28% | 2.56% | 2.38% |

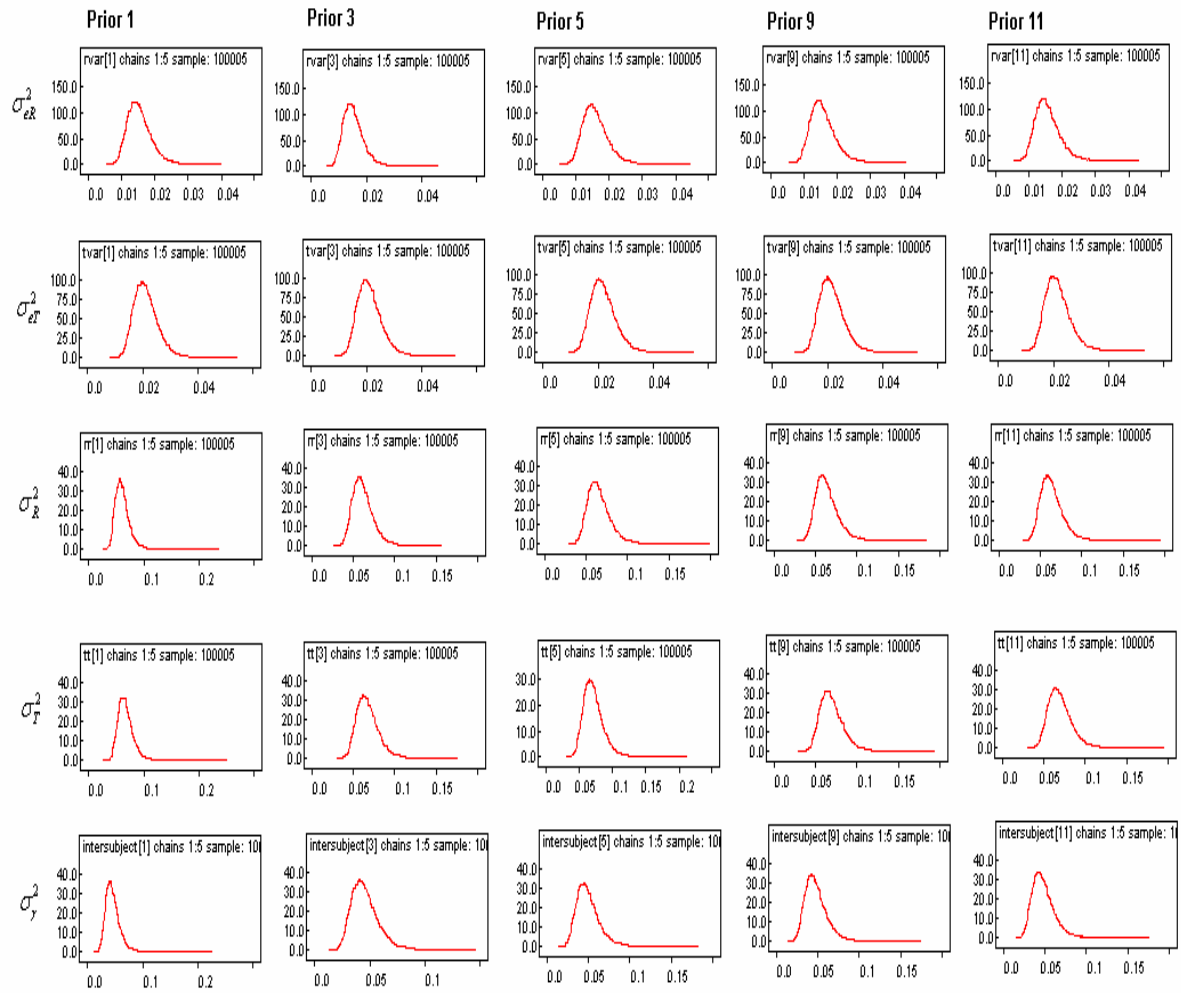
| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| PAB | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | - |
| PJT | 0.03% | 0.05% | 0.06% | 0.04% | 0.02% | - |
| PRV | 0.03% | 0.05% | 0.06% | 0.04% | 0.02% | - |
| $\mu_R$ | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | - |
| $\mu_T$ | 0.02% | 0.02% | 0.02% | 0.02% | 0.02% | - |
| $\sigma_\gamma^2$ | 5.81% | 2.38% | 2.36% | 2.44% | 2.32% | - |
| $\sigma_R^2$ | 4.56% | 1.52% | 1.55% | 1.55% | 1.46% | - |
| $\sigma_{eR}^2$ | 0.82% | 1.01% | 0.82% | 1.01% | 1.01% | - |
| $\sigma_T^2$ | 4.73% | 1.81% | 1.81% | 1.79% | 1.70% | - |
| $\sigma_{eT}^2$ | 2.38% | 0.51% | 0.61% | 0.37% | 0.42% | - |




**<u>FIGURE 4:</u> Figure 4 above shows posterior distributions of the variance parameters obtained using the model in (1) on the Chow and Liu data for prior distributions 1, 3, 5, 9, and 11 on the scale parameters.**




**<u>FIGURE 5:</u> Figure 5 above shows posterior distributions of the variance parameters obtained using the model in (1) on the FDA drug 8 data for prior distributions 1, 3, 5, 9, and 11 on the scale parameters.**




**<u>FIGURE 6:</u> Figure 6 above shows posterior distributions of the variance parameters obtained using the model in (1) on the FDA drug 14c data for prior distributions 1, 3, 5, 9, and 11 on the scale parameters.**

**TABLE 4: Table 4 below shows the WinBUGS Deviance Information Criterion (DIC) for the model in (1) on the Chow and Liu data.**

| Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes | | | | |
|---|---|---|---|---|
| | **Dbar** | **Dhat** | **pD** | **DIC** |
| z | -285.534 | -515.809 | 230.275 | -55.260 |
| total | -277.217 | -507.491 | 230.275 | -46.942 |

**TABLE 5: Table 5 below shows the WinBUGS Deviance Information Criterion (DIC) for the model in (1) on the FDA drug 8 data.**

| Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes | | | | |
|---|---|---|---|---|
| | **Dbar** | **Dhat** | **pD** | **DIC** |
| z | 2.386 | -275.606 | 277.992 | 280.378 |
| total | 10.704 | -267.289 | 277.992 | 288.696 |

**TABLE 6: Table 6 below shows the WinBUGS Deviance Information Criterion (DIC) for the model in (1) on the FDA drug 14c data.**

| Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes | | | | |
|---|---|---|---|---|
| | **Dbar** | **Dhat** | **pD** | **DIC** |
| z | -2353.300 | -2878.040 | 524.738 | -1828.560 |
| total | -2344.980 | -2869.720 | 524.738 | -1820.240 |

### 5.2. Individual Bioequivalence

The scale parameters of the random effects in the Bayesian Model for assessing individual bioequivalence presented by Ghosh and Ntzoufras are tested on the prior distributions presented by Lambert *et al*. We consider two different data sets to test this model. The first data set is drug 8 from the FDA's website. The second data set is drug 14c from the FDA's website. Since each treatment immediately precedes every other treatment the same number of times in the data of drug 14c, this data set is balanced with respect to first-order carry-over effects. Thus, the data of drug 14c is also used to examine the change in the common carry-over effect $\lambda$ as the prior distributions change on the variance parameters. To analyze these data sets we use 1,000 burn-in iterations and 10,000 updates as suggested by the paper by Ghosh and Ntzoufras.

The model in (2) was used to aggregately assess Individual Bioequivalence for the data of drug 8. Figure 7 shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, population variance, and subject-by-formulation interaction variance for each prior distribution and Table 7.A shows the results. The model in (2) was also used to aggregately assess Individual Bioequivalence for the data of drug 14c, and Figure 8 shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, population variance, and subject-by-formulation interaction variance for each prior distribution and Table 8.A shows the results. Figures 7 and 8 both show how the credible intervals differ for each prior distribution on the scale parameters. Table 7.B and Table 8.B show the Percent Deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13). These tables show how the Individual Bioequivalence inference (IBEH0) is changing for each prior

distribution on the scale parameters. Figure 9 and Figure 10 show the posterior densities of the variance parameters for prior distributions 1, 3, 5, 9, and 11 for the FDA drug 8 data, and FDA drug 14c data respectively. Table 9 and Table 10 show the Deviance Information Criterion (DIC) for each prior distribution on the scale parameters of the model in (2) on the FDA drug 8 data and the FDA drug 14c data respectively.

The model in (3) was used on the data of drug 14c to examine the change the common carry-over effect $\lambda$. Figure 11 shows the medians and 95 percent credible intervals for each $\lambda$ obtained by changing the prior distributions on the variance parameters and Table 11 shows the results.

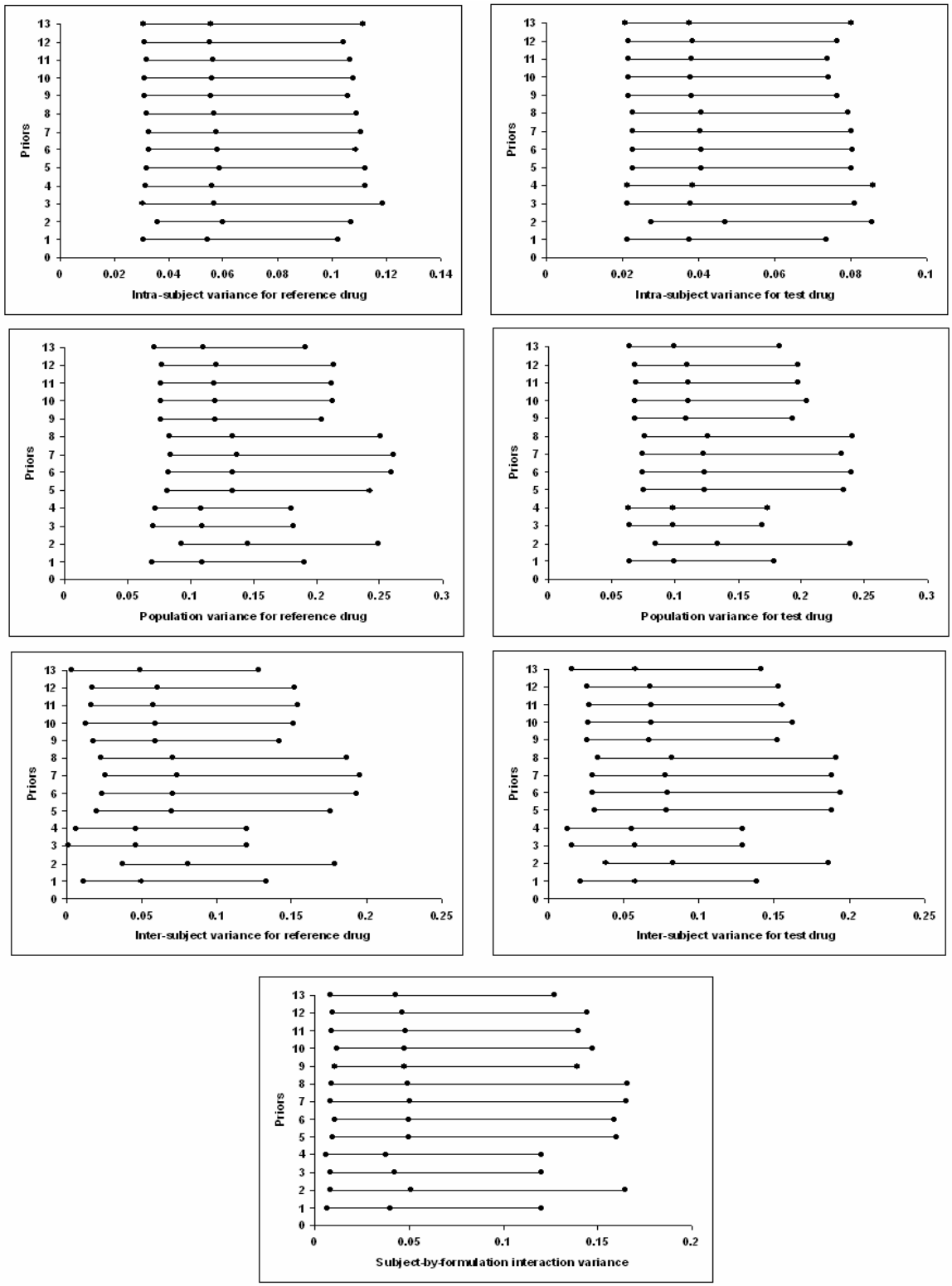



**FIGURE 7: Figure 7 above shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance obtained using the model in (2) on the FDA drug 8 data for each prior distribution on the scale parameters.**

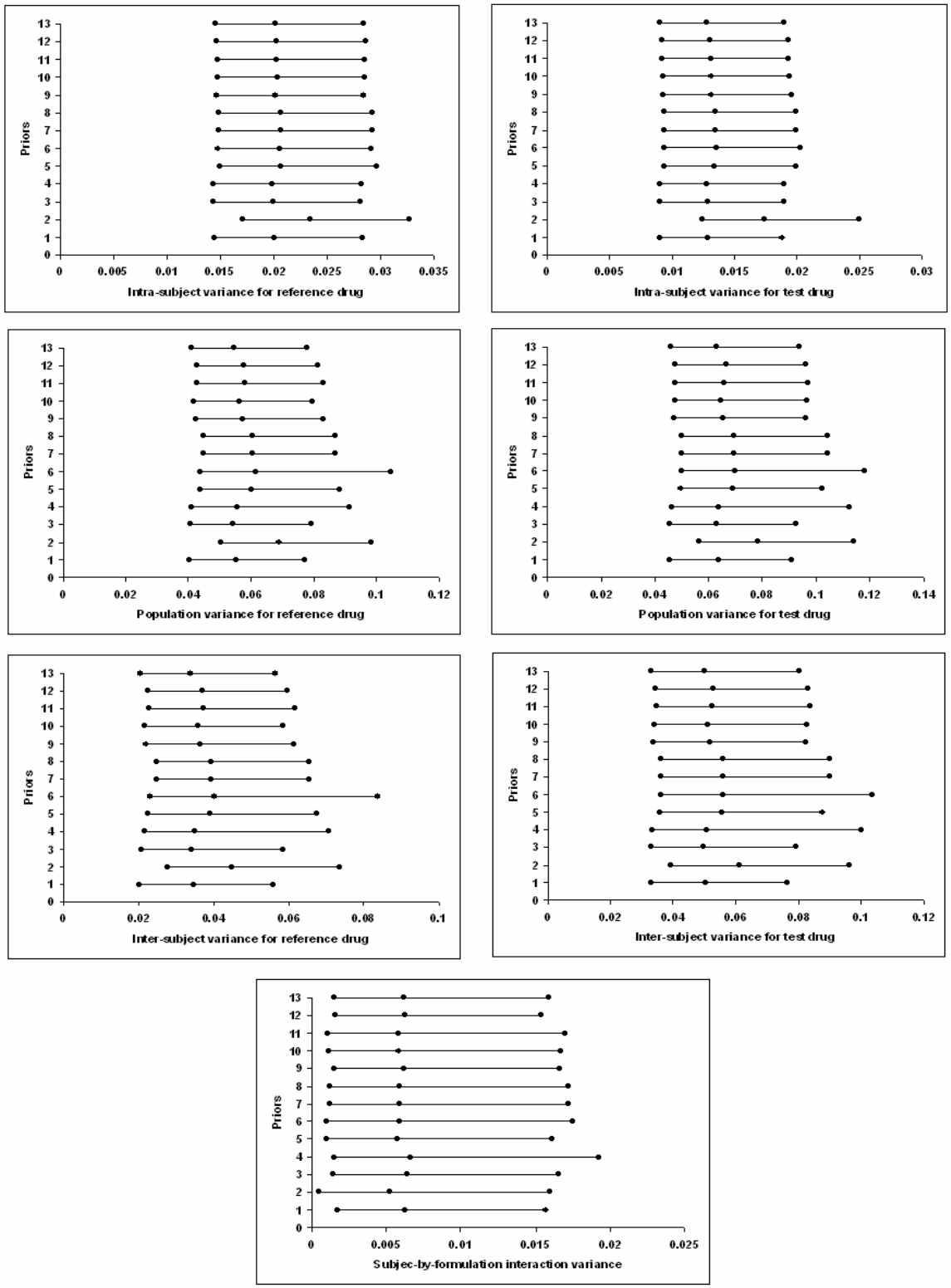



**FIGURE 8: Figure 8 above shows the medians and 95 percent credible intervals for inter-subject variance, intra-subject variance, and population variance obtained using the model in (2) on the FDA drug 14c data for each prior distribution on the scale parameters.**

**TABLE 7.A: Table 7.A below shows the estimated values using the aggregate methodology for assessing Individual bioequivalence, population means, inter-subject variances, intra-subject variances, population variances, subject-by-formulation interaction variance, and correlation for the FDA drug 8 data for each prior distribution on the scale parameters.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 0.8901 | 1.164 | 0.8745 | 0.836 | 1.083 | 1.123 | 1.125 |
| IBEH0 | 0.91821 | 0.8733 | 0.91671 | 0.92611 | 0.8865 | 0.8745 | 0.8721 |
| $\sigma^2_{BR}$ | 0.05732 | 0.09105 | 0.05193 | 0.05364 | 0.08049 | 0.08482 | 0.08731 |
| $\sigma^2_{BT}$ | 0.06604 | 0.09393 | 0.06328 | 0.06168 | 0.09105 | 0.09187 | 0.09014 |
| $\sigma^2_{D}$ | 0.04919 | 0.06413 | 0.05055 | 0.04721 | 0.06301 | 0.06297 | 0.06387 |
| $\sigma^2_{TR}$ | 0.1165 | 0.1554 | 0.1153 | 0.1154 | 0.1438 | 0.1475 | 0.1501 |
| $\sigma^2_{TT}$ | 0.1075 | 0.1444 | 0.1056 | 0.1056 | 0.1357 | 0.1366 | 0.1348 |
| $\sigma^2_{WR}$ | 0.05918 | 0.06431 | 0.06335 | 0.06175 | 0.06333 | 0.0627 | 0.06282 |
| $\sigma^2_{WT}$ | 0.04144 | 0.05052 | 0.04237 | 0.04393 | 0.04468 | 0.04471 | 0.04467 |
| $\mu_T$ | 7.465 | 7.464 | 7.458 | 7.471 | 7.463 | 7.474 | 7.466 |
| $\mu_R$ | 7.507 | 7.513 | 7.513 | 7.516 | 7.507 | 7.52 | 7.509 |
| $\rho$ | 0.6416 | 0.6722 | 0.5928 | 0.6198 | 0.6579 | 0.661 | 0.6639 |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 1.158 | 1.046 | 1.031 | 1.026 | 1.042 | 0.9136 |
| IBEH0 | 0.8649 | 0.8926 | 0.8934 | 0.8965 | 0.8948 | 0.91231 |
| $\sigma^2_{BR}$ | 0.08297 | 0.06666 | 0.06814 | 0.0676 | 0.06987 | 0.05666 |
| $\sigma^2_{BT}$ | 0.09407 | 0.0753 | 0.07834 | 0.07743 | 0.07587 | 0.06597 |
| $\sigma^2_{D}$ | 0.06405 | 0.05806 | 0.05917 | 0.05802 | 0.05828 | 0.0521 |
| $\sigma^2_{TR}$ | 0.145 | 0.127 | 0.129 | 0.1285 | 0.1296 | 0.118 |
| $\sigma^2_{TT}$ | 0.1386 | 0.1173 | 0.12 | 0.1192 | 0.1181 | 0.1084 |
| $\sigma^2_{WR}$ | 0.06205 | 0.06031 | 0.06086 | 0.06092 | 0.05978 | 0.06135 |
| $\sigma^2_{WT}$ | 0.0445 | 0.04203 | 0.04166 | 0.0418 | 0.04228 | 0.04246 |
| $\mu_T$ | 7.475 | 7.469 | 7.463 | 7.472 | 7.481 | 7.468 |
| $\mu_R$ | 7.517 | 7.515 | 7.507 | 7.517 | 7.523 | 7.513 |
| $\rho$ | 0.667 | 0.6223 | 0.6252 | 0.6308 | 0.63 | 0.605 |

In Table 7.A we see that IBEH0 $\geq$ 0.90 for priors 1, 3, 4, and 13, and IBEH0 < 0.90 for all other priors, thus, the Individual Bioequivalence inference is affected by changing the prior distribution of the scale parameters of the random effects for this data.

**<u>TABLE 7.B:</u> Table 7.B below shows the percent deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13) for the results in Table 7.A. We see that changing the prior distribution on the scale parameters of the random effects causes large percent deviations from the original diffuse priors.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 2.57% | 27.41% | 4.28% | 8.49% | 18.54% | 22.92% | 23.14% |
| IBEH0 | 6.73% | 44.49% | 5.02% | 15.74% | 29.43% | 43.12% | 45.85% |
| $\sigma^2_{BR}$ | 1.16% | 60.70% | 8.35% | 5.33% | 42.06% | 49.70% | 54.09% |
| $\sigma^2_{BT}$ | 0.11% | 42.38% | 4.08% | 6.50% | 38.02% | 39.26% | 36.64% |
| $\sigma^2_{D}$ | 5.59% | 23.09% | 2.98% | 9.39% | 20.94% | 20.86% | 22.59% |
| $\sigma^2_{TR}$ | 1.27% | 31.69% | 2.29% | 2.20% | 21.86% | 25.00% | 27.20% |
| $\sigma^2_{TT}$ | 0.83% | 33.21% | 2.58% | 2.58% | 25.18% | 26.01% | 24.35% |
| $\sigma^2_{WR}$ | 3.54% | 4.82% | 3.26% | 0.65% | 3.23% | 2.20% | 2.40% |
| $\sigma^2_{WT}$ | 2.40% | 18.98% | 0.21% | 3.46% | 5.23% | 5.30% | 5.20% |
| $\mu_T$ | 0.04% | 0.05% | 0.13% | 0.04% | 0.07% | 0.08% | 0.03% |
| $\mu_R$ | 0.08% | 0.00% | 0.00% | 0.04% | 0.08% | 0.09% | 0.05% |
| $\rho$ | 6.05% | 11.11% | 2.02% | 2.45% | 8.74% | 9.26% | 9.74% |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 26.75% | 14.49% | 12.85% | 12.30% | 14.05% | - |
| IBEH0 | 54.07% | 22.48% | 21.56% | 18.03% | 19.97% | - |
| $\sigma^2_{BR}$ | 46.43% | 17.65% | 20.26% | 19.31% | 23.31% | - |
| $\sigma^2_{BT}$ | 42.60% | 14.14% | 18.75% | 17.37% | 15.01% | - |
| $\sigma^2_{D}$ | 22.94% | 11.44% | 13.57% | 11.36% | 11.86% | - |
| $\sigma^2_{TR}$ | 22.88% | 7.63% | 9.32% | 8.90% | 9.83% | - |
| $\sigma^2_{TT}$ | 27.86% | 8.21% | 10.70% | 9.96% | 8.95% | - |
| $\sigma^2_{WR}$ | 1.14% | 1.70% | 0.80% | 0.70% | 2.56% | - |
| $\sigma^2_{WT}$ | 4.80% | 1.01% | 1.88% | 1.55% | 0.42% | - |
| $\mu_T$ | 0.09% | 0.01% | 0.07% | 0.05% | 0.17% | - |
| $\mu_R$ | 0.05% | 0.03% | 0.08% | 0.05% | 0.13% | - |
| $\rho$ | 10.25% | 2.86% | 3.34% | 4.26% | 4.13% | - |

**TABLE 8.A: Table 8.A below shows the estimated values using the aggregate methodology for assessing Individual bioequivalence, population means, inter-subject variances, intra-subject variances, population variances, subject-by-formulation interaction variance, and correlation for the FDA drug 14c data for each prior distribution on the scale parameters.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 0.01382 | 0.02506 | 0.02138 | 0.1336 | 0.002207 | 0.02325 | 0.01477 |
| IBEH0 | 1 | 1 | 1 | 0.9786 | 1 | 1 | 1 |
| $\sigma^2_{BR}$ | 0.03586 | 0.04696 | 0.03602 | 0.1002 | 0.04105 | 0.06534 | 0.04148 |
| $\sigma^2_{BT}$ | 0.05225 | 0.06322 | 0.05202 | 0.149 | 0.05786 | 0.08464 | 0.05833 |
| $\sigma^2_{D}$ | 0.007146 | 0.006364 | 0.007358 | 0.01095 | 0.006768 | 0.007216 | 0.007148 |
| $\sigma^2_{TR}$ | 0.05637 | 0.07091 | 0.05647 | 0.1206 | 0.06229 | 0.08641 | 0.06262 |
| $\sigma^2_{TT}$ | 0.06548 | 0.08108 | 0.06527 | 0.1623 | 0.07173 | 0.09863 | 0.07223 |
| $\sigma^2_{WR}$ | 0.02051 | 0.02395 | 0.02044 | 0.0204 | 0.02124 | 0.02107 | 0.02114 |
| $\sigma^2_{WT}$ | 0.01324 | 0.01786 | 0.01325 | 0.01326 | 0.01387 | 0.01399 | 0.0139 |
| $\mu_T$ | 5.601 | 5.604 | 5.602 | 5.574 | 5.598 | 5.583 | 5.597 |
| $\mu_R$ | 5.612 | 5.615 | 5.614 | 5.58 | 5.61 | 5.594 | 5.608 |
| $\rho$ | 0.9415 | 0.9589 | 0.9375 | 0.9414 | 0.9515 | 0.9506 | 0.9463 |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 0.01477 | 0.02267 | 0.01071 | 0.01297 | 0.01183 | 0.01128 |
| IBEH0 | 1 | 1 | 1 | 1 | 1 | 1 |
| $\sigma^2_{BR}$ | 0.04148 | 0.03853 | 0.03725 | 0.03904 | 0.03859 | 0.03557 |
| $\sigma^2_{BT}$ | 0.05833 | 0.05409 | 0.05377 | 0.05475 | 0.0548 | 0.05234 |
| $\sigma^2_{D}$ | 0.007148 | 0.00724 | 0.006946 | 0.006998 | 0.007061 | 0.007097 |
| $\sigma^2_{TR}$ | 0.06262 | 0.05916 | 0.05805 | 0.05975 | 0.05934 | 0.05616 |
| $\sigma^2_{TT}$ | 0.07223 | 0.0677 | 0.06738 | 0.06828 | 0.06828 | 0.06556 |
| $\sigma^2_{WR}$ | 0.02114 | 0.02062 | 0.02081 | 0.02071 | 0.02074 | 0.02059 |
| $\sigma^2_{WT}$ | 0.0139 | 0.01361 | 0.01362 | 0.01353 | 0.01349 | 0.01322 |
| $\mu_T$ | 5.597 | 5.599 | 5.6 | 5.602 | 5.6 | 5.603 |
| $\mu_R$ | 5.608 | 5.61 | 5.611 | 5.615 | 5.612 | 5.615 |
| $\rho$ | 0.9463 | 0.9409 | 0.9455 | 0.9435 | 0.9432 | 0.9428 |

In Table 7.A we see that IBEH0 $\geq$ 0.90 for all thirteen prior distributions, thus, the Individual Bioequivalence inference is not affected by changing the prior distribution of the scale parameters of the random effects for this data.

**<u>TABLE 8.B:</u> Table 8.B below shows the percent deviation of the first twelve priors to the diffuse priors presented in the original papers (prior 13) for the results in Table 8.A.**

| Parameter | Prior 1 | Prior 2 | Prior 3 | Prior 4 | Prior 5 | Prior 6 | Prior 7 |
|---|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 22.52% | 122.16% | 89.54% | 1084.40% | 80.43% | 106.12% | 30.94% |
| IBEH0 | 0.00% | 0.00% | 0.00% | 2.14% | 0.00% | 0.00% | 0.00% |
| $\sigma^2_{BR}$ | 0.82% | 32.02% | 1.27% | 181.70% | 15.41% | 83.69% | 16.62% |
| $\sigma^2_{BT}$ | 0.17% | 20.79% | 0.61% | 184.68% | 10.55% | 61.71% | 11.44% |
| $\sigma^2_{D}$ | 0.69% | 10.33% | 3.68% | 54.29% | 4.64% | 1.68% | 0.72% |
| $\sigma^2_{TR}$ | 0.37% | 26.26% | 0.55% | 114.74% | 10.92% | 53.86% | 11.50% |
| $\sigma^2_{TT}$ | 0.12% | 23.67% | 0.44% | 147.56% | 9.41% | 50.44% | 10.17% |
| $\sigma^2_{WR}$ | 0.39% | 16.32% | 0.73% | 0.92% | 3.16% | 2.33% | 2.67% |
| $\sigma^2_{WT}$ | 0.15% | 35.10% | 0.23% | 0.30% | 4.92% | 5.82% | 5.14% |
| $\mu_T$ | 0.04% | 0.02% | 0.02% | 0.52% | 0.09% | 0.36% | 0.11% |
| $\mu_R$ | 0.05% | 0.00% | 0.02% | 0.62% | 0.09% | 0.37% | 0.12% |
| $\rho$ | 0.14% | 1.71% | 0.56% | 0.15% | 0.92% | 0.83% | 0.37% |

| Parameter | Prior 8 | Prior 9 | Prior 10 | Prior 11 | Prior 12 | Prior 13 |
|---|---|---|---|---|---|---|
| $\Theta_{IBE}$ | 30.94% | 100.98% | 5.05% | 14.98% | 4.88% | - |
| IBEH0 | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | - |
| $\sigma^2_{BR}$ | 16.62% | 8.32% | 4.72% | 9.76% | 8.49% | - |
| $\sigma^2_{BT}$ | 11.44% | 3.34% | 2.73% | 4.60% | 4.70% | - |
| $\sigma^2_{D}$ | 0.72% | 2.01% | 2.13% | 1.39% | 0.51% | - |
| $\sigma^2_{TR}$ | 11.50% | 5.34% | 3.37% | 6.39% | 5.66% | - |
| $\sigma^2_{TT}$ | 10.17% | 3.26% | 2.78% | 4.15% | 4.15% | - |
| $\sigma^2_{WR}$ | 2.67% | 0.15% | 1.07% | 0.58% | 0.73% | - |
| $\sigma^2_{WT}$ | 5.14% | 2.95% | 3.03% | 2.34% | 2.04% | - |
| $\mu_T$ | 0.11% | 0.07% | 0.05% | 0.02% | 0.05% | - |
| $\mu_R$ | 0.12% | 0.09% | 0.07% | 0.00% | 0.05% | - |
| $\rho$ | 0.37% | 0.20% | 0.29% | 0.07% | 0.04% | - |

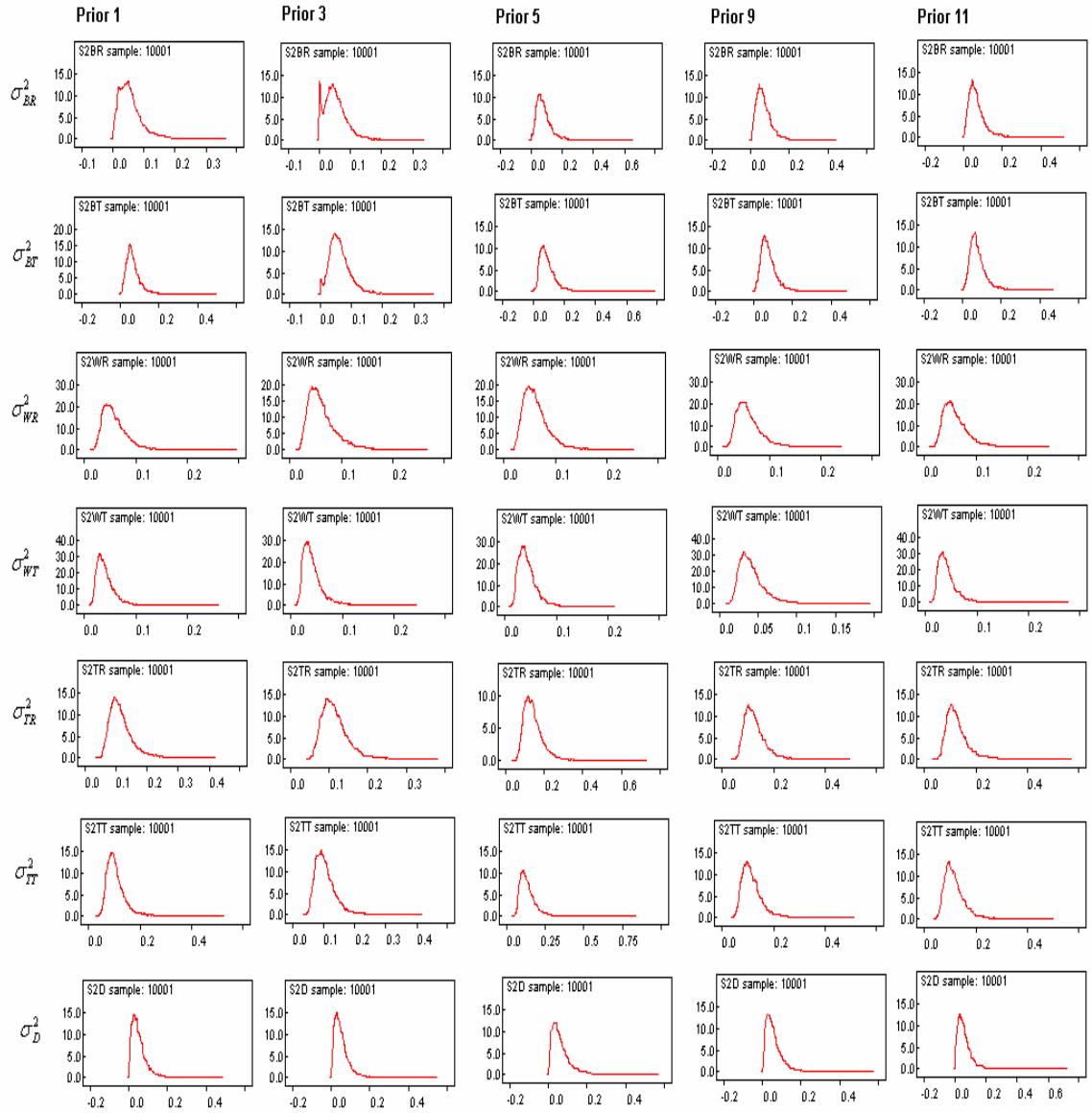
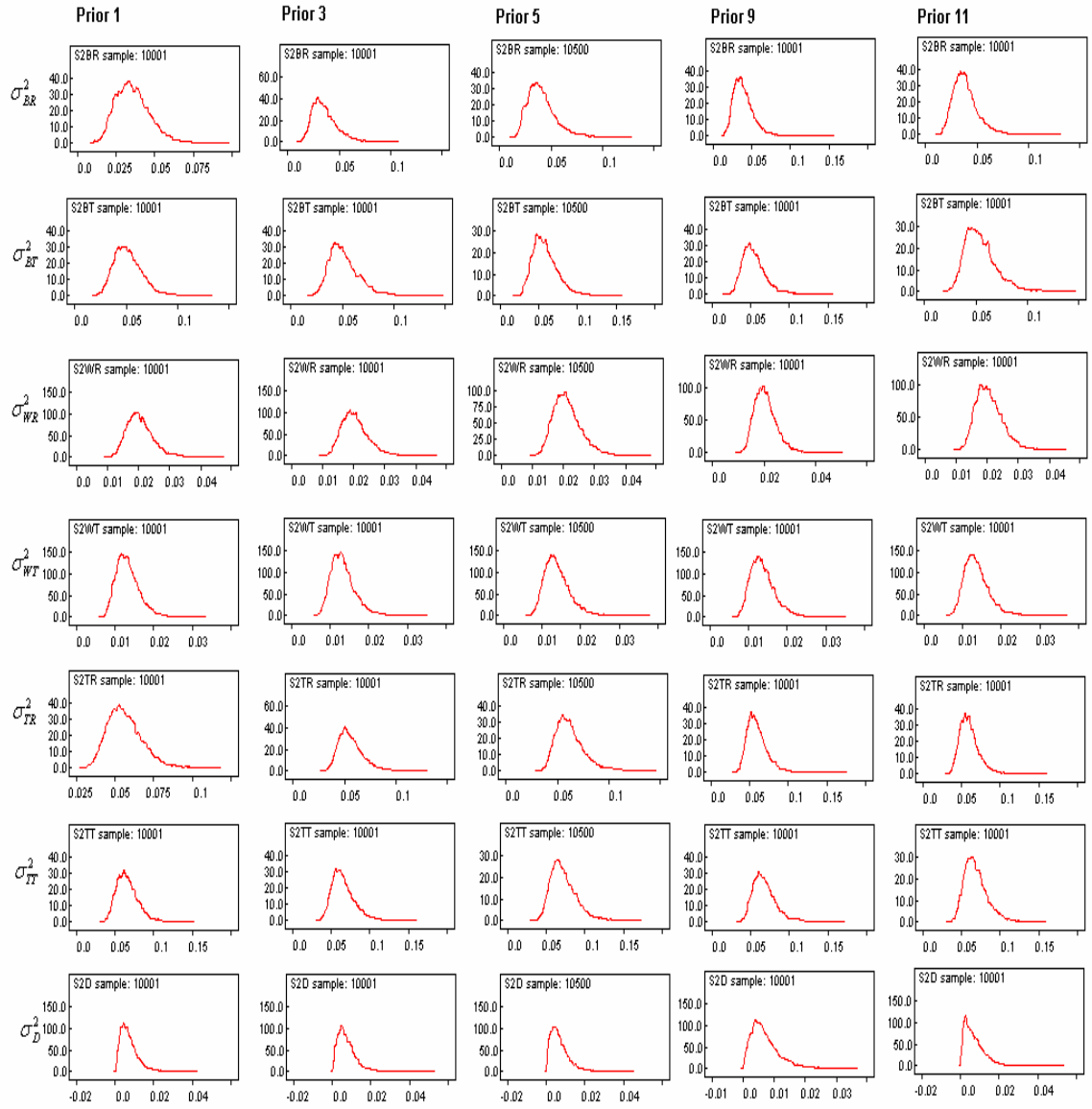



**FIGURE 9:** **Figure 9 above shows posterior distributions of the variance parameters obtained using the model in (2) on the FDA drug 8 data for prior distributions 1, 3, 5, 9, and 11 on the scale parameters.**




**<u>FIGURE 10:</u> Figure 10 above shows posterior distributions of the variance parameters obtained using the model in (2) on the FDA drug 14c data for prior distributions 1, 3, 5, 9, and 11 on the scale parameters.**

**TABLE 9: Table 9 below shows the Deviance Information Criterion (DIC) for each prior distribution on the scale parameters for the model in (2) on the FDA drug 8 data.**

| | | Dbar | Dhat | pD | DIC |
|---|---|---|---|---|---|
| **Prior 1** | z | -18.346 | -57.117 | 38.77 | 20.424 |
| | total | -18.346 | -57.117 | 38.77 | 20.424 |
| **Prior 2** | z | -13.935 | -53.332 | 39.398 | 25.463 |
| | total | -13.935 | -53.332 | 39.398 | 25.463 |
| **Prior 3** | z | -15.96 | -51.904 | 35.944 | 19.984 |
| | total | -15.96 | -51.904 | 35.944 | 19.984 |
| **Prior 4** | z | -15.666 | -51.357 | 35.691 | 20.026 |
| | total | -15.666 | -51.357 | 35.691 | 20.026 |
| **Prior 5** | z | -16.924 | -51.236 | 34.312 | 17.388 |
| | total | -16.924 | -51.236 | 34.312 | 17.388 |
| **Prior 6** | z | -17.269 | -51.528 | 34.258 | 16.989 |
| | total | -17.269 | -51.528 | 34.258 | 16.989 |
| **Prior 7** | z | -17.281 | -57.659 | 40.378 | 23.097 |
| | total | -17.281 | -57.659 | 40.378 | 23.097 |
| **Prior 8** | z | -17.624 | -57.85 | 40.226 | 22.602 |
| | total | -17.624 | -57.85 | 40.226 | 22.602 |
| **Prior 9** | z | -19.049 | -54.574 | 35.525 | 16.475 |
| | total | -19.049 | -54.574 | 35.525 | 16.475 |
| **Prior 10** | z | -18.813 | -54.478 | 35.665 | 16.852 |
| | total | -18.813 | -54.478 | 35.665 | 16.852 |
| **Prior 11** | z | -18.685 | -54.29 | 35.604 | 16.919 |
| | total | -13.14 | -48.745 | 35.604 | 22.464 |
| **Prior 12** | z | -18.959 | -54.75 | 35.79 | 16.831 |
| | total | -13.414 | -49.204 | 35.79 | 22.376 |
| **Prior 13** | z | -16.866 | -56.044 | 39.178 | 22.312 |
| | total | -16.866 | -56.044 | 39.178 | 22.312 |

Deviance Information Criteria or DIC is used for model selection and determining the sensitivity of the results to the prior specification. DIC is the Bayesian equivalent to AIC. DIC = Dbar+pD where small values of Dbar indicate that the model fits the data and pD measures the complexity of the model. In the table above we see that Prior 9, which has a Uniform distribution, has the best DIC, and is therefore better in this case than the inverse gamma distribution on the variance parameters.

**TABLE 10: Table 10 below shows the Deviance Information Criterion (DIC) for each prior distribution on the scale parameters of the model in (2) on the FDA drug 14c data.**

| | | Dbar | Dhat | pD | DIC |
|---|---|---|---|---|---|
| **Prior 1** | z | -196.576 | -248.332 | 51.757 | -144.819 |
| | total | -196.576 | -248.332 | 51.757 | -144.819 |
| **Prior 2** | z | -181.451 | -231.217 | 49.766 | -131.684 |
| | total | -181.451 | -231.217 | 49.766 | -131.684 |
| **Prior 3** | z | -196.619 | -247.739 | 51.12 | -145.5 |
| | total | -196.619 | -247.739 | 51.12 | -145.5 |
| **Prior 4** | z | -196.783 | -247.911 | 51.128 | -145.655 |
| | total | -196.783 | -247.911 | 51.128 | -145.655 |
| **Prior 5** | z | -193.95 | -242.954 | 49.005 | -144.945 |
| | total | -193.95 | -242.954 | 49.005 | -144.945 |
| **Prior 6** | z | -194.098 | -243.575 | 49.477 | -144.62 |
| | total | -194.098 | -243.575 | 49.477 | -144.62 |
| **Prior 7** | z | -194.371 | -246.423 | 52.052 | -142.318 |
| | total | -194.371 | -246.423 | 52.052 | -142.318 |
| **Prior 8** | z | -194.371 | -246.423 | 52.052 | -142.318 |
| | total | -194.371 | -246.423 | 52.052 | -142.318 |
| **Prior 9** | z | -195.73 | -246.156 | 50.427 | -145.303 |
| | total | -195.73 | -246.156 | 50.427 | -145.303 |
| **Prior 10** | z | -195.102 | -244.785 | 49.683 | -145.42 |
| | total | -195.102 | -244.785 | 49.683 | -145.42 |
| **Prior 11** | z | -195.653 | -245.8 | 50.147 | -145.505 |
| | total | -190.108 | -240.255 | 50.147 | -139.96 |
| **Prior 12** | z | -195.841 | -246.059 | 50.218 | -145.623 |
| | total | -190.296 | -240.514 | 50.218 | -140.078 |
| **Prior 13** | z | -196.333 | -248.013 | 51.68 | -144.653 |
| | total | -196.333 | -248.013 | 51.68 | -144.653 |

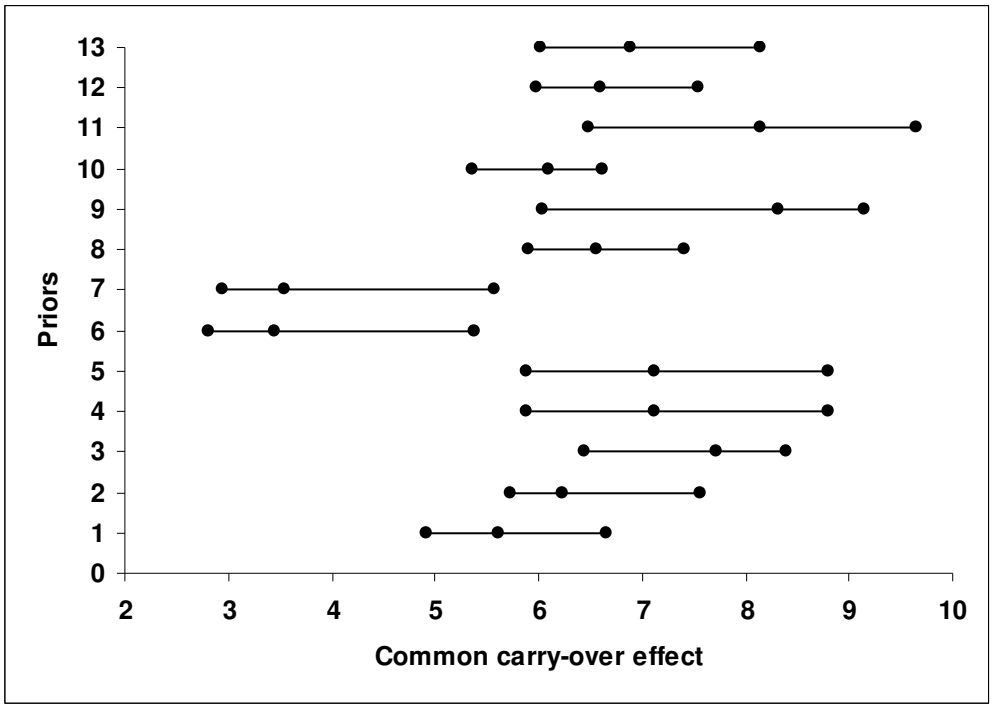



**FIGURE 11: Figure 11 above shows the medians and 95 percent credible intervals for the common carry-over effect $\lambda$ obtained using the model in (3) on the FDA drug 14c data for each prior distribution on the scale parameters.**

**TABLE 11: Table 11 below shows the estimated values, standard deviation, median, and 95% credible interval for the common carry-over effect $\lambda$ obtained using the model in (3) on the FDA drug 14c data for each prior distribution on the scale parameters.**

| | Common Carry-over effect $\lambda$ | | | | |
|---|---|---|---|---|---|
| **Prior** | **mean** | **sd** | **5.0%** | **median** | **95.0%** |
| **1** | 5.641 | 0.5223 | 4.914 | 5.608 | 6.65 |
| **2** | 6.364 | 0.5575 | 5.731 | 6.235 | 7.564 |
| **3** | 7.654 | 0.5449 | 6.439 | 7.715 | 8.403 |
| **4** | 7.212 | 0.9108 | 5.891 | 7.117 | 8.794 |
| **5** | 7.212 | 0.9108 | 5.891 | 7.117 | 8.794 |
| **6** | 3.834 | 0.8588 | 2.811 | 3.455 | 5.387 |
| **7** | 3.867 | 0.83 | 2.949 | 3.544 | 5.574 |
| **8** | 6.602 | 0.4638 | 5.895 | 6.556 | 7.414 |
| **9** | 7.881 | 1.074 | 6.039 | 8.324 | 9.144 |
| **10** | 6.07 | 0.3742 | 5.361 | 6.094 | 6.62 |
| **11** | 7.989 | 1.051 | 6.488 | 8.142 | 9.653 |
| **12** | 6.687 | 0.4846 | 5.987 | 6.605 | 7.539 |
| **13** | 6.93 | 0.5651 | 6.022 | 6.887 | 8.145 |

## 6. DISCUSSION

We have assessed the performance of several different models for determining Bioequivalence by changing the prior distribution on the variance parameters. We used thirteen different prior distributions for the variance parameters. Three data sets were used for our assessment. We also examined the effect that changing the prior distribution on the variance parameters had on the IBE model with and without the assumption of a carry-over effect.

For the disaggregate model for determining ABE and PBE, Prior 2 consistently gave the largest deviation from the original diffuse priors for the estimates of the variance parameters as well as Population Bioequivalence for the three data sets examined. The model estimates on the FDA drug 14c data were least affected and the model estimates on the Chow and Liu data were most affected by changing the prior distribution of the variance parameters.

For the aggregate model for determining IBE with no carry-over effect, Prior 2 and Prior 6 tended to give the largest deviation from the original diffuse priors for the variance parameters as well as IBE. For the two data sets examined for this model, the within-subject variances were least affected by changing the prior distribution on the variance parameters. In examining the DIC, we see that for the FDA drug 8 data, Prior 9 has the best DIC. For the FDA drug 14c data we see that there is no prior that clearly has a better DIC than another. For the aggregate model for determining IBE with carry-over effect, we see that the carry-over parameter is most sensitive to Prior 6 and Prior 7.

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# APPENDIX

## WINBUGS CODES

### A.1. WinBUGS Code for Average and Population Bioequivalence

### A.1.0. Prior Distributions

```
#-------------------------------------------------------------
#           PRIOR DISTRIBUTIONS ON SCALE PARAMETERS
#-------------------------------------------------------------

#-------------------------------------------
# PRIOR 1 - GAMMA(0.001,0.001) ON PRECISION
#-------------------------------------------
tau1[1]~dgamma(0.001,0.001)
tau2[1]~dgamma(0.001,0.001)
tau3[1]~dgamma(0.001,0.001)

rvar[1]<-1/tau1[1]
tvar[1]<-1/tau2[1]
intersubject[1]<-1/tau3[1]

sdr[1]<-sqrt(rvar[1])
sdt[1]<-sqrt(tvar[1])
sdi[1]<-sqrt(intersubject[1])

lvis[1]<-log(intersubject[1])
lvr[1]<-log(rvar[1])
lvt[1]<-log(tvar[1])

#----------------------------------------
# PRIOR 2 - GAMMA(0.1, 0.1) ON PRECISION
#----------------------------------------
tau1[2]~dgamma(0.1,0.1)
tau2[2]~dgamma(0.1,0.1)
tau3[2]~dgamma(0.1,0.1)

rvar[2]<-1/tau1[2]
tvar[2]<-1/tau2[2]
intersubject[2]<-1/tau3[2]

sdr[2]<-sqrt(rvar[2])
sdt[2]<-sqrt(tvar[2])
sdi[2]<-sqrt(intersubject[2])

lvis[2]<-log(intersubject[2])
lvr[2]<-log(rvar[2])
lvt[2]<-log(tvar[2])

#-------------------------------------------
# PRIOR 3 - UNIFORM(-10,10) ON LOG VARIANCE
#-------------------------------------------
lvis[3] ~ dunif(-10,10)
lvr[3] ~ dunif(-10,10)
lvt[3] ~ dunif(-10,10)

log(intersubject[3])<-lvis[3]
log(rvar[3])<-lvr[3]
log(tvar[3])<-lvt[3]
```

```
tau1[3]<-1/rvar[3]
tau2[3]<-1/tvar[3]
tau3[3]<-1/intersubject[3]

sdr[3]<-sqrt(rvar[3])
sdt[3]<-sqrt(tvar[3])
sdi[3]<-sqrt(intersubject[3])

#-------------------------------------------
# PRIOR 4 - UNIFORM(-10,4) ON LOG VARIANCE
#-------------------------------------------
lvis[4] ~ dunif(-10,4)
lvr[4] ~ dunif(-10,4)
lvt[4] ~ dunif(-10,4)

log(intersubject[4])<-lvis[4]
log(rvar[4])<-lvr[4]
log(tvar[4])<-lvt[4]

tau1[4]<-1/rvar[4]
tau2[4]<-1/tvar[4]
tau3[4]<-1/intersubject[4]

sdr[4]<-sqrt(rvar[4])
sdt[4]<-sqrt(tvar[4])
sdi[4]<-sqrt(intersubject[4])

#----------------------------------------
# PRIOR 5 - UNIFORM(0, 1000) ON VARIANCE
#----------------------------------------
rvar[5] ~ dunif(0,1000)
tvar[5] ~ dunif(0,1000)
intersubject[5] ~ dunif(0,1000)

tau1[5]<-1/rvar[5]
tau2[5]<-1/tvar[5]
tau3[5]<-1/intersubject[5]

sdr[5]<-sqrt(rvar[5])
sdt[5]<-sqrt(tvar[5])
sdi[5]<-sqrt(intersubject[5])

lvis[5]<-log(intersubject[5])
lvr[5]<-log(rvar[5])
lvt[5]<-log(tvar[5])

#----------------------------------------
# PRIOR 6 - UNIFORM(0, 4) ON VARIANCE
#----------------------------------------
rvar[6] ~ dunif(0,4)
tvar[6] ~ dunif(0,4)
intersubject[6] ~ dunif(0,4)

tau1[6]<-1/rvar[6]
tau2[6]<-1/tvar[6]
tau3[6]<-1/intersubject[6]

sdr[6]<-sqrt(rvar[6])
sdt[6]<-sqrt(tvar[6])
sdi[6]<-sqrt(intersubject[6])

lvis[6]<-log(intersubject[6])
lvr[6]<-log(rvar[6])
```

```
lvt[6]<-log(tvar[6])

#-----------------------------------------
# PRIOR 7 - PARETO(1,0.001) ON PRECISION
#-----------------------------------------

tau1[7] ~ dpar(1,0.001)
tau2[7] ~ dpar(1,0.001)
tau3[7] ~ dpar(1,0.001)

rvar[7]<-1/tau1[7]
tvar[7]<-1/tau2[7]
intersubject[7]<-1/tau3[7]

sdr[7]<-sqrt(rvar[7])
sdt[7]<-sqrt(tvar[7])
sdi[7]<-sqrt(intersubject[7])

lvis[7]<-log(intersubject[7])
lvr[7]<-log(rvar[7])
lvt[7]<-log(tvar[7])

#-----------------------------------------
# PRIOR 8 - PARETO(1,0.25) ON PRECISION
#-----------------------------------------

tau1[8] ~ dpar(1, 0.1)
tau2[8] ~ dpar(1, 0.1)
tau3[8] ~ dpar(1, 0.1)

rvar[8]<-1/tau1[8]
tvar[8]<-1/tau2[8]
intersubject[8]<-1/tau3[8]

sdr[8]<-sqrt(rvar[8])
sdt[8]<-sqrt(tvar[8])
sdi[8]<-sqrt(intersubject[8])

lvis[8]<-log(intersubject[8])
lvr[8]<-log(rvar[8])
lvt[8]<-log(tvar[8])

#--------------------------------------------
# PRIOR 9 - UNIFORM(0,100) ON SD
#--------------------------------------------

tau1[9]<-1/rvar[9]
tau2[9]<-1/tvar[9]
tau3[9]<-1/intersubject[9]

rvar[9]<-pow(sdr[9],2)
tvar[9]<-pow(sdt[9],2)
intersubject[9]<-pow(sdi[9],2)

sdr[9] ~ dunif(0,100)
sdt[9] ~ dunif(0,100)
sdi[9] ~ dunif(0,100)

lvis[9]<-log(intersubject[9])
lvr[9]<-log(rvar[9])
lvt[9]<-log(tvar[9])

#--------------------------------------------
# PRIOR 10 - UNIFORM(0,2) ON SD
```

```
#-------------------------------------------

tau1[10]<-1/rvar[10]
tau2[10]<-1/tvar[10]
tau3[10]<-1/intersubject[10]

rvar[10]<-pow(sdr[10],2)
tvar[10]<-pow(sdt[10],2)
intersubject[10]<-pow(sdi[10],2)

sdr[10] ~ dunif(0,2)
sdt[10] ~ dunif(0,2)
sdi[10] ~ dunif(0,2)

lvis[10]<-log(intersubject[10])
lvr[10]<-log(rvar[10])
lvt[10]<-log(tvar[10])

#-------------------------------------------
# PRIOR 11 - HALF NORMAL ON SD - VAR=100
#-------------------------------------------

tau1[11]<-1/rvar[11]
tau2[11]<-1/tvar[11]
tau3[11]<-1/intersubject[11]

rvar[11]<-pow(sdr[11],2)
tvar[11]<-pow(sdt[11],2)
intersubject[11]<-pow(sdi[11],2)

sdr[11] ~ dnorm(0,0.01)I(0,)
sdt[11] ~ dnorm(0,0.01)I(0,)
sdi[11] ~ dnorm(0,0.01)I(0,)

lvis[11]<-log(intersubject[11])
lvr[11]<-log(rvar[11])
lvt[11]<-log(tvar[11])

#-------------------------------------------
# PRIOR 12 - HALF NORMAL ON SD - VAR=1
#-------------------------------------------

tau1[12]<-1/rvar[12]
tau2[12]<-1/tvar[12]
tau3[12]<-1/intersubject[12]

rvar[12]<-pow(sdr[12],2)
tvar[12]<-pow(sdt[12],2)
intersubject[12]<-pow(sdi[12],2)

sdr[12] ~ dnorm(0,1)I(0,)
sdt[12] ~ dnorm(0,1)I(0,)
sdi[12] ~ dnorm(0,1)I(0,)

lvis[12]<-log(intersubject[12])
lvr[12]<-log(rvar[12])
lvt[12]<-log(tvar[12])

#-----------------------------------------------
# PRIOR 13 - ORIGINAL DIFFUSE PRIORS FROM PAPER
#-----------------------------------------------

tau1[13]~dgamma(0.01,0.01)
tau2[13]~dgamma(0.01,0.01)
```

```
tau3[13]~dgamma(0.01,0.01)

rvar[13]<-1/tau1[13]
tvar[13]<-1/tau2[13]
intersubject[13]<-1/tau3[13]

sdr[13]<-sqrt(rvar[13])
sdt[13]<-sqrt(tvar[13])
sdi[13]<-sqrt(intersubject[13])

lvis[13]<-log(intersubject[13])
lvr[13]<-log(rvar[13])
lvt[13]<-log(tvar[13])
```

### A.1.1. ABE and PBE WinBUGS code for Chow and Liu Data

```
#BAYESIAN METHODS FOR BIOEQUIVALENCE ALENCES STUDIES
#CODE FOR MODELS I1 USING cHOW AND LIU DATA ON 13 PRIORS

#alpha is a common intercept parameter
#x[i,1] are the sequence indicators
#x[i,2] are the period indicators
#x[i,3] is treatment indicator
#s[g[i]] corresponds to the random subject (sequence) effect
#g[i] is a variable that assigns a common subject number to each set of
two observations taken from the same subject


model {

for (m in 1:13){

for (i in 1:24) {
z[i,m]<-log(y[i])
z[i,m]~dnorm(mu[i,m], tau1[m])
mu[i,m]<-beta[1,m]*x[i,1]+beta[2,m]*x[i,2]+beta[3,m]*x[i,3]+s[g[i],m]
      }
for (i in 25:N){
z[i,m]<-log(y[i])
z[i,m]~dnorm(mu[i,m], tau2[m])
mu[i,m]<-beta[1,m]*x[i,1]+beta[2,m]*x[i,2]+beta[3,m]*x[i,3]+s[g[i],m]
      }
for (k in 1:24){
      s[k,m]~dnorm (alpha[m],tau3[m])
      }

#Here we calculate the means for each formulation

rbar[m]<-mean(mu[1:24,m])
tbar[m]<-mean(mu[25:48,m])

#Here we calculate the difference in means, ratio of variances, and the
intra-subject correlation

tt[m]<-tvar[m]+intersubject[m]
rr[m]<-rvar[m]+intersubject[m]
diff12[m]<-tbar[m]-rbar[m]
ratio[m]<-tt[m]/rr[m]

#Here we calculate the probability of equivalence in means, equivalence
in variances, the intra-subject correlation and the joint occurrence

PAB[m]<-step(diff12[m]-log(0.8))-step(diff12[m]-log(1.25))
PRV[m]<-step(ratio[m]-0.7)-step(ratio[m]-1.43)
PJT[m]<-PAB[m]*PRV[m]

#The fixed effects parameters get diffuse normal prior distributions
and the precision on the random effects parameters get gamma prior
distributions

alpha[m]~dnorm(0,0.0001)
beta[1,m]~dnorm(0,0.0001)
beta[2,m]~dnorm(0,0.0001)
beta[3,m]~dnorm(0,0.0001)

}

#-----------------------------------------------------------
```

```
#           PRIOR DISTRIBUTIONS ON SCALE PARAMETERS
#-----------------------------------------------------------
    ***PRIOR DISTRIBUTION FOR SCALE PARAMETERS FROM A.1.0 GO HERE***
}
```

## Initial Values

```
list(alpha = c(0,0,0,0,0,0,0,0,0,0,0,0,0),
beta=structure(.Data=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,0),.Dim=c(3,13)), tau1 =
c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1), tau2 =
c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1), tau3 =
c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1),
rvar=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA),
tvar=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA) ,
intersubject=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA),
sdr=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
sdt=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
sdi=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
lvis=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA),
lvr=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA),
lvt=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA))
```

### A.1.2. ABE and PBE WinBUGS Code for FDA Drug 8 Data

```
#BAYESIAN METHODS FOR BIOEQUIVALENCE ALENCES STUDIES
#CODE FOR MODELS I1 USING FDA DRUG 8 DATA ON 13 PRIORS

#alpha is a common intercept parameter
#x[i,1]-x[i,3] are the sequence indicators
#x[i,4]-x[i,6] are the period indicators
#x[i,7] is treatment indicator
#s[g[i]] corresponds to the random subject (sequence) effect
#g[i] is a variable that assigns a common subject number to each set of
two observations taken from the same subject


model {

for (m in 1:13){

for (i in 1:38) {
z[i,m]<-log(y[i])
z[i,m]~dnorm(mu[i,m], tau1[m])
mu[i,m]<-
beta[1,m]*x[i,1]+beta[2,m]*x[i,2]+beta[3,m]*x[i,3]+beta[4,m]*x[i,4]+bet
a[5,m]*x[i,5]+beta[6,m]*x[i,6]+beta[7,m]*x[i,7]+s[g[i],m]
      }
for (i in 39:N){
z[i,m]<-log(y[i])
z[i,m]~dnorm(mu[i,m], tau2[m])
mu[i,m]<-
beta[1,m]*x[i,1]+beta[2,m]*x[i,2]+beta[3,m]*x[i,3]+beta[4,m]*x[i,4]+bet
a[5,m]*x[i,5]+beta[6,m]*x[i,6]+beta[7,m]*x[i,7]+s[g[i],m]
      }
for (k in 1:19){
      s[k,m]~dnorm (alpha[m],tau3[m])          #assumption of normal
random subject effects
      }

#Here we calculate the means for each formulation

rbar[m]<-mean(mu[1:38,m])
tbar[m]<-mean(mu[39:76,m])

#Here we calculate the difference in means, ratio of variances, and the
intra-subject correlation

tt[m]<-tvar[m]+intersubject[m]
rr[m]<-rvar[m]+intersubject[m]
diff12[m]<-tbar[m]-rbar[m]
ratio[m]<-tt[m]/rr[m]
cor[m]<-intersubject[m]/sqrt(tt[m]*rr[m])

#Here we calculate the probability of equivalence in means, equivalence
in variances, the intra-subject correlation and the joint occurrence

PAB[m]<-step(diff12[m]-log(0.8))-step(diff12[m]-log(1.25))
PRV[m]<-step(ratio[m]-0.7)-step(ratio[m]-1.43)
PJT[m]<-PAB[m]*PRV[m]

#The fixed effects parameters get diffuse normal prior distributions
and the precision on the random effects parameters get gamma prior
distributions

alpha[m]~dnorm(0,0.0001)
beta[1,m]~dnorm(0,0.0001)
```

```
beta[2,m]~dnorm(0,0.0001)
beta[3,m]~dnorm(0,0.0001)
beta[4,m]~dnorm(0,0.0001)
beta[5,m]~dnorm(0,0.0001)
beta[6,m]~dnorm(0,0.0001)
beta[7,m]~dnorm(0,0.0001)

}

#-------------------------------------------------------------
#           PRIOR DISTRIBUTIONS ON SCALE PARAMETERS
#-------------------------------------------------------------
    ***PRIOR DISTRIBUTION FOR SCALE PARAMETERS FROM A.1.0 GO HERE***
}
```

## Initial Values

```
list(alpha = c(0,0,0,0,0,0,0,0,0,0,0,0,0),
beta=structure(.Data=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0
,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0),.Dim=c(
7,13)), tau1 = c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1), tau2 =
c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1), tau3 =
c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1),
rvar=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA),
tvar=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA) ,
intersubject=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA),
sdr=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
sdt=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
sdi=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
lvis=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA),
lvr=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA),
lvt=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA))
```

### A.1.3. ABE and PBE WinBUGS Code for FDA Drug 14c Data

```
#BAYESIAN METHODS FOR BIOEQUIVALENCE ALENCES STUDIES
#CODE FOR MODELS I1 USING FDA DRUG 14C DATA ON 13 PRIORS

#alpha is a common intercept parameter
#x[i,1] are the sequence indicators
#x[i,2]-x[i,4] are the period indicators
#x[i,5] is treatment indicator
#s[g[i]] corresponds to the random subject (sequence) effect
#g[i] is a variable that assigns a common subject number to each set of
two observations taken from the same subject


model {

for (m in 1:13){

for (i in 1:76) {
      z[i,m]<-log(y[i])
      z[i,m]~dnorm(mu[i,m], tau1[m])            #assumption of normally
distributed erros
      mu[i,m]<-
beta[1,m]*x[i,1]+beta[2,m]*x[i,2]+beta[3,m]*x[i,3]+beta[4,m]*x[i,4]+bet
a[5,m]*x[i,5]+s[g[i],m]
      }
for (i in 77:N){
      z[i,m]<-log(y[i])
      z[i,m]~dnorm(mu[i,m], tau2[m])            #assumption of normally
distributed erros
      mu[i,m]<-
beta[1,m]*x[i,1]+beta[2,m]*x[i,2]+beta[3,m]*x[i,3]+beta[4,m]*x[i,4]+bet
a[5,m]*x[i,5]+s[g[i],m]
      }
for (k in 1:38){
      s[k,m]~dnorm (alpha[m],tau3[m])           #assumption of normal
random subject effects
      }

#Here we calculate the means for each formulation

rbar[m]<-mean(mu[1:76,m])
tbar[m]<-mean(mu[77:152,m])

#Here we calculate the difference in means, ratio of variances, and the
intra-subject correlation

tt[m]<-tvar[m]+intersubject[m]
rr[m]<-rvar[m]+intersubject[m]
diff12[m]<-tbar[m]-rbar[m]
ratio[m]<-tt[m]/rr[m]
cor[m]<-intersubject[m]/sqrt(tt[m]*rr[m])

#Here we calculate the probability of equivalence in means, equivalence
in variances, the intra-subject correlation and the joint occurrence

PAB[m]<-step(diff12[m]-log(0.8))-step(diff12[m]-log(1.25))
PRV[m]<-step(ratio[m]-0.7)-step(ratio[m]-1.43)
PJT[m]<-PAB[m]*PRV[m]

#The fixed effects parameters get diffuse normal prior distributions
and the precision on the random effects parameters get gamma prior
distributions
```

```
alpha[m]~dnorm(0,0.0001)
beta[1,m]~dnorm(0,0.0001)
beta[2,m]~dnorm(0,0.0001)
beta[3,m]~dnorm(0,0.0001)
beta[4,m]~dnorm(0,0.0001)
beta[5,m]~dnorm(0,0.0001)

}

#-----------------------------------------------------------
#           PRIOR DISTRIBUTIONS ON SCALE PARAMETERS
#-----------------------------------------------------------
    ***PRIOR DISTRIBUTION FOR SCALE PARAMETERS FROM A.1.0 GO HERE***
}
```

## Initial Values

```
list(alpha = c(0,0,0,0,0,0,0,0,0,0,0,0,0),
beta=structure(.Data=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0
,0,0,0,0,0),.Dim=c(5,13)), tau1 = c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1),
tau2 =  c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1), tau3 =
c(1,1,NA,NA,NA,NA,1,1,NA,NA,NA,NA,1),
rvar=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA),
tvar=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA) ,
intersubject=c(NA,NA,NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA),
sdr=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
sdt=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
sdi=c(NA,NA,NA,NA,NA,NA,NA,NA,1,1,1,1,NA),
lvis=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA),
lvr=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA),
lvt=c(NA,NA,1,1,NA,NA,NA,NA,NA,NA,NA,NA,NA))
```

## A.2. WinBUGS Code for Individual Bioequivalence

### A.2.0. Prior Distributions

```
#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR #1 - GAMMA(0.001,0.001) ON
PRECISION
#-----------------------------------------------------------------------
TAUBR ~ dgamma(0.001, 0.001)
TAUBT ~ dgamma(0.001, 0.001)
tau[1] ~ dgamma( 0.001, 0.001)
tau[2] ~ dgamma( 0.001, 0.001)

S2BR<-1/TAUBR
S2BT<-1/TAUBT
S2WR<-1/tau[1]
S2WT<-1/tau[2]

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR #2 - GAMMA(0.1,0.1) ON PRECISION
#-----------------------------------------------------------------------
TAUBR ~ dgamma(0.1, 0.1)
TAUBT ~ dgamma(0.1, 0.1)
tau[1] ~ dgamma( 0.1, 0.1)
tau[2] ~ dgamma( 0.1, 0.1)

S2BR<-1/TAUBR
S2BT<-1/TAUBT
S2WR<-1/tau[1]
S2WT<-1/tau[2]

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR #3 - UNIFORM(-10,10) ON LOG
VARIANCE
#-----------------------------------------------------------------------
lvWR ~ dunif(-10,10)
lvWT ~ dunif(-10,10)
lvBR ~ dunif(-10,10)
lvBT ~ dunif(-10,10)

log(S2WR)<-lvWR
log(S2WT)<-lvWT
log(S2BR)<-lvBR
log(S2BT)<-lvBT

tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 4 - UNIFORM(-10,4) ON LOG VARIANCE
#-----------------------------------------------------------------------
lvWR ~ dunif(-10,4)
lvWT ~ dunif(-10,4)
lvBR ~ dunif(-10,4)
lvBT ~ dunif(-10,4)

log(S2WR)<-lvWR
log(S2WT)<-lvWT
log(S2BR)<-lvBR
log(S2BT)<-lvBT
```

```
tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 5 - UNIFORM(0, 1000) ON VARIANCE
#-----------------------------------------------------------------------
S2WR ~ dunif(0,1000)
S2WT ~ dunif(0,1000)
S2BR ~ dunif(0,1000)
S2BT ~ dunif(0,1000)

tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 6 - UNIFORM(0, 4) ON VARIANCE
#-----------------------------------------------------------------------
S2WR ~ dunif(0,4)
S2WT ~ dunif(0,4)
S2BR ~ dunif(0,4)
S2BT ~ dunif(0,4)

tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 7 - PARETO(1,0.001) ON PRECISION
#-----------------------------------------------------------------------
tau[1] ~ dpar(1,0.001)
tau[2] ~ dpar(1,0.001)
TAUBR ~ dpar(1,0.001)
TAUBT ~ dpar(1,0.001)

S2WR<-1/tau[1]
S2WT<-1/tau[2]
S2BR<-1/TAUBR
S2BT<-1/TAUBT

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 8 - PARETO(1,0.25) ON PRECISION
#-----------------------------------------------------------------------
tau[1] ~ dpar(1,0.1)
tau[2] ~ dpar(1,0.1)
TAUBR ~ dpar(1,0.1)
TAUBT ~ dpar(1,0.1)

S2WR<-1/tau[1]
S2WT<-1/tau[2]
S2BR<-1/TAUBR
S2BT<-1/TAUBT

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 9 - UNIFORM(0,100) ON SD
#-----------------------------------------------------------------------
tau[1]<-1/S2WR
tau[2]<-1/S2WT
```

```
TAUBR<-1/S2BR
TAUBT<-1/S2BT

S2WR<-pow(sdWR,2)
S2WT<-pow(sdWT,2)
S2BR<-pow(sdBR,2)
S2BT<-pow(sdBT,2)

sdWR ~ dunif(0,100)
sdWT ~ dunif(0,100)
sdBR ~ dunif(0,100)
sdBT ~ dunif(0,100)

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 10 - UNIFORM(0,2) ON SD
#-----------------------------------------------------------------------
tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

S2WR<-pow(sdWR,2)
S2WT<-pow(sdWT,2)
S2BR<-pow(sdBR,2)
S2BT<-pow(sdBT,2)

sdWR ~ dunif(0,2)
sdWT ~ dunif(0,2)
sdBR ~ dunif(0,2)
sdBT ~ dunif(0,2)

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 11 - HALF NORMAL ON SD - VAR=100
#-----------------------------------------------------------------------
tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

S2WR<-pow(sdWR,2)
S2WT<-pow(sdWT,2)
S2BR<-pow(sdBR,2)
S2BT<-pow(sdBT,2)

sdWR ~ dnorm(0,0.01)I(0,)
sdWT ~ dnorm(0,0.01)I(0,)
sdBR ~ dnorm(0,0.01)I(0,)
sdBT ~ dnorm(0,0.01)I(0,)

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 12 - HALF NORMAL ON SD - VAR=1
#-----------------------------------------------------------------------
tau[1]<-1/S2WR
tau[2]<-1/S2WT
TAUBR<-1/S2BR
TAUBT<-1/S2BT

S2WR<-pow(sdWR,2)
S2WT<-pow(sdWT,2)
S2BR<-pow(sdBR,2)
S2BT<-pow(sdBT,2)

sdWR ~ dnorm(0,1)I(0,)
sdWT ~ dnorm(0,1)I(0,)
```

```
sdBR ~ dnorm(0,1)I(0,)
sdBT ~ dnorm(0,1)I(0,)

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  PRIOR 13 - ORIGINAL DIFFUSE PRIORS
#-----------------------------------------------------------------------
TAUBR ~ dgamma(0.0001, 0.0001)
TAUBT ~ dgamma(0.0001, 0.0001)
tau[1] ~ dgamma( 0.0001, 0.0001)
tau[2] ~ dgamma( 0.0001, 0.0001)

S2BR<-1/TAUBR
S2BT<-1/TAUBT
S2WR<-1/tau[1]
S2WT<-1/tau[2]
```

### A.2.1. WinBUGS Code without carry-over effect for FDA Drug 8 Data

```
# Aggregate Criteria Method test for Individual Bioequivalence

model bioeq;
{
#
# Likelihood
for (i in 1:(n*REP*DRUGS)){
z[i]<-log(y[i])
z[i]~dnorm( mu[i], tau[trt[i]])
mu[i] <- m[ trt[i] ] + gamma[ seq[i], trt[i], rep[i] ] + delta[
subj[i], seq[i], trt[i] ];
      }

for (j in 1:n){
      for (i in 1:SEQ){
            delta[j,i,1:DRUGS]~dmnorm( meand[] , T[,] );
            }
      }

meand[1]<-0.0;
meand[2]<-0.0;
T[1:DRUGS,1:DRUGS]<-inverse(omega[,]);
#
#-----------------------------------------------------------------------
# VARIANCES:
#-----------------------------------------------------------------------
# S2BR : Between-subject variance for Test drug formulation treatment
# S2BT : Between-subject variance for Reference drug formulation
Treatment
# S2WR : within-subject variance for reference drug formulation
treatment
# S2WT : within-subject variance for test drug formulation treatment
# S2D : variance treatment difference
# S2TT : total variance from Test drug formulation population
# S2TR : total variance from Reference drug formulation
#-----------------------------------------------------------------------

omega[1,1]<-S2BR
omega[2,2]<-S2BT
omega[1,2]<-rho*sqrt(S2BT*S2BR)
omega[2,1]<-omega[1,2]

rho ~ dunif(-1, 1)
S2D<-S2BT+S2BR-2*omega[1,2]
S2TT<-S2BT+S2WT
#
# variances within ref+test treatments

S2TR<-S2BR+S2WR
#
# SECOND STAGE OF HYPERPRIORS
for (k in 1:DRUGS) {
# constraint
      gamma[1,k,1]<- -gamma[1,k,2] -gamma[2,k,1]-gamma[2,k,2]

      for (i in 2:SEQ){ gamma[i,k,1] ~ dnorm( g[k], taug[k]) }
      for (l in 2:REP){ gamma[1,k,l] ~ dnorm( g[k], taug[k]) }
      for (i in 2:SEQ){ for (l in 2:REP){ gamma[i,k,l] ~ dnorm( g[k],
taug[k] ) }}
      g[k]<-0.0
      taug[k]<-0.0001
      m[k] ~ dnorm( m00, tau0[k])
```

```
      tau0[k] ~ dgamma(0.0001, 0.0001)
      }

m00 ~ dnorm(0.0, 0.0001)

#-------------------------------------------------------
# BIOEQUIVALENCE PARAMETERS
#-------------------------------------------------------

# INDIVIDUAL BIOEQUIVALENCE

S2W0 <- 0.04
THETAI <- 2.4948
IBE <- ( (m[2]-m[1])*(m[2]-m[1]) + S2D + S2WT - S2WR) / max(S2WR, S2W0)
IBEH0 <- step( IBE-THETAI )

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:
#-----------------------------------------------------------------------
    ***PRIOR DISTRIBUTION FOR SCALE PARAMETERS FROM A.2.0 GO HERE***
}
```

**Initial Values**

```
list(m00 = 0, rho = 0, tau0 = c(1,1),***Initial Values for Scale
Parameters Go Here***)
```

***NOTE: The initial values for the scale parameters will depend on which scale parameter is being modeled stochastically. The initial values for the scale parameters used were:

<u>For Priors 1, 2, 7, 8, and 13:</u>

```
tau = c(1,1)
TAUBR = 1
TAUBT = 1
```

<u>For Priors 3 and 4:</u>

```
lvWR = 1
lvWT = 1
lvBR = 1
lvBT = 1
```

<u>For Priors 5 and 6:</u>

```
S2WR = 1
S2WT = 1
S2BR = 1
S2BT = 1
```

<u>For Priors 9, 10, 11, and 12:</u>

```
sdWR = 1
sdWT = 1
sdBR = 1
sdBT = 1
```

### A.2.2. WinBUGS Code without carry-over effect for FDA Drug 14c Data

```
# Aggregate Criteria Method test for Individual Bioequivalence

model bioeq;
{
#
# Likelihood
for (i in 1:(n*REP*DRUGS)){
      z[i]<-log(y[i])
      z[i]~dnorm( mu[i], tau[trt[i]])
      mu[i] <- m[ trt[i] ] + gamma[ seq[i], trt[i], rep[i] ] + delta[
subj[i], seq[i], trt[i] ];
      }

for (j in 1:n){
      for (i in 1:SEQ){
            delta[j,i,1:DRUGS]~dmnorm( meand[] , T[,] );
            }
      }

meand[1]<-0.0;
meand[2]<-0.0;
T[1:DRUGS,1:DRUGS]<-inverse(omega[,]);
#
#-----------------------------------------------------------------------
# VARIANCES:
#-----------------------------------------------------------------------
# S2BR : Between-subject variance for Test drug formulation treatment
# S2BT : Between-subject variance for Reference drug formulation
Treatment
# S2WR : within-subject variance for reference drug formulation
treatment
# S2WT : within-subject variance for test drug formulation treatment
# S2D : variance treatment difference
# S2TT : total variance from Test drug formulation population
# S2TR : total variance from Reference drug formulation
#-----------------------------------------------------------------------

omega[1,1]<-S2BR
omega[2,2]<-S2BT
omega[1,2]<-rho*sqrt(S2BT*S2BR)
omega[2,1]<-omega[1,2]

rho ~ dunif(-1, 1)
S2D<-S2BT+S2BR-2*omega[1,2]
S2TT<-S2BT+S2WT
#
# variances within ref+test treatments

S2TR<-S2BR+S2WR
#
# SECOND STAGE OF HYPERPRIORS
for (k in 1:DRUGS) {
# constraint
      gamma[1,k,1]<- -gamma[1,k,2] -gamma[2,k,1]-gamma[2,k,2]

      for (i in 2:SEQ){ gamma[i,k,1] ~ dnorm( g[k], taug[k]) }
      for (l in 2:REP){ gamma[1,k,l] ~ dnorm( g[k], taug[k]) }
      for (i in 2:SEQ){ for (l in 2:REP){ gamma[i,k,l] ~ dnorm( g[k],
taug[k] ) }}
      g[k]<-0.0
      taug[k]<-0.0001
      m[k] ~ dnorm( m00, tau0[k])
```

```
      tau0[k] ~ dgamma(0.0001, 0.0001)

      }
m00 ~ dnorm(0.0, 0.0001)

#-------------------------------------------------------
# BIOEQUIVALENCE PARAMETERS
#-------------------------------------------------------

# INDIVIDUAL BIOEQUIVALENCE

S2W0 <- 0.04
THETAI <- 2.4948
IBE <- ( (m[2]-m[1])*(m[2]-m[1]) + S2D + S2WT - S2WR) / max(S2WR, S2W0)
IBEH0 <- step( IBE-THETAI )

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:
#-----------------------------------------------------------------------
    ***PRIOR DISTRIBUTION FOR SCALE PARAMETERS FROM A.2.0 GO HERE***
}
```

**Initial Values**

```
list(m00 = 0, rho = 0, tau0 = c(1,1),***Initial Values for Scale
Parameters Go Here***)
```

***NOTE: The initial values for the scale parameters will depend on which scale parameter is being modeled stochastically. The initial values for the scale parameters used were:

<u>For Priors 1, 2, 7, 8, and 13:</u>

```
tau = c(1,1)
TAUBR = 1
TAUBT = 1
```

<u>For Priors 3 and 4:</u>

```
lvWR = 1
lvWT = 1
lvBR = 1
lvBT = 1
```

<u>For Priors 5 and 6:</u>

```
S2WR = 1
S2WT = 1
S2BR = 1
S2BT = 1
```

<u>For Priors 9, 10, 11, and 12:</u>

```
sdWR = 1
sdWT = 1
sdBR = 1
sdBT = 1
```

### A.2.3. WinBUGS Code with carry-over effect for FDA Drug 14c Data

```
# Aggregate Criteria Method test for Individual Bioequivalence

model bioeq;
{
#
# Likelihood
for (i in 1:(n*REP*DRUGS)){
      z[i]<-log(y[i])
      z[i]~dnorm( mu[i], tau[trt[i]])
      mu[i] <- m[ trt[i] ]+gamma[ seq[i], trt[i], rep[i] ]+delta[
subj[i], seq[i], trt[i] ]+r[i]*lambda;
      }

# Prior Distribution for carry-over effect lambda
lambda~dnorm(0,0.0001)

for (j in 1:n){
      for (i in 1:SEQ){
            delta[j,i,1:DRUGS]~dmnorm( meand[] , T[,] );
            }
      }

meand[1]<-0.0;
meand[2]<-0.0;
T[1:DRUGS,1:DRUGS]<-inverse(omega[,]);
#
#-----------------------------------------------------------------------
# VARIANCES:
#-----------------------------------------------------------------------
# S2BR : Between-subject variance for Test drug formulation treatment
# S2BT : Between-subject variance for Reference drug formulation
Treatment
# S2WR : within-subject variance for reference drug formulation
treatment
# S2WT : within-subject variance for test drug formulation treatment
# S2D : variance treatment difference
# S2TT : total variance from Test drug formulation population
# S2TR : total variance from Reference drug formulation
#-----------------------------------------------------------------------

omega[1,1]<-S2BR
omega[2,2]<-S2BT
omega[1,2]<-rho*sqrt(S2BT*S2BR)
omega[2,1]<-omega[1,2]

rho ~ dunif(-1, 1)
S2D<-S2BT+S2BR-2*omega[1,2]
S2TT<-S2BT+S2WT
#
# variances within ref+test treatments
S2TR<-S2BR+S2WR

#-----------------------------------------------------------------
# Prior Distribution for gamma
#-----------------------------------------------------------------
# SECOND STAGE OF HYPERPRIORS
for (k in 1:DRUGS) {
# constraint
      gamma[1,k,1]<- -gamma[1,k,2] -gamma[2,k,1]-gamma[2,k,2]

      for (i in 2:SEQ){ gamma[i,k,1] ~ dnorm( g[k], taug[k]) }
      for (l in 2:REP){ gamma[1,k,l] ~ dnorm( g[k], taug[k]) }
```

```
      for (i in 2:SEQ){ for (l in 2:REP){ gamma[i,k,l] ~ dnorm( g[k],
taug[k] ) }}
      g[k]<-0.0
      taug[k]<-0.0001
      m[k] ~ dnorm( m00, tau0[k])
      tau0[k] ~ dgamma(0.0001, 0.0001)
      }
m00 ~ dnorm(0.0, 0.0001)

#-------------------------------------------------------
# BIOEQUIVALENCE PARAMETERS
#-------------------------------------------------------

# INDIVIDUAL BIOEQUIVALENCE

S2W0 <- 0.04
THETAI <- 2.4948
IBE <- ( (m[2]-m[1])*(m[2]-m[1]) + S2D + S2WT - S2WR) / max(S2WR, S2W0)
IBEH0 <- step( IBE-THETAI )

#-----------------------------------------------------------------------
# PRIORS ON SCALE PARAMETERS:  ORIGINAL DIFFUSE PRIORS
#-----------------------------------------------------------------------
    ***PRIOR DISTRIBUTION FOR SCALE PARAMETERS FROM A.2.0 GO HERE***
}
```

**Initial Values**

```
list(m00 = 0, rho = 0, lambda = 0, tau0 = c(1,1),***Initial Values for
Scale Parameters Go Here***)
```

***NOTE: The initial values for the scale parameters will depend on which scale parameter is being modeled stochastically. The initial values for the scale parameters used were:

<u>For Priors 1, 2, 7, 8, and 13:</u>

```
tau = c(1,1)
TAUBR = 1
TAUBT = 1
```

<u>For Priors 3 and 4:</u>

```
lvWR = 1
lvWT = 1
lvBR = 1
lvBT = 1
```

<u>For Priors 5 and 6:</u>

```
S2WR = 1
S2WT = 1
S2BR = 1
S2BT = 1
```

<u>For Priors 9, 10, 11, and 12:</u>

```
sdWR = 1
sdWT = 1
sdBR = 1
sdBT = 1
```

## DATA SETS

### A.3.1. Chow and Liu Data for ABE and PBE

```
#Chow & Liu data
#input y[]=AUCt   seq indicators(X1), per indicators(X2), trt
indicator(X3), subj(g)

#           CODING OF VARIABLES
#-----------------------------------------------------------
#     seq   x[,1]
#     1     0
#     2     1
#-----------------------------------------------------------
#     per   x[,2]
#     1     0
#     2     1
#-----------------------------------------------------------
#     trt   x[,3]
#     1     0
#     2     1

list(N=48)

y[]         x[,1] x[,2] x[,3] g[]
74.675      0     0     0     1
96.4        0     0     0     4
101.95      0     0     0     5
79.05       0     0     0     6
79.05       0     0     0     11
85.95       0     0     0     12
69.725      0     0     0     15
86.275      0     0     0     16
112.675     0     0     0     19
99.525      0     0     0     20
89.425      0     0     0     23
55.175      0     0     0     24
37.35       1     1     0     2
51.925      1     1     0     3
72.175      1     1     0     7
77.5        1     1     0     8
71.875      1     1     0     9
94.025      1     1     0     10
124.975     1     1     0     13
85.225      1     1     0     14
95.925      1     1     0     17
67.1        1     1     0     18
59.425      1     1     0     21
114.05      1     1     0     22
73.675      0     1     1     1
93.25       0     1     1     4
102.125     0     1     1     5
69.45       0     1     1     6
69.025      0     1     1     11
68.7        0     1     1     12
59.425      0     1     1     15
76.125      0     1     1     16
114.875     0     1     1     19
116.25      0     1     1     20
64.175      0     1     1     23
74.575      0     1     1     24
74.825      1     0     1     2
86.875      1     0     1     3
81.675      1     0     1     7
```

```
92.7        1     0     1     8
50.45       1     0     1     9
66.125      1     0     1     10
122.45      1     0     1     13
99.075      1     0     1     14
86.35       1     0     1     17
49.925      1     0     1     18
42.7        1     0     1     21
91.725      1     0     1     22
END
```

### A.4.1. FDA Drug 8 Data for ABE and PBE

```
#DRUG #8

#Input y[]=AUCt, seq=(x[,1]-x[,3]), per=(x[,4]-x[,6]), trt=x[,7],
g[]=subj

#           CODING OF VARIABLES
#-------------------------------------------------------
# Sequence Coding
#     2211=1
#     1221=2
#     1122=3
#     2112=4
#
#     seq   x[,1] x[,2] x[,3]
#     1     0     0     0
#     2     0     0     1
#     3     0     1     0
#     4     1     0     0
#-------------------------------------------------------
# Period Coding
#     per   x[,4] x[,5] x[,6]
#     1     0     0     0
#     2     0     0     1
#     3     0     1     0
#     4     1     0     0
#-------------------------------------------------------
# Treatment Coding
#     Trt 1= Test
#     Trt 2= Reference
#
#     trt   x[,7]
#     1     0
#     2     1

list(N=76)

y[]         x[,1] x[,2] x[,3] x[,4] x[,5] x[,6] x[,7] g[]
1927.4      0     0     0     0     0     0     1     1
1526.5      0     0     0     0     0     1     1     1
3219.1      0     0     1     0     0     1     1     2
2933        0     0     1     0     1     0     1     2
2816.6      0     1     0     0     1     0     1     3
3078.3      0     1     0     1     0     0     1     3
1477.2      1     0     0     0     0     0     1     4
1948.3      1     0     0     1     0     0     1     4
2177.7      0     0     0     0     0     0     1     5
1780.6      0     0     0     0     0     1     1     5
2354.3      1     0     0     0     0     0     1     6
3275        1     0     0     1     0     0     1     6
667.4       0     0     1     0     0     1     1     7
1274.4      0     0     1     0     1     0     1     7
2332.5      0     1     0     0     1     0     1     8
2310.9      0     1     0     1     0     0     1     8
2137        0     1     0     0     1     0     1     9
2035.1      0     1     0     1     0     0     1     9
2106.1      1     0     0     0     0     0     1     10
2335.8      1     0     0     1     0     0     1     10
1344.8      0     0     1     0     0     1     1     11
1608.3      0     0     1     0     1     0     1     11
2962.7      0     0     0     0     0     0     1     12
1403.7      0     0     0     0     0     1     1     12
1968.9      0     0     0     0     0     0     1     13
```

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1971.6 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 13 |
| 1661.4 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 14 |
| 2226.2 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 14 |
| 1664.4 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 15 |
| 1881.6 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 15 |
| 2082.5 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 16 |
| 2085.5 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 16 |
| 2125.1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 17 |
| 1245.9 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 17 |
| 2211.8 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 18 |
| 3123.3 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 18 |
| 2074.6 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 19 |
| 1828.6 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 19 |
| 1880.4 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| 1522.5 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| 1065.3 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| 2131.3 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| 5091.9 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 |
| 4193.4 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 3 |
| 2985.1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 4 |
| 2157.7 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 4 |
| 2509.7 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 5 |
| 2885.3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 5 |
| 2416.6 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 6 |
| 3092.6 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 6 |
| 1212 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 7 |
| 963.6 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 7 |
| 1850.6 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 8 |
| 2785 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 8 |
| 1607.3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 9 |
| 1538.8 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 9 |
| 2374.4 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 10 |
| 1674.1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 10 |
| 1110.8 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 11 |
| 1536.2 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 11 |
| 2238.7 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 12 |
| 2354.9 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 12 |
| 1374.3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 13 |
| 1608 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 13 |
| 2524.7 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 14 |
| 1526.1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 14 |
| 2096.4 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 15 |
| 2147.7 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 15 |
| 1537.1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 16 |
| 1768.8 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 16 |
| 2050.4 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 17 |
| 2082.3 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 17 |
| 3631.3 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 18 |
| 2880.2 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 18 |
| 1743.2 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 19 |
| 1568.3 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 19 |

END

### A.4.2. FDA Drug 8 Data for IBE

```
#       Drug 8
#     Trt 1= Test
#     Trt 2= Reference

list(n=19,REP=2,DRUGS=2,SEQ=4)

subj[]      seq[] rep[] trt[] y[]
1     1     1     2     1927.4
1     1     2     2     1526.5
1     1     1     1     1880.4
1     1     2     1     1522.5
2     2     1     1     1065.3
2     2     1     2     3219.1
2     2     2     2     2933
2     2     2     1     2131.3
3     3     1     1     5091.9
3     3     2     1     4193.4
3     3     1     2     2816.6
3     3     2     2     3078.3
4     4     1     2     1477.2
4     4     1     1     2985.1
4     4     2     1     2157.7
4     4     2     2     1948.3
5     1     1     2     2177.7
5     1     2     2     1780.6
5     1     1     1     2509.7
5     1     2     1     2885.3
6     4     1     2     2354.3
6     4     1     1     2416.6
6     4     2     1     3092.6
6     4     2     2     3275
7     2     1     1     1212
7     2     1     2     667.4
7     2     2     2     1274.4
7     2     2     1     963.6
8     3     1     1     1850.6
8     3     2     1     2785
8     3     1     2     2332.5
8     3     2     2     2310.9
9     3     1     1     1607.3
9     3     2     1     1538.8
9     3     1     2     2137
9     3     2     2     2035.1
10    4     1     2     2106.1
10    4     1     1     2374.4
10    4     2     1     1674.1
10    4     2     2     2335.8
11    2     1     1     1110.8
11    2     1     2     1344.8
11    2     2     2     1608.3
11    2     2     1     1536.2
12    1     1     2     2962.7
12    1     2     2     1403.7
12    1     1     1     2238.7
12    1     2     1     2354.9
13    1     1     2     1968.9
13    1     2     2     1971.6
13    1     1     1     1374.3
13    1     2     1     1608
14    2     1     1     2524.7
14    2     1     2     1661.4
14    2     2     2     2226.2
```

| | | | | |
|---|---|---|---|---|
| 14 | 2 | 2 | 1 | 1526.1 |
| 15 | 4 | 1 | 2 | 1664.4 |
| 15 | 4 | 1 | 1 | 2096.4 |
| 15 | 4 | 2 | 1 | 2147.7 |
| 15 | 4 | 2 | 2 | 1881.6 |
| 16 | 2 | 1 | 1 | 1537.1 |
| 16 | 2 | 1 | 2 | 2082.5 |
| 16 | 2 | 2 | 2 | 2085.5 |
| 16 | 2 | 2 | 1 | 1768.8 |
| 17 | 3 | 1 | 1 | 2050.4 |
| 17 | 3 | 2 | 1 | 2082.3 |
| 17 | 3 | 1 | 2 | 2125.1 |
| 17 | 3 | 2 | 2 | 1245.9 |
| 18 | 4 | 1 | 2 | 2211.8 |
| 18 | 4 | 1 | 1 | 3631.3 |
| 18 | 4 | 2 | 1 | 2880.2 |
| 18 | 4 | 2 | 2 | 3123.3 |
| 19 | 2 | 1 | 1 | 1743.2 |
| 19 | 2 | 1 | 2 | 2074.6 |
| 19 | 2 | 2 | 2 | 1828.6 |
| 19 | 2 | 2 | 1 | 1568.3 |

END

### A.5.1. FDA Drug 14c Data for ABE and PBE

```
#     DRUG 14C FROM FDA WEBSITE
#     input y[]=AUCt    g[]=SUBJ
#           CODING OF VARIABLES
#-------------------------------------------------------
#     seq   x[,1]
#     1     0
#     2     1
#-------------------------------------------------------
#     per   x[,2] x[,3] x[,4]
#     1     0     0     0
#     2     1     0     0
#     3     0     1     0
#     4     0     0     1
#-------------------------------------------------------
#     trt   x[,5]
#     1     0
#     2     1

list(N=152)

y[]   x[,1] x[,2] x[,3] x[,4] x[,5] g[]
346.657     1     0     0     0     1     1
333.783     1     0     0     1     1     1
271.828     1     0     0     0     1     2
330.27      1     0     0     1     1     2
295.662     0     1     0     0     1     3
272.292     0     0     1     0     1     3
347.456     1     0     0     0     1     4
377.844     1     0     0     1     1     4
329.069     1     0     0     0     1     5
270.104     1     0     0     1     1     5
385.956     0     1     0     0     1     6
376.274     0     0     1     0     1     6
311.421     1     0     0     0     1     7
331.277     1     0     0     1     1     7
266.97      0     1     0     0     1     8
209.216     0     0     1     0     1     8
193.216     0     1     0     0     1     9
210.969     0     0     1     0     1     9
313.162     0     1     0     0     1     10
293.487     0     0     1     0     1     10
287.225     0     1     0     0     1     11
327.839     0     0     1     0     1     11
312.111     0     1     0     0     1     12
330.896     0     0     1     0     1     12
272.382     0     1     0     0     1     13
252.822     0     0     1     0     1     13
319.934     1     0     0     0     1     14
342.512     1     0     0     1     1     14
197.386     0     1     0     0     1     15
224.63      0     0     1     0     1     15
317.494     0     1     0     0     1     16
314.604     0     0     1     0     1     16
353.662     0     1     0     0     1     17
345.82      0     0     1     0     1     17
189.886     1     0     0     0     1     18
245.583     1     0     0     1     1     18
214.754     0     1     0     0     1     19
142.514     0     0     1     0     1     19
263.031     1     0     0     0     1     20
271.879     1     0     0     1     1     20
273.088     1     0     0     0     1     21
```

| | | | | | | |
|---|---|---|---|---|---|---|
| 253.794 | 1 | 0 | 0 | 1 | 1 | 21 |
| 307.58 | 0 | 1 | 0 | 0 | 1 | 22 |
| 364.567 | 0 | 0 | 1 | 0 | 1 | 22 |
| 279.311 | 1 | 0 | 0 | 0 | 1 | 23 |
| 298.579 | 1 | 0 | 0 | 1 | 1 | 23 |
| 398.39 | 0 | 1 | 0 | 0 | 1 | 24 |
| 352.844 | 0 | 0 | 1 | 0 | 1 | 24 |
| 314.791 | 1 | 0 | 0 | 0 | 1 | 25 |
| 326.895 | 1 | 0 | 0 | 1 | 1 | 25 |
| 381.913 | 1 | 0 | 0 | 0 | 1 | 26 |
| 268.906 | 1 | 0 | 0 | 1 | 1 | 26 |
| 217.423 | 0 | 1 | 0 | 0 | 1 | 27 |
| 186.125 | 0 | 0 | 1 | 0 | 1 | 27 |
| 176.912 | 1 | 0 | 0 | 0 | 1 | 28 |
| 169.195 | 1 | 0 | 0 | 1 | 1 | 28 |
| 274.946 | 1 | 0 | 0 | 0 | 1 | 29 |
| 245.503 | 1 | 0 | 0 | 1 | 1 | 29 |
| 386.77 | 0 | 1 | 0 | 0 | 1 | 30 |
| 325.938 | 0 | 0 | 1 | 0 | 1 | 30 |
| 207.374 | 1 | 0 | 0 | 0 | 1 | 31 |
| 304.305 | 1 | 0 | 0 | 1 | 1 | 31 |
| 313.213 | 0 | 1 | 0 | 0 | 1 | 32 |
| 253.484 | 0 | 0 | 1 | 0 | 1 | 32 |
| 179.864 | 1 | 0 | 0 | 0 | 1 | 33 |
| 186.623 | 1 | 0 | 0 | 1 | 1 | 33 |
| 188.034 | 1 | 0 | 0 | 0 | 1 | 34 |
| 198.137 | 1 | 0 | 0 | 1 | 1 | 34 |
| 320.177 | 0 | 1 | 0 | 0 | 1 | 35 |
| 243.794 | 0 | 0 | 1 | 0 | 1 | 35 |
| 139.147 | 1 | 0 | 0 | 0 | 1 | 36 |
| 188.801 | 1 | 0 | 0 | 1 | 1 | 36 |
| 321.509 | 1 | 0 | 0 | 0 | 1 | 37 |
| 325.621 | 1 | 0 | 0 | 1 | 1 | 37 |
| 341.441 | 1 | 0 | 0 | 0 | 1 | 38 |
| 329.299 | 1 | 0 | 0 | 1 | 1 | 38 |
| 295.793 | 1 | 1 | 0 | 0 | 0 | 1 |
| 307.487 | 1 | 0 | 1 | 0 | 0 | 1 |
| 268.853 | 1 | 1 | 0 | 0 | 0 | 2 |
| 297.293 | 1 | 0 | 1 | 0 | 0 | 2 |
| 288.982 | 0 | 0 | 0 | 0 | 0 | 3 |
| 288.023 | 0 | 0 | 0 | 1 | 0 | 3 |
| 315.592 | 1 | 1 | 0 | 0 | 0 | 4 |
| 368.771 | 1 | 0 | 1 | 0 | 0 | 4 |
| 267.528 | 1 | 1 | 0 | 0 | 0 | 5 |
| 259.507 | 1 | 0 | 1 | 0 | 0 | 5 |
| 313.583 | 0 | 0 | 0 | 0 | 0 | 6 |
| 409.134 | 0 | 0 | 0 | 1 | 0 | 6 |
| 260.449 | 1 | 1 | 0 | 0 | 0 | 7 |
| 255.399 | 1 | 0 | 1 | 0 | 0 | 7 |
| 251 | 0 | 0 | 0 | 0 | 0 | 8 |
| 276.414 | 0 | 0 | 0 | 1 | 0 | 8 |
| 200.429 | 0 | 0 | 0 | 0 | 0 | 9 |
| 234.662 | 0 | 0 | 0 | 1 | 0 | 9 |
| 300.113 | 0 | 0 | 0 | 0 | 0 | 10 |
| 349.199 | 0 | 0 | 0 | 1 | 0 | 10 |
| 259.098 | 0 | 0 | 0 | 0 | 0 | 11 |
| 274.848 | 0 | 0 | 0 | 1 | 0 | 11 |
| 292.694 | 0 | 0 | 0 | 0 | 0 | 12 |
| 271.354 | 0 | 0 | 0 | 1 | 0 | 12 |
| 382.436 | 0 | 0 | 0 | 0 | 0 | 13 |
| 290.16 | 0 | 0 | 0 | 1 | 0 | 13 |
| 286.001 | 1 | 1 | 0 | 0 | 0 | 14 |
| 284.307 | 1 | 0 | 1 | 0 | 0 | 14 |
| 165.711 | 0 | 0 | 0 | 0 | 0 | 15 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 216.986 | 0 | 0 | 0 | 1 | 0 | 15 |
| 321.386 | 0 | 0 | 0 | 0 | 0 | 16 |
| 343.271 | 0 | 0 | 0 | 1 | 0 | 16 |
| 324.899 | 0 | 0 | 0 | 0 | 0 | 17 |
| 311.822 | 0 | 0 | 0 | 1 | 0 | 17 |
| 202.821 | 1 | 1 | 0 | 0 | 0 | 18 |
| 379.1 | 1 | 0 | 1 | 0 | 0 | 18 |
| 182.509 | 0 | 0 | 0 | 0 | 0 | 19 |
| 237.114 | 0 | 0 | 0 | 1 | 0 | 19 |
| 285.758 | 1 | 1 | 0 | 0 | 0 | 20 |
| 309.356 | 1 | 0 | 1 | 0 | 0 | 20 |
| 201.809 | 1 | 1 | 0 | 0 | 0 | 21 |
| 232.005 | 1 | 0 | 1 | 0 | 0 | 21 |
| 254.868 | 0 | 0 | 0 | 0 | 0 | 22 |
| 233.719 | 0 | 0 | 0 | 1 | 0 | 22 |
| 320.763 | 1 | 1 | 0 | 0 | 0 | 23 |
| 253.281 | 1 | 0 | 1 | 0 | 0 | 23 |
| 343.725 | 0 | 0 | 0 | 0 | 0 | 24 |
| 290.404 | 0 | 0 | 0 | 1 | 0 | 24 |
| 340.947 | 1 | 1 | 0 | 0 | 0 | 25 |
| 306.799 | 1 | 0 | 1 | 0 | 0 | 25 |
| 314.845 | 1 | 1 | 0 | 0 | 0 | 26 |
| 288.623 | 1 | 0 | 1 | 0 | 0 | 26 |
| 192.33 | 0 | 0 | 0 | 0 | 0 | 27 |
| 174.125 | 0 | 0 | 0 | 1 | 0 | 27 |
| 170.607 | 1 | 1 | 0 | 0 | 0 | 28 |
| 179.668 | 1 | 0 | 1 | 0 | 0 | 28 |
| 285.287 | 1 | 1 | 0 | 0 | 0 | 29 |
| 205.17 | 1 | 0 | 1 | 0 | 0 | 29 |
| 382.929 | 0 | 0 | 0 | 0 | 0 | 30 |
| 337.494 | 0 | 0 | 0 | 1 | 0 | 30 |
| 242.771 | 1 | 1 | 0 | 0 | 0 | 31 |
| 257.696 | 1 | 0 | 1 | 0 | 0 | 31 |
| 225.137 | 0 | 0 | 0 | 0 | 0 | 32 |
| 447.483 | 0 | 0 | 0 | 1 | 0 | 32 |
| 202.77 | 1 | 1 | 0 | 0 | 0 | 33 |
| 202.892 | 1 | 0 | 1 | 0 | 0 | 33 |
| 236.78 | 1 | 1 | 0 | 0 | 0 | 34 |
| 263.08 | 1 | 0 | 1 | 0 | 0 | 34 |
| 239.068 | 0 | 0 | 0 | 0 | 0 | 35 |
| 299.003 | 0 | 0 | 0 | 1 | 0 | 35 |
| 144.593 | 1 | 1 | 0 | 0 | 0 | 36 |
| 188.394 | 1 | 0 | 1 | 0 | 0 | 36 |
| 323.345 | 1 | 1 | 0 | 0 | 0 | 37 |
| 312.701 | 1 | 0 | 1 | 0 | 0 | 37 |
| 355.642 | 1 | 1 | 0 | 0 | 0 | 38 |
| 400.55 | 1 | 0 | 1 | 0 | 0 | 38 |

END

### A.5.2. FDA Drug 14c Data for IBE without carry-over

```
#        Drug 14c.
#        Replicate Design
#        Trt 1: Test
#        Trt 2: Reference

list(n=38,REP=2,DRUGS=2,SEQ=2)

seq[] subj[]      trt[] rep[] y[]
2     1     1     1     295.793
2     1     2     1     346.657
2     1     1     2     307.487
2     1     2     2     333.783
2     2     1     1     268.853
2     2     2     1     271.828
2     2     1     2     297.293
2     2     2     2     330.27
1     3     1     1     288.982
1     3     2     1     295.662
1     3     1     2     288.023
1     3     2     2     272.292
2     4     1     1     315.592
2     4     2     1     347.456
2     4     1     2     368.771
2     4     2     2     377.844
2     5     1     1     267.528
2     5     2     1     329.069
2     5     1     2     259.507
2     5     2     2     270.104
1     6     1     1     313.583
1     6     2     1     385.956
1     6     1     2     409.134
1     6     2     2     376.274
2     7     1     1     260.449
2     7     2     1     311.421
2     7     1     2     255.399
2     7     2     2     331.277
1     8     1     1     251
1     8     2     1     266.97
1     8     1     2     276.414
1     8     2     2     209.216
1     9     1     1     200.429
1     9     2     1     193.216
1     9     1     2     234.662
1     9     2     2     210.969
1     10    1     1     300.113
1     10    2     1     313.162
1     10    1     2     349.199
1     10    2     2     293.487
1     11    1     1     259.098
1     11    2     1     287.225
1     11    1     2     274.848
1     11    2     2     327.839
1     12    1     1     292.694
1     12    2     1     312.111
1     12    1     2     271.354
1     12    2     2     330.896
1     13    1     1     382.436
1     13    2     1     272.382
1     13    1     2     290.16
1     13    2     2     252.822
2     14    1     1     286.001
2     14    2     1     319.934
```

| | | | | |
|---|---|---|---|---|
| 2 | 14 | 1 | 2 | 284.307 |
| 2 | 14 | 2 | 2 | 342.512 |
| 1 | 15 | 1 | 1 | 165.711 |
| 1 | 15 | 2 | 1 | 197.386 |
| 1 | 15 | 1 | 2 | 216.986 |
| 1 | 15 | 2 | 2 | 224.63 |
| 1 | 16 | 1 | 1 | 321.386 |
| 1 | 16 | 2 | 1 | 317.494 |
| 1 | 16 | 1 | 2 | 343.271 |
| 1 | 16 | 2 | 2 | 314.604 |
| 1 | 17 | 1 | 1 | 324.899 |
| 1 | 17 | 2 | 1 | 353.662 |
| 1 | 17 | 1 | 2 | 311.822 |
| 1 | 17 | 2 | 2 | 345.82 |
| 2 | 18 | 1 | 1 | 202.821 |
| 2 | 18 | 2 | 1 | 189.886 |
| 2 | 18 | 1 | 2 | 379.1 |
| 2 | 18 | 2 | 2 | 245.583 |
| 1 | 19 | 1 | 1 | 182.509 |
| 1 | 19 | 2 | 1 | 214.754 |
| 1 | 19 | 1 | 2 | 237.114 |
| 1 | 19 | 2 | 2 | 142.514 |
| 2 | 20 | 1 | 1 | 285.758 |
| 2 | 20 | 2 | 1 | 263.031 |
| 2 | 20 | 1 | 2 | 309.356 |
| 2 | 20 | 2 | 2 | 271.879 |
| 2 | 21 | 1 | 1 | 201.809 |
| 2 | 21 | 2 | 1 | 273.088 |
| 2 | 21 | 1 | 2 | 232.005 |
| 2 | 21 | 2 | 2 | 253.794 |
| 1 | 22 | 1 | 1 | 254.868 |
| 1 | 22 | 2 | 1 | 307.58 |
| 1 | 22 | 1 | 2 | 233.719 |
| 1 | 22 | 2 | 2 | 364.567 |
| 2 | 23 | 1 | 1 | 320.763 |
| 2 | 23 | 2 | 1 | 279.311 |
| 2 | 23 | 1 | 2 | 253.281 |
| 2 | 23 | 2 | 2 | 298.579 |
| 1 | 24 | 1 | 1 | 343.725 |
| 1 | 24 | 2 | 1 | 398.39 |
| 1 | 24 | 1 | 2 | 290.404 |
| 1 | 24 | 2 | 2 | 352.844 |
| 2 | 25 | 1 | 1 | 340.947 |
| 2 | 25 | 2 | 1 | 314.791 |
| 2 | 25 | 1 | 2 | 306.799 |
| 2 | 25 | 2 | 2 | 326.895 |
| 2 | 26 | 1 | 1 | 314.845 |
| 2 | 26 | 2 | 1 | 381.913 |
| 2 | 26 | 1 | 2 | 288.623 |
| 2 | 26 | 2 | 2 | 268.906 |
| 1 | 27 | 1 | 1 | 192.33 |
| 1 | 27 | 2 | 1 | 217.423 |
| 1 | 27 | 1 | 2 | 174.125 |
| 1 | 27 | 2 | 2 | 186.125 |
| 2 | 28 | 1 | 1 | 170.607 |
| 2 | 28 | 2 | 1 | 176.912 |
| 2 | 28 | 1 | 2 | 179.668 |
| 2 | 28 | 2 | 2 | 169.195 |
| 2 | 29 | 1 | 1 | 285.287 |
| 2 | 29 | 2 | 1 | 274.946 |
| 2 | 29 | 1 | 2 | 205.17 |
| 2 | 29 | 2 | 2 | 245.503 |
| 1 | 30 | 1 | 1 | 382.929 |
| 1 | 30 | 2 | 1 | 386.77 |

| | | | | |
|---|---|---|---|---|
| 1 | 30 | 1 | 2 | 337.494 |
| 1 | 30 | 2 | 2 | 325.938 |
| 2 | 31 | 1 | 1 | 242.771 |
| 2 | 31 | 2 | 1 | 207.374 |
| 2 | 31 | 1 | 2 | 257.696 |
| 2 | 31 | 2 | 2 | 304.305 |
| 1 | 32 | 1 | 1 | 225.137 |
| 1 | 32 | 2 | 1 | 313.213 |
| 1 | 32 | 1 | 2 | 447.483 |
| 1 | 32 | 2 | 2 | 253.484 |
| 2 | 33 | 1 | 1 | 202.77 |
| 2 | 33 | 2 | 1 | 179.864 |
| 2 | 33 | 1 | 2 | 202.892 |
| 2 | 33 | 2 | 2 | 186.623 |
| 2 | 34 | 1 | 1 | 236.78 |
| 2 | 34 | 2 | 1 | 188.034 |
| 2 | 34 | 1 | 2 | 263.08 |
| 2 | 34 | 2 | 2 | 198.137 |
| 1 | 35 | 1 | 1 | 239.068 |
| 1 | 35 | 2 | 1 | 320.177 |
| 1 | 35 | 1 | 2 | 299.003 |
| 1 | 35 | 2 | 2 | 243.794 |
| 2 | 36 | 1 | 1 | 144.593 |
| 2 | 36 | 2 | 1 | 139.147 |
| 2 | 36 | 1 | 2 | 188.394 |
| 2 | 36 | 2 | 2 | 188.801 |
| 2 | 37 | 1 | 1 | 323.345 |
| 2 | 37 | 2 | 1 | 321.509 |
| 2 | 37 | 1 | 2 | 312.701 |
| 2 | 37 | 2 | 2 | 325.621 |
| 2 | 38 | 1 | 1 | 355.642 |
| 2 | 38 | 2 | 1 | 341.441 |
| 2 | 38 | 1 | 2 | 400.55 |
| 2 | 38 | 2 | 2 | 329.299 |

END

### A.5.3. FDA Drug 14c Data for IBE with carry-over

```
#        Drug 14c.
#        Replicate Design
#        Trt 1: Test
#        Trt 2: Reference

#     CODING OR INDICATOR VARIABLE r
#----------------------------------------
#     IF PERIOD >1 THEN r=1 ELSE r=0
#----------------------------------------

list(n=38,REP=2,DRUGS=2,SEQ=2)

seq[] subj[]      trt[] rep[] r[]   y[]
2     1     1     1     1     295.793
2     1     2     1     0     346.657
2     1     1     2     1     307.487
2     1     2     2     1     333.783
2     2     1     1     1     268.853
2     2     2     1     0     271.828
2     2     1     2     1     297.293
2     2     2     2     1     330.27
1     3     1     1     0     288.982
1     3     2     1     1     295.662
1     3     1     2     1     288.023
1     3     2     2     1     272.292
2     4     1     1     1     315.592
2     4     2     1     0     347.456
2     4     1     2     1     368.771
2     4     2     2     1     377.844
2     5     1     1     1     267.528
2     5     2     1     0     329.069
2     5     1     2     1     259.507
2     5     2     2     1     270.104
1     6     1     1     0     313.583
1     6     2     1     1     385.956
1     6     1     2     1     409.134
1     6     2     2     1     376.274
2     7     1     1     1     260.449
2     7     2     1     0     311.421
2     7     1     2     1     255.399
2     7     2     2     1     331.277
1     8     1     1     0     251
1     8     2     1     1     266.97
1     8     1     2     1     276.414
1     8     2     2     1     209.216
1     9     1     1     0     200.429
1     9     2     1     1     193.216
1     9     1     2     1     234.662
1     9     2     2     1     210.969
1     10    1     1     0     300.113
1     10    2     1     1     313.162
1     10    1     2     1     349.199
1     10    2     2     1     293.487
1     11    1     1     0     259.098
1     11    2     1     1     287.225
1     11    1     2     1     274.848
1     11    2     2     1     327.839
1     12    1     1     0     292.694
1     12    2     1     1     312.111
1     12    1     2     1     271.354
1     12    2     2     1     330.896
1     13    1     1     0     382.436
```

| | | | | | |
|---|---|---|---|---|---|
| 1 | 13 | 2 | 1 | 1 | 272.382 |
| 1 | 13 | 1 | 2 | 1 | 290.16 |
| 1 | 13 | 2 | 2 | 1 | 252.822 |
| 2 | 14 | 1 | 1 | 1 | 286.001 |
| 2 | 14 | 2 | 1 | 0 | 319.934 |
| 2 | 14 | 1 | 2 | 1 | 284.307 |
| 2 | 14 | 2 | 2 | 1 | 342.512 |
| 1 | 15 | 1 | 1 | 0 | 165.711 |
| 1 | 15 | 2 | 1 | 1 | 197.386 |
| 1 | 15 | 1 | 2 | 1 | 216.986 |
| 1 | 15 | 2 | 2 | 1 | 224.63 |
| 1 | 16 | 1 | 1 | 0 | 321.386 |
| 1 | 16 | 2 | 1 | 1 | 317.494 |
| 1 | 16 | 1 | 2 | 1 | 343.271 |
| 1 | 16 | 2 | 2 | 1 | 314.604 |
| 1 | 17 | 1 | 1 | 0 | 324.899 |
| 1 | 17 | 2 | 1 | 1 | 353.662 |
| 1 | 17 | 1 | 2 | 1 | 311.822 |
| 1 | 17 | 2 | 2 | 1 | 345.82 |
| 2 | 18 | 1 | 1 | 1 | 202.821 |
| 2 | 18 | 2 | 1 | 0 | 189.886 |
| 2 | 18 | 1 | 2 | 1 | 379.1 |
| 2 | 18 | 2 | 2 | 1 | 245.583 |
| 1 | 19 | 1 | 1 | 0 | 182.509 |
| 1 | 19 | 2 | 1 | 1 | 214.754 |
| 1 | 19 | 1 | 2 | 1 | 237.114 |
| 1 | 19 | 2 | 2 | 1 | 142.514 |
| 2 | 20 | 1 | 1 | 1 | 285.758 |
| 2 | 20 | 2 | 1 | 0 | 263.031 |
| 2 | 20 | 1 | 2 | 1 | 309.356 |
| 2 | 20 | 2 | 2 | 1 | 271.879 |
| 2 | 21 | 1 | 1 | 1 | 201.809 |
| 2 | 21 | 2 | 1 | 0 | 273.088 |
| 2 | 21 | 1 | 2 | 1 | 232.005 |
| 2 | 21 | 2 | 2 | 1 | 253.794 |
| 1 | 22 | 1 | 1 | 0 | 254.868 |
| 1 | 22 | 2 | 1 | 1 | 307.58 |
| 1 | 22 | 1 | 2 | 1 | 233.719 |
| 1 | 22 | 2 | 2 | 1 | 364.567 |
| 2 | 23 | 1 | 1 | 1 | 320.763 |
| 2 | 23 | 2 | 1 | 0 | 279.311 |
| 2 | 23 | 1 | 2 | 1 | 253.281 |
| 2 | 23 | 2 | 2 | 1 | 298.579 |
| 1 | 24 | 1 | 1 | 0 | 343.725 |
| 1 | 24 | 2 | 1 | 1 | 398.39 |
| 1 | 24 | 1 | 2 | 1 | 290.404 |
| 1 | 24 | 2 | 2 | 1 | 352.844 |
| 2 | 25 | 1 | 1 | 1 | 340.947 |
| 2 | 25 | 2 | 1 | 0 | 314.791 |
| 2 | 25 | 1 | 2 | 1 | 306.799 |
| 2 | 25 | 2 | 2 | 1 | 326.895 |
| 2 | 26 | 1 | 1 | 1 | 314.845 |
| 2 | 26 | 2 | 1 | 0 | 381.913 |
| 2 | 26 | 1 | 2 | 1 | 288.623 |
| 2 | 26 | 2 | 2 | 1 | 268.906 |
| 1 | 27 | 1 | 1 | 0 | 192.33 |
| 1 | 27 | 2 | 1 | 1 | 217.423 |
| 1 | 27 | 1 | 2 | 1 | 174.125 |
| 1 | 27 | 2 | 2 | 1 | 186.125 |
| 2 | 28 | 1 | 1 | 1 | 170.607 |
| 2 | 28 | 2 | 1 | 0 | 176.912 |
| 2 | 28 | 1 | 2 | 1 | 179.668 |
| 2 | 28 | 2 | 2 | 1 | 169.195 |
| 2 | 29 | 1 | 1 | 1 | 285.287 |

| | | | | | |
|---|---|---|---|---|---|
| 2 | 29 | 2 | 1 | 0 | 274.946 |
| 2 | 29 | 1 | 2 | 1 | 205.17 |
| 2 | 29 | 2 | 2 | 1 | 245.503 |
| 1 | 30 | 1 | 1 | 0 | 382.929 |
| 1 | 30 | 2 | 1 | 1 | 386.77 |
| 1 | 30 | 1 | 2 | 1 | 337.494 |
| 1 | 30 | 2 | 2 | 1 | 325.938 |
| 2 | 31 | 1 | 1 | 1 | 242.771 |
| 2 | 31 | 2 | 1 | 0 | 207.374 |
| 2 | 31 | 1 | 2 | 1 | 257.696 |
| 2 | 31 | 2 | 2 | 1 | 304.305 |
| 1 | 32 | 1 | 1 | 0 | 225.137 |
| 1 | 32 | 2 | 1 | 1 | 313.213 |
| 1 | 32 | 1 | 2 | 1 | 447.483 |
| 1 | 32 | 2 | 2 | 1 | 253.484 |
| 2 | 33 | 1 | 1 | 1 | 202.77 |
| 2 | 33 | 2 | 1 | 0 | 179.864 |
| 2 | 33 | 1 | 2 | 1 | 202.892 |
| 2 | 33 | 2 | 2 | 1 | 186.623 |
| 2 | 34 | 1 | 1 | 1 | 236.78 |
| 2 | 34 | 2 | 1 | 0 | 188.034 |
| 2 | 34 | 1 | 2 | 1 | 263.08 |
| 2 | 34 | 2 | 2 | 1 | 198.137 |
| 1 | 35 | 1 | 1 | 0 | 239.068 |
| 1 | 35 | 2 | 1 | 1 | 320.177 |
| 1 | 35 | 1 | 2 | 1 | 299.003 |
| 1 | 35 | 2 | 2 | 1 | 243.794 |
| 2 | 36 | 1 | 1 | 1 | 144.593 |
| 2 | 36 | 2 | 1 | 0 | 139.147 |
| 2 | 36 | 1 | 2 | 1 | 188.394 |
| 2 | 36 | 2 | 2 | 1 | 188.801 |
| 2 | 37 | 1 | 1 | 1 | 323.345 |
| 2 | 37 | 2 | 1 | 0 | 321.509 |
| 2 | 37 | 1 | 2 | 1 | 312.701 |
| 2 | 37 | 2 | 2 | 1 | 325.621 |
| 2 | 38 | 1 | 1 | 1 | 355.642 |
| 2 | 38 | 2 | 1 | 0 | 341.441 |
| 2 | 38 | 1 | 2 | 1 | 400.55 |
| 2 | 38 | 2 | 2 | 1 | 329.299 |

END