

Collection of Biostatistics Research Archive
COBRA Preprint Series

Year 2007

Paper 30

An Example of How to Write the Statistical
Section of a Bioequivalence Study Protocol for
FDA Review

William F. McCarthy*

*Maryland Medical Research Institute, dr.w.f.mccarthy@gmail.com

This working paper is hosted by The Berkeley Electronic Press (bepress) and may not be commercially reproduced without the permission of the copyright holder.

<http://biostats.bepress.com/cobra/art30>

Copyright ©2007 by the author.

An Example of How to Write the Statistical Section of a Bioequivalence Study Protocol for FDA Review

William F. McCarthy

Abstract

This paper provides a detailed example of how one should write the statistical section of a bioequivalence study protocol for FDA review. Three forms of bioequivalence are covered: average bioequivalence (ABE), population bioequivalence (PBE) and individual bioequivalence (IBE). The method of analysis is based on Jones and Kenward (2003) and a modification of their SAS Macro is provided.

Statistical Approach to Establishing Bioequivalence

If one assumes an orally administered drug is being considered, pharmacokinetics (PK) is concerned with obtaining information on the absorption, distribution, metabolism and elimination of the drug under consideration. PK is the study of what the body does to the drug. An important outcome of a PK study is the assessment of how much of the active constituents of the drug reaches its site of action. Since this type of assessment cannot be easily made, the concentration of the drug under consideration that reaches the circulating bloodstream is taken as a surrogate. This concentration of the drug in the blood is referred to as its bioavailability. Two drugs that have the same bioavailability are termed bioequivalent.

Following FDA Guidelines, the statistical analysis should be based on the non-compartmental PK parameters AUC_{0-t} (Area Under the Curve from time 0 to last measurable time point), $AUC_{0 \text{ to } \infty}$ (Area Under the Curve from time 0 to infinity) and C_{\max} (maximum concentration) derived from the drug concentration-time curve.

Three Forms of Bioequivalence

In the following narrative, we refer to the original or innovator version of the drug under consideration as the "Reference" or R. The new or alternative version of the drug we will refer to as the "Test" or T.

1. Average Bioequivalence (ABE):

To show that T and R are average bioequivalent it is only necessary to show that the mean $\ln(AUC)$ and the mean $\ln(C_{\max})$ for T is not significantly different from the mean $\ln(AUC)$ and the mean $\ln(C_{\max})$ for R.

In other words we need to show that, "on average", in the population of intended patients, the two drugs are bioequivalent.

This measure does not take into account the variability of T and R. It is possible for one drug to be much more variable than the other, yet similar in terms of mean $\ln(AUC)$ and the mean $\ln(C_{\max})$.

It is for this reason that Population Bioequivalence (PBE) was introduced.

2. Population Bioequivalence (PBE):

The measure of PBE is a mixture of the mean and variance of the $\ln(AUC)$ and the $\ln(C_{\max})$.

PBE can be considered as a measure that permits patients who have not yet been treated with T or R to be safely prescribed either.

3. Individual Bioequivalence (IBE):

Two drugs could be similar in mean and variance over the population of potential patients, but be such that they produce different effects when a patient is switched from formulation T to formulation R or vice-versa.

In other words, there is a significant subject-by-formulation interaction.

To show that this is not the case T and R have to be shown to be Individual Bioequivalence (IBE).

The measure of IBE is an aggregate measure involving the means and variances of T and R and the subject-by-formulation interaction.

IBE can be considered as a measure that permits a patient who is currently being treated with R to be safely switched to T.

NOTE: If T is IBE to R it does not imply that R is IBE to T.

Study Design

A replicated crossover design (four-period, two-sequence, two-formulation) will be used that will allow for the assessment of ABE, PBE and IBE.

		PERIOD			
		1	2	3	4
SEQUENCE	1	T	R	T	R
	2	R	T	R	T

Sample Size and Dropouts

Sample size determination was based on the use of the sample size tables provided in Appendix C of the FDA Guidance Statistical Approaches to Establishing Bioequivalence (January 2001). Please refer to Appendix A.

Since this document is a generic template, no specificity is provided in this section by this author. In this section, the biostatistician using this template would add a narrative regarding estimated sample size to use based on information from literature and/or pilot studies. The sample size tables in Appendix A would be used and referenced. A discussion of dropouts would be presented as well, with appropriate adjustments to sample size for such anticipated dropouts.

Method of Analysis

The methodology proposed by Jones and Kenward (2003) will be used to assess ABE, IBE and PBE. For IBE and PBE, the FDA recommended aggregate metric for IBE and PBE is used.

For IBE the aggregate metric is:

$$\frac{(\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2}{\max(0.04, \sigma_{WR}^2)}$$

which tests the following linearized null hypotheses:

$$\text{if } \hat{\sigma}_{WR}^2 > 0.04 \text{ then } H_0 : \nu_{IBE} = \delta^2 + \sigma_D^2 + \sigma_{WT}^2 - (1 + C_{FDA})\sigma_{WR}^2 \geq 0.$$

$$\text{If } \hat{\sigma}_{WR}^2 \leq 0.04 \text{ then } H_0 : \nu_{C.IBE} = \delta^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2 - 0.04(C_{FDA}) \geq 0.$$

The value C_{FDA} in H_0 is a regulatory goalpost equal to 2.49. It assumes a within-subject variance for R of 0.04, a difference of means of $\ln(1.25)$, $\sigma_D^2=0.03$ and $\sigma_{WT}^2 - \sigma_{WR}^2=0.02$. The denominator is set at 0.04.

Using the methodology proposed by Jones and Kenward (2003), the asymptotic upper bound of the 90% confidence interval can be calculated as:

$$\hat{v}_{IBE} + 1.645\sqrt{\hat{Var}[\hat{v}_{IBE}]} \text{ or } \hat{v}_{C.IBE} + 1.645\sqrt{\hat{Var}[\hat{v}_{C.IBE}]},$$

where each component of the 90% confidence interval can be obtained from SAS code developed by Jones and Kenward (2003).

If the asymptotic upper bound of the 90% confidence interval for both $\ln(\text{AUC})$ and $\ln(\text{Cmax})$ are below zero, IBE can be claimed.

For PBE the aggregate metric is:

$$\frac{(\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2}{\max(0.04, \sigma_R^2)}$$

where $\sigma_T^2 = \sigma_{WT}^2 + \sigma_{BT}^2$, $\sigma_R^2 = \sigma_{WR}^2 + \sigma_{BR}^2$.

which tests the following linearized null hypotheses:

if $\hat{\sigma}_R^2 > 0.04$ then $H_0 : v_{PBE} = \delta^2 + \sigma_T^2 - (1 + C_{FDA})\sigma_R^2 \geq 0$.

If $\hat{\sigma}_R^2 \leq 0.04$ then $H_0 : v_{C.PBE} = \delta^2 + \sigma_T^2 - \sigma_R^2 - 0.04(C_{FDA}) \geq 0$.

The value C_{FDA} in H_0 is a regulatory goalpost equal to 1.75. It assumes a difference of means of $\ln(1.25)$, and $\sigma_T^2 - \sigma_R^2=0.02$. The denominator is set at 0.04.

Using the methodology proposed by Jones and Kenward (2003), the asymptotic upper bound of the 90% confidence interval can be calculated as:

$$\hat{v}_{PBE} + 1.645\sqrt{\hat{Var}[\hat{v}_{PBE}]} \text{ or } \hat{v}_{C.PBE} + 1.645\sqrt{\hat{Var}[\hat{v}_{C.PBE}]},$$

where each component of the 90% confidence interval can be obtained from SAS code developed by Jones and Kenward (2003).

If the asymptotic upper bound of the 90% confidence interval for both $\ln(\text{AUC})$ and $\ln(\text{Cmax})$ are below zero, PBE can be claimed.

ABE is based on the “two one-sided test” (TOST), the asymptotic 90% confidence interval around the geometric mean ratio of the test and reference formulations is required to fall within bioequivalence limits of 0.80 to 1.25 (or ± 0.2231 on the natural log scale). If the asymptotic 90% confidence interval around the geometric mean ratio of the test and reference formulations falls within bioequivalence limits of 0.80 to 1.25 (or ± 0.2231 on the natural log scale) for both $\ln(\text{AUC})$ and $\ln(\text{Cmax})$, ABE can be claimed.

The TOST results can be obtained from SAS code developed by Jones and Kenward (2003). TOST is based on Schuirmann (1981; 1987).

Patterson and Jones (2002b, page 55) noted the following: “ Variance estimates are of less concern in ABE testing, but in alternative criteria where estimates are important to interpretation (i.e., for IBE and PBE) method-of-moments estimates should be viewed cautiously. Method-of-moment estimation, as expected, yields unbiased estimates in complete data sets, but results in positively biased $\hat{\sigma}_D^2$ in some sample with missing data. Bias in method-of-moment $\hat{\sigma}_D^2$ (with certain patterns of missing data) and constrained REML procedures increases as drugs become more highly variable and decreases with increasing sample size. Biased method-of-moment estimates in data sets with missing data exhibit a greater degree of bias than those found in CSH REML, and the estimates from an alternative constrained (FAO(2)) REML are similarly questionable. Only the unconstrained REML procedure (Type='UN') was found to yield unbiased estimates for σ_D^2 , σ_{WT}^2 , and σ_{WR}^2 in complete data sets and those with missing data.”

Strategy for Establishing Bioequivalence

With respect to FDA guidelines, bioequivalence is established for T if the following occurs:

- When the individual BE approach is used, in addition to meeting the IBE limit based on confidence bounds, the point estimate of the geometric test/reference mean ratio should fall within 80-125%. In other words, both IBE and ABE need to be demonstrated for both $\ln(\text{AUC})$ and $\ln(\text{Cmax})$.
- When the population BE approach is used, in addition to meeting the PBE limit based on confidence bounds, the point estimate of the geometric test/reference mean ratio should fall within 80-125%. In other words, both PBE and ABE need to be demonstrated for both $\ln(\text{AUC})$ and $\ln(\text{Cmax})$.

Since this document is a generic template, no specificity is provided in this section by this author. In this section, the biostatistician using this template would add a narrative regarding which approach would be used to demonstrate BE. Typically, one of the above approaches (highlighted above with bullets) is used and the biostatistician should consult with FDA in terms of which approach FDA would prefer to have used.

Statistical Modeling Issues

In general, replicated cross-over design trials that have been used to test for IBE and PBE have used sample sizes in excess of 20 to 30 subjects (Patterson and Jones, 2002a). Therefore, it is reasonable to consider asymptotic testing and there is a precedent for the use of such a procedure in the study of pharmacokinetics (Machado et al., 1999). Thus, asymptotic normal theory using restricted maximum likelihood (REML) will be used based on the modeling approach outlined by Jones and Kenward (2003).

All the appropriate estimates required to determine IBE, PBE and ABE can be obtained from the use of SAS code, in particular, PROC MIXED using the REML option. In addition, using the modeling approach outlined by Jones and Kenward (2003), an unstructured covariance structure using the PROC MIXED option "Type=UN" is used. The FDA recommended reference-scaled metric is used, in accordance with the FDA Guidance (2001). The Jones and Kenward (2003) SAS code for assessing IBE, PBE and ABE is found in Appendix B.

Logarithmic Transformation

The FDA Guidance recommends that BE measures (e.g., AUC and Cmax) be log-transformed using either common logarithms to base 10 or natural logarithms. This study will use the natural logarithm. Per advice of the FDA Guidance, there will be no test for normality of the error distribution after log-transformation.

Presentation of Data

In addition to the output from the Jones and Kenward (2003) SAS code for assessing IBE, PBE and ABE, the drug concentration in biological fluid determined at each sampling time point will be furnished on the original scale for each subject participating in the study. The pharmacokinetic measures of systemic exposure will be furnished on the original scale. The mean, standard deviation, and coefficient of variation for each pharmacokinetic measure will be computed and tabulated in the final report.

The arithmetic mean and associated standard deviation for the T and R products and the geometric means will be calculated.

To facilitate BE comparisons, the pharmacokinetic measures for each subject will be displayed in parallel for the formulation tested. In particular, for each BE measure the ratio of the individual geometric mean of the T product to the individual geometric mean of the R product will be tabulated side by side for each subject. The summary tables will indicate in which sequence each subject received the product.

Carryover Effects

It is assumed that carryover effects are either absent (the response to a formulation administered in a particular period of the design is unaffected by formulations administered in earlier periods) or equal for each formulation and preceding formulation.

Outlier Considerations

The FDA Guidance suggests that the existence of a subject outlier with no protocol violations could indicate one of the following situations:

1. Product Failure – a subject exhibits an unusually high or low response to one or the other products because of a problem with the specific dosage unit administered.
2. Subject-by-Formulation Interaction – a subject is representative of subjects present in the general population in low numbers, for whom the relative bioavailability of the two products is markedly different than for the majority of the population, and for whom the two products are not bioequivalent, even though they might be bioequivalent in the majority of the population.

If this type of data should occur, the sponsor will review how to handle such outliers with the appropriate FDA review staff.

Appendix A.

APPENDIX C of the FDA Guidance Statistical Approaches to Establishing Bioequivalence (January 2001).

Sample Size Determination

Sample sizes for average BE should be obtained using published formulas. Sample sizes for population and individual BE should be based on simulated data. The simulations should be conducted using a default situation allowing the two formulations to vary as much as 5% in average BA with equal variances and certain magnitude of subject-by-formulation interaction. The study should have 80 or 90% power to conclude BE between these two formulations. Sample size also depends on the magnitude of variability and the design of the study. Variance estimates to determine the number of subjects for a specific drug can be obtained from the biomedical literature and/or pilot studies.

Tables 1-4 below give sample sizes for 80% and 90% power using the specified study design, given a selection of within-subject standard deviations (natural log scale), between-subject standard deviations (natural log scale), and subject-by-formulation interaction, as appropriate.

Notation used below:

$$\Delta = \mu_T - \mu_R$$

μ_T = the true mean value of log(AUC) [or log(Cmax)] for T

μ_R = the true mean value of log(AUC) [or log(Cmax)] for R

σ_{WT} = within-subject standard deviation for T

σ_{WR} = within-subject standard deviation for R

σ_{BT} = between-subject standard deviation for T

σ_{BR} = between-subject standard deviation for R

σ_D = subject-by-formulation interaction standard deviation

$$\sigma_D^2 = \sigma_{BT}^2 + \sigma_{BR}^2 - 2\rho\sigma_{BT}\sigma_{BR}$$

ρ = between-subject correlation of T and R

$$\varepsilon_P = \sigma_T^2 - \sigma_R^2$$

$$\sigma_T^2 = \sigma_{WT}^2 + \sigma_{BT}^2$$

$$\sigma_R^2 = \sigma_{WR}^2 + \sigma_{BR}^2$$

$$\varepsilon_I = \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2$$

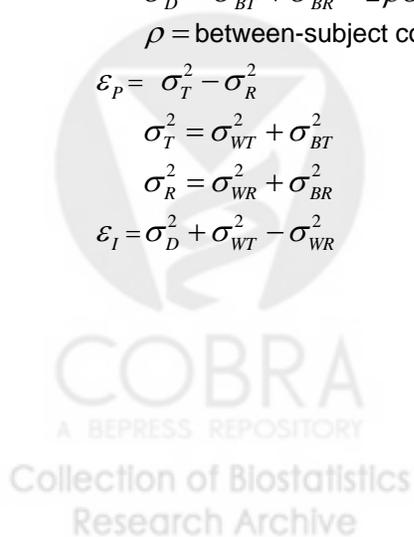


Table 1
Average Bioequivalence
Estimated Numbers of Subjects
 $\Delta = 0.05$

$\sigma_{WT} =$	$\sigma_D =$	80% Power		90% Power	
		2P	4P	2P	4P
0.15	0.01	12	6	16	8
	0.10	15	10	18	12
	0.15	16	12	22	16
0.23	0.01	24	12	32	16
	0.10	26	16	36	20
	0.15	30	18	38	24
0.30	0.01	40	20	54	28
	0.10	42	24	56	30
	0.15	44	26	60	34
0.50	0.01	108	54	144	72
	0.10	110	58	148	76
	0.15	112	60	150	80

Results for the 2P (two-period) designs use the method of Diletti et al (1991).
 Results for the 4P (four-period) designs use relative efficiency data of Liu (1995).

Table 2
Population Bioequivalence
Four-Period Design (RTRT/TRTR)
Estimated Numbers of Subjects
 $\varepsilon_p = 0.02, \Delta = 0.05$

$\sigma_{WR} = \sigma_{WT}$	$\sigma_{BR} = \sigma_{BT}$	80% Power	90% Power
0.15	0.15	18	22
	0.30	24	32
0.23	0.23	22	28
	0.46	24	32
0.30	0.30	22	28
	0.60	26	34
0.50	0.50	22	28
	1.00	26	34

Results for population BE are approximate from simulation studies (1,540 simulations for each parameter combination), assuming two-sequence, four-period trials with a balanced design across sequences.

Table 3
Individual Bioequivalence
Estimated Numbers of Subjects
 $\varepsilon_I = 0.05, \Delta = 0.05$

$\sigma_{WT} =$	$\sigma_D =$	80% Power		90% Power	
		3P	4P	3P	4P
0.15	0.01	14	10	18	12
	0.10	18	14	24	16
	0.15	28	22	36	26
0.23	0.01	42	22	54	30
	0.10	56	30	74	40
	0.15	76	42	100	56
0.30	0.01	52	28	70	36
	0.10	60	32	82	42
	0.15	76	42	100	56
0.50	0.01	52	28	70	36
	0.10	60	32	82	42
	0.15	76	42	100	56

Results for individual BE are approximate using simulations (5,000 simulations for each parameter combination). The designs used in simulations are RTR/TRT (3P) and RTRT/TRTR (4P) assuming two-sequence trials with a balanced design across sequences.

While the above sample sizes assume within-subject standard deviations, simulation studies for 3-period and 4-period designs reveal that if $\Delta = 0$ and $\sigma_{WT}^2 - \sigma_{WR}^2 = 0.05$, the sample sizes given will provide either 80% or 90% power for these studies.

To maintain consistency with FDA requirements, which specify a minimum of 12 subjects in all BE studies, the one case above where $n=10$ for 80% power should be increased to $n=12$.



Table 4
Individual Bioequivalence
Estimated Numbers of Subjects

$\varepsilon_1 = 0.05, \Delta = 0.10$

With Constraint on Δ ($0.8 \leq \exp(\Delta) \leq 1.25$)

		80% Power	90% Power
$\sigma_{WT} =$	$\sigma_D =$	4P	4P
0.30	0.01	30	40
	0.10	36	48
	0.15	42	56
0.50	0.01	34	46
	0.10	36	48
	0.15	42	56

Results for individual BE are approximate using simulations (5,000 simulations for each parameter combination). The designs used in simulations are RTRT/TRTR (4P), assuming two-sequence trials with a balanced design across sequences. When $\Delta = 0.05$, sample sizes remain the same as given in Table 3. This is because the studies are already powered for variance estimation and inference, and therefore, a constraint on the point estimate Δ has little influence on the sample size for small values of Δ .



Appendix B.

Assessing ABE, PBE and IBE using SAS

```

/*****
/*
/*          SAS Code for Assessing ABE, IBE and PBE          */
/*          in Replicate Cross-over Trials                    */
/*
/*          Jones and Kenward (2003) code                    */
/*          modified by W. McCarthy for this protocol        */
/*          log(AUC) Model shown                             */
*****/

data bio2x4;
input subject sequence$ period form$ AUC CMAX;
logauc=log(AUC);
logcmax=log(CMAX);
datalines;
1 RTRT 1 R 5269 1366
1 RTRT 2 T 3848 1251
1 RTRT 3 R 3262 922
1 RTRT 4 T 4140 1101
. . . . .
. . . . .
. . . . .
29 TRTR 1 T 2142 488
29 TRTR 2 R 1517 292
29 TRTR 3 T 2348 555
29 TRTR 4 R . .
;
run;
title 'data';
run;
title 'ABE, PBE and IBE for AUC, UNstructured covariance matrix,
KR adjusted df';
run;
proc mixed data=bio2x4 method=reml ITDETAILS CL=WALD ALPHA=0.1
          scoring=50 maxiter=200 IC ASYCOV;
class sequence subject period form;
model logauc=sequence period form/ddfm=kenwardroger;
random form/type=UN subject=subject G;
repeated/group=form subject=subject;
lsmeans form/pdiff cl alpha=0.1;
estimate 'T-R'
form 1 -1 /CL ALPHA=0.1;
ods output Estimates=BLUEUN CovParms=COVUN AsyCov=ascovun;
run;
data covdun (keep=delta2 asigdel);
set blueun;
delta2=ESTIMATE*ESTIMATE;
asigdel=STDERR*STDERR;

```

```

run;
data covunBT (keep=l_BT l_BTxw l_BTxBR l_BTxWT l_BTxWR);
set ascovun;
if COVPARAM='UN(2,2)';
l_BT=COVP3; l_BTxw=COVP2;
l_BTxBR=COVP1; l_BTxWT=COVP5;
l_BTxWR=COVP4;
run;
data covunw (keep=l_w l_BRxw l_wxWT l_wxWR);
set ascovun;
if COVPARAM='UN(2,1)';
l_w=COVP2;
l_BRxw=COVP1;
l_wxWT=COVP5;
l_wxWR=COVP4;
run;
data covunBR (keep=l_BR l_BRxWT l_BRxWR);
set ascovun;
if COVPARAM='UN(1,1)';
l_BR=COVP1;
l_BRxWT=COVP5;
l_BRxWR=COVP4;
run;
data covunWT (keep=l_WT l_WTxWR);
set ascovun;
if COVPARAM='Residual' and Row=5;
l_WT=COVP5;
l_WTxWR=COVP4;
run;
data covunWR (keep=l_WR);
set ascovun;
if COVPARAM='Residual' and Row=4;
l_WR=COVP4;
run;
data blueUN (keep=undiff unlow unup unratio unrlow unrup);
set blueun;
undiff=ESTIMATE;
unratio=exp(undiff);
unlow=LOWER;
unrlow=exp(unlow);
unup=UPPER;
unrup=exp(unup);
run;
data bsigaun (keep=bsdaun bsigaun);
set covun; if
substr(COVPARAM,1,6)='UN(2,2)';
bsigaun=ESTIMATE;
bsdaun=SQRT(ESTIMATE);
run;
data bsigbun (keep=bsdbun bsigbun);
set covun;
if substr(COVPARAM,1,6)='UN(1,1)';
bsigbun=ESTIMATE;
bsdbun=SQRT(ESTIMATE);

```

```

run;
data wsigaun (keep=wsdaun wsigaun);
set covun;
if substr(GROUP,6,1)='T';
wsigaun=ESTIMATE;
wsdaun=SQRT(ESTIMATE);
run;
data wsigbun (keep=wsdbun wsigbun);
set covun;
if substr(GROUP,6,1)='R';
wsigbun=ESTIMATE;
wsdbun=SQRT(ESTIMATE);
run;
data covun (keep=covun);
set covun;
if substr(COVPARM,1,6)='UN(2,1)';
covun=ESTIMATE;
run;
data covun (keep=bsigaun bsdaun bsigbun bsdbun covun wsigaun
wsdaun wsigbun wsdbun sigdun rhoun);
merge bsigaun bsigbun wsigaun wsigbun covun;
sigdun=bsigaun+bsigbun-(2*covun);
rhoun=covun/(bsdaun*bsdbun);
run;
data ascovun (keep=v_ibeun v_cibeun f_ibeun f_cibeun ubibeun
ubcibeun v_pbeun v_cpbeun f_pbeun f_cpbeun ubpbeun
ubcpbeun);
merge covdun covunBT covunw covunBR covunWT covunWR covun;
theta=((log(1.25))**2)+0.05)/0.04;
thetap=((log(1.25))**2)+0.02)/0.04;

v_ibeun=delta2+sigdun+wsigaun-((1+theta)*wsigbun);
v_cibeun=delta2+sigdun+wsigaun-wsigbun-(0.04*theta);
f_ibeun=(4*asigdel*delta2)+l_BT+l_BR+(4*l_w)+l_WT+((1+theta)
*(1+theta)*l_WR)+(2*l_BTxBR)-(4*l_BT*xw)+(2*l_BTxWT)-
(2*(1+theta)*l_BTxWR)-(4*l_BRxw)+(2*l_BRxWT)-(2*(1+theta)*
l_BRxWR)-(4*l_wxWT)+(4*(1+theta)*l_wxWR)-(2*(1+theta)*
l_WTxWR);
f_cibeun=(4*asigdel*delta2)+l_BT+l_BR+(4*l_w)+l_WT+l_WR+(2*l_BTxBR)-
(4*l_BRxw)+(2*l_BRxWT)-(2*l_BRxWR)-(4*l_wxWT)+(4*l_wxWR)-
(2*l_WTxWR);
ubibeun=v_ibeun+((probit(0.95))*sqrt(f_ibeun));
ubcibeun=v_cibeun+((probit(0.95))*sqrt(f_cibeun));

v_pbeun=delta2+bsigaun+wsigaun-((1+thetap)*(wsigbun+bsigbun));
v_cpbeun=delta2+bsigaun+wsigaun-(wsigbun+bsigbun)-(0.04*thetap);
f_pbeun=(4*asigdel*delta2)+l_BT+l_WT+((1+thetap)*(1+thetap)*l_BR)+
((1+thetap)*(1+thetap)*l_WR)+(2*l_BTxWT)-
(2*(1+thetap)*l_BTxBR)
-(2*(1+thetap)*l_BTxWR)-(2*(1+thetap)*l_BRxWT)-(2*(1+thetap)
*l_WTxWR)+(2*(1+thetap)*(1+thetap)*l_BRxWR);
f_cpbeun=(4*asigdel*delta2)+l_BT+l_WT+l_BR+l_WR+(2*l_BTxWT)-(2*l_BTxBR)
-(2*l_BTxWR)-(2*l_BRxWT)-(2*l_WTxWR)+(2*l_BRxWR);
ubpbeun=v_pbeun+((probit(0.95))*sqrt(f_pbeun));

```

```

ubcpbeun=v_cpbeun+((probit(0.95))*sqrt(f_cpbeun));
run;
proc print data=ascovun;
var ubibeun ubcibeun ubpbeun ubcpbeun;
run;

```

Example of Edited Results from SAS OUTPUT

	Upper bound 90% CI For FDA IBE Criterion	Upper bound 90% CI For FDA PBE Criterion	TOST CI For FDA ABE
log(AUC _{0-t})	-0.0603	-0.2392	0.8477, 0.9848
log(AUC _{0-inf})	-0.0408	-0.1985	0.8200, 0.9600
log(Cmax)	-0.0549	-0.1904	0.7804, 0.9516
	IBE claimed	PBE claimed	ABE not claimed

If upper bound for 90% CI for FDA IBE criterion for both log(AUC) and log(Cmax) are below zero, IBE can be claimed.

If upper bound for 90% CI for FDA PBE criterion for both log(AUC) and log(Cmax) are below zero, PBE can be claimed.

If TOST CI for both log(AUC) and log(Cmax) are contained within the limits of 0.80 to 1.25, ABE can be claimed.



References

Guidance for Industry, Statistical Approaches to Establishing Bioequivalence. U.S. Department of health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). January 2001.

Jones B and Kenward MG (2003). Design and Analysis of Cross-Over Trials, Second Edition. Chapman & Hall/CRC, New York.

Machado S, Miller R and Hu C (1999). A Regulatory Perspective on Pharmacokinetic and Pharmacodynamic Modelling. *Statistical Methods in Medical Research*, 8: 217-245.

Patterson SD and Jones B (2002a). Bioequivalence and the Pharmaceutical Industry. *Pharmaceutical Statistics*, 1:83-95.

Patterson SD and Jones B (2002b). Replicated Designs and Average, Individual, and Population Bioequivalence. GlaxoSmithKline BDS Technical Report 2002-05, 11 December 2002.

Schuurmann DJ (1981). On hypothesis testing to determine if the mean of a normal distribution is contained in a known interval. *Biometrics* 37:617.

Schuurmann DJ (1987). A comparison of the two one sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokin. Biopharm.* 15: 657-680.

