US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

New Drug Application

Biometrics Division: VI

NDA NO.:	204412
DATE RECEIVED BY OB:	03/31/2015
DRUG NAME:	Delzicol(mesalamine) delayed release capsules
INDICATION:	Treatment Of Mildly To Moderately Active Ulcerative Colitis; Maintenance Of Remission Of Ulcerative Colitis.
SPONSOR:	Warner Chilcott
REVIEW FINISHED:	07/31/2015
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1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1.1 Purpose of this review

On March 31, 2015, Office of Clinical Pharmacology (OCP) requests CMC statistics team in the Office of Biostatistics (OB) to evaluate Warner Chilcott Company's 5-period crossover bioequivalence trial for the relative bioavailability of a new Delzicol (mesalamine) delayed release formulation WC3079 vs. the approved Delzicol 400 mg formulation. The sponsor proposed to remove the food-effect period and then collapse the 5-period design into a 4-period design. Particularly, OCP requests OB to conduct analyses without removing the food-effect period for the bioequivalence portion of the study (primary objective) in order to determine if this approach by the sponsor has affected the outcomes of the BE analysis.

1.2 Sponsor's crossover design

In order to evaluate the bioavailability of Delzicol delayed-release capsules, 400 mg, vs Asacol (mesalamine) delayed-release tablets, 400mg, a 4-sequence, 5-period, 3-treatment crossover study was conducted. The specific design is shown in **Table 1**,

Table 1: Study Design

	Period p_j				
Sequence g_i	1	2	3	4	5
1	Trt_1	Trt_3	Trt_2	Trt_1	Trt_2
2	Trt_2	Trt_1	Trt_2	Trt_3	Trt_1
3	Trt_1	Trt_2	Trt_3	Trt_1	Trt_2
4	Trt_2	Trt_1	Trt_3	Trt_2	Trt_1

Trt_1 = Asacol, fasted; Trt_2 = Delzicol, fasted; Trt_3 = Delzicol, fed

Note that we denote the population mean of Delzicol as μ_T , fasted and denote the population mean of Asacol as μ_R in the following sections.

1.3 FDA's information requests and the sponsor's responses to FDA IRs

During the review cycle, FDA (CMC statistics team) sent multiple information requests to the sponsor in order to facility the review.

On April 22, 2015, FDA sent out information request below,

"With regard to NDA 204412/S-006, it appears that during your statistical analyses to test for bioequivalence under fasting conditions, you've re-numbered periods by removing the fed-treatment period. A similar approach was used in the analysis to evaluate the food-effect. This assumes absence of a period effect. In this regard, we recommend that you repeat the statistical analyses for each of the two objectives without eliminating periods. Please submit your new

analyses and conclusions within two weeks after receipt of this information request. If this date cannot be met, please contact us as soon as possible."

On April 30, 2015, the sponsor submitted their request for clarification,

"For the 2 objectives, bioequivalence (BE) of Delzicol vs Asacol, and food effect of fed vs fasted Delzicol, the relevant PK parameters are analyzed in 2 different ways:

1. Reference-scaled BE, the primary analysis discussed in the body of the CSR, and the correct model given the high variability (the within-reference SD > 0.294 for all parameters, corresponding to CV > 30%)
2. Unscaled average BE, which is not correct given the high variability, but is the standard model under low variability: these additional analyses are provided only in after-text tables and not discussed in the CSR

The CSR for study PR-07513 only discusses the reference-scaled approach and all conclusions are based on these models. The study was powered under these assumptions as well, so the protocol developers were aware at that time that these drugs are highly variable, and as such, followed the guidance for highly variable drug products, described here:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm209294.pdf

By the nature of the reference-scaled approach, each patient's individual log PK scores for the 5 periods are reduced to a single term for the respective BE and FE models:

1. Bioequivalence of Delzicol vs Asacol:

T_{ijk} = kth observation (k = 1 or 2) on T for subject j within sequence i

R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i

$$I_{ij} = \frac{T_{ij1} + T_{ij2}}{2} - \frac{R_{ij1} + R_{ij2}}{2}$$

2. Food effect of fed vs fasted Delzicol:

T_{ij} = the observation on T for subject j within sequence i

R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i

$$I_{ij} = T_{ij} - \frac{R_{ij1} + R_{ij2}}{2}$$

The ANOVA models used in this approach cannot contain either treatment or period (or carryover), since each patient's data is reduced to a single term for each respective model. The ANOVA models only controls for sequence per the guidance.

Request for Clarification of the statistical information request:

We would like to request clarification of which model part 1 of the information request refers to. If the statistical reviewer's question pertains to the reference-scaled BE model, treatment or period cannot be added to the reference scaled-model and therefore we would like to verify if the information request in part 2 of the information request (pdf attachment) is relevant since the estimators outlined in the pdf attachment, treatment and period, are not applicable to the reference scaled-model.

Please confirm the statistical reviewer's main objective of the information request. Is the goal of the fulfillment of the statistical information request to support the study data analysis conclusion that there was a lack of carryover effect?"

On May 11, 2015, we sent out our clarification below:

"Since Delzicol is a highly variable drug, use of the reference-scaled average BE approach is appropriate. However, the methods in the reference-scaled average BE guidance are only applicable to the particular designs (with balanced periods) as specified in that guidance, and not to any other designs. For those particular designs, the estimator for the treatment difference between the test and the reference is unbiased even if no carryover effect is assumed. Because your design is different from those specified in the reference-scaled average BE guidance, your estimator for the treatment difference between the test and the reference is biased when you assume no carryover effect. You must therefore find the unbiased estimator for the treatment difference between the test and the reference without any assumption of the period effect. Please refer to the previous communication for details on the appropriate methods."

On May 28, 2015, the sponsor submitted their response to information request. They provided their methods in terms of statistical formula.

For the bioavailability analysis, the sponsor removed Trt_3, as shown in Table 2,

Table 2: Study Design excluding $\mathbf{Trt_3}$

	Period p_j				
Sequence g_i	1	2	3	4	5
1	Trt_1	~~Trt_3~~	Trt_2	Trt_1	Trt_2
2	Trt_2	Trt_1	Trt_2	~~Trt_3~~	Trt_1
3	Trt_1	Trt_2	~~Trt_3~~	Trt_1	Trt_2
4	Trt_2	Trt_1	~~Trt_3~~	Trt_2	Trt_1

Trt_1 = Asacol, fasted; Trt_2 = Delzicol, fasted; ~~Trt_3 = Delzicol, fed~~

The statistical model for response y_{ijk}, sample means, and expectations are given below:

$$y_{ijk} = \tau + \mu_{(j,i)} + g_i + pj + c_{(j-1,i)} + s_{ki} + \epsilon_{ijk}$$

$$\bar{y}_{ij.} = \frac{\sum_{k=1}^{n_i} y_{ijk}}{n_i}, \text{ sample mean for sequence } i \text{ in period } j$$

$$E\left[y_{ijk}\right] = \tau + \mu_{(j,i)} + g_i + pj + c_{(j-1,i)}$$

where

y_{ijk} = response of subject k in sequence i and period j
$i \in \{1,2,3,4\}, j \in \{1,2,3,4,5\}, k \in \{1,2,\ldots,n_i\}$

τ = overall mean effect

$\mu_{(j,i)}$ = direct effect of treatment in sequence i and period j

g_i = fixed effect of sequence i

p_j = fixed effect of period j

$c_{(j-1,i)}$ = fixed effect of first-order carryover of treatment in sequence i from period $j-1$ for $j \in \{2,3,4,5\}$; we assume no higher-order carryover effects

s_{ki} = between-subject random effect, subject within sequence i

ϵ_{ijk} = within-subject random error for response y_{ijk}

n_i = number of subjects randomized to sequence i

The sample means and their expectations for the sequence-by-period cells are given in Table 1

Table 3, sample means and expected values by sequence and period

	Period p_j				
Sequence g_i	1	2	3	4	5
1	$\bar{y}_{11.}$ $\tau+\mu_1+g_1+p_1$	$\bar{y}_{12.}$ $\tau+\mu_3+g_1+p_2+c_1$	$\bar{y}_{13.}$ $\tau+\mu_2+g_1+p_3+c_3$	$\bar{y}_{14.}$ $\tau+\mu_1+g_1+p_4+c_2$	$\bar{y}_{15.}$ $\tau+\mu_2+g_1+p_5+c_1$
2	$\bar{y}_{21.}$ $\tau+\mu_2+g_2+p_1$	$\bar{y}_{22.}$ $\tau+\mu_1+g_2+p_2+c_2$	$\bar{y}_{23.}$ $\tau+\mu_2+g_2+p_3+c_1$	$\bar{y}_{24.}$ $\tau+\mu_3+g_2+p_4+c_2$	$\bar{y}_{25.}$ $\tau+\mu_1+g_2+p_5+c_3$
3	$\bar{y}_{31.}$ $\tau+\mu_1+g_3+p_1$	$\bar{y}_{32.}$ $\tau+\mu_2+g_3+p_2+c_1$	$\bar{y}_{33.}$ $\tau+\mu_3+g_3+p_3+c_2$	$\bar{y}_{34.}$ $\tau+\mu_1+g_3+p_4+c_3$	$\bar{y}_{35.}$ $\tau+\mu_2+g_3+p_5+c_1$
4	$\bar{y}_{41.}$ $\tau+\mu_2+g_4+p_1$	$\bar{y}_{42.}$ $\tau+\mu_1+g_4+p_2+c_2$	$\bar{y}_{43.}$ $\tau+\mu_3+g_4+p_3+c_1$	$\bar{y}_{44.}$ $\tau+\mu_2+g_4+p_4+c_3$	$\bar{y}_{45.}$ $\tau+\mu_1+g_4+p_5+c_2$

Based on this study design, the naïve estimator for $\mu_2 - \mu_1$, $\widehat{D}_1$ and expected value, $\mathrm{E}[\widehat{D}_1]$ are respectively given below,

$$\hat{D}_1 = \frac{1}{4}\begin{bmatrix} +\left(\frac{\bar{y}_{13.}+\bar{y}_{15.}}{2}\right) & - & \left(\frac{\bar{y}_{11.}+\bar{y}_{14.}}{2}\right) \\ +\left(\frac{\bar{y}_{21.}+\bar{y}_{23.}}{2}\right) & - & \left(\frac{\bar{y}_{22.}+\bar{y}_{25.}}{2}\right) \\ +\left(\frac{\bar{y}_{32.}+\bar{y}_{35.}}{2}\right) & - & \left(\frac{\bar{y}_{31.}+\bar{y}_{34.}}{2}\right) \\ +\left(\frac{\bar{y}_{41.}+\bar{y}_{44.}}{2}\right) & - & \left(\frac{\bar{y}_{42.}+\bar{y}_{45.}}{2}\right) \end{bmatrix} = \frac{1}{4}\left(\frac{1}{2}\right)\begin{bmatrix} -\bar{y}_{11.} & & +\bar{y}_{13.} & -\bar{y}_{14.} & +\bar{y}_{15.} \\ +\bar{y}_{21.} & -\bar{y}_{22.} & +\bar{y}_{23.} & & -\bar{y}_{25.} \\ -\bar{y}_{31.} & +\bar{y}_{32.} & & -\bar{y}_{34.} & +\bar{y}_{35.} \\ +\bar{y}_{41.} & -\bar{y}_{42.} & & +\bar{y}_{44.} & -\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_1\right] = (\mu_2 - \mu_1) + \frac{1}{8}(-p_2 + 2p_3 - p_4) + \frac{1}{2}(c_1 - c_2)$$

.

The sponsor also proposed another design excluding more cells in the original design in order to use the guidance method on partial reference-replicated 3-way design. The naïve estimator for$\mu_2 - \mu_1$, $\widehat{D}_{1B}$ and expected value, E[$\widehat{D}_{1B}$] are giving below,

$$\hat{D}_{1B} = \frac{1}{4}\begin{bmatrix} +\left(\bar{y}_{15.} & - & \frac{\bar{y}_{11.}+\bar{y}_{14.}}{2}\right) \\ +\left(\bar{y}_{21.} & - & \frac{\bar{y}_{22.}+\bar{y}_{25.}}{2}\right) \\ +\left(\bar{y}_{32.} & - & \frac{\bar{y}_{31.}+\bar{y}_{34.}}{2}\right) \\ +\left(\bar{y}_{44.} & - & \frac{\bar{y}_{42.}+\bar{y}_{45.}}{2}\right) \end{bmatrix} = \frac{1}{4}\left(\frac{1}{2}\right)\begin{bmatrix} -1\bar{y}_{11.} & & -1\bar{y}_{14.} & +2\bar{y}_{15.} \\ +2\bar{y}_{21.} & -1\bar{y}_{22.} & & -1\bar{y}_{25.} \\ -1\bar{y}_{31.} & +2\bar{y}_{32.} & -1\bar{y}_{34.} & \\ & -1\bar{y}_{42.} & +2\bar{y}_{44.} & -1\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_{1B}\right] = (\mu_2 - \mu_1) + \frac{1}{2}(c_1 - c_2)$$

On June 8, 2015, FDA sent out the information request as below,

"For the BE evaluation, your unbiased estimate is incorrect because it appears that you intentionally take away some observations for the test product (See Page 5 in your response). It is possible to find an unbiased estimator with all observations in Periods 1, 2, 4, and 5. It is acceptable to remove the observations in Period 3. Find another unbiased estimator for the treatment difference and submit the mathematical and statistical formulas and SAS codes for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$ *."*

On June 11, 2015, FDA sent out the information request regarding the unbalanced number of number of nonzero concentrations (⩽3) for the reference product than those for the test product,

"1)

*Table **4** shows that there are more cases with the small number of nonzero concentrations (⩽3) for the reference product than those for the test product.*

Can you scientifically justify the observed differences?

How do you justify your analysis to support the equivalence between the reference product and the test product when 23% of subjects have at least one case with the small number of nonzero concentration (⩽3)?

2)

*Table **5** shows that the naïve biased estimate for* μ_T / μ_R *in the subgroup with >3 nonzero concentrations is 0.72, which is much smaller than 0.96 if all observations are included. In other words, the geometric mean of the responding subjects with >3 nonzero concentrations in the test group is too small compared to that of the responding subjects in the reference group.*

How do you assure the efficacy of the test product for the responding subgroup with >3 nonzero concentrations since the equivalence trial does not address either the efficacy or the safety issue?

Table 4: Distribution of the number of nonzero concentrations

Number of nonzero concentrations	*Number of subjects*	
	Reference	*Test*
0	*15*	*2*
≤1	*17*	*8*
≤2	*20*	*9*
≤3	*26*	*12*

Table 5: Sample mean and sample standard deviation of log(AUC) of the subgroup with >3 nonzero concentrations for each treatment

Treatment	*Number of subjects*	*Sample mean of log(AUC)*	*Sample standard deviation of log(AUC)*
R1 (first trt1 in each sequence)	*112*	*6.662*	*0.730*
R2 (second trt1 in each sequence)	*112*	*6.716*	*0.677*
T1(first trt2 in each sequence)	*112*	*6.417*	*0.703*
T2 (second trt2 in each sequence)	*112*	*6.308*	*0.854*

”

The sponsor submitted their response on June 24, 2015.

“Sponsor Response to questions 1:

The reference product (Asacol tablets, 400mg) and test product (WC3079, 4x100 mg) utilize a delayed-release pH-dependent delivery system to release the drug in the lower gastrointestinal tract (mostly in the colon). Given the typically lower volumes of fluid present in the colon and variable pH profiles & gastric transit times of the GI tract between and within patients, the release of the drug is expected to be somewhat variable and possibly incomplete at times. The use of 4 tablets (100 mg each) of the test product as compared to a single tablet of the reference product, is expected to provide a more robust release profile. This is based on the understanding

that the drug release from 4 units should buffer against any inherent variability and result in a more uniform profile as compared to release from a single unit.

Sponsor Response to questions 2:

The BE analysis was a prospectively planned statistical analysis, in compliance with the "Statistical Approaches to Establishing Bioequivalence" guidance from the FDA. Although there are more cases with a small number of nonzero concentrations ($\leqslant 3$) for the reference product compared to the test product, removing these data from either group cannot be justified since it is probably a reflection of observations in a real-world setting and since, as per the above-referenced guidance, deletion of outlier data, e.g. subjects with 0-3 measurable concentrations, is generally discouraged in pivotal BE studies. Deleting the observed data from subjects with only 0-3 measurable concentrations results in a biased overestimation of the mean for the reference product as compared to the test product.

Sponsor Response to questions 3:

As noted in the response above, removing the data from subjects with <=3 concentrations cannot be justified; this results in a biased overestimation of the reference product mean which does not reflect a real-world setting. Based on the prespecified analysis and in accordance with recommendations in the FDA guidance "Statistical Approaches to Establishing Bioequivalence", there is no significant difference in overall exposure between the test and reference products."

On June 24, 2015, FDA sent out the information request as follows,

"Since your study is not properly designed to obtain unbiased estimate of treatment difference, you may only be able to obtain unbiased estimate by using a fraction of the data collected in the study. However, there may be various ways to achieve this objective. Please provide all the possible unbiased estimators for the treatment difference without removing any of the treatments from Periods 1, 2, 4, 5. Justify the unbiased estimators in terms of mathematical and statistical formulas and conduct hypothesis testing using all unbiased estimators. Submit the mathematical and statistical formulas, SAS codes for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$ *and the SAS output to support bioequivalence. Submit this information within 3 weeks. "*

On July 1, 2015, we had a TCON with the sponsor. After the teleconference, FDA sent out another information request, "Since you are proposing modeling approach for estimation, please provide both analyses for only fasted data and the combined data of the fasted and fed studies" on July 7, 2015

On July 15, 2105, the sponsor submitted their response with another four modified design and estimators. The sponsor removed the third period, and the naïve estimator for$\mu_2 - \mu_1$, $\widehat{D}_{1C}$ and expected value, E[$\widehat{D}_{1C}$] are giving below,

$$\hat{D}_{1C} = \frac{1}{5}\begin{bmatrix} +\left(\bar{y}_{15.} - \frac{\bar{y}_{11.}+\bar{y}_{14.}}{2}\right) \\ +\left(\bar{y}_{21.} - \frac{\bar{y}_{22.}+\bar{y}_{25.}}{2}\right) \\ +\left(\frac{2\bar{y}_{32.}+\bar{y}_{35.}}{2} - \frac{2\bar{y}_{31.}+\bar{y}_{34.}}{2}\right) \\ +\left(\frac{\bar{y}_{41.}+2\bar{y}_{44.}}{2} - \frac{\bar{y}_{42.}+2\bar{y}_{45.}}{2}\right) \end{bmatrix} = \frac{1}{5}\left(\frac{1}{2}\right)\begin{bmatrix} -1\bar{y}_{11.} & & -1\bar{y}_{14.} & +2\bar{y}_{15.} \\ +2\bar{y}_{21.} & -1\bar{y}_{22.} & & -1\bar{y}_{25.} \\ -2\bar{y}_{31.} & +2\bar{y}_{32.} & -1\bar{y}_{34.} & +1\bar{y}_{35.} \\ +1\bar{y}_{41.} & -1\bar{y}_{42.} & +2\bar{y}_{44.} & -2\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_{1C}\right] = (\mu_2 - \mu_1) + \frac{1}{2}(c_1 - c_2)$$

For the fourth estimator, the sponsor kept all the cells in the design. The naïve estimator for$\mu_2 - \mu_1$, $\widehat{D}_{1D}$ and expected value, E[$\widehat{D}_{1D}$] are giving below,

$$\hat{D}_{1D} = \frac{1}{5}\begin{bmatrix} +\left(\frac{\bar{y}_{13.}+\bar{y}_{15.}}{2} - \frac{3\bar{y}_{11.}+3\bar{y}_{14.}}{4} + \frac{\bar{y}_{12.}}{2}\right) \\ +\left(\frac{\bar{y}_{21.}+\bar{y}_{23.}}{2} - \frac{3\bar{y}_{22.}+3\bar{y}_{25.}}{4} + \frac{\bar{y}_{24.}}{2}\right) \\ +\left(\frac{3\bar{y}_{32.}+3\bar{y}_{35.}}{4} - \frac{\bar{y}_{31.}+\bar{y}_{34.}}{2} - \frac{\bar{y}_{33.}}{2}\right) \\ +\left(\frac{3\bar{y}_{41.}+3\bar{y}_{44.}}{4} - \frac{\bar{y}_{42.}+\bar{y}_{45.}}{2} - \frac{\bar{y}_{43.}}{2}\right) \end{bmatrix} = \frac{1}{5}\left(\frac{1}{4}\right)\begin{bmatrix} -3\bar{y}_{11.} & +2\bar{y}_{12.} & +2\bar{y}_{13.} & -3\bar{y}_{14.} & +2\bar{y}_{15.} \\ +2\bar{y}_{21.} & -3\bar{y}_{22.} & +2\bar{y}_{23.} & +2\bar{y}_{24.} & -3\bar{y}_{25.} \\ -2\bar{y}_{31.} & +3\bar{y}_{32.} & -2\bar{y}_{33.} & -2\bar{y}_{34.} & +3\bar{y}_{35.} \\ +3\bar{y}_{41.} & -2\bar{y}_{42.} & -2\bar{y}_{43.} & +3\bar{y}_{44.} & -2\bar{y}_{45.} \end{bmatrix}$$

$$E\left[\hat{D}_{1D}\right] = (\mu_2 - \mu_1) + \frac{1}{2}(c_1 - c_2)$$

In addition to the estimators above, the sponsor provides two estimators based on the standard average bioequivalence MMRM model, $\widehat{D}_{1E}$, based on all data and $\widehat{D}_{1F}$, excluding fed data.

Table 6 shows the ranges of the geometric mean ratio and linearized upper confidence bound estimates over the presented estimators for each parameter obtained by the sponsor.

Table 6: Ranges of Geometric Mean Ratio and Linearized Upper Confidence Bound Estimates over Estimators by Parameter

	Ratio		LUCB	
Parameter	Min	Max	Min	Max
C_{max}	111.88	119.10	-1.138	-1.077
AUC_{8-48}	93.24	97.41	-1.583	-1.531
AUC_{0-tldc}	102.09	106.22	-1.573	-1.525
AUC_{0-inf}	84.97	94.78	-0.256	-0.189

Ratio = geometric mean ratio Trt2/Trt1; LUCB = linearized upper confidence bound.

1.4 Statistical issues

There are multiple statistical issues from the sponsor's crossover design and the response to the FDA IRs:

1. Imbalance of the number of zero profiles in WC3079 (test) and Asacol (reference)

As we pointed out in the information request dated on June 11, 2015, there are more cases with the small number of nonzero concentrations ($\leqslant 3$) for the reference product than those for the test product (see Table 4).

2. The naïve biased estimate for μ_T / μ_R in the subgroup with >3 nonzero concentrations smaller than 0.8

   From Table 5, the naïve biased estimate for μ_T / μ_R in the subgroup with >3 nonzero concentrations is 0.72, which is smaller than 0.8 (point estimate criteria in Scaled-average BE) and is much smaller than 0.96 if all observations are included. Hence, the geometric mean of the responding subjects with >3 nonzero concentrations in the test group is too small compared to that of the responding subjects in the reference group.

3. Design flaw and biased estimator $\widehat{\mathrm{D}}_1$

   The sponsor made a strong assumption of zero or equal period effect. The methods in the reference-scaled average BE guidance [1] do not have the assumption of zero or equal period effect. Hence, the sponsor cannot make such assumptions. The sponsor must provide the theoretical proof for zero or equal period effect if the sponsor uses the guidance method. If the sponsor could not provide such proof, the estimator $\widehat{\mathrm{D}}_1$ is not an unbiased estimator which cannot be used to analyze the crossover design.

4. Partial data used in the sponsor's estimators $\widehat{\mathrm{D}}_{1\mathrm{B}}$ *and* $\widehat{\mathrm{D}}_{1\mathrm{C}}$

   The sponsor removed cells from the study design, which is not acceptable because such a modification is a way of manipulating data which will result in a favorable analysis comparing to the analysis using all the data.

5. An infinite number of unbiased estimates for the mean difference: $\mu_T - \mu_R$

   There are infinite unbiased estimators from this design and $\widehat{\mathrm{D}}_{1\mathrm{C}}$ is only one of them. In order to find the unbiased estimator $\widehat{D}$, we need to assign weights on the cells. We have the following formula,

$$\widehat{D} = \frac{1}{a_{15}+a_{21}+a_{32}+a_{35}+a_{41}+a_{44}} \begin{bmatrix} +(a_{15}\bar{y}_{15} - a_{11}\bar{y}_{11} - a_{14}\bar{y}_{14}) \\ +(a_{21}\bar{y}_{21} - a_{22}\bar{y}_{22} - a_{25}\bar{y}_{25}) \\ +(a_{32}\bar{y}_{32} + a_{35}\bar{y}_{35} - a_{31}\bar{y}_{31} - a_{34}\bar{y}_{34}) \\ +(a_{41}\bar{y}_{41} + a_{44}\bar{y}_{44} - a_{42}\bar{y}_{42} - a_{45}\bar{y}_{45}) \end{bmatrix}$$

$$= \frac{1}{a_{15}+a_{21}+a_{32}+a_{35}+a_{41}+a_{44}} \begin{bmatrix} -a_{11}\bar{y}_{11} & & -a_{14}\bar{y}_{14} & +a_{15}\bar{y}_{15} \\ +a_{21}\bar{y}_{21} & -a_{22}\bar{y}_{22} & & -a_{25}\bar{y}_{25} \\ -a_{31}\bar{y}_{31} & +a_{32}\bar{y}_{32} & -a_{34}\bar{y}_{34} & +a_{35}\bar{y}_{35} \\ +a_{41}\bar{y}_{41} & -a_{42}\bar{y}_{42} & +a_{44}\bar{y}_{44} & -a_{45}\bar{y}_{45} \end{bmatrix}$$

$$\mathrm{E}\left[\widehat{D}\right] = \mu_T - \mu_R - \frac{1}{2}(c_1 - c_2)$$

   To determine the weights, we just need to solve the following equations,

$$-a_{11} - a_{14} + a_{15} = 0$$
$$a_{21} - a_{22} - a_{25} = 0$$
$$-a_{31} + a_{32} - a_{34} + a_{35} = 0$$

$$a_{41} - a_{42} + a_{44} - a_{45} = 0$$
$$-a_{11} + a_{21} - a_{31} + a_{41} = 0$$
$$-a_{22} + a_{32} - a_{42} = 0$$
$$-a_{14} - a_{34} + a_{44} = 0$$
$$a_{15} - a_{25} + a_{35} - a_{45} = 0$$

Since there are night equations and fourteen variables, the system of equations has infinitely many solutions.

Not all the estimators from this design can be between 80%-125%. For example, if we chose weights for the cells as follows,

$$\begin{bmatrix} -\bar{y}_{11} & & -6\bar{y}_{14} & +2\bar{y}_{15} \\ +3\bar{y}_{21} & -1\bar{y}_{22} & & -2\bar{y}_{25} \\ -3\bar{y}_{31} & +11\bar{y}_{32} & -9\bar{y}_{34} & +1\bar{y}_{35} \\ +1\bar{y}_{41} & -10\bar{y}_{42} & +10\bar{y}_{44} & -\bar{y}_{45} \end{bmatrix}.$$

For the end point AUC, the mean difference $\bar{\mu}_T - \bar{\mu}_R$ is -0.2828571. The geometric mean ratio is 0.7536274, which is lower than 0.80. Hence, the bioequivalence cannot be concluded.

6. Food effect data used in the sponsor's estimator $\widehat{D}_{1D}$

   The sponsor kept all the cells in the original study design and derived an unbiased estimator. In FDA IR, we suggested the sponsor use all data for model fit in order to estimate the period effect and variability, etc. We did not ask the sponsor to use the food effect for estimating the contrast between the test product and reference product. Indeed, the contrast should not use any data from $\mathbf{Trt_3}$ (food effect). It is not acceptable to estimate the contrast using data from food effect between test and reference.

7. No proper formula for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$ There is no proper formula for calculating the confidence interval for , where σ_{WR}^2 is the within-subject variation for the sponsor's estimators $\widehat{D}_{1E}$ and $\widehat{D}_{1F}$.

1.5 Conclusion and recommendation

In conclusion, the original crossover design is uninterpretable and the WC3079 and Asacol responded differently. The bioequivalence cannot be concluded due to the following reasons. First, the proposed estimators will not make up for the deficiency of the design. We found one unbiased estimator using weight different the sponsor's weight, whose point estimate is smaller than 0.8. Second, there are no proper statistical methods for calculating the confidence interval for $(\mu_T - \mu_R)^2 - \theta\sigma_{WR}^2$. Third, there are more cases with the small number of nonzero concentrations (≤3) for the reference product than those for the test product and the point

estimate of μ_T / μ_R for nonzero group is 0.72. Therefore, the test product WC3097 and reference product Asacol are not bioequivalent.

Reference:

1. Draft Guidance on Progesterone.

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