



September 23, 2002

Docket Management Branch (HFA-305), Docket No. 02D-0307  
Food and Drug Administration  
5630 Fishers Lane, Room 1061 – HFA-305  
Rockville, MD, USA, 20852

SUBJECT: Comments and suggestions regarding the Potassium Chloride guidance posted August, 2002

Please find enclosed our comments and suggestions regarding the guidance for industry entitled "Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vivo Dissolution Testing".

We hope that these comments will be helpful to the FDA in the development of the final guidance. Please do not hesitate to contact us if you need any additional information.

Sincerely,

A handwritten signature in black ink, appearing to read "Josee Morin".

Josee Morin, M.Sc.  
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**Guidance for Industry**  
Potassium Chloride Modified-Release  
Tablets and Capsules: In Vivo  
Bioequivalence and In Vivo Dissolution  
Testing

**GENERAL COMMENTS**

Please find our comments in the sequence that they appear in the Guidance.

**SPECIFIC COMMENTS**

**Comment #1**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**1. Objectives**

The Draft Guidance states:

Lines 92-93 "*The objective of a single-dose bioequivalence study should be to compare the rate and extent of absorption of a generic potassium chloride formulation with that of a reference formulation.*"

Comment:

Bioequivalence between 2 formulations is proven scientifically by looking at both the rate and extent of bioavailability. Using noncompartmental pharmacokinetics on urinary data, one can look at the total amount of drug excreted unchanged over the entire period of sample collection (TAe 0-24) and the maximum excretion rate (R<sub>max</sub>). These parameters only reflect robustly the extent of bioavailability.

If needed, a compartmental pharmacokinetic analysis may allow for an accurate assessment of the rate of bioavailability, when using urinary data for KCl.

**Comment #2**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**2. Methodology**

The Draft Guidance states:

Lines 99-101 "*Extensive urine sampling for determination of urinary potassium excretion should be performed before and after each dose. Creatinine clearance should be determined to ensure that urine collection has been adequate.*"

Comment:

The criteria for ensuring that urine collection has been adequate are not defined. In addition, no guidance is given as to how to treat data when urine collection is determined to be inadequate. This should be clarified in the Guidance.

Inadequate urine collection leads to errors in volume and concentration determinations, which ultimately adversely affects the amount excreted and the rate of excretion calculations, thereby impacting the BE assessment.

**Comment #3**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**3. Inclusion/Exclusion Criteria**

The Draft Guidance states:

Line 106: *“Subjects eligible for participation should be between the ages of 20 and 40 years, within ”*

Comment:

The rationale for this narrow age limit is not clear.

Proposed change:

*“should be between the ages of 18 and 45 years,...”*

**Comment #4**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**6. Study Design**

**Diet Equilibration Days, Days 1-4 and 9-12**

The Draft Guidance states:

Lines 167-169 *“Diets should be standardized to provide the following daily intake of potassium, sodium, and calories*

*Potassium 50-60 mEq*

*Sodium 160-180 mEq*

*Calories 2500-3500”*

Comment:

If the diet is not rich enough in K<sup>+</sup>, it might create a potassium deficiency that can affect the urinary excretion of K<sup>+</sup>. This deficiency might not be the same for the two dosing periods, engendering spurious bioequivalence conclusions.

Proposed change.

The subjects should receive a rich potassium diet of 100mEq / day for the equilibration, baseline and post-dose days. If the FDA is concerned about safety, the daily requirements could be broken up by age, weight and gender.

**Comment #5**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**6. Study Design**

**Baseline Days, Days 5-6 and 13-14**

The Draft Guidance states:

Lines 191-193, 4<sup>th</sup> Bullet *“Urine collection should begin at 7 00 hours. On Day 5 and 13, subjects can dispose of this sample On Day 6 and 14, the urine collected at 7.00 hours complete the 16-24 hour sample”*

Comment:

Clarification is required

Proposed change:

“Urine collection should begin at 7:00 hours. On Day 5 and 13, subjects can dispose of this sample. On Days 6 and 14, the urine collected at 7:00 hours complete the 16-24 hour sample for Baseline days 5 and 13. On Days 7 and 15, the urine collected at 7:00 hours complete the 16-24 hour sample for Baseline days 6 and 14.

**Comment #6**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**6. Study Design**

**Baseline Days, Days 5-6 and 13-14**

The Draft Guidance states:

Line 195, 5<sup>th</sup> Bullet “Sample for creatinine clearance determination should be collected on Days 6 and 14”.

Comment:

The usual creatinine clearance formula is based on the mid-point clearance method. This means that the creatinine plasma concentration theoretically has to be taken at the mid-point interval. In addition, the FDA may want to specify that it is a plasma sample used for the determination of the creatinine clearance.

Proposed change:

Please clarify the procedure

**Comment #7**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**6. Study Design**

**Drug Dosing Days, Days 7 and 15**

The Draft Guidance states:

Line 208, 4<sup>th</sup> Bullet “*Urine collection times should be as on Days 6 and 14*”.

Comment:

It is not clear as to why Days 5 and 13 were omitted.

Proposed change:

“Urine collection times should be as on Days 5, 6, 13 and 14”.

**Comment #8**

**III. IN VIVO STUDIES**

**B. Single-Dose Bioavailability Study**

**6. Study Design**

**Post-Drug Dosing Days, Days 8 and 16**

The Draft Guidance states:

Line 220, 2<sup>nd</sup> Bullet “*Urine collection times should be as on Days 7 and 15*”.

Comment:

On post-drug dosing Days 8 and 16, it is not necessary to have the same urine collection times as dosing Days 7 and 15 since there is no dose given and the R<sub>max</sub> occurs on the dosing day (Days 7 and 15).

Proposed change:

Urine collection intervals of 24-36 and 36-48 hours should be adequate and robust BE assessment is not required for total amount excreted over 48 hours.

For the post-dose 24-36 and 36-48 hour collection intervals, the sum of the corresponding 12-hour intervals from baseline days (0-12 and 12-24 hours) should be used to adjust post-dose data.

**Comment #9**

**IV. DATA ANALYSIS**

The Draft Guidance states:

Lines 252-253, 1<sup>st</sup> paragraph: “ *Although fluctuation in the baseline are expected, differences in baseline excretion amounts for the two baseline days should not differ by more than 100 percent* ”

Comment:

The FDA should provide a rationale for this cutoff of 100%. It sure looks like a high number to us.

A less than 100% difference between the two baseline days does not appear to be a sound scientific reason to justify the use of the mean of the baseline days for adjustment. Moreover, the guidance does not specify if the 100% difference is applicable to the net day amount or by time interval.

In order to use an interval adjustment with the mean of both baseline days, the diet should be controlled to have the exact same meals for both baseline days and post-dose day. This should be sufficient to justify the use of the mean of the two baseline days.

#### **Comment #10**

#### **IV. DATA ANALYSIS**

The Draft Guidance states:

Line 255, “*The following information on urine potassium concentration data should be recorded for each subject*

- ..

Line 262-*Area under the excretion rate vs. time curve (AUCr = [(R<sub>1</sub>+R<sub>2</sub>)\*(t<sub>2</sub>-t<sub>1</sub>)/2])*

-...”

#### **Comment.**

This should be equal to the cumulative urinary excretion from 0-48 hours (Ae<sub>0-48h</sub>) which is already indicated in line 259. Therefore, we would suggest that Line 262 be removed.

Moreover, the guidance should outline which mean and individual plots should be presented in the report. In addition, it should specify if both linear and semi-log plots are required.

#### **Comment #11**

#### **IV. DATA ANALYSIS**

The Draft Guidance states:

Lines 266-270: “*All data should be calculated using baseline adjusted and non-baseline adjusted data. Statistical analysis (p=0.05) should be done by ANOVA for baseline adjusted parameters, and the 90 percent confidence intervals generated for natural log-transformed and nontransformed cumulative urinary excretion from 0-34 (Ae<sub>0-24</sub>) and maximal rate of urinary excretion data (R<sub>max</sub>)*”

Comment:

Sample processing deviations affecting volume and Not Reportable concentrations generally affect amount excreted and rate of excretion calculations whether they occur during baseline or post-dosing days. This may ultimately affect the total amount excreted and R<sub>max</sub> pharmacokinetic parameters by which BE is assessed. There is no guidance on appropriate ways to treat such data.

#### **Comment #12**

#### **IV. DATA ANALYSIS**

Comment:

Analysis of Covariance (ANCOVA) should be allowed on baseline-adjusted PK parameters as it was clearly demonstrated that no bias occurs when using the ANCOVA appropriately. The advantage of the ANCOVA is to increase the power to meet bioequivalence, but without increasing the type I error (see poster included).

**Comment #13**

**IV. DATA ANALYSIS**

Comment:

The guidance does not specify the criteria to use for the selection between the analyses on the natural log-transformed parameters and the analyses on the nontransformed parameter as main analysis to conclude on bioequivalence.

Proposed change:

Residual diagnostic should be performed and the transformation having the best normality and homogeneity of variance should be chosen as main analysis.

**Comment #14**

**Appendix A: STUDY SCHEDULE**

Comment:

We believe that samples for creatinine clearance determination should be taken on Days 9 and 17 in order to determine if urine collection was adequate on Days 8 and 16.

Also, there should be a line distinction between the 24-hour creatinine clearance determination and the timing of the plasma creatinine concentration.

# ANALYSIS OF COVARIANCE (ANCOVA) AND ANALYSIS OF VARIANCE (ANOVA) TO ASSESS BIOEQUIVALENCE (BE) OF ENDOGENOUS COMPOUNDS

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MDS Pharma Services, Université de Montréal

## ABSTRACT

### INTRODUCTION

To demonstrate BE between 2 formulations of an endogenous compound ANOVA on baseline-adjusted baseline subtracted parameters is generally performed and 90% confidence intervals are constructed. ANCOVA can also be performed when the main advantage lies in decreasing the variance.

### PURPOSE

To evaluate and compare the type I error and power between the following three methods: ANOVA performed on baseline adjusted parameters, ANCOVA performed on unadjusted parameters and ANCOVA performed on baseline adjusted parameters.

### METHODS

1000 2-way crossover studies were simulated under relative bioavailability (F<sub>r</sub>) of 1 (bioequivalent conditions: 1) and 0.75 using a one-compartment PK model. Simulations were performed with and without endogenous feedback.

### RESULTS

#### Ln AUC with Endogenous Feedback

Methods	F <sub>r</sub> ratio 1.00			F <sub>r</sub> ratio 1.30			F <sub>r</sub> ratio 0.75		
	%Base	%BE	%CV	%Base	%BE	%CV	%Base	%BE	%CV
ANOVA adj.	37	15	0	24	0	0	30	0	0
ANOVA unadj.	64	100	8	84	98	9	99	100	8
ANCOVA adj.	18	38	23	39	0	23	51	0	28

#### Ln AUC without Endogenous Feedback

Methods	F <sub>r</sub> ratio 1.50			F <sub>r</sub> ratio 1.30			F <sub>r</sub> ratio 0.75		
	%Base	%BE	%CV	%Base	%BE	%CV	%Base	%BE	%CV
ANOVA adj.	80	17	0	11	0	19	0	0	0
ANOVA unadj.	68	100	8	97	99	8	99	100	8
ANCOVA adj.	9	16	17	17	0	17	17	0	18

The mean baseline endogenous concentration was approximately 55% of the post-dose average concentration. A type I error of 5% was used. %Base and %BE refer to the percentage of studies where the baseline was statistically significant and where BE was met, respectively. %CV is the mean intra-subject coefficient of variation. Results suggest that the pre-determined 80% power was well respected for both ANOVA and ANCOVA on baseline adjusted parameters when there was no endogenous feedback. In the presence of endogenous feedback, the power decreased to 40% for both methods. When F<sub>r</sub>=1.3 or 0.75 the type I error was less than 5% in both baseline adjusted methods but approximately 100% when using the ANCOVA on unadjusted data. The introduction of the baseline as a covariate was mostly justified when a negative feedback was simulated.

### CONCLUSION

The ANCOVA on the unadjusted data should not be used to assess BE of endogenous compounds due to its high type I error. The ANCOVA on baseline adjusted parameters should be favored over the ANOVA when a significant baseline is observed, which seems to occur mostly when endogenous feedback is present.

## INTRODUCTION

In the context of bioavailability and bioequivalence assessment, adjustment of measured plasma concentrations is required following exogenous administration of an endogenous compound. A generally accepted approach to adjust the plasma concentration of the endogenous compound is to subtract a mean baseline concentration from each post-dose concentration. An analysis of variance (ANOVA) is then performed on the baseline adjusted responses to assess bioequivalence. Another sound approach is the use of an ANCOVA on the baseline adjusted or unadjusted responses.

## OBJECTIVE

To compare the following three methods of adjustment in order to determine the type I error and power:

1. ANOVA on baseline adjusted response
2. ANCOVA on unadjusted response
3. ANCOVA on baseline adjusted response

## METHODOLOGY

### SIMULATED DATA SET

- Exogenous level: Monte Carlo simulations were performed to produce 1000 treatments for each of the 1000 studies (crossover single dose studies). A standard 1-compartment model with first-order absorption and elimination was used to simulate the exogenous concentration in the data using the following equation:

$$E(t) = \frac{C_0 \cdot K_a}{K_a - K_e} \left( e^{-K_e t} - e^{-K_a t} \right)$$

$E(t)$ : the drug concentration at time  $t$   
 $C_0$ : the bioavailability (Dose on  $t=0$  divided by the initial  $K_e$  in the first-order absorption rate constant)  
 $K_a$ : the first-order absorption rate constant  
 $K_e$ : the terminal rate constant

- $K_a$  and  $K_e$  were assumed to follow a log-normal distribution. A correlation between  $K_a$  and  $K_e$  was simulated.

- No negative feedback: A constant endogenous level (Endo) was simulated from a lognormal distribution and added directly to the exogenous level (Exo):

$$C(t) = E(t) + \text{Endo}$$

- Negative feedback: An endogenous level (Endo) was simulated from a lognormal distribution and added to the exogenous level (Exo) according to the following equation:

$$C(t) = E(t) + \text{Endo} \cdot e^{-k_f t}$$

Thus, the endogenous level (Endo) decreased by  $k_f$  (k<sub>f</sub> = k<sub>in</sub> - k<sub>out</sub>) increased by half at an exogenous concentration equivalent to the endogenous level (100%). The figure below is an example of the simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 1: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 2: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 3: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 4: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 5: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 6: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 7: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 8: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 9: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 10: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 11: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 12: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 13: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 14: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 15: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 16: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 17: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 18: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 19: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 20: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 21: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 22: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 23: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 24: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 25: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 26: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 27: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 28: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 29: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 30: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 31: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 32: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 33: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 34: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 35: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 36: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 37: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 38: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 39: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 40: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 41: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 42: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 43: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 44: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 45: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 46: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 47: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 48: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

Figure 49: Simulated curves with end level and without (blue) and negative feedback with an endogenous level of 1000 pg.

The endogenous levels were simulated according to different scenarios:

- Mean baseline of 1000 and 10000
- Relative bioavailability (F<sub>r</sub>) of 1.0, 1.30 and 0.75
- Sampling times at 7.5, 3, 4.5, 5, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 60 and 72 hours post dose
- Three pre-dose values measured at 48, 72 and 0 hours
- 1000 studies were simulated by scenario
- 17 subjects per study, were simulated for the F<sub>r</sub> of 1.0 and 30 subjects per study were simulated for the F<sub>r</sub> of 1.30 and 0.75 in order to maintain a minimum power of 80% when no negative feedback was simulated.

### PK parameter

### AUC

### STATISTICAL ANALYSIS

#### Model: Linear

#### Error: Lognormal

#### ANCOVA

#### Fixed effects: Period, Sequence, Formulation

#### Random effect: Subject (sequence)

#### ANCOVA with interaction

#### Fixed effects: Random effect + Covariate + Covariate \* Formulation

#### ANCOVA without interaction

#### Fixed effects: Random effect + Covariate

#### Covariate

It transformed mean of baseline concentrations specific to subject and period.

## RESULTS

The % of studies where:

1. the covariate is significant (%Base) using a type I error of 5% and
2. bioequivalence is met (%BE)

were calculated as well as the intra-subject %CV. Results are summarized by % of mean baseline values to the average concentration (C<sub>0</sub>) for AUC.

%Base, %BE and %CV were also presented for a subgroup of studies where the covariate was statistically significant using the ANCOVA on baseline adjusted data.

Table 1: Ln AUC, no negative feedback

F <sub>r</sub>	Methods	0.9%			12.4%		
		%Base	%BE	%CV	%Base	%BE	%CV
F <sub>r</sub> = 1	ANOVA baseline adjusted	22	141	79.6	17.1		
	ANOVA unadjusted	6.4	84.5	12.8	0.8	100.0	7.7
	ANCOVA baseline adjusted	5.9	80.1	11.1	0.0	75.9	10.0
Studies where %Base significant					72.3	88.3	
F <sub>r</sub> = 0.75	ANOVA baseline adjusted	100	96.1	9.5	100	100	7.2
	ANOVA unadjusted	100	96.4	10.2	100	81.9	81.4
	ANCOVA baseline adjusted	100	96.4	10.2	100	81.9	81.4
Studies where %Base significant					100.0	100.0	
F <sub>r</sub> = 1.3	ANOVA baseline adjusted	6.7	1.1	13.1	49.0	99.1	8.4
	ANOVA unadjusted	4.4	0.1	18.3	12.2	0.1	18.7
	ANCOVA baseline adjusted	100	0.0	12.9	100	88.1	17.2
Studies where %Base significant					0.0	14.0	
%Base (C <sub>0</sub> )					7.9%	49.2%	

Table 2: Ln AUC, negative feedback

F <sub>r</sub>	Methods	0.9%			61.5%		
		%Base	%BE	%CV	%Base	%BE	%CV
F <sub>r</sub> = 1	ANOVA baseline adjusted	53.5	14.1	36.6	25.4		
	ANOVA unadjusted	4.8	84.8	12.6	64.2	100	8.0
	ANCOVA baseline adjusted	5.8	80.6	14.3	18.1	37.7	23.3
Studies where %Base significant					78.9	77.7	
F <sub>r</sub> = 0.75	ANOVA baseline adjusted	100	93.5	10.6	100	100	7.6
	ANOVA unadjusted	100	99.1	11.7	100	47.4	20.4
	ANCOVA baseline adjusted	100	99.1	11.7	100	47.4	20.4
Studies where %Base significant					100.0	100.0	
F <sub>r</sub> = 1.3	ANOVA baseline adjusted	0.2	14.8	0.2	23.9		
	ANOVA unadjusted	6.2	1.1	13.5	84.2	99.7	8.9
	ANCOVA baseline adjusted	7.5	0.2	14.7	30.1	0.0	22.0
Studies where %Base significant					0.0	14.9	
%Base (C <sub>0</sub> )					100	0.0	

Table 3: Ln AUC, negative feedback with interaction

F <sub>r</sub>	Methods	0.9%			12.4%		
		%Base	%BE	%CV	%Base	%BE	%CV
F <sub>r</sub> = 1	ANOVA baseline adjusted	22	141	79.6	17.1		
	ANOVA unadjusted	6.4	84.5	12.8	0.8	100.0	7.7
	ANCOVA baseline adjusted	5.9	80.1	11.1	0.0	75.9	10.0
Studies where %Base significant					72.3	88.3	
F <sub>r</sub> = 0.75	ANOVA baseline adjusted	100	96.1	9.5	100	100	7.2
	ANOVA unadjusted	100	96.4	10.2	100	81.9	81.4
	ANCOVA baseline adjusted	100	96.4	10.2	100	81.9	81.4
Studies where %Base significant					100.0	100.0	
F <sub>r</sub> = 1.3	ANOVA baseline adjusted	6.7	1.1	13.1	49.0	99.1	8.4
	ANOVA unadjusted	4.4	0.1	18.3	12.2	0.1	18.7
	ANCOVA baseline adjusted	100	0.0	12.9	100	88.1	17.2
Studies where %Base significant					0.0	14.0	
%Base (C <sub>0</sub> )					7.9%	49.2%	

• The power was quite similar across all the three methods when the % of baseline (C<sub>0</sub>) was lower than 10%.

### UNDER BIOEQUIVALENT CONDITIONS (F<sub>r</sub> = 0.75 & 1.30)

• The type I error was less than 5% in both baseline adjusted method. It approached 100% when using the ANCOVA on unadjusted data for "Baseline(C<sub>0</sub>)" more than 10%.

### USE OF THE ANCOVA

• The introduction of the baseline as a covariate was mostly justified when a negative feedback was simulated.

• When the covariate is statistically significant, the ANCOVA on baseline adjusted data has a type I error equivalent to the ANOVA and a higher power than the ANOVA, especially for large % baseline(C<sub>0</sub>).

## CONCLUSION

• When an endogenous feedback is suspected or when the % of baseline to unadjusted response is large, the ANCOVA on the baseline adjusted response should be favored when assessing bioequivalence for endogenous compounds. If the baseline is found to be statistically not significant, the ANCOVA on the baseline adjusted response should be performed.

• The ANCOVA on the unadjusted data should not be used to assess BE of endogenous compounds due to its high type I error.

ORIG. ID: YULA (514)333-0033 DATE: 09/23/02 | / |  
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