CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-698

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-698
Drug Product Name	Metolazone Tablets USP
Strength	2.5 mg
Applicant Name	Mylan Pharmaceuticals
Address	Morgantown, WV
Submission Date(s)	March 27, 2003
Amendment Date(s)	September 24, 2003
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	**V:\firmsam\mylan\ltrs&rev\76698n0303.doc**

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study comparing the test product, Metolazone Tablets USP, 2.5 mg, with the RLD product, Celltech's Zaroxolyn® Tablets, 2.5 mg. The fasting study was performed in 34 normal males and 12 normal females at a dose of 4x2.5 mg (46 completing subjects from 52 enrolled subjects) and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (AUCt 1.02, 97.2-106.2; AUCinf 1.00, 96.0-104.6; Cmax 1.14, 105.6-123.7). The firm has also submitted comparative dissolution data for the test and reference products using the FDA-recommended dissolution method. The dissolution data met the FDA-recommended specification.

This application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Mylan's Metolazone Tablets USP, 2.5 mg* ***NOTE:** Although the RLD product is also available in the 5 mg and 10 mg strengths, the current ANDA is only for the 2.5 mg strength.
Reference Product	Zaroxolyn® Tablets, 2.5 mg (Other strengths available are 5 mg and 10 mg)
RLD Manufacturer	Celltech Pharmaceuticals
NDA No.	17-386
RLD Approval Date	11/27/73
Indication	Indicated for the treatment of salt and water retention including edema accompanying congestive heart failure and renal diseases, and for the treatment of hypertension.

B. PK/PD Information

Bioavailability	40-65%
Food Effect	Not known; no statement of food effect in the RLD product labeling.
Tmax	8 hours
Metabolism	Only small fraction of the dose is metabolized at unspecified site.
Excretion	Approximately 28% to 45% is excreted unchanged in the urine.
Half-life	8-14 hours
Relevant OGD or DBE History	**ANDA #75-543(Copley; 12/30/98):** The fasting bioequivalence study on 10 mg was found acceptable. Metolazone was measured. However, based on the significantly different *in vitro* dissolution profiles between the 10 mg strength and the lower strengths, 2.5 mg and 5 mg, of the RLD product, and due to the lack of dose propotionality studies for the RLD product, the DBE recommended a separate fasting bio study for the 2.5 mg strength. Biowaiver for the 5 mg strength is considered based on the bio study of the 2.5 mg strength, formulation proportionality and comparable dissolution profiles. **Protocol #00-046 (Roxane Laboratories; 10/31/2000) and Control Document #02-049 (** (b) (4)**; 01/29/02)::** The DBE accepted the fasting study protocol by Roxane, informed the firms that a food effect study is not requested for the drug product, recommended Roxane develop a dissolution method, and both firms conduct a separate fasting bio study for the 2.5 mg strength. **ANDA #76-466 (Eon; 07/26/02):** The submitted fasting bio study was found acceptable. Metolazone was measured. The firm was also recommended to develop a dissolution method and conduct a separate fasting bio study for the 5 mg strength. The firm was informed that a biowaiver for the 2.5 mg strength may be requested based on the fasting study of the 5 mg strength, as well as formulation proportionality and comparable dissolution profiles between the two lower strengths. **NOTE:** Currently, both 10 mg and 5 mg strengths of Zaroxolyn® tablets are listed as RLD products in the Orange Book.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	No	
Amendments	Yes	1 (Telephone Amendment to provide additional dissolution data)

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Metolazone
Internal Standard	(b) (4)
Method description	HPLC/Fluorescence detection
QC range	1.5 ng/mL to 50 ng/mL (1.5, 3.0, 10 and 50 ng/mL)
Standard curve range	1.5 to 80.0 ng/mL
Limit of quantitation	1.5 ng/mL
Average recovery of Drug (%)	78-8-86.3%
Average Recovery of Int. Std (%)	83.8%
Intraday precision range (%CV)	2.1-2.8%
Intraday accuracy range (%)	98.3-102.8%
Interday precision range (%CV)	4.1-7.5%
Interday accuracy range (%)	96.8-104.8%
Bench-top stability (hrs)	4.5 hours
Stock stability (days)	48 days for (b) (4) 33 days for (b) (4) at 4°C
Processed stability (hrs)	96 hours
Freeze-thaw stability (cycles)	7 cycles
Long-term storage stability (days)	260 days
Dilution integrity	1:1 (95.9-101.4%)
Specificity	Acceptable
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Chromatograms included (Y/N)	Yes
Random Selection of Serial Chrom	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	METO-02110
Study Design	Two-way crossover
No. of subjects enrolled	52
No. of subjects completing	46
No. of subjects analyzed	46
Subjects (Normal/Patients?)	Normal, healthy subjects
Sex(es) included (how many?)	Male: 34 Female: 12
Test product	Mylan's Metolazone Tablets USP, 2.5 mg
Reference product	Celltech's Zaroxolyn® Tablets USP, 2.5 mg
Strength tested	2.5 mg
Dose	4x2.5 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	97.2-106.2
AUC_{∞}	1.00	96.0-104.6
C_{max}	1.14	105.6-123.7

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Samples were repeated for analytical reasons only. There was no PK repeat.	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on Fasting Study: The fasting study is acceptable.

2. Single-dose Fed Bioequivalence Study: None

F. Formulation

Location in appendix	Section B, Page 15
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	No
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	No
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method *	FDA*
Medium	0.05M Sodium Phosphate Buffer, pH 7.5 with 2% Sodium Lauryl Sulfate
Volume (mL)	900 mL
USP Apparatus type	Paddle
Rotation (rpm)	75 rpm
Firm's proposed specifications	N/A
FDA-recommended specifications	NLT (b) (4)% (Q) dissolved in 120 minutes
F2 metric calculated (yes or no)	Yes
If no, reason why F2 not calculated	
Method is acceptable (yes or no)	Yes

***NOTE:** The firm had originally submitted dissolution data using the firm's proposed dissolution method. However, the firm was requested to conduct additional dissolution testing using the FDA-recommended method. The original dissolution data by the firm's method are not reviewed.

F2 metric, test compared to reference	
Strength	F2 metric
2.5 mg	Not calculated due to high CV% (>15%) at early time points in the test product's dissolution profile

H. Waiver Request(s)

Strengths for which waivers requested	None
Regulation cited	
Proportional to strength tested in vivo (yes or no)	
Dissolution is acceptable (yes or no)	
Waiver granted (yes or no)	

I. Deficiency Comments: None

J. Recommendations

1. The single-dose, fasting bioequivalence conducted by Mylan on the test product, Metolazone Tablets USP, 2.5 mg, lot # R1K4377, comparing it with the reference product, Celltech's Zaroxolyn® Tablets, 2.5 mg, lot # X-847, has been found **acceptable** by the Division of Bioequivalence. The test product, Mylan's Metolazone Tablets USP, 2.5 mg, is deemed bioequivalent to the reference product, Celltech's Zaroxolyn® Tablets, 2.5 mg.

2. The dissolution testing conducted by Mylan on its Metolazone Tablets USP is acceptable. The dissolution testing should be incorporated into the firm's stability and quality control programs.

The dissolution testing should be conducted in 900 mL of 0.05M sodium phosphate buffer, pH 7.5 with 2% Sodium Lauryl Sulfate, at 37°C using USP apparatus II(paddle) at 75 rpm. The test product should meet the following specification:

Not less than (b) (4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 120 minutes.

10/28/03
Hoainhon Nguyen, Review Branch I, Date

10/31/2003
Yih Chain Huang, Review Branch I, Date

11/4/03
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	METO-02110
Study Title	Single-Dose Fasting In Vivo Bioequivalence Study of Metolazone Tablets (2.5 mg; Mylan) and Zaroxolyn® Tablets (2.5 mg; Celltech) in Healthy Volunteers
Clinical Site	Gateway Medical Research, St. Charles, MO
Principal Investigator	Thomas Siler, M.D.
Study/Dosing Dates	Period I: 12/13/02-12/17/02; Period II: 12/20/02-12/24/02
Analytical Site	Bioanalytical Department, Mylan Pharmaceuticals
Analytical Director	(b) (6) Ph.D.
Analysis Dates	01/20/03-03/14/03
Storage Period (no. of days from first sample to final analysis)	90 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metolazone Tablets USP	Zaroxolyn® Tablets
Manufacturer	Mylan	Celltech
Batch/Lot No.	R1K4377	X-847
Manufacture Date	11/27/02	
Expiration Date		09/03
Strength	2.5 mg	2.5 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	
Potency	98.1%	99.3%
Content Uniformity	98.4%(RSD=2.0%)	99.1%(RSD=1.3%)
Formulation	See Appendix Section B	
Dose Administered	4x2.5 mg	4x2.5 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	Predose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours postdose
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	Samples were collected in heparinized tubes, cooled in an ice bath, centrifuged and harvested for plasma which was stored at -70°C and protected from light.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours prior to until 5 hours after dosing.
Length of Confinement	At least 16 hours prior to until 24 hours postdose
Safety Monitoring	Vital signs were measured at approximately 4, 6, 8, 10,12, 24 and 48 hours postdose and at study exit.

Table 1 Demographics of Study Subjects (N=46)

Age		Weight (lbs)		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	26 M 7 F
Mean	23.7 M 30.5 F	Mean	184.3 M 141.7 F	18-40	32 M 10 F	Male	34	Afr. Amer.	8 M 5 F
SD	6.5 M 12.0 F	SD	18.8 M 20.7 F	41-64	2 M 2 F	Female	12	Hispanic	
Range	18-47 M 20-57 F	Range	144-217 M 110-172 F	65-75	0			Asian	
				>75	0			Others	

Study Results

Table 2 Dropout Information

Subject No	3	13	23	28	46	47
Reason	Personal reasons	Schedule conflict	Schedule conflict	Oral surgery	Schedule conflict	Adverse event
Period	II	II	I	I	II	I
Replacement	No	No	No	No	No	No

Was there a difference in side effects for the test versus the reference? The reference product had a higher number of adverse events observed. Most adverse reactions were mild to

moderate except for three severe reactions: cracked tooth (Subject #28, Reference Treatment), vomiting (Subject #47, Reference Treatment) and headache (Subject #50, Test Treatment).

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Weakness	0	3
Headache	8	12
Lightheadedness	4	3
Nausea	0	4
Stomach cramp	1	1
Dizziness	1	0
Upset stomach	0	3
Fever	0	1
Cracked tooth	0	1
Stomache ache	1	0
Vertigo	1	0
Rash	1	0
Nose bleed	2	1
Muscle twitching	1	0
Blurred vision	1	0
Joint pain	1	0
Shortness of breath	0	1
Vomiting	0	1
Anxiety	0	1
Total:	**22**	**32**

Comments: (*on adverse events)*: None

Was there a difference in protocol deviations for the test versus the reference? No

Table 4 Protocol Deviations: No significant deviation.

Comments: The integrity of the study was not compromised.

Table 5 Assay Validation – Within Study

	Parent		
QC Conc. (ng/mL)	3.0(n=113)	10.0(n=118)	50.0(n=115)
Inter day Precision (%CV)	5.4	4.7	3.9
Inter day Accuracy (%)	104.6	102.1	104.1
Cal. Standards Conc. (ng/mL)	1.50, 3.00, 5.00, 7.50, 10.0, 25.0, 50.0 and 80.0 (n=36)		
Inter day Precision (%CV)	1.8-4.1		
Inter day Accuracy (%)	98.1-102.7		
Linearity Range (range of R^2 values)	1.50-80.0 (0.9933-0.9996)		

Chromatograms: Any interfering peaks? No

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
D-400-02	**09/24/02**	**Reassay or Reinjection of Clinical Samples**
D-401-04	**03/21/02**	**Evaluation and Acceptance Criteria for Standard Curves, Quality Controls and Biostudy Sample Batches.**
D-416-01	**06/18/02**	**Reassay of Whole Subjects**

Comments on repeat assays.

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. N/A
- Did recalculation of plasma concentrations change the study outcome? No recalculation of the study results was done based on the original values since no samples were repeated for PK reasons.
- Does the reviewer agree with the outcome of the repeat assays? The repeat assays were done for analytical reasons, and with adequate explanations.
- Provide any other comments about repeat assays: None

Comments on Within-Study Validation: None

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	Ng.hr/mL	639.2	43	615.9	36	1.04
AUC_{∞}	Ng.hr/mL	702.7	46	685.5	37	1.02
C_{max}	Ng/mL	67.42	45	57.93	42	1.16
T_{max}	Hrs	3.11	37	3.17	31	0.98
$T_{1/2}$	hrs	14.82	49	17.56	44	0.84

Table 8 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	593.8	584.4	1.02	97.2-106.2
AUC_{∞}	650.5	649.1	1.00	96.0-104.6
C_{max}	60.95	53.34	1.14	105.6-123.7

Table 9 Additional Study Information

Root mean square error, AUC_{0-t}	0.12650	
Root mean square error, AUC_{∞}	0.12142	
Root mean square error, C_{max}	0.22542	
mean ratio AUC_{0-t}/AUC_{∞}	T =0.913	R =0.901
Range of values, ratio AUC_{0-t}/AUC_{∞}	T =0.768-0.971	R =0.637-0.977

Comments: (on pharmacokinetic analysis)

- k_{el} and AUC_{∞} were determined for how many subjects: 46
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as T_{max}: None, and
  c. first measurable drug concentration as C_{max}: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? Yes, there were statistically significant period effects for AUC_{0-t}, AUC_{∞} and C_{max}, and there was statistically significant sequence effect for C_{max},. However, these effects are not considered to affect the integrity of the study. (See Don Schuirmann's comments on period effect and sequence effect in a consult for a similar case in the Appendix (D. Consult Reviews on page 17).

- Are the 90% confidence intervals for AUC_{0-t}, AUC_{∞}, C_{max} within the acceptable limits of 80-125%? Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Table 10 Metolazone Mean Plasma Concentrations

Single-Dose Fasting Bioequivalence Study

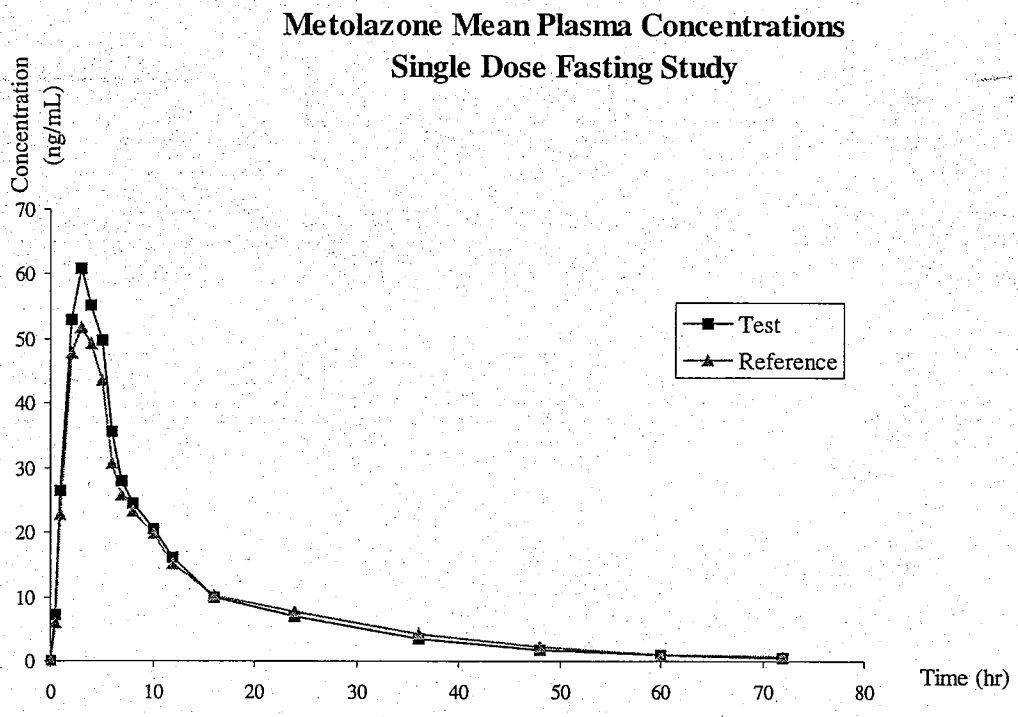
TRT=A

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	46	0	.	0	0
Hour0.50	46	7.1321304	134.3472754	0	55.3920000
Hour1	46	26.5282826	86.4582029	0	127.3390000
Hour2	46	52.8411522	57.9523140	8.4000000	161.8780000
Hour3	46	60.7968696	51.7618135	13.8700000	170.6350000
Hour4	46	55.0932826	46.5643388	23.0550000	122.7220000
Hour5	46	49.7540217	46.8987560	21.8860000	137.5050000
Hour6	46	35.6030435	43.8738563	17.2770000	104.7110000
Hour7	46	27.9571739	35.3875166	15.6630000	67.1050000
Hour8	46	24.5589565	33.1191843	13.9360000	58.3080000
Hour10	46	20.4153261	38.9569082	11.8700000	61.5920000
Hour12	46	16.0190217	31.2445911	10.0420000	38.1920000
Hour16	46	9.8212826	36.1862103	5.4130000	23.5670000
Hour24	46	6.9825652	48.4834984	3.2630000	22.9850000
Hour36	46	3.5119783	79.3751733	0	14.6950000
Hour48	46	1.8373478	112.3356025	0	10.2560000
Hour60	46	1.0801522	191.9875024	0	10.2770000
Hour72	46	0.4448696	240.7816456	0	4.8910000

TRT=B

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	46	0	.	0	0
Hour0.50	46	6.0010435	136.7125338	0	42.0260000
Hour1	46	22.7028043	94.6999428	0	129.2390000
Hour2	46	47.7158043	53.8887847	5.8300000	131.1720000
Hour3	46	51.7640000	43.7049172	11.2800000	120.1920000
Hour4	46	49.3248913	37.5501141	23.6230000	92.4870000
Hour5	46	43.6527609	41.8961028	18.8960000	105.4900000
Hour6	46	30.7561957	41.0433641	17.0000000	65.4330000
Hour7	46	25.6108261	37.6758745	13.5610000	53.1930000
Hour8	46	23.1647826	37.0660384	12.6620000	52.3730000
Hour10	46	19.7168696	38.6416588	11.1450000	50.1980000
Hour12	46	15.1557391	29.2218402	8.7000000	26.5920000
Hour16	46	10.0261087	41.9046502	4.8490000	29.7610000
Hour24	46	7.7031522	46.7920135	2.4160000	21.1880000
Hour36	46	4.1048696	60.9436805	0	11.9340000
Hour48	46	2.1116739	94.5031201	0	8.4950000
Hour60	46	0.9764348	182.2068843	0	7.6200000
Hour72	46	0.7584130	215.6171016	0	7.0640000

Figure 1



B. Formulation Data

Ingredients	Amount per tablet	%w/w
Metalazone USP (b) (4)	(b) (4)	
Magnesium Stearate NF		
Colloidal Silicon Dioxide NF		
Microcrystalline Cellulose NF		
FD&C Yellow #6 Lake HT (b) (4)		
Total Theoretical Weight	100.0	100%

(b) (4)

C. Dissolution Data

Table 1

Sampling Time, min.	Test Product, Strength: 2.5 mg Lot No. R1K4377			Reference Product, Strength: 2.5 mg Lot No. X-847		
	Mean	%CV	Range	Mean	%CV	Range
15	38	21.9	(b) (4)	47	13.8	(b) (4)
30	60	15.8		68	12.5	
60	80	8.5		83	7.6	
90	90	5.2		90	5.4	
120	97	3.8		95	4.3	

Similarity Factor F2 could not be calculated since %CV's for two of the earlier time points for the test product exceed 15%.

D. Consult Reviews: The following consult was from ANDA 76-520 and deals with similar issue of signicant period and sequence effects encountered in the current ANDA.

From: Schuirmann, Donald J
Sent: Wednesday, March 19, 2003 9:09 AM
To: Nguyen, Hoainhon T
Cc: Li, Huaixiang; Huang, Yih Chain; Conner, Dale P; Davit, Barbara M; Patnaik, Rabindra N; Machado, Stella G
Subject: RE: Statistical Consult: Significant Period and Sequence Effects

Hello Hoai,

Regarding the occurrence of a statistically significant Period effect, this is something that happens regularly in crossover bioequivalence (BE) studies. If, as a matter of scientific curiosity, you wanted to investigate WHY a significant period effect occurred, that could be done. But as a general rule, the occurrence of a significant period effect has never been regarded as a reason to distrust the validity of the 90% confidence interval computed using standard methods. The only possible exception to this that I can think of would be the case where there is some sort of blood sample preparation that is done after the sample is drawn (The example that I can think of was a case where the blood samples were treated with some sort of ultrasound, in order to break up the red blood cells and release the drug into the plasma. The drug in that case was chlorthalidone.) In this situation, a significant period effect could possibly indicate that the sample preparation was not done with the same thoroughness in all periods. Nevertheless, in the absence of such a sample-preparation issue, my advice would be not to worry about the significant period effect.

Regarding the occurrence of a statistically significant Sequence effect, you may recall that the issue with significant Sequence effects in standard two-period crossover BE studies was that a significant Sequence effect test might be evidence of unequal carryover effects. If there are unequal carryover effects, the usual estimate of the difference between the means for ln(Cmax) (or ln(AUC)) may be biased. You will recall that the Center considered this issue and presented recommendations at the September 1991 Generic Drugs Advisory Committee. These recommendations were incorporated in the well-known July 1992 Guidance "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design". Basically, the 1992 Guidance said that a significant Sequence effect should be ignored if a number of conditions hold (I often refer to this list of conditions as "the laundry list".) One of the listed conditions was that the study must be a single-dose study in healthy subjects, but shortly after the Guidance was issued OPS (through the initiative of Dr. Williams) decided that a significant Sequence effect could also be discounted in multiple-dose studies and/or studies in patients.

This language from the 1992 Guidance is also contained in the more recent "Statistical Approaches to Establishing Bioequivalence" Guidance. The more recent Guidance states:

In most cases, for both replicated and nonreplicated crossover designs, the possibility of unequal carryover effects is considered unlikely in a BE study under the following circumstances:

It is a single-dose study.

The drug is not an endogenous entity.

More than an adequate washout period has been allowed between periods of the study and in the subsequent periods the predose
biological matrix samples do not exhibit a detectable drug level in any of the subjects.

The study meets all scientific criteria (e.g., it is based on an acceptable study protocol and it contains sufficient validated assay
methodology).

The possibility of unequal carryover effects can also be discounted for multiple-dose studies and/or studies in patients, provided that the drug is not an endogenous entity and the studies meet all scientific criteria as described above. Under all other circumstances, the sponsor or applicant could be asked to consider the possibility of unequal carryover effects, including a direct-by-carryover interaction. If there is evidence of carryover effects, sponsors should describe their proposed approach in the study protocol, including statistical tests for the presence of such effects and procedures to be followed. Sponsors who suspect that carryover effects might be an issue may wish to conduct a BE study with parallel designs.

In your description (below) of the study, you indicate that the washout period is adequate and that there were no detected blood levels of drug in the pre-dose blood samples from periods after period 1. That makes it sound to me that the above conditions have been fulfilled, and that the computed confidence interval may be used to make a decision regarding bioequivalence. Since the confidence interval falls within the "goalposts" of 0.80 to 1.25, it looks like the sponsor has passed the test for Cmax.

Regarding the significant Treatment effect, that has never been considered a reason to discount an acceptable confidence interval. I can understand that you might be concerned about the point estimate of 1.11. The significant Treatment effect may be regarded as evidence that the mean ln(Cmax) is not the same for Test and Reference, but it is NOT evidence that the ratio of means is truly 1.11. Actually, given the confidence interval, we cannot rule out the possibility that the ratio of means is as large as 1.17. But we CAN rule out the possibility that the ratio of means is as large as 1.25, which is the standard requirement for approval of an ANDA (together, of course, with the requirement that we may rule out the possibility that the ratio of means is as small as 0.80.)

Don Schuirmann

-----Original Message-----
From: Nguyen, Hoainhon T
Sent: Friday, February 28, 2003 10:53 AM
To: Machado, Stella G
Cc: Li, Huaixiang; Schuirmann, Donald J; Huang, Yih Chain; Conner, Dale P; Davit, Barbara M; Patnaik, Rabindra N
Subject: Statistical Consult: Significant Period and Sequence Effects

Hi Stella,
Per preliminary discussion between Helen and me, I am requesting a statistical consult for the following question: For ANDA #76-520 (Par Pharmaceutical's Fenofibrate Tablets, 160 mg), in the nonfasting bio study, ANOVA results for lnCMAX showed significant period effect (p=0.0303) and significant sequence effect (p=0.0185). The treatment effect for lnCMAX was also significant (p=0.0203). The 90% C.I. for CMAX was [1.05-1.17] (point estimate of 1.11). The drug's half-life is 20 hours and the washout period was 14 days. There was no non-zero predose plasma concentration. Should we do a further carryover effect analysis on the data?
Thanks in advance for your assistance.
Hoai Nguyen

Following this page, 19 pages withheld in full (b)(4) SAS output

BIOEQUIVALENCY COMMENTS

ANDA: 76-698 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Metolazone Tablets USP, 2.5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

Please incorporate the following dissolution testing into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.05M sodium phosphate buffer, pH 7.5 with 2% Sodium Lauryl Sulfate, at 37°C using USP apparatus II(paddle) at 75 rpm. The test product should meet the following specification:

Not less than (b) (4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 120 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara M Saul

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:ANDA 76-698
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 10/31/2003
HFD-617/ A. Sigler
HFD-650/ D. Conner 10/31/03

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BIOEQUIVALENCY - ACCEPTABLE Submission date: 03-27-03 & 09-24-03

1. FASTING STUDY (STF) 01C Strength: 2.5 mg
   Clinical: Gateway Medical Research **Outcome: AC**
   Analytical: Mylan Bioanalytical Dept.

2. STUDY AMENDMENT (STA) Telephone amendment to provide additional dissolution data. 01C Strength: 2.5 mg
   Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable **NC** - No credit

9/24/03 -
2.1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-698 SPONSOR : Mylan Pharmaceuticals
DRUG AND DOSAGE FORM : Metolazone Tablets USP
STRENGTH(S) : 2.5 mg
TYPES OF STUDIES : Fasting Study
CINICAL STUDY SITE(S) : Gateway Medical Research
ANALYTICAL SITE(S) : Mylan Bioanalytical Dept.

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: N/A

DSI INSPECTION STATUS

Inspection needed: ~~YES~~ NO	Inspection status:	Inspection results:
First Generic NO	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HHN DATE : 10/28/03

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YH DATE : 10/31/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : BWD DATE : 11/4/03