CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076640

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	January 15, 2003
Amendment Date(s)	July 28, 2003, October 3, 2003 & ~~October 21, 2003~~
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\kv\ltrs&rev\76640n0103.doc**

I. Executive Summary

The firm has submitted a single-dose, 3-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing Formulations A and B of the test product, Metoprolol Succinate ER Tablets, 200 mg, with the RLD product, AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets, 200 mg. The Test Formulation A is different from Formulation B and only Formulation A is the subject of the current ANDA. The fasting study was performed in 29 normal males and 4 normal females at a dose of 1x200 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE, ***between Formulation A and the RLD formulation***, in the fasted state (AUCt 0.98, 88.7-108.2; AUCinf 0.91, 81.8-102.0; Cmax 0.95, 87.3-103.3). The fasting study does ***not*** show BE between Formulation B and the RLD formulation in the fasted state (AUCt 1.06, 96.4-117.6; AUCinf 1.00, 90.4-111.0; Cmax 1.21, 111.3-131.8). The nonfasting study was performed prior to the fed BE guidance, comparing the Test Formulation A with the RLD formulation, in 18 normal males and 17 normal females at a dose of 1x200 mg and resulted in acceptable data (point-estimate) that demonstrate BE in the fed state (AUCt 1.06; AUCinf 1.04; Cmax 0.87).

The firm has also submitted comparative dissolution data for the whole and half tablets of 100 mg and 200 strengths of the test and reference products using the firm's proposed method and the USP method. In addition, the dissolution testing was performed in aqueous media of pH of 1.2, 4.5 and 6.8. Since the compendial method is available for the drug product, this method is recommended for the test product instead of the firm's proposed method.

The formulations of the 100 mg and 200 mg strengths of the test product are proportionally similar. However, due to the high variability in the dissolution data of the test product as well as the difference in dissolution profile between the two strengths, the firm is requested to provide explanations for the observations. In addition, dissolution data of the 200 mg strength based on the USP method showed that at Hour 20, only 61-64% of the labeled amount of the 200 mg strength was dissolved. The firm is requested

to submit additional dissolution data for the 200 mg strength, using the USP method, at the final time point, at which at least 80% of the labeled amount is dissolved.

This application is deficient pending satisfactory responses from the firm concerning the dissolution data for both strengths.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information (based on the PDR labeling of the RLD product and NDA 19-962's 1993-1994 reviews)

Bioavailability	50% (after first pass); 65-70% (relative bioavailability as compared with conventional IR metoprolol tablets)
Food Effect	Food does not significantly affect the bioavailability.
Tmax	4.4-14.0 hours
Metabolism	Extensive first-pass metabolism in the liver to yield inactive metabolites.
Excretion	Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites.
Half-life	3-7 hours
Relevant OGD or DBE History	**(1) Control Documents # 01-423 ((b) (4) ; 08/31/01) and 01-470 ((b) (4) ; 09/20/01):** The DBE recommended a replicate, single-dose fasting bioequivalence study for the 200 mg and 50 mg strengths of the test product, a crossover, single-dose nonfasting bioequivalence study for the 200 mg strength. Biowaiver request for the 25 mg and 100 mg strengths may be considered based on formulation proportionality, comparable dissolution profiles and acceptable *in vivo* testing of the 200 mg and 50 mg strengths. **(2) Control Document #02-105 ((b) (4) ; 02/27/02):** The DBE recommended the same as above except that replicate design was no longer requested for the fasting study, and metoprolol was determined to be the only analyte to be measured.
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	
Waiver requests	Yes	1
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies		
Amendments	Yes	3 (1 amendment to add the 100 mg strength, 1 telephone amendment to provide additional dissolution data and formulation information, and 1 telephone amendment to provide additional dissolution data)

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Metoprolol
Internal Standard	(b) (4)
Method description	HPLC/Fluorescence spectroscopy
QC range	6.00 to 60.00 ng/mL
Standard curve range	5.00 to 150.00 ng/mL
Limit of quantitation	6.00 ng/mL
Average recovery of Drug (%)	99.4%
Average Recovery of Int. Std (%)	64.6%
Intraday precision range (%CV)	1.2%-7.9%
Intraday accuracy range (%)	85.9%-111.8%
Interday precision range (%CV)	8.5%-10.7%
Interday accuracy range (%)	93.4%-99.4%
Bench-top stability (hrs)	5 hours
Stock stability (days)	2 days
Processed stability (hrs)	33 hours
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	133 days
Dilution integrity	3:1 (96.8%), 1:1 (97.6%), 1:3 (96.4%)
Specificity	Yes
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.	R02-586
Study Design	Three-way crossover
No. of subjects enrolled	33
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 4
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)* and R416-059A (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment C)
Strength tested	200 mg
Dose	1x200 mg

*NOTE: Only Test Formulation A is currently submitted for approval. Comparison between Test Formulations A and B is provided in the Appendix.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.98	88.67-108.2
AUC_{∞}	0.91	81.83-102.0
C_{max}	0.95	87.28-103.3

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	96.40-117.6
AUC_{∞}	1.00	90.44-111.0
C_{max}	1.21	111.3-131.8

Reanalysis of Study Samples Additional information in Appendix, Table 6								
There was no samples reanalyzed for PK reasons.	**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 with respect to Test Formulation A.

2. Single-dose Fed Bioequivalence Study

Study No.	RA2-102
Study Design	Two-way crossover
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 17
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment B)
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 17 and Table 18		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	99.0-114.2
AUC_{∞}	1.04	97.9-110.3
C_{max}	0.87	77.5-96.9*

Reanalysis of Study Samples Additional information in Appendix, Table 16								
There was no samples repeated for PK reasons	**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 fed study: The nonfasting study is acceptable based on point estimate. The study was conducted before the issuance of the food guidance.

F. Formulation

Location in appendix	Section B, Page 26
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)	Yes
If yes, which strengths are scored?	200 mg and 100 mg
Is scoring of RLD the same as test? (yes or no)	Both 200 mg and 100 mg strengths of the RLD product are scored.
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

G. In Vitro Dissolution

The firm has originally submitted dissolution data using its proposed dissolution method which is the same as the USP method except for the volume of dissolution medium, 900 mL versus 500 mL as specified in the USP. The firm was requested through telephone to submit additional dissolution data using the USP dissolution method as is (with 500 mL of dissolution medium). The dissolution data based on the firm's proposed method, USP method, as well as dissolution testing using aqueous media of different pH's are summarized in the Appendix C. Dissolution Data (Tables 21-30).

Please note that the summary of dissolution testing given immediately below is based on the final testing using the USP method only.

Source of Method	USP
Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
USP specifications	Hour 1: NMT 25% Hour 4: 20-40% Hour 8: 40-60% Hour 20: NLT 80%
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Due to high variability (CV%>15) of most of the time points in the test dissolution profiles.
Method is acceptable (yes or no)	See Deficiency Comments

H. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Pending

I. Deficiency Comments

1. As requested, the firm has submitted the dissolution testing of the test and reference products using aqueous solutions of different pH's and the dissolution testing of the whole tablets and half tablets of the 200 mg and 100 mg strengths of the test and reference products using the USP method. The 200 mg and 100 mg strengths appeared to have different dissolution profiles. The 100 mg strength of the test product appeared to dissolve much faster than the 200 mg strength. The dissolution rate of the 100 mg strength appeared to be more similar to that of the RLD product (of both strengths) and also met the USP specifications. However, the 200 mg strength, of which the *in vivo* bioequivalence study has been found acceptable, did not meet the USP specifications. In addition, the dissolution data of both strengths of the test product are highly variable. Especially, for the whole tablets of the 100 mg strength and the half tablets of both strengths, the CV%'s were greater than 10% for most time points. The firm is requested to provide explanation for the high variability of the dissolution data based on the USP method.

2. The firm has proposed a different dissolution method for the test product. However, since currently there is a compendial method available for the drug product, this method is recommended for the test product.

3. The firm has not submitted dissolution data, using the USP method, for the final time point at which at least 80% of the labeled amount of the test product is dissolved. Therefore, the firm is requested to submit the dissolution data for the 200 mg strength at the final time point.

4. The formulations of the 100 mg and 200 mg strengths of the test product are proportionally similar. However, due to the deficiencies cited in Comments 1 and 3 above, the waiver request for the 100 mg strength is not considered at this time pending satisfactory responses from the firm concerning the dissolution data for both strengths.

J. Recommendations

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by KV Pharmaceutical on the test product, Metoprolol Succinate ER Tablets, 200 mg, lot # R416-055, comparing it with the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg, lot # 3698H, have been found **acceptable** by the Division of Bioequivalence. The test product,

KV's Metoprolol Succinate ER Tablets, 200 mg, is deemed bioequivalent to the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg.

2. The dissolution testing conducted by KV Pharmaceutical on its Metoprolol Succinate ER Tablets, 200 mg, has been found **incomplete** for the reasons cited in Deficiency Comment #3 above.

For the 200 mg: The dissolution testing should be conducted in 500 mL of pH 6.8 phosphate buffer at 37°C using USP apparatus II(paddle) at 50 rpm. The *interim* specifications for the 200 mg strength are not recommended pending the firm's submission of the dissolution data for the 200 mg strength at the final time point at which at least 80% of the labeled amount of the drug in the dosage form is dissolved.

For the 100 mg: The dissolution testing should be conducted in 500 mL of pH 6.8 phosphate buffer at 37°C using USP apparatus II(paddle) at 50 rpm. The 100 mg strength of the test product should meet the following USP specifications:

Hour 1: NMT 25%
Hour 4: 20-40%
Hour 8: 40-60%
Hour 20: NLT 80%

3. The formulations of the 100 mg and 200 mg strengths of the test product are proportionally similar. However, due to the deficiencies cited in Comments 1 and 3 above, the waiver request for the 100 mg strength is not considered at this time pending satisfactory responses from the firm concerning the dissolution data for both strengths.

1-20-04
Hoainhon Nguyen, Review Branch I, Date

1/20/2004
Yih Chain Huang, Team Leader, Review Branch I, Date

for
1/20/04
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Hnguyen/01-06-04/v:\firmsam\kv\ltrs&rev\76640n0103.doc

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	R02-586
Study Title	A Relative Bioavailability Study of 200 mg Metoprolol Succinate Extended Release Tablets Under Fasting Conditions
Clinical Site	PRACS Institute, East Grand Forks, MN
Principal Investigator	Thomas Cariveau, M.D.
Study/Dosing Dates	Period I: 09/15-17/02; Period II: 09/22-24/02; Period III: 09/29-10/01/02
Analytical Site	PRACS Institute, Fargo, ND
Analytical Director	(b) (6) M.S.
Analysis Dates	10/07-17/02
Storage Period (no. of days from first sample to final analysis)	32 days

Treatment ID	A	B	C
Test or Reference	Test	Test	Reference
Product Name	Metoprolol Succinate ER Tablets USP	Metoprolol Succinate ER Tablets USP	Toprol-XL®
Manufacturer	KV	KV	AstraZeneca
Batch/Lot No.	R416-055A	R416-059A	3698H
Manufacture Date	07/19/02	08/23/02	
Expiration Date			02/05
Strength	200 mg	200 mg	200 mg
Dosage Form	ER Tablets	ER Tablets	ER Tablets
Batch Size		(b) (4)	
Potency	100.2%	97.2	96.7%
Content Uniformity	103.2%(RSD=4.5%)	97.2%(RSD=3.9%)	98.4%(RSD=1.8%)
Formulation	See Appendix Section B		
Dose Administered	1x200 mg	1x200 mg	1x200 mg
Route of Administration		Oral	

No. of Sequences	3
No. of Periods	3
No. of Treatments	3
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	Predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 38 and 48 hours postdose
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	Samples were collected in EDTA vacutainers, centrifuged and harvested for plasma which was stored at -70°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Approximately 10 hours predose until at least 4 hours postdose
Length of Confinement	Approximately 10 hours predose until at least 24 hours postdose
Safety Monitoring	Vital signs were measured at predose, 4, 8, 12 and 24 hours postdose. Pregnancy screen was done for female subjects prior to each period of the study.

Table 1 Demographics of Study Subjects (N=33)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	31
Mean	25.1	Mean	76.0	18-40	31	Male	29	Afr. Amer.	0
SD	8.2	SD	11.3	41-64	2	Female	4	Hispanic	0
Range	18-47	Range	48.9-97.4	65-75	0			Asian	0
				>75	0			Others	2

Study Results

Table 2 Dropout Information

Subject No	N/A There was no dropout.
Reason	Provide brief description
Period	
Replacement	Y/N; explain if appropriate

Was there a difference in side effects for the test versus the reference? Yes, see Comments below.

Table 3 Study Adverse Events

Adverse Event Description	# in Test (A) Group	# in Test (B) Group	# in Reference (c) Group
Abscess Tooth Socket	0	1	0
Dizziness	1	0	0
Dyspepsia	1	0	0
Headache	2	1	0
Malaise (Head Cold)	0	1	0
Pharyngitis (Sore Throat)	0	2	0
Rhinitis (Stuffy Nose)	0	1	0
Syncope (Fainted)	1	0	0
Total:	**5**	**6**	**0**

Comments: (*on adverse events)* Adverse events were only observed in Test Treatments (both A and B) and not in Reference Treatment. The study investigator considered all the adverse events listed above as not related to the study drug. The dizziness and syncope events reported for Subject #28 at approximately study hour 3 of Period I were contributed to painful phlebotomy. It should be noted that headache, dizziness, syncope and heartburn have been listed as some of the adverse effects observed for immediate release metoprolol tartrate, according to the PDR labeling of Toprol-XL®.

Was there a difference in protocol deviations for the test versus the reference?

Table 4 Protocol Deviations

Type	Subject #s (Test A)	Subject #s (Test B)	Subject #s (Reference)
Repeat/Additional Vital Signs Measurements	6	7	5
Concurrent Medications Used for Adverse Events	0	3	0

Comments: (*indicate whether protocol deviations compromised the integrity of study*) The concurrent medications given (pseudoephedrine HCl, Sudafed Cold & Sinus (pseudoephedrine HCl/acetaminophen) and Pencillin V Potassium) are not known to interact adversely with the study drug. No protocol deviations appeared to compromise the integrity of the study.

Table 5 Assay Validation – Within Study

	Parent			
QC Conc. (ng/mL)	15.00 (n=132)	30.00 (n=132)	70.00 (n=132)	120.00 (n=132)
Inter day Precision (%CV)	6.7	8.7	7.0	7.1
Inter day Accuracy (%)	98.9	97.5	97.2	97.5
Cal. Standards Conc. (ng/mL)	5.00, 10.00, 25.00, 50.00, 75.00, 100.00, 150.00			
Inter day Precision (%CV)	1.16-2.40			
Inter day Accuracy (%)	97.7-102.8			
Linearity Range (range of R^2 values)	5.00-150.00 (0.998-1.000)			

Chromatograms: Any interfering peaks? None

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

SOP No.	Date of SOP	SOP Title
090-01	**05/13/02**	**Sample Re-Analysis (NOTE:** The SOP was listed but not submitted. The firm is requested to submit the SOP for review in future submissions.)

Comments on repeat assays.

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. None
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? If no, explain reason(s). Yes
- Provide any other comments about repeat assays. Samples were repeated for analytical reasons only. There were 28 subject samples reassayed mainly due to exceeding the curves. The samples were repeated with dilution. Dilution integrity was validated during prestudy validation. The standard curves and QC concentration ranges as selected are acceptable.

Comments on Within-Study Validation:

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 A		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	Ng.hr/mL	1050	104	1164	113	0.90
AUC_{∞}	Ng.hr/mL	1225	99	1339	108	0.91
C_{max}	Ng/mL	49.76	83	53.06	91	0.94
T_{max}	Hr	13.36	33	7.21	40	1.85
$T_{1/2}$	Hr	8.41	38	10.29	48	0.82

Parameter	Units	Test B		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	Ng.hr/mL	1169	101	1164	113	1.00
AUC_{∞}	Ng.hr/mL	1290	97	1339	108	0.96
C_{max}	Ng/mL	61.92	74	53.06	91	1.17
T_{max}	Hr	12.91	17	7.21	40	1.79
$T_{1/2}$	Hr	7.31	35	10.29	48	0.71

Table 8 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test A	Reference	T/R	90% CI
AUC_{0-t}	712.1	727.0	0.98	88.67-108.2
AUC_{∞}	818.2	895.7	0.91	81.83-102.0
C_{max}	37.66	39.66	0.95	87.28-103.3

Parameter	Test B	Reference	T/R	90% CI
AUC_{0-t}	774.2	727.0	1.06	96.40-117.6
AUC_{∞}	897.4	895.7	1.00	90.44-111.0
C_{max}	48.04	39.66	1.21	111.3-131.8

Table 9 Additional Study Information

Root mean square error, AUC_{0-t}	0.2422	
Root mean square error, AUC_{∞}	0.2491	
Root mean square error, C_{max}	0.2050	
mean ratio AUC_{0-t}/AUC_{∞}	T (A)=0.8526; T (B)=0.8668	**R** =0.8240
Range of values, ratio AUC_{0-t}/AUC_{∞}	T (A) =0.6047-0.9839 T (B)=0.6880-0.9760	**R** =0.4283-0.9816

Comments: (on pharmacokinetic analysis)

- k_{el} and AUC_{∞} were determined for how many subjects: 33. If there are cases in which k_{el} cannot be calculated (Subjects #10 (Test A), 17 (Test A) and 27 (Test A)). The reviewer agrees with firm's decision.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None , and
  c. first measurable drug concentration as Cmax: 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? If so, did these affect the integrity of the study? No
- Are the 90% confidence intervals for AUC_{0-t}, AUC_{∞}, C_{max} within the acceptable limits of 80-125%: All but the 90% confidence interval for Cmax of Test B Treatment as compared with Reference Treatment.
- 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 with respect to the Test Formulation A which is the subject of the original ANDA. Comparison between Test Formulations A and B is given in the Appendix.

Table 10 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

TRT=A:TEST

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	33	0	.		(b) (4)
Hour1	33	10.7036364	81.2566959		
Hour2	33	21.3560606	72.0870976		
Hour3	33	26.0709091	83.4339734		
Hour4	33	25.5021212	90.4149488		
Hour5	33	27.0442424	91.6128859		
Hour6	33	28.8769697	93.4406631		
Hour8	33	32.8236364	86.0832773		
Hour10	33	35.0400000	83.6928025		
Hour12	33	42.6303030	79.5788312		
Hour14	33	43.8048485	87.1976580		
Hour16	33	41.1903030	92.4021317		
Hour18	33	35.4696970	97.5582760		
Hour20	33	32.6090909	107.5623939		
Hour24	33	27.6775758	120.3648837		
Hour30	33	19.8957576	143.3420054		
Hour38	33	6.5578788	224.7528485		
Hour48	33	2.4936364	325.0682028		

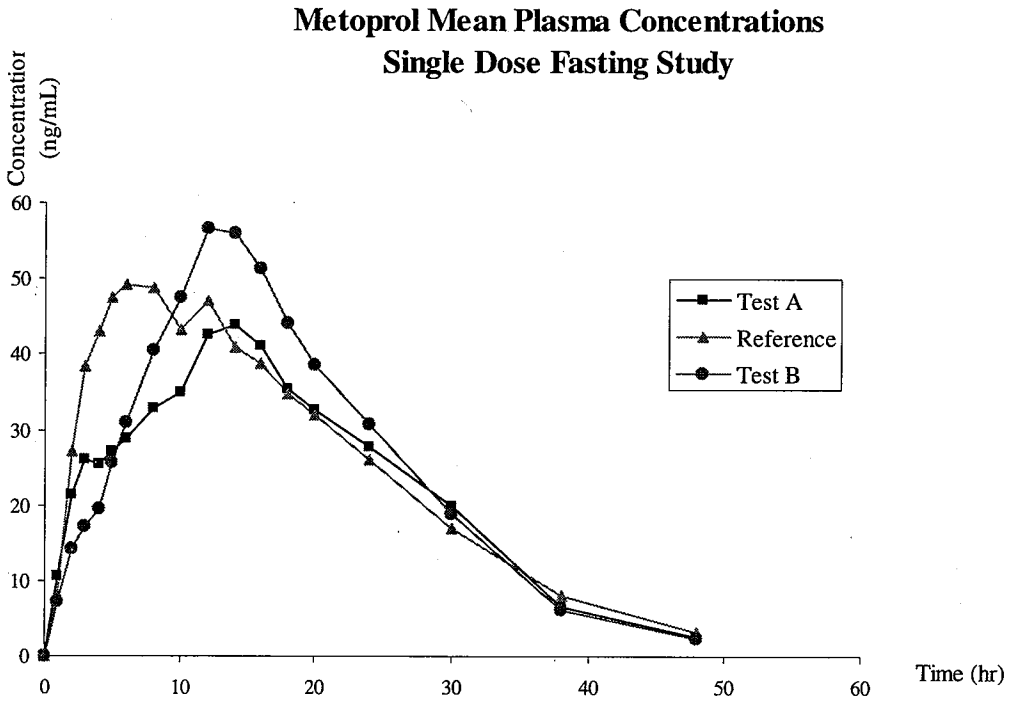
TRT=B:TEST

Time	N	Mean	Coeff of Variation	Minimum	Maximum
Hour0	33	0	.		(b) (4)
Hour1	33	7.2303030	99.3802826		
Hour2	33	14.2896970	89.7193562		
Hour3	33	17.2400000	93.9337290		
Hour4	33	19.5109091	99.1204566		
Hour5	33	25.5657576	91.8932958		
Hour6	33	30.9521212	90.3871315		
Hour8	33	40.4048485	86.0784660		
Hour10	33	47.5172727	84.8700395		
Hour12	33	56.6024242	73.2072406		
Hour14	33	56.0081818	75.4695112		
Hour16	33	51.2212121	81.3503931		
Hour18	33	44.0157576	90.6057169		
Hour20	33	38.6275758	97.9048024		
Hour24	33	30.7354545	112.5323302		
Hour30	33	18.8366667	157.1568497		
Hour38	33	6.1563636	233.5022705		
Hour48	33	2.3363636	290.8879438		

TRT=C:REF

Time	N	Mean	Coeff of Variation	Minimum	Maximum
					(b) (4)
Hour0	33	0	.		
Hour1	33	8.0115152	68.0488516		
Hour2	33	27.2421212	68.9926224		
Hour3	33	38.4233333	75.8982831		
Hour4	33	42.9812121	83.9878287		
Hour5	33	47.4096970	81.2033165		
Hour6	33	49.2818182	83.4306796		
Hour8	33	48.7596970	93.2340504		
Hour10	33	43.3045455	95.8292467		
Hour12	33	46.9854545	103.8397757		
Hour14	33	40.8581818	100.5845846		
Hour16	33	38.8530303	105.2756756		
Hour18	33	34.7830303	113.5736183		
Hour20	33	31.9272727	117.2498584		
Hour24	33	26.1469697	122.6258484		
Hour30	33	17.0221212	154.5324388		
Hour38	33	7.9969697	214.3587173		
Hour48	33	3.1684848	295.4590351		

Figure 1


Metoprol Mean Plasma Concentrations
Single Dose Fasting Study
Concentration (ng/mL)
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (hr)
Test A
Reference
Test B

2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	RA2-102
Study Title	A Relative Bioavailability Study of 200 mg Metoprolol Succinate Extended Release Tablets Under Non-Fasting Conditions
Clinical Site	PRACS Institute, East Grand Forks, MN
Principal Investigator	Thomas Cariveau, M.D.
Study/Dosing Dates	Period I: 11/09-11/02; Period II: 11/16-18/02
Analytical Site	PRACS Institute, Fargo, ND
Analytical Director	(b) (6) M.S.
Analysis Dates	12/10-19/02
Storage Period (no. of days from first sample to final analysis)	40 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metoprolol Succinate ER Tablets USP	Toprol-XL®
Manufacturer	KV	AstraZeneca
Batch/Lot No.	R416-055A	3698H
Manufacture Date	07/19/02	
Expiration Date		02/05
Strength	200 mg	200 mg
Dosage Form	ER Tablets	ER Tablets
Batch Size	(b) (4)	
Potency	100.2%	96.7%
Content Uniformity	103.2%(RSD=4.5%)	98.4%(RSD=1.8%)
Formulation	See Appendix Section B	
Dose Administered	1x200 mg	1x200 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	0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 38 and 48 hours postdose
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	Samples were collected in EDTA vacutainers, centrifuged and harvested for plasma which was stored at -70°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table
Length of Fasting	Approximately 10 hours prior to dosing. A standardized breakfast* was given 30 minutes before dosing.
Length of Confinement	Approximately 10 hours predose to 24 hours postdose
Safety Monitoring	Vital signs were measured at predose, 4, 8, 12 and 24 hours postdose. Pregnancy screen was done for female subjects prior to each period of the study.

*The standardized breakfast consisted of one buttered English muffin, one slice of American cheese, one serving of hash brown potatoes, one fried egg, one slice of Canadian bacon, 8 fl. oz. of whole milk and 6 fl. oz. of orange juice.

Table 11 Demographics of Study Subjects (N=35)

Age		Weight, kg		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	33
Mean	28.5	Mean	73.1	18-40	29	Male	18	Afr. Amer.	0
SD	10.8	SD	11.6	41-64	6	Female	17	Hispanic	2
Range	18-58	Range	48.9-106.5	65-75	0			Asian	0
				>75	0			Others	0

Study Results

Table 12 Dropout Information

Subject No.	No. 9
Reason	Due to personal reasons.
Period	Prior to Period II
Replacement	No

Was there a difference in side effects for the test versus the reference?
There was no significant difference in side effects between the test and reference products.

Table 13 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Dizziness	1	0
Headache	0	2
Hot	0	1
Pain (in both arms)	1	0
Total:	2	3

Comments: (*on adverse events)* None

Was there a difference in protocol deviations for the test versus the reference?

Table 14 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Reference)
Repeat/Additional Vital Signs Measurements	9	10
Concurrent medication usage	0	1(Ibuprofen for headache)

Comments: (*indicate protocol deviations compromised the integrity of study*) Protocol deviations did not appear to compromise the integrity of the study.

Table 15 Assay Validation – Within Study

	Parent				
QC Conc. (ng/mL)	15.00 (n=63)	25.00 (n=63)	70.00 (n=63)	120.00 (n=59)	120.00dil. (n=4)
Inter day Precision (%CV)	7.7	7.0	8.7	8.1	1.1
Inter day Accuracy (% Accuracy)	102.1	101.4	104.6	102.8	86.4
Cal. Standards Conc. (ng/mL)	5.00, 10.00, 25.00, 50.00, 75.00, 100.00, 150.00				
Inter day Precision (%CV)	1.06-3.02				
Inter day Accuracy (% Accuracy)	98.2-102.6				
Linearity Range (range of R^2 values)	5.00-150.0 (0.998-1.000)				

Chromatograms: Any interfering peaks? No

Table 16 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
090-01	05/13/02	**Sample Re-Analysis (NOTE:** The SOP was listed but not submitted. The firm is requested to submit the SOP for review in future submissions.)

Comments on repeat assays.

- Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. None
- Did recalculation of plasma concentrations change the study outcome? N/A
- Does the reviewer agree with the outcome of the repeat assays? If no, explain reason(s). Yes
- Provide any other comments about repeat assays. Samples were repeated for analytical reasons only. There were 21 subject samples reassayed mainly due to exceeding the curves. The samples were repeated with dilution. Dilution integrity was validated during prestudy validation. The standard curves and QC concentration ranges as selected are acceptable.

Comments on Within-Study Validation:

Conclusion: Analytical method is acceptable.

Table 17 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 20 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	Ng.hr/mL	1038	99	1010	101	1.03
AUC_{∞}	Ng.hr/mL	1247	94	1160	100	1.08
C_{max}	Ng/mL	49.84	79	53.73	61	0.93
T_{max}	Hrs	11.54	40	6.37	39	1.81
$T_{1/2}$	Hrs	11.73	95	10.42	32	1.13

Table 18 Least Squares Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	795.2	747.6	1.06	99.0-114.2
AUC_{∞}	921.0	886.3	1.04	97.9-110.3
C_{max}	40.02	46.17	0.87	77.5-96.9*

*The 90% confidence interval for Cmax was outside the [0.80-1.25] limit. However, since the study was conducted (11/02) prior to the issuance of the Food Study Guidance (1/2003), the point estimate criteria are applied to the nonfasting study results.

Table 19 Additional Study Information

Root mean square error, AUC0-t	0.1766	
Root mean square error, AUC∞	0.1353	
Root mean square error, Cmax	0.2754	
Mean ratio AUC0-t/AUC∞	T =0.8759	R =0.8478
Range of values, ratio AUC0-t/AUC∞	T =0.7304-0.9656	R =0.6602-0.9663

Comments: (on pharmacokinetic analysis)

- ke and AUC∞ were determined for how many subjects: 32 for Test Treatment, 35 for Reference Treatment. The reviewer agreed with firm's decision that the following subjects' ke and AUC∞ could not be determined: 2(Test), 19 (Test) and 28 (Test).
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None, and
  c. first measurable drug concentration as Cmax: None.

- Did pharmacokinetic parameters and point estimates calculated by the reviewer agree with firm's calculations? Yes.
- Were there statistically significant sequence or period effects? No. If so, did these affect the integrity of the study? N/A
- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%? *The 90% confidence interval for Cmax was outside the [0.80-1.25] limit. However, since the study was conducted (11/02) prior to the issuance of the Food Study Guidance (1/2003), the point estimate criteria are applied to the nonfasting study results.
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

Conclusion: The single-dose fed bioequivalence study is acceptable. The point estimates of AUC0-t, AUC∞ and Cmax fall within the [0.80-1.25] limit.

Table 20 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

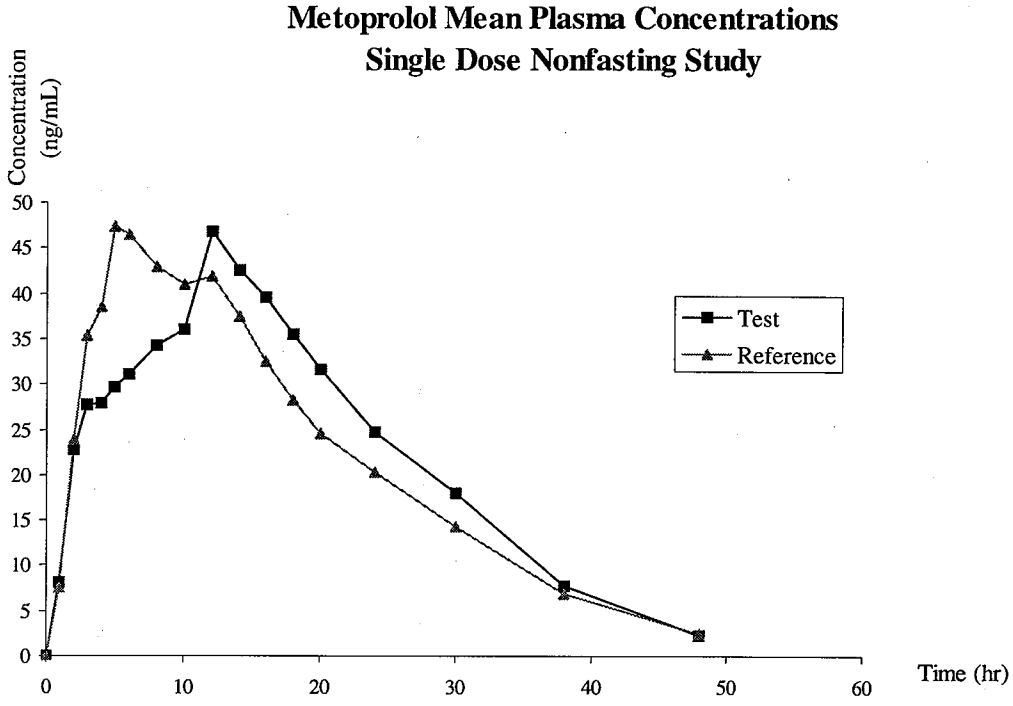
TRT=A:TEST

Time	N	Mean	Coeff of Variation	Minimum	Maximum
					(b) (4)
Hour0	35	0	.		
Hour1	35	8.1068571	145.5154549		
Hour2	35	22.8008571	70.2622633		
Hour3	35	27.8185714	79.1168306		
Hour4	35	27.8934286	82.5442922		
Hour5	35	29.6202857	84.2505235		
Hour6	35	31.0614286	80.6481932		
Hour8	34	34.2264706	80.8944275		
Hour10	35	36.0714286	88.2839984		
Hour12	34	46.7400000	81.9652040		
Hour14	35	42.6520000	82.2797744		
Hour16	35	39.6165714	81.6459161		
Hour18	35	35.4597143	94.2891530		
Hour20	35	31.5960000	95.4699264		
Hour24	35	24.8054286	116.4952308		
Hour30	35	18.0242857	135.4415003		
Hour38	34	7.7282353	195.1482271		
Hour48	33	2.2369697	380.9880762		

TRT=B:REF

Time	N	Mean	Coeff of Variation	Minimum	Maximum
					(b) (4)
Hour0	35	0	.		
Hour1	35	7.6091429	113.7353513		
Hour2	35	23.8197143	81.9339254		
Hour3	35	35.3465714	71.4874328		
Hour4	35	38.4768571	69.5915279		
Hour5	35	47.3457143	66.2425067		
Hour6	35	46.5397143	64.0838676		
Hour8	35	42.9697143	71.9447505		
Hour10	35	40.9042857	75.1524565		
Hour12	35	41.9122857	80.6149839		
Hour14	35	37.5025714	83.1273786		
Hour16	35	32.5148571	92.1387460		
Hour18	35	28.1900000	91.8556066		
Hour20	35	24.4951429	105.5924446		
Hour24	35	20.2734286	116.2160885		
Hour30	35	14.3825714	166.2497259		
Hour38	35	6.8971429	214.4538280		
Hour48	33	2.4612121	336.0692355		

Figure 2


Metoprolol Mean Plasma Concentrations
Single Dose Nonfasting Study
Concentration (ng/mL)
50
45
40
35
30
25
20
15
10
5
0
0
10
20
30
40
50
60
Time (hr)
Test
Reference

B. Formulation Data (For Test Formulations, 200 mg (Formulation A) and 100 mg)

Ingredient	100 mg		200 mg	
	Quantity to weigh (in mg/tab)	% in Exhibit Batch	Quantity to weigh (in mg/tab)	% in Exhibit Batch
Metoprolol Succinate, USP	95.0	28.27	190.0	28.3 %
Microcrystalline Cellulose, NF (b) (4)				(b) (4)
Croscarmellose Sodium, NF				
Sodium Stearyl Fumarate, NF				
(b) (4)				
(b) (4)				
(b) (4)				
Wax, Carnauba, NF (b) (4)				
Vinyl Acetate Copolymer (b) (4)				
Methacrylic Acid Copolymer (b) (4)				
Triethyl Citrate, NF				
Hydrogenated Vegetable Oil (b) (4)				
Calcium Stearate, NF				
(b) (4)				
Carboxymethylcellulose Sodium, NF (b) (4)				
Glyceryl Behenate, NF				
(b) (4)				
Povidone, USP (b) (4)				
TOTAL (mg)	336.09	100 %	671.5	100.0 %

NOTE: The amounts of metoprolol succinate, 95.0 mg/tablet and 190.0 mg/tablets, in the formulations of the 100 mg and 200 mg strengths above are equivalent to the amount of 100 mg and 200 mg of metoprolol tartrate, respectively

Following this page, 1 page withheld in full (b)(4)

C. Dissolution Data

1. Firm's Proposed Dissolution Method:

Medium	Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 21

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055			Reference Product, Strength: 200 mg Lot No. 3698H		
	Mean	%CV	Range	Mean	%CV	Range
1	11	14.5	(b) (4)	12	5.8	(b) (4)
2	15	11.3		18	2.8	
4	19	11.0		30	1.7	
8	27	7.8		49	1.4	
12	37	7.3		66	1.8	
16	47	6.4		79	1.5	
24	57	36.1*		92	2.3	

F2 between the test and reference lots: 31.89

F2 between the 200 mg and 100 mg strengths of the test product: 34.50

***NOTE:** The dissolution data for the 24-hour time point were highly variable for the test product and not consistent with the data of the earlier time points.

Table 22

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	15	11.3	(b) (4)	9	8.9	(b) (4)
2	21	11.4		15	7.3	
4	31	11.0		27	6.3	
8	47	7.9		49	4.9	
12	62	4.4		69	4.2	
16	74	2.6		84	3.3	
24	88	1.9		96	2.8	

F2 between the test and reference lots: 58.77

2. Dissolution Testing in Different pH media: pH 1.2 & 4.5

Medium	pH 1.2 buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 23

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	9.2	(b) (4)	12	6.7	(b) (4)
2	15	9.3		19	6.8	
4	19	8.4		34	5.3	
12	33	5.5		80	3.5	
24	61	4.6		97	3.7	

F2 between the test and reference lots: 28.12
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 24

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079B			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	15	22.7	(b) (4)	11	7.3	(b) (4)
2	24	11.2		19	4.2	
4	34	17.9		32	2.8	
12	64	14.1		78	2.2	
24	94	4.9		98	2.0	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Medium	pH 4.5 acetate buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 25

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	13.0	(b) (4)	10	11.0	(b) (4)
2	14	8.6		17	8.2	
4	19	8.4		28	7.5	
12	37	5.9		69	5.7	
24	69	5.2		93	4.8	

F2 between the test and reference lots: 36.75

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 26

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079B			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	14	25.0	(b) (4)	9	6.7	(b) (4)
2	25	34.4		15	4.7	
4	33	19.1		26	4.6	
12	68	14.7		67	3.0	
24	95	6.6		96	2.8	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

3. USP Method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Whole Tablets:

Table 27

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	15.0	(b) (4)	9	10.0	(b) (4)
2	14	12.9		15	8.0	
4	19	10.5		27	6.7	
8	26	8.5		48	5.4	
12	36	6.9		67	4.9	
20	64	5.8		90	3.3	

F2 between the test and reference lots: 35.93
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 28

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079B			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	14	20.0	(b) (4)	8	7.5	(b) (4)
2	22	19.1		14	7.9	
4	33	16.7		26	5.0	
8	52	14.4		47	3.4	
12	72	11.7		68	3.4	
20	93	8.9		92	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Half Tablets:

Table 29

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	17.5	(b) (4)	9	15.6	(b) (4)
2	15	17.3		16	12.5	
4	20	15.0		27	9.3	
8	28	11.8		48	6.9	
12	38	8.9		68	5.6	
20	61	6.9		90	3.4	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.
F2 between the test half and whole tablets (of 200 mg): Not calculated due to high CV%'s in the test profile data of the 200 mg half tablets.
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data.

Table 30

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079B			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	18	20.6	(b) (4)	11	10.9	(b) (4)
2	26	19.2		17	10.0	
4	37	17.6		29	6.9	
8	56	14.3		50	4.2	
12	72	10.8		70	3.3	
20	91	7.2		93	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.
F2 between the test half and whole tablets (of 100 mg): Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the half-tablets of the100 mg and 200 strengths of the test product were highly variable and more variable than those of the whole tablets of the 200 mg strength of the test product and the RLD product.

Following this page, 18 pages withheld in full (b)(4)-SAS Output

F. Additional Attachments

None

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The dissolution data of both strengths of the test product are highly variable. Especially, for the whole tablets of the 100 mg strength and the half tablets of both strengths, the coefficients of variation were greater than 10% for most time points. Please provide explanation for the high variability of the dissolution data. In addition, the dissolution profiles of the 100 mg and 200 mg strengths of the test product are not similar, with the 100 mg having a much faster rate. Please provide explanation for the difference in the dissolution rate between the two strengths.

2. Please note that the Division of Bioequivalence recommends that you use the compendial method of USP 27 for stability and quality controls testing of your product.

3. You have not submitted dissolution data for the 200 mg strength, using the USP method, **for the final time point at which at least 80% of the labeled amount of the test product is dissolved.** Please submit the dissolution data for the 200 mg strength at the final time point.

4. Due to the deficiencies cited in Comments 1 and 3 above, the waiver request for the 100 mg strength is not considered at this time pending satisfactory responses concerning the dissolution data for both strengths.

Sincerely yours,

for

Barbara M. Saunt

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

CC:ANDA 76-640
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
HFD-617/ A. Sigler
HFD-650/ D. Conner

V:\FIRMSAM\KV\ltrs&rev\76640n0103.doc
Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE
DISSOLUTION - INCOMPLETE

Submission date: 01-05-03
07-28-03
10/03/03
~~10/21/03~~
11/05/03

1. FASTING STUDY (STF)
   Clinical: PRACS Institute
   Analytical: PRACS Institute
   Strength: 200 mg
   Outcome: AC

2. NON-FASTING STUDY (STP)
   Clinical: PRACS Institute
   Analytical: PRACS Institute
   Strength: 200 mg
   Outcome: AC

3. DISSOLUTION WAIVER (DIW)
   Strength: 100 mg
   Outcome : IC

4. STUDY AMENDMENT (STA): For additional dissolution data obtained using USP method 10/03/03
   Strength: 200 mg & 100 mg
   Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	April 14, 2004
Amendment Date(s)	May 7, 2004 (Telephone Amendment)
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\kv\ltrs&rev\76640a0404.doc**

I. Executive Summary

This is a review of an amendment. The firm has submitted its responses to the DBE's previous deficiency comments concerning the dissolution variability, dissolution profile difference between strengths and determination of the final time point of the dissolution specifications. The firm has identified the source of the dissolution profile difference as due to the use of [redacted] (b) (4) for the 100 mg and 200 mg strengths of the test product. This manufacturing process difference has been corrected in the Master Batch Record and the firm has submitted a replacement lot for the 100 mg strength, manufactured using the correct [redacted] (b) (4). Dissolution data for the replacement lot were provided in the current amendment. The dissolution profile of the replacement lot was found more similar to that of the bio lot of the 200 mg strength. Although the dissolution data of the test product were more variable than the RLD product, the 200 mg strength met the *in vivo* bioequivalence testing criteria.

With respect to determination of the final time point for the dissolution specification using the USP dissolution method, it has been found appropriate to recommend a much lower release percent (Q= [redacted] (b) (4) at 20 hours) for the test product since the submitted data showed that 80% of the labeled amount of the test product was not released until approximately 30 hours. The release rate was found not dependent on the paddle speed or volume of the medium.

The firm had previously submitted a single-dose, 3-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing the test product, Metoprolol Succinate ER Tablets, 200 mg, with the RLD product, AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets, 200 mg. These studies were found acceptable (See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

The formulations of the 100 mg and 200 mg strengths of the test product are proportionally similar. The dissolution profiles of the two strengths were similar. Therefore, the waiver request for the 100 mg strength is granted.

This application is deficient pending the firm's response to the Agency's dissolution specification recommendation.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information (based on the PDR labeling of the RLD product and NDA 19-962's 1993-1994 reviews)

Bioavailability	50% (after first pass); 65-70% (relative bioavailability as compared with conventional IR metoprolol tablets)
Food Effect	Food does not significantly affect the bioavailability.
Tmax	4.4-14.0 hours
Metabolism	Extensive first-pass metabolism in the liver to yield inactive metabolites.
Excretion	Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites.
Half-life	3-7 hours
Relevant OGD or DBE History	**(1) Control Documents # 01-423 ((b) (4) 08/31/01) and 01-470 ((b) (4) 09/20/01):** The DBE recommended a replicate, single-dose fasting bioequivalence study for the 200 mg and 50 mg strengths of the test product, a crossover, single-dose nonfasting bioequivalence study for the 200 mg strength. Biowaiver request for the 25 mg and 100 mg strengths may be considered based on formulation proportionality, comparable dissolution profiles and acceptable *in vivo* testing of the 200 mg and 50 mg strengths. **(2) Control Document #02-105 ((b) (4) 02/27/02):** The DBE recommended the same as above except that replicate design was no longer requested for the fasting study, and metoprolol was determined to be the only analyte to be measured.
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	1
Single-dose fed	No	1
Steady-state	No	0
In vitro dissolution	No	
Waiver requests	No	1
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies		
Amendments	Yes	2 (1 amendment to respond to the DBE deficiency letter and 1 telephone amendment to provide additional dissolution data)

D. Pre-Study Bioanalytical Method Validation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	R02-586
Study Design	Three-way crossover
No. of subjects enrolled	33
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 4
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)* and R416-059A (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment C)
Strength tested	200 mg
Dose	1x200 mg

*NOTE: Only Test Formulation A is currently submitted for approval.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.98	88.67-108.2
AUC_{∞}	0.91	81.83-102.0
C_{max}	0.95	87.28-103.3

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	96.40-117.6
AUC_{∞}	1.00	90.44-111.0
C_{max}	1.21	111.3-131.8

Comments on Fasting Study: The fasting study is acceptable with respect to Test Formulation A.

2. Single-dose Fed Bioequivalence Study

Study No.	RA2-102
Study Design	Two-way crossover
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 17
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment B)
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=35		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	99.0-114.2
AUC_{∞}	1.04	97.9-110.3
C_{max}	0.87	77.5-96.9*

Comments on fed study: The nonfasting study is acceptable based on point estimate. The study was conducted before the issuance of the food guidance.

F. Formulation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

G. In Vitro Dissolution

Source of Method	USP
Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
USP specifications	Hour 1: NMT 25% Hour 4: 20-40% Hour 8: 40-60% Hour 20: NLT 80%
Firm's proposed specifications	Hour 2: (b) (4) Hour 4: Hour 12: Hour 24:
FDA specifications for the test product based on the submitted data	Hour 1: (b) (4) Hour 4: Hour 8: Hour 20:
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Not calculated due to high CV%'s in the test profile data.
Method is acceptable (yes or no)	Yes

H. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

I. Comments

The DBE has communicated the following deficiencies to the firm in the letter dated 01/23/04:

"1. The dissolution data of both strengths of the test product are highly variable. Especially, for the whole tablets of the 100 mg strength and the half tablets of both strengths, the coefficients of variation were greater than 10% for most time points. Please provide explanation for the high variability of the dissolution data. In addition, the dissolution profiles of the 100 mg and 200 mg strengths of the test product are not similar, with the 100 mg having a much faster rate. Please provide explanation for the difference in the dissolution rate between the two strengths.

2. Please note that the Division of Bioequivalence recommends that you use the compendial method of USP 27 for stability and quality controls testing of your product.

3. You have not submitted dissolution data for the 200 mg strength, using the USP method, for the final time point at which at least 80% of the labeled amount of the test product is dissolved. Please submit the dissolution data for the 200 mg strength at the final time point.

4. Due to the deficiencies cited in Comments 1 and 3 above, the waiver request for the 100 mg strength is not considered at this time pending satisfactory responses concerning the dissolution data for both strengths. "

The firm's responses are summarized below:

1. *"Metoprolol Succinate Extended-Release Tablets, USP, is manufactured by the use of an extended-release* (b) (4) *tablets formulation. The finished tablet has* (b) (4) (b) (4) *ER pellets which may break upon cutting the tablet into halves. The act of cutting may increase the variability and CV% by damaging some of the ER pellets in the tablet* (b) (4) *The number of ER pellets that break upon cutting may be slightly different from tablet to tablet.*

The Metoprolol Succinate Extended-Release Tablets, USP, whole tablet dissolution is less variable than the half tablet dissolution." In addition, *"In vitro variability is unrelated to the performance of the product in vivo."* The test product is found bioequivalent to the reference product, with similar CV%'s for most of the important PK parameters.

2. The following response was also submitted to the Division of Chemistry: The significant difference observed between the dissolution profiles of the 100 mg and 200 mg was found to be due to the (b) (4)

For this reason, KV is proposing a replacement lot #R429-081 for the 100 mg. The replacement lot #R429-081 used (b) (4) (b) (4) *and has similar dissolution data to the 200 mg.*

(b) (4)

The firm has submitted the dissolution data for the replacement lot#R429-081 of the 100 mg strength. The dissolution profiles of 100 mg whole tablets were submitted in four different media and also using the USP dissolution method. The dissolution profile of

100 mg half tablets was also submitted using the USP dissolution method. The data are summarized in the review Appendix.

3. The firm acknowledges that the USP dissolution method is recommended for the test product.

4. The firm did not submit the dissolution data for the final time point at which at least 80% of the labeled amount of the test product is dissolved for the reason that the DBE had previously instructed the firm to perform the testing *"up to 80% or 20 hours whichever comes first."* Upon reviewing the amendment, the DBE contacted the firm by telephone on April 20, 2004 to clarify that in order to set the specifications for the test product, especially for the final time point, it is necessary to determine the time at which 80% of the test product is dissolved. The firm was suggested to try dissolution testing using higher paddle speeds (i.e., 75 rpm and 100 rpm). Subsequently, the firm submitted the Telephone Amendment dated 05/07/04 to provide the requested additional dissolution data.

Although the firm did not submit individual data for the additional dissolution testing, two dissolution graphs were provided along with the experiment conditions (See the review Appendix). The 80% release point was found to be approximately 30 hours and 100% release eventually happens at around 41.5 hours. It was also found that the release of metoprolol succinate from the test tablets was not dependent on the volume or speed of the paddle.

DBE's Comments on the Firm's Current Responses:

1. The firm's responses concerning the variability in dissolution data of the test product are adequate and acceptable. Although the dissolution data of the 100 mg strength remains highly variable, the dissolution profile of the replacement lot of the 100 mg strength is considered more similar to that of the 200 mg. In addition, there is no dose dumping observed for the half tablets.

2. Based on the additional dissolution data submitted, the DBE recognizes the test product is slow-release and 80% of the labeled amount is not released at reasonable testing time using the USP dissolution method. The current USP specifications are not appropriate for the test product. The DBE recommends the following dissolution specifications based on the data submitted for both the 100 mg and 200 mg strengths of the test product.

	(b) (4)
Hour 1:	
Hour 4:	
Hour 8:	
Hour 20:	

Although the specification recommended for the final time point of 20 hours is lower than usual, similar specification has been recommended for at least another drug product

with similar slow-release profile when compared with the reference product (Q= (b) (4) at 24 hours was recommended for ANDA 40-539, Theophylline ER Tablets, 600 mg (Able Laboratories; 03/15/04)).

The firm is requested to respond to the FDA-recommended specifications which are different from the firm's proposed specifications (Hour 2: (b) (4) Hour 4: (b) (4) Hour 12: (b) (4) Hour 24: (b) (4)).

J. Recommendations

From the review of the original submission:

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by KV Pharmaceutical on the test product, Metoprolol Succinate ER Tablets, 200 mg, lot # R416-055, comparing it with the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg, lot # 3698H, have been found **acceptable** by the Division of Bioequivalence. The test product, KV's Metoprolol Succinate ER Tablets, 200 mg, is deemed bioequivalent to the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg.

From the review of the current amendment:

2. The dissolution testing is considered **incomplete**. The firm has conducted the dissolution testing on its Metoprolol Succinate ER Tablets, 200 mg and 100 mg, using the USP dissolution method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50

The firm proposed the following specifications:

Hour 2:	(b) (4)
Hour 4:	
Hour 12:	
Hour 24:	

However, the Agency recommends the following specifications (based on the submitted data):

Hour 1:	(b) (4)
Hour 4:	
Hour 8:	
Hour 20:	

The firm is requested to provide response to the Agency's specification recommendations.

3. The formulations of the 100 mg and 200 mg strengths of the test product are proportionally similar. The dissolution testing of the 100 mg strength is acceptable. The waiver request for the 100 mg strength is granted. The test product, KV's Metoprolol Succinate ER Tablets, 100 mg, is deemed bioequivalent to the reference product, Astra Zeneca's Toprol-XL® Tablets, 100 mg.

6/25/04

Hoainhon Nguyen, Review Branch I, Date

6/25/2004

Shriniwas Nerurkar, Ph.D., Team Leader, Review Branch I, Date

Barbara M Davis 6/25/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Hnguyen/06-01-04/v:\firmsam\kv\ltrs&rev\76640a0404.doc

IV. Appendix

A. Dissolution Data

1. Dissolution Testing in Different pH media: pH 1.2 & 4.5

Medium	pH 1.2 buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 1

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	9.2	(b) (4)	12	6.7	(b) (4)
2	15	9.3		19	6.8	
4	19	8.4		34	5.3	
12	33	5.5		80	3.5	
24	61	4.6		97	3.7	

F2 between the test and reference lots: 28.12
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the profile data of the 100 mg.

Table 2

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	9	23.3	(b) (4)	11	7.3	(b) (4)
2	12	22.5		19	4.2	
4	16	20.0		32	2.8	
12	36	12.5		78	2.2	
24	74	5.8		98	2.0	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Medium	pH 4.5 acetate buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 3

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	13.0	(b) (4)	10	11.0	(b) (4)
2	14	8.6		17	8.2	
4	19	8.4		28	7.5	
12	37	5.9		69	5.7	
24	69	5.2		93	4.8	

F2 between the test and reference lots: 36.75

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 4

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	10	26.0	(b) (4)	9	6.7	(b) (4)
2	13	23.1		15	4.7	
4	18	20.0		26	4.6	
12	43	11.4		67	3.0	
24	79	7.6		96	2.8	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

2. USP Method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Whole Tablets:

Table 5

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	15.0	(b) (4)	9	10.0	(b) (4)
2	14	12.9		15	8.0	
4	19	10.5		27	6.7	
8	26	8.5		48	5.4	
12	36	6.9		67	4.9	
20	64	5.8		90	3.3	

F2 between the test and reference lots: 35.93

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 6

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	9	18.9	(b) (4)	8	7.5	(b) (4)
2	12	20.8		14	7.9	
4	17	20.0		26	5.0	
8	28	16.8		47	3.4	
12	42	12.6		68	3.4	
20	68	8.8		92	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Half Tablets:

Table 7

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	17.5	(b) (4)	9	15.6	(b) (4)
2	15	17.3		16	12.5	
4	20	15.0		27	9.3	
8	28	11.8		48	6.9	
12	38	8.9		68	5.6	
20	61	6.9		90	3.4	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.
F2 between the test half and whole tablets (of 200 mg): Not calculated due to high CV%'s in the test profile data of the 200 mg half tablets.
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data.

Table 8

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	12	28.3	(b) (4)	11	10.9	(b) (4)
2	16	21.2		17	10.0	
4	21	18.6		29	6.9	
8	31	14.2		50	4.2	
12	44	11.1		70	3.3	
20	71	8.2		93	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.
F2 between the test half and whole tablets (of 100 mg): Not calculated due to high CV%'s in the test profile data.

NOTE: The variability of the dissolution data for the half-tablets and whole tablets of the100 mg and 200 strengths of the test product were similar, and higher compared with the dissolution data of the RLD product. There was no dose dumping for either the 100 mg or 200 mg strength of the test and reference products.

B. Attachment: The Firm's Investigation of the Dissolution of KV's Metoprolol Succinate Tablets

76640dissolutionamendment.pdf

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The dissolution testing is considered **incomplete**. You have conducted the dissolution testing on its Metoprolol Succinate ER Tablets, 200 mg and 100 mg, using the USP dissolution method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus Type	II (paddle)
Rotation (rpm)	50

You have proposed the following specifications:

Hour 2:	(b) (4)
Hour 4:	
Hour 12:	
Hour 24:	

However, the Agency recommends the following specifications (based on the submitted data):

Hour 1:	(b) (4)
Hour 4:	
Hour 8:	
Hour 20:	

Please provide your response to the Agency's specification recommendations.

Sincerely yours,

/s/ Barbara M. Davit

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

CC:ANDA 76-640
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen HNC
HFD-652/ SNerurkar
HFD-617/ A. Sigler
HFD-650/ D. Conner BZD 6/25/04

6/25/04

V:\FIRMSAM\KV\ltrs&rev\76640a0404.doc
Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE
DISSOLUTION - INCOMPLETE

Submission date: 04-14-04
05-07-04

1. STUDY AMENDMENTS (STA)

Strength: 200 mg & 100 mg

To provide additional dissolution data, explanations for the dissolution data variability and profile difference between strengths.

Outcome: ~~AC~~ IC

OUTCOME DECISIONS: **IC** - Incomplete (fatal flaw) **UN** - Unacceptable
AC - Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	July 30, 2004
Amendment Date(s)	
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\kv\ltrs&rev\76640a0704.doc**

I. Executive Summary

This is a review of an amendment. The firm has submitted its responses to the DBE's recommended dissolution method and specifications. The FDA-recommended method is the same as the USP method; however, the specifications are different. The firm concurred with the recommended specifications for the first three time points but disagreed with the Agency on specification for the 20-hour time point (NLT (b) (4) in 20 hours).

The firm has proposed a different specification for the 20-hour time point (NLT (b) (4) in 20 hours). This specification was found unacceptable since it was based on dissolution data obtained using the firm's dissolution method (which is different from the USP's method), and on extrapolated data.

The determination of the specifications for the test product using the USP method has been confounded by the fact that the dissolution testing using the USP method was conducted only after the test lots were already 14-15 months old. (The DBE generally requests USP method be used, if available, on a fresh bio lot. However, the bio lot for this ANDA was no longer fresh at the time the firm received the DBE request concerning the USP method.)

In the original submission, the firm had proposed dissolution testing using its own dissolution method and specifications. The DBE was not able to determine specifications for the firm's dissolution method based on the data submitted since there was questionable variability at the last time point (24-hour time point) for the 200 mg strength.

For the reasons cited above, the firm is requested to conduct dissolution testing using both USP and its own methods for one fresh lot of each of the strengths, 200 mg and 100 mg. If fresh lots are not available, the firm is requested to manufacture a new lot for each of the strengths and conduct the requested dissolution testing. The dissolution

specifications will be determined by the DBE based on the dissolution data of the fresh lots tested at Stage 2 (using 12 units).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information (based on the PDR labeling of the RLD product and NDA 19-962's 1993-1994 reviews)

Bioavailability	50% (after first pass); 65-70% (relative bioavailability as compared with conventional IR metoprolol tablets)
Food Effect	Food does not significantly affect the bioavailability.
Tmax	4.4-14.0 hours
Metabolism	Extensive first-pass metabolism in the liver to yield inactive metabolites.
Excretion	Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites.
Half-life	3-7 hours
Relevant OGD or DBE History	**(1) Control Documents # 01-423 ((b) (4) 08/31/01) and 01-470 ((b) (4) 09/20/01):** The DBE recommended a replicate, single-dose fasting bioequivalence study for the 200 mg and 50 mg strengths of the test product, a crossover, single-dose nonfasting bioequivalence study for the 200 mg strength. Biowaiver request for the 25 mg and 100 mg strengths may be considered based on formulation proportionality, comparable dissolution profiles and acceptable *in vivo* testing of the 200 mg and 50 mg strengths. **(2) Control Document #02-105 ((b) (4) 02/27/02):** The DBE recommended the same as above except that replicate design was no longer requested for the fasting study, and metoprolol was determined to be the only analyte to be measured.
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	
Waiver requests	No	0
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies		
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	R02-586
Study Design	Three-way crossover
No. of subjects enrolled	33
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 4
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)* and R416-059A (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment C)
Strength tested	200 mg
Dose	1x200 mg

*NOTE: Only Test Formulation A is currently submitted for approval.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.98	88.67-108.2
AUC_{∞}	0.91	81.83-102.0
C_{max}	0.95	87.28-103.3

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	96.40-117.6
AUC_{∞}	1.00	90.44-111.0
C_{max}	1.21	111.3-131.8

Comments on Fasting Study: The fasting study is acceptable with respect to Test Formulation A.

2. Single-dose Fed Bioequivalence Study

Study No.	RA2-102
Study Design	Two-way crossover
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 17
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment B)
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=35		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	99.0-114.2
AUC_{∞}	1.04	97.9-110.3
C_{max}	0.87	77.5-96.9*

Comments on fed study: The nonfasting study is acceptable based on point estimate. The study was conducted before the issuance of the food guidance.

F. Formulation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

G. In Vitro Dissolution

Source of Method	USP
Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
USP specifications	Hour 1: NMT 25% Hour 4: 20-40% Hour 8: 40-60% Hour 20: NLT 80%
Firm's proposed specifications (in the current amendment)	Hour 1: (b) (4) Hour 4: Hour 8: Hour 20:
FDA specifications for the test product based on the submitted data	Hour 1: Hour 4: Hour 8: Hour 20:
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Not calculated due to high CV%'s in the test profile data.
Method is acceptable (yes or no)	Yes

*NOTE: The specification at 20 hours as proposed by the firm was based on *estimated* data. The firm's previously proposed specification at 24 hour time point, using the USP method, was (b) (4) (See the review of the submission dated 04/14/04, v:\firmsam\kv\ltrs&rev\76640a0404.doc). See Comments section below for further discussion of the firm's previous and current proposed specifications.

H. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

I. Firm's Responses in Current Amendment

The DBE has communicated the following deficiencies to the firm in the letter dated 06/30/04:

*"The dissolution testing is considered **incomplete**. You have conducted the dissolution testing on its Metoprolol Succinate ER Tablets, 200 mg and 100 mg, using the USP dissolution method:*

Medium *pH 6.8 phosphate buffer*
Volume (mL) *500 mL*
USP Apparatus Type *II (paddle)*
Rotation (rpm) *50*

You have proposed the following specifications:

Hour 2: (b) (4)
Hour 4:
Hour 12:
Hour 24:

However, the Agency recommends the following specifications (based on the submitted data):

Hour 1: (b) (4)
Hour 4:
Hour 8:
Hour 20:

Please provide your response to the Agency's specification recommendations."

The firm's responses are summarized below:

1. The firm concurs with the above FDA specifications for 1, 2, and 8 hour time points. However, the firm does not concur with the Agency on the recommended specification at 20 hours for the following reasons:

"At release, the proposed product was not tested at 20 hours. In order to access the percent dissolved at 20 hours, at release time, we estimated the 20 hour percent dissolved, from the 24 hr actual data with the following formula: (24 hr percent dissolved X 20)/24=20 hr percent dissolved.

Strength/Lot	24 hr Actual Value	20 hr Estimated Value
200 mg/R416055	(b) (4)	
100 mg/R429081		

As can be seen there is one value per strength below the FDA proposed specification. Further, there is an additional unit per strength right at the lower limit of the proposed specification.

FDA based their proposal on dissolution profiles which were submitted to FDA on a bio amendment dated 10/03/03. These profiles were made at the request from the Bioequivalence Division on a letter dated 09/05/03. The profiles were tested at 14 and 15.5 months from the date of manufacture, for the 200 and 100 mg strengths respectively. Thus, these profiles are not a reflection of the product at the time of manufacture.

It is therefore, KV's recommendation that the proposed specification for the 20 hour time point be NLT (b) (4)"

2. The firm also wishes to keep the medium volume of 900 mL, as proposed in the original submission, for routine testing. The firm justified the use of 900 mL volume by citing the data submitted in the Telephone Amendment dated 05/07/04 which showed that changes in medium volume had no effect on percent dissolved, and the fact that *"the release and stability data generated in support of the approval of the proposed product was generated using 900 mL media volume".*

J. Deficiency Comments:

1. The firm has proposed a different specification for the 20-hour time point (NLT (b) (4) in 20 hours). This specification has been found **unacceptable** since it was based on dissolution data obtained using the firm's dissolution method (which is different from the USP's method), and on extrapolated data. The firm should note that although the firm's and USP methods may be considered equivalent, the specifications for each method are determined based on the *actual* dissolution data of 12 units obtained using each method separately, and not by transplanting estimated data from the firm's method into the data obtained by the USP method.

2. The determination of the specifications for the test product using the USP method has been confounded by the fact that the dissolution testing using the USP method was conducted only after the test lots were already 14-15 months old. (The DBE generally requests USP method be used, if available, on a fresh bio lot. However, the bio lot for this ANDA was no longer fresh at the time the firm received the DBE request concerning the USP method.)

3. In the original submission, the firm had proposed dissolution testing using its own dissolution method and specifications. The DBE was not able to determine specifications for the firm's dissolution method based on the data submitted since there was questionable variability at the last time point (24-hour time point) for the 200 mg strength. In the original submission dated January 15, 2003 (Vol. A1.1, Section VI, page 104), based on 12 units, the dissolution data at the 24- hour time point for the 200 mg strength (Lot No. R416-055) were highly variable and not consistent with the data of the earlier time points (mean=57%, with CV%=36.1 and range of (b) (4), whereas the CV%'s of earlier time points were less than 15%).

In addition, there were no acceptable dissolution data submitted for the 100 mg strength using the firm's method. The lot used in the original dissolution testing (using the firm's method) for the 100 mg strength (Lot No. R416-079) was later replaced due to the manufacturing process deficiency. There were no other dissolution data submitted for the replacement lot (R416081) of the 100 mg strength, **based on 12 units**, and **using the firm's method.**

4. For the reasons cited above, the firm is requested to conduct dissolution testing using both USP method (for sampling up to 20 hours) and the firm's own methods (for sampling up to 24 ours) for one fresh lot of each of the strengths, 200 mg and 100 mg. If fresh lots are not available, the firm is requested to manufacture a new lot for each of the strengths and conduct the requested dissolution testing. The dissolution specifications will be determined by the DBE based on the dissolution data of the fresh lots tested at Stage 2 (using 12 units).

K. Recommendations

From the review of the previous submissions:

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by KV Pharmaceutical on the test product, Metoprolol Succinate ER Tablets, 200 mg, lot # R416-055, comparing it with the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg, lot # 3698H, have been found **acceptable** by the Division of Bioequivalence. The test product, KV's Metoprolol Succinate ER Tablets, 200 mg, is deemed bioequivalent to the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg.

2. The formulations of the 100 mg and 200 mg strengths of the test product are proportionally similar. The dissolution testing of the 100 mg strength is acceptable. The waiver request for the 100 mg strength is granted. The test product, KV's Metoprolol Succinate ER Tablets, 100 mg, is deemed bioequivalent to the reference product, Astra Zeneca's Toprol-XL® Tablets, 100 mg.

From the review of the current amendment:

3. The dissolution testing is considered **incomplete** due to reasons cited in the Deficiency Comments above. The firm should be informed of the Comments.

1/21/05

Hoainhon Nguyen, Review Branch I, Date

1/24/2005

Shriniwas Nerurkar, Ph.D., Team Leader, Review Branch I, Date

1/24/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Hnguyen/11-30-04/v:\firmsam\kv\ltrs&rev\76640a0704.doc

IV. Appendix

A. Dissolution Data

1. Dissolution Testing in Different pH media: pH 1.2 & 4.5

Medium	pH 1.2 buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 1

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	9.2	(b) (4)	12	6.7	(b) (4)
2	15	9.3		19	6.8	
4	19	8.4		34	5.3	
12	33	5.5		80	3.5	
24	61	4.6		97	3.7	

F2 between the test and reference lots: 28.12
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the profile data of the 100 mg.

Table 2

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	9	23.3	(b) (4)	11	7.3	(b) (4)
2	12	22.5		19	4.2	
4	16	20.0		32	2.8	
12	36	12.5		78	2.2	
24	74	5.8		98	2.0	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Medium	pH 4.5 acetate buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 3

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	13.0	(b) (4)	10	11.0	(b) (4)
2	14	8.6		17	8.2	
4	19	8.4		28	7.5	
12	37	5.9		69	5.7	
24	69	5.2		93	4.8	

F2 between the test and reference lots: 36.75
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 4

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	10	26.0	(b) (4)	9	6.7	(b) (4)
2	13	23.1		15	4.7	
4	18	20.0		26	4.6	
12	43	11.4		67	3.0	
24	79	7.6		96	2.8	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

2. USP Method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Whole Tablets:

Table 5

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	15.0	(b) (4)	9	10.0	(b) (4)
2	14	12.9		15	8.0	
4	19	10.5		27	6.7	
8	26	8.5		48	5.4	
12	36	6.9		67	4.9	
20	64	5.8		90	3.3	

F2 between the test and reference lots: 35.93

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 6

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	9	18.9	(b) (4)	8	7.5	(b) (4)
2	12	20.8		14	7.9	
4	17	20.0		26	5.0	
8	28	16.8		47	3.4	
12	42	12.6		68	3.4	
20	68	8.8		92	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Half Tablets:

Table 7

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	17.5	(b) (4)	9	15.6	(b) (4)
2	15	17.3		16	12.5	
4	20	15.0		27	9.3	
8	28	11.8		48	6.9	
12	38	8.9		68	5.6	
20	61	6.9		90	3.4	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

F2 between the test half and whole tablets (of 200 mg): Not calculated due to high CV%'s in the test profile data of the 200 mg half tablets.

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data.

Table 8

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	12	28.3	(b) (4)	11	10.9	(b) (4)
2	16	21.2		17	10.0	
4	21	18.6		29	6.9	
8	31	14.2		50	4.2	
12	44	11.1		70	3.3	
20	71	8.2		93	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

F2 between the test half and whole tablets (of 100 mg): Not calculated due to high CV%'s in the test profile data.

NOTE: The variability of the dissolution data for the half-tablets and whole tablets of the100 mg and 200 strengths of the test product were similar, and higher compared with the dissolution data of the RLD product. There was no dose dumping for either the 100 mg or 200 mg strength of the test and reference products.

3. Firm's Originally Proposed Dissolution Method: (Submitted in the original submission dated 01/15/03, Vol. A1.1, Section VI, page 104)

NOTE: This is the same method that in the current amendment the firm wishes to use for its stability and release testing. The F2 Similarity Factor comparing the dissolution data of the 200 mg strength of the test product (Lot No. R416-055) between the USP and firm's methods was 85.51, using the sampling times of 1, 2, 4, 8 and 12 hours. Similarly, F2 comparing the 100 mg strength of the reference product (Lot No. 3603J) was 89.63. There are no available dissolution data for similar comparison of the 200 mg strength of the RLD product or the 100 mg strength of the test product since different lots were tested using the USP and firm's methods. Also, comparison can not be made after the 12 hour sampling time since the USP method uses 20-hour as the last time point whereas the firm's uses 16-hour and 24-hour as the last time points. However, based on the F2 values above calculated from the available data, **the firm and USP methods appeared equivalent.**

Medium	Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 9

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055			Reference Product, Strength: 200 mg Lot No. 3698H		
	Mean	%CV	Range	Mean	%CV	Range
1	11	14.5	(b) (4)	12	5.8	(b) (4)
2	15	11.3		18	2.8	
4	19	11.0		30	1.7	
8	27	7.8		49	1.4	
12	37	7.3		66	1.8	
16	47	6.4		79	1.5	
24	57	36.1*		92	2.3	

F2 between the test and reference lots: 31.89

F2 between the 200 mg and 100 mg strengths of the test product: 34.50

***NOTE:** The dissolution data for the 24-hour time point were highly variable for the test product and not consistent with the data of the earlier time points.

Table 10

NOTE: The below 100 mg lot No. R416-079 was later replaced with the 100 mg lot No. R429081 due to a deficiency in the manufacturing process. See the review of the submission dated 04/14/04, v:\firmsam\kv\ltrs&rev\76640a0404.doc.

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	15	11.3	(b) (4)	9	8.9	(b) (4)
2	21	11.4		15	7.3	
4	31	11.0		27	6.3	
8	47	7.9		49	4.9	
12	62	4.4		69	4.2	
16	74	2.6		84	3.3	
24	88	1.9		96	2.8	

F2 between the test and reference lots: 58.77

4. **Firm's Dissolution Method: (Submitted in the original submission dated 01/15/03, Vol. A1.10, Section XIV, page 4973 and the amendment dated 04/14/04, Vol. A5.1, Attachment 2, page 50)**

NOTE: The following dissolution data were presented under Certificate of Analysis. For Lot No. R416-055 (200 mg), the Certificate was dated 08/22/02. The lot was manufactured on 07/19/02 according to the Certificate. For Lot No. R429-081 (Replacement lot, 100 mg), the Certificate was dated 11/20/03. The lot was manufactured on 08/02/02 according to the Certificate. The dissolution data were based on **6 units** for each lot. In the current amendment, the firm referred to these data as *release data.*

Medium	Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 11

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055		
	Mean	%CV	Range
1	11	14.5	(b) (4)
2	15	10	
4	20	6.5	
8	29	3.1	
12	38	0.80	
16	49	1.2	
24	68	3.4	

Table 12

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R429-081		
	Mean	%CV	Range
1	7	8.6	(b) (4)
2	10	9.0	
4	14	7.1	
8	24	6.2	
12	36	5.6	
16	50	5.2	
24	69	5.4	

Similarity Factor F2 between the 200 mg and 100 mg lots: 69.61

B. Attachment: The Firm's Investigation of the Dissolution of KV's Metoprolol Succinate Tablets (Submitted in the Telephone Amendment dated 05/07/04)

76640dissolutionamendment.pdf

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have proposed a different specification for the 20-hour time point (NLT (b)(4) in 20 hours). This specification has been found **unacceptable** since it was based on dissolution data obtained using your dissolution method (which is different from the USP's method), and on extrapolated data. Please note that although your and the USP methods may be considered equivalent, the specifications for each method are determined based on the *actual* dissolution data of 12 units obtained using each method separately, and not by transplanting estimated data from your method into the data obtained by the USP method.

2. The determination of the specifications for the test product using the USP method has been confounded by the fact that the dissolution testing using the USP method was conducted only after the test lots were already 14-15 months old (The DBE generally requests USP method be used, if available, on a fresh bio lot. However, the bio lot for this ANDA was no longer fresh at the time you received our request concerning the USP method).

3. In the original submission, you had proposed dissolution testing using its own dissolution method and specifications. The DBE was not able to determine specifications for your dissolution method based on the data submitted since there was questionable variability at the last time point (24-hour time point) for the 200 mg strength. In the original submission dated January 15, 2003 (Vol. A1.1, Section VI, page 104), based on 12 units, the dissolution data at the 24- hour time point for the 200 mg strength (Lot No. R416-055) were highly variable and not consistent with the data of the earlier time points (mean=57%, with CV%=36.1 and range of (b)(4), whereas the CV%'s of earlier time points were less than 15%).

In addition, there were no acceptable dissolution data submitted for the 100 mg strength using your method. The lot used in the original dissolution testing (using your method) for the 100 mg strength (Lot No. R416-079) was later replaced due to the manufacturing process deficiency. There were no other dissolution data submitted for the replacement lot (R416081) of the 100 mg strength, **based on 12 units**, and **using your method.**

4. For the reasons cited above, the Division of Bioequivalence(DBE) requests that you conduct dissolution testing using both USP method (for sampling up to 20 hours) and your own methods (for sampling up to 24 hours) for one fresh lot of each of the strengths, 200 mg and 100 mg. If fresh lots are not available, please manufacture a new lot for each of the strengths and conduct the requested dissolution testing. The dissolution specifications will be determined by the DBE based on the dissolution data of the fresh lots tested at Stage 2 (using 12 units).

Sincerely yours,

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

CC:ANDA 76-640
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen 1/21/05
HFD-652/ SNerurkar
HFD-617/ A. Sigler
HFD-650/ D. Conner 1/24/05

1/24/05

V:\FIRMSAM\KV\ltrs&rev\76640a0704.doc
Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE
DISSOLUTION - INCOMPLETE

Submission date: 07-30-04

1. STUDY AMENDMENTS (STA)

Strength: 200 mg & 100 mg

Firm disagreed with the FDA-recommended dissolution specifications and provided rationale for the firm's own proposed dissolution method and specifications.

✓ **Outcome: IC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable
(fatal flaw)
AC - Acceptable

7.1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	July 22, 2005
Amendment Date(s)	~~June 26, 2006~~
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\kv\ltrs&rev\76640a0705.doc**

I. Executive Summary

This is a review of amendments. The firm has submitted its responses to the DBE's deficiency comments concerning the dissolution testing communicated in the letter dated January 28, 2005, and also in the teleconference dated April 5, 2006. There is a USP method for the drug product. The firm proposed its own dissolution method. For either of the methods, there were insufficient valid data for the DBE to determine appropriate specifications for the test product. The original bio lots had been now expired and the DBE requested that the firm conduct dissolution testing using both USP and its own methods for one fresh lot of each of the strengths, 200 mg and 100 mg. If fresh lots are not available, the firm was asked to manufacture a new lot for each of the strengths and conduct dissolution testing using both the USP and the firm's method.

In the July 22, 2005 amendment, the firm submitted the dissolution data based on both methods for a freshly manufactured "experimental" lot for each of the strengths. Based on the data submitted in this amendment, the DBE found that the test product was slow-release and 80% of the labeled amount was not released at reasonable testing time using either the USP or the firm's dissolution method. Subsequently, on April 5, 2006, the DBE initiated a teleconference with KV to suggest that the firm performs further development of a dissolution method that would improve the release rate of the test product and would give at least 80% dissolved at a reasonable time. In the amendment dated June26, 2006, the firm responded by proposing to use the current USP method with its own specifications for approval of the application, and to develop a new dissolution method post approval. This proposal is not acceptable. The firm is informed that BE requirements for approval of the test product are not considered complete without acceptable dissolution testing. In addition, the waiver request for the lower strengths of the test product will not be considered without acceptable dissolution data. Again, the firm is recommended to perform further development of dissolution methodology for the test product.

In the current review, a clinical consult was also requested concerning the clinical significance of large Tmax difference between the test and RLD products observed in the fasting and nonfasting BE studies. The OGD clinical reviewer recommended that the test product be considered therapeutically interchangeable with the RLD product despite of the substantial Tmax difference.

The application is **incomplete.**

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	
Waiver requests	No	0
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies		
Amendments	Yes	2

D. Pre-Study Bioanalytical Method Validation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

E. In Vivo Studies

1. *Original* Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	R02-586
Study Design	Three-way crossover
No. of subjects enrolled	33
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 4
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)* and R416-059A (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment C)
Strength tested	200 mg
Dose	1x200 mg

*NOTE: Only Test Formulation A is currently submitted for approval.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.98	88.67-108.2
AUC_{∞}	0.91	81.83-102.0
C_{max}	0.95	87.28-103.3

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	1.06	96.40-117.6
AUC∞	1.00	90.44-111.0
Cmax	1.21	**111.3-131.8**

Comments on Fasting Study: The fasting study is acceptable with respect to Test Formulation A.

2. *Original* Single-dose Fed Bioequivalence Study

Study No.	RA2-102
Study Design	Two-way crossover
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 17
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment B)
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=35		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	1.06	99.0-114.2
AUC∞	1.04	97.9-110.3
Cmax	0.87	**77.5-96.9***

Comments on fed study: The nonfasting study is acceptable based on point estimate. The study was conducted before the issuance of the food guidance.

F. Formulation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

G. In Vitro Dissolution

Source of Method	Firm's
Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications (in the current amendment)	Hour 1: (b) (4) Hour 4: Hour 8: Hour 20:
F2 metric calculated (yes or no)	Yes
Method is acceptable (yes or no)	No. See Deficiency Comments.

H. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	No. See Deficiency Comments.
Waiver granted (yes or no)	No. See Deficiency Comments.

I. Comments:

1. According to the firm, the "experimental" lots, R449-028 (100 mg) and R449-027 (200 mg) were manufactured using the same process, same equipment and same personnel as the submission lots. They were manufactured only to generate more dissolution data and *"do not serve as replacement batches"*.

2. In the amendment dated June 26, 2006, the firm stated the following in the cover letter: *"In correspondence which KV has previously submitted, the KV batch R449-027 was referred to as an "experimental" batch". As previously indicated in the March 27, 2006 amendment, KV should not have characterized those batches as "experimental". These batches were manufactured at the same scale as the original exhibit lot and are cGMP demonstration batches, consistent with the manufacturing process as established in the original exhibit batch and consistent with the proposed commercial master record. KV respectfully requests that the replacement batches of the 200 mg strength (lot R449-027) and the 100 mg strength (lot R449-028) be the exhibit batches for the purpose of this application for review and subsequent approval."* The firm has submitted additional fasting and nonfasting BE studies for the new lot R449-027 in the June 26, 2006 amendment and these studies were reviewed in a separate review (v:\firmsam\kv\ltrs&rev\ 76640a0606.doc). The new BE studies were reviewed separately because of the complex history of dissolution testing of the test product, and for purpose of keeping the DBE issues of dissolution testing separate from the chemistry

issues concerning the *original* bio lots (See further discussion of the chemistry issue in the review v:\firmsam\kv\ltrs&rev\ 76640a0606.doc)

3. Due to concerns raised by the DBE on the significant difference in Tmax between the test and RLD product, a consult was sent to the OGD Clinical Team on September 1, 2005. The consult recommendations by the clinical reviewer were as follows (See the complete consult response in this review's Appendix):

1. *A proposed generic sustained release metoprolol succinate product may be considered therapeutically interchangeable with the RLD even if Tmax differs substantially from the RLD.*
2. *The experience of the new drug division suggests that sustained release metoprolol formulations may exhibit substantial intraindividual variability in pharmacokinetic profiles from dose to dose. This potential variability should be considered in reviewing and determining the approvability of generic metoprolol succinate products.*

Based on the above recommendations, the DBE's previous recommendations concerning the outcome of the BE studies remain the same: **The fasting and nonfasting studies are acceptable**.

J. Deficiency Comments:

Based on the additional dissolution data submitted in the July 22, 2005, the DBE found that the test product was slow-release and 80% of the labeled amount was not released at reasonable testing time using either the USP or the firm's dissolution method. The firm proposed the following specifications for the data based on the firm's proposed dissolution method[1]:

1 hr:	(b) (4)
4 hr:	
8 hr:	
20 hr:	

The firm's specifications as proposed in the July 22, 2005 amendment were found unacceptable by the DBE. On April 5, 2006, the DBE initiated a teleconference with KV to suggest that the firm performs further development of a dissolution method that would improve the release rate of the test product and would give at least 80% dissolved at a reasonable time. The DBE suggested using faster paddle speed with pH 6.8 buffer

---

[1] The current USP specifications are:

1 hr:	NMT 25%
4 hr:	20-40%
8 hr:	40-60%
20 hr:	NLT 80%

medium, or using higher pH, or using surfactants. See the teleconference memorandum attached below.

76640DissolutionTele con.doc

In the amendment dated June 26, 2006, the firm responded to the DBE's April 5, 2006 request for additional dissolution testing by proposing to use the current USP method for the test product, and the following specifications:

	(b) (4)
1 hr:	
4 hr:	
8 hr:	
20 hr:	

It should be noted that these specifications are the same specifications proposed by the firm previously for the data generated using its own proposed method.

In addition, the firm has proposed that *"a post approval commitment to attempt to develop a new dissolution methodology which would address Dr. Nerurkar's request. The results from this evaluation would be provided in the annual reports, post approval."*

The firm's proposal for postponed development of acceptable dissolution methodology until post approval, as stated in the June 26, 2006 amendment, is unacceptable. The BE requirements for approval of the test product are not considered complete without acceptable dissolution testing. In addition, the waiver request for the lower strengths of KV's Metoprolol Succinate ER Tablet product will not be considered without acceptable dissolution data. The firm is recommended to perform further development of dissolution methodology.

K. Recommendations

The dissolution testing on the test product, Metoprolol Succinate ER Tablets, 200 mg and 100 mg, conducted by KV is **incomplete.**

The firm is recommended to perform further development of dissolution methodology.

9/19/06

Hoainhon Nguyen, Review Branch I, Date

9/19/2006

Shriniwas Nerurkar, Ph.D., Team Leader, Review Branch I, Date

9/19/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Hnguyen/08-18-06/v:\firmsam\kv\ltrs&rev\76640a0705.doc

IV. Appendix

A. Dissolution Data from the Current Submission (07/22/05)

1. USP Method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Whole Tablets:

Table 1

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R449-027			Test Product, Strength: 100 mg Lot No. R449-028		
	Mean	%CV	Range	Mean	%CV	Range
1	7	11	(b) (4)	7	8.6	(b) (4)
2	8	11		9	14	
4	10	10		13	13	
8	18	6.1		24	12	
12	31	6.1		41	9.8	
20	61	3.9		69	7.7	

F2 between the 200 mg and 100 mg strengths of the test product: 61.09 (based on all time points)

2. Firm's Method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	**900 mL**
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
Firm's Proposed Specifications	Hour 1: (b) (4) Hour 4: Hour 8: Hour 20:

Whole Tablets:

Table 2

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R449-027			Test Product, Strength: 100 mg Lot No. R449-028		
	Mean	%CV	Range	Mean	%CV	Range
1	7	23	(b) (4)	6	22	(b) (4)
2	8	22		8	19	
4	11	16		10	18	
8	18	9.4		20	12	
12	30	6.7		35	8.0	
20	59	4.4		64	5.9	
24	70	4.1		74	6.1	

F2 between the 200 mg and 100 mg strengths of the test product: 68.32 (based on the last 4 time points with CV% less than 15)

B. Dissolution Data from Previous Submissions:

1. Dissolution Testing in Different pH media: pH 1.2 & 4.5

Medium	pH 1.2 buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 3

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	9.2	(b) (4)	12	6.7	(b) (4)
2	15	9.3		19	6.8	
4	19	8.4		34	5.3	
12	33	5.5		80	3.5	
24	61	4.6		97	3.7	

F2 between the test and reference lots: 28.12

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the profile data of the 100 mg.

Table 4

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	9	23.3	(b) (4)	11	7.3	(b) (4)
2	12	22.5		19	4.2	
4	16	20.0		32	2.8	
12	36	12.5		78	2.2	
24	74	5.8		98	2.0	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Medium	pH 4.5 acetate buffer
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 5

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	13.0	(b) (4)	10	11.0	(b) (4)
2	14	8.6		17	8.2	
4	19	8.4		28	7.5	
12	37	5.9		69	5.7	
24	69	5.2		93	4.8	

F2 between the test and reference lots: 36.75

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 6

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	10	26.0	(b) (4)	9	6.7	(b) (4)
2	13	23.1		15	4.7	
4	18	20.0		26	4.6	
12	43	11.4		67	3.0	
24	79	7.6		96	2.8	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

2. USP Method:

Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Whole Tablets:

Table 7

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	10	15.0	(b) (4)	9	10.0	(b) (4)
2	14	12.9		15	8.0	
4	19	10.5		27	6.7	
8	26	8.5		48	5.4	
12	36	6.9		67	4.9	
20	64	5.8		90	3.3	

F2 between the test and reference lots: 35.93

F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data of the 100 mg strength.

Table 8

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	9	18.9	(b) (4)	8	7.5	(b) (4)
2	12	20.8		14	7.9	
4	17	20.0		26	5.0	
8	28	16.8		47	3.4	
12	42	12.6		68	3.4	
20	68	8.8		92	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.

NOTE: The dissolution data for the 100 mg strength of the test product were highly variable at this pH and more variable than the 200 mg strength of the test product and the RLD product.

Half Tablets:

Table 9

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055B			Reference Product, Strength: 200 mg Lot No. 4063F		
	Mean	%CV	Range	Mean	%CV	Range
1	12	17.5	(b) (4)	9	15.6	(b) (4)
2	15	17.3		16	12.5	
4	20	15.0		27	9.3	
8	28	11.8		48	6.9	
12	38	8.9		68	5.6	
20	61	6.9		90	3.4	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.
F2 between the test half and whole tablets (of 200 mg): Not calculated due to high CV%'s in the test profile data of the 200 mg half tablets.
F2 between the 200 mg and 100 mg strengths of the test product: Not calculated due to high CV%'s in the test profile data.

Table 10

Sampling Time(hr)	Test Product (Replacement Lot), Strength: 100 mg Lot No. R429-081			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	12	28.3	(b) (4)	11	10.9	(b) (4)
2	16	21.2		17	10.0	
4	21	18.6		29	6.9	
8	31	14.2		50	4.2	
12	44	11.1		70	3.3	
20	71	8.2		93	2.6	

F2 between the test and reference lots: Not calculated due to high CV%'s in the test profile data.
F2 between the test half and whole tablets (of 100 mg): Not calculated due to high CV%'s in the test profile data.

NOTE: The variability of the dissolution data for the half-tablets and whole tablets of the100 mg and 200 strengths of the test product were similar, and higher compared with the dissolution data of the RLD product. There was no dose dumping for either the 100 mg or 200 mg strength of the test and reference products.

3. Firm's Originally Proposed DissolutionMethod: (Submitted in the original submission dated 01/15/03, Vol. A1.1, Section VI, page 104)

NOTE: This is the same method that in the current amendment the firm wishes to use for its stability and release testing. The F2 Similarity Factor comparing the dissolution data of the 200 mg strength of the test product (Lot No. R416-055) between the USP and firm's methods was 85.51, using the sampling times of 1, 2, 4, 8 and 12 hours. Similarly, F2 comparing the 100 mg strength of the reference product (Lot No. 3603J) was 89.63. There are no available dissolution data for similar comparison of the 200 mg strength of the RLD product or the 100 mg strength of the test product since different lots were tested using the USP and firm's methods. Also, comparison can not be made after the 12 hour sampling time since the USP method uses 20-hour as the last time point whereas the firm's uses 16-hour and 24-hour as the last time points. However, based on the F2 values above calculated from the available data, **the firm and USP methods appeared equivalent.**

Medium	Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 11

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055			Reference Product, Strength: 200 mg Lot No. 3698H		
	Mean	%CV	Range	Mean	%CV	Range
1	11	14.5	(b) (4)	12	5.8	(b) (4)
2	15	11.3		18	2.8	
4	19	11.0		30	1.7	
8	27	7.8		49	1.4	
12	37	7.3		66	1.8	
16	47	6.4		79	1.5	
24	57	36.1*		92	2.3	

F2 between the test and reference lots: 31.89
F2 between the 200 mg and 100 mg strengths of the test product: 34.50

***NOTE:** The dissolution data for the 24-hour time point were highly variable for the test product and not consistent with the data of the earlier time points.

Table 12

NOTE: The below 100 mg lot No. R416-079 was later replaced with the 100 mg lot No. R429081 due to a deficiency in the manufacturing process. See the review of the submission dated 04/14/04, v:\firmsam\kv\ltrs&rev\76640a0404.doc.

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R416-079			Reference Product, Strength: 100 mg Lot No. 3603J		
	Mean	%CV	Range	Mean	%CV	Range
1	15	11.3	(b) (4)	9	8.9	(b) (4)
2	21	11.4		15	7.3	
4	31	11.0		27	6.3	
8	47	7.9		49	4.9	
12	62	4.4		69	4.2	
16	74	2.6		84	3.3	
24	88	1.9		96	2.8	

F2 between the test and reference lots: 58.77

4. Firm's Dissolution Method: (Submitted in the original submission dated 01/15/03, Vol. A1.10, Section XIV, page 4973 and the amendment dated 04/14/04, Vol. A5.1, Attachment 2, page 50)

NOTE: The following dissolution data were presented under Certificate of Analysis. For Lot No. R416-055 (200 mg), the Certificate was dated 08/22/02. The lot was manufactured on 07/19/02 according to the Certificate. For Lot No. R429-081 (Replacement lot, 100 mg), the Certificate was dated 11/20/03. The lot was manufactured on 08/02/02 according to the Certificate. The dissolution data were based on **6 units** for each lot. In the current amendment, the firm referred to these data as *release data.*

Medium	Phosphate buffer, pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Table 13

Sampling Time(hr)	Test Product, Strength: 200 mg Lot No. R416-055		
	Mean	%CV	Range
1	11	14.5	(b) (4)
2	15	10	
4	20	6.5	
8	29	3.1	
12	38	0.80	
16	49	1.2	
24	68	3.4	

Table 14

Sampling Time(hr)	Test Product, Strength: 100 mg Lot No. R429-081		
	Mean	%CV	Range
1	7	8.6	(b) (4)
2	10	9.0	
4	14	7.1	
8	24	6.2	
12	36	5.6	
16	50	5.2	
24	69	5.4	

Similarity Factor F2 between the 200 mg and 100 mg lots: 69.61

B. Attachment: The Firm's Investigation of the Dissolution of KV's Metoprolol Succinate Tablets (Submitted in the Telephone Amendment dated 05/07/04)

76640dissolutionamendment.pdf

C. Clinical Consult on Tmax Difference

76640clinicalconsultemail.rtf

metaprololclinicalconsult76640C0705 mor.c

BIOEQUIVALENCE DEFICIENCY

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies concerning the dissolution testing have been identified:

Your dissolution testing for the test product is incomplete. Your proposal for postponed development of acceptable dissolution methodology until post approval, as stated in the June 26, 2006 amendment, is unacceptable. The bioequivalence requirements for approval of the test product are not considered complete without acceptable dissolution testing. In addition, the waiver request for the lower strengths of your Metoprolol Succinate ER Tablet product will not be considered without acceptable dissolution data. Please perform further development of dissolution methodology as requested in our teleconference dated April 5, 2006.

Please note that the DBE will review the additional bioequivalence studies submitted on June 26, 2006 separately.

Sincerely yours,

/s/ Barbara M Davit

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

CC:ANDA 76-640
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen HMC 9/19/06
HFD-652/ SNerurkar
HFD-617/ Suh Keri
HFD-650/ D. Conner BMD 9/19/06

9/19/06

V:\FIRMSAM\KV\ltrs&rev\76640a0705.doc
Printed in final on / /

BIOEQUIVALENCE - INCOMPLETE Submission date: 07-22-05 & 06-26-06

1. STUDY AMENDMENT (STA) (July 22, 2005) Additional dissolution data for freshly manufactured lots Strength: 200 mg & 100 mg

✓ **Outcome: IC**

2. STUDY AMENDMENT (STA) (June 26, 2006) Additional BE studies

Strength: 200 mg & 100 mg
Outcome: NC*

OUTCOME DECISIONS: **IC** - Incomplete

***NC** - No credit. The studies will be reviewed separately and the review credits for the additional BE studies will be entered in this separate review. The June 26, 2006 amendment was entered here since some content of this amendment concerning dissolution testing only was reviewed in the current review.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	June 26, 2006
Amendment Date(s)	
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\kv\ltrs&rev\76640a0606.doc**

I. Executive Summary

This is a review of an amendment.

Previously, in the review of the original submission dated January 15, 2003, the fasting and nonfasting BE studies for the 200 mg strength of the test product were acceptable (v:\firmsam\kv\ltrs&rev\76640n0103.doc). A clinical consult was also requested concerning the clinical significance of large Tmax difference between the test and RLD products observed in the *original* fasting and nonfasting BE studies. The OGD clinical reviewer recommended that the test product be considered therapeutically interchangeable with the RLD product despite of the substantial Tmax difference.

However, as the results of chemistry review, the original bio lot of the 200 mg strength for the BE studies above was found unacceptable. The firm was asked to manufacture a new lot for the 200 mg strength and conduct BE studies for the new lot. In the current amendment dated June 26, 2006, the firm has submitted the BE fasting and nonfasting studies for the new lot. It should be noted that the new lot was actually manufactured prior to the request of the Chemistry division, for the purpose of generating additional dissolution data requested by the DBE. The dissolution data for the new lot were submitted in the July 22, 2006 and reviewed separately in the review v:\firmsam\kv\ltrs&rev\76640a0705.doc.

The *new* single dose, two-way, crossover, fasting bioequivalence (BE) study and single dose, two-way crossover, nonfasting BE study comparing the test product, Metoprolol Succinate ER Tablets, 200 mg from KV Pharmaceutical to AstraZeneca's Toprol-XL® ER Tablets are **acceptable**. The study results are summarized below.

Summary of Statistical Analysis, *New* Fasting Bioequivalence Study (N=39)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	1.02	94.8-109.8
AUC∞	1.03	96.0-110.7
Cmax	1.12	103.3-121.2

Summary of Statistical Analysis, *New* Fed Bioequivalence Study (N=63)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	1.06	102.6-109.9
AUC∞	1.06	102.7-109.6
Cmax	1.12	103.9-120.7

It should be noted that the significant Tmax differences observed in the *original* BE studies were also seen in the current *new* BE studies.

At this time, the dissolution testing for the test product is **incomplete.** The DBE has currently requested that the firm conduct further development of dissolution methodology (See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc). The waiver request for the 100 mg strength is not considered pending satisfactory dissolution testing.

The application is **incomplete.**

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information (based on the PDR labeling of the RLD product and NDA 19-962's 1993-1994 reviews)

Bioavailability	50% (after first pass); 65-70% (relative bioavailability as compared with conventional IR metoprolol tablets)
Food Effect	Food does not significantly affect the bioavailability.
Tmax	4.4-14.0 hours
Metabolism	Extensive first-pass metabolism in the liver to yield inactive metabolites.
Excretion	Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites.
Half-life	3-7 hours
Relevant OGD or DBE History	**(1) Control Documents # 01-423 ((b) (4) 08/31/01) and 01-470 ((b) (4) 09/20/01):** The DBE recommended a replicate, single-dose fasting bioequivalence study for the 200 mg and 50 mg strengths of the test product, a crossover, single-dose nonfasting bioequivalence study for the 200 mg strength. Biowaiver request for the 25 mg and 100 mg strengths may be considered based on formulation proportionality, comparable dissolution profiles and acceptable *in vivo* testing of the 200 mg and 50 mg strengths. **(2) Control Document #02-105 ((b) (4) 02/27/02):** The DBE recommended the same as above except that replicate design was no longer requested for the fasting study, and metoprolol was determined to be the only analyte to be measured.
ANDA Issues	1. Based on the chemistry review of the original bio lot used in the original BE studies of this ANDA 76-

640, the lot was found unacceptable. The firm was asked to manufacture a new lot and conduct new BE studies. See the files attached below.


76640 KV Metoprolol Maj Amend Response


76640ChemDeficiencyletter.doc


76640DBETelecon.doc

The firm has submitted the requested new BE studies in the current amendment.

2. In addition to the chemistry issues of the bio lot mentioned above, the dissolution testing for the ANDA was found unsatisfactory to date. See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	No	
Waiver requests	No	0
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	N/A	
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation


76640PrestudyValidation.pdf

COMMENTS: The method was based on reverse-phase HPLC with MS/MS spectroscopy. The validation data are acceptable.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	PRACS R06-0598
Study Design	Two-way crossover
No. of subjects enrolled	40
No. of subjects completing	39
No. of subjects analyzed	39
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 21 Female: 18
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot No. R449-027A
Reference product	Toprol-XL® Tablets, Lot No. LN0094
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=39		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	94.8-109.8
AUC_{∞}	1.03	96.0-110.7
Cmax	1.12	103.3-121.2

Reanalysis of Study Samples, Fasting Bioequivalence Study

76640NewFastReanalysis.pdf

Did use of recalculated plasma concentration data change study outcome? There was no PK repeat. No recalculation was necessary.

Comments on Fasting Study: The fasting study is acceptable.

2. Single-dose Fed Bioequivalence Study

Study No.	PRACS R06-0599
Study Design	Two-way crossover
No. of subjects enrolled	66
No. of subjects completing	63
No. of subjects analyzed	63
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 44 Female: 19
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot No. R449-027A
Reference product	Toprol-XL® Tablets, Lot No. LN0094
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=63		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	102.6-109.9
AUC_{∞}	1.06	102.7-109.6
Cmax	1.12	103.9-120.7

Reanalysis of Study Samples, Fed Bioequivalence Study

76640NewFedReanalysis.pdf

Did use of recalculated plasma concentration data change study outcome? There was no PK repeat. No recalculation was necessary.

Comments on fed study: The nonfasting study is acceptable.

F. Formulation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc. Although the firm manufactured new lot for the new BE studies, there was no change from the original formulation.

G. In Vitro Dissolution

Source of Method	USP
Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications (in the current amendment)	Hour 1: (b) (4) Hour 4: Hour 8: Hour 20:
USP specifications	Hour 1: NMT 25% Hour 4: 20-40% Hour 8: 40-60% Hour 20: NLT 80%
Method is acceptable (yes or no)	No. See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc

H. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	No. See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc
Waiver granted (yes or no)	No. See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc

I. Deficiency Comments:

Although the *new* BE studies submitted currently are acceptable, the dissolution testing for the test product is **incomplete.** The firm has recently been requested to conduct further development of dissolution methodology for the test product. The waiver request for the lower strength, 100 mg, is not considered at this time pending acceptable dissolution methodology and data. See the review v:\firmsam\kv\ltrs&rev\ 76640a0705.doc

The application is **incomplete.**

J. Recommendations

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by KV Pharmaceutical on the test product, Metoprolol Succinate ER Tablets, 200 mg, lot # R449-027A, comparing it with the reference product, Astra Zeneca's Toprol-XL® Tablets, 200 mg, lot # LN0094, have been found **acceptable** by the Division of Bioequivalence.

2. The dissolution testing for the test product is **incomplete.** The firm is currently requested to conduct further development of dissolution methodology for the test product. See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc

3. The waiver request for the lower strength, 100 mg, is not considered at this time pending acceptable dissolution methodology and data.

The application is **incomplete.**

9/22/06

Hoainhon Nguyen, Review Branch I, Date

Moheb H. Makary 9/22/06

Moheb H. Makary, Ph.D., Team Leader, Review Branch I, Date

for Barbara M. Davit 9/22/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a. Study Design

Study Information	
Study Number	PRACS 06-0598
Study Title	A Relative Bioavailability Study of 200 mg Metoprolol Succinate ER Tablets Under Fasting Conditions.
Clinical Site	PRACS Institute, Ltd., East Grand Forks, MN
Principal Investigator	Craig R. Sprenger, M.D.
Study/Dosing Dates	Period I: May 13-15, 2006 Period II: May 20-22, 2006
Analytical Site	PRACS Inst. Ltd., Fargo, ND
Analytical Director	(b) (6)
Analysis Dates	May 25, 2006 – June 7, 2006
Storage Period	25 days maximum

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metoprolol Succinate ER	Toprol-XL®
Manufacturer	KV Pharmaceutical	AstraZeneca
Batch/Lot No.	R449-027A	LN0094
Manufacture Date	03/08/2005	NA
Expiration Date	NA	09/2008
Strength	200 mg	200 mg
Dosage Form	ER Tablet	ER Tablet
Batch Size	(b) (4)	NA
Potency	101.2%	97.3%
Content Uniformity	100.9%(RSD=3.7%)	97.9%(RSD=2.1%)
Formulation	See Appendix 0	
Dose Administered	1x200 mg	1x200 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	76640NewFastRandomization.pdf
Blood Sampling Times	Pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 42 and 48 hours
Blood Volume Collected/Sample	6 mL Vacutainers® (K_2EDTA).
Blood Sample Processing/Storage	Centrifuged at 2400 RPM for 15 minutes at 4°C, plasma divided into polypropylene tubes, stored at -20°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours before to 4.25 hours after dosing
Length of Confinement	10 hours before to 48 hours after dosing
Safety Monitoring	Heart rate and blood pressure will be monitored predose and postdose at 6, 8, 12 and 24 hours.

Comments on Study Design:

Acceptable.

b. Clinical Results

Table 1: Demographics of Study Subjects

76640NewFastDemographics.pdf

Table 2 Dropout Information

Subject No.	Reason	Period	Replaced?
29	Personal reasons	Period I	No

Table 3 Study Adverse Events

76640NewBEAdverseEvents.pdf

Comments: None of the adverse events was serious. There appeared no significant difference in number of adverse reactions between the test and reference treatments.

Table 4 Protocol Deviations

There was no significant protocol deviation that might have affected the integrity of the study. The blood sampling time deviations were corrected by using the actual sampling times.

c. Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent (metoprolol)			
QC Conc. (ng/mL)	1.50 (n=43)	80.0 (n=44)	150.0 (n=44)	4.00 (n=44)
Inter day Precision (%CV)	8.4	2.7	2.7	5.1
Inter day Accuracy (%)	97.4	97.3	107.2	100.6
Cal. Stds. Conc. (ng/mL)	0.50, 1.00, 5.00, 10.00, 50.00, 100.0, 150.0, 200.0			
Inter day Precision (%CV)	1.59-12.1			
Inter day Accuracy (%)	98.2-101.1			
Linearity Range (R^2 values)	0.9989-0.9998			

Comments on Study Assay Quality Control: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable

Table 6 SOP's Dealing with Analytical Repeats

SOP No.	Date of SOP	SOP Title
405_05 Version 01	08/15/05	Study Subject Sample Analysis

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	N/A. There was no PK repeat and therefore, no recalculation.
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Acceptable.

d. Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=39)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng·hr/mL	1220	88	1223	93	1.00
AUC∞	ng·hr/mL	1276	91	1255	94	1.02
Cmax	ng/mL	58.18	79	53.24	81	1.09
Tmax	hrs	17.23	33	9.436	38	1.83*
T1/2	hrs	5.76	32	6.06	25	0.95
Kel	hr-1	0.1313	29	0.1228	29	1.07

***NOTE:** The significant difference in Tmax between the test and RLD product was also observed in the original fasting study. The Tmax difference was consulted with the OGD Clinical group. The clinical reviewer found that *"A proposed generic sustained release metoprolol succinate product may be considered therapeutically interchangeable with the RLD even if Tmax differs substantially from the RLD."* See the complete consult report below.

metaprololclinicalcons
ult76640C0705 mor.c

Table 9 Geometric Means and 90% Confidence Intervals (N=39)

Parameter	Test Mean	Reference Mean	T/R	90% CI
AUC0-t	895.1	877.1	1.02	94.8-109.8
AUC∞	923.6	896.2	1.03	96.0-110.7
Cmax	45.21	40.40	1.12	103.3-121.2

Table 10 Additional Study Information

Root mean square error, AUC0-t	0.192509
Root mean square error, AUC∞	0.186253
Root mean square error, Cmax	0.208809
Kel and AUC∞ determined for how many subjects?	All 39 subjects
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
measurable drug concentrations at 0 hr	0
first measurable drug concentration as Cmax	0

Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: Acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The study results met the confidence interval criteria. The fasting study is **acceptable.**

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Test Treatment

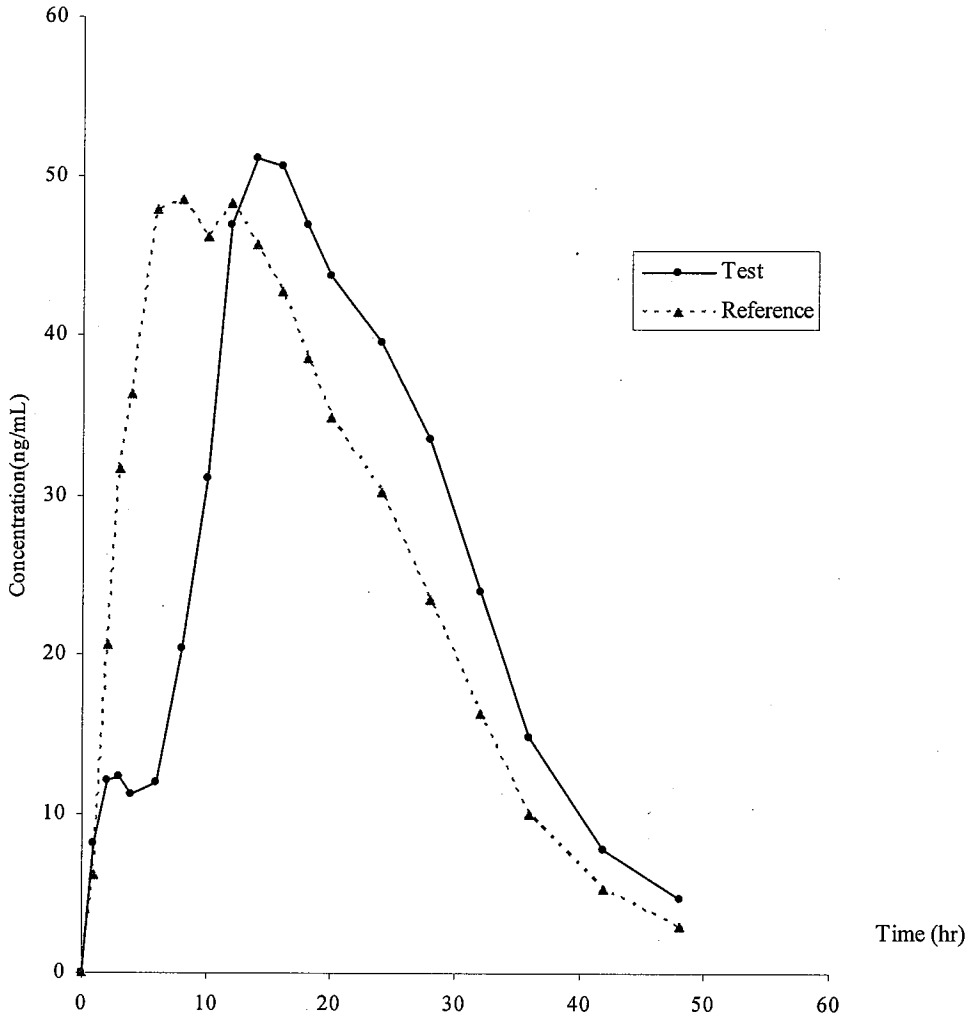
Time	N	Mean	Std Dev	Minimum	Maximum
					(b) (4)
Hour0	39	0.000	0.000		
Hour1	39	8.187	7.252		
Hour2	39	12.096	8.312		
Hour3	39	12.264	8.224		
Hour4	39	11.253	8.249		
Hour6	39	11.935	9.284		
Hour8	39	20.318	19.028		
Hour10	39	31.018	32.198		
Hour12	39	46.906	41.008		
Hour14	39	51.113	44.572		
Hour16	39	50.661	45.797		
Hour18	39	46.960	43.856		
Hour20	39	43.699	40.522		
Hour24	39	39.528	37.398		
Hour28	39	33.537	31.309		
Hour32	39	23.872	23.952		
Hour36	39	14.746	16.951		
Hour42	39	7.758	10.569		
Hour48	39	4.727	7.126		

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
					(b) (4)
Hour0	39	0.000	0.000		
Hour1	39	6.111	3.402		
Hour2	39	20.558	13.103		
Hour3	39	31.693	23.736		
Hour4	39	36.391	28.331		
Hour6	39	47.895	36.517		
Hour8	39	48.547	38.987		
Hour10	39	46.230	40.062		
Hour12	39	48.318	41.939		
Hour14	39	45.731	41.248		
Hour16	39	42.796	40.071		
Hour18	39	38.559	36.958		
Hour20	39	34.888	35.303		
Hour24	39	30.182	32.161		
Hour28	39	23.398	27.081		
Hour32	39	16.265	19.862		
Hour36	39	10.025	12.902		
Hour42	39	5.237	7.293		
Hour48	39	2.988	4.327		

Figure 1

Metoprolol Mean Plasma Concentrations
Single Dose New Fasting Study



2. Single-dose Nonfasting Bioequivalence Study

a. Study Design

Study Information	
Study Number	PRACS 06-0599
Study Title	A Relative Bioavailability Study of 200 mg Metoprolol Succinate ER Tablets Under Non-Fasting Conditions.
Clinical Site	PRACS Institute, Ltd., East Grand Forks, MN
Principal Investigator	Craig R. Sprenger, M.D.
Study/Dosing Dates	Period I: May 13-15, 2006 Period II: May 20-22, 2006
Analytical Site	PRACS Inst. Ltd., Fargo, ND
Analytical Director	(b) (6)
Analysis Dates	May 23, 2006 – June 2, 2006
Storage Period	20 days maximum

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metoprolol Succinate ER	Toprol-XL®
Manufacturer	KV Pharmaceutical	AstraZeneca
Batch/Lot No.	R449-027A	LN0094
Manufacture Date	03/08/2005	NA
Expiration Date	NA	09/2008
Strength	200 mg	200 mg
Dosage Form	ER Tablet	ER Tablet
Batch Size	(b) (4)	NA
Potency	101.2%	97.3%
Content Uniformity	100.9%(RSD=3.7%)	97.9%(RSD=2.1%)
Formulation	See Appendix 0	
Dose Administered	1x200 mg	1x200 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	 76640NewFedRandomization.pdf
Blood Sampling Times	Pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 42 and 48 hours
Blood Volume Collected/Sample	6 mL Vacutainers® (K_2EDTA).
Blood Sample Processing/Storage	Centrifuged at 2400 RPM for 15 minutes at 4°C, plasma divided into polypropylene tubes, stored at -20°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 12
Length of Fasting Before Meal	10 hours
Length of Confinement	10 hours before to 48 hours after dosing
Safety Monitoring	Heart rate and blood pressure will be monitored predose and postdose at 6, 8, 12 and 24 hours.
Standard FDA Meal Used?	Yes

Comments on Study Design:

Acceptable.

b. Clinical Results

Table 12 Demographics of Study Subjects

76640NewFedDemographics.pdf

Table 13 Dropout Information

Subject No.	Reason	Period	Replaced?
12	Adverse events (pharyngitis streptococcal)	Period II	No
18	Family emergency	Period II	No
57	Family emergency	Period II	No

Table 14 Study Adverse Events

76640NewBEAdverseEvents.pdf

Comments: None of the adverse events was serious. There appeared no significant difference in number of adverse reactions between the test and reference treatments.

Table 15 Protocol Deviations

There was no significant protocol deviation that might have affected the integrity of the study. The blood sampling time deviations were corrected by using the actual sampling times.

c. Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Parent (metoprolol)			
QC Conc. (ng/mL)	1.50 (n=61)	80.0 (n=66)	150.0 (n=62)	4.00 (n=65)
Inter day Precision (%CV)	7.3	3.8	4.4	4.4
Inter day Accuracy (%)	95.8	97.3	106.8	99.8
Cal. Stds. Conc. (ng/mL)	0.50, 1.00, 5.00, 10.00, 50.00, 100.0, 150.0, 200.0			
Inter day Precision (%CV)	3.02-10.5			
Inter day Accuracy (%)	99.7-101.0			
Linearity Range (R^2 values)	0.9937-0.9998			

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable

Table 17 SOP's Dealing with Analytical Repeats

SOP No.	Date of SOP	SOP Title
405_05 Version 01	08/15/05	Study Subject Sample Analysis

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	N/A
Did recalculation of plasma concentrations change the study outcome?	There was no PK repeat.
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Acceptable.

d. Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters (N=63)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng·hr/mL	930.5	100	886.7	104	1.05
AUC∞	ng·hr/mL	966.9	104	916.7	106	1.05
Cmax	ng/mL	47.84	83	41.33	86	1.16
Tmax	hrs	16.73	28	7.730	52	2.16*
Kel	hrs	0.1374	31	0.1139	38	1.21
T1/2	hr-1	5.54	31	6.76	28	0.82

***NOTE:** See the comments concerning the Tmax difference under the Fasting Study above.

Table 20 Geometric Means and 90% Confidence Intervals (N=63)

Parameter	Test Mean	Reference Mean	T/R	90% CI
AUC0-t	684.4	644.6	1.06	102.6-109.9
AUC∞	703.5	663.0	1.06	102.7-109.6
Cmax	36.38	32.49	1.12	103.9-120.7

Table 21 Additional Study Information

Root mean square error, AUC0-t	0.114681
Root mean square error, AUC∞	0.109450
Root mean square error, Cmax	0.251061
Kel and AUC∞ determined for how many subjects?	All 63 subjects
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
measurable drug concentrations at 0 hr	1
first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: Acceptable.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The study results met the confidence interval criteria. The nonfasting study is **acceptable.**

Table 22 Mean Plasma Concentrations, Single-Dose Nonfasting Bioequivalence Study

Test Treatment

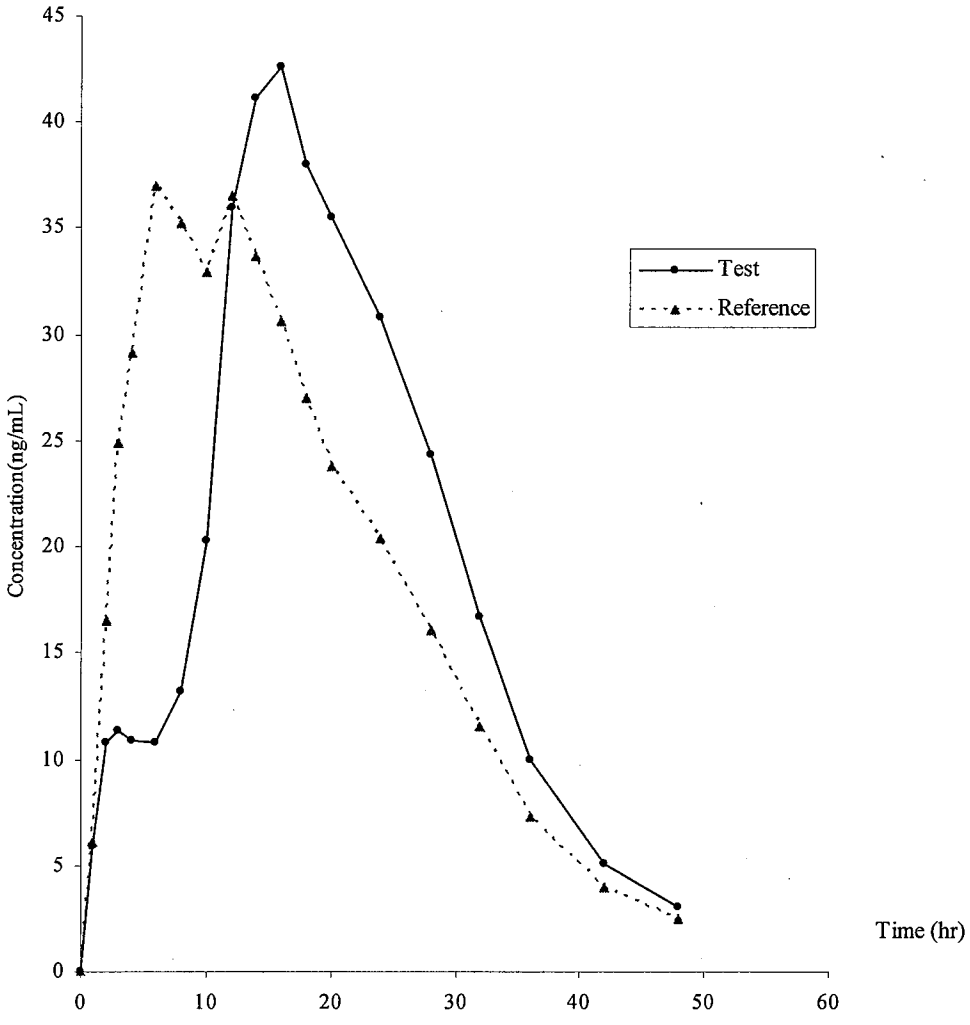
Time	N	Mean	Std Dev	Minimum	Maximum
					(b) (4)
Hour0	63	0.000	0.000		
Hour1	63	5.936	7.113		
Hour2	63	10.820	8.601		
Hour3	63	11.344	8.784		
Hour4	63	10.897	9.698		
Hour6	63	10.781	10.095		
Hour8	63	13.163	13.518		
Hour10	63	20.254	22.389		
Hour12	63	35.990	28.791		
Hour14	63	41.143	30.123		
Hour16	63	42.613	35.825		
Hour18	63	37.946	33.587		
Hour20	63	35.547	34.531		
Hour24	63	30.784	33.363		
Hour28	63	24.301	30.943		
Hour32	63	16.666	26.197		
Hour36	63	9.963	18.077		
Hour42	63	5.112	11.170		
Hour48	63	3.037	7.354		

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
					(b) (4)
Hour0	63	0.010	0.077		
Hour1	63	6.110	4.687		
Hour2	63	16.512	9.839		
Hour3	63	24.853	16.536		
Hour4	63	29.158	22.249		
Hour6	63	36.947	29.923		
Hour8	63	35.220	30.036		
Hour10	63	32.919	30.958		
Hour12	63	36.496	34.577		
Hour14	63	33.640	33.478		
Hour16	63	30.635	31.138		
Hour18	63	26.987	29.389		
Hour20	63	23.759	27.044		
Hour24	63	20.412	25.359		
Hour28	63	16.091	23.421		
Hour32	63	11.490	17.802		
Hour36	63	7.247	12.387		
Hour42	63	3.931	7.689		
Hour48	63	2.478	4.776		

Figure 2

Metoprolol Mean Plasma Concentrations
Single Dose New Nonfasting Study



B. Formulation Data

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc. Although the firm manufactured new lot for the new BE studies, there was no change from the original formulation.

C. Dissolution Data

See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc. The dissolution data submitted previously are summarized in the file attached below.

76640Dissolution.pdf

D. SAS Output

1. Fasting Study:

76640NEWFAST.txt

2. Nonfasting Study:

76640NEWFED.txt

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies concerning the dissolution testing have been identified:

Your dissolution testing for the test product is incomplete. Your proposal for postponed development of acceptable dissolution methodology until post approval, as stated in the June 26, 2006 amendment, is unacceptable. The bioequivalence requirements for approval of the test product are not considered complete without acceptable dissolution testing. In addition, the waiver request for the lower strengths of your Metoprolol Succinate ER Tablet product will not be considered without acceptable dissolution data. Please perform further development of dissolution methodology as requested in our teleconference dated April 5, 2006.

At this time we have no further questions concerning the new fasting and nonfasting bioequivalence studies conducted for the test lot No. R449-027A.

Sincerely yours,

Barbara M. Davit

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

CC:ANDA 76-640
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ MMakary

Endorsements: (Final with Dates)
HFD-652/ HNguyen HNC
HFD-652/ MMakary MMM 09/22/06
HFD-617/ ASigler
HFD-650/ DPConner BMD 9/22/06

V:\FIRMSAM\KV\ltrs&rev\76640a0606.doc
Printed in final on / /

BIOEQUIVALENCE - ACCEPTABLE Submission date: 06-26-06
DISSOLUTION - INCOMPLETE

1. Fasting Study (STF): *New Study*
Clinical Site: PRACS Institute, East Grand Forks MN
Analytical Site: PRACS Institute, Fargo ND

Strength: 200 mg
Outcome: AC*

2. Nonfasting Study (STP): *New Study*
Clinical Site: PRACS Institute, East Grand Forks MN
Analytical Site: PRACS Institute, Fargo ND

Strength: 200 mg
Outcome: AC*

OUTCOME DECISIONS: **AC** - Acceptable

*NOTE: Although the *new* BE studies are acceptable, the dissolution testing is **incomplete.** See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	**October 18, 2006 (Current Submission)**
Amendment Date(s)	
Reviewer	Hoainhon Nguyen
First Generic	Yes

I. Executive Summary

This is a review of an amendment. The firm has submitted its responses to the DBE's deficiency comments concerning the dissolution testing communicated in the letter dated October 3, 2006. The current USP dissolution method for the drug product and the firm's originally proposed dissolution method (both using pH 6.8 phosphate buffer as dissolution medium) had been determined by the DBE to be inappropriate for the test product: The dissolution data did not meet the USP specification of NLT 80%(Q) in 20 hours (the last time point) and less than 60% label claim (LC) was dissolved at 20 hours in both of these methods. The firm had been asked to develop an alternate method that would allow at least 80% LC to be dissolved in 20 hours. In the last amendment dated June 26, 2006, the firm requested that the development of an appropriate, alternate dissolution method be postponed until after approval of the test product. This request was denied.

In the current amendment that was faxed to the DBE on October 18, 2006, the firm informed the Agency that it has finally developed a dissolution method that uses Sodium Laurel Sulfate (SLS) as surfactant in the dissolution medium and therefore allows at least 80% LC to be dissolved in 20 hours. However, the firm has presented two different options for adopting this newly developed dissolution method, and would like to discuss the options with the DBE via a telephone conference. Option #1 proposes to use the current USP method as the official application method and adding the new dissolution method as *"an alternate method"* which would be used for ANDA information and post-approval changes only. Option #2 proposes the use the new dissolution method as the official application method.

Since the USP method had been determined to be inappropriate method for the test product, Option #1 is therefore considered inappropriate and unacceptable. Option #2 is consistent with the DBE's past and current practice for establishing an official dissolution method for an application, and therefore, is acceptable. The DBE recommends that the firm finalizes its dissolution method development, provides individual and mean data (with CV% and range), based on the finalized method, using 12 units of the test and RLD

product, of each strength, and of batches within expiry dates. The DBE will determine appropriate dissolution specifications based on the submitted data.

The firm is informed of the DBE's above recommendations in a letter, and the teleconference is deemed unnecessary at this time.

The dissolution testing is **incomplete.**

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	
Waiver requests	No	0
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies		
Amendment	Yes	1

D. In Vivo Studies

1. *Original* Single-dose Fasting Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

Study Summary	
Study No.	R02-586
Study Design	Three-way crossover
No. of subjects enrolled	33
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 4
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)* and R416-059A (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment C)
Strength tested	200 mg
Dose	1x200 mg

*NOTE: Only Test Formulation A is currently submitted for approval.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.98	88.67-108.2
AUC_{∞}	0.91	81.83-102.0
C_{max}	0.95	87.28-103.3

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	96.40-117.6
AUC_{∞}	1.00	90.44-111.0
C_{max}	1.21	**111.3-131.8**

Comments on Fasting Study: The fasting study is acceptable with respect to Test Formulation A.

2. *Original* Single-dose Fed Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

Study No.	RA2-102
Study Design	Two-way crossover
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 17
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment B)
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=35		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	99.0-114.2
AUC_{∞}	1.04	97.9-110.3
C_{max}	0.87	**77.5-96.9***

Comments on fed study: The nonfasting study is acceptable based on point estimate. The study was conducted before the issuance of the food guidance.

3. *Second* Single-dose Fasting Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640a0606.doc.

Study Summary	
Study No.	PRACS R06-0598
Study Design	Two-way crossover
No. of subjects enrolled	40
No. of subjects completing	39
No. of subjects analyzed	39
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 21 Female: 18
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot No. R449-027A
Reference product	Toprol-XL® Tablets, Lot No. LN0094
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=39		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	94.8-109.8
AUC_{∞}	1.03	96.0-110.7
C_{max}	1.12	103.3-121.2

Comments on Fasting Study: The fasting study is acceptable.

4. *Second* Single-dose Fed Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640a0606.doc.

Study No.	PRACS R06-0599
Study Design	Two-way crossover
No. of subjects enrolled	66
No. of subjects completing	63
No. of subjects analyzed	63
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 44 Female: 19
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot No. R449-027A
Reference product	Toprol-XL® Tablets, Lot No. LN0094
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=63		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	102.6-109.9
AUC_{∞}	1.06	102.7-109.6
C_{max}	1.12	103.9-120.7

Comments on fed study: The nonfasting study is acceptable.

E. Formulation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

F. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	No. See Deficiency Comments.
Waiver granted (yes or no)	No. See Deficiency Comments.

G. In Vitro Dissolution Development

Following are the current USP dissolution method for the drug product and the firm's originally proposed dissolution method. Both methods were unacceptable because the dissolution data did not meet the USP specification of NLT 80%(Q) in 20 hours (the last time point) and less than 60% label claim (LC) was dissolved at 20 hours in both of these methods. Eighty percent (80%) dissolution was not achieved using pH 6.8 phosphate buffer and USP apparatus II (paddle) until at least 35 hours. The paddle speeds or the dissolution volumes had no effect on the dissolution rate. (See the review v:\firmsam\kv\ltrs&rev\76640a0705.doc.)

USP Method:

Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	***500 mL***
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

Firm's Originally Proposed Method

Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP)
Volume (mL)	***900 mL***
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm

In the current amendment, the firm has submitted preliminary method development data to show that with addition of SLS, the dissolution rate could be increased to the desired level (i.e., at least 80% dissolved in 20 hours). The data included experiments with effect of volume and paddle speed, different buffer salt concentrations and SLS concentrations. The data presented for the dissolution conditions of 900 mL of pH 6.8 phosphate buffer

with 0.2% SLS, and USP apparatus II (paddle) at 50 rpm, for 6 units of two test lots showed the most promising results. See the review Appendix.

However, the firm has not proposed a final dissolution method and provided sufficient dissolution data (i.e., individual and mean data for 12 units of the test and RLD product, of both 100 mg and 200 mg strengths) necessary for establishing final specifications.

In addition, the firm has presented two different options for adopting a newly developed dissolution method, and requested to discuss the options with the DBE via a telephone conference. Option #1 proposes to use the current USP method as the official application method and adding any finalized new dissolution method as *"an alternate method"* which would be used for ANDA information and post-approval changes only. Option #2 proposes the use of the finalized new dissolution method as the official application method.

H. Deficiency Comments

The firm's proposed options for adopting a new dissolution method and dissolution data provided in the current amendment were discussed at the Bio Management meeting of 10/24/2006. (See the meeting minutes on v:\division\bio\Management Mtg\24Oct06.doc) Since the USP method has been determined to be inappropriate method for the test product, Option #1 is therefore considered inappropriate and unacceptable. Option #2 is consistent with the DBE's past and current practice for establishing an official dissolution method for an application, and therefore, is acceptable. The DBE recommends that the firm finalizes its dissolution method development, provides individual and mean data (with CV% and range), based on the finalized method, using 12 units of the test and RLD product, of each strength, and of batches within expiry dates. The DBE will determine appropriate dissolution specifications based on the submitted data.

The firm is informed of the DBE's above recommendations in a letter, and the teleconference is deemed unnecessary at this time.

The dissolution testing is **incomplete.**

I. Recommendations

The dissolution testing on the test product, Metoprolol Succinate ER Tablets, 200 mg and 100 mg, conducted by KV is **incomplete** due to the reasons cited in the Deficiency Comments above**.**

The firm is informed of the DBE recommendations and Deficiency Comments.

IV. Appendix

A. Dissolution Method Development Data as Submitted in the Current Amendment

(b) (4)

[redacted]

Following this page, 7 pages withheld in full (b)(4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies concerning the dissolution testing have been identified:

You have presented two different options for adopting your newly developed dissolution method which uses pH 6.8 phosphate buffer with Sodium Lauryl Sulfate as dissolution medium. Option #1 proposes the use the current USP method as the official application method and adding the new dissolution method as *"an alternate method"* which would be used for ANDA information and post-approval changes only. Option #2 proposes the use of the new dissolution method as the official application method.

The USP method has been determined to be inappropriate method for the test product due to the fact that the dissolution data for the test product did not meet the USP specification of NLT 80% in 20 hours (the last time point)and 80% of the label claim was not dissolved until at least 35 hours of testing based on the USP method. Option #1 is therefore considered inappropriate and unacceptable. Option #2 is consistent with the DBE's past and current practice for establishing an official dissolution method for an application, and is the only acceptable option.

It is noted that in the current amendment, you have only submitted preliminary dissolution method development data and have not finalized your new method. We recommend that you complete your dissolution method development and provide individual and mean data (with CV% and range included)from this finalized method, using 12 units of the test and RLD product, of both strengths, and of batches within expiry dates. The DBE will determine appropriate dissolution specifications based on the submitted data.

Sincerely yours,

{See appended electronic signature page}

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

ANDA 76-640

BIOEQUIVALENCE - INCOMPLETE Submission date: 10-18-06

1. DISSOLUTION AMENDMENT (OTH) Strength: 200 mg & 100 mg

Outcome: IC

OUTCOME DECISIONS: **IC** – Incomplete

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hoainhon T. Nguyen
11/14/2006 10:38:12 AM
BIOPHARMACEUTICS

Moheb H. Makary
11/14/2006 12:50:41 PM
BIOPHARMACEUTICS

Barbara Davit
11/14/2006 06:18:01 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-640
Drug Product Name	Metoprolol Succinate ER Tablets USP
Strength	200 mg and 100 mg
Applicant Name	KV Pharmaceutical Company
Address	St. Louis, MO
Submission Date(s)	**November 21, 2006 & December 15, 2006 (Current Submissions)**
Amendment Date(s)	October 18, 2006
Reviewer	Hoainhon Nguyen
First Generic	Yes

I. Executive Summary

This is a review of an amendment. The firm has submitted its responses to the DBE's deficiency comments concerning the dissolution testing communicated in the letter dated October 3, 2006 and November 21, 2006. The current USP dissolution method for the drug product and the firm's originally proposed dissolution method (both using pH 6.8 phosphate buffer as dissolution medium) had been previously determined by the DBE to be inappropriate for the test product: The dissolution data did not meet the USP specification of NLT 80%(Q) in 20 hours (the last time point) and less than 60% label claim (LC) was dissolved at 20 hours in both of these methods. Subsequently, in the amendment that was faxed to the DBE on October 18, 2006, the firm informed the Agency that it has finally developed a dissolution method that uses surfactant in the dissolution medium and therefore allows at least 80% LC to be dissolved in 20 hours. The DBE then recommended that the firm finalizes its dissolution method development, provides individual and mean data (with CV% and range), based on the finalized method, using 12 units of the test and RLD product, of each strength, and of batches within expiry dates.

In the current amendment, the firm has submitted the dissolution data generated during the method development as well as the dissolution data based on the finalized, proposed dissolution method. The dissolution method and data are **acceptable**. The DBE agrees with the *interim* specifications as proposed by the firm. The *interim* specifications will be finalized with the dissolution data of three fresh commercial lots of each strength that the firm proposes to submit following approval. The dissolution testing is therefore considered **complete**.

The fasting and nonfasting bioequivalence studies have previously been found **acceptable.** The formulations of both strengths of the test product have also previously been found **acceptable.** The waiver request for the 100 mg strength of the test product is granted.

The application is **complete.**

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	KV's Metoprolol Succinate ER Tablets USP, 200 mg
Reference Product	Toprol-XL® Tablets
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	01/10/92
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	
Waiver requests	No	0
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies		
Amendment	Yes	1

D. In Vivo Studies

1. *Original* Single-dose Fasting Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

Study Summary	
Study No.	R02-586
Study Design	Three-way crossover
No. of subjects enrolled	33
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 29 Female: 4
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)* and R416-059A (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment C)
Strength tested	200 mg
Dose	1x200 mg

*NOTE: Only Test Formulation A is currently submitted for approval.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.98	88.67-108.2
AUC_{∞}	0.91	81.83-102.0
C_{max}	0.95	87.28-103.3

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) N=33		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	96.40-117.6
AUC_{∞}	1.00	90.44-111.0
C_{max}	1.21	**111.3-131.8**

Comments on Fasting Study: The fasting study is acceptable with respect to Test Formulation A.

2. *Original* Single-dose Fed Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640n0103.doc.

Study No.	RA2-102
Study Design	Two-way crossover
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 18 Female: 17
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot Nos. R416-055A (Treatment A)
Reference product	Toprol-XL® Tablets, Lot No. 3698H (Treatment B)
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=35		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	99.0-114.2
AUC_{∞}	1.04	97.9-110.3
C_{max}	0.87	**77.5-96.9***

Comments on fed study: The nonfasting study is acceptable based on point estimate. The study was conducted before the issuance of the food guidance.

3. *Second* Single-dose Fasting Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640a0606.doc.

Study Summary	
Study No.	PRACS R06-0598
Study Design	Two-way crossover
No. of subjects enrolled	40
No. of subjects completing	39
No. of subjects analyzed	39
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 21 Female: 18
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot No. R449-027A
Reference product	Toprol-XL® Tablets, Lot No. LN0094
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=39		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	94.8-109.8
AUC_{∞}	1.03	96.0-110.7
C_{max}	1.12	103.3-121.2

Comments on Fasting Study: The fasting study is acceptable.

4. *Second* Single-dose Fed Bioequivalence Study

See the review v:\firmsam\kv\ltrs&rev\76640a0606.doc.

Study No.	PRACS R06-0599
Study Design	Two-way crossover
No. of subjects enrolled	66
No. of subjects completing	63
No. of subjects analyzed	63
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 44 Female: 19
Test product	KV's Metoprolol Succinate ER Tablets USP, 200 mg, Lot No. R449-027A
Reference product	Toprol-XL® Tablets, Lot No. LN0094
Strength tested	200 mg
Dose	1x200 mg

Summary of Statistical Analysis N=63		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.06	102.6-109.9
AUC_{∞}	1.06	102.7-109.6
C_{max}	1.12	103.9-120.7

Comments on fed study: The nonfasting study is acceptable.

E. Formulation

See the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

F. Waiver Request(s)

Strengths for which waivers requested	100 mg
Regulation cited	Not cited by the firm.
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

G. In Vitro Dissolution Development

During the development of the firm's original dissolution method and a new dissolution method, the firm has investigated the following:

- ***Extending Dissolution Time:*** Based on the firm's original method (900 mL of pH 6.8 buffer, with USP apparatus II (paddle) @ 50 rpm, the data showed it took at least 36 hours for the test product (Lot Nos. R416-055, R449-027 and R449-028) to reach 80% released, and at least 47 hours to reach approximately 100% released.
- ***Effect of Volume and Agitation:*** The firm has compared dissolution volume of 500 mL versus 900 mL, and paddle speeds of 50 rpm, 75 rpm and 100 rpm, using pH 6.8 phosphate buffer and USP apparatus II (paddle) and the test Lot No. R416-055. The data showed that the different dissolution volumes and paddle speeds produced similar dissolution profiles.
- ***Effect of Salt Concentration:*** Using the firm's original dissolution method, the firm added different concentrations of NaCl: 10 mM, 50 mM and 100 mM. The data showed addition of salt did not increase the dissolution rate of the test product (Lot No. R416-055).
- ***Effect of Surfactant (SLS):*** Dissolution testing was conducted in 500 mL of pH 6.8 phosphate buffer, with USP apparatus II (paddle) @ 50 rpm, with 0%, 0.2% and 0.25% SLS added to the medium. The data showed that there was significant increase in dissolution rate with addition of 0.2% and 0.25% SLS compared with no addition of SLS. However, increase in SLS concentration from 0.2% to 0.25 % did not result in significant change in the dissolution rate. Dissolution testing was also conducted in 900 mL of pH 6.8 phosphate buffer containing 0.2% SLS, with USP apparatus II (paddle) @ 50 rpm, using test Lot Nos. R449-027 and R449-028. The dissolution profiles of the two lots were similar, with the profile of Lot No. R449-028 (100 mg) being slightly faster compared with that of Lot No. R449-027 (200 mg). Similar Factor F2 was 63.32.

- ***Effect of Another Surfactant (Triton X-100):*** Dissolution testing was also conducted in 900 mL of pH 6.8 phosphate buffer, with USP apparatus II (paddle) @ 50 rpm, with 0.2% Triton X-100 (octoxynol), another surfactant sometimes used in dissolution testing[1,2,3] Compared with the dissolution profile generated using 0.2% SLS where the test product reached 80% dissolved in approximately 7 hours, the dissolution profile based on 0.2% Triton X-100 was slower, with the test product reaching 80% dissolved in approximately 14 hours. Due to concern of the discriminatory ability of the method using of 0.2% SLS, the firm has selected the method using 0.2% Triton X-100. The firm's currently proposed dissolution method is, therefore, as follows: 900 mL of pH 6.8 buffer with 0.2% Triton X-100, with USP apparatus II (paddle) @ 50 rpm.
- ***Additional Validation Data:*** The firm conducted comparative dissolution testing between the strengths of 50 mg (Lot No. R429-098), 100 mg (Lot No. R449-028) and 200 mg (R449-027), using the currently proposed method. Firm's calculation of the Similarity Factor F2 was as follows: Between 50 mg and 100 mg strengths, F2=40.39; between 50 mg and 200 mg strengths, F2=44.20; and between 100 mg and 200 mg strengths, F2=77.13. It should be noted that the 50 mg strength of KV's Metoprolol Succinate ER Tablets is currently filed under a separate ANDA 77-176.

  In addition to comparison of dissolution profile between strengths, the firm also conducted dissolution testing using 100 mg strength (Lot No. R449-028) and 200 mg strength (Lot No. R449-027) on three different days for interday variability assessment. The interday CV% from combining data of 3 days for each time point (n=6) ranged from 5.4% to 29%. The intraday CV% for each time point (n=6) ranged from 3.2% to 29%.

[1] Noory, C. et al. Steps for development of a dissolution test for sparingly water-soluble drug products. Dissol. Technol. 7(1): 16-18, 2000.
[2] Brown, C. et al. Acceptable analytical practices for dissolution testing of poorly soluble compounds. Pharm. Tech., December 2004, 56-65.
[3] Brown, W. et al. Question and Answer Section. Dissol. Technol. 12(3), August 2005 (online; pages not given).

H. Dissolution Data Based on Firm's Currently Proposed Method

Medium	Phosphate buffer, pH 6.8 (prepared as specified in USP) with 0.2% Triton X-100
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
Firm's Currently Proposed Specifications	1 hr (b) (4) 4 hr 8 hr 20 hr 24 hr

Whole Tablets:

Product Lot No.	Strength	No. of Units	Collection Times				
			Mean, Range, CV%				
			1 hr	4 hr	8 hr	20 hr	24 hr
Test R449-028	100 mg	12	6	11	34	87	97
			(b) (4)				
			30%	23%	11%	8.5%	7.2%
RLD ML0135	100 mg	12	8	25	49	90	98
			(b) (4)				
			6.4%	4.6%	3.9%	4.8%	4.2%
Test R449-027	200 mg	12	7	12	34	91	101
			(b) (4)				
			11%	15%	25%	11%	5.8%
RLD LN0094	200 mg	12	10	29	53	93	97
			(b) (4)				
			7.4%	6.3%	7.5%	3.6%	3.4%

F2 between 100 mg and 200 mg of RLD product: 72.80.

NOTE: F2 cannot be calculated for the test product due to high CV%.

Half Tablets:

Product Lot No.	Strength	No. of Units	Collection Times				
			Mean, Range, CV%				
			1 hr	4 hr	8 hr	20 hr	24 hr
Test R449-028	100 mg	12	9	26	50	87	97
			(b) (4)				
			13%	8.5%	5.6	4.5%	4.0%
RLD ML0135	100 mg	12	9	13	33	85	99
			(b) (4)				
			24%	22%	12.4%	7.1%	5.3%
Test R449-027	200 mg	12	6	10	29	85	94
			(b) (4)				
			20%	18%	12%	4.6%	3.3%
RLD LN0094	200 mg	12	8	23	45	80	94
			(b) (4)				
			15%	10%	8.2%	9.0%	9.5%

NOTE: F2 cannot be calculated for the test or RLD product due to high CV%.

I. Comments

1. The dissolution data for both strengths of the test product are more variable than the data of both strengths of the RLD product, based on the firm's currently proposed dissolution method. The difference in variability between the test and RLD product was previously observed in dissolution testing conducted using USP method, or in media of different pH's.

2. With respect to the dissolution rate, the currently proposed method provided more acceptable, faster profile.

3. The dissolution data for ***half-tablets*** of the test and RLD product, based on the firm's currently proposed method, showed no dose-dumping.

4. The dissolution method as proposed by the firm in the current amendment is acceptable. The dissolution testing for the 100 mg and 200 mg strengths of the test and RLD products is **acceptable.** Based on the data submitted, the DBE agrees with the firm's proposed *interim* specifications as follows:

	(b) (4)
1 hr	
4 hr	
8 hr	
20 hr	
24 hr	

5. The DBE also agrees with the firm's following proposal concerning the finalized dissolution specifications: *"These tentative dissolution specifications will be finalized after release data from ten commercial lots per strength is generated and room temperature 24 month stability data is generated on the first three (3) commercial batches per strength. At which point KV is proposing to submit the data in a supplement CBE-30 to either confirm or request modifications to the tentative dissolution specifications."* However, if the firm requests modifications of the *interim* dissolution specifications, the firm should submit the data of the new lots in a Prior Approval supplement, not CBE-30 supplement. If there is no revision proposed to the *interim* specifications, the firm may submit the data of the new lots in a CBE-30 supplement.

6. NOTE: The test lots No. R449-027 (200 mg) and R-449-028 (100 mg) were manufactured April 2005 according to the Chemistry review, v:\firmsam\KV\ltrs&rev\ 76640N05_rms.doc and the bioequivalence review, v:\firmsam\kv\ltrs&rev\ 76640a0606.doc.. Therefore, they were within the expiry period of 2 years at the time of dissolution testing using the firm's currently proposed method.

7. The waiver request for the 100 mg strength of the test product is granted at this time. For comparative formulations of the 100 mg and 200 mg strengths, see the review of the original submission, v:\firmsam\kv\ltrs&rev\76640n0103.doc.

J. Deficiency Comments

None

K. Recommendations

1. The dissolution testing on the test product, Metoprolol Succinate ER Tablets, 200 mg and 100 mg, conducted by KV is **acceptable.**

The dissolution testing should be conducted in 900 mL of pH 6.8 phosphate buffer with 0.2% Triton X-100 at 37°C using the USP apparatus II (paddle) at 50 rpm. The test product should meet the following *interim* specifications:

	(b) (4)
1 hr	
4 hr	
8 hr	
20 hr	
24 hr	

2. The fasting and nonfasting bioequivalence studies have previously been found **acceptable.** The formulations of both strengths of the test product have also previously been found **acceptable.** The waiver request for the 100 mg strength of the test product is granted at this time.

BIOEQUIVALENCE COMMENTS

ANDA: 76-640 APPLICANT: KV Pharmaceutical

DRUG PRODUCT: Metoprolol Succinate Extended-Released Tablets USP, 200 mg and 100 mg

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

Your proposed dissolution method as presented in the current amendment is **acceptable.**

The dissolution testing should be conducted in 900 mL of pH 6.8 phosphate buffer with 0.2% Triton X-100 at 37°C using the USP apparatus II (paddle) at 50 rpm.

The test product should meet the following *interim* specifications:

	(b) (4)
1 hr	
4 hr	
8 hr	
20 hr	
24 hr	

The Agency agrees with you that the *interim* specifications will be finalized based on the dissolution data of three *fresh* production lots of each strength, and you will submit the data of the new lots in a Prior Approval supplement if you request revisions of the current *interim* specifications. If there is no revision proposed to the *interim* specifications, please submit the dissolution data of the new lots in a CBE-30 supplement.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

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

ANDA 76-640

BIOEQUIVALENCE - ACCEPTABLE Submission date: 11-21-06 & 12-15-06

1. STUDY AMENDMENT (OTH) Strength: 200 mg & 100 mg

Outcome: AC

OUTCOME DECISIONS: **AC** – Acceptable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hoainhon T. Nguyen
12/27/2006 10:25:18 AM
BIOPHARMACEUTICS

Moheb H. Makary
12/27/2006 10:27:53 AM
BIOPHARMACEUTICS

Barbara Davit
12/27/2006 02:18:59 PM
BIOPHARMACEUTICS