CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077779

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-176 and 77-779
Drug Product Name	Metoprolol Succinate Extended-Release Tablets USP
Strength	50 mg (#77-176) and 25 mg (#77-779)
Applicant Name	KV Pharmaceutical Company
Address	2503 South Hanley Road, St. Louis, MO 63144
Submission Date(s)	June 4, 2004 (#77-176), June 30, 2005 (#77-779)
Amendment Date(s)	Aug. 5, 2005 (#77-176)
Reviewer	Xiaojian Jiang, Ph.D.
First Generic	No
File Location	V:\firmsam\KV\ltrs&rev\77176N0604 V:\firmsam\KV\ltrs&rev\77779N0605

I. Executive Summary

This document has a review for two ANDAs from KV Pharmaceutical Company. Those are 77-779 for metoprolol succinate 25 mg ER tablet and 77-176 for metoprolol succinate 50 mg ER tablet.

For ANDA 77-176 (50 mg ER tablet)

The firm has submitted a single-dose, 3-way crossover fasting bioequivalence (BE) study comparing Formulations A and B of the test product, Metoprolol Succinate ER Tablets, 50 mg, with the RLD product, AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets, 50 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 31 normal males and 31 normal females at a dose of 1x50 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE, between Formulation A and the RLD formulation, in the fasted state (LAUCt 0.98, 93.13-102.67%; LAUCinf 0.97, 92.34-101.96%; LCmax 1.12, 105.32-118.70%). The fasting study does not show BE between Formulation B and the RLD formulation in the fasted state (LAUCt 1.06, 101.19-111.57%; LAUCinf 1.05, 100.06-110.49%; LCmax 1.20, 112.88-**127.23**%).

The firm has also submitted comparative dissolution data for the whole and half tablets of 50 mg strength 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 and 4.5. The dissolution testing is not acceptable because dissolution data show that at Hour 20, only approximately 60% of the labeled amount of the drug is dissolved. The DBE requests the firm to submit additional dissolution data to explore the possibility to raise the dissolution specifications at the final time point.

For ANDA 77779 (25 mg ER tablet)

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study comparing the test product, Metoprolol Succinate ER Tablets, 25 mg, with the reference listed drug (RLD), AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets, 25 mg. The fasting study was

performed in 13 normal males and 22 normal females at a dose of 2x25 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (LAUCt 0.99, 93.33-104.87%; LAUCinf 1.00, 94.85-105.09%; LCmax 0.98, 90.64-105.52%).

The firm has also submitted comparative dissolution data for the whole and half tablets of 25 mg strength of the test and reference products using USP method (500 ml of pH 6.8 buffer, paddle at 50 rpm) and non-USP method (900 ml of pH 1.2, 4.5 and 6.8 buffers, paddle at 50 rpm). The dissolution testing is acceptable and a new specification (different from USP specification) is recommended. The firm has submitted its acceptance of this FDA-recommended specification (1 hr: NMT 25%, 4hr: (b) (4) 8 hr: (b) (4) 20 hr: (b) (4)) in the amendment dated 12/07/05.

Summary for both ANDAs

As per the Electronic Orange Book, there are 4 strengths of ER metoprolol succinate Tablets (25 mg, 50 mg, 100 mg and 200 mg). Of these the 200 mg and 50 mg ER tablets are designated as the RLDs. That means if a generic firm wants all four strengths, it conducts 2 acceptable BE studies on the 200 mg ER tablet, an acceptable fasting study on the 50 mg ER tablet and multimedia dissolution testing on all four strengths. With these tests firm gets waiver for the 100 mg and 25 mg ER tablets and acceptance of all four strengths. Thus only the 200 mg ER tablet is a stand-alone strength while remaining three strengths (100 mg, 50 mg and 25 mg) are not because their acceptance depends on the acceptability of the 200 mg ER tablet. KV conducted a fasting BE study on the 25 mg strength because it did not formulate its 25 mg ER tablet proportionally similar to the 50 mg ER tablet.

KV had previously submitted two acceptable BE studies (fasting and fed) on its 200 mg ER tablet (ANDA 76640 See V:\firmsam\KV\ltrs&rev\76640N0103) but according to the current telecommunication with the firm those studies are invalid because the Chemistry Division found the manufacturing of the biolot of 200 mg ER tablet unacceptable. The firm therefore manufactured a new biolot of the 200 mg ER tablet and planning to conduct 2 new BE studies on that lot (see attachment# 2 on page 40).

Therefore, both applications are deficient pending satisfactory responses from the firm concerning the dissolution testing (ANDA 77-176 only) and the DBE's acceptance of the 2 BE studies on newly manufactured bio lot of the 200 mg ER tablet.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Metoprolol Succinate Extended-Release Tablets USP, EQ 25 and 50 mg Tartrate
Reference Product	Toprol-XL® ER Tablets, EQ 50 mg Tartrate (also available as 25 mg, 100 mg and 200 mg ER Tablets, the 200 mg strength is also designated as RLD)
RLD Manufacturer	Astrazeneca
NDA No.	19-962
RLD Approval Date	Jan 10, 1992 for 200 mg, 100 mg and 50 mg strengths, Feb. 5, 2001 for 25 mg strength.
Indication	For the treatment of hypertension, angina pectoris and heart failure.

B. PK/PD Information

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	The following is a summary for KV's metoprolol ER tablets submitted in three different ANDAs: As mentioned in the Executive Summary, in ANDA 76-640 (200 mg and 100 mg Metoprolol ER tablets), the firm submitted two BE studies (fasting and fed) on its 200 mg ER tablet and waiver request for the 100 mg strength. These studies are invalid because the Chemistry Division found the manufacturing of the biolot of 200 mg ER tablet unacceptable. The firm therefore manufactured a new biolot of the 200 mg ER tablet and planning to conduct 2 new BE studies on that lot. The firm submitted a fasting BE study on its 50 mg ER tablets in ANDA 77-176 per request of the DBE. However, the firm also submitted a fasting BE study on its 25 ER tablets in ANDA 77-779 because it did not formulate its 25 mg ER tablet proportionally similar to the 50 mg ER tablet. The formulations of KV's Metoprolol Succinate ER Tablets 200 mg and 100 mg are proportionally similar. However, the formulations of its 50 mg and 25 mg strengths are not proportionally similar to each other or to that of the 200 mg/100 mg strength (see additional attachment#1 on page 40 for the formulation comparison across the strengths). Similar dissolution behavior was observed between 50 mg and 200 mg/100 mg strengths. The dissolution of these strengths is so slow in the conventional media that the DBE is unable to set proper dissolution specifications. Thus the firm may have to use a dissolution medium with surfactant to obtain reasonable dissolution profiles. Thus dissolution testing for these three strengths is still incomplete. Totally different dissolution characteristic was observed for the 25 mg strength. The dissolution is faster than that of the RLD. More

	than 80% of the labeled amount of the drug is released at 20 hrs. 2. The DBE has received following ANDAs for Metoprolol Succinate ER Tablets, USP. 76-640 (KV, 01/15/03, 200 mg and 100 mg); 76-969 (Eon,12/18/03, 200 mg, 100 mg, 50 mg and 25 mg); (b) (4) 76-862 (Andrx, 11/26/03, 50 mg); 77-118 (Andrx, 04/01/04, 25 mg); 77-298 (Andrx, 09/30/04, 200 mg and 100 mg); 3. The Division of Bioequivalence (DBE) has reviewed the following control documents regarding this product: #01-423 (8/13/01- #01-470 (9/20/01- #02-035 (1/11/02, Andrx) #02-105 (2/27/02- #03-299 (4/17/03- #03-313 (4/22/03- #03-563 (7/16/03- #03-642 (8/1/03 #03-641 (8/1/03 #03-971 (12/15/03-Mylan) #04-393 (4/27/04- #04-437 (5/13/04- #04-548 (5/28/04- #04-630 (6/10/04- #04-635 (6/17/04- #05-0174 (02/09/05- #05-0336 (03/03/05- #05-0478 (04/25/05- #05-0579 (05/04/05- #05-0912 (06/14/05-
Agency Guidance	Currently, the DBE recommends the following: -A single-dose, two-way crossover or replicate-design fasting in-vivo bioequivalence study comparing Metoprolol Succinate Extended Release Tablets, 200 mg, to the reference listed drug (RLD), Toprol-XL® (Metoprolol Succinate) Extended Release Tablets, 200 mg. -A single-dose, two-way crossover fed in-vivo bioequivalence study comparing Metoprolol Succinate Extended Release Tablets, 200 mg, to the RLD.

	-A single-dose, two-way crossover or replicate-design fasting in-vivo bioequivalence study comparing Metoprolol Succinate Extended Release Tablets, 50 mg, to the RLD. -Only the parent compound, metoprolol, should be measured. -Metoprolol Succinate Extended Release Tablets, 25 mg and 100 mg, are eligible for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 50 mg and 200 mg strengths, (2) acceptable dissolution testing of the 25 mg, 50 mg, 100 mg, and 200 mg strengths, and (3) proportional similarity in the formulations of the 25 mg, 50 mg, 100 mg, and 200 mg strengths. *Reviewer's comments: Toprol-XL® ER Tablets, 100 mg and 200 mg are bioequivalent and Toprol-XL® ER Tablets, 25 mg and 50 mg are bioequivalent, based on studies submitted in NDA 19-962[1]. The formulations of the reference product are not proportional across strengths. However, dissolution profiles across all strengths are comparable in a variety of media*
ANDA-Specific Issue	NA
Drug Specific Issues (if any)	NA

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	2
Single-dose fed	No	---
Steady-state	No	---
In vitro dissolution	Yes	2
Waiver requests	No	---
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	Yes	1 (additional dissolution data)
CTD Tables	Yes	Not submitted for ANDA 77-176 Partially submitted for ANDA 77-779

[1] DBE review of Control document#01-423

D. Pre-Study Bioanalytical Method Validation*

For ANDA 77-176

	Parent
Analyte name	Metoprolol
Internal Standard	(b) (4)
Method description	LC/MS/MS
QC range	1.50, 80.0 and 150 ng/mL
Standard curve range	0.500 to 200 ng/mL
Limit of quantitation	0.50 ng/mL
Average recovery of Drug (%)	89.8%
Average Recovery of Int. Std (%)	95.2%
Intraday precision range (%CV)	2.82%-7.95%
Intraday accuracy range (%)	92.6%-108.7%
Interday precision range (%CV)	3.73%-8.20%
Interday accuracy range (%)	94.1%-104.9%
Bench-top stability (hrs)	12 hours 45 min
Stock stability (days)	2 days and 5 days for drug and internal standard respectively at 4°C
Processed stability (hrs)	68 hours 24 min at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	34 days at -20°C
Dilution integrity	3:1-1:3
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Chromatograms included (Y/N)	Yes
Random Selection of Serial Chrom	Yes

* The same method validation data were previously found acceptable in ANDA (b) (4). The analytical lab used for that application and this submission is the same.

For ANDA 77-779: a little different from that submitted in ANDA 77-176 above.

	Parent
Analyte name	Metoprolol
Internal Standard	(b) (4)
Method description	LC/MS/MS
QC range	1.50, 80.0 and 150 ng/mL
Standard curve range	0.500 to 200 ng/mL
Limit of quantitation	0.50 ng/mL
Average recovery of Drug (%)	89.8%
Average Recovery of Int. Std (%)	95.2%
Intraday precision range (%CV)	2.82%-7.95%
Intraday accuracy range (%)	92.6%-108.7%
Interday precision range (%CV)	1.18%-8.26%
Interday accuracy range (%)	98.5%-103.2%
Bench-top stability (hrs)	12 hours 45 min
Stock stability (days)	7 days and 5 days for drug and internal standard respectively at 4°C
Processed stability (hrs)	93 hours 51 min at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	**112 days at -20°C**
Dilution integrity	3:1-1:3
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 (#77-176)

Study Summary	
Study No.	R04-096
Study Design	Single-Dose, randomized, open-label, three-treatment, three-period, three-sequence crossover
No. of subjects enrolled	63
No. of subjects completing	62
No. of subjects analyzed	62
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 31, Female: 31.
Test product	KV's Metoprolol Succinate ER Tablets USP, 50 mg, Lot Nos. R429-098 (Treatment A)* and R440-015 (Treatment B)
Reference product	Toprol-XL® Tablets, Lot No. 3871J (Treatment C)
Strength tested	50 mg
Dose	1x50 mg

*NOTE: Only Test Formulation A is currently submitted for approval. Comparison between Test Formulations A and B was not provided.

Summary of Statistical Analysis (Test Treatment A vs. Reference Treatment C) Additional Information in Appendix, Table 9		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC∞	0.97	92.34-101.96
AUC0-t	0.98	93.13-102.67
Cmax	1.12	105.32-118.70

Summary of Statistical Analysis (Test Treatment B vs. Reference Treatment C) Additional Information in Appendix, Table 9		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC∞	1.05	100.06-110.49
AUC0-t	1.06	101.19-111.57
Cmax	1.20	112.88-**127.23**

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	A**	**C****	**A**	**C**	**A**	**C**	**A**	**C**
PK repeat	9	1	0.27	0.03	9	1	0.27	0.03
Low internal standard	2	1	0.06	0.03	2	1	0.06	0.03
Incomplete analysis	4	3	0.12	0.09	4	3	0.12	0.09
Total	15	5	0.45	0.15	15	5	0.45	0.15

*Total # samples assayed = 3348
** A: Test Formulation A; C: Reference Formulation. Samples re-assayed for Test Formulation B were not listed.

Did use of recalculated serum concentration data change study outcome? **No.**

Based on the reviewer's calculations, the 90% confidence intervals for lnAUC0-t, lnAUC∞ and lnCmax are within the acceptable limits of 80-125% using the original values of samples re-assayed for PK reason.

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

2. **Single-dose Fasting Bioequivalence Study (#77-779)**

Study Summary	
Study No.	R05-0036
Study Design	Single-Dose, randomized, open-label, two-way crossover
No. of subjects enrolled	36*
No. of subjects completing	36
No. of subjects analyzed	35**
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 13, Female: 22.
Test product	KV's Metoprolol Succinate ER Tablets USP
Reference product	Toprol-XL® Tablets
Strength tested	25 mg
Dose	2x25 mg

* The protocol requested 40 subjects. However, only 36 subjects were qualified for enrollment.
** Subject 07 was excluded from the statistical analysis due to emesis during the recommended dosing interval.

Summary of Statistical Analysis, Fasting Bioequivalence Study			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		LowCI	**UppCI**
AUC∞	1.00	94.85	105.09
AUC0-t	0.99	93.33	104.87
Cmax	0.98	90.64	105.52

Reanalysis of Study Samples Additional information in Appendix, Table 17								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
No Internal standard response		1	0	0.08		1	0	0.08
Processing error	1	1	0.08	0.08	1	1	0.08	0.08
Total	1	2	0.08	0.16	1	2	0.08	0.16

*Total # samples assayed =1290

Did use of recalculated serum concentration data change study outcome? **No.**

F. Formulation

Location in appendix	Section a)A.2, Page 33
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	25 mg and 50 mg strength
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

For ANDA 77-176

Source of Method (USP, FDA or Firm)	Firm's proposed method
Medium	pH 6.8 phosphate buffer
Volume (mL)	900 mL
USP Apparatus type	USP apparatus 2 (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications	2 hour: (b) (4) 4 hours: 12 hours: (b) (4) 24 hours:
USP dissolution method and specifications	500 ml of pH 6.8 phosphate buffer, USP apparatus 2 (Paddle) at 50 rpm. The firm's proposed method is the same as the USP method except for the volume of the medium 900 ml vs. 500 ml. 1 hour: not more than 25% 4 hours: between 20% and 40% 8 hours: between 40% and 60% 20 hours: not less than 80%
F2 metric calculated?	Yes
If no, reason why F2 not calculated	NA
Is method acceptable?	**Not acceptable**

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
50 mg (whole tablet)	50 mg (half tablet)	70.48	85.50

F2 metric, test compared to reference	
Strength	F2 metric
50 mg, Phosphate buffer pH 1.2, 900 ml	27.13
50 mg, Phosphate buffer pH 4.5, 900 ml	38.17
50 mg, Phosphate buffer pH 6.8, 900 ml	34.09
50 mg (whole tablet), Phosphate buffer pH 6.8, 500 ml	36.89
50 mg (half tablet), Phosphate buffer pH 6.8, 500 ml	34.61

History from previous ANDAs

Firm	**AstraZeneca**	**Andrx**	**Eon**
	INNOVATOR: NDA 19-962	ANDAs 76-862, 77-118, and 77-298	ANDA 76-969
Source of Method	**USP method**		
Medium	pH 6.8 phosphate buffer	SGF pH 1.2 (without enzyme)	Acetate buffer at pH 4.5
Volume (mL)	500	500	500
Apparatus	Paddle	paddle	paddle
Rotation (rpm)	50	75	50
Specifications	1 hour: NMT 25% 4 hours: 20% - 40% 8 hours: 40% - 60% 20 hours: NLT 80%	1 hour: (b) (4) 4 hours: 20% - 40% 8 hours: (b) (4) 20 hours: NLT 80%	1 hour: (b) (4) 4 hours: 8 hours: 20 hours: NLT 80%
Strength	200 mg, 100 mg, 50 mg and 25 mg (all strengths)	All strengths	All strengths

Comments on Dissolution of the 50 mg strength:

1. The DBE previously reviewed dissolution data of this ANDA. The firm has conducted comparative dissolution testing using USP method (500 ml of pH 6.8 buffer) and in two other media (pH 1.2 and pH 4.5 phosphate buffers). The dissolution data with the USP method indicated that the test product did not meet the USP specifications at 8 hrs and 20 hrs. The DBE Review of the dissolution data is archived at V:\firmsam\KV\ltrs&rev\77176D09604. The firm was asked to conduct additional dissolution testing using its proposed method (900 ml pH 6.8 phosphate buffer) and include time point at 24 hrs.

2. The firm submitted an amendment dated Aug.5, 2005 in response to the DBE dissolution deficiency comments of Apr. 7, 2005. The firm has provided dissolution data using the firm's proposed method. The data are similar to those conducted at USP method.

3. The 50 mg strength test product is slow-release with 63% dissolution reached at 24 hrs. The dissolution data are also highly variable. The coefficients of variation are greater than 10% up to 20 hrs. The dissolution behavior of the 50 mg tablets is very similar to that of the 200 mg and 100 mg tablets, although the formulation of the KV's 50 mg tablets is not proportional to that of its 200 mg and 100 mg tablets submitted in ANDA 76-640.

4. For ANDA 76-640 (V:\firmsam\KV\ltrs&rev\76640N0103, 76640A0404, 76640A0704), the following conclusions were made based on firm's responses:

1) The high variation of the dissolution data is due to the manufacture process. When the ER (b) (4) tablets, different numbers of ER pellets may be broken from tablet to tablet. However, 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% for all the PK parameters.
2) The test product is slow-release and 80% of the labeled amount is not released at reasonable testing time using either the USP or the firm's dissolution method. The firm's data show that the 80% of the drug is released at approximately 30 hrs and 100% release is eventually reached at around 41.5 hrs.
3) *The release of drug from the test product was found not dependent on the volume, type of media and speed of the paddle.*

5. For ANDA 76-640, up to this date, the dissolution testing of the KV's 200 mg and 100 tablets are still not acceptable because of the slow release. The DBE has asked the firm to explore other dissolution methods that are suitable for these products (see additional attachment#3 for the Teleconference memo). Because of the similarity in the dissolution behavior between KV's 50 mg tablets and 200 mg/100 mg strengths, the DBE will inquire the firm to do the same thing for 50 mg strength.

For ANDA 77-779

Source of Method (USP, FDA or Firm)	USP
Medium	pH 6.8 phosphate buffer
Volume (mL)	500 mL
USP Apparatus type	USP apparatus 2 (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications	The firm did not propose specifications.
USP specifications	1 hour: not more than 25% 4 hours: between 20% and 40% 8 hours: between 40% and 60% 20 hours: not less than 80%
FDA-recommended specification for this product	1 hour: not more than 25% 4 hours: (b) (4) 8 hours: 20 hours
F2 metric calculated?	Yes
If no, reason why F2 not calculated	NA
Is method acceptable?	Yes

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
25 mg (whole tablet)	25 mg (half tablet)	98.02	57.71

F2 metric, test compared to reference	
Strength	F2 metric
25 mg, Phosphate buffer pH 1.2, 900 ml	43.47
25 mg, Phosphate buffer pH 4.2, 900 ml	48.26
25 mg, Phosphate buffer pH 6.8, 900 ml	45.52
25 mg (whole tablet), Phosphate buffer pH 6.8, 500 ml	45.99
25 mg (half tablet), Phosphate buffer pH 6.8, 500 ml	47.21

Comments on Dissolution of the 25 mg strength:

6. The DBE previously reviewed dissolution data of this ANDA. The firm has conducted comparative dissolution testing using USP method (500 ml of pH 6.8 buffer) and non-USP method (900 ml of pH 1.2, pH 4.5 and pH 6.8 phosphate buffers). The dissolution data with the USP method indicated that the test product did not meet the USP specifications. Based on the dissolution data submitted and consultation with Dr. Nhan Tran (the dissolution focal point), the DBE recommends the USP method and the following modified specifications for the test product: 1 hr: NMT 25%, 4hr: (b) (4) 8 hr: (b) (4) 20 hr: (b) (4). In the amendment dated 12/07/05, the firm acknowledged the USP method and FDA-recommended dissolution specification. The DBE Review of the dissolution data is archived at V:\firmsam\KV\ltrs&rev\ 77779D0605.

H. Waiver Request(s)

Strength for which waiver is requested	NA
Regulation cited	NA
Proportional to strength tested in vivo?	NA
Is dissolution acceptable?	NA
Waivers granted?	NA
If not then why?	NA

I. Deficiency Comments

For ANDA 77-176

1. The dissolution testing is not acceptable because dissolution data using both the USP and the firm's proposed method show that at Hour 20, only approximately 60% of the labeled amount of the drug is dissolved. In order to explore the possibility to raise the dissolution specifications at the final time point, the DBE inquired whether the firm has dissolution data under the following conditions:

   A. with a paddle speed higher than the speed in the current data
   B. with a pH of medium higher than the pH in the current data
   C. with dual pHs viz. acid medium followed by the alkaline medium
   D. with any surfactant in the medium and

E. with combination of "a through d"

For ANDA 77-779

1. For ANDA 76-640, the Division of Chemistry has issued a letter on Apr. 2006 stating that the biobatch is not representative of what the firm plan to manufacture because of lack of manufacturing product with consistent quality (see additional attachment#2 for the letter and firm's telecommunication accepting to manufacture new biobatch for the 200 mg ER tablet). Since this ANDA is linked to the ANDA 76-640 (200 mg ER tablet), which is still incomplete, this ANDA ((b) (4)) is also incomplete.

J. Recommendations

For ANDA 77-176

1. The single-dose, fasting bioequivalence study submitted by KV Pharmaceutical on its test product, Metoprolol Succinate ER Tablets USP, 50 mg (lot # R429-098) comparing it to AstraZeneca's Toprol-XL® ER Tablets, 50 mg (lot # 3871J), has been found **acceptable** by the Division of Bioequivalence.

2. The *in vitro* dissolution testing conducted by the firm on its Metoprolol Succinate ER Tablets, 50 mg is not acceptable due to Deficiency Comments#1.

This application is incomplete pending satisfactory responses from the firm concerning the dissolution testing and the DBE's acceptance of the 2 BE studies on newly manufactured bio lot of the 200 mg ER tablet.

For ANDA 77-779

3. The single-dose, fasting bioequivalence study submitted by KV Pharmaceutical on its test product, Metoprolol Succinate ER Tablets USP, 25 mg (lot # R449-017A) comparing it to AstraZeneca's Toprol-XL® ER Tablets, 25 mg (lot#3725J), has been found **acceptable** by the Division of Bioequivalence.

4. The *in vitro* dissolution testing conducted by the firm on its Metoprolol Succinate ER Tablets, 25 mg is acceptable. The dissolution testing should be conducted as per USP 28 (500 ml of phosphate buffer, pH 6.8 using apparatus II (paddle) at 50 rpm). The test product should meet the following FDA-recommended specification:

1 h: NMT 25%
4 h: (b) (4)
8 h:
20 h

This application is still incomplete pending the DBE's acceptance of the 2 BE studies on newly manufactured bio lot of the 200 mg ER tablet.

9/8/06

Xiaojian Jiang, Ph.D. Date Signed
Review Branch II

9/11/2006

Shriniwas Nerurkar, Ph.D. Date Signed
Team Leader, Review Branch II

9/8/06

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

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study (#77-176)

a) Study Design

Study Information	
Study Number	R04-096
Study Title	A relative bioavailability study of Metoprolol Succinate 50 mg ER Tablets under fasting conditions.
Clinical Site	PRACS Institute, East Grand Forks, MN 56721
Principal Investigator	Thomas Cariveau, M.D.
Study/Dosing Dates	Period 1: Feb. 14, 2004 Period 2: Feb. 21, 2004 Period 3: Feb. 28, 2004
Analytical Site	PRACS Institute, 4666 Amber Valley Parkway, Fargo, ND
Analytical Director	(b) (6) M.S.
Analysis Dates	March 5, 2004 –March 17, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	33

Treatment ID	A	B	C
Test or Reference	Test	Test	Reference
Product Name	Metoprolol Succinate Extended-Release Tablets USP	Metoprolol Succinate Extended-Release Tablets USP	Toprol-XL® ER Tablets
Manufacturer	KV Pharma	KV Pharma	Astrazeneca
Batch/Lot No.	R429-098	R440-015	3871J
Manufacture Date	12/05/03	01/30/04	NA
Expiration Date	NA	NA	05/06
Strength	50 mg	50 mg	50 mg
Dosage Form	Tablet	Tablet	Tablet
Batch Size	(b) (4)	Not reported	NA
Production Batch Size		Not reported	NA
Potency	97.2%	Not reported	97.9%
Content Uniformity (mean, %CV)	98.6%, (87.7%-107.5%, 5.8%CV)	Not reported	99.6% (95.2%-104.4, 3.4%RSD)
Formulation	See Appendix Section 2		
Dose Administered	1x50 mg	1x50 mg	1x50 mg
Route of Administration	Oral with 240 ml water		

No. of Sequences	3
No. of Periods	3
No. of Treatments	3
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**A-B-C:** Subjects 2, 11, 12, 15, 16, 17, 20, 23, 24, 25, 26, 30, 31, 33, 36, 41, 48, 51, 53, 54, 61 **B-C-A:** Subjects 3, 10, 14, 19, 29, 32, 34, 37, 39, 40, 42, 44, 46, 49, 50, 56, 57, 58, 60, 62, 63 **C-A-B:** 1, 4, 5, 6, 7, 8, 9, 13, 18, 21, 22, 27, 28, 35, 38, 43, 45, 47, 52, 55, 59.
Blood Sampling Times	0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 38, and 48 hrs post-dose
Blood Volume Collected/Sample	10 mL Vacutainers containing EDTA
Blood Sample Processing/Storage	Samples were collected in EDTA vacutainers, centrifuged and harvested for plasma which was stored at -20°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours pre-dose and 4 hours post-dose
Length of Confinement	At least 10 hours pre-dose until 24 hours post-dose.
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.

Comments on Study Design: acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects (n=62)

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	100.0
Mean	23.05	Mean	160.45	18-40	93.5	Male	50.0	Afr. Amer.	0.0
SD	6.74	SD	24.67	41-64	6.5	Female	50.0	Hispanic	0.0
Range	18	Range	114	65-75	0.0			Asian	0.0
	46		211	>75	0.0			Others	0.0

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
58	Dropped from the study prior to Period II dose administration due to a urinary tract infection.	Prior to Period 2 dosing	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test (A) Group	# in Test (B) Group	# in Reference (c) Group
Abdominal Pain Upper (Stomach Pain)	2		1
Diarrhea		1	
Dizziness (light-headed)	1		
Dysmenorrhea (Menstrual Cramps)			1
Genitourinary Chlamydial Infection (Urinary Tract Infection)		1	
Headache	3	5	2
Joint Sprain (Left Ankle Sprain)		1	
Myalgia (left shoulder muscle pain)	1		
Pharyngolaryngeal Pain (Sore Throat)	1	1	1
Sinus Congestion			1
Throat Irritation (Scratchy Throat)			1
Tinnitus (left Ear Ringing)		1	
Toothache			1
Vaginal Mycosis (Yeast Infection)		1	
Total:	**8**	**11**	**8**

Table 4 Protocol Deviations

Type	Subject #s (Test A)	Subject #s (Test B)	Subject #s (Reference C)
Sampling deviation	A few	A few	A few
Concurrent Medications Used for Adverse Events		Ibuprofen: 10, 26; Micronazole:24	Ibuprofen: 10, 49 Zithromax: 58

Comments on Dropouts/Adverse Events/Protocol Deviations:

A total of 27 post-dose adverse events were reported (19 following administration of the test product and 8 following administration of the reference product). All of the reported adverse events were deemed mild to moderate in severity. No serious adverse events occurred during the conduct of the study.

The sampling time deviations were adjusted for PK analysis.

The protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Metoprolol							
QC Conc. (ng/mL)	1.50	80.00	150.0	5.00				
Inter day Precision (%CV)	7.2	3.0	3.4	4.3				
Inter day Accuracy (%)	104.7	101.8	99.5	107.6				
Cal. Standards Conc. (ng/mL)	0.500	1.00	5.00	10.0	50.0	100.0	150.0	200.0
Inter day Precision (%CV)	7.58	4.87	4.12	2.90	3.43	2.30	2.85	2.66
Inter day Accuracy (%)	95.8	100.8	101.5	102.5	99.2	100.8	98.9	100.4
Linearity Range (ng/ml)	0.50 to 200.0 ng/ml (Quadratic regression)							
Range of R values	0.9910-0.99998							

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, Subjects# 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14.

Comments on Chromatograms: Acceptable.

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

SOP No.	Date of SOP	SOP Title
098-01	11/22/02	Summary of validation and study acceptance criteria

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=62)

Mean plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test-A		Reference-C		T/R
		Mean	%CV	Mean	% CV	A/C
AUC∞	ng-hr/ml	345.18	110.93*	341.52	101.67*	1.01
AUC0-t	ng-hr/ml	325.20	111.25*	319.70	100.94*	1.02
Cmax	ng/ml	15.57	96.85	13.00	82.69	1.20
Kel	1/hr	0.09	33.33	0.09	22.22	1.07
T1/2	hr	8.09	33.25	8.47	28.45	0.95
Tmax	hr	**12.61**	26.33	**8.13**	46.62	**1.55****

Parameter	Units	Test-B		Reference-C		T/R
		Mean	% CV	Mean	% CV	B/C
AUC∞	ng-hr/ml	376.40	111.79	341.52	101.67	1.10
AUC0-t	ng-hr/ml	358.19	112.97	319.70	100.94	1.12
Cmax	ng/ml	16.66	94.90	13.00	82.69	1.28
Kel	1/hr	0.10	30.00	0.09	22.22	1.13
T1/2	hr	8.04	48.26	8.47	28.45	0.95
Tmax	hr	10.74	32.03	8.13	46.62	1.32

* The high intersubject variability of the AUC values has been observed for its sister product, 200 mg metoprolol succinate ER tablets (ANDA 76-640) and also other generic metoprolol succincate ER tablets (ANDAs 76-862, 76969 and (b) (4)).
** The test product has higher Tmax than the reference product (12.61 hr vs. 8.31 hr). It was also observed in ANDA 76-640 (13.36 hr vs. 7.21 hr).

For ANDA 76-640, 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 Clinical Consultation section):

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.

Table 9 Least Squares Geometric Means and 90% Confidence Intervals (N=62)

Comparison of Test A to Reference C

Parameter	Test A	Reference C	A/C	90% CI	
				LowCI	UppCI
AUC∞	224.96	231.84	0.97	92.34	101.96
AUC0-t	207.29	211.99	0.98	93.13	102.67
Cmax	10.89	9.74	1.12	105.32	118.70

Comparison of Test B to Reference C

Parameter	Test B	Reference C	B/C	90% CI	
				LowCI	UppCI
AUC∞	243.77	231.84	1.05	100.06	110.49
AUC0-t	225.24	211.99	1.06	101.19	111.57
Cmax	11.67	9.74	1.20	112.88	127.23

Table 10 Additional Study Information (N=62)

Root mean square error, AUC0-t	0.163915
Root mean square error, AUC∞	0.166382
Root mean square error, Cmax	0.200859
Ke and AUCi determined for how many subjects?	62
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:

The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations. The 90% confidence intervals for lnAUC0-t, lnAUC∞, and lnCmax are within the acceptable limits of 80-125%.

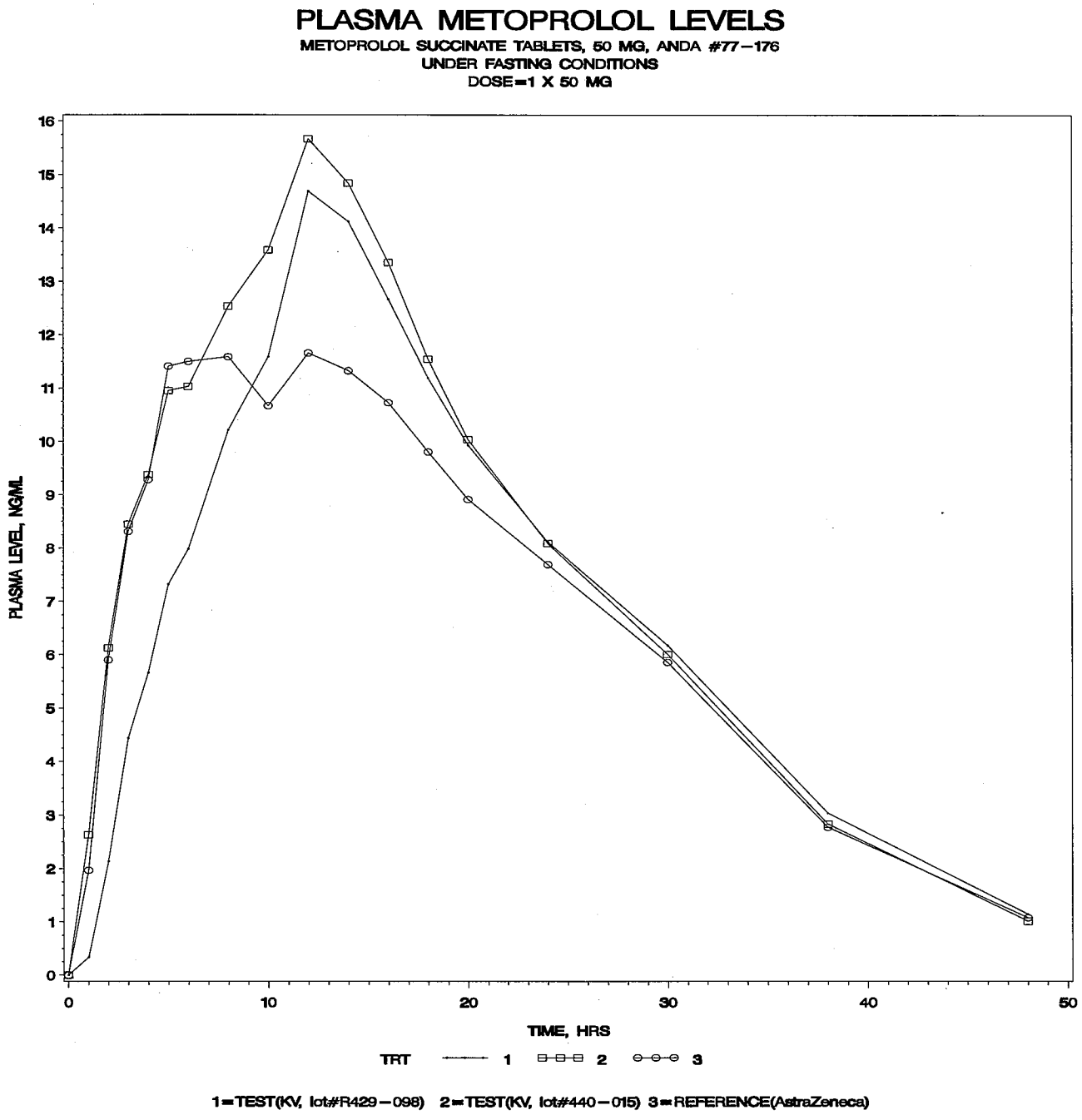
A statistically significant treatment and period effect was observed for LAUC0-t, LAUC∞ and LCmax.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasting bioequivalence study is acceptable with respect to the Test Formulation A which is the subject of the original ANDA.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (ng/mL)

TIME (hour)	TEST A		TEST B		REFERENCE C		TEST/REFERENCE		
	MEAN	CV%	MEAN	CV%	MEAN	CV%	A/B	A/C	B/C
0	0	.	0	.	0	.	.	.	.
1	0.33	133	2.63	79	1.97	81	0.13	0.17	1.34
2	2.13	85	6.13	77	5.90	70	0.35	0.36	1.04
3	4.43	75	8.45	79	8.31	69	0.52	0.53	1.02
4	5.66	78	9.38	83	9.28	75	0.60	0.61	1.01
5	7.32	77	10.95	83	11.41	75	0.67	0.64	0.96
6	7.98	84	11.03	85	11.50	75	0.72	0.69	0.96
8	10.22	105	12.54	94	11.59	84	0.81	0.88	1.08
10	11.59	106	13.59	99	10.67	91	0.85	1.09	1.27
12	14.69	97	15.67	98	11.66	93	0.94	1.26	1.34
14	14.12	99	14.84	106	11.33	95	0.95	1.25	1.31
16	12.67	105	13.36	112	10.73	95	0.95	1.18	1.25
18	11.19	110	11.54	119	9.81	99	0.97	1.14	1.18
20	9.93	116	10.04	123	8.91	102	0.99	1.11	1.13
24	8.12	127	8.09	129	7.69	105	1.00	1.06	1.05
30	6.18	143	6.00	143	5.86	122	1.03	1.05	1.02
38	3.03	162	2.83	161	2.77	158	1.07	1.09	1.02
48	1.14	190	1.01	181	1.08	198	1.13	1.06	0.94

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fasting Bioequivalence Study (#77-779)

a) Study Design

Study Information	
Study Number	R05-0036
Study Title	A relative bioavailability study of Metoprolol Succinate 25 mg ER Tablets under fasting conditions.
Clinical Site	PRACS Institute, East Grand Forks, MN 56721
Principal Investigator	James Carlson
Study/Dosing Dates	Period 1: March. 6, 2005 Period 2: March 13, 2005
Analytical Site	PRACS Institute, 4801 Amber Valley Parkway, Fargo, ND 58104
Analytical Director	(b) (6)
Analysis Dates	March 16, 2005 –March 25, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	20

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metoprolol Succinate Extended-Release Tablets USP	Toprol-XL® ER Tablets
Manufacturer	KV Pharma	Astrazeneca
Batch/Lot No.	R449-017A	3725J
Manufacture Date	01/19/05	NA
Expiration Date	NA	03/06
Strength	25 mg	25 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	NA
Production Batch Size		NA
Potency	101.1%	100.4%
Content Uniformity (mean, %CV)	99.8%, (91.4%-111.3%, 5.9%CV)	96.1% (93.6%-98.3, 1.7%RSD)
Formulation	See Appendix Section 2	
Dose Administered	2x25 mg	2x25 mg
Route of Administration	Oral with 240 ml water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**A-B:** Subjects 4, 7, 11, 12, 14, 15, 19, 20, 22, 23, 24, 25, 26, 27, 29, 31, 32, 35. **B-A:** Subjects 1, 2, 3, 5, 6, 8, 9, 10, 13, 16, 17, 18, 21, 28, 30, 33, 34, 36.
Blood Sampling Times	0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 38, and 48 hrs post-dose
Blood Volume Collected/Sample	10 mL Vacutainers containing EDTA
Blood Sample Processing/Storage	Samples were collected in EDTA vacutainers, centrifuged and harvested for plasma which was stored at -20°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 12
Length of Fasting	At least 10 hours pre-dose and 4 hours post-dose
Length of Confinement	At least 10 hours pre-dose until 24 hours post-dose.
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.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 12 Demographics of Study Subjects (n=36)

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	97.22
Mean	23.2	Mean	153.2	18-40	88.9	Male	38.9	Afr. Amer.	0.0
SD	7.6	SD	27.8	41-64	11.1	Female	61.1	Hispanic	2.78
Range	18	Range	106.0	65-75				Asian	0.0
	48		216.0	>75				Others	0.0

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
None			

Table 14 Study Adverse Events

Adverse Event Description	# in Test (A) Group	# in Reference Group
Abdominal Pain Upper		1
Chest discomfort		1
Dizziness		1
Headache	4	3
Nasal congestion	2	
Vomiting		1
Total:	**6**	**7**

Table 15 Protocol Deviations

Type	Subject #s (Test A)	Subject #s (Reference B)
Sampling deviation	A few	A few
Samples were not obtained	36 (3, 10 and 38 hrs)	13 (38 and 48 hrs), 18(48 hrs)
Concurrent Medications Used for Adverse Events		Ibuprofen: 21

Comments on Dropouts/Adverse Events/Protocol Deviations:

A total of 13 post-dose adverse events were reported (6 following administration of the test product and 7 following administration of the reference product). All of the reported adverse events were deemed mild to moderate in severity. No serious adverse events occurred during the conduct of the study.

Subject# 7 vomited 12 hrs after dose. It was excluded from the statistical analysis according to general BA/BE guidance. However, inclusion of this subject did not change the study outcome.
The sampling time deviations were adjusted for PK analysis.

The protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Metoprolol			
QC Conc. (ng/mL)	1.50	80.00	150.0	15.00
Inter day Precision (%CV)	4.7	2.2	2.8	3.0
Inter day Accuracy (%)	99.3	100.0	100.0	100.4

Cal. Standards Conc. (ng/mL)	0.500	1.00	5.00	10.0	50.0	100.0	150.0	200.0
Inter day Precision (%CV)	5.36	4.05	3.18	2.69	1.74	2.04	1.83	1.54
Inter day Accuracy (%)	103.1	98.6	98.8	99.2	100.1	100.4	99.7	100.1
Linearity Range (ng/ml)	0.50 to 200.0 ng/ml (Quadratic regression)							
Range of R values	0.9992-0.9999							

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, Subjects# 1, 2, 3, 4, 5, 6, 7, and 8.

Comments on Chromatograms: Acceptable.

Table 17 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
007-24	12/29/04	Study subject sample analysis

Table 18 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters (N=35)

Mean plasma concentrations are presented in Table 22 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	ng-hr/ml	453.71	99.32	459.40	102.66	0.99
AUCt	ng-hr/ml	436.82	100.79	442.66	103.14	0.99
Cmax	ng/ml	22.82	86.34	22.67	84.89	1.01
Kel	1/hr	0.10	25.26	0.10	22.22	1.00
T1/2	hr	7.26	27.92	7.14	22.48	1.02
Tmax	hr	**7.20**	**45.56**	**9.14**	38.53	**0.79***

* The test product has lower Tmax than the reference product (7.20 hr vs. 9.14 hr). It was totally opposite to its sister applications [ANDA 76-640 (13.36 hr vs. 7.21 hr) and ANDA 77-176 (12.61 hr vs. 8.31 hr)].

Table 20 Least Squares Geometric Means and 90% Confidence Intervals (N=35)

Parameter	Test	Reference	T/R	90% CI	
				LowCI	UppCI
AUC∞	309.51	310.01	1.00	94.85	105.09
AUCt	290.82	293.96	0.99	93.33	104.87
Cmax	16.57	16.94	0.98	90.64	105.52

Table 21 Additional Study Information (N=35)

Root mean square error, AUC0-t	0.144083
Root mean square error, AUC∞	0.126622
Root mean square error, Cmax	0.187824
Ke and AUCi determined for how many subjects?	35 (all subjects)
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:

The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations. The 90% confidence intervals for lnAUC0-t, lnAUC∞, and lnCmax are within the acceptable limits of 80-125%.

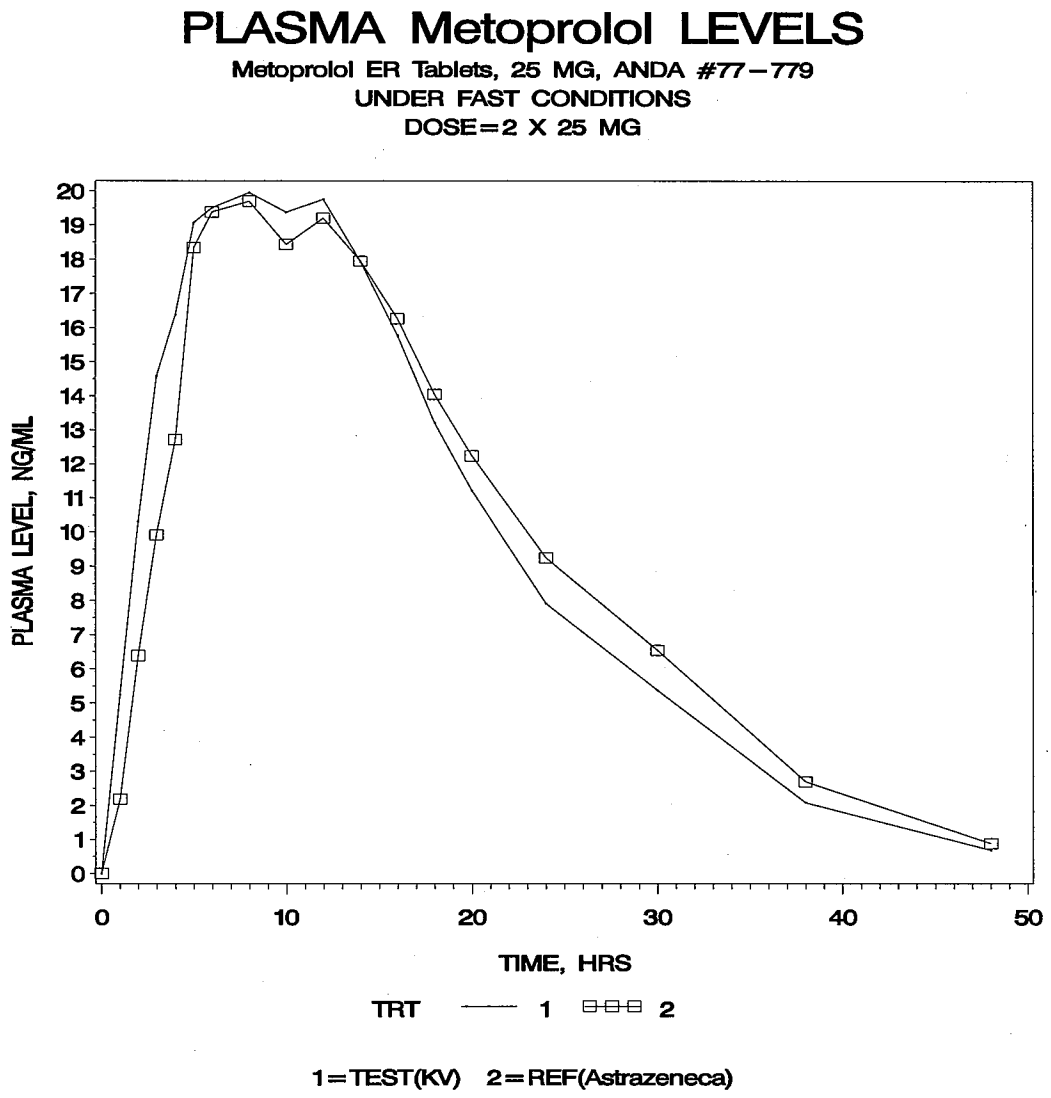
A statistically significant period effect was observed for LAUC0-t and LCmax.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasting bioequivalence study is acceptable.

Table 22 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (ng/mL)

Time (hr)	Test (n=35)		Reference (n=35)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	-	0	-	0.00
1	5.25	82.46	2.19	74.49	2.40
2	10.30	65.05	6.38	60.18	1.61
3	14.58	72.38	9.92	64.02	1.47
4	16.38	76.08	12.71	79.92	1.29
5	19.07	76.13	18.34	84.13	1.04
6	19.50	81.50	19.38	83.71	1.01
8	19.95	89.52	19.70	87.63	1.01
10	19.38	100.42	18.43	88.02	1.05
12	19.75	93.82	19.20	88.75	1.03
14	17.92	97.90	17.94	97.58	1.00
16	15.77	103.91	16.26	103.59	0.97
18	13.20	108.86	14.03	110.88	0.94
20	11.21	114.00	12.23	115.73	0.92
24	7.90	121.56	9.24	124.77	0.86
30	5.37	136.36	6.54	147.59	0.82
38	2.08	184.31	2.69	178.43	0.77
48	0.68	228.11	0.88	210.24	0.78

Figure 2 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



B. Formulation Data

1. Formulation for the Test Product (Not to be released under FOI)

Ingredient	50 mg Metoprolol Succinate ER Tablets		
	Function	Amount per Tablet (mg)	% in Exhibit Batch
Metoprolol Succinate, USP	Active ingredient	47.50*	6.4
Microcrystalline Cellulose, NF (b) (4) (b) (4)	(b) (4)		(b) (4)
Croscarmellose Sodium, NF			
Sodium Stearyl Fumarate, NF			
(b) (4)			
Wax Carnauba, NF			
Vinyl Acetate Copolymer (b) (4)			
Methacrylic Acid Copolymer (b) (4) (b) (4)			
Triethyl Citrate, NF			
Hydrogenated vegetable oil, NF			
Calcium Stearate, NF			
(b) (4) Carboxy methylcellulose, Sodium, NF (b) (4) (b) (4)			
Glyceryl Behenate, NF			
(b) (4)			
Povidone, USP (b) (4)			
Total (mg)		738.27	100

*Equivalent to 50 mg Metoprolol Tartrate

Ingredient	25 mg Metoprolol Succinate ER Tablets	
	Quantity to weigh (in mg/tab)	% in Exhibit Batch
(b) (4)		
Metoprolol Succinate, USP	23.75*	6.92
(b) (4) Carboxymethylcellulose Sodium, NF (b) (4) (b) (4) (b) (4)		(b) (4)
Vinyl Acetate Copolymer (b) (4)		
Methacrylic Acid Copolymer (b) (4)		
Triethyl Citrate, NF		
Hydrogenated Vegetable Oil (b) (4)		
Calcium Stearate, NF		

Microcrystalline Cellulose, NF (b) (4)		(b) (4)
Glyceryl Behenate, NF		
(b) (4)		
Croscarmellose Sodium, NF		
Povidone, USP (b) (4)		
Sodium Stearyl Fumarate, NF		
(b) (4)		
Wax, Carnauba, NF (b) (4)		
TOTAL (mg)	343.09	100.00

*Equivalent to 25 mg Metoprolol Tartrate

Description of the test product:

Strength	**Product Description**
50 mg	White, Lightly mottled, film-coated, oval, debossed "369" on one side with a bisect on the other site.
25 mg	White, Lightly mottled, film-coated, oval, debossed "293" on one side with a bisect on the other site.

Comment on the formulation:

1. The OGD had a telecon in reference to the inactive ingredients level in the 50 mg ER tablets on 7/19/2004. KV Pharmaceuticals submitted a new correspondence (Volume 2.1, 7/23/04), justifying all levels of inactive ingredients. Pharm-Tox review by Thomas Papoin dated 10/18/2004, concluded that the proposed level of Glyceryl Behenate in the drug product would not result in any unforeseen safety issues.

2. **Formulation for the Reference Product* (Not to be released under FOI)**

Formulation Comparison of Different Strengths of Toprol®-XL Tablets

Strength	25 mg	50 mg	100 mg	200 mg
Ingredient	mg/tab. (%)	mg/tab. (%)	mg/tab. (%)	mg/tab. (%)
*Metoprolol Succinate	23.75 (14)	47.5 (22)	95 (26)	190 (27)
(b) (4)				
Total Weight	169.4 (100)	219.3 (102)	375.3 (103)	710.3 (102)

*Metoprolol Succinate, 23.75, 47.5, 95 and 190 mg is equivalent to 25, 50, 100 and 250 mg of Metoprolol Tartrate, USP respectively.

(b) (4)

* Formulation obtained from review of control document#01-423
Description of the reference product:

Strength	Product Description
50 mg	White, biconvex, round, engraving" A mo", film-coated and scored.
25 mg	White, biconvex, Oval, engraving" A β", film-coated and scored on both sides.

C. **Dissolution Data**

For ANDA 77-176

Table 1: *In Vitro* Comparative Drug Release for the whole tablets

Medium:	pH 1.2 at 37°C ± 0.5°C
Volume:	**900** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098 (Mfg: 12/03)			Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. 3871J (Exp. 05/06)		
	Mean	%CV	Range	Mean	%CV	Range
1	4	30	(b) (4)	13	11	(b) (4)
2	9	31		20	11	
4	18	25		32	8.75	
12	33	19		74	4.32	
24	49	12		94	3.62	

Medium:	pH 4.5 buffer at 37°C ± 0.5°C
Volume:	**900** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098			Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. 3871J		
	Mean	%CV	Range	Mean	%CV	Range
1	4	20	(b) (4)	10	10	(b) (4)
2	10	16		16	8.75	
4	20	13.5		27	7.4	
12	41	8.5		65	4.46	
24	63	6.3		91	3.42	

	USP method
Medium:	pH 6.8 buffer at 37°C ± 0.5°C
Volume:	**500** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098			Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. 3871J		
	Mean	%CV	Range	Mean	%CV	Range
1	4	17.5	(b) (4)	10	10	(b) (4)
2	10	17		16	9.4	
4	20	15		28	6.4	
8	33	14		48	4.6	
12	43	13		67	3.6	
20	60	9.3		87	4.5	

Table 2: *In Vitro* Comparative Drug Release for the half tablets

	USP method
Medium:	pH 6.8 buffer at 37°C ± 0.5°C
Volume:	**500** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

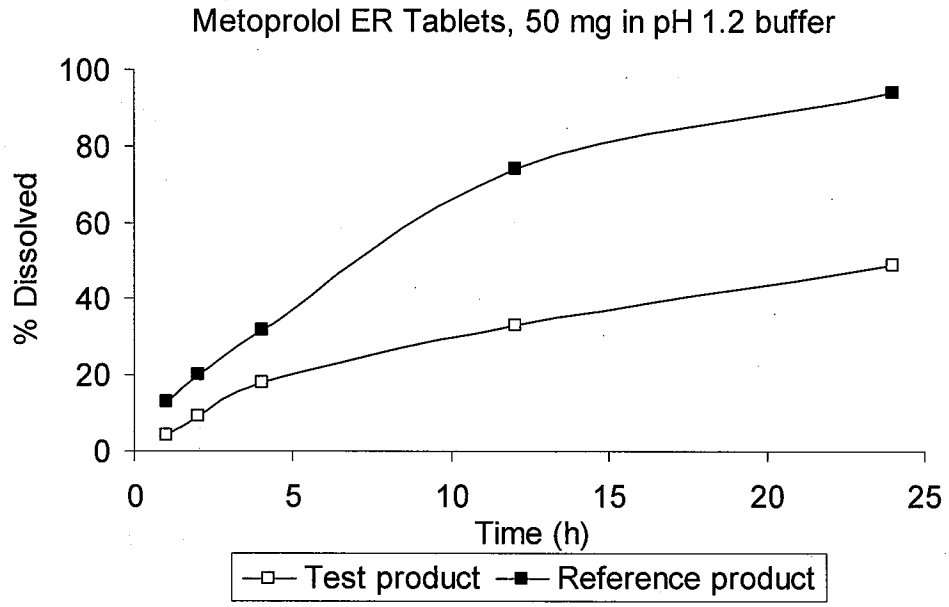
Sampling Time (Hr)	**Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098**			**Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. 3871J**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
1	4	27.5	(b) (4)	12	17.5	(b) (4)
2	10	26		18	13.3	
4	20	25.5		29	8.96	
8	32	24.1		50	5.2	
12	43	21.6		68	4.26	
20	61	16.4		91	4.29	

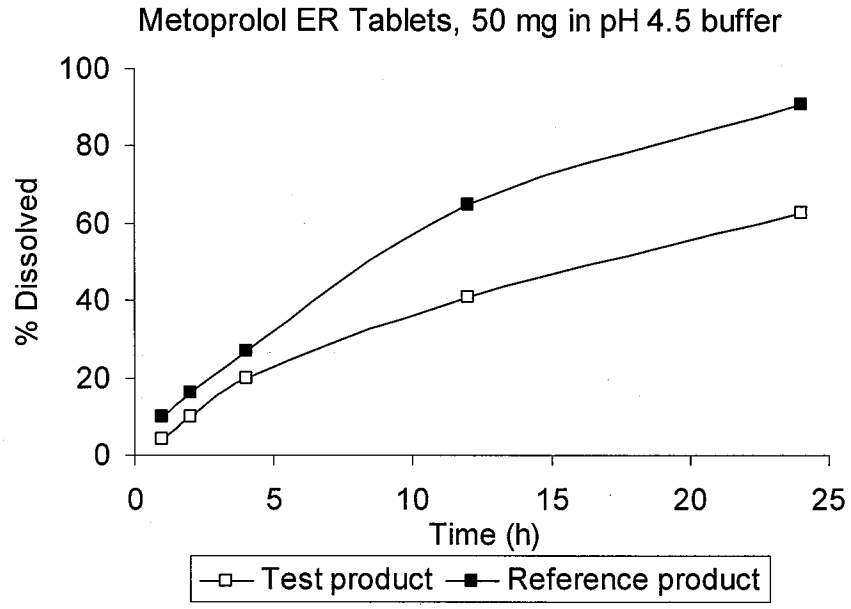
Table 3: *In Vitro* Comparative Drug Release for the whole tablets submitted in the amendment dated Aug.5, 2005.

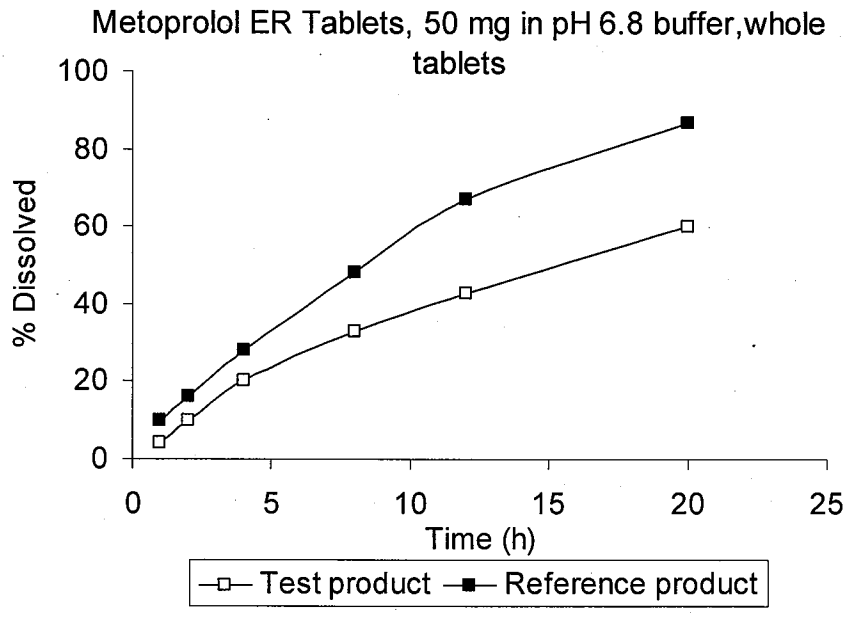
	Firm's proposed method
Medium:	pH 6.8 buffer at 37°C ± 0.5°C
Volume:	**900** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

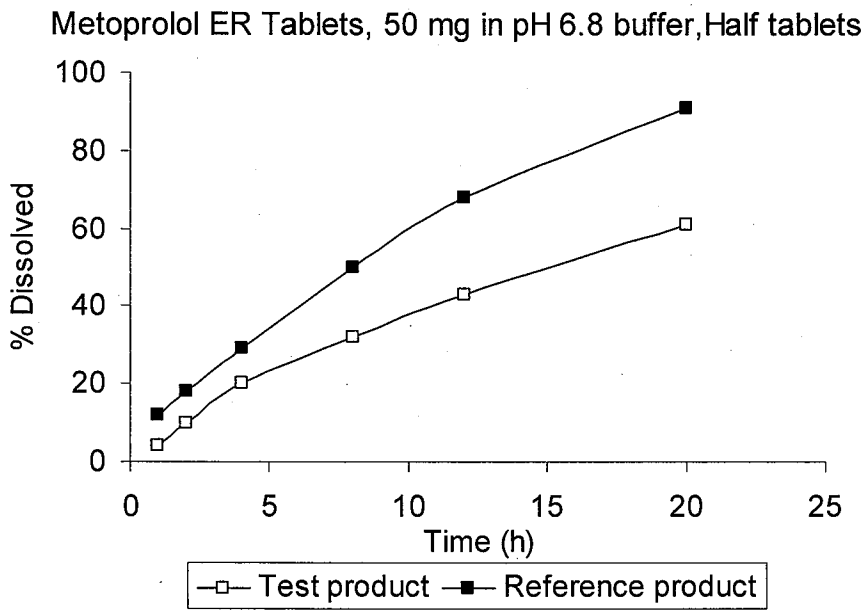
Sampling Time (Hr)	**Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098**			**Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. 3871J**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
1	4	30.0	(b) (4)	9	10	(b) (4)
2	9	30.0		15	9.3	
4	19	21.6		27	8.1	
8	31	17.7		48	5.8	
12	41	15.1		66	5.2	
20	57	10.9		89	4.7	
24	63	9.7		94	4.6	

Figure 3: Dissolution Profiles test vs. reference


Metoprolol ER Tablets, 50 mg in pH 1.2 buffer
% Dissolved
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)
Test product
Reference product


Metoprolol ER Tablets, 50 mg in pH 4.5 buffer
% Dissolved
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)
Test product
Reference product





For ANDA 77-776

The dissolution data submitted in the original review was previously reviewed by the DBE. Files were attached below. Please also see comments under In vitro dissolution section for details.

77779d0605.doc

D. Clinical Consultation

76640clinicalconsultemail.rtf

metaprololclinicalconsult76640C0705 mor.c

E. SAS Output

Fasting Bioequivalence Study

Active Component	SAS DATA	SAS PROGRAM	SAS OUTPUT
Metoprolol (50 mg)	data.xls	3wayxiaojian.txt	output.txt
Metoprolol (25 mg)	data.xls	fastprogram.txt	fastoutput.txt

F. Additional Attachments

Attachment#1

	25 mg	50 mg	100 mg	200 mg	25 mg	50 mg	100 mg	200 mg
	Mg/tablets	Mg/tablets	Mg/tablets	Mg/tablets	%w/w	%w/w	%w/w	%w/w
Metoprolol Succinate, USP	23.75	47.5	95	190	6.92	6.43	28.27	28.29
Microcrystalline Cellulose, NF (b) (4)	(b) (4)							
Croscarmellose Sodium, NF								
Sodium Stearyl Fumarate, NF (b) (4)								
Vinyl Acetate Copolymer (b) (4)								
Methacrylic Acid Copolymer (b) (4) (b) (4)								
Triethyl Citrate, NF								
Hydrogenated vegetable oil, NF								
Calcium Stearate, NF								
(b) (4) Carboxy methylcellulose, Sodium, NF (b) (4)								

Glyceryl Behenate, NF (b) (4)	(b) (4)							
Povidone, USP (b) (4) (b) (4)								
Total weight	343.09	738.27	336.09	671.5	100.00	100.00	100.00	100.00

Attachment #2 (teleconference on chemistry issue)

76640_KV letter_final_14apr

telecon with KV on metoprolol

Attachment#3 (dissolution teleconference memo)

76-640.doc
(52 KB)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-176 and 77-779 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Metoprolol Succinate Extended-Release Tablets USP 25 and 50 mg

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

For ANDA 77-176, Metoprolol Succinate ER Tablets USP, 50 mg.

1. Your dissolution testing is not acceptable because dissolution data using both the USP and your proposed method show that at Hour 20, only approximately 60% of the labeled amount of the drug is dissolved. Similarly for your 200 mg and 100 mg Metoprolol Succinate ER Tablets submitted under ANDA 76-640, in order to explore a possibility of raising the dissolution specifications of the test product, the DBE inquired whether you have dissolution data under the following conditions:

   A. with a paddle speed higher than the speed in the current data
   B. with a pH of medium higher than the pH in the current data
   C. beginning with low pH followed by higher pH; that is, acid medium followed by neutral medium
   D. with any surfactant in the medium and
   E. with combination of "a through d"

For ANDA 77-779, Metoprolol Succinate ER Tablets USP, 25 mg

1. In order for the DBE to deem acceptable a stand alone ANDA for any strength of a modified-release tablet, the submission should contain 2 acceptable BE studies (fasting and fed) and multimedia dissolution testing on that strength. This ANDA cannot be deemed acceptable on its own because it contains only an acceptable fasting study and acceptable multimedia dissolution testing. The acceptance of this product therefore is linked to your ANDA 76-640 for the 200 mg ER tablet. Since your ANDA 76-640 has not yet been deemed acceptable by the DBE, the status of this ANDA (77-779) is still incomplete.

Sincerely yours,

Barbara McDavitt

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

CC: ANDA 77-176 and ANDA 77-779
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Xiaojian Jiang X.J. 9/8/06
HFD-655/S.Nerurkar
HFD-650/Dale Conner BMD 9/11/06

9/11/06

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V:\firmsam\KV\ltrs&rev\77779N0605
Printed in final on

BIOEQUIVALENCE - incomplete Submission Date: 06/04/2004 (#77-176)

1. **FASTING STUDY** (STF) Strengths: 50 mg
Outcome: AC

Clinical: PRACS Institute, East Grand Forks, MN 56721
Analytical: PRACS Institute, 4666 Amber Valley Parkway, Fargo, ND

2. **Study Amendment** (STA) Aug.5,05 Strengths: all strengths
(Dissolution data, not previously reviewed) **Outcome: IC**

Submission Date: 06/30/2005(#77-779)

3. **FASTING STUDY** (STF) Strengths: 25 mg
Outcome: AC

Clinical: PRACS Institute, East Grand Forks, MN 56721
Analytical: PRACS Institute, 4801 Amber Valley Parkway, Fargo, ND

Outcome Decisions: Incomplete
WinBio Comments: Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-176 and 77-779
Drug Product Name	Metoprolol Succinate Extended-Release Tablets USP
Strength	50 mg (#77-176) and 25 mg (#77-779)
Applicant Name	KV Pharmaceutical Company
Address	2503 South Hanley Road, St. Louis, MO 63144
Point of Contact	David Jespesen
Phone Number	314-645-6600 ext. 5778
Fax Number	314-567-0704
Original Submission Date(s) and previous Amendment	June 4, 2004 (#77-176), June 30, 2005 (#77-779), Aug. 5, 2005 (#77-176) and Dec. 07, 2005 (#77-779)
Current Amendment Date(s)	**12/21/06 and 1/22/07 (**#77-176), **11/22/06** (#77-779)
Reviewer	Xiaojian Jiang, Ph.D.
DSI Inspection	**Not scheduled and not necessary (routine or for cause)**
First Generic	**no**
File Location	DFS

I. Executive Summary

This document is a review of amendments for two ANDAs from KV Pharmaceutical Company. Those are 77-779 for metoprolol succinate 25 mg ER tablet and 77-176 for metoprolol succinate 50 mg ER tablet.

For ANDA 77-176 (50 mg ER tablet)

The firm had previously submitted a single-dose, 3-way crossover fasting bioequivalence (BE) study comparing Formulations A and B of the test product, Metoprolol Succinate ER Tablets, 50 mg, with the RLD product, AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets, 50 mg. The Test Formulation A was different from Formulation B and only the Formulation A is the subject of this ANDA. The fasting study demonstrated BE between Formulation A and the RLD. A fed BE study is not needed for this product because it is linked to the firm's 200 mg ER tablet (submitted under the ANDA 76640) that has two acceptable BE studies (fasting and fed). However, the dissolution testing was not acceptable. Both the firm's proposed dissolution method and the USP method were inappropriate for this test product because dissolution data showed that at Hour 20, only approximately 60% of the labeled amount of the drug was dissolved. The DBE requested the firm to submit additional dissolution data to explore the possibility to raise the dissolution specifications at the final time point. (V:\firmsam\KV\ltrs&rev\77176N0604).

The firm submitted the current amendments in response to the Division of Bioequivalence (DBE) deficiency comments, dated 10/23/06. 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 (900 ml of pH 6.8 phosphate buffer with 0.2% Triton X-100, paddle at 50 rpm). The dissolution method and data are acceptable. The DBE also agrees with the *interim*

specifications as proposed by the firm (1 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 20 hr: (b) (4) (b) (4) and 24 hr: (b) (4)). 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**.

For ANDA 77779 (25 mg ER tablet)

The firm had previously submitted a single-dose, 2-way crossover fasting bioequivalence study comparing the test product, Metoprolol Succinate ER Tablets, 25 mg, with the reference listed drug (RLD), AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets, 25 mg. The fasting BE study was found acceptable. A fed BE study is not needed for this product because it is linked to the firm's 200 mg ER tablet (submitted under the ANDA 76640) that has two acceptable BE studies (fasting and fed). The dissolution testing using the USP method was also found acceptable. The firm had submitted its acceptance of the DBE-recommended specification (modified USP specification, 1 hr: NMT 25%, 4hr: (b) (4) 8 hr: (b) (4) 20 hr: (b) (4)) in the amendment dated 12/07/05. (V:\firmsam\KV\ltrs&rev\77779N0605)

Summary for both ANDAs

As per the Electronic Orange Book, there are 4 strengths of ER metoprolol succinate Tablets (25 mg, 50 mg, 100 mg and 200 mg). Of these the 200 mg and 50 mg ER tablets are designated as the RLDs. That means if a generic firm wants all four strengths, it conducts 2 acceptable BE studies (fasting and fed) on the 200 mg ER tablet, an acceptable fasting study on the 50 mg ER tablet and multimedia dissolution testing on all four strengths. With these tests firm gets waiver for the 100 mg and 25 mg ER tablets and acceptance of all four strengths. Thus only the 200 mg ER tablet is a stand-alone strength while remaining three strengths (100 mg, 50 mg and 25 mg) are not because their acceptance depends on the acceptability of the 200 mg ER tablet. KV conducted a fasting BE study on the 25 mg strength because it did not formulate its 25 mg ER tablet proportionally similar to the 50 mg ER tablet.

KV had previously submitted two acceptable BE studies (fasting and fed) on its 200 mg ER tablet (ANDA 76640, reviewed by a different reviewer, See V:\firmsam\KV\ltrs&rev\76640N0103) but due to CMC issue, the firm manufactured a new biolot of the 200 mg ER tablet and conducted 2 new BE studies on that lot. The new fasting and fed study were found acceptable (V:\firmsam\KV\ltrs&rev\76640a0606). The dissolution testing of this product was also found acceptable in the amendment of Nov. 21, 2006 (DFS N076640 N 000 AB 21-Nov-2006). The recommended dissolution method and specification is 900 ml of pH 6.8 phosphate buffer with 0.2% Triton X-100, paddle at 50 rpm and 1 hr: NMT (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 20 hr: (b) (4) and 24 hr: (b) (4)

Therefore, both applications (77-176 and 77-779) are acceptable and complete with no deficiencies

These ANDAs are not scheduled for DSI inspection and do not need it (for cause or routine).

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information and Relevant OGD or DBE History

See the review of the original submission.

[V:\firmsam\KV\ltrs&rev\77176N0604, V:\firmsam\KV\ltrs&rev\77779N0605]

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	---
Single-dose fed	No	---
Steady-state	No	---
In vitro dissolution	No	---
Waiver requests	No	---
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	Yes	3

C. Review of Submission

For ANDA 77-176 (50 mg ER tablet): Amendments of **12/21/06 (dissolution data) and 1/22/07 (correction of the proposed specification from (b) (4) to (b) (4) at 20 and 24 hrs).**

Deficiency-1:

Your dissolution testing is not acceptable because dissolution data using both the USP and your proposed method show that at Hour 20, only approximately 60% of the labeled amount of the drug is dissolved. Similarly for your 200 mg and 100 mg Metoprolol Succinate ER Tablets submitted under ANDA 76-640, in order to explore a possibility of raising the dissolution specifications of the test product, the DBE inquired whether you have dissolution data under the following conditions:

A. with a paddle speed higher than the speed in the current data
B. with a pH of medium higher than the pH in the current data

C. beginning with low pH followed by higher pH; that is, acid medium followed by neutral medium
D. with any surfactant in the medium and
E. with combination of "a through d"

Firm's Response:

A. As requested, the firm worked on different dissolution conditions in order to obtain an in vitro procedure which would yield 80% or greater release at the last sampling time interval. The firm provided the summary of this work. Please note that the same investigation report was submitted in the amendment dated 11/21/06 of ANDA 76-640 and reviewed by the DBE (DFS N076640 N 000 AB 21-Nov-2006). The following information was extracted from that review.

- ***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. *(Lot Nos. R416-055, R449-027 and R449-028 are the 200 mg and 100 mg strength ER tablets)*
- ***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, 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.

  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%.

B. The firm proposed the following dissolution method and interim dissolution specifications for its 50 mg strength product.

Medium:	pH 6.8 phosphate buffer with 0.2% Triton X-100
Volume:	900 mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm
Specification:	1 hour: (b) (4) 4 hours 8 hours 20 hours: (b) (4) 24 hours:

1. The firm conducted dissolution testing on the biobatch#**R429-098** and new batch# **R449-067** using the new method. The biobatch was over 34 months old when the testing was conducted. The firm thus manufactured a new batch, lot#R449-067. The firm stated that this batch was manufactured, controlled and tested according to the

[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).

submission batch process and it was manufactured for the purpose of commercialization. Because the timing of that approval had not occurred as anticipated but the batch was available for analysis.

The dissolution data of both batches using the new method are presented in Table 1

Table 1 dissolution data with the new proposed method

For the Whole Tablets

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098 (Mfg: 12/03)			RLD was not tested		
	Mean*	%CV	Range	Mean	%CV	Range
1	4	27.50	(b) (4)			
4	20	21.00				
8	35	12.86				
20	68	6.03				
24	77	3.25				

* data from 6 units and this batch was expired when the above data were generated.

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R449-067 (Mfg: 7/18/05)			Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. MN0025* (Exp. 07/09)		
	Mean	%CV	Range	Mean	%CV	Range
1	3	26.67	(b) (4)	12	20.83	(b) (4)
4	18	22.22		30	12.00	
8	40	14.50		54	6.48	
20	83	8.67		91	4.84	
24	93	5.38		95	4.74	
F2	**50.131**					

* The RLD biolot#387931J was expired at the time of testing. A new RLD lot was used in the testing.

For the Half Tablets: both test and reference product are scored.

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R449-067 (Mfg: 7/18/05)	Reference Product Toprol-XL® ER Tablets Strength 50 mg Lot No. MN0025 (Exp. 07/09)

	Mean	%CV	Range	Mean	%CV	Range
1	7	31.43	(b) (4)	14	17.86	(b) (4)
4	28	19.29		32	11.88	
8	49	15.92		53	7.17	
20	87	11.26		86	5.23	
24	97	8.97		92	4.78	
F2	**66.244**					

F2 calculation between whole tablet and half tables for the new batch and between biobatch and new batch

Low strength	Highest strength	F2 metric
50 mg, **R449-067** (whole tablet)	50 mg, **R449-067** (half tablet)	58.24
50 mg, **R449-067**	50 mg, **R429-098**	**49.69**

C. In order to demonstrate similarity of these two batches, the firm provided multimedia dissolution profile data comparing the batch# R449-067 with the biobatch#R429-098. The dissolution data for the biolot is historic data submitted in the original application. The data are presented in Tablet 2.

For the Whole Tablets

Medium:	pH 1.2 phosphate buffer at 37ºC ± 0.5ºC
Volume:	900 mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	**Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R449-067 (Mfg: 7/18/05)**			**Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098 (Mfg: 12/03)**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
1	2	30.00	(b) (4)	4	30.00	(b) (4)
2	8	11.25		9	31.11	
4	17	10.59		18	25.00	
12	38	8.68		33	19.09	
24	64	6.25		49	12.04	
F2	**57.058**					

Medium:	pH 4.5 phosphate buffer at 37ºC ± 0.5ºC
Volume:	900 mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R449-067 (Mfg: 7/18/05)			Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098 (Mfg: 12/03)		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
1	3	23.33	(b) (4)	4	20.00	(b) (4)
2	7	22.86		10	16.00	
4	15	18.67		20	13.50	
12	42	10.24		41	8.54	
24	70	5.4		63	6.35	
F2	**66.945**					

	USP method
Medium:	pH 6.8 phosphate buffer at 37ºC ± 0.5ºC
Volume:	**500** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R449-067 (Mfg: 7/18/05)			Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098 (Mfg: 12/03)		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
1	4	57.50	(b) (4)	5	14.00	(b) (4)
2	8	25.00		10	17.00	
4	17	18.24		20	15.00	
8	32	11.56		33	13.64	
12	46	10.43		43	12.56	
20	69	8.26		60	9.33	
F2	**68.321**					

<u>for the half tablets</u>

	USP method
Medium:	pH 6.8 buffer at 37ºC ± 0.5ºC
Volume:	**500** mL
Apparatus:	USP apparatus 2 (Paddles)
Speed:	50 rpm

Sampling Time (Hr)	Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R449-067 (Mfg: 7/18/05)			Test Product, Metoprolol Succinate ER Tablets USP Strength 50 mg Lot No. R429-098 (Mfg: 12/03)		
	Mean	%CV	Range	Mean	%CV	Range
1	4	30.00	(b) (4)	4	27.50	(b) (4)
2	8	32.50		10	26.00	
4	17	25.88		20	25.50	
8	32	19.06		32	24.06	
12	46	15.87		43	21.63	
20	70	11.71		61	16.39	
F2	**68.518**					

Review's Comment

1. The dissolution data for the test product are highly variable. The variability was observed in dissolution testing conducted using firm's currently proposed method, USP method, or in media of different pHs. With respect to the dissolution rate, the currently proposed method provided more acceptable, faster profile. The same variability was also observed for 200 mg and 100 mg ER tablets that are the subject of ANDA 76-640.

2. The dissolution behavior of the 50 mg tablets is very similar to that of the 200 mg and 100 mg tablets, although the formulation of the KV's 50 mg tablets is not proportional to those strengths. The same dissolution method was found acceptable for KV's 200 mg and 100 mg ER Tablets (DFS N076640 N 000 AB 21-Nov-2006). A slightly different specification was recommended to those strengths.

3. The firm stated that this batch was manufactured, controlled and tested according to the submission batch process and it was manufactured for the purpose of commercialization. Based on the multimedia dissolution data, it appears that dissolution profile of the biobatch and the new batch are comparable. However, using the firm's currently proposed method, the biobatch seems release drug slowly at 20 and 24 hrs. At this time, there are no chemistry review available regarding the manufacture and control similarity of these two batches. The chemistry reviewer should be aware of this issue. Please also note that the F2 calculation may not be statistically meaningful due to the high variation of the dissolution data.

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

5. The dissolution method as proposed by the firm in the current amendment is acceptable. The dissolution testing for the 50 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:

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

6. 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.
7. The firm's responses to this deficiency is acceptable. Since ANDA 76-640 was found acceptable and complete, ANDA 77-179 is also complete with no deficiencies.

For ANDA 77-779 (25 mg ER tablet): amendment of 11/22/06

Deficiency-1:

In order for the DBE to deem acceptable a stand alone ANDA for any strength of a modified-release tablet, the submission should contain 2 acceptable BE studies (fasting and fed) and multimedia dissolution testing on that strength. This ANDA cannot be deemed acceptable on its own because it contains only an acceptable fasting study and acceptable multimedia dissolution testing. The acceptance of this product therefore is linked to your ANDA 76-640 for the 200 mg ER tablet. Since your ANDA 76-640 has not yet been deemed acceptable by the DBE, the status of this ANDA (77-779) is still incomplete.

Firm's Response:

The firm indicated that they submitted several amendments to address issues in ANDA 76-640. After review, they believed that this ANDA will be found acceptable.

Review's Comment:

The firm recently submitted three amendments to address issues raised by the DBE for ANDA 76-640.

June 26, 2006 Amendment: fasting and fed study on the new biolot of the 200 mg strengths (V:\firmsam\KV\ltrs&rev\76640a0606)

October 18, 2006 Amendment: proposal for the official dissolution method (DFS N076640 N 000 AB 10-OCT-2006)
November 21 and December 15, 2006 Amendment: dissolution data using the currently proposed method (DFS N076640 N 000 AB 21-OCT-2006).

All the above amendments were found acceptable. The DBE accepted the firm's proposed dissolution method and interim dissolution specification. This application is considered complete.

Therefore, ANDA 77-779 is complete with no deficiencies.

D. Waiver Request(s)-NA

E. Deficiency Comments

None

F. Recommendations

For ANDA 77-176

1. The single-dose, fasting bioequivalence study submitted by KV Pharmaceutical on its test product, Metoprolol Succinate ER Tablets USP, 50 mg (lot # R429-098) comparing it to AstraZeneca's Toprol-XL® ER Tablets, 50 mg (lot # 3871J), has been previously found **acceptable** by the Division of Bioequivalence.

2. The dissolution testing on the test product, Metoprolol Succinate ER Tablets, 50 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	

For ANDA 77-779

3. The single-dose, fasting bioequivalence study submitted by KV Pharmaceutical on its test product, Metoprolol Succinate ER Tablets USP, 25 mg (lot # R449-017A)

comparing it to AstraZeneca's Toprol-XL® ER Tablets, 25 mg (lot#3725J), has been previously found **acceptable** by the Division of Bioequivalence.

4. The *in vitro* dissolution testing conducted by the firm on its Metoprolol Succinate ER Tablets, 25 mg was previously found **acceptable**. The dissolution testing should be conducted as per USP 29 (500 ml of phosphate buffer, pH 6.8 using apparatus II (paddle) at 50 rpm). The test product should meet the following DBE-recommended specification:

1 h: NMT 25%
4 h: (b) (4)
8 h:
20 h

Both applications are complete with no deficiencies.

G. Comments for Other OGD Disciplines

Discipline	Comment
CMC	The firm stated that the new batch lot#449-067 was manufactured, controlled and tested according to the submission batch process and it was manufactured for the purpose of commercialization. However, due to slightly difference in the dissolution at 20 and 24 hrs using firm's currently proposed dissolution method between the biolot and this new lot, a careful examination of similarity of the chemistry, manufacture and control between these two batches might be necessary. **These ANDAs are not scheduled for DSI inspection and do not need it (for cause or routine).**

BIOEQUIVALENCE COMMENTS

ANDA: 77-176 and 77-779 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Metoprolol Succinate Extended-Release Tablets USP
25 and 50 mg

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

For ANDA 77-176, Metoprolol Succinate ER Tablets USP, 50 mg.

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:

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

The DBE 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.

For ANDA 77-779, Metoprolol Succinate ER Tablets USP, 25 mg

We acknowledge that you have accepted the DBE-recommended dissolution method and specification as follows:

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

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

1 hr	NMT 25%
4 hr	(b) (4)
8 hr	
20 hr	

Please note that the bioequivalence comments provide 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 77-176 and 77-779

BIOEQUIVALENCE - ACCEPTABLE Submission date: 12-21-06 & 1-22-06 (77-179)

1. STUDY AMENDMENT (STF) Strength: 50 mg

Outcome: AC

2. STUDY AMENDMENT (STF) Strength: 50 mg

Outcome: WC

Submission date: 11/22/06 (ANDA 77-779)

3. STUDY AMENDMENT (STF) Strength: 50 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/

Xiaojian Jiang
3/2/2007 05:22:57 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
3/5/2007 08:00:10 AM
BIOPHARMACEUTICS

Barbara Davit
3/5/2007 02:08:05 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW - ADDENDUM

ANDA No.	77-176 and 77-779
Drug Product Name	Metoprolol Succinate Extended-Release Tablets USP
Strength	50 mg (#77-176) and 25 mg (#77-779)
Applicant Name	KV Pharmaceutical Company
Address	2503 South Hanley Road, St. Louis, MO 63144
Point of Contact	David Jespesen
Phone Number	314-645-6600 ext. 5778
Fax Number	314-567-0704
Original Submission Date(s) and previous Amendments	June 4, 2004 (#77-176), Aug. 5, 2005 (#77-176), 12/21/06, 1/12/07 and 1/22/07 (#77-176), Mar. 19, 2007 (#77-176: dissolution acknowledgement) June 30, 2005 (#77-779), and Dec. 07, 2005 (#77-779), 11/22/06 (#77-779),
Current Amendment Date(s)	NA
Reviewer	Xiaojian Jiang, Ph.D.
DSI Inspection	**Not scheduled and not necessary (routine or for cause)**
First Generic	**no**
File Location	DFS

I. Executive Summary

This is an addendum to the review (DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006). Due to concern of dose dumping for the drug product, the Agency currently requests that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The testing conditions are described for the additional testing.

The application has previously been found **complete** with other bioequivalence requirement aspects (see the review in DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006).

II. Table of Contents

III. Submission Summary

A. Drug Product Information, PK/PD Information and Relevant OGD or DBE History

See the review of the original submission.

[V:\firmsam\KV\ltrs&rev\77176N0604, V:\firmsam\KV\ltrs&rev\77779N0605]

A. Deficiency Comments

Due to concern of dose dumping for the drug product (See memo referenced in this review), the Agency currently requests that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus II (paddle) @ 50 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

B. Recommendations

The dissolution testing conducted by KV on its Metoprolol Succinate Extended Release Tablets, 25 mg and 50 mg, is **incomplete** for the reasons cited in the Deficiency Comments above**.**

The firm is requested to conduct additional dissolution testing as described in the Deficiency Comments above.

C. Additional attachment

Memorandum: Please see the memo to the ANDA 77176 and 77779 files, written by Drs. Barbara M. Davit and Dale P. Conner, archived electronically in DFS at N 077176 N 000 AB 05-Aug-2005 and N 077779 N 000 AB 07-Dec-2005.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-176 and 77-779 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Metoprolol Succinate Extended-Release Tablets 25 and 50 mg

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

There is evidence that some extended-release drug products "dose dump" when ingested with alcoholic beverages. Therefore, the Agency is concerned that dose-dumping may potentially result if extended-release metoprolol succinate tablets are taken with alcoholic beverages. This is a potential safety concern because high levels of metoprolol can produce serious adverse events in cardiac patients. Cardiac patients are dosed to tolerability, rather than to a blood pressure goal. It is possible that patients exposed to sudden elevations in plasma metoprolol concentrations (which might occur as a result of dose-dumping) could be at risk for excessive bradycardia, hypotension, and perhaps ischemic stress. An in vitro dose dumping test is a simple way to screen the performance of generic formulations of metoprolol succinate extended-release tablets compared to the performance of the RLD.

The Agency requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 2 (paddle) @ 50 rpm, with and without the alcohol:

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both strengths of the test and RLD products must be tested accordingly.

Please submit standard operating procedures (SOPs) for the dissolution testing above, individual dissolution data, mean values, standard deviations, coefficient of variation (CV%), and plots of the percent dissolved data.

We ask that these studies be performed as post approval commitments. Please acknowledge your agreement to perform these studies. Please complete these studies within 6 months of approval.

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 77-176 and 77-779

1.	**Addendum**	Strength(s):	25 mg & 50 mg
	(OTH)	Outcome:	**IC & WC (Addendum for Additional Dissolution Request)**
	Submission Date(s)	**12/21/06 and 11/22/06**	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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/s/

Xiaojian Jiang
5/17/2007 02:46:56 PM
BIOPHARMACEUTICS

Surendra P. Shrivastava
5/17/2007 02:49:59 PM
BIOPHARMACEUTICS

Barbara Davit
5/17/2007 03:16:48 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-176 and 77-779
Drug Product Name	Metoprolol Succinate Extended-Release Tablets USP
Strength(s)	50 mg (#77-176) and 25 mg (#77-779)
Applicant Name	KV Pharmaceutical Company
Address	2503 South Hanley Road, St. Louis, MO 63144
Applicant's Point of Contact **Contact's Telephone Number** **Contact's Fax Number**	Scarlett Tumulty 314-645-6600 ext. 5585 314-567-0704
Original Submission Date(s) and previously reviewed amendments	June 4, 2004 (#77-176), Aug. 5, 2005 (#77-176), 12/21/06, 1/12/07 and 1/22/07 (#77-176), Mar. 19, 2007 (#77-176: dissolution acknowledgement) June 30, 2005 (#77-779), and Dec. 07, 2005 (#77-779), 11/22/06 (#77-779),
Submission Date(s) of Amendment(s) Under Review	**May, 22 (plan to send dissolution by Nov. 18, 2007) and Nov. 5, 2007 (77-176)** **May, 22 (plan to send dissolution by Nov. 18, 2007) and Nov. 5, 2007 (77-779)**
Reviewer	Xiaojian Jiang, Ph.D.
First Generic	No
DSI Inspection	Not scheduled and not necessary
Location	DFS
Outcome	**Incomplete**

Review of an Amendment

I. Executive Summary:

The applications of KV's Metoprolol Succinate Extended-Release Tablets, 25 mg and 50 mg (the RLD is AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets) had previously been found **acceptable** with other bioequivalence requirement aspects (V:\firmsam\KV\ltrs&rev\77176N0604 and 77779N0605, DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006).

Due to concern of dose dumping for the drug product, the Agency asked, on May 18, 2007, that the firm conduct additional dissolution testing using various concentrations of ethanol in the recommended dissolution medium of 0.1 N HCl for both strengths of test and reference products.

[Addendum review in DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006**]**

In the current supplement, the firm submitted the in vitro alcohol dose dumping testing, as requested by the DBE. The DBE first compared the % dissolution of the test product at 2 hr without alcohol to the % dissolution of the test product at 2 hrs with alcohol. Since the % dissolution of the test product increased as the amount of alcohol in the medium increased, there was a possibility of dose-dumping. The DBE then compared 2 hr mean and range % dissolution of the test product to the same of the reference product at all three concentrations of alcohol. The DBE considered i) whether there was overlap between dissolution range for the test product and the dissolution range for the reference product and ii) whether the mean% dissolution of the test product was comparable to that of the mean% dissolution of the reference product, Using this criterion, the test 25mg ER Table dissolution data would have been acceptable but the firm has not provided the date of manufacture for the test 25 mg ER Tablet, the expiry date for the reference 25 mg ER tablet and the date of the dissolution testing. Similarly using this criterion, the in vitro alcohol dose-dumping test results for the 50 mg ER tablet are not acceptable because the test product releases more metoprolol in 20% alcohol than does the reference product [T = 66% (b) (4)) and R = 47% ((b) (4))]. The firm also has not provided the date of the dissolution testing and the expiration date for the Reference 50 mg ER Tablet. The firm should provide these data.

Therefore, both applications are **incomplete**.

II. Table of Contents

III. Background and References:

A. Drug Product Information, PK/PD Information and Relevant OGD or DBE History

See the review in V:\firmsam\KV\ltrs&rev\77176N0604 and 77779N0605,
DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006

IV. Current Submission:

DEFICIENCY COMMENT #1

There is evidence that some extended-release drug products "dose dump" when ingested with alcoholic beverages. Therefore, the Agency is concerned that dose-dumping may potentially result if extended-release metoprolol succinate tablets are taken with alcoholic beverages. This is a potential safety concern because high levels of metoprolol can produce serious adverse events in cardiac patients. Cardiac patients are dosed to tolerability, rather than to a blood pressure goal. It is possible that patients exposed to sudden elevations in plasma metoprolol concentrations (which might occur as a result of dose-dumping) could be at risk for excessive bradycardia, hypotension, and perhaps ischemic stress. An in vitro dose dumping test is a simple way to screen the performance of generic formulations of metoprolol succinate extended-release tablets compared to the performance of the RLD.

The Agency requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 2 (paddle) @ 50 rpm, with and without the alcohol:

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both strengths of the test and RLD products must be tested accordingly.

Please submit standard operating procedures (SOPs) for the dissolution testing above, individual dissolution data, mean values, standard deviations, coefficient of variation (CV%), and plots of the percent dissolved data.

We ask that these studies be performed as post approval commitments. Please acknowledge your agreement to perform these studies. Please complete these studies within 6 months of approval.

FIRM'S RESPONSE: The additional dissolution data for both test and reference products are summarized below:

Table 1 ANDA 77-176 KV's Metoprolol Succinate Extended-Release Tablets, **50 mg** versus Toprol-XL® (metoprolol succinate) 50 mg ER Tablets

Conditions: USP Apparatus II (Paddle), 50 rpm, 900 mL, 37°C. Media composition and sampling times are shown in the tables below

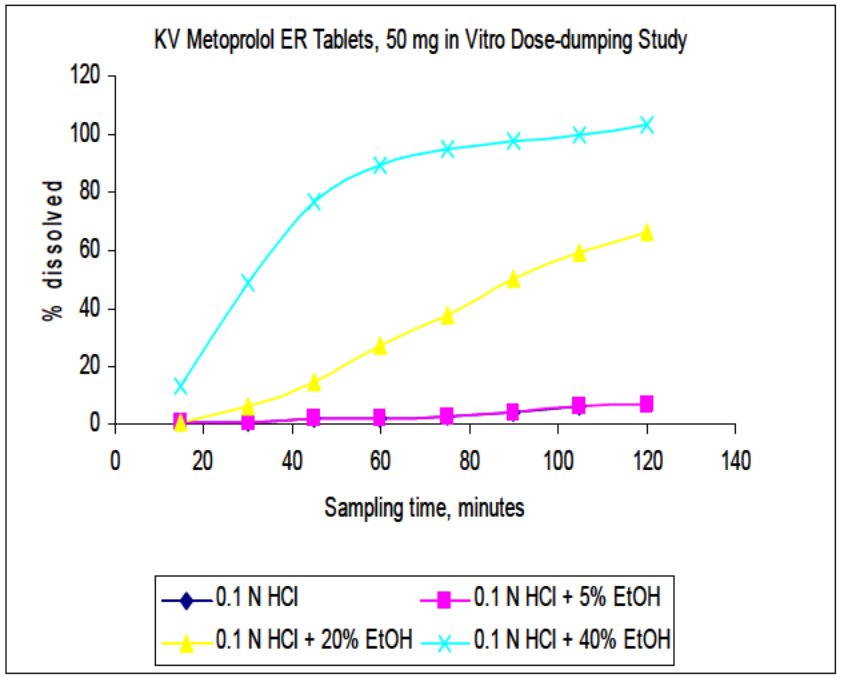
Mean % of labeled amount of metoprolol succinate dissolved at various sampling times (n=12)										
Product	Medium	0 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
KV	0.1 N HCl	0	1	1	2	2	3	4	6	7
	5% EtOH/95% 0.1N HCl	0	1	1	2	2	3	4	6	7
	20% EtOH/80% 0.1N HCl	0	1	6	15	27	38	50	59	66
	40% EtOH/60% 0.1N HCl	0	13	49	77	89	95	98	100	103
Toprol-XL® (metoprolol succinate) ER Tablets	0.1 N HCl	0	6	9	12	14	16	18	20	21
	5% EtOH/95% 0.1N HCl	0	8	11	14	17	19	22	24	27
	20% EtOH/80% 0.1N HCl	0	4	8	13	19	27	34	42	47
	40% EtOH/60% 0.1N HCl	0	6	25	50	70	82	88	92	94

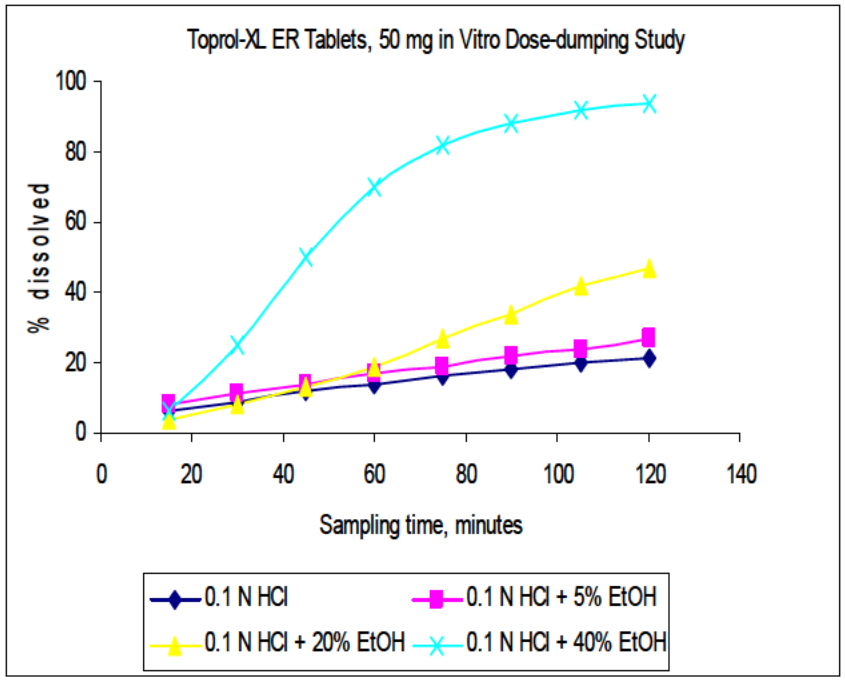
Table 2 ANDA 77-776 KV's Metoprolol Succinate Extended-Release Tablets, **25 mg** versus Toprol-XL® (metoprolol succinate) 25 mg ER Tablets

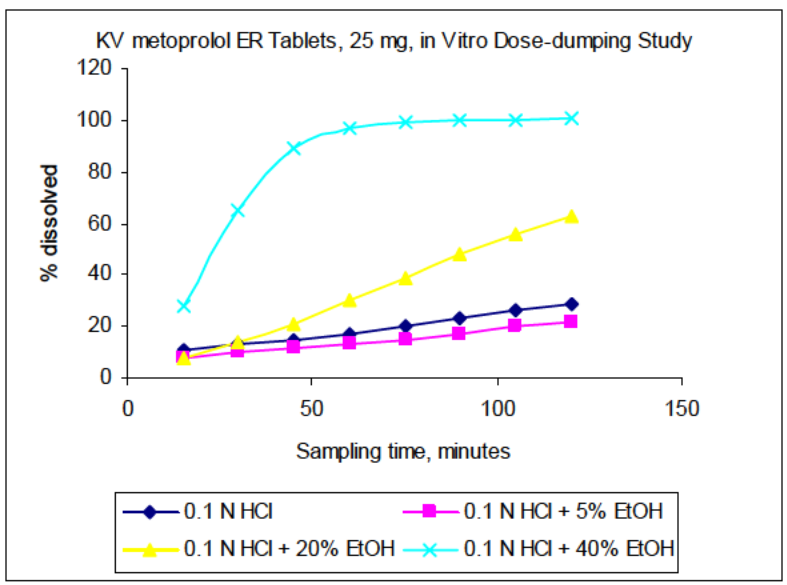
Conditions: USP Apparatus II (Paddle), 50 rpm, 900 mL, 37°C. Media composition and sampling times are shown in the tables below

Mean % of labeled amount of metoprolol succinate dissolved at various sampling times (n=12)										
Product	Medium	0 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
KV	0.1 N HCl	0	11	13	15	17	20	23	26	29
	5% EtOH/95% 0.1N HCl	0	8	10	12	13	15	17	20	22
	20% EtOH/80% 0.1N HCl	0	8	14	21	30	39	48	56	63
	40% EtOH/60% 0.1N HCl	0	28	65	89	97	99	100	100	101
Toprol-XL® (metoprolol succinate) ER Tablets	0.1 N HCl	0	3	7	9	12	14	16	19	21
	5% EtOH/95% 0.1N HCl	0	3	6	9	12	15	18	22	26
	20% EtOH/80% 0.1N HCl	0	3	8	15	25	37	50	61	70
	40% EtOH/60% 0.1N HCl	0	6	31	57	74	83	88	91	94

Figure 1: Dissolution comparison between media with alcohol and without alcohol







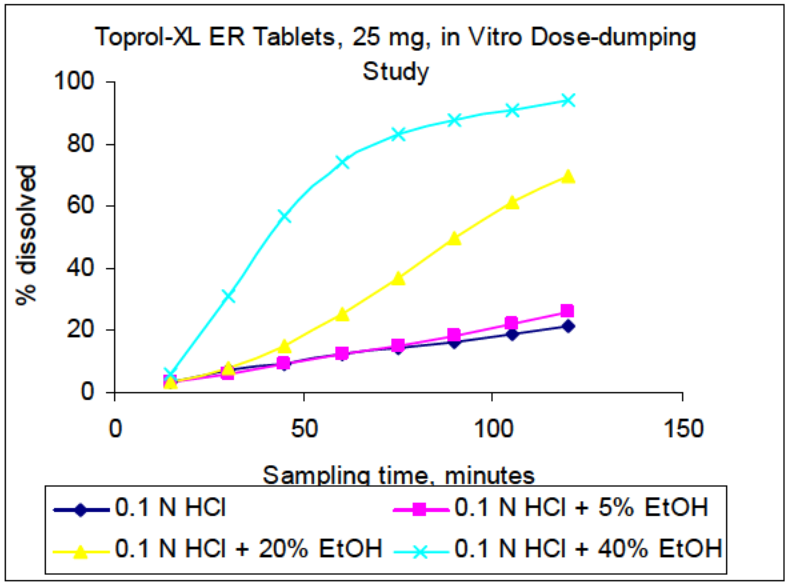
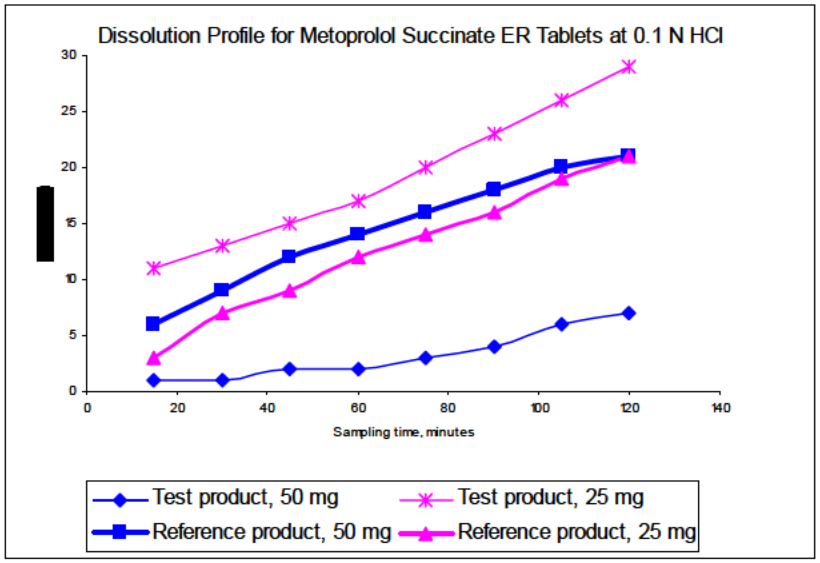
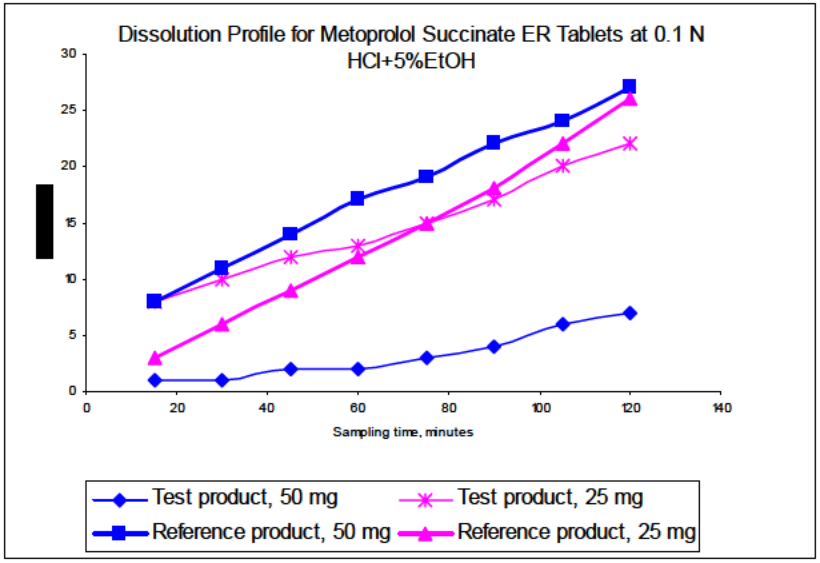
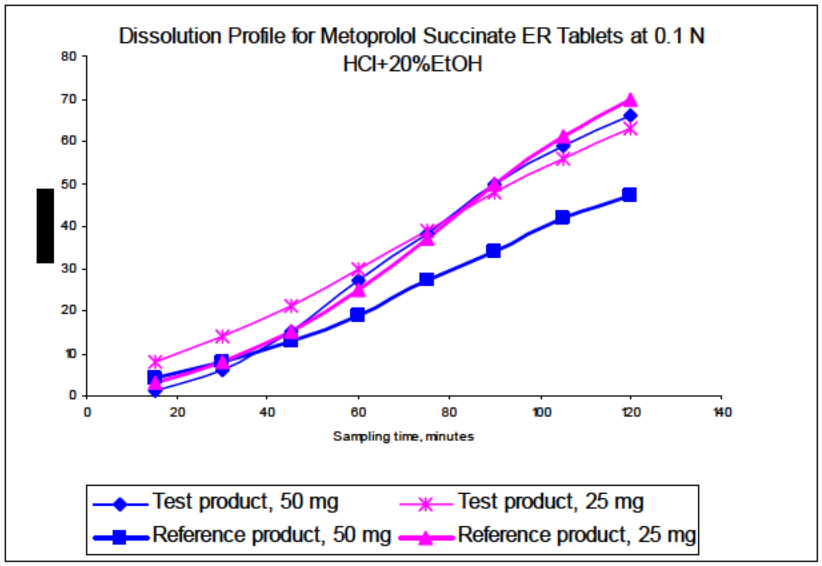


Figure 1: Dissolution comparison between test and reference in various alcohol concentrations






Dissolution Profile for Metoprolol Succinate ER Tablets at 0.1 N HCl+20%EtOH
Sampling time, minutes
Test product, 50 mg
Test product, 25 mg
Reference product, 50 mg
Reference product, 25 mg

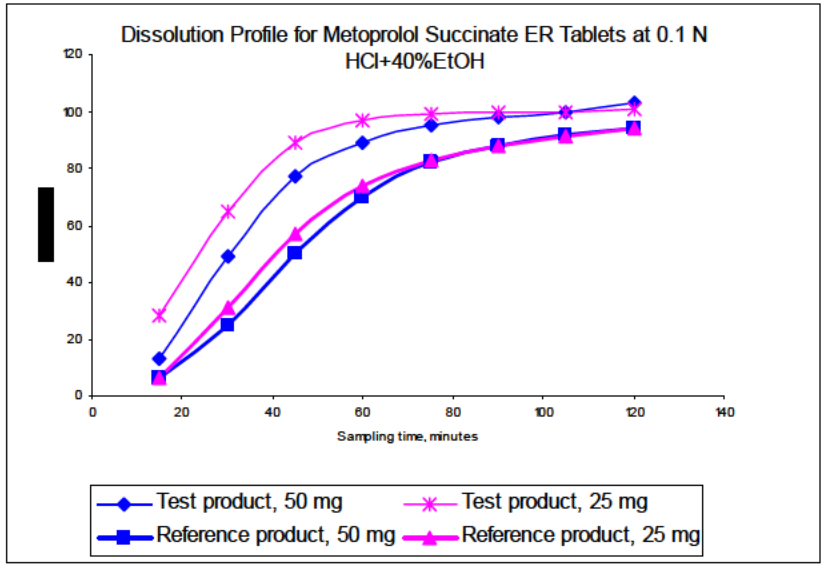

Dissolution Profile for Metoprolol Succinate ER Tablets at 0.1 N HCl+40%EtOH
Sampling time, minutes
Test product, 50 mg
Test product, 25 mg
Reference product, 50 mg
Reference product, 25 mg

Table 4: Percentage Drug Release of 50 mg Metoprolol Succinate ER tablets in 0.1 N HCl with various alcohol levels **at 120 minutes (n=12 tablets)**									
Alcohol Level (% V/V)	KV Metoprolol Succinate ER tablets, 50 mg (Lot#R449-067, Mfg: 7/18/05)				Toprol-XL® (metoprolol succinate) ER Tablets, 50 mg (Lot#NF0053)				Mean Differences between test and Reference (%)
	Mean (%)	Range (%)	%SD	Mean Difference between with alcohol and without alcohol (%)	Mean (%)	Range (%)	%SD	Mean Difference between with alcohol and without alcohol	
0%	**7**	(b) (4)	1.3	---	**21**	(b) (4)	2.9	---	**-15**
5%	**7**		1.3	0	**27**		2.4	6	**-20**
20%	**66**		5.7	59	**47**		1.5	26	**19**
40%	**103**		5.6	96	**94**		2.9	73	**9**

REVIEWER'S COMMENT:

The DBE first compared the % dissolution of the test product at 2 hr without alcohol to the % dissolution of the test product at 2 hrs with alcohol. Since the % dissolution of the test product increased as the amount of alcohol in the medium increased, there was a possibility of dose-dumping. The DBE then compared 2 hr mean and range % dissolution of the test product to the same of the reference product at all three concentrations of alcohol. If i) there is no overlap between dissolution range for the test product and the dissolution range for the reference product and ii) the mean% dissolution of the test product is not comparable to the mean% dissolution for the reference product, then this test is unacceptable. Using this criterion, the in vitro alcohol dose-dumping test results for the 50 mg ER tablet are not acceptable because the test product releases more metoprolol in 20% alcohol than does the reference product [T = 66% ((b) (4)) and R = 47% ((b) (4))]. The firm also has not provided the date of the dissolution testing and the expiration date for the Reference 50 mg ER Tablet. The firm should provide these data.

Table 5: Percentage Drug Release of 25 mg Metoprolol Succinate ER tablets in 0.1 N HCl with various alcohol levels **at 120 minutes (n=12 tablets)**									
Alcohol Level (% V/V)	KV Metoprolol Succinate ER tablets, 25 mg (Lot#R449-063)				Toprol-XL® (metoprolol succinate) ER Tablets, 25 mg (Lot#MP0061)				Mean Differences between test and Reference (%)
	Mean (%)	Range (%)	%SD	Mean Difference between with alcohol and without alcohol (%)	Mean (%)	Range (%)	%SD	Mean Difference between with alcohol and without alcohol	
0%	**29**	(b) (4)	4.7	---	**21**	(b) (4)	1.0	---	**8**
5%	**22**		4.0	-7	**26**		1.1	5	**-4**
20%	**63**		7.8	34	**70**		2.8	49	**-7**
40%	**101**		5.6	72	**94**		2.9	73	**7**

REVIEWER'S COMMENT:

The DBE first compared the % dissolution of the test product at 2 hr without alcohol to the % dissolution of the test product at 2 hrs with alcohol. Since the % dissolution of the test product increased as the amount of alcohol in the medium increased there was a possibility of dose-dumping. The DBE then compared 2 hr mean and range % dissolution of the test product to the same of the reference product at all three concentrations of alcohol. If i) there is no overlap between dissolution range for the test product and the dissolution range for the reference product and ii) the mean% dissolution of the test product is not comparable to the mean% dissolution of the reference product, then this test is unacceptable. Using this criterion, the test 25mg ER Table dissolution data would have been acceptable but the firm has not provided the date of manufacture for the test 25mg ER Tablet, the expiry date for the reference 25 mg ER tablet and the date of the dissolution testing. The firm should provide these data.

The reviewer also notes the following regarding the additional dissolution testing:

- Drug release profiles are different between the 25 mg strength and 50 mg strength for the test products because the formulation of the 25 mg strength is not proportionally similar to the 50 mg strength. These two products have different dissolution method and specification.

- For both the test and reference products, there is substantial increase of % drug release with increasing ethanol concentration in the medium.

    - For the 50 mg strength, there is a 96% and 73% greater release of drug at 2 hrs in 40% alcohol, respectively for test and reference product, compared to no alcohol,
    - For the 25 mg strength, there is a 72% and 73% greater release of drug at 2 hrs in 40% alcohol, respectively for the test and reference product, compared to no alcohol.

- For both strength, the test product releases similar amount as the corresponding RLD in 40% alcohol at 2 hours.
- For the 50 mg strength, the test product releases **19% more** than the corresponding RLD in 20% alcohol at 2 hours. The ranges do not overlap between the test and reference products.
- For the 25 mg strength, the test product releases 7% less than the corresponding RLD in 20% alcohol at 2 hours. The ranges overlap between the test and reference products.
- For the 25 mg strength, the test product and RLD product showed **comparable** dissolution at 2 hrs in all alcohol media.

Reviewer's Note:

1) KV has submitted 3 ANDAs for Metoprolol Succinate ER Tablets:
ANDA 76-640 - Metoprolol Succinate ER Tablets, USP, 200 mg and 100 mg

ANDA 77-176 - Metoprolol Succinate ER Tablets, USP, 50 mg

ANDA 77-779 - Metoprolol Succinate ER Tablets, USP, 25 mg

The Division of Bioequivalence (DBE) has deemed the 200 mg product as the stand alone product and so approval of ANDA 76-640 is necessary before approval of ANDAs 77-176 and 77-779 are considered.

ANDA 76-640 was approved on 5/18/2007. The alcohol dose dumping testing of ANDA 76-640 as a post approval commitment has not yet reviewed.

2) DBE has reviewed dose dumping study for other two generic metoprolol ER Tablets (Andrx's ANDA 76-862, 77118 and 77-298 and Sandoz's ANDA 76-969). The reference product release data at different alcohol concentration are consistent with the current application. Both dose-dumping tests were found acceptable because the test product release less drug at 2 hours compared to reference product in all alcohol media.

B. Deficiency Comments

The DBE first compared the % dissolution of the test product at 2 hr without alcohol to the % dissolution of the test product at 2 hrs with alcohol. Since the % dissolution of the test product increased as the amount of alcohol in the medium increased there was a possibility of dose-dumping. The DBE then compared 2 hr mean and range % dissolution of the test product to the same of the reference product at all three concentrations of alcohol. If i) there is no overlap between dissolution range for the test product and the dissolution range for the reference product and ii) the mean% dissolution of the test product is not comparable to the mean % dissolution for the reference product, then this test is unacceptable. Using this criterion, the test 25mg ER Table dissolution data would have been acceptable but the firm has not provided the date of manufacture for the test 25mg ER Tablet, the expiry date for the reference 25 mg ER tablet and the date of the dissolution testing. Similarly using this criterion, the results of the in vitro alcohol dose dumping test for the 50 mg ER in 20% alcohol are unacceptable [T = 66% ((b) (4)) and R = 47% ((b) (4))]. The firm also has not provided the date of the dissolution testing and the expiration date for the Reference 50 mg ER Tablet. The firm should provide these data.

C. Recommendations

1. Due to concern of dose dumping for the drug product, the Agency had previously requested that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The in vitro alcohol dose dumping testing for the 50 mg strength is **not acceptable** due to reason stated in Deficiency comment above.
2. The in vitro alcohol dose dumping testing for the 25 mg strength is **incomplete** due to deficiency comments above

D. Comments for Other OGD Disciplines

Discipline	Comment
CMC	There is a typographic error of the volume of the dissolution method in the letter to the firm in the DBE review (archived in DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006). It should be **500 ml** instead of 900 ml.

BIOEQUIVALENCE DIFFICIENCIES

ANDA: 77-176 and 77-779 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Metoprolol Succinate Extended-Release Tablets USP
25 and 50 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:

The DBE first compared the % dissolution of the test product at 2 hr without alcohol to the % dissolution of the test product at 2 hrs with alcohol. Since the % dissolution of the test product increased as the amount of alcohol in the medium increased there was a possibility of dose-dumping. The DBE then compared 2 hr mean and range % dissolution of the test product to the same of the reference product at all three concentrations of alcohol. If i) there is no overlap between dissolution range for the test product and the dissolution range for the reference product and ii) the mean% dissolution of the test product is not comparable to that of the reference product, then the DBE concludes that the results of this test are unacceptable.

1. Using this criterion, the test 25 mg ER Table dissolution data would have been acceptable but you have not provided the date of manufacture for the test 25 mg ER Tablet, the expiry date for the reference 25 mg ER tablet and the date of the dissolution testing. Please provide these data.

2. Similarly using the above mentioned criterion, your 50-mg ER tablet appears to "dose-dump" in vitro compared to the reference product. In 20% alcohol, your product releases more metoprolol than the 50-mg strength of the reference product [T = 66% ((b) (4)) and R = 47% ((b) (4))]. Therefore the results of the in vitro alcohol dose-dumping test for your 50 mg ER Tablet are not acceptable. Moreover, you have not provided the date of the dissolution testing and the expiration date for the Reference 50 mg ER Tablet.

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

Completed Assignment for 77176 ID: 1039

Reviewer: Jiang, Xiaojian **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
1039	11/5/2007	Other	Study Amendment	1	1
				Bean Total:	1

Completed Assignment for 77779 ID: 1040

Reviewer: Jiang, Xiaojian **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
1040	11/5/2007	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Xiaojian Jiang
12/19/2007 01:41:40 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
12/20/2007 07:49:21 AM
BIOPHARMACEUTICS

Barbara Davit
12/20/2007 05:42:13 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-176 and 77-779
Drug Product Name	Metoprolol Succinate Extended-Release Tablets USP
Strength(s)	50 mg (#77-176) and 25 mg (#77-779)
Applicant Name	KV Pharmaceutical Company
Address	2503 South Hanley Road, St. Louis, MO 63144
Applicant's Point of Contact **Contact's Telephone Number** **Contact's Fax Number**	Scarlett Tumulty 314-645-6600 ext. 5585 314-567-0704
Original Submission Date(s) and previously reviewed amendments	June 4, 2004, Aug. 5, 2005, 12/21/06, 1/12/07 and 1/22/07, Mar. 19, 2007, May 22, 2007, Nov. 5, 2007 (#77-176) June 30, 2005, and Dec. 07, 2005, 11/22/06, and May, 22, 2007 and Nov.5, 2007 (#77-776)
Submission Date(s) of Amendment(s) Under Review	**Feb. 4, 2008 (77-176)** **Jan.4, 2008 (77-779)**
Reviewer	Xiaojian Jiang, Ph.D.
First Generic	No
DSI Inspection	Not scheduled and not necessary
Location	DFS
Outcome	**Incomplete (77176)** **Acceptable (77779)**

Review of an Amendment

I. Executive Summary:

The applications of KV's Metoprolol Succinate Extended-Release Tablets, 25 mg and 50 mg (the RLD is AstraZeneca's Toprol-XL® (metoprolol succinate) ER Tablets) had previously been found **acceptable** with other bioequivalence requirement aspects (V:\firmsam\KV\ltrs&rev\77176N0604 and 77779N0605, DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006).

Due to concern of dose dumping for the drug product, the Agency asked, on May 18, 2007, that the firm conduct additional dissolution testing using various concentrations of ethanol in the recommended dissolution medium of 0.1 N HCl for both strengths of test and reference products. [Addendum review in DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006]

In the previous amendment, the firm had submitted the in vitro alcohol dose dumping testing, as requested by the DBE. The DBE found the in vitro alcohol dose dumping testing incomplete because 1) the firm did not provide the date of manufacture for the test 25 mg ER Tablets, the expiry date for the reference 25 mg ER Tablets and the date of the dissolution testing; 2) the in vitro alcohol dose-dumping test results for the 50 mg ER tablet were not acceptable because the test product released more metoprolol in 20% alcohol than did the reference product [T = 66% ((b) (4)) and R = 47% ((b) (4))].[DFS N077176 N000 AB 05-Nov-2007 and N077776 N000 AB 05-Nov-2007]

For ANDA 77-176 (50 mg ER tablet)

The firm submitted the current amendment in responses to the above deficiencies. The firm repeated the testing in the 20% alcohol media. The retest results show that the KV product gave substantially lower dissolution results compared to the original test, and the dissolution profile of the KV product was now comparable to that of the reference listed drug. To investigate the differences between the original and retest results, the firm found that the peaks of the chromatograms in the original run were much broader than those in the retest and therefore hypothesized that the HPLC column degraded during the analysis of the KV product. The firm also recalculated the original test results using peak heights and the results were found similar to the retest values.

Because the firm did not indicate the condition of the peaks for the standard curve and quality control samples (e.g. broader or normal compared with the test samples), it is unclear if the firm's statement regarding the unreliability of the original test results is accurate. Therefore, to further support its conclusion, the DBE requests the firm to submit the following:

1) A statement regarding the condition of the peaks (broad or normal) of the calibration standards and quality control samples in the original dissolution testing compared to the peaks of test product samples (the statement provided by the firm about the peaks of the original dissolution test is not clear).

2) A statement clarifying whether the same HPLC equipment and HPLC column were used for analyzing the samples of both the test and reference product *in the retest.* Ideally, the dissolution samples of the test and reference product should be analyzed under the same analytical conditions, unless a sound logistical justification can be provided for using different analytical conditions. In spite of the logistical justification, the firm should have a separate calibration curve with quality controls for each HPLC and/or HPLC column used during the retest.

3) All chromatograms of the original R449-067 run and retest run of both the test and reference product, which exhibit peak heights and peak areas of all calibration standards, quality controls and testing samples (of both the test and reference products). The print out for the raw data should clearly show the numerical values, pertinent calculations as well as HPLC equipment identification, HPLC column identification.

The DBE notes that the tentative expiration dating for this product is 24 months. However, this alcohol dose dumping testing was conducted after the test product was stored for 27 months. To

further support the retest data, the DBE suggests the firm repeat the alcohol dose dumping testing in 20% alcohol on other unexpired batches if available.
Therefore, this application is **incomplete**.

For ANDA 77779 (25 mg ER tablet)

In the current amendment, the firm provided the requested data and the alcohol dose dumping testing for 25 mg strength is acceptable.

Therefore, this application is **acceptable.**

II. Table of Contents

III. Background and References:

A. Drug Product Information, PK/PD Information and Relevant OGD or DBE History

See the reviews: V:\firmsam\KV\ltrs&rev\77176N0604 and 77779N0605,
DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006, DFS N077176 N000 AB 05-Nov-2007 and N077776 N000 AB 05-Nov-2007

IV. Current Submission:

DEFICIENCY COMMENT #1

The DBE first compared the % dissolution of the test product at 2 hr without alcohol to the % dissolution of the test product at 2 hrs with alcohol. Since the % dissolution of the test product increased as the amount of alcohol in the medium increased there was a possibility of dose-dumping. The DBE then compared 2 hr mean and range % dissolution of the test product to the same of the reference product at all three concentrations of alcohol. If i) there is no overlap between dissolution range for the test product and the dissolution range for the reference product and ii) the mean% dissolution of the test product is not comparable to that of the reference product, then the DBE concludes that the results of this test are unacceptable.

1. Using this criterion, the test 25 mg ER Table dissolution data would have been acceptable but you have not provided the date of manufacture for the test 25 mg ER Tablet, the expiry date for the reference 25 mg ER tablet and the date of the dissolution testing. Please provide these data.

2. Similarly using the above mentioned criterion, your 50-mg ER tablet appears to "dose-dump" in vitro compared to the reference product. In 20% alcohol, your product releases more metoprolol than the 50-mg strength of the reference product [T = 66% ((b) (4)) and R = 47% (b) (4) (b) (4))]. Therefore the results of the in vitro alcohol dose-dumping test for your 50 mg ER Tablet are not acceptable. Moreover, you have not provided the date of the dissolution testing and the expiration date for the Reference 50 mg ER Tablet.

FIRM'S RESPONSE:

50 mg strength, ANDA 77-176

After evaluation of the alcohol dose-dumping dissolution testing that was performed on 10/24/07 and 10/31/07 of the KV and RLD product, it was apparent that the KV peak shape of appeared were much broader compared to peaks of other runs. The KV product only appeared to release more metoprolol than the RLD in the 20% alcohol concentration. All testing of the other strengths (25 mg, 100 mg and 200 mg) at all the required alcohol concentrations of the KV product yielded similar results to the brand. Additionally, all other alcohol concentrations produced similar results to the brand product.

The KV and RLD products were run at different times on different HPLC units. It was hypothesized that the HPLC column degraded during the analysis of the KV product. To confirm that these KV results were unreliable, a recalculation was performed of the KV and RLD products using peak height. The recalculation demonstrated peak broadening was a factor in the KV HPLC chromatograms.

Therefore, the KV and RLD product were both re-tested in the 20% alcohol media (1/9/2008 and 1/4/2008). The results included in this report show that the KV product has a similar effect of the 20% alcohol dissolution rate as the RLD at the 120 minute time point.

Also, the requested date of manufacture, expiry date of the reference listed drug and date of the dissolution testing is provided in the table below.

KV 50* mg date of manufacture lot#R449-067	7/18/05
Toprol XL expiration date	Expired 1/31/10
Dissolution testing occurred between the following date	10/20/2007 and 1/1/2007

* misidentified in the text as 25 mg

Reviewer's note : *The reviewer summarized the alcohol dumping test at 20% in Table 1 and Figure 1, including the original results tested in 10/07, recalculated results tested in 10/07 using peak height and the re-test results conducted in 01/08.*

As can be observed in Figure 1, the repeat dissolution of the KV product (01/09/08) gave substantially lower dissolution results at all time points compared to the original test (10/24/07), and the dissolution profile of the KV product was now lower -rather than higher - than that of the reference listed drug. However, the repeat dissolution of the reference listed drug (01/04/08) did not change much; it was very similar and slightly higher than the dissolution profile of the original test (10/31/07).

The difference between the original dissolution test result for KV lot R449-067 from 10/24/07 and the retest on 01/09/08 was therefore investigated. On comparing chromatograms, the peak shape of the original R449-067 run appeared to be different than other runs. The peaks in the original run were much broader than those in the retest, indicating that the HPLC column used in the original analysis of the KV sample had degraded. (The peaks in the original run of the reference listed drug were also examined and found to be normal; the original runs of the KV product and the reference listed drug were made at different times on different HPLCs with different columns.) A recalculation of both original runs was computed using peak height instead of peak area, to see if the peak broadening in the original KV run affected the calculated results. (***Reviewer's note***: *The data are included in Table 1 and Figure 1*).

As can be observed in Figure 1, when calculated by peak heights, the dissolution profiles of the KV product and the reference listed drug are essentially identical. The release rate of Metoprolol Succinate ER Tablets and the reference listed drug both increase to a similar extent as the concentration of alcohol in the dissolution vessel is raised.

The initial results reported previously were found to be unreliable due to the failing peak shape. This is evidenced by the significant change in result when compared to the same data calculated by peak height.

The most recent results of the repeated dissolutions of the KV product and the reference listed drug have comparable means at 120 minutes (44 to 51) and the ranges overlap, showing a similar influence of the 20% alcohol on the dissolution rate of Metoprolol Succinate on both dosage forms. All other data presented in the original report are believed to be correct and therefore supporting the conclusion that the effect of alcohol is similar between KV's 47.5 mg formulation and the reference listed drug, 47.5 mg Toprol XL®.

25 mg strength, ANDA 77-779

The requested date of manufacture, expiry date of the reference listed drug and date of the dissolution testing is provided in the table below.

KV 25 mg date of manufacture lot#R449-063*	9/8/05
Toprol XL expiration date	Expired 9/30/09
Dissolution testing occurred between the following date	9/19/2007 and 11/5/2007

* misidentified in the text as R449-067

Table 1 ANDA 77-176 KV's Metoprolol Succinate Extended-Release Tablets, **50 mg** versus Toprol-XL® (metoprolol succinate) 50 mg ER Tablets

Conditions: USP Apparatus II (Paddle), 50 rpm, 900 mL, 37°C. Media composition and sampling times are shown in the tables below

Mean % of labeled amount of metoprolol succinate dissolved at various sampling times (n=12)											
Product		Medium	0 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
KV	Original data	**20% EtOH/80% 0.1N HCl**	**0**	**1**	**6**	**15**	**27**	**38**	**50**	**59**	**66**
	Recalculated original data	**20% EtOH/80% 0.1N HCl**	**0**	**1**	**5**	**11**	**19**	**28**	**35**	**43**	**49**
	Retest data	**20% EtOH/80% 0.1N HCl**	**0**	**0**	**2**	**6**	**12**	**20**	**28**	**36**	**44**
Toprol-XL® (metoprolol succinate) ER Tablets	Original data	**20% EtOH/80% 0.1N HCl**	**0**	**4**	**8**	**13**	**19**	**27**	**34**	**42**	**47**
	Recalculated original data	**20% EtOH/80% 0.1N HCl**	**0**	**4**	**8**	**14**	**20**	**27**	**35**	**43**	**49**
	Retest data	**20% EtOH/80% 0.1N HCl**	**0**	**4**	**9**	**15**	**21**	**29**	**37**	**44**	**51**

Figure 1: Dissolution comparison between test and reference in 20% alcohol concentrations

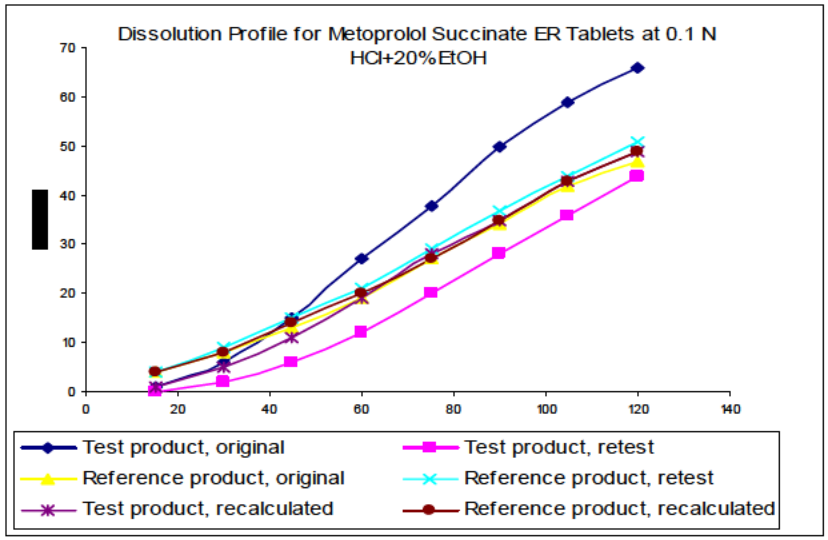


Table 4: Percentage Drug Release of 50 mg Metoprolol Succinate ER tablets in 0.1 N HCl with 20% alcohol levels **at 120 minutes (n=12 tablets)**									
Alcohol Level (% V/V)	KV Metoprolol Succinate ER tablets, 50 mg (Lot#R449-067, Mfg: 7/18/05)				Toprol-XL® (metoprolol succinate) ER Tablets, 50 mg (Lot#NF0053, Exp. 1/31/10)				Mean Differences between test and Reference (%)
	Mean (%)	Range (%)	%SD	Mean Difference between with alcohol and without alcohol (%)	Mean (%)	Range (%)	%SD	Mean Difference between with alcohol and without alcohol	
20% (original)	**66**	(b) (4)	5.7	59	**47**	(b) (4)	1.5	26	**19**
20% (retest)	**44**		4.0	37	**51**		2.6	30	**-7**
20% (recalculated)	**49**		4.4	42	**49**		1.6	28	**0**

REVIEWER'S COMMENT:

50 mg strength, ANDA 77-176

The firm stated that the peaks in the original R449-067 run were much broader than those in the retest run indicating that the HPLC column used in the original analysis of the KV sample had degraded. However, the firm did not indicate the peak condition of the calibration standard and quality control samples, e.g. if the peaks of the calibration standards and quality controls used in that run were as broad as the test samples. If so, the calculated concentrations should not be different using either peak height or peak area. Otherwise if the test samples had broader peaks than the standard curve samples, the calculated concentrations using the peak areas should be more close to the actual values than those using the peak heights because a broader peak would have a lower peak height. The analytical run should have included standard or quality controls at the end of the run to monitor the deterioration of the column or any other changes to the pre-validated system. Only the results of the quality control samples provide the basis of accepting or rejecting the run. The broadness of peaks of the test samples should not be used as the criteria.

Therefore, to further support the explanation that the original test results were unreliable and to confirm the validity of the retest data, the DBE requests the firm to submit the following:

1) A statement regarding the condition of the peaks (broad or normal) of the calibration standards and quality control samples in the original dissolution testing compared to the peaks of test product samples (the statement provided by the firm about the peaks of the original dissolution test is not clear).

2) A statement clarifying whether the same HPLC equipment and HPLC column were used for analyzing the samples of both the test and reference product *in the retest.* Ideally, the dissolution samples of the test and reference product should be analyzed under the same analytical conditions, unless a sound logistical justification can be provided for using different analytical conditions. In spite of the logistical justification, the firm should have a separate calibration curve with quality controls for each HPLC and/or HPLC column used during the retest.

3) All chromatograms of the original R449-067 run and retest run of both the test and reference product, which exhibit peak heights and peak areas of all calibration standards, quality controls and testing samples (of both the test and reference products). The print out for the raw data should clearly show the numerical values, pertinent calculations as well as HPLC equipment identification, HPLC column identification.

The DBE notes that the tentative expiration dating for this product is 24 months. However, this alcohol dose dumping testing was conducted after the test product was stored for 27 months. To further support the retest data, the DBE suggests the firm repeat the alcohol dose dumping testing in 20% alcohol on other unexpired batches if available.

25 mg strength, ANDA 77-779

The firm provided the requested data and the alcohol dose dumping testing for the 25 mg strength is acceptable.

Additional submission history:

1) KV has submitted 3 ANDAs for Metoprolol Succinate ER Tablets:
ANDA 76-640 - Metoprolol Succinate ER Tablets, USP, 200 mg and 100 mg

ANDA 77-176 - Metoprolol Succinate ER Tablets, USP, 50 mg

ANDA 77-779 - Metoprolol Succinate ER Tablets, USP, 25 mg

The Division of Bioequivalence (DBE) has deemed the 200 mg product as the stand alone product and so approval of ANDA 76-640 is necessary before approval of ANDAs 77-176 and 77-779 are considered.

ANDA 76-640 was approved on 5/18/2007. The alcohol dose dumping testing of ANDA 76-640 as a post approval commitment has not yet reviewed.

2) DBE has reviewed dose dumping study for other two generic metoprolol ER Tablets (Andrx's ANDA 76-862, 77118 and 77-298 and Sandoz's ANDA 76-969). The reference product release data at different alcohol concentration are consistent with the current application. Both dose-dumping tests were found acceptable because the test product release less drug at 2 hours compared to reference product in all alcohol media.

B. Deficiency Comments

50 mg strength, ANDA 77-176

See the reviewer's comments on page 8

C. Recommendations

1. Due to concern of dose dumping for the drug product, the Agency had previously requested that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The in vitro alcohol dose dumping testing for the 50 mg strength is **incomplete** due to reason stated in the reviewer's comment section above.
2. The in vitro alcohol dose dumping testing for the 25 mg strength is **acceptable.**

D. Comments for Other OGD Disciplines

Discipline	Comment
CMC	There is a typographic error of the volume of the dissolution method in the letter to the firm in the DBE review (archived in DFS N077176 N000 AB 21-Dec-2006 and N077776 N000 AB 22-Nov-2006). It should be **500 ml** instead of 900 ml.

BIOEQUIVALENCE DEFFICIENCIES

ANDA: 77-176 and 77-779 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Metoprolol Succinate Extended-Release Tablets USP
25 and 50 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:

50 mg strength, ANDA 77-176

You stated that the peaks for the test samples in the original R449-067 run were much broader than those in the retest run indicating that the HPLC column used in the original analysis of the KV sample had degraded. The analytical run should have included standard or quality controls at the end of the run to monitor the deterioration of the column or any other changes to the pre-validated system. Moreover, you did not indicate the condition of the peaks for the standard curve and quality control samples, for example, whether the peaks of the standard curve and quality control samples used in that original run were as broad as the test samples. Therefore, to further support your statement that the original test results were unreliable and to confirm the validity of the retest data, the DBE requests you to submit the following:

1) A statement regarding the condition of the peaks (broad or normal) of the calibration standards and quality control samples in the original dissolution testing compared to the peaks of test product samples (the statement provided by you about the peaks of the original dissolution test is not clear).

2) A statement clarifying whether the same HPLC equipment and HPLC column were used for analyzing the samples of both the test and reference product in the retest. Ideally, the dissolution samples of the test and reference product should be analyzed under the same analytical conditions, unless a sound logistical justification can be provided for using different analytical conditions. In spite of the logistical justification, you should have a separate calibration curve with quality controls for each HPLC and/or HPLC column used during the retest.

3) All chromatograms of the original R449-067 run and retest run of both the test and reference product, which exhibit peak heights and peak areas of all calibration standards, quality controls and testing samples (of both the test and reference products). The print out for the raw data should clearly show the numerical values, pertinent calculations as well as HPLC equipment identification, HPLC column identification.

The DBE notes that the tentative expiration dating for this product is 24 months. However, this alcohol dose dumping testing was conducted after the test product was stored for 27 months. To further support your retest data, the DBE suggests you repeat the alcohol dose dumping testing in 20% alcohol on other unexpired batches if available.

25 mg strength, ANDA 77-779

The DBE has completed its review of the in vitro alcohol dose dumping test on the 25 mg strength of the test and reference products and has no further questions at this time.

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 Researcn

Completed Assignment for 77176 ID: 4956

Reviewer: Jiang, Xiaojian **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4956	2/4/2008	Other	In-vitro dose-dumping in alcohol	1	1
				Bean Total:	1

Completed Assignment for 77779 ID: 4957

Reviewer: Jiang, Xiaojian **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4957	1/4/2008	Other	In-vitro dose-dumping in alcohol	0	0
				Bean Total:	0

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/s/

Xiaojian Jiang
3/11/2008 04:28:01 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
3/11/2008 04:29:19 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
3/11/2008 04:30:21 PM
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