CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090615

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90615			
Drug Product Name	Metoprolol Succinate Extended Release Tablets USP			
Strength (s)	25 mg, 50 mg, 100 mg, 200 mg			
Applicant Name	Wockhardt Limited			
Address	Wockhardt Towers, Bandra–Kurla Complex Bandra (East), Mumbai-400051 Maharashtra, INDIA.			
Applicant's Point of Contact	US Agent Address Dr. Brij Khera Wockhardt USA Inc., 135 Route 202/206, Bedminster, NJ 07921, USA			
Contact's Phone Number	908-234-9761			
Contact's Fax Number	908-234-9748			
Submission Date(s)	07-May-2008			
First Generic	No			
Reviewer	Z.Z. Wahba, Ph.D.			
Study Number (s)	CPB-058-2007	CPB-059-2007	CPB-152-2007	CPB-153-2007
Study Type (s)	Fasting	Fed	Fasting	fed
Strength(s)	50 mg	50 mg	200 mg	200 mg
Clinical Site	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited			
Clinical Site Address	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India.			
Analytical Site	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited			
Analytical Address	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India			
OUTCOME DECISION	Incomplete			

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is a USP method for this product. The firm's dissolution testing (500 mL of pH 6.8 phosphate buffer with paddle at 50 rpm) data with the USP method are acceptable.
In addition, the firm provided dissolution data generated from three different dissolution media (pH 4.5 acetate buffer, 0.1 N HCl, and water) per BA/BE general guidance (issued on 03/2003). The firm's proposed specifications are the same as the USP recommended specifications (1 hr: NMT 25%, 4 hr: 20-40%, 8 hr: 40-60%, and 20 hr: NLT 80%). Therefore, the DBE acknowledges that the firm will follow the USP method and specifications for its test products, Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg, 200 mg.

There is evidence that some extended-release drug products may cause "dose dump" when ingested with alcoholic beverages. Therefore, the Agency is concerned that dose-dumping may potentially result if Metoprolol Succinate Extended Release Tablets are taken with alcoholic beverages. The firm is requested to conduct additional dissolution testing to address Agency's concerns of dose dumping from this product.

In addition, the firm has not submitted the dissolution data in eCTD format tables for three different dissolution media (pH 4.5 acetate buffer, 0.1 N HCl, and water); therefore, the firm will be requested to submit these tables.

Note: The firm will be informed with the DBE acknowledgments of the test products' dissolution testing method and specifications once the Agency receives satisfactory response to the deficiencies cited in the deficiency section.

The firm's dissolution testing is incomplete.

No Division of Scientific Investigations (DSI) inspection is pending or necessary

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☐	☒
Did the firm use the USP dissolution method			☒	☐	☐
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☒
SAS datasets submitted to the electronic document room (edr)	Fasting BE study (50 & 200 mg)	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study (50 & 200 mg)	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Source of dissolution method	USP
Dissolution Medium	pH 6.8 phosphate buffer
Volume	500 mL
Apparatus	2
Rotation	50 rpm
Time	1, 4, 8 and 20 hours
Specifications	1 hr: NMT 25%, 4 hr: 20-40%, 8 hr: 40-60%, and 20 hr: NLT 80%

The following are summary tables of In Vitro Dissolution Studies - Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg, 200 mg

Dissolution conditions:	
Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	pH 6.8 Phosphate Buffer
Volume:	500 mL
Temperature:	37 ± 0.5º C
Firm's proposed specification:	
1 Hour	Not more than 25% of labeled amount of Metoprolol succinate dissolved
4 Hour	Between 20 and 40% of labeled amount of Metoprolol succinate dissolved
8 Hour	Between 40 and 60% of labeled amount of Metoprolol succinate dissolved
20 Hour	Not less than 80% of labeled amount of Metoprolol succinate dissolved
Site of testing : Wockhardt Limited, L-1, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Hours) 1 Hour	4 Hour	8 Hour	20 Hour	Study Report Location
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LGS13220 Manufacturing Date: Oct. 2007 Date of testing : Jan 07, 2008	25 mg Tablets	12	Mean	4	23	56	97	Module 5, 1.1, Pages 73-76
				Range	(b) (4)				
				%CV	25	7	7	6	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / MA0004 Expiry Date: Nov. 2008 Date of testing : Jan 06, 2008	25 mg Tablets	12	Mean	10	28	54	94	
				Range	(b) (4)				
				%CV	10	7	6	4	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Hours)				Study Report Location
					1 Hour	4 Hour	8 Hour	20 Hour	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LGS13222 Manufacturing Date: Oct. 2007 Date of testing : Nov 06, 2007	50 mg Tablets	12	Mean	3	21	53	96	Module 5, 1.1, Pages 90-93
				Range	(b) (4)				
				%CV	33	14	8	4	
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / LT0026 Expiry Date: Nov.07 Date of testing : Nov 05, 2007	50 mg Tablets	12	Mean	8	26	51	94	
				Range	(b) (4)				
				%CV	13	8	4	2	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LGS13223 Manufacturing Date: Oct. 2007 Date of testing : Jan 09, 2008	100 mg Tablets	12	Mean	4	22	53	95	Module 5, 1.1, Pages 107-110
				Range	(b) (4)				
				%CV	25	9	6	3	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / MA0091 Expiry Date: Oct. 2008 Date of testing : Jan 08, 2008	100 mg Tablets	12	Mean	8	26	51	95	
				Range	(b) (4)				
				%CV	9	4	4	2	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LGS13224 Manufacturing Date: Oct. 2007 Date of testing : Nov 19, 2007	200 mg Tablets	12	Mean	3	21	53	97	Module 5, 1.1, Pages 124-127
				Range	(b) (4)				
				%CV	0	5	4	4	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / MA0081 Expiry Date: Dec.2008 Date of testing : Nov 20, 2007	200 mg Tablets	12	Mean	10	28	50	90	
				Range	(b) (4)				
				%CV	10	4	2	3	

II. COMMENTS:

1. There is a USP method for this product. The firm conducted the dissolution testing (500 mL of pH 6.8 phosphate buffer with paddle at 50 rpm) according to the USP method for this drug. It was noticed that the 50 mg and 200 mg test tablets at the 4-hr sampling time point exhibit dissolution release outside the range of 20-40%. This observation was discussed with the DBE dissolution focal point. It was decided that the firm's dissolution data are acceptable (for details please see email of the dissolution consult in the Attachment section).

2. In light of Agency's concerns of dose dumping from this product when taken with alcohol, the DBE requests the firm to conduct additional dissolution testing on all strengths of the test and reference products 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:

   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.

3. In addition, the firm provided dissolution data generated from three different dissolution media (pH 4.5 acetate buffer, 0.1 N HCl, and water) per BA/BE general guidance (issued on 03/2003). Although the individual dissolution data generated in these additional media are included in the submission (volume 1.3, pages 71-139), the firm did not submit these in the eCTD format tables. Therefore, the firm will be requested to submit the missing eCTD format tables for all strengths of the test and reference products.

4. The firm's proposed specifications are the same as the USP recommended specifications (1 hr: NMT 25%, 4 hr: 20-40%, 8 hr: 40-60%, and 20 hr: NLT 80%).

5. The firm will be informed with the DBE acknowledgments of the test products' dissolution testing method and specifications once the Agency receives satisfactory response to the deficiencies cited in the deficiency section.

III. DEFICIENCY COMMENTS:

1. In light of Agency's concerns of dose dumping from this product when taken with alcohol, the DBE requests the firm to conduct additional dissolution testing on all strengths of the test and reference products 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:

   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.

2. The firm is requested to submit the dissolution data in the eCTD format tables for three different dissolution media (pH 4.5 acetate buffer, 0.1 N HCl, and water) of all strengths of the test and reference products.

IV. RECOMMENDATIONS:

The in vitro dissolution testing and data conducted by Wockhardt Limited on its test products, Metoprolol Succinate Extended Release Tablets USP, 25 mg (lot # LGS13220), 50 mg (lot # LGS13222), 100 mg (lot # LGS13223), 200 mg (lot # LGS13224), are incomplete due to the deficiencies cited in the deficiency section above.

V. ATTACHMENTS:

From: Seo, Paul
Sent: Wednesday, November 05, 2008 4:58 PM
To: Wahba, Zakaria Z
Cc: Chaurasia, Chandra S; Seo, Paul
Subject: RE: Request for dissolution consult on 90615 (Metoprolol Succinate E R Tablets USP - Wockhardt)

Hi Zak.
This is acceptable for several reasons. Typically it is our practice to allow, and in fact attempt to set specs such that products will pass at S1/L1/A1/B1. However, when a USP monograph is present, in my opinion, all attempts should be made to not pollute the monograph w/ too many potential future tests, particularly if the test product meets the monograph specs at level 1 or 2. Unless grossly poor dissolution (i.e. level 3 or more), USP testing at level 1 or 2 should be acceptable. Furthermore, the firm knows this, and is obviously comfortable w/ their product passing at L2 and therefore is also in my opinion a justificaiton to allow the USP specs.

This is just a recommendation, please consult your TL as well.

Thanks,
Paul

From: Wahba, Zakaria Z
Sent: Wednesday, November 05, 2008 4:47 PM
To: Seo, Paul
Cc: Chaurasia, Chandra S; Wahba, Zakaria Z
Subject: Request for dissolution consult on 90615 (Metoprolol Succinate E R Tablets USP - Wockhardt)

Hi Paul:
There is a USP method for this product. The firm designated its drug as USP product. The firm's dissolution testing data with the USP method are acceptable. The firm's proposed specifications are the same as the USP recommended specifications (1 hr: NMT 25%, 4 hr: 20-40%, 8 hr: 40-60%, and 20 hr: NLT 80%). However, the 50 mg and 200 mg strengths of the test drug at the 4 hr sampling time point exhibit dissolution release (for the 50 mg tablet: mean=21, range= (b) (4) and for the 200 mg tablet: mean=21, range= (b) (4)) outside the range of 20-40%. Dr. Makary suggests that I should check with you, if this is acceptable to DBE. Enclosed is the dissolution review which contains the summary eCTD format tables, all individual dissolution data for all strengths and 90% CI PK parameters results.
Thank you very much.
Zak

From: Chaurasia, Chandra S
Sent: Wednesday, November 05, 2008 10:30 AM
To: Wahba, Zakaria Z
Cc: Makary, Moheb H
Subject: RE: Review [DBE2] 90615 (Metoprolol Succinate E R Tablets USP - Wockhardt)

Zak:
As the 50 mg and 200 mg test tablets at the 4 hr sampling time point exhibit dissolution release outside the range of 20-40%, Moheb suggests that you should check with Paul, if this is acceptable to DBE.

My initial ok was based on the following specification at the L2 level (for 12 units tested), although I might have interpreted it differently.
Thanks,
Chandra

L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	90615
APPLICANT:	Wockhardt Limited
DRUG PRODUCT:	Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg, 200 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies and waiver request will be conducted later. The following deficiencies have been identified:

1. There is evidence that some extended-release drug products may cause "dose dump" when ingested with alcoholic beverages. Therefore, the Agency is concerned that dose-dumping may potentially result if Metoprolol Succinate Extended Release Tablets are taken with alcoholic beverages. 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 reference listed drug (RLD). The Agency requests that additional dissolution testing on all strengths of the test and reference products be conducted using various concentrations of ethanol in the dissolution medium, as follows:

   Testing Conditions: 900 mL, 0.1 N HCl, Apparatus II (Paddle) at 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.

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 at each time point for twelve tablets.

In addition to providing the individual dissolution data in the submission, please also submit all generated dissolution results in the electronic CTD format tables as requested by DBE.

2. Please submit the dissolution data in electronic CTD format tables for three different dissolution media (pH 4.5 acetate buffer, 0.1 N HCl, and water) for all strengths of the test and reference products.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA: 90615

Completed Assignment for 90615 ID: 6783

Reviewer: Wahba, Zakaria **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6783	5/7/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY
ANDA 90615

Dissolution Review	
Dissolution Review	1
Dissolution Review 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/

Zakaria Z. Wahba
11/7/2008 03:53:00 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
11/8/2008 01:47:12 PM
BIOPHARMACEUTICS

Moheb H. Makary
11/10/2008 11:18:46 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-615			
Drug Product Name	Metoprolol Succinate Extended Release Tablets, USP			
Strength(s)	25 mg, 50 mg, 100 mg and 200 mg			
Applicant Name	Wockhardt Limited			
Address	Wockhardt Towers, Bandra-Kurla Complex Bandra (East) Mumbai – 400051, India			
Applicant's Point of Contact	Dr. Brij Khera Wockhardt USA Inc., 135 Route 202/206 Bedminster, NJ 07921			
Contact's Telephone Number	908.234.9761 (973.257.4998)			
Contact's Fax Number	908.234.9748 (973.257.4999)			
Original Submission Date(s)	May 7, 2008			
Submission Date(s) of Amendment(s) Under Review	January 8, 2009			
Reviewer	Jennifer N. Albano, Ph.D.			
Study Number (s)	CPB-058-2007	CPB-059-2007	CPB-152-2007	CPB-153-2007
Study Type (s)	Fasting	Fed	Fasting	Fed
Strength (s)	50 mg	50 mg	200 mg	200 mg
Clinical Site	Clinical Pharmacokinetics & Biopharmaceutics Department, Wockhardt Limited			
Clinical Site Address	Mulund-Goregaon Link Road Bhandup (West), Mumbai – 400 078, India			
Analytical Site	Clinical Pharmacokinetics & Biopharmaceutics Department, Wockhardt Limited			
Analytical Site Address	Mulund-Goregaon Link Road Bhandup (West), Mumbai – 400 078, India			
OUTCOME DECISION	**INCOMPLETE**			

1 EXECUTIVE SUMMARY

This application contains the results of two fasting (50 mg and 200 mg) and one fed (200 mg) bioequivalence (BE) studies comparing Wockhardt Limited's Metoprolol Succinate Extended Release Tablets, USP, to the corresponding reference listed drug, Toprol-XL® (Metoprolol Succinate Extended Release Tablets, 50 mg and 200 mg) by AstraZeneca. The firm also conducted a fed study using the 50 mg strength; however, this study is not requested by the DBE for determination of bioequivalence. Additionally, the application includes two waiver requests for the 25 mg and 100 mg strengths. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

Metoprolol Succinate Extended Release Tablets, 1 x 50 mg
Fasting Bioequivalence Study No. CPB-058-2007, N=32 (Male=32 and Female=0)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	993.2960	999.6142	0.9937	93.60	105.49
AUC∞ (ng·hr/mL)	1010.2472	1017.9099	0.9925	93.46	105.39
Cmax (ng/mL)	47.8325	50.3799	0.9494	90.22	99.91

Metoprolol Succinate Extended Release Tablets, 1 x 200 mg
Fasting Bioequivalence Study No. CPB-152-2007, N=27 (Male=27 and Female=0)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	3453.0009	3660.0143	0.9434	82.64	107.71
AUC∞ (ng·hr/mL)	3499.6640	3703.2112	0.9450	82.71	107.98
Cmax (ng/mL)	183.8432	183.8080	1.0002	92.59	108.04

Metoprolol Succinate Extended Release Tablets, 1 x 200 mg
Fed Bioequivalence Study No. CPB-153-2007, N=35 (Male=35 and Female=0)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	3193.3486	3070.1501	1.0401	97.53	110.93
AUC∞ (ng·hr/mL)	3227.0858	3101.6639	1.0404	97.50	111.02
Cmax (ng/mL)	173.6725	159.4156	1.0894	103.54	114.63

The firm's dissolution testing using the USP method is incomplete (DFS N 090615 N 000 07-May-2008). The firm did not submit dissolution testing on half tablets. The firm is asked to conduct dissolution testing on half tablets using the current USP method for Metoprolol Succinate Extended Release Tablets:

> The dissolution testing should be conducted in 500 ml of phosphate buffer (pH 6.8) using USP apparatus II (Paddle) at 50 rpm.

In light of the Agency's concerns of dose dumping from this product when taken with alcohol, the DBE requested the firm on November 23, 2008 to conduct additional dissolution testing on all strengths of the test and reference products 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:
>
> **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.

On January 8, 2009, the firm submitted alcohol dose dumping dissolution testing. For the test and reference products, the % dissolved at 2 hours in 5%, 20% and 40% ethanol is comparable. Therefore, the DBE concludes that the risk of dose dumping from the test product is the same as for Toprol-XL®.

In the January 8, 2009 amendment, the firm also submitted the dissolution data in electronic CTD format tables for three different dissolution media (pH 4.5 acetate buffer, 0.1N HCl and water) for all strengths of the test and reference product.

The DBE denies the waiver requests for in vivo BE study requirements for the following strengths, 25 mg and 100 mg, based on criteria set forth in 21 CFR § 320.24 (b) (6).

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is **incomplete** with deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Metoprolol Succinate Extended Release Tablets, USP 50 mg and 200 mg
Reference Product	Toprol-XL® (metoprolol succinate) Extended Release Tablets, USP 50 mg and 200 mg
RLD Manufacturer	AstraZeneca
NDA No.	19-962
RLD Approval Date	January 10, 1992
Indication	For the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Also indicated in the long-term treatment of angina pectoris and for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin.

3.2 PK/PD Information[2,3]

Bioavailability	Absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose.
Food Effect	Not significantly affected by food.
Tmax	~7 hours
Metabolism	Occurs primarily in the liver, which is characterized extensively by first-pass metabolism. Metoprolol is primarily metabolized by cytochrome P450 CYP2D6.
Excretion	Excreted mainly via the kidney as metabolites, with 95% of an oral dose excreted renally, primarily via glomerular filtration, within 72 hours.
Half-life	3-7 hours
Drug Specific Issues (if any)	See Appendix for Black Box Warning

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	3, two fasting and one fed

[1] Electronic Orange Book, December 2008
[2] Clinical Pharmacology Online, December 2008
[3] Label from RLD

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-way crossover *in vivo*
	Strength:	50 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fasting
	Design:	Single-dose, two-way crossover *in vivo*
	Strength:	200 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

3.	**Type of study:**	Fed
	Design:	Single-dose, two-way crossover *in vivo*
	Strength:	200 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Metoprolol in plasma
Bioequivalence based on:	90% CI: $LAUC_T$, $LAUC_I$, LC_{max}
Waiver request of in-vivo testing:	25 mg and 100 mg
Source of most recent recommendations:	Draft Guidance: http://www.fda.gov/cder/guidance/bioequivalence/default htm Protocol 08-066 Control 01-423 ANDAs 76-640, 77-176 and 77-779

Summary of OGD or DBE History (for details, see Appendix 4.4):	1. The following studies are recommended to establish bioequivalence of metoprolol succinate extended release tablets: a. A single-dose, two-way crossover 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. b. A single-dose, two-way crossover fed *in vivo* bioequivalence study comparing Metoprolol Succinate Extended Release Tablets, 200 mg, to the RLD. c. A single-dose, two-way crossover design fasting *in vivo* bioequivalence study comparing Metoprolol Succinate Extended Release Tablets, 50 mg, to the 50 mg strength of the RLD. 2. Please measure only the parent compound, metoprolol. 3. Metoprolol Succinate Extended-Release Tablets, 25 mg and 100 mg, may be considered for a waiver of *in vivo* bioequivalence testing based on (i) acceptable bioequivalence studies on the 50 mg and 200 mg strengths, (ii) acceptable dissolution testing of the 25 mg, 50 mg, 100 mg, and 200 mg strengths, and (iii) proportional similarity in the formulations of the 25 mg, 50 mg, 100 mg, and 200 mg strengths. 4. Please conduct comparative *in vitro* dissolution testing on 12 dosage units of each strength of the test and reference products using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The recommended sampling times are: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. For scored tablets, additional dissolution testing is recommended on half tablets.

In addition, please conduct dissolution testing using the following FDA method:

Apparatus: USP apparatus II (paddle)
Speed: 50 rpm
Medium: Phosphate buffer pH 6.8
Volume: 500 mL
Sampling times: 1, 4, 8 and 20 hours and until at least 80% of the labeled content is dissolved.

5. Due to concerns of dose dumping in the presence of alcohol for this drug product, the Agency currently 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 (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.

Reviewer's Notes: 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[4]. The formulations of the reference product are not proportional across strengths. However, dissolution profiles across all strengths are comparable in a variety of media.

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

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	**Yes**	**2**
Single-dose fed	**Yes**	**2**
Steady-state	No	0
In vitro dissolution	**Yes**	**4**
Waiver requests	**Yes**	**2**
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

3.5 Pre-Study Bioanalytical Method Validation

3.5.1 50 mg Studies

Information Requested	Analyte 1
Bioanalytical method validation report location	Page No. 631-679, Module 5, Volume 1.3 Page No. 3525-3543, Module 5, Volume 1.9
Study Report Number	MVR-METO-001-07
Analyte	Metoprolol
Internal standard (IS)	(b) (4)
Method description	High Performance Liquid Chromatography Mass Spectrometric Method
Lower Limit of Quantification (ng/mL)	0.502
% recovery (and %CV) at each concentration tested	1.503 ng/mL: 26.75% 85.380 ng/mL: 29.28% 170.761 ng/mL: 30.32% Overall Recovery: 28.783% (6.38%)
Average recovery of IS (%) (and %CV)	32.22%
Standard curve concentrations (ng/mL)	0.502, 2.511, 5.001, 10.002, 25.006, 50.011, 100.023, 200.045
QC concentrations (ng/mL)	LLOQ: 0.502 LQC: 1.503 MQC: 85.380 HQC: 170.761
QC Intra-day precision range (%)	1.65 to 15.20%
QC Intra-day accuracy range (%)	108.95 to 110.17%
QC Inter-day precision range (%)	3.44 to 13.48%
QC Inter-day accuracy range (%)	107.15 to 108.25%

Bench-top stability (6 hrs) Precision (%) Accuracy (%)	 1.58 to 6.80% 101.77 to 102.12%
Stock stability Room Temperature for 8 hrs (%) Refrigerated for 7 days (%)	 100.93% 104.17%
Processed stability (24 hrs) Precision (%) Accuracy (%)	 1.40 to 2.53% 102.33 to 102.38%
Freeze-thaw stability (3 cycles) Precision (%) Accuracy (%)	 1.21 to 9.01% 99.14 to 103.13%
Long-term storage stability (7 days) **Below -50°C** Precision (%) Accuracy (%) **Below -20°C** Precision (%) Accuracy (%)	 1.54 to 10.00% 105.64 to 108.33% 0.45 to 3.12% 105.40 to 110.17%
Long-term storage stability (126 days) **Below -50°C** Precision (%) Accuracy (%) **Below -20°C** Precision (%) Accuracy (%)	 0.96 to 6.48% 92.43 to 102.45% 1.24 to 3.36% 88.34 to 101.70%
Dilution integrity **Four times dilution** Precision (%) Accuracy (%) **Two times dilution** Precision (%) Accuracy (%)	 1.66% 101.55% 3.25% 103.40%
Selectivity	No significant interference from endogenous components was observed at retention time of analyte and IS in all the human plasma batches screened.
Sensitivity Precision (%) Accuracy (%)	 5.00% 105.12%

SOPs submitted	Yes	Bioanalytical Method Validation (CPB-AP-009-01); Effective May 24, 2006
Bioanalytical method is acceptable	Yes	

3.5.2 200 mg Studies

Information Requested	Analyte 1
Bioanalytical method validation report location	Page No. 6247-6315, Module 5, Volume 1.15 Page No. 8583-8651, Module 5, Volume 1.20
Study Report Number	MVR-METO-002-08
Analyte	Metoprolol
Internal standard (IS)	(b) (4)
Method description	High Performance Liquid Chromatography Mass Spectrometric Method
Lower Limit of Quantification (ng/mL)	0.527
% recovery (and %CV) at each concentration tested	1.534 ng/mL: 92.61% 159.791 ng/mL: 87.01% 332.899 ng/mL: 82.66% Overall Recovery: 87.427% (5.71%)
Average recovery of IS (%) (and %CV)	100.98%
Standard curve concentrations (ng/mL)	0.527, 1.110, 6.001, 20.004, 50.010, 200.041, 400.083
QC concentrations (ng/mL)	LLOQ: 0.527 LQC: 1.534 MQC: 159.791 HQC: 332.899
QC Intra-day precision range (%)	2.01 to 8.07%
QC Intra-day accuracy range (%)	96.43 to 103.57%
QC Inter-day precision range (%)	1.93 to 7.57%
QC Inter-day accuracy range (%)	96.13 to 102.98%
Bench-top stability (6 hrs) Precision (%) Accuracy (%)	 0.95 to 3.69% 96.54 to 102.31%
Stock stability Room Temperature for 8 hrs (%) Refrigerated for 7 days (%)	 102.13% 95.60%
Processed stability (25 hrs) Precision (%) Accuracy (%)	 1.75 to 3.32% 100.35 to 110.56%
Freeze-thaw stability (3 cycles) Precision (%) Accuracy (%)	 2.55 to 2.82% 97.03 to 111.51%
Long-term storage stability (7 days) **Below -50°C** Precision (%) Accuracy (%) **Below -20°C**	 1.92 to 3.30% 93.34 to 108.41%

Precision (%) Accuracy (%)	1.81 to 3.08% 92.59 to 108.47%
Long-term storage stability (60 days) **Below -50°C** Precision (%) Accuracy (%) **Below -20°C** Precision (%) Accuracy (%)	 1.31 to 2.80% 94.38 to 96.04% 1.56 to 3.41% 95.80 to 97.62%
Dilution integrity **Four times dilution** Precision (%) Accuracy (%) **Two times dilution** Precision (%) Accuracy (%)	 1.89% 100.79% 6.56% 94.89%
Selectivity	No significant interference from endogenous components was observed at retention time of analyte and IS in all the human plasma batches screened.
Sensitivity Precision (%) Accuracy (%)	 4.03% 104.59%

SOPs submitted	Yes	Bioanalytical Method Validation (CPB-AP-009-02); Effective December 26, 2007
Bioanalytical method is acceptable	Yes	

Comments on the Pre-Study Method Validation:

The average percent recovery of drug is significantly lower for the 50 mg pre-study method validation (overall recovery: 28.783%) than for the 200 mg pre-study method validation (overall recovery: 87.427%). The recovery of drug for each study is consistent with the respective recovery of internal standard and the %CV is within acceptable limits. It should be noted that the firm uses two different HPLC columns: [redacted] (b) (4) for the 50 mg study and [redacted] (b) (4) for the 200 mg study.

The pre-study method validation is acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	T½ (hr)	K_{el} (hr^{-1})	
CPB-058-2007	**Efficacy:** To assess bioavailability of Metoprolol succinate 50 mg extended release tablets (Wockhardt Limited, India) and compare with Toprol-XL® (containing Metoprolol succinate 50 mg) tablets (AstraZeneca, USA) in 32 normal, adult, human subjects under fasting condition.	A single center, randomized, single dose, open-label, analyst-blind, two-treatment, two-period, two-sequence, crossover comparative bioavailability study under fasting condition	**Test Product (A):** Metoprolol succinate 50 mg ER tablets (Manufactured by Wockhardt Limited, India) Oral Batch No: LG10845 **Reference Product (B):** Toprol-XL® tablets (containing Metoprolol succinate 50 mg) (Manufactured by: AstraZeneca, USA) Oral Batch no: LT0026	**Participated Subjects:** 32 male healthy subjects **Mean age:** 24.1 ± 5.63 (19 - 41) **Clinical Phase Completed Subjects:** 32 male healthy subjects **Mean age:** 24.1 ± 5.63 (19 - 41) **Considered for PK & Statistical Analyses:** 32 male healthy subjects **Mean age:** 24.1 ± 5.63 (19 - 41)	50.43 (34.64)	13.00 (5.00 – 24.00)	1088.06 (45.38)	1110.82 (46.50)	5.80 (24.98)	0.13 (23.90)	**Page No. 200, Module 5, Volume 1.2**
					52.81 (33.12)	12.00 (3.00 – 24.00)	1094.84 (45.50)	1119.14 (46.94)	5.82 (23.05)	0.12 (21.26)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	T½ (hr)	K_{el} (hr^{-1})	
CPB-152-2007	**Efficacy:** To assess bioavailability of Metoprolol succinate 200 mg extended release tablet (Wockhardt Limited, India) and compare with Toprol-XL® 200 mg (containing Metoprolol succinate 200 mg) tablet (AstraZeneca, USA) in 28 normal, adult, human subjects under fasting condition.	A single center, randomized, single dose, open-label, analyst-blind, two-treatment, two-period, two-sequence, crossover comparative bioavailability study under fasting condition.	**Test Product (A):** Metoprolol succinate 200 mg ER tablets (Manufactured by Wockhardt Limited, India) Oral Batch No: LG10896 **Reference Product (B):** Toprol-XL® 200 mg tablets (containing Metoprolol succinate 200 mg) (Manufactured by: AstraZeneca, USA) Oral Batch no: MA0081	**Participated Subjects:** 28 male healthy subjects **Mean age:** 24.1 ± 3.08 (19 - 31) **Clinical Phase Completed Subjects:** 27 male healthy subjects **Mean age:** 24.1 ± 3.14 (19 - 31) **Considered for PK & Statistical Analyses:** 27 male healthy subjects **Mean age:** 24.1 ± 3.14 (19 - 31)	191.33 (27.37)	12.00 (5.00 – 16.00)	3730.87 (40.13)	3789.60 (40.76)	6.11 (14.55)	0.12 (13.33)	**Page No. 5847, Module 5, Volume 1.14**
					189.97 (25.80)	10.00 (4.00 – 16.00)	3919.31 (36.62)	3971.95 (37.30)	6.17 (15.32)	0.11 (14.08)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	T½ (hr)	K_{el} (hr^{-1})	
CPB-153-2007	**Efficacy:** To assess bioavailability of Metoprolol succinate 200 mg extended release tablets (Wockhardt Limited, India) and compare with Toprol-XL® 200 mg (containing Metoprolol succinate 200 mg) tablets (AstraZeneca, USA) in 36 normal, adult, human subjects under fed condition.	A single center, randomized, single dose, open-label, analyst-blind, two-treatment, two-period, two-sequence, crossover comparative bioavailability study under fed condition.	**Test Product (A):** Metoprolol succinate 200 mg ER tablets (Manufactured by Wockhardt Limited, India) Oral Batch No: LG10896 **Reference Product (B):** Toprol-XL® 200 mg tablets (containing Metoprolol succinate 200 mg) (Manufactured by: AstraZeneca, USA) Oral Batch no: MA0081	**Participated Subjects:** 36 healthy male subjects **Mean age:** 24.5 ± 4.91 (19 - 37) **Clinical Phase Completed Subjects:** 35 healthy male subjects **Mean age:** 24.6 ± 4.96 (19 - 37) **Considered for PK & Statistical Analyses:** 35 healthy male subjects **Mean age:** 24.6 ± 4.96 (19 - 37)	179.01 (24.24)	12.00 (5.00 – 16.00)	3419.95 (35.92)	3461.35 (36.44)	5.74 (12.13)	0.12 (12.12)	**Page No. 8147, Module 5, Volume 1.19**
					162.98 (21.01)	6.00 (4.00 – 14.00)	3229.86 (30.76)	3267.66 (31.26)	5.99 (12.42)	0.12 (11.77)	

Reviewer's Comment:

On March 16, 2006, a medical consult for ANDA 76640 (Metoprolol Succinate ER Tablets, 100 mg and 200 mg, submitted by KV Pharmaceutical) was issued by OGD concerning a difference in Tmax values. In both BE studies, the mean Test Tmax was almost twice of the Reference Tmax (fasting: 13.4 versus 7.2 hours; fed: 11.5 versus 6.4 hours, respectively). Drs. Nancy Chang and Dena Hixon determined: "…in the context of current clinical use and labeling, sustained release metoprolol

succinate products that otherwise meet standard bioequivalence criteria (i.e. for Cmax and AUC) could still be considered therapeutically interchangeable even with a significant difference in Tmax."

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Metoprolol Succinate Extended Release Tablets 1 x 50 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. CPB-058-2007)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	993.30	998.16	1.00	93.72	105.66
AUC∞ (ng·hr/mL)	1010.25	1016.47	0.99	93.59	105.55
Cmax (ng/mL)	47.83	50.15	0.95	90.84	100.16

Metoprolol Succinate Extended Release Tablets 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. CPB-152-2007)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	3452.76	3657.41	0.94	82.67	107.81
AUC∞ (ng·hr/mL)	3499.43	3700.59	0.95	82.74	108.08
Cmax (ng/mL)	183.84	183.81	1.00	92.59	108.04

Metoprolol Succinate Extended Release Tablets 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. CPB-153-2007)					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	3193.38	3070.15	1.04	97.53	110.93
AUC∞ (ng·hr/mL)	3227.13	3101.66	1.04	97.50	111.03
Cmax (ng/mL)	173.67	159.42	1.09	103.54	114.63

Table 3. Reanalysis of Study Samples

50 mg Fasted Study, Study No. CPB-058-2007 Location: Page No. 597 and 610-617, Module 5, Volume 1.3								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
ASV (Anomalous Sample Value)	2	2	0.14	0.14	2	2	0.14	0.14
ESP (Error in Sample Processing)	0	1	0.00	0.07	0	1	0.00	0.07
RAB (Rejected Analytical Batch)	60	60	4.25	4.25	60	60	4.25	4.25
SCR (Sample Value Outside Concentration Range)	1	1	0.07	0.07	1	1	0.07	0.07
UAC (Unacceptable Chromatography)	3	2	0.21	0.14	3	2	0.21	0.14
Total	**66**	**66**	**4.67**	**4.67**	**66**	**66**	**4.67**	**4.67**

Note: 66 samples of test product and 66 samples of reference product were reanalyzed.
Total no. of samples analyzed: 1412 (excluding 70 PD & 69 PD+IS samples, as these cannot be assigned to either test or reference formulation).

200 mg Fasted Study, Study No. CPB-152-2007 Location: Page No. 6216 and 6228-6229, Module 5, Volume 1.14								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
ASV (Anomalous Sample Value)	1	1	0.10	0.10	1	1	0.10	0.10
ESP (Error in Sample Processing)	0	5	0.00	0.51	0	5	0.00	0.51
Total	**1**	**6**	**0.10**	**0.61**	**1**	**6**	**0.10**	**0.61**

Note: 1 sample of test product and 6 samples of reference product were reanalyzed.
Total no. of samples analyzed: 979 (excluding 54 PD & 55 PD+IS samples, as these cannot be assigned to either test or reference formulation).

200 mg Fed Study, Study No. CPB-153-2007 Location: Page No. 8549 and 8564-8570, Module 5, Volume 1.20								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
ESP (Error in Sample Processing)	36	46	2.61	3.33	36	46	2.61	3.33
ISV (Internal Standard Variation)	1	1	0.07	0.07	1	1	0.07	0.07
RAB (Rejected Analytical Batch)	18	18	1.30	1.30	18	18	1.30	1.30
Total	**55**	**65**	**3.98**	**4.70**	**55**	**65**	**3.98**	**4.70**

Note: 55 samples of test product and 65 samples of reference product were reanalyzed.
Total no. of samples analyzed: 1380 (excluding 76 PD & 76 PD+IS samples, as these cannot be assigned to either test or reference formulation).

Did use of recalculated plasma concentration data change study outcome?

No

Comments from the Reviewer:

For the 50 mg fasting study (CPB-058-2007), the firm reanalyzed 4 samples due to Anomalous Sample Value (ASV), which the reviewer considers to be pharmacokinetic repeats. For three of the samples, the initial value was used for the firm's calculations. The reviewer conducted statistical analysis using both the original and repeat value. The use of reanalyzed plasma concentration data did not change the study outcome. The firm followed all appropriate SOPs.

For the 200 mg fasting study (CPB-152-2007), the firm reanalyzed 2 samples due to Anomalous Sample Value (ASV), which the reviewer considers to be pharmacokinetic repeats. The reviewer conducted statistical analysis using both the original and repeat value. The use of reanalyzed plasma concentration data did not change the study outcome. The firm followed all appropriate SOPs.

Samples repeated due to "Rejected Analytical Batch" contained quality control samples that did not meet batch acceptance criteria established in SOP No. CPB-AP-005.

3.7 Formulation

Location in appendix	Section 4.2, Page 58
If a tablet, is the RLD scored?	Yes
If a tablet, is the test product biobatch scored	Yes
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS N 090615 N 000 07-May-2008
Source of Method (USP, FDA or Firm)	USP
Medium	pH 6.8 Phosphate Buffer
Volume (mL)	500 mL
USP Apparatus type	Apparatus II (Paddle)
Rotation (rpm)	50
DBE-recommended specifications	1 Hour: NMT 25%; 4 Hour: 20-40%; 8 Hour: 40-60%; 20 Hour: NLT 80%
If a modified-release tablet, was testing done on ½ tablets?	No
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	**METHOD INCOMPLETE**
If not then why?	Firm did not conduct dissolution testing on ½ tablets

F2 metric calculated by reviewer, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
50 mg	25 mg	91.20	80.85
200 mg	100 mg	95.60	71.35

3.9 Waiver Request(s)

Strengths for which waivers are requested	25 mg and 100 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	**WAIVERS DENIED**
If not then why?	See deficiency comments

3.10 Deficiency Comments

Because the test and reference products are scored and can be divided, dissolution testing should be conducted on half tablets of all strengths of the test and reference products using the compendial USP method.

3.11 Recommendations

1. The Division of Bioequivalence (DBE) accepts the fasting BE study (CPB-058-2007) conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 50 mg, Batch #LG10845, comparing it to AstraZeneca's Toprol-XL® (Metoprolol Succinate) ER Tablets, 50 mg, Batch #LT0026.

2. The DBE accepts the fasting BE study (CPB-152-2007) conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 200 mg, Batch #LG10896, comparing it to AstraZeneca's Toprol-XL® (Metoprolol Succinate) Extended Release Tablets, 200 mg, Batch #MA0081.

3. The DBE accepts the fed BE study (CPB-153-2007) conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 200 mg, Batch #LG10896, comparing it to AstraZeneca's Toprol-XL® (Metoprolol Succinate) Extended Release Tablets, 200 mg, Batch #MA0081.

4. Dissolution testing conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 50 mg and 25 mg is **incomplete** due to the above deficiencies. The formulation for the 25 mg strength is proportionally similar to the 50 mg strength of the test product which underwent bioequivalence testing. Therefore, the DBE does not find the 25 mg strength test product to be bioequivalent to the RLD under the Section 21 CFR §320.24 (b) (6) at this time.

5. Dissolution testing conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 200 mg and 100 mg is **incomplete** due to the above deficiencies. The formulation for the 100 mg strength is proportionally similar to the 200 mg strength of the test product which underwent bioequivalence testing. Therefore, the DBE does not find the 100 mg strength test product to be bioequivalent to the RLD under the Section 21 CFR §320.24 (b) (6) at this time.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose 50 mg Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	CPB-058-2007
Study Title	A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover, comparative bioavailability study on Metoprolol succinate 50 mg extended release tablets (Wockhardt Limited, India) compared with Toprol-XL® (containing Metoprolol succinate 50 mg) tablets (AstraZeneca, USA) in 32 normal, adult, human subjects under fasting condition
Clinical Site (Name & Address)	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India. Tel: +91-22-6652 4444, Fax: +91-22-6652 4545
Principal Investigator	Dr. Ilesh Changela
Dosing Dates	Period-I: 16/11/2007 & Period-II: 23/11/2007
Analytical Site (Name & Address)	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India. Tel: +91-22-6652 4444, Fax: +91-22-6652 4545
Analysis Dates	26/11/2007 to 13/12/2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	16/11/2007 to 13/12/2007 (28 days)

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	**A**	**B**
Product Name	Metoprolol Succinate Extended Release Tablets	Toprol-XL® Tablets
Manufacturer	Wockhardt Limited, India	AstraZeneca, USA
Batch/Lot No.	Batch No: LG10845	Batch No: LT0026
Manufacture Date	October 2007	N/AV
Expiration Date	September 2009	November 2007
Strength	50 mg	50 mg

Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	98.9%	101.8% [Based on Wockhardt's analysis]
Content Uniformity (mean, %CV)	103.0, 101.3, 100.4, 99.5, 101.0, 101.6, 98.2, 96.2, 100.2, 102.0 L1=4.8	102.4, 100.8, 98.1, 96.8, 94.3, 97.2, 100.9, 100.9, 10.6, 98.7 L1=6.3 [Based on Wockhardt's analysis]
Dose Administered	1 x 50 mg	1 x 50 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled:** 32 **Dosed:** 32 **Completed:** 32 **Analyzed:** 32
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**AB:** 2, 4, 7, 8, 9, 10, 13, 16, 18, 19, 21, 22, 27, 28, 30, 31 **BA:** 1, 3, 5, 6, 11, 12, 14, 15, 17, 20, 23, 24, 25, 26, 29, 32
Blood Sampling Times	Pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 20.0, 24.0, 30.0, 36.0 and 48.0 hours post-dose
Blood Volume Collected/Sample	1 x 5 mL
Blood Sample Processing/Storage	Blood samples were collected in K_3EDTA vacutainers after discarding the first 0.5 mL of saline mixed blood from the cannula. Blood samples were then centrifuged at 4°C, 3000 rpm for 10 minutes. Plasma samples were transferred in duplicates to pre-labeled storage vials. Vials were stored upright in deep freezers between -79.4°C and -59.1°C until analysis.
Central Ethics Committee Approval	September 17, 2007
Informed Consent	September 14, 2007
Length of Fasting	Overnight fast of at least 10 hours before initial dose and for 4 hours post-dose.
Length of Confinement	Subjects will be housed in the facility from at least 11 hours prior to dosing and further till 48 hours after dosing in each period.

Safety Monitoring	Medical examination will be carried out at check-in and check out of each period and whenever felt necessary by the attending medical professional. Sitting blood pressure, oral temperature, respiratory rate and radial pulse will be measured at the time of check-in prior to drug administration and around 2, 4, 6, 8, 12, 24, 36 and 48 hours post dose in each period.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. CPB-058-2007			
		Treatment Groups	
		Test Product N = 32	Reference Product N = 32
Age (years)	Mean ± SD	24.1 ± 5.63	24.1 ± 5.63
	Range	19-41	19-41
Age Groups	< 18	0	0
	18 – 40	31 (97 %)	31 (97 %)
	41 – 64	1 (3 %)	1 (3 %)
	65 – 75	0	0
	> 75	0	0
Sex	Male	32 (100 %)	32 (100 %)
	Female	0	0
Race	Asian	32 (100 %)	32 (100 %)
	Black	0	0
	Caucasian	0	0
	Hispanic	0	0
	Other	0	0
BMI (kg/m^2)	Mean + SD	21.65 ± 2.234	21.65 ± 2.234
	Range	18.2 - 25.0	18.2 - 25.0
Other Factors		Nil	Nil

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
There were no dropout/withdrawn subjects in this project.			

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. CPB-058-2007	
	Test	Reference
Body as a whole	Nil	
Cardiovascular	Nil	
Gastrointestinal	Nil	
Post Study Assessment		
Eosinophilia	2 (6.25 %)*	
Lymphocytosis	1 (3.13 %)*	
Anemia	1 (3.13 %)*	
Total	**4 (12.50 %)**	

Note:
32 subjects participated in this study.
*- Adverse events are related unlikely to studied drug.
- Percentage values are rounded off.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
No protocol deviations observed during the course of the study.		

Comments on Dropouts/Adverse Events/Protocol Deviations:

No serious adverse events (AEs) were reported. A total of four (4) AEs were reported by 4 of the 32 subjects during the post study assessment. All were mild in nature and were unrelated to the study medication.

All subjects dosed completed the study.

No protocol deviations were observed during the course of this study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study (CPB-058-2007) Metoprolol								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.506	1.264	2.504	5.007	12.518	25.036	50.071	100.143
Inter day Precision (%CV)	2.80	6.90	8.11	3.14	4.14	3.74	3.48	4.24
Inter day Accuracy (%Actual)	100.69	99.30	99.45	98.70	100.30	100.76	101.14	100.85
Linearity	0.993 to 1.000							
Linearity Range (ng/mL)	0.506 to 100.143							
Sensitivity/LOQ (ng/mL)	0.502							

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	1.489	41.365	82.730
Inter day Precision (%CV)	10.50	8.35	7.09
Inter day Accuracy (%Actual)	94.24	104.15	103.05

Comments on Study Assay Validation:

Acceptable.

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

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CPB-AP-011-01	05/24/2006	Reporting of Bioanalytical Results

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The study assay is acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	1088.06	45.38	397.18	2436.46	1093.98	45.62	476.49	2274.61	0.99
AUCI	ng hr/mL	1110.82	46.50	404.97	2520.91	1118.28	47.06	484.71	2394.05	0.99
CMAX	ng/mL	50.43	34.64	28.25	102.71	52.63	33.53	30.94	106.86	0.96
TMAX	hr	13.00	.	5.00	24.00	12.00	.	3.00	24.00	1.08
KE	hr-1	0.13	23.90	0.07	0.19	0.12	21.27	0.07	0.19	1.01
THALF	hr	5.80	24.97	3.71	9.90	5.82	23.07	3.60	9.85	1.00

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Metoprolol Succinate Extended Release Tablets 1 x 50 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. CPB-058-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	993.2960	999.6142	0.9937	93.60	105.49
AUC∞ (hr *ng/ml)	1010.2472	1017.9099	0.9925	93.46	105.39
Cmax (ng/ml)	47.8325	50.3799	0.9494	90.22	99.91

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Metoprolol Succinate Extended Release Tablets 1 x 50 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. CPB-058-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	993.30	998.16	1.00	93.72	105.66
AUC∞ (hr *ng/ml)	1010.25	1016.47	0.99	93.59	105.55
Cmax (ng/ml)	47.83	50.15	0.95	90.84	100.16

Table 17. Additional Study Information, Fasting Study No. CPB-058-2007

Root mean square error, AUC0-t	0.1412	
Root mean square error, AUC∞	0.1417	
Root mean square error, Cmax	0.1150	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	32	32
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	1
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	32	0.98	0.94	1.00
Reference	32	0.98	0.94	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. One subject had a drug concentration of 1.485 ng/mL at 0 hours. This concentration is less than 5% Cmax; therefore, the subject was not dropped from analysis.

2. The reviewer conducted statistical analysis using the original and repeat values. Results using the original values are given in Table 16. No significant difference was observed by using the repeat values for $LAUC_t$, $LAUC_i$, and LC_{max} for metoprolol.

3. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, T_{max}, KE and $t_{1/2}$) and confidence intervals of AUC_t, AUC_i and C_{max} for metoprolol as calculated by the reviewer were in agreement with the values reported by the firm.

4. The 90% confidence intervals for metoprolol of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

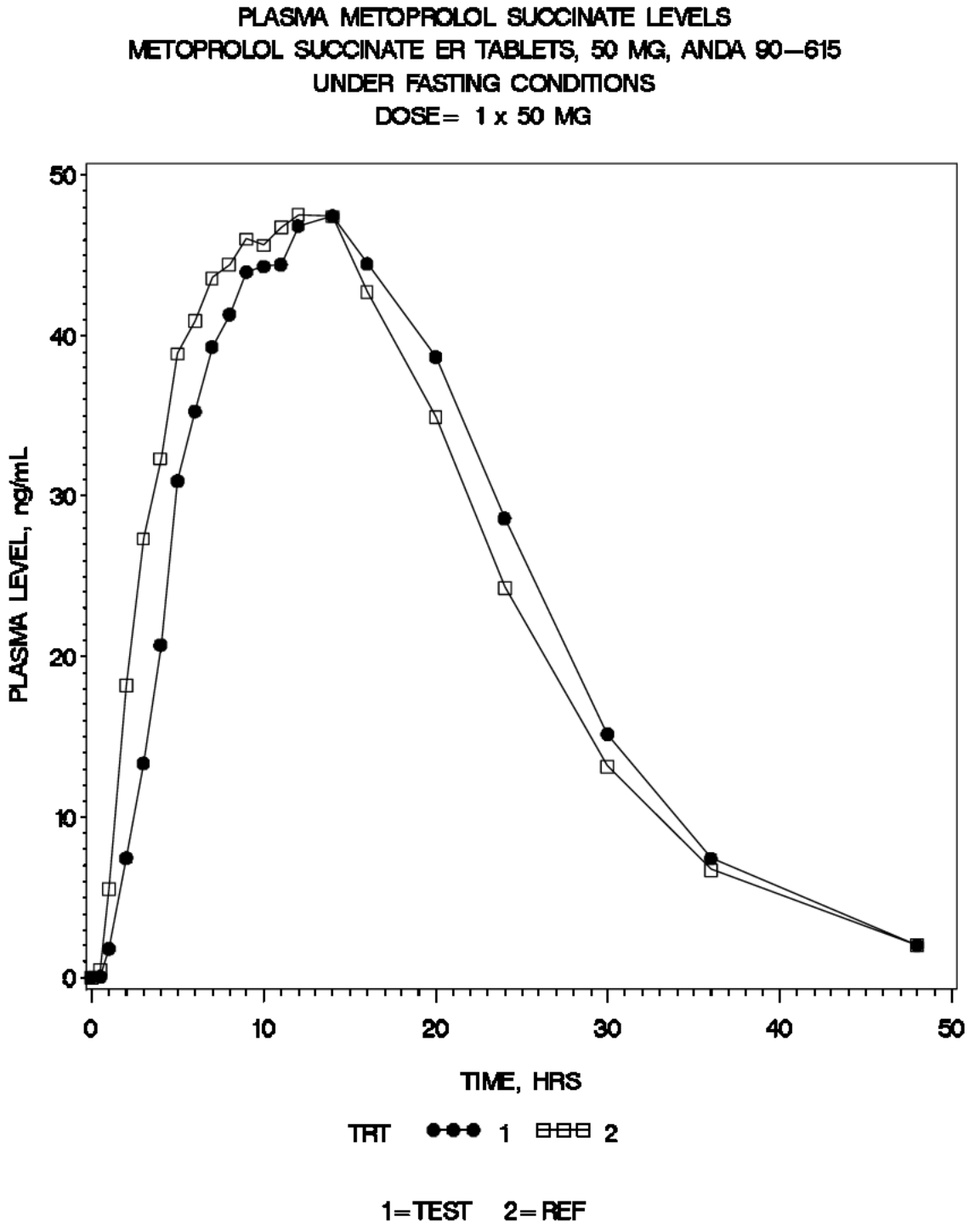
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting bioequivalence study is acceptable

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=32)		Reference (n=32)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.05	565.69	0.00	.	.
0.50	0.08	323.88	0.48	163.73	0.17
1.00	1.83	94.47	5.56	71.82	0.33
2.00	7.47	51.60	18.20	38.18	0.41
3.00	13.37	31.71	27.36	27.11	0.49
4.00	20.74	24.94	32.35	22.93	0.64
5.00	30.96	24.44	38.88	21.31	0.80
6.00	35.28	26.82	40.91	23.31	0.86
7.00	39.30	27.04	43.60	26.82	0.90
8.00	41.33	28.87	44.41	29.82	0.93
9.00	43.98	29.88	46.03	31.71	0.96
10.00	44.32	33.69	45.64	32.93	0.97
11.00	44.43	35.61	46.77	33.88	0.95
12.00	46.84	37.80	47.52	38.02	0.99
14.00	47.45	41.18	47.43	38.18	1.00
16.00	44.48	44.54	42.70	49.18	1.04
20.00	38.68	51.27	34.96	56.62	1.11
24.00	28.63	58.57	24.31	68.38	1.18
30.00	15.19	76.12	13.19	94.00	1.15
36.00	7.45	95.67	6.74	111.55	1.11
48.00	2.05	120.00	2.04	136.71	1.01

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



4.1.2 Single-dose 200 mg Fasting Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	CPB-152-2007
Study Title	A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover bioavailability study on Metoprolol succinate 200 mg extended release tablet (Wockhardt Limited, India) compared with Toprol-XL® (containing Metoprolol succinate 200 mg) tablet (AstraZeneca, USA) in 28 normal, adult, human subjects under fasting condition.
Clinical Site (Name & Address)	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India. Tel: +91-22-6652 4444, Fax: +91-22-6652 4545
Principal Investigator	Dr. Ilesh Changela
Dosing Dates	Period-I: 14/01/2008 & Period-II: 21/01/2008
Analytical Site (Name & Address)	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India. Tel: +91-22-6652 4444, Fax: +91-22-6652 4545
Analysis Dates	25/02/2008 to 06/03/2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	14/01/2008 to 06/03/2008 (53 days)

Table 20. Product information

Product	**Test**	**Reference**
Treatment ID	**A**	**B**
Product Name	Metoprolol succinate	Toprol-XL®
Manufacturer	Wockhardt Limited, India	AstraZeneca, USA
Batch/Lot No.	Batch No: LG10896	Batch No: MA0081
Manufacture Date	October 2007	N/AV
Expiration Date	September 2009	December 2008
Strength	200 mg	200 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	102.7%	99.4%

		[Based on Wockhardt's analysis]
Content Uniformity (Individual values & % RSD)	102.9, 96.9, 101.8, 95.5, 97.5, 96.7, 95.2, 96.8, 95.6, 95.5 L1=7.1	90.6, 94.3, 94.9, 95.2, 92.2, 94.0, 99.7, 101.7, 97.6, 97.1 L1=8.6 [Based on Wockhardt's analysis]
Dose Administered	1 x 200 mg	1 x 200 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled:** 30 **Dosed:** 28 **Completed:** 27 **Analyzed:** 27
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**AB:** 2, 3, 5, 7, 9, 12, 14, 15, 17, 18, 21, 24, 25, 26 **BA:** 1, 4, 6, 8, 10, 11, 13, 16, 19, 20, 22, 23, 27, 28
Blood Sampling Times	Pre-dose, 0.5, 1.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 24.0, 30.0, 36.0 and 48.0 hours post-dose
Blood Volume Collected/Sample	1 x 5 mL
Blood Sample Processing/Storage	Blood samples were collected in K_3EDTA vacutainers after discarding the first 0.5 mL of saline mixed blood from the cannula. Blood samples were then centrifuged at 4°C, 3000 rpm for 10 minutes. Plasma samples were transferred in duplicates to pre-labeled storage vials. Vials were stored upright in deep freezers at -50°C or colder until analysis.
Central Ethics Committee Approval	January 1, 2008
Informed Consent	December 19, 2007
Length of Fasting	Overnight fast of at least 10 hours before initial dose and for 4 hours post-dose.
Length of Confinement	Subjects will be housed in the facility from at least 11 hours prior to dosing and further till 48 hours after dosing in each period.

Safety Monitoring	Medical examination will be carried out at check-in and check out of each period and whenever felt necessary by the attending medical professional. Sitting blood pressure, oral temperature, respiratory rate and radial pulse will be measured at the time of check-in prior to drug administration and around 2, 4, 6, 8, 12, 24, 36 and 48 hours post dose in each period.

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. CPB-152-2007			
		Treatment Groups	
		Test Product N = 27	Reference Product N = 27
Age (years)	Mean ± SD	24.1 ± 3.14	24.1 ± 3.14
	Range	19-31	19-31
Age Groups	< 18	0	0
	18 – 40	27 (100 %)	27 (100 %)
	41 – 64	0	0
	65 – 75	0	0
	> 75	0	0
Sex	Male	27 (100 %)	27 (100 %)
	Female	0	0
Race	Asian	27 (100 %)	27 (100 %)
	Black	0	0
	Caucasian	0	0
	Hispanic	0	0
	Other	0	0
BMI (kg/m^2)	Mean + SD	21.53 ± 2.191	21.53 ± 2.191
	Range	18.5 - 25.0	18.5 - 25.0
Other Factors		Nil	Nil

Table 23. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
15	Did not report to facility for check-in (dropout)	II	N/AP

Table 24. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. CPB-152-2007	
	Test	Reference
Body as a whole		
Headache	---	2 (7.14%)*
Weakness	---	1 (3.57%)*
Cardiovascular		
Low Blood Pressure	3 (10.71%)*	6 (21.43%)*
Gastrointestinal	Nil	
Post Study Assessment		
Eosinophilia	1 (3.57%)**	
Elevated TLC	1 (3.57%)**	
Elevated level of Alkaline Phosphatase	1 (3.57%)*	
Elevated level of SGPT	2 (7.14%)*	
Elevated level of SOPT	2 (7.14%)*	
Total	**19 (67.86%)**	

Note:
28 subjects participated in this study.
* -Adverse events are related probable to studied drug.
**- Adverse events are related unlikely to studied drug.
-Percentage values are rounded off.

Table 25. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time point deviations	03	06 & 08
Deviation in Refrigerator temperature during subject sample analyses		

Comments on Dropouts/Adverse Events/Protocol Deviations:

No serious adverse events (AEs) were reported. A total of ten (10) AEs were reported by 6 of the 28 subjects, with 7 AEs occurring during the post study assessment. All were mild in severity. Eight events were most likely due to the study drug, while two were unrelated to the study drug.

27 of the 28 dosed subjects completed the study. The dropout subject was not replaced.

Protocol deviations did not affect the outcome of the study.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study (CPB-152-2007) Metoprolol								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.528	1.106	5.980	19.933	49.833	99.665	199.330	398.660
Inter day Precision (%CV)	1.37	3.22	2.14	1.86	1.47	1.87	1.71	1.50
Inter day Accuracy (%Actual)	102.75	94.86	96.40	100.32	98.92	100.98	101.72	104.05
Linearity (range of r^2)	0.996 to 0.999							
Linearity Range (ng/mL)	0.528 to 398.660							
Sensitivity/LOQ (ng/mL)	0.527							

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	1.536	160.034	332.020
Inter day Precision (%CV)	11.18	7.13	6.79
Inter day Accuracy (%Actual)	101.96	98.64	100.76

Comments on Study Assay Validation:

Acceptable.

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

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CPB-AP-011-02	12/26/2007	Reporting of Bioanalytical Results

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The study assay is acceptable.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18and Figure 12.

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	3730.65	40.13	1436.20	7280.57	3918.15	36.68	1414.31	7639.81	0.95
AUCI	ng hr/mL	3789.39	40.76	1463.31	7437.54	3970.80	37.36	1419.35	7988.96	0.95
CMAX	ng/mL	191.33	27.37	107.12	298.07	189.97	25.80	103.68	289.92	1.01
TMAX	hr	12.00	.	5.00	16.00	10.00	.	4.00	16.00	1.20
KE	hr-1	0.12	13.34	0.09	0.14	0.11	14.09	0.08	0.14	1.01
THALF	hr	6.11	14.56	4.94	8.14	6.17	15.32	4.88	8.21	0.99

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Metoprolol Succinate Extended Release Tablets 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. CPB-152-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	3453.0009	3660.0143	0.9434	82.64	107.71
AUC∞ (hr *ng/ml)	3499.6640	3703.2112	0.9450	82.71	107.98
Cmax (ng/ml)	183.8432	183.8080	1.0002	92.59	108.04

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Metoprolol Succinate Extended Release Tablets 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. CPB-152-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	3452.76	3657.41	0.94	82.67	107.81
AUC∞ (hr *ng/ml)	3499.43	3700.59	0.95	82.74	108.08
Cmax (ng/ml)	183.84	183.81	1.00	92.59	108.04

Table 32. Additional Study Information, Fasting Study No. CPB-152-2007

Root mean square error, AUC0-t	0.2853	
Root mean square error, AUC∞	0.2871	
Root mean square error, Cmax	0.1659	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	27	27
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	27	0.99	0.97	1.00
Reference	27	0.99	0.96	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The reviewer conducted statistical analysis using the original and repeat values. Results using the original values are given in Table 31. No significant difference was observed by using the repeat values for $LAUC_t$, $LAUC_i$, and LC_{max} for metoprolol.

2. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, T_{max}, KE and $t_{1/2}$) and confidence intervals of AUC_t, AUC_i and C_{max} for metoprolol as calculated by the reviewer were in agreement with the values reported by the firm.

3. The 90% confidence intervals for metoprolol of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

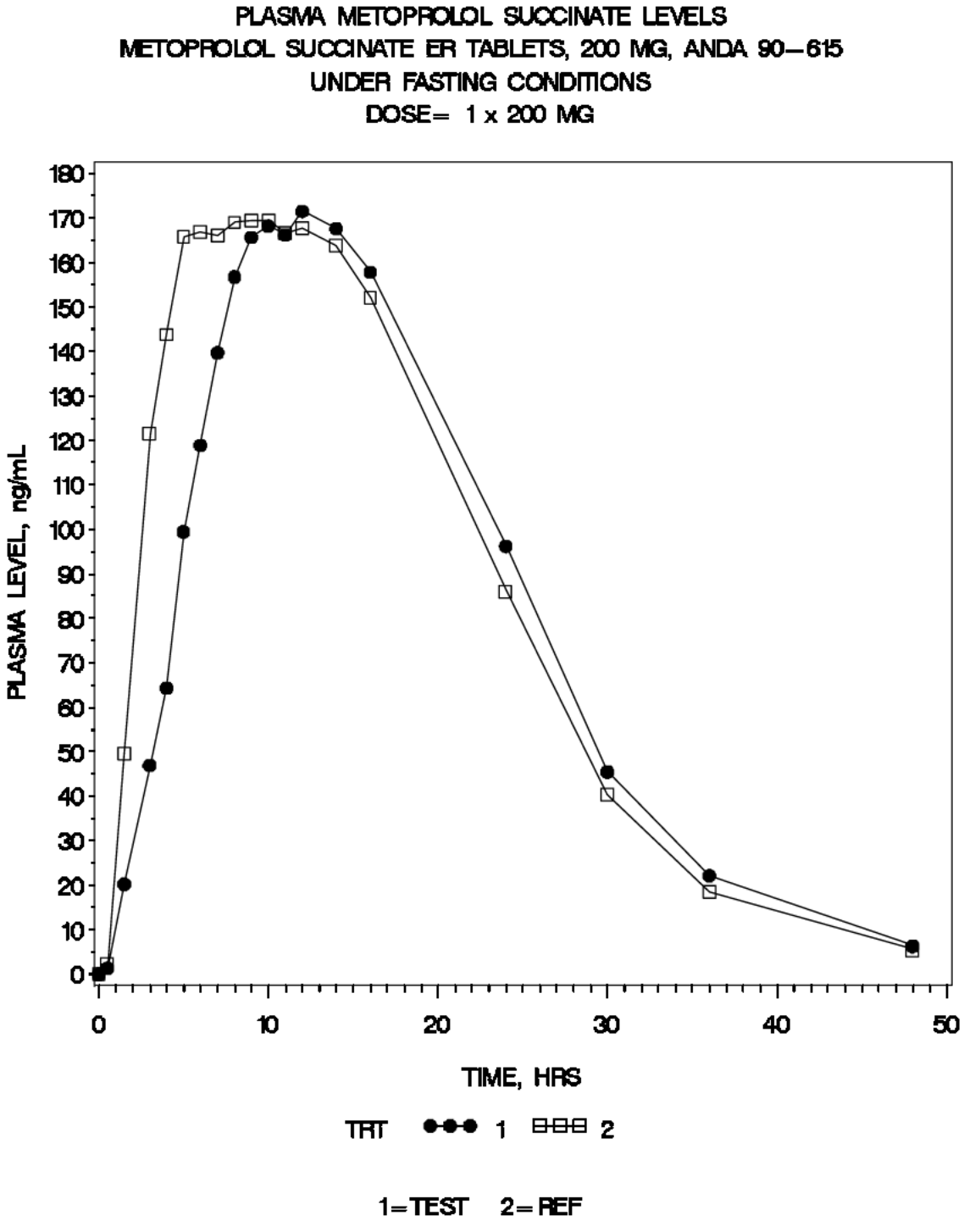
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting bioequivalence study is acceptable.

Table 33. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=27)		Reference (n=27)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	1.38	94.50	2.30	106.77	0.60
1.50	20.28	27.85	49.68	32.40	0.41
3.00	46.97	17.95	121.59	17.23	0.39
4.00	64.37	16.79	143.85	20.32	0.45
5.00	99.48	15.99	165.83	22.87	0.60
6.00	118.94	17.34	166.86	24.09	0.71
7.00	139.72	21.09	166.06	29.30	0.84
8.00	156.81	23.87	169.07	29.32	0.93
9.00	165.68	26.46	169.38	31.86	0.98
10.00	168.26	28.01	169.45	34.59	0.99
11.00	166.24	28.65	166.72	34.67	1.00
12.00	171.54	29.46	167.78	34.48	1.02
14.00	167.64	35.85	163.90	38.90	1.02
16.00	157.85	41.49	152.18	42.07	1.04
24.00	96.22	63.00	86.13	54.40	1.12
30.00	45.53	85.02	40.31	67.89	1.13
36.00	22.17	93.20	18.56	82.22	1.19
48.00	6.32	91.97	5.49	98.88	1.15

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



4.1.3 Single-dose 200 mg Fed Bioequivalence Study

4.1.3.1 Study Design

Table 34. Study Information

Study Number	CPB-153-2007
Study Title	A randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover bioavailability study on Metoprolol succinate 200 mg extended release tablets (Wockhardt Limited, India) compared with Toprol-XL® (containing Metoprolol succinate 200 mg) tablets (AstraZeneca, USA) in 36 normal, adult, human subjects under fed condition.
Clinical Site (Name & Address)	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India. Tel: +91-22-6652 4444, Fax: +91-22-6652 4545
Principal Investigator	Dr. Ilesh Changela
Dosing Dates	Period-I: 15/01/2008 & Period-II: 22/01/2008
Analytical Site (Name & Address)	Clinical Pharmacokinetics & Biopharmaceutics Department Wockhardt Limited, Mulund-Goregaon Link Road, Bhandup (West), Mumbai – 400 078, India. Tel: +91-22-6652 4444, Fax: +91-22-6652 4545
Analysis Dates	04/02/2008 to 22/02/2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	15/01/2008 to 22/02/2008 (39 days)

Table 35. Product Information

Product	**Test**	**Reference**
Treatment ID	**A**	**B**
Product Name	Metoprolol succinate	Toprol-XL®
Manufacturer	Wockhardt Limited, India	AstraZeneca, USA
Batch/Lot No.	Batch No: LG10896	Batch No: MA0081
Manufacture Date	October 2007	N/AV
Expiration Date	September 2009	December 2008
Strength	200 mg	200 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	102.7%	99.4%

		[Based on Wockhardt's analysis]
Content Uniformity (Individual values & % RSD)	102.9, 96.9, 101.8, 95.5, 97.5, 96.7, 95.2, 96.8, 95.6, 95.5 L1=7.1	90.6, 94.3, 94.9, 95.2, 92.2, 94.0, 99.7, 101.7, 97.6, 97.1 L1=8.6 [Based on Wockhardt's analysis]
Dose Administered	1 x 200 mg	1 x 200 mg
Route of Administration	Oral	Oral

Table 36. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	**Enrolled:** 38 **Dosed:** 36 **Completed:** 35 **Analyzed:** 35
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**AB:** 3, 4, 5, 7, 9, 11, 13, 16, 17, 19, 22, 23, 26, 27, 29, 32, 35, 36 **BA:** 1, 2, 6, 8, 10, 12, 14, 15, 18, 20, 21, 24, 25, 28, 30, 31, 33, 34
Blood Sampling Times	Pre-dose, 0.5, 1.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 24.0, 30.0, 36.0 and 48.0 hours post-dose
Blood Volume Collected/Sample	1 x 5 mL
Blood Sample Processing/Storage	Blood samples were collected in K_3EDTA vacutainers after discarding the first 0.5 mL of saline mixed blood from the cannula. Blood samples were then centrifuged at 4°C, 3000 rpm for 10 minutes. Plasma samples were transferred in duplicates to pre-labeled storage vials. Vials were stored upright in deep freezers at -50°C or colder until analysis.
Central Ethics Committee Approval	January 11, 2008
Informed Consent	December 19, 2007
Length of Fasting Before Meal	Subjects are required to undergo an overnight fast for at least 10 hours before serving of standard test meal and for 4 hours post-dose.
Length of Confinement	Subjects will be housed in the facility from at least 11 hours prior to dosing and further till 48 hours after dosing in each period.
Safety Monitoring	Medical examination will be carried out at check-in and check out of each period and whenever felt necessary by the attending medical professional. Sitting blood pressure, oral temperature, respiratory rate and radial pulse will be measured at the time of check-in prior to drug administration and around 2, 4, 6, 8, 12, 24, 36 and 48 hours post dose in each period.

Standard FDA Meal Used?	No
If No, then meal components and composition is listed in the tables below	

Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	57.3%	544
Carbohydrate	26.4%	251
Protein	15.8%	150
Total		**945**

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study	
Component	**Kcal**
Bread & Butter	310
Omelet	246
French Fries	118
Whole Milk	270
Total	**944**

Comments on Study Design:

The study design is acceptable.

4.1.3.2 Clinical Results

Table 37. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. CPB-153-2007			
		Treatment Groups	
		Test Product N = 35	Reference Product N = 35
Age (years)	Mean ± SD	24.6 ± 4.96	24.6 ± 4.96
	Range	19-37	19-37
Age Groups	< 18	0	0
	18 – 40	35 (100 %)	35 (100 %)
	41 – 64	0	0
	65 – 75	0	0
	> 75	0	0
Sex	Male	35 (100 %)	35 (100 %)
	Female	0	0
Race	Asian	35 (100 %)	35 (100 %)
	Black	0	0
	Caucasian	0	0
	Hispanic	0	0
	Other	0	0
BMI (kg/m^2)	Mean + SD	21.36 ± 1.658	21.36 ± 1.658
	Range	18.2 – 24.5	18.2 – 24.5
Other Factors		Nil	Nil

Table 38. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
29	Did not report to facility for check-in (dropout)	II	N/AP

Table 39. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. CPB-153-2007	
	Test	Reference
Body as a whole		
Fever	---	1 (2.78 %) **
Headache	3 (8.33 %)*	2 (5.56 %)*
Tiredness	-	1 (2.78 %)*
Weakness	1(2.78 %)*	2 (5.56 %)*
Cardiovascular		
Low Blood Pressure	10 (27.78)*	12 (33.33)*
Gastrointestinal		
Post Study Assessment		
Eosinophilia	1 (2.78 %) **	
Neutropenia	2 (5.56 %) **	
Lymphocytosis	1 (2.78 %) **	
Elevated level of Alkaline Phosphatase	1 (2.78 %)*	
Elevated level of SGPT	3 (8.33 %)*	
Total	**40 (111.11%)**	

Note:
36 subjects participated in this study.
* -Adverse events are related probable to studied drug.
**- Adverse events are related unlikely to studied drug.
- Percentage values are rounded off.

Table 40. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time point deviations	06	---
Deviation in Refrigerator temperature during subject sample analyses	---	

Comments on Adverse Events/Protocol Deviations:

No serious adverse events (AEs) were reported. A total of twenty two (22) AEs were reported by 14 of the 36 subjects, with 8 AEs occurring during the post study assessment. All were mild in severity. Eighteen events were most likely due to the study drug, while 4 were unrelated to the study drug.

35 of the 36 dosed subjects completed the study. The dropout subject was not replaced.

Protocol deviations did not affect the outcome of the study.

4.1.3.3 Bioanalytical Results

Table 41. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study (CPB-153-2007) Metoprolol								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.528	1.106	5.980	19.933	49.833	99.665	199.330	398.660
Inter day Precision (%CV)	1.35	3.14	1.93	2.05	3.83	2.77	2.55	2.04
Inter day Accuracy (%Actual)	103.03	94.43	95.84	99.67	100.32	100.31	101.46	104.96
Linearity (range of r^2)	0.995 to 0.999							
Linearity Range (ng/mL)	0.528 to 398.660							
Sensitivity/LOQ (ng/mL)	0.527							

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	1.536	160.034	332.020
Inter day Precision (%CV)	11.17	13.09	7.27
Inter day Accuracy (%Actual)	100.61	97.87	99.42

Comments on Study Assay Validation:

Acceptable.

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

Comments on Chromatograms:

Acceptable.

Table 42. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CPB-AP-011-02	12/26/2007	Reporting of Bioanalytical Results

Table 43. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

The study assay is acceptable.

4.1.3.4 Pharmacokinetic Results

Table 44. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 48 and Figure 3.

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	ng hr/mL	3419.98	35.92	1159.65	6172.48	3229.86	30.76	1189.60	4894.21	1.06
AUCI	ng hr/mL	3461.38	36.44	1172.89	6291.66	3267.66	31.26	1193.98	5044.77	1.06
CMAX	ng/mL	179.01	24.24	103.48	279.25	162.98	21.01	91.92	241.14	1.10
TMAX	hr	12.00	.	5.00	16.00	6.00	.	4.00	14.00	2.00
KE	hr-1	0.12	12.12	0.09	0.15	0.12	11.77	0.09	0.14	1.04
THALF	hr	5.74	12.13	4.63	7.37	5.99	12.42	4.89	7.79	0.96

* Tmax values are presented as median, range

Table 45. Geometric Means and 90% Confidence Intervals - Firm Calculated

Metoprolol Succinate Extended Release Tablets 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. CPB-153-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	3193.3486	3070.1501	1.0401	97.53	110.93
AUC∞ (hr *ng/ml)	3227.0858	3101.6639	1.0404	97.50	111.02
Cmax (ng/ml)	173.6725	159.4156	1.0894	103.54	114.63

Table 46. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Metoprolol Succinate Extended Release Tablets 1 x 200 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. CPB-153-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	3193.38	3070.15	1.04	97.53	110.93
AUC∞ (hr *ng/ml)	3227.13	3101.66	1.04	97.50	111.03
Cmax (ng/ml)	173.67	159.42	1.09	103.54	114.63

Table 47. Additional Study Information, Fed Study No. CPB-153-2007

Root mean square error, AUC0-t	0.1591	
Root mean square error, AUC∞	0.1605	
Root mean square error, Cmax	0.1256	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	35	35
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	35	0.99	0.97	1.00
Reference	35	0.99	0.97	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, T_{max}, KE and $t_{1/2}$) and confidence intervals of AUC_t, AUC_i and C_{max} for metoprolol as calculated by the reviewer were in agreement with the values reported by the firm.

2. The 90% confidence intervals for metoprolol of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

3. Please refer to reviewer's comments in Section 3.6 regarding difference in Test and Reference T_{max}. In addition, the median Tmax for the reference product is 10 hrs under fasting conditions and 6 hrs under fed conditions. Therefore, the median Tmax for the test product of 12 hrs under fed conditions is acceptable since the labeling for Toprol-XL® tablets states that "The bioavailability of metoprolol is not significantly affected by food following TOPROL-XL administration", i.e., TOPROL-XL can be administered without regard to food.

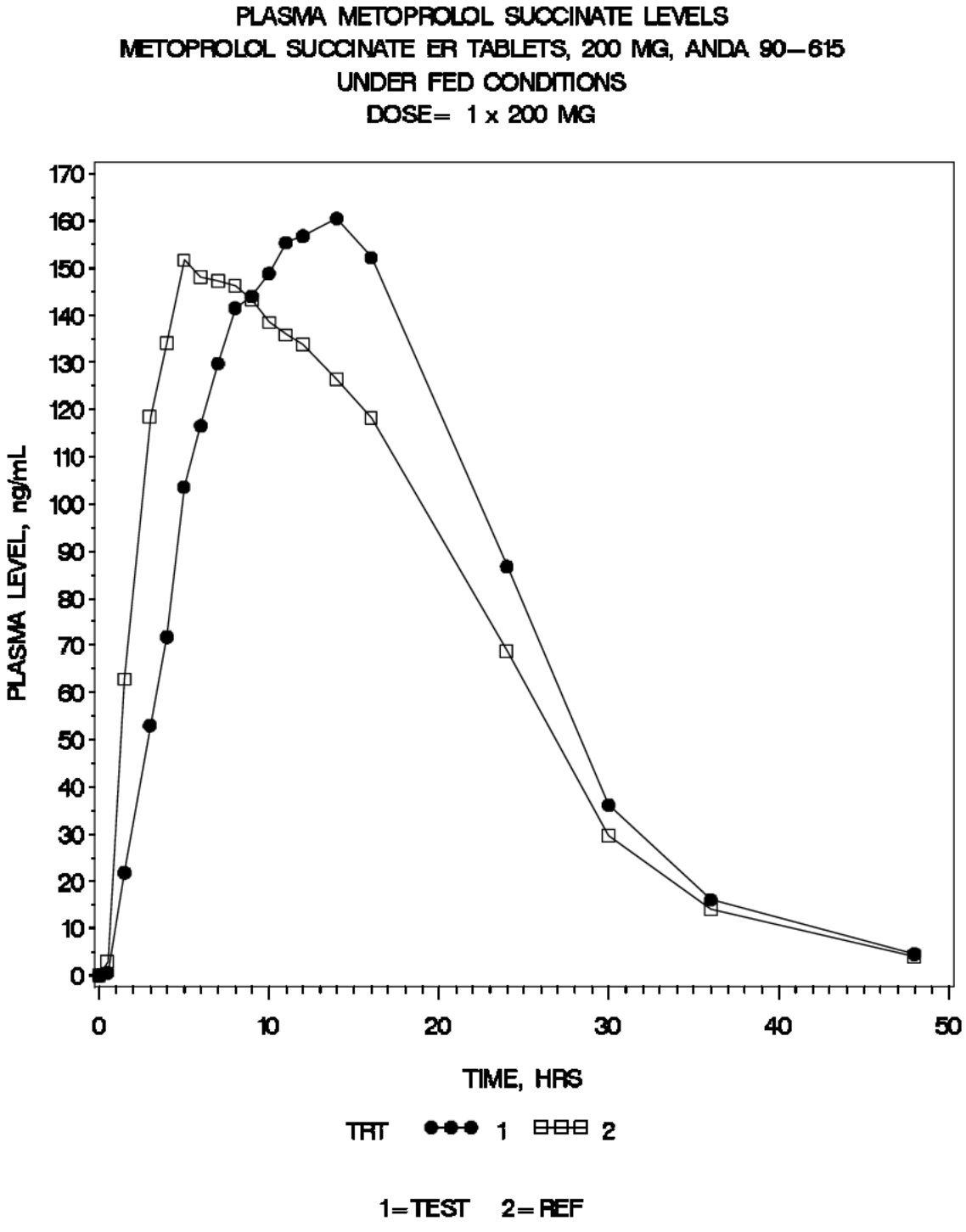
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The fasting bioequivalence study is acceptable.

Table 48. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=35)		Reference (n=35)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.61	189.40	3.03	124.85	0.20
1.50	21.84	60.94	62.90	45.88	0.35
3.00	53.06	24.51	118.56	25.04	0.45
4.00	71.83	23.65	134.07	23.24	0.54
5.00	103.63	18.73	151.75	20.46	0.68
6.00	116.61	19.04	148.06	19.15	0.79
7.00	129.80	20.56	147.28	19.73	0.88
8.00	141.56	22.45	146.37	22.68	0.97
9.00	144.09	24.43	143.34	24.07	1.01
10.00	148.88	27.55	138.52	26.77	1.07
11.00	155.42	29.95	135.89	26.66	1.14
12.00	156.81	31.45	133.90	29.35	1.17
14.00	160.55	34.82	126.39	33.29	1.27
16.00	152.24	39.81	118.20	36.75	1.29
24.00	86.75	57.28	68.74	49.11	1.26
30.00	36.18	68.71	29.67	61.97	1.22
36.00	16.10	81.19	14.13	74.18	1.14
48.00	4.60	86.33	4.09	77.86	1.13

Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

(b) (4)

Following this page, 5 pages withheld in full (b)(4)- formulation data

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	None of the excipients used in the formulation exceed the IIG limit. The chemistry review has not been completed at the time of this review.

4.3 Dissolution Data

Dissolution Review Path	DFS N 090615 N 000 07-May-2008

Table 49. Dissolution Data

Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	pH 6.8 Phosphate Buffer
Volume:	500 mL
Temperature:	37 ± 0.5° C
1 Hour: Not more than 25% of labeled amount of Metoprolol succinate dissolved 4 Hour: Between 20 and 40% of labeled amount of Metoprolol succinate dissolved 8 Hour: Between 40 and 60% of labeled amount of Metoprolol succinate dissolved 20 Hour: Not less than 80% of labeled amount of Metoprolol succinate dissolved	
Wockhardt Limited, L-1, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 1 Hour	4 Hour	8 Hour	20 Hour	Study Report Location
Study Report #: N/A	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LGS13220 Manufacturing Date: Oct. 2007 Date of testing : Jan 07, 2008	25 mg Tablets	12	Mean	4	23	56	97	Module 5, 1.1, Pages 73-76
				Range	(b) (4)				
				%CV	25	7	7	6	
Study Report #: N/A	TOPROL-XL ® Tablets, 25mg / MA0004 Expiry Date: Nov. 2008 Date of testing : Jan 06, 2008	25 mg Tablets	12	Mean	10	28	54	94	
				Range	(b) (4)				
				%CV	10	7	6	4	
Study Report #:N/A	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LGS13222	50 mg Tablets	12	Mean	3	21	53	96	Module 5, 1.1,
				Range	(b) (4)				

	Manufacturing Date: Oct. 2007 Date of testing : Nov 06, 2007			%CV	33	14	8	4	Pages 90-93
Study Report #:N/A	TOPROL-XL ® Tablets, 50mg / LT0026 Expiry Date: Nov.07 Date of testing : Nov 05, 2007	50 mg Tablets	12	Mean	8	26	51	94	
				Range	(b) (4)				
				%CV	13	8	4	2	
Study Report #:N/A	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LGS13223 Manufacturing Date: Oct. 2007 Date of testing : Jan 09, 2008	100 mg Tablets	12	Mean	4	22	53	95	Module 5, 1.1, Pages 107-110
				Range	(b) (4)				
				%CV	25	9	6	3	
Study Report #:N/A	TOPROL-XL ® Tablets, 100 mg / MA0091 Expiry Date: Oct. 2008 Date of testing : Jan 08, 2008	100 mg Tablets	12	Mean	8	26	51	95	
				Range	(b) (4)				
				%CV	9	4	4	2	
Study Report #:N/A	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LGS13224 Manufacturing Date: Oct. 2007 Date of testing : Nov 19, 2007	200 mg Tablets	12	Mean	3	21	53	97	Module 5, 1.1, Pages 124-127
				Range	(b) (4)				
				%CV	0	5	4	4	
Study Report #:N/A	TOPROL-XL ® Tablets, 200 mg / MA0081 Expiry Date: Dec.2008 Date of testing : Nov 20, 2007	200 mg Tablets	12	Mean	10	28	50	90	
				Range	(b) (4)				
				%CV	10	4	2	3	

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37 ± 0.5° C
Firm's Proposed Specifications	1 Hour: Not more than 25% of labeled amount of Metoprolol succinate dissolved 4 Hour: Between 20 and 40% of labeled amount of Metoprolol succinate dissolved 8 Hour: Between 40 and 60% of labeled amount of Metoprolol succinate dissolved 20 Hour: Not less than 80% of labeled amount of Metoprolol succinate dissolved	
Dissolution Testing Site (Name, Address)	Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis**	**Dosage Form& Strength**	**No. of Dosage Units Tested**		**Collection Times (Hours)** 1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	10 hr.	12 hr.	16 hr.	20 hr.	24 hr.	**Location**
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Dec. 19, 2007	25 mg Tablets	12	Mean	4	6	16	31	45	56	67	81	92	96	Module 5 , Volume 1.1, Page No. 81-84 of Original ANDA submission
				Range	(b) (4)										
				%CV	15	15	6	5	5	4	4	5	5	4	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / MA0004 Expiry Date: Nov. 2008 Date of testing : Dec. 01, 2007	25 mg Tablets	12	Mean	10	18	40	64	80	88	93	94	98	100	
				Range	(b) (4)										
				%CV	11	10	5	4	3	3	3	3	3	3	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007	50 mg Tablets	12	Mean	3	7	17	30	42	52	61	74	83	88	Module 5 , Volume 1.1, Page No. 98-101 of Original
				Range	(b) (4)										
				%CV	20	13	8	6	5	4	3	3	3	3	

	Date of testing : Nov 02, 2007			%CV	20	13	8	6	5	4	3	3	3	3	ANDA submission
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / LT0026 Expiry Date: Nov.2007 Date of testing : Oct. 29, 2007	50 mg Tablets	12	Mean	10	17	32	48	63	75	84	90	95	97	
				Range	(b) (4)										
				%CV	12	9	7	6	6	5	5	4	4	4	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Dec. 12, 2007	100 mg Tablets	12	Mean	5	8	17	31	44	55	66	78	89	93	Module 5 , Volume 1.1, Page No. 115-118 of Original ANDA submission
				Range	(b) (4)										
				%CV	16	10	6	4	3	3	3	3	3	3	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / MA0091 Expiry Date: Oct. 2008 Date of testing : Nov. 26, 2007	100 mg Tablets	12	Mean	9	16	32	48	63	75	83	90	95	97	
				Range	(b) (4)										
				%CV	10	15	5	4	4	3	3	2	3	4	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Nov 21, 2007	200 mg Tablets	12	Mean	4	6	15	30	42	55	64	78	89	95	Module 5 , Volume 1.1, Page No. 132-135 of Original ANDA submission
				Range	(b) (4)										
				%CV	12	10	6	3	3	3	3	4	2	3	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / MA0081 Expiry Date: Dec.2008 Date of testing : Nov 15, 2007	200 mg Tablets	12	Mean	13	19	36	53	67	79	86	91	97	99	
				Range	(b) (4)										
				%CV	18	7	6	6	5	4	5	4	4	5	

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	pH 4.5 Acetate Buffer
	Volume:	500 mL
	Temperature:	37 ± 0.5° C
Firm's Proposed Specifications	1 Hour: Not more than 25% of labeled amount of Metoprolol succinate dissolved 4 Hour: Between 20 and 40% of labeled amount of Metoprolol succinate dissolved 8 Hour: Between 40 and 60% of labeled amount of Metoprolol succinate dissolved 20 Hour: Not less than 80% of labeled amount of Metoprolol succinate dissolved	
Dissolution Testing Site (Name, Address)	Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis**	**Dosage Form& Strength**	**No. of Dosage Units Tested**		**Collection Times (Hours)**										**Location**
					1 hr.	**2 hr.**	**4 hr.**	**6 hr.**	**8 hr.**	**10 hr.**	**12 hr.**	**16 hr.**	**20 hr.**	**24 hr.**	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Dec. 20, 2007	25 mg Tablets	12	Mean	3	6	25	44	59	70	78	85	91	94	Module 5 , Volume 1.1, Page No. 85-88 of Original ANDA submission
				Range	(b) (4)										
				%CV	16	12	4	4	4	4	4	4	4	4	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / MA0004 Expiry Date: Nov. 2008 Date of testing : Dec. 03, 2007	25 mg Tablets	12	Mean	10	18	40	63	79	88	91	94	97	98	
				Range	(b) (4)										
				%CV	14	11	7	5	5	5	5	4	4	5	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007	50 mg Tablets	12	Mean	3	10	28	45	59	70	78	86	93	96	Module 5 , Volume 1.1, Page No. 102-105 of Original
				Range	(b) (4)										
				%CV	32	15	11	7	5	4	4	3	2	2	

	Date of testing : Nov 01, 2007			%CV	32	15	11	7	5	4	4	3	2	2	ANDA submission
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / LT0026 Expiry Date: Nov.2007 Date of testing : Oct. 31, 2007	50 mg Tablets	12	Mean	8	17	35	52	66	77	88	93	97	101	
				Range	(b) (4)										
				%CV	11	7	5	4	4	3	3	3	3	3	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Dec. 13, 2007	100 mg Tablets	12	Mean	3	7	23	40	56	68	80	85	91	94	Module 5 , Volume 1.1, Page No. 119-122 of Original ANDA submission
				Range	(b) (4)										
				%CV	9	8	3	3	3	3	3	3	3	3	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / MA0091 Expiry Date: Oct. 2008 Date of testing : Nov. 28, 2007	100 mg Tablets	12	Mean	8	16	34	51	66	79	86	90	95	97	
				Range	(b) (4)										
				%CV	9	7	5	5	5	4	4	3	4	4	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Nov 22, 2007	200 mg Tablets	12	Mean	3	6	23	42	57	72	80	86	92	95	Module 5 , Volume 1.1, Page No. 136-139 of Original ANDA submission
				Range	(b) (4)										
				%CV	16	9	4	4	4	3	3	3	3	3	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / MA0081 Expiry Date: Dec.2008 Date of testing : Nov 17, 2007	200 mg Tablets	12	Mean	11	19	37	53	68	80	90	92	97	99	
				Range	(b) (4)										
				%CV	15	4	4	3	3	2	3	3	3	3	

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	Water
	Volume:	500 mL
	Temperature:	37 ± 0.5° C
Firm's Proposed Specifications	1 Hour: Not more than 25% of labeled amount of Metoprolol succinate dissolved 4 Hour: Between 20 and 40% of labeled amount of Metoprolol succinate dissolved 8 Hour: Between 40 and 60% of labeled amount of Metoprolol succinate dissolved 20 Hour: Not less than 80% of labeled amount of Metoprolol succinate dissolved	
Dissolution Testing Site (Name, Address)	Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis**	**Dosage Form& Strength**	**No. of Dosage Units Tested**		**Collection Times (Hours)**										**Location**
					1 hr.	**2 hr.**	**4 hr.**	**6 hr.**	**8 hr.**	**10 hr.**	**12 hr.**	**16 hr.**	**20 hr.**	**24 hr.**	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Dec. 17, 2007	25 mg Tablets	12	Mean	2	3	12	22	30	38	45	52	57	61	Module 5, Volume 1.1, Page No. 77-80 of Original ANDA submission.
				Range	(b) (4)										
				%CV	33	14	5	5	8	5	5	4	4	5	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / MA0004 Expiry Date: Nov. 2008 Date of testing : Nov. 29, 2007	25 mg Tablets	12	Mean	9	16	30	44	58	70	77	81	89	95	
				Range	(b) (4)										
				%CV	13	9	7	6	5	5	5	4	4	4	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007	50 mg Tablets	12	Mean	1	3	11	21	30	36	43	52	56	59	Module 5, Volume 1.1, Page No. 94-97 of Original
				Range	(b) (4)										
				%CV	33	32	15	10	8	7	4	3	3	3	

	Date of testing : Nov 03, 2007			%CV	33	32	15	10	8	7	4	3	3	3	ANDA submission
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / LT0026 Expiry Date: Nov.2007 Date of testing : Oct. 27, 2007	50 mg Tablets	12	Mean	8	14	28	42	55	66	77	85	91	95	
				Range	(b) (4)										
				%CV	16	9	7	6	5	3	5	6	5	4	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Nov. 21, 2007	100 mg Tablets	12	Mean	1	2	9	19	29	38	49	56	62	68	Module 5 , Volume 1.1, Page No. 111-114 of of Original ANDA submission
				Range	(b) (4)										
				%CV	0	14	9	6	6	5	6	4	5	3	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / MA0091 Expiry Date: Oct. 2008 Date of testing : Nov. 21, 2007	100 mg Tablets	12	Mean	8	14	27	41	55	68	77	86	92	96	
				Range	(b) (4)										
				%CV	7	7	6	4	4	3	3	3	2	2	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Nov 19, 2007	200 mg Tablets	12	Mean	1	2	8	18	29	38	48	57	64	68	Module 5 , Volume 1.1, Page No. 128-131 of Original ANDA submission
				Range	(b) (4)										
				%CV	0	26	6	4	3	3	3	2	2	2	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / MA0081 Expiry Date: Dec.2008 Date of testing : Nov 14, 2007	200 mg Tablets	12	Mean	9	16	30	43	57	69	78	87	94	98	
				Range	(b) (4)										
				%CV	16	11	8	7	6	5	4	5	5	4	

Dissolution conditions:	
Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	0.1 N HCl with 5% v/v of Alcohol USP
Volume:	900 mL (855 mL 0.1 HCl + 45 mL Alcohol USP)
Temperature:	37 ± 0.5° C
Site of testing : Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes) 15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	Location
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Dec. 31, 2008	25 mg Tablets	12	Mean	1	2	3	4	4	5	6	7	Refer Page No. 28-30, Exhibit-II of the same submission.
				Range								(b) (4)	
				%CV	36	28	22	24	20	22	20	18	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / PP0025 Expiry Date: June 2011 Date of testing : Dec. 26, 2008	25 mg Tablets	12	Mean	4	8	11	14	17	20	23	26	
				Range								(b) (4)	
				%CV	13	12	12	10	10	10	8	7	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007 Date of testing : Dec. 23, 2008	50 mg Tablets	12	Mean	1	2	2	3	3	4	5	6	Refer Page No. 41-43, Exhibit-II of the same submission.
				Range								(b) (4)	
				%CV	0	15	18	10	15	11	12	8	
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / PN0016 Expiry Date: April 2012 Date of testing : Dec. 20, 2008	50 mg Tablets	12	Mean	4	7	11	14	16	18	21	23	
				Range								(b) (4)	
				%CV	16	16	14	13	14	13	13	13	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes)								Location
					15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Dec. 11, 2008	100 mg Tablets	12	Mean	2	3	4	5	6	7	8	10	Refer Page No. 56-58, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	26	14	12	12	10	9	8	8	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / PN0019 Expiry Date: May 2012 Date of testing : Dec. 13, 2008	100 mg Tablets	12	Mean	4	7	9	11	14	15	17	19	
				Range	(b) (4)								
				%CV	13	8	8	7	8	8	8	7	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Dec.11, 2008	200 mg Tablets	12	Mean	1	2	3	4	5	6	7	8	Refer Page No. 70-72, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	36	28	23	18	20	19	16	14	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / PN0149 Expiry Date: May 2012 Date of testing : Dec. 05, 2008	200 mg Tablets	12	Mean	3	7	9	12	15	17	20	22	
				Range	(b) (4)								
				%CV	15	12	8	8	8	6	6	6	

Dissolution conditions:	
Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	0.1 N HCl with 20% v/v of Alcohol USP
Volume:	900 mL (720 mL 0.1 HCl + 180 mL Alcohol USP)
Temperature:	37 ± 0.5° C
Site of testing : Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes) 15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	Location
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Jan. 01, 2009	25 mg Tablets	12	Mean	1	2	4	8	17	27	36	44	Refer Page No. 31-33, Exhibit-II of the same submission.
				Range								(b) (4)	
				%CV	33	38	33	19	13	12	11	10	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / PP0025 Expiry Date: June 2011 Date of testing : Dec. 27, 2008	25 mg Tablets	12	Mean	4	9	16	25	37	48	57	66	
				Range								(b) (4)	
				%CV	15	9	7	5	2	2	2	1	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007 Date of testing : Dec. 24, 2008	50 mg Tablets	12	Mean	1	1	3	7	16	25	35	43	Refer Page No. 44-46, Exhibit-II of the same submission.
				Range								(b) (4)	
				%CV	60	36	25	15	15	11	10	9	
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / PN0016 Expiry Date: April 2012 Date of testing : Dec. 22, 2008	50 mg Tablets	12	Mean	3	7	12	17	24	31	37	43	
				Range								(b) (4)	
				%CV	23	19	15	12	9	8	7	7	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes)								Location
					15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Dec. 17, 2008	100 mg Tablets	12	Mean	1	2	4	9	19	28	38	47	Refer Page No. 59-61, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	0	20	11	10	7	6	5	4	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / PN0019 Expiry Date: May 2012 Date of testing : Dec. 15, 2008	100 mg Tablets	12	Mean	4	8	12	17	24	32	38	45	
				Range	(b) (4)								
				%CV	21	11	6	5	3	3	3	3	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Dec.12, 2008	200 mg Tablets	12	Mean	1	2	4	9	19	28	39	49	Refer Page No. 73-75, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	0	18	18	9	7	7	5	7	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / PN0149 Expiry Date: May 2012 Date of testing : Dec. 08, 2008	200 mg Tablets	12	Mean	3	8	13	19	26	33	41	49	
				Range	(b) (4)								
				%CV	12	7	4	5	4	4	4	4	

Dissolution conditions:	
Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	0.1 N HCl with 40% v/v of Alcohol USP
Volume:	900 mL (540 mL 0.1 HCl + 360 mL Alcohol USP)
Temperature:	37 ± 0.5° C
Site of testing : Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes) 15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	Location
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Jan. 02, 2009	25 mg Tablets	12	Mean	5	33	55	65	72	76	80	82	Refer Page No. 34-36, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	12	9	5	5	4	4	4	4	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / PP0025 Expiry Date: June 2011 Date of testing : Dec. 29, 2008	25 mg Tablets	12	Mean	7	40	68	81	87	91	94	96	
				Range	(b) (4)								
				%CV	9	5	3	3	3	3	3	3	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007 Date of testing : Dec. 18, 2008	50 mg Tablets	12	Mean	3	29	52	64	72	77	81	84	Refer Page No. 47-50, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	15	10	4	4	4	4	4	4	
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / PN0016 Expiry Date: April 2012 Date of testing : Dec. 24, 2008	50 mg Tablets	12	Mean	6	31	60	76	84	89	92	93	
				Range	(b) (4)								
				%CV	11	6	5	4	4	4	4	4	

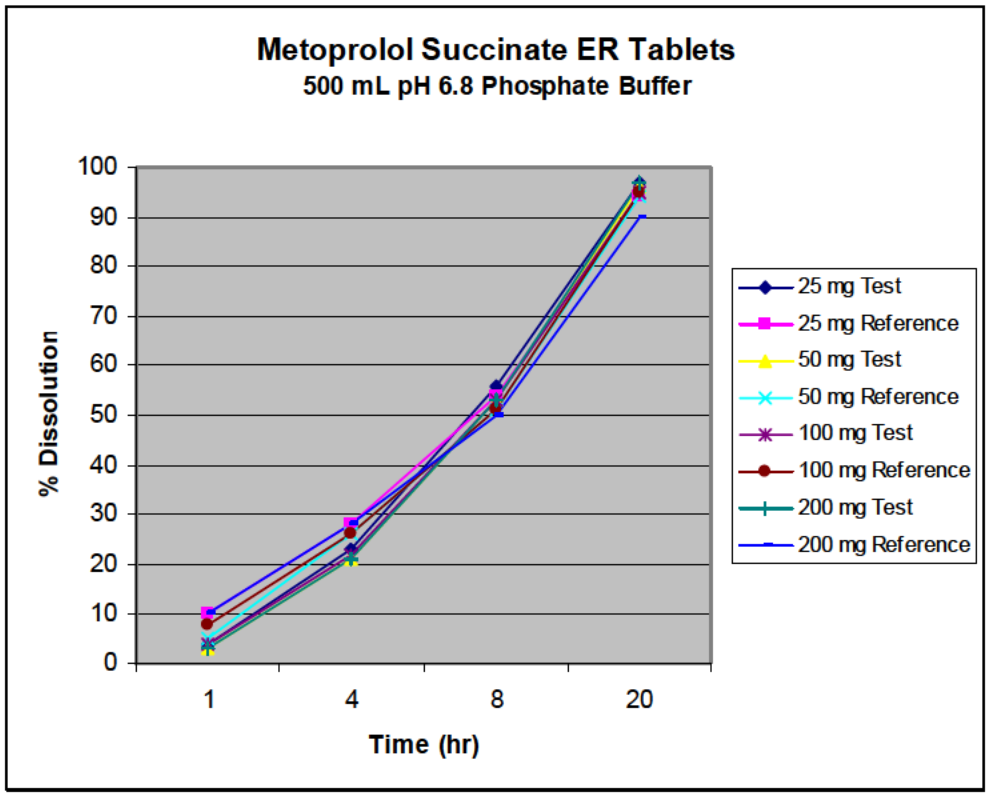
Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes)								Location
					15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Dec. 18, 2008	100 mg Tablets	12	Mean	5	32	51	61	67	72	75	77	Refer Page No.62-64, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	16	9	7	6	6	5	5	4	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / PN0019 Expiry Date: May 2012 Date of testing : Dec. 15, 2008	100 mg Tablets	12	Mean	6	30	59	75	84	89	92	94	
				Range	(b) (4)								
				%CV	17	8	5	4	3	3	3	3	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Dec.12, 2008	200 mg Tablets	12	Mean	6	33	55	64	70	75	78	81	Refer Page No. 76-78, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	9	9	6	5	5	5	5	5	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / PN0149 Expiry Date: May 2012 Date of testing : Dec. 09, 2008	200 mg Tablets	12	Mean	7	33	61	76	84	88	91	92	
				Range	(b) (4)								
				%CV	17	8	5	3	3	3	3	3	

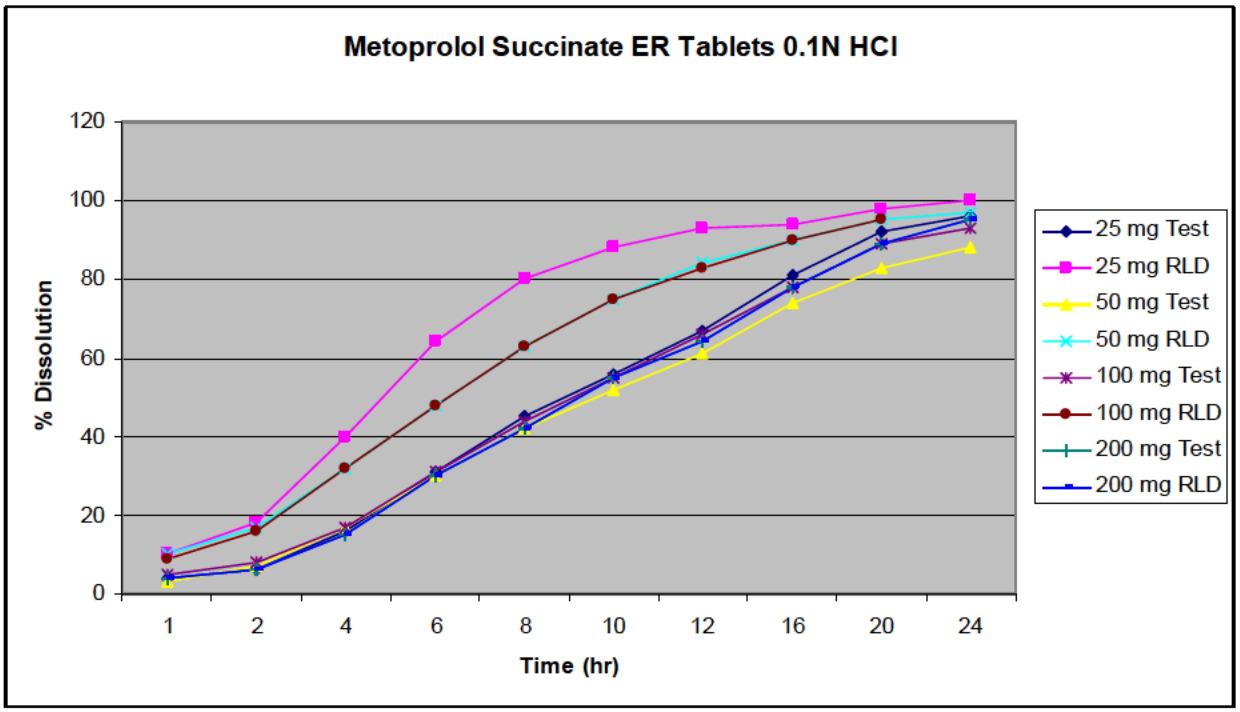
Dissolution conditions:	
Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	0.1 N HCl
Volume:	900 mL
Temperature:	37 ± 0.5° C
Site of testing : Wockhardt Limited, D-4, MIDC Area, Chikalthana, Aurangabad, Maharashtra, India	

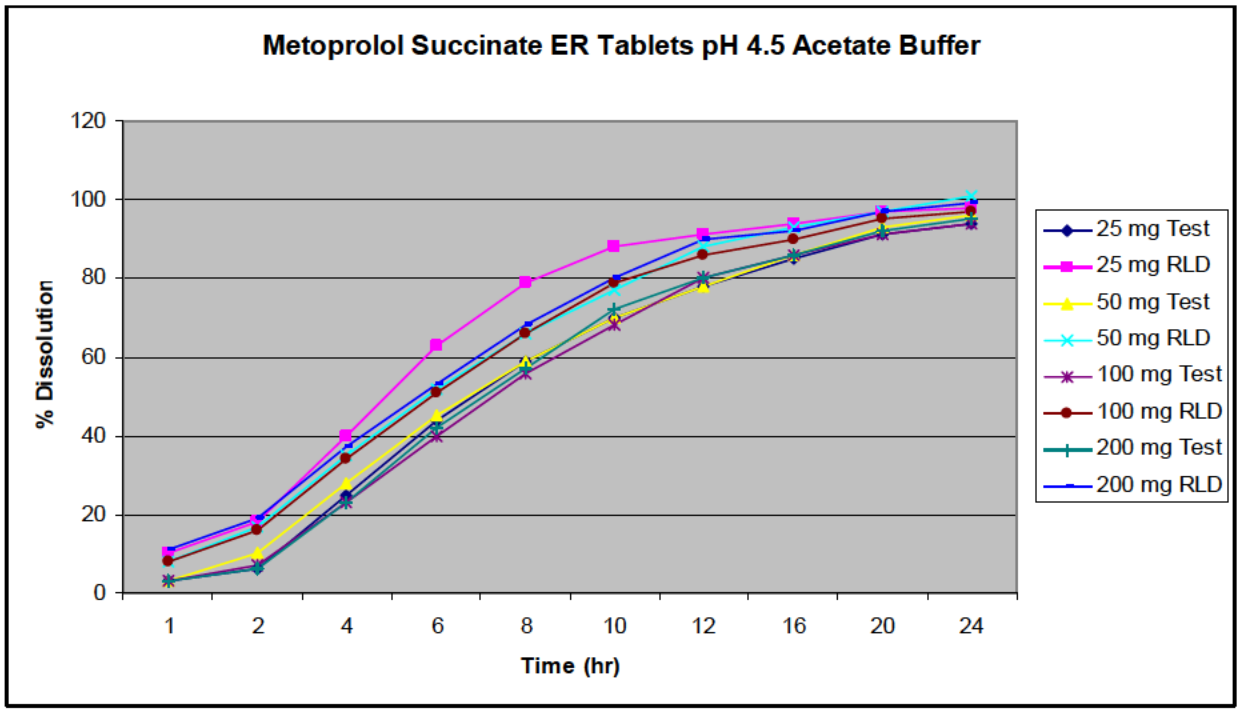
Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes) 15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	Location
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : Dec. 30, 2008	25 mg Tablets	12	Mean	2	2	3	4	5	5	6	6	Refer Page No. 23-27, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	30	28	31	20	26	21	17	18	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / PP0025 Expiry Date: June 2011 Date of testing : Dec. 25, 2008	25 mg Tablets	12	Mean	3	7	10	13	15	17	19	21	
				Range	(b) (4)								
				%CV	23	15	11	9	8	6	7	7	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007 Date of testing : Dec. 23, 2008	50 mg Tablets	12	Mean	1	2	2	3	3	4	4	5	Refer Page No. 36/1-40, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	47	50	28	25	26	19	22	19	
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / PN0016 Expiry Date: April 2012 Date of testing : Dec. 19, 2008	50 mg Tablets	12	Mean	4	7	9	11	13	14	16	18	
				Range	(b) (4)								
				%CV	22	19	17	17	15	15	14	14	

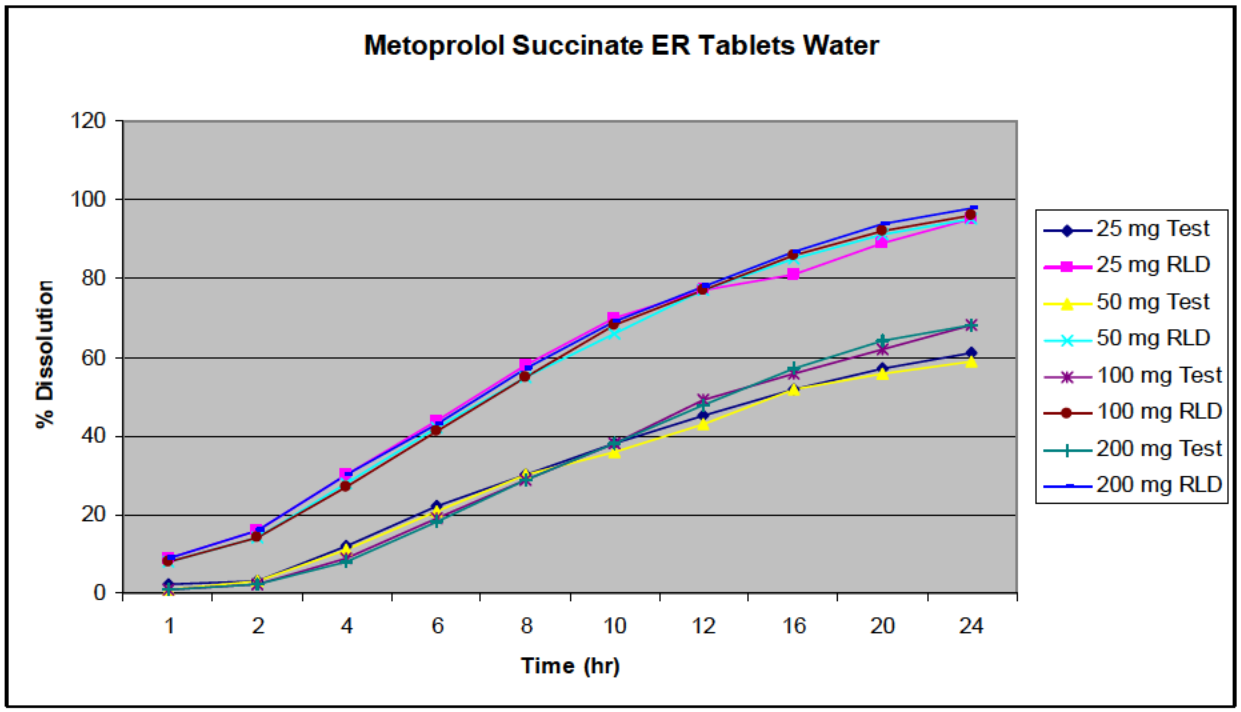
Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Minutes)								Location
					15 mins.	30 mins.	45 mins.	60 mins.	75 mins.	90 mins.	105 mins.	120 mins.	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : Dec. 10, 2008	100 mg Tablets	12	Mean	1	3	4	5	6	7	7	8	Refer Page No. 51-55, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	36	20	17	12	16	13	11	13	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg / PN0019 Expiry Date: May 2012 Date of testing : Dec. 13, 2008	100 mg Tablets	12	Mean	4	7	9	11	13	15	16	18	
				Range	(b) (4)								
				%CV	15	10	9	9	9	7	8	7	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : Dec.10, 2008	200 mg Tablets	12	Mean	1	2	3	4	5	6	6	7	Refer Page No. 65-69, Exhibit-II of the same submission.
				Range	(b) (4)								
				%CV	27	21	15	11	10	9	10	8	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / PN0149 Expiry Date: May 2012 Date of testing : Dec. 04, 2008	200 mg Tablets	12	Mean	4	7	10	12	14	16	18	20	
				Range	(b) (4)								
				%CV	12	0	5	6	5	5	4	3	

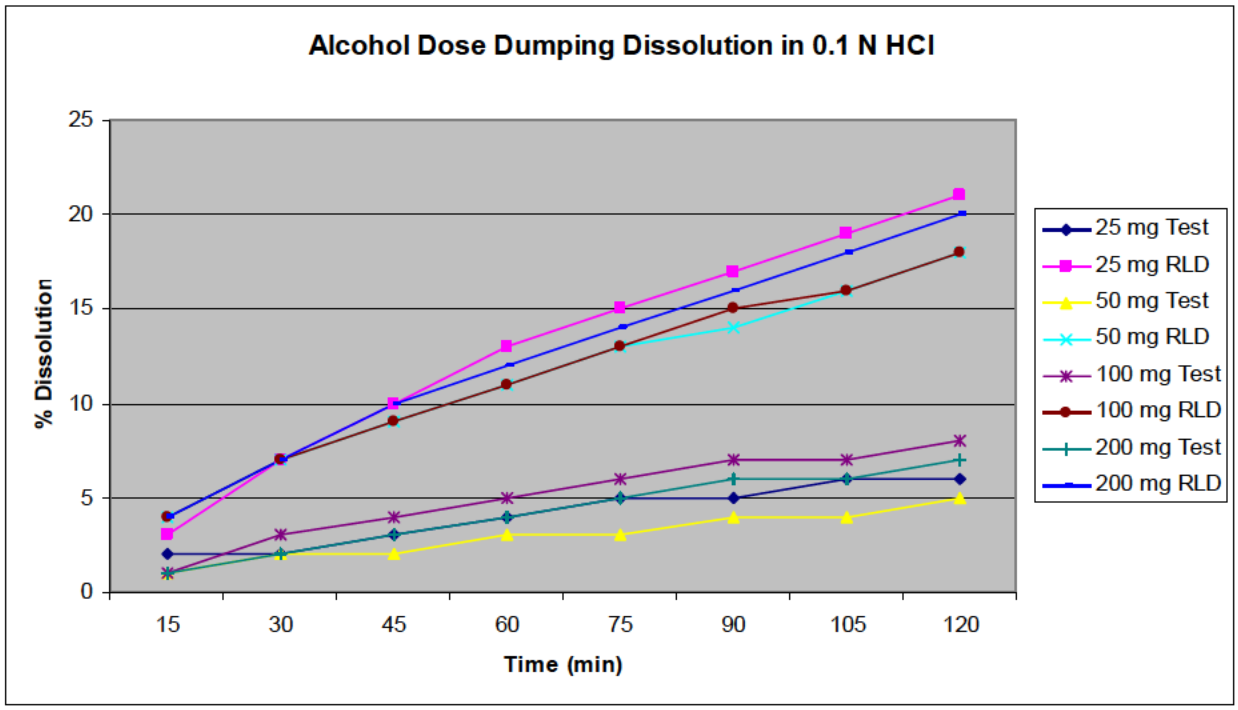
Figure 4. Dissolution Profiles

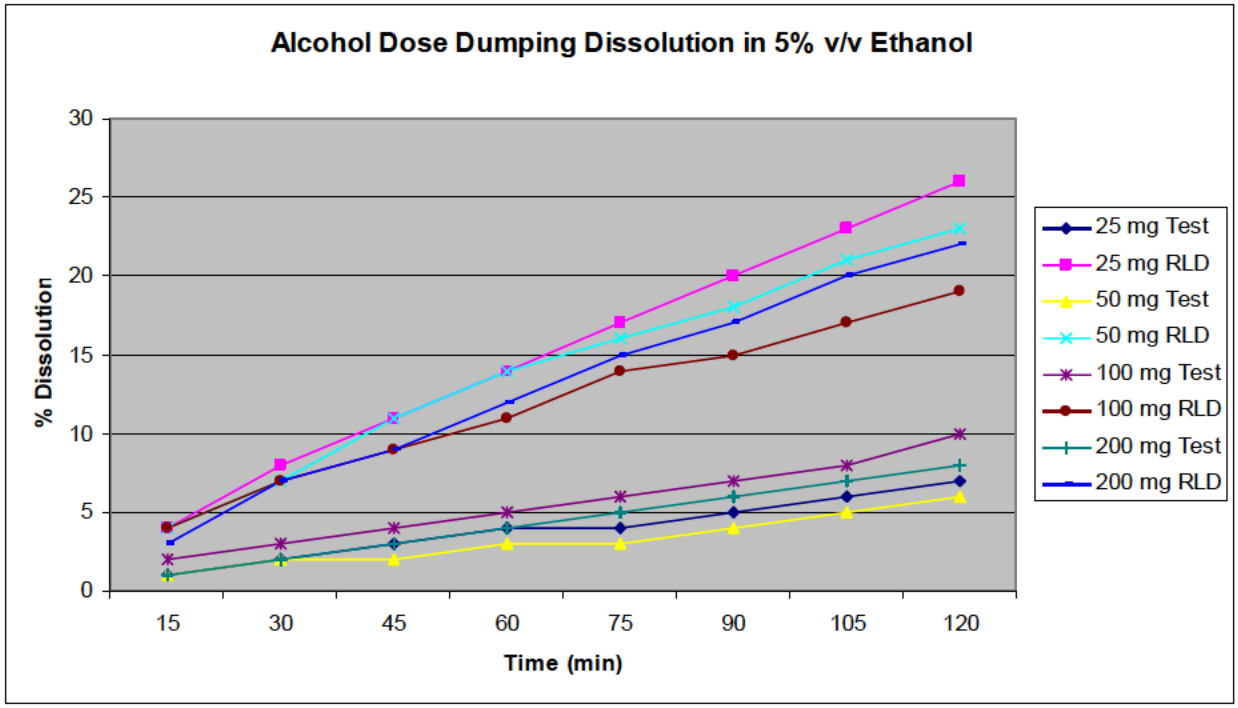


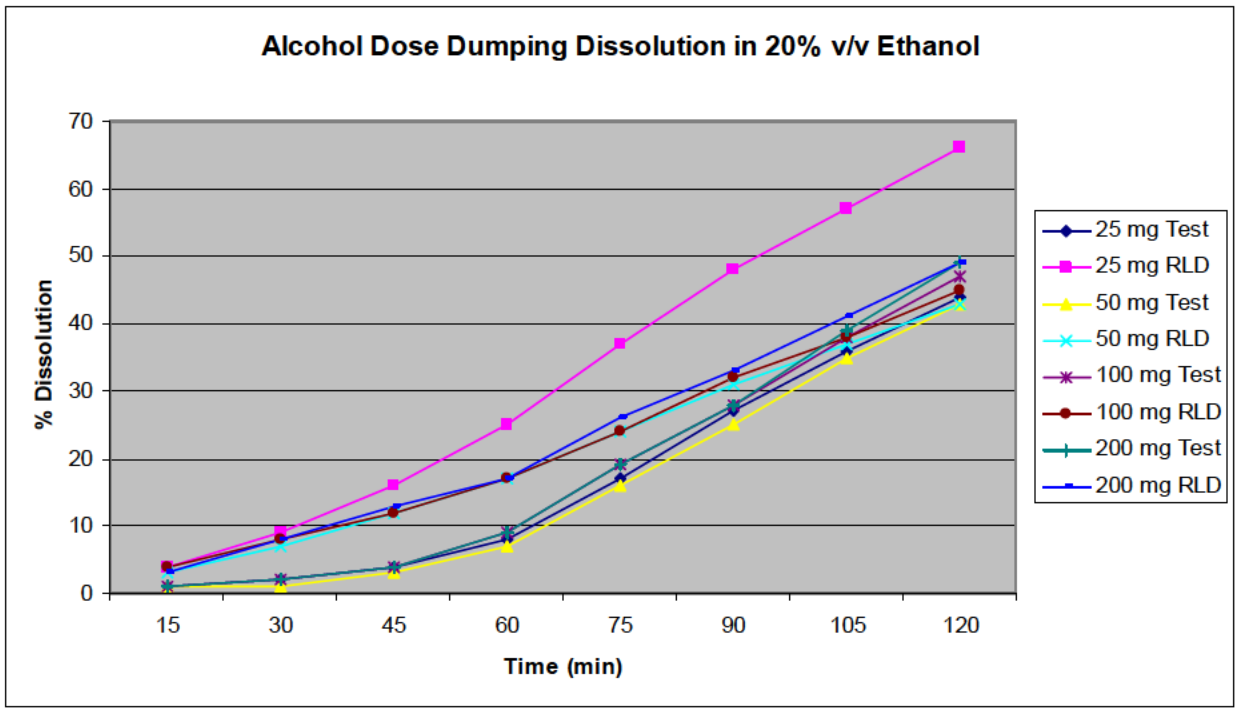


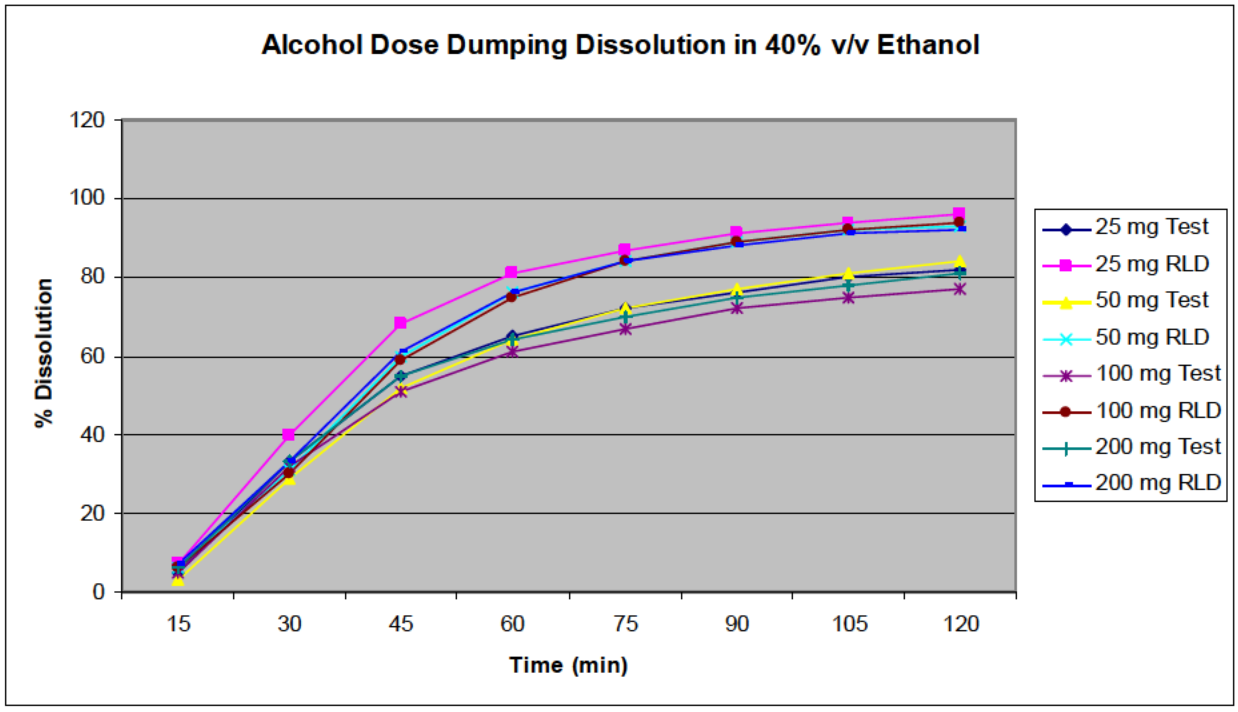

Metoprolol Succinate ER Tablets pH 4.5 Acetate Buffer
% Dissolution
120
100
80
60
40
20
0
1
2
4
6
8
10
12
16
20
24
Time (hr)
25 mg Test
25 mg RLD
50 mg Test
50 mg RLD
100 mg Test
100 mg RLD
200 mg Test
200 mg RLD

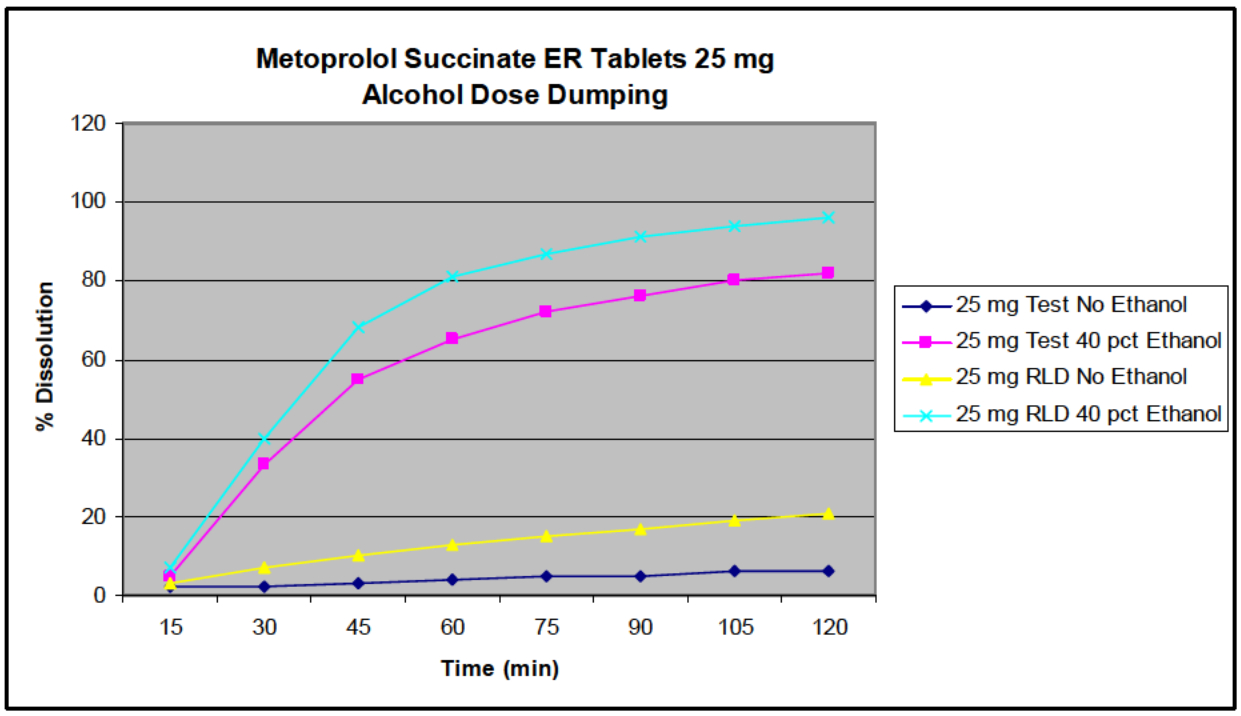

Metoprolol Succinate ER Tablets Water
% Dissolution
120
100
80
60
40
20
0
1
2
4
6
8
10
12
16
20
24
Time (hr)
25 mg Test
25 mg RLD
50 mg Test
50 mg RLD
100 mg Test
100 mg RLD
200 mg Test
200 mg RLD

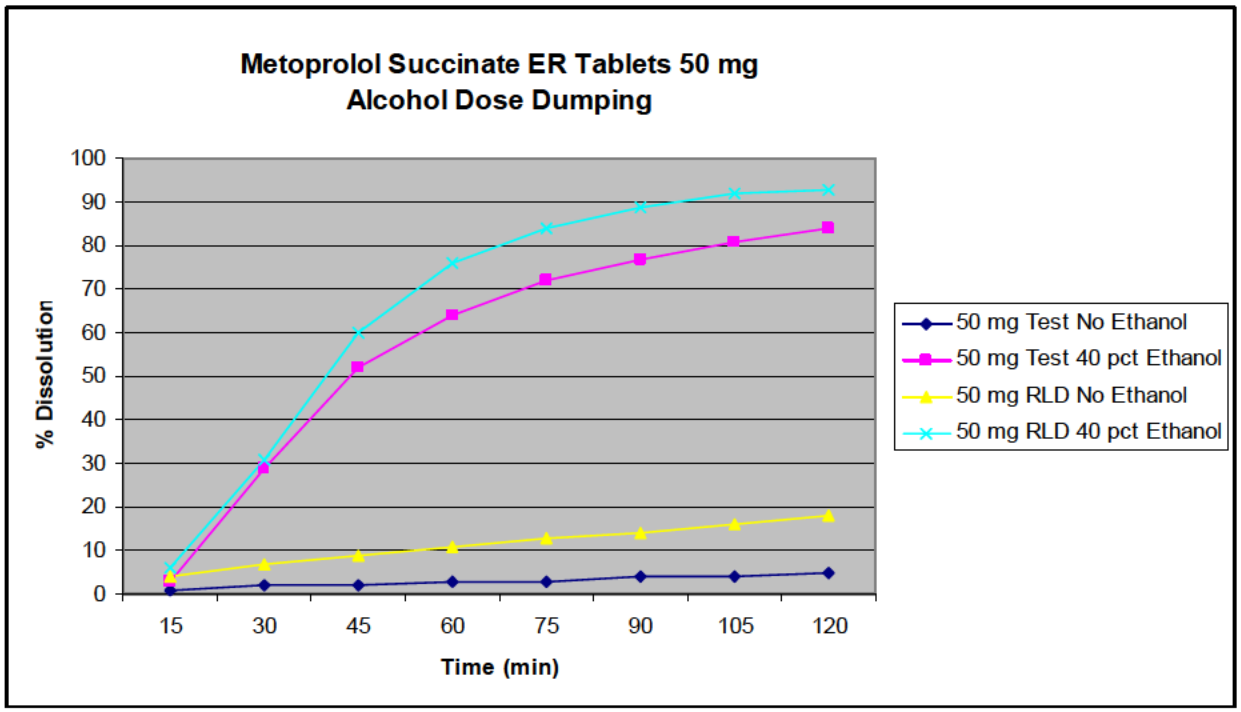

Alcohol Dose Dumping Dissolution in 0.1 N HCl
% Dissolution
Time (min)
0
5
10
15
20
25
15
30
45
60
75
90
105
120
25 mg Test
25 mg RLD
50 mg Test
50 mg RLD
100 mg Test
100 mg RLD
200 mg Test
200 mg RLD

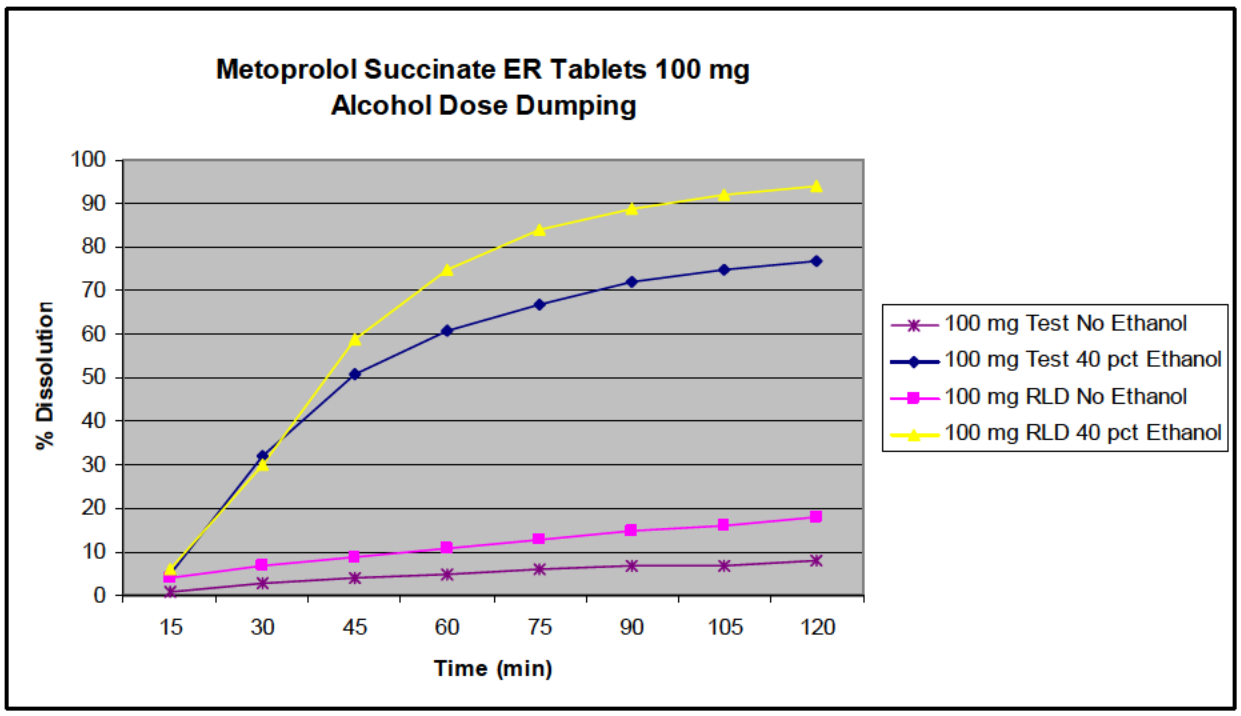

Alcohol Dose Dumping Dissolution in 5% v/v Ethanol
% Dissolution
Time (min)
0
5
10
15
20
25
30
15
30
45
60
75
90
105
120
25 mg Test
25 mg RLD
50 mg Test
50 mg RLD
100 mg Test
100 mg RLD
200 mg Test
200 mg RLD

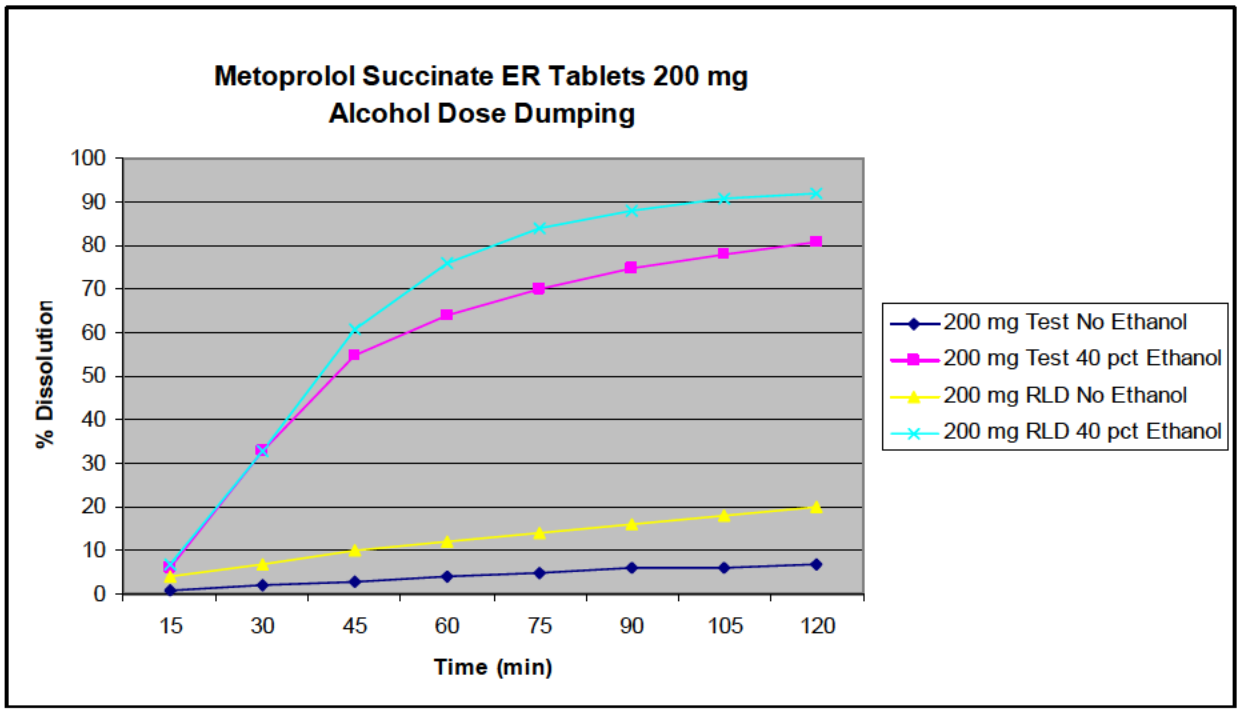

Alcohol Dose Dumping Dissolution in 20% v/v Ethanol
% Dissolution
Time (min)
0
10
20
30
40
50
60
70
15
30
45
60
75
90
105
120
25 mg Test
25 mg RLD
50 mg Test
50 mg RLD
100 mg Test
100 mg RLD
200 mg Test
200 mg RLD


Alcohol Dose Dumping Dissolution in 40% v/v Ethanol
% Dissolution
Time (min)
0
20
40
60
80
100
120
15
30
45
60
75
90
105
120
25 mg Test
25 mg RLD
50 mg Test
50 mg RLD
100 mg Test
100 mg RLD
200 mg Test
200 mg RLD


Metoprolol Succinate ER Tablets 25 mg
Alcohol Dose Dumping
% Dissolution
120
100
80
60
40
20
0
15
30
45
60
75
90
105
120
Time (min)
25 mg Test No Ethanol
25 mg Test 40 pct Ethanol
25 mg RLD No Ethanol
25 mg RLD 40 pct Ethanol


Metoprolol Succinate ER Tablets 50 mg
Alcohol Dose Dumping
% Dissolution
100
90
80
70
60
50
40
30
20
10
0
15
30
45
60
75
90
105
120
Time (min)
50 mg Test No Ethanol
50 mg Test 40 pct Ethanol
50 mg RLD No Ethanol
50 mg RLD 40 pct Ethanol


Metoprolol Succinate ER Tablets 100 mg
Alcohol Dose Dumping
% Dissolution
Time (min)
100 mg Test No Ethanol
100 mg Test 40 pct Ethanol
100 mg RLD No Ethanol
100 mg RLD 40 pct Ethanol


Metoprolol Succinate ER Tablets 200 mg
Alcohol Dose Dumping
% Dissolution
Time (min)
200 mg Test No Ethanol
200 mg Test 40 pct Ethanol
200 mg RLD No Ethanol
200 mg RLD 40 pct Ethanol

% Metoprolol Succinate ER Tablet Dissolved in No Ethanol at 2 Hours				
	25 mg	**50 mg**	**100 mg**	**200 mg**
Test Product	6%	5%	8%	7%
RLD	21%	18%	18%	20%

% Metoprolol Succinate ER Tablet Dissolved in 5% Ethanol at 2 Hours				
	25 mg	**50 mg**	**100 mg**	**200 mg**
Test Product	7%	6%	10%	8%
RLD	26%	23%	19%	22%

% Metoprolol Succinate ER Tablet Dissolved in 20% Ethanol at 2 Hours				
	25 mg	**50 mg**	**100 mg**	**200 mg**
Test Product	44%	43%	47%	49%
RLD	66%	43%	45%	49%

% Metoprolol Succinate ER Tablet Dissolved in 40% Ethanol at 2 Hours				
	25 mg	**50 mg**	**100 mg**	**200 mg**
Test Product	82%	84%	77%	81%
RLD	96%	93%	94%	92%

Reviewer's Comment:

For products that exhibit alcohol dose dumping, the DBE compares the % dissolved at 2 hours in 0.1 N HCl with no alcohol to the % dissolved at 2 hours in 40% ethanol/60% 0.1 N HCl (v/v) for the test product. For all strengths of the test product, Metoprolol Succinate ER Tablets, the % dissolved at 2 hours is not comparable for no ethanol versus 40% ethanol. However, for the all strengths of the test and reference products, the % dissolved at 2 hours in 40% ethanol is comparable. Therefore, the DBE concludes that the risk of dose dumping from the test product is the same as for Toprol-XL®.

4.4 Detailed Regulatory History (If Applicable)

Protocols Reviewed
08-066: [redacted](b) (4) (Completed 11/8/2008)

Controls Reviewed (Since 2003)

03-313	[redacted](b) (4)	4/22/2003
03-642		8/1/2003
03-971		12/15/2003
04-548		5/28/2004
04-630		6/10/2004
04-635		6/17/2004
05-0174		2/9/2005
05-0478		4/25/2005
05-0579		5/4/2005
05-0912		7/14/2005
05-1214		9/19/2005
05-1225		9/20/2005
06-0871		6/5/2006
06-1192		8/18/2006
07-0400		2/15/2007
07-0506		3/23/2007

Other ANDA's

76-640 (KV): Approved 5/18/2007 (200 mg, 100 mg)
77-779 (KV): Approved 3/20/2008 (25 mg)
77-176 (KV): Approved 5/14/2008 (50 mg)
76-969 (Sandoz): Approved 7/31/2006 (25 mg)
76-969 (Sandoz): Approved 5/18/2007 (50 mg)
76-969 (Sandoz): Approved 3/20/2008 (100 mg, 200 mg)

4.5 Consult Reviews

None.

4.6 SAS Output

4.6.1 50 mg Fasting Study Data

FASTING CONCENTRATION DATASET

(b) (4)

Following this page, 106 pages withheld in full (b)(4)-SAS Output

4.7 Abbreviated Review of Metoprolol 50 mg Fed Study

4.7.1 Single-dose 50 mg Fed Bioequivalence Study

4.7.1.1 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1
Bioanalytical method validation report location	Page No. 631-679, Module 5, Volume 1.3 Page No. 3525-3543, Module 5, Volume 1.9
Study Report Number	MVR-METO-001-07
Analyte	Metoprolol
Internal standard (IS)	(b) (4)
Method description	High Performance Liquid Chromatography Mass Spectrometric Method
Lower Limit of Quantification (ng/mL)	0.502
% recovery (and %CV) at each concentration tested	1.503 ng/mL: 26.75% 85.380 ng/mL: 29.28% 170.761 ng/mL: 30.32% Overall Recovery: 28.783% (6.38%)
Average recovery of IS (%) (and %CV)	32.22%
Standard curve concentrations (ng/mL)	0.502, 2.511, 5.001, 10.002, 25.006, 50.011, 100.023, 200.045
QC concentrations (ng/mL)	LLOQ: 0.502 LQC: 1.503 MQC: 85.380 HQC: 170.761
QC Intra-day precision range (%)	1.65 to 15.20%
QC Intra-day accuracy range (%)	108.95 to 110.17%
QC Inter-day precision range (%)	3.44 to 13.48%
QC Inter-day accuracy range (%)	107.15 to 108.25%
Bench-top stability (6 hrs) Precision (%) Accuracy (%)	 1.58 to 6.80% 101.77 to 102.12%
Stock stability Room Temperature for 8 hrs (%) Refrigerated for 7 days (%)	 100.93% 104.17%
Processed stability (24 hrs) Precision (%) Accuracy (%)	 1.40 to 2.53% 102.33 to 102.38%
Freeze-thaw stability (3 cycles) Precision (%) Accuracy (%)	 1.21 to 9.01% 99.14 to 103.13%
Long-term storage stability (7 days)	

Below -50°C Precision (%) Accuracy (%) **Below -20°C** Precision (%) Accuracy (%)	 1.54 to 10.00% 105.64 to 108.33% 0.45 to 3.12% 105.40 to 110.17%
Long-term storage stability (126 days) **Below -50°C** Precision (%) Accuracy (%) **Below -20°C** Precision (%) Accuracy (%)	 0.96 to 6.48% 92.43 to 102.45% 1.24 to 3.36% 88.34 to 101.70%
Dilution integrity **Four times dilution** Precision (%) Accuracy (%) **Two times dilution** Precision (%) Accuracy (%)	 1.66% 101.55% 3.25% 103.40%
Selectivity	No significant interference from endogenous components was observed at retention time of analyte and IS in all the human plasma batches screened.
Sensitivity Precision (%) Accuracy (%)	 5.00% 105.12%

4.7.1.2 In Vivo Studies

Table 50. Summary of *in vivo* Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{∞} (ng*hr/mL)	$T½$ (hr)	K_{el} (hr^{-1})	
CPB-059-2007	**Efficacy:** To assess bioavailability of Metoprolol succinate 50 mg extended release tablets (Wockhardt Limited, India) and compare with Toprol-XL® (containing Metoprolol succinate 50 mg) tablets (AstraZeneca, USA) in 32 normal, adult, human subjects under fed condition.	A single center, randomized, single dose, open-label, analyst-blind, two-treatment, two-period, two-sequence, crossover comparative bioavailability study under fed condition.	**Test Product (A):** Metoprolol succinate 50 mg ER tablets (Manufactured by Wockhardt Limited, India) Oral Batch No: LG10845 **Reference Product (B):** Toprol-XL® tablets (containing Metoprolol succinate 50 mg) (Manufactured by: AstraZeneca, USA) Oral Batch no: LT0026	**Participated Subjects:** 32 healthy male subjects **Mean age:** 24.1 ± 4.10 (19 - 33) **Clinical Phase Completed Subjects:** 30 healthy male subjects **Mean age:** 24.1 ± 4.03 (19 - 33) **Considered for PK & Statistical Analyses:** 30 healthy male subjects **Mean age:** 24.1 ± 4.03 (19 - 33)	47.23 (23.86)	12.00 (5.00 – 20.00)	935.47 (38.14)	951.81 (39.84)	5.51 (20.17)	0.13 (19.01)	**Page No. 3053, Module 5, Volume 1.8**
					45.72 (28.04)	7.50 (3.00 – 16.00)	912.34 (43.00)	934.47 (44.19)	6.12 (32.80)	0.12 (27.59)	

Table 51. Reanalysis of Study Samples

50 mg Fed Study, Study No. CPB-059-2007 Location: Page No. 3450 and 3460-3463, Module 5, Volume 1.8								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
ISV (Internal Standard Variation)	0	1	0.00	0.08	0	1	0.00	0.08
RAB (Rejected Analytical Batch)	20	20	1.56	1.56	20	20	1.56	1.56
UAC (Unacceptable Chromatography)	20	20	1.56	1.56	20	20	1.56	1.56
Total	**40**	**41**	**3.12**	**3.20**	**40**	**41**	**3.12**	**3.20**

Note: 40 samples of test product and 41 samples of reference product were reanalyzed.
Total no. of samples analyzed: 1281 (excluding 64 PD & 64 PD+IS samples, as these cannot be assigned to either test or reference formulation).

4.7.1.3 Clinical Results

Table 52. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. CPB-059-2007			
		Treatment Groups	
		Test Product N = 30	Reference Product N = 30
Age (years)	Mean ± SD	24.1 ± 4.03	24.1 ± 4.03
	Range	19-33	19-33
Age Groups	< 18	0	0
	18 – 40	30 (100 %)	30 (100 %)
	41 – 64	0	0
	65 – 75	0	0
	> 75	0	0
Sex	Male	30 (100 %)	30 (100 %)
	Female	0	0
Race	Asian	30 (100 %)	30 (100 %)
	Black	0	0
	Caucasian	0	0
	Hispanic	0	0
	Other	0	0
BMI (kg/m^2)	Mean + SD	21.99 ± 2.001	21.99 ± 2.001
	Range	18.4 – 24.9	18.4 – 24.9
Other Factors		Nil	Nil

Table 53. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
30	Withdrawn from study due to adverse event of vomiting	I	N/AP
31	Not reported to facility (dropout)	II	N/AP

Table 54. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. CPB-059-2007	
	Test	Reference
Body as a whole		
Fever	---	1 (3.13%)*
Cardiovascular	Nil	
Gastrointestinal		
Vomiting	1 (3.13%)*	---
Post Study Assessment		
Anaemia	1 (3.13 %)*	
Eosinophilia	2 (6.25 %)*	
Rise in Alkaline Phosphatase levels	1 (3.13 %)*	
Neutropenia	1 (3.13 %)*	
Lymphocytosis	1 (3.13 %)*	
Total	**8 (25.00 %)**	

Note:
32 subjects participated in this study.
*- Adverse events are related unlikely to studied drug.
- Percentage values are rounded off.

Table 55. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling time point deviations	-	08
Deviation in deep freezer temperature	-	-

4.7.1.4 Bioanalytical Results

Table 56. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study (CPB-059-2007) Metoprolol								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.506	1.264	2.504	5.007	12.518	25.036	50.071	100.143
Inter day Precision (%CV)	2.86	6.92	4.98	3.81	3.56	4.57	3.46	3.07
Inter day Accuracy (%Actual)	100.83	99.04	98.33	99.40	97.94	100.04	100.40	103.89
Linearity (range of r^2)	0.992 to 0.999							
Linearity Range (ng/mL)	0.506 to 100.143							
Sensitivity/LOQ (ng/mL)	0.502							

Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (ng/mL)	1.489	41.365	82.730
Inter day Precision (%CV)	9.89	6.10	5.58
Inter day Accuracy (%Actual)	99.70	104.06	104.25

Table 57. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CPB-AP-011-01	05/24/2006	Reporting of Bioanalytical Results
CPB-AP-011-02	12/26/2007	Reporting of Bioanalytical Results

4.7.1.5 Pharmacokinetic Results

Table 58. Geometric Means and 90% Confidence Intervals - Firm Calculated

Metoprolol Succinate Extended Release Tablets 1 x 50 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. CPB-059-2007					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	880.2313	831.7400	1.0583	96.26	116.35
AUC∞ (hr *ng/ml)	892.6747	850.3326	1.0498	95.57	115.31
Cmax (ng/ml)	46.0255	44.0164	1.0456	98.50	111.00

4.8 Additional Attachments

4.8.1 Black Box Warning

Ischemic Heart Disease:

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1−2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TOPROL-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TOPROL-XL therapy abruptly even in patients treated only for hypertension.

4.8.2 Memorandum on Alcohol Dose-Dumping

(V:\DIVISION\BIO\farrarj\Xiaojian\New reviewer tool\alcohol dose dumping\barbaramemo.pdf)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 16, 2007

FROM: Barbara M. Davit, J.D., Ph.D.
Deputy Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

SUBJECT: In vitro study to compare potential for dose-dumping in the presence of ethanol between Toprol-XL® and potential generic Metoprolol Succinate Extended-Release Tablets

TO: ANDA 76640
ANDA 76862
ANDA 76969
ANDA 77176
ANDA 77779

Introduction: Under normal conditions of use, extended-release drug products are intended to release drug slowly into the systemic circulation. The drug plasma profile observed following administration of an extended-release drug product is frequently characterized by a slow rise, followed by sustained levels, after which there is a slow decline. Thus, extended-release formulations offer the advantage to patients that fluctuations in plasma concentrations are minimized. Many extended-release drug products are intended for administration once a day.

Dose-dumping is a term that describes the rapid release of an active ingredient from an extended release oral drug product into the bloodstream. In 2005, the FDA acquired information that when the extended-release tablet formulation Palladone®

(hydromorpone hydrochloride) was taken with alcohol, the extended-release mechanism was harmed, leading to dose-dumping. As the consequences of dose-dumping could lead to serious or even fatal adverse events in some patients, the FDA asked the marketer of Palladone® to withdraw the product from the market.

Due to FDA's concerns that ingested alcohol can potentially cause dose-dumping from certain extended-release drug products, a CDER interdisciplinary working group developed an in vitro test to evaluate the potential for dose-dumping in the presence of alcohol (in vitro dose-dumping test).[5] Briefly, the test evaluates the effect of increasing ethanol content on drug release from the dosage form. The in vitro dose dumping test will help to assure that any potential for dose dumping in the presence of alcohol would be comparable for a generic extended-release drug product and its corresponding reference listed drug (RLD). Where appropriate, OGD will ask applicants who submitted ANDAs for generic modified release solid oral dosage forms to use the test and submit it to the Division of Bioequivalence (DBE) for evaluation.

This memo (1) describes the in vitro dose-dumping test; (2) explains why the test is necessary to evaluate the performance of generic metoprolol succinate ER tablets; and (3) clarifies how in vitro test results will be analyzed.

Background: For metoprolol succinate ER tablets, the RLD is Toprol-XL®. Toprol-XL® is indicated for the treatment of hypertension.[6] The active ingredient in Toprol-XL®, metoprolol, is a beta$_1$-selective (cardioselective) adrenoceptor blocking agent. Because it is an extended-release formulation, Toprol-XL® is given once daily. The usual initial dosages are 25 to 100 mg/day for hypertension, 100 mg/day for angina pectoris, 25 mg/day for patients with NYHA Class II heart failure, and 12.5 mg/day in patients with more severe heart failure. For hypertension and angina, the dosage may be increased at weekly or longer intervals until optimum clinical response is optimal. Dosages above 400 mg/day have not been studied for hypertension or angina. For heart failure patients, the dosage may be increased once every two weeks either up to the highest level tolerated by the patient or up to 200 mg/day. Dosage must be individualized and closely monitored during up-titration. Worsening cardiac failure may occur during up-titration of Toprol-XL®.

Thus, high levels of metoprolol can produce serious adverse events in cardiac patients. As stated above, 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

[5] The interdisciplinary working group was comprised of CDER scientists from the Office of Generic Drugs (OGD), Office of Drug Evaluation II (ODEII), Office of New Drug Quality Assessment (ONDQA), and Office of Testing.

[6] Toprol-XL® package insert, ©2005, Astra-Zeneca LP, Wilmington, DE.

excessive bradycardia, hypotension, and perhaps ischemic stress.[7] It is not known if ethanol will cause extended-release formulations of metoprolol succinate to dose-dump. However, because patients may be switched from Toprol- XL® to generic metoprolol succinate ER tablets (once these products are on the market), it is important to provide assurance that ethanol will have the same effects on metoprolol release from a generic metoprolol succinate ER tablet and Toprol-XL®. The in vitro dose dumping test is a simple way to screen the performance of the generic formulations compared to the performance of the RLD.

Description of the in vitro dose dumping test: The DBE recommends that the starting conditions for the in vitro dose dumping test of metoprolol succinate ER tablets used the following initial conditions: (1) 900 mL of 0.1 N hydrochloric acid (HCl) media; (2) the USP Apparatus II (paddles) at a rotational speed of 50 rpm: (3) a temperature of 37ºC.[8] For the in vitro dose dumping test, increasing amounts of ethanol are added to the 0.1 N HCl medium.[9] The same dissolution conditions are used as for the regulatory method. The dissolution performance of the generic (test) product and Toprol-XL® are compared at the various ethanol concentrations. Differing amounts of ethanol are added to the 0.1 N HCl media on a volume/volume (v/v) basis to give the following percentages:

- % ethanol (no ethanol added)
- 5% ethanol
- 20% ethanol
- 40% ethanol

Twelve (12) units of the test product and 12 units of Toprol-XL® are tested separately in 900 mL volumes of each medium. Samples of the media are taken once every 15 minutes until 2 hours is reached. The percent of labeled amount of metoprolol succinate dissolved in the medium (% dissolved) is calculated for each sample. Dissolution data are expressed as % dissolved.

Data analysis: The DBE compares the % dissolved at 2 hours in 0.1 N HCl with no ethanol to the % dissolved at 2 hours in 40% ethanol/60% 0.1 N HCl (v/v) for the test product. If the % dissolved is comparable for no ethanol versus 40% ethanol, the test product is considered robust and no further comparisons are needed. If, however, the % dissolved from the test product increases as the amount of ethanol in the media increases, then the DBE compares % dissolved data at 2 hours in 40% ethanol for the test product and Toprol-XL®. If for both products, the % dissolved at 2 hours in 40% ethanol is comparable, then the DBE concludes that the risk of dose dumping from the generic product is the same as for Toprol-XL®.

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[7] Email correspondence between Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products, CDER, FDA, and Mr. Gary Buehler, Director of the Office of Generic Drugs, CDER, FDA, April 27, 2007.

[8] The rotational speed of 50 rpm (using USP Apparatus II) was chosen by DBE scientific staff based on dissolution data submitted to ANDAs for generic metoprolol succinate ER tablets. See email from Dr. Barbara Davit to Dr. Moheb Makary et. al., May 2, 2007.

[9] The CDER interdisciplinary working group recommended that 0.1 N HCl be used as the basic medium because it approximates the acidic solution that exists in the stomach in vivo.

OGD requests to generic applicants: OGD will ask all applicants who submitted ANDAs for generic metoprolol succinate ER tablet formulations to conduct an in vitro alcohol dose-dumping study. OGD will also ask applicants to submit: standard operating procedures (SOPs) for the dissolution testing, individual dissolution data, mean values, standard deviations, and plots of the % dissolved data. The requests will be to perform these studies as post approval commitments.[10]

[10] ANDA 76969 was approved on July 31, 2006. OGD regulatory evaluations of ANDAs 76440, 76862, 77176, and 77779 are pending.

4.8.3 Medical Consultation For ANDA 76-640

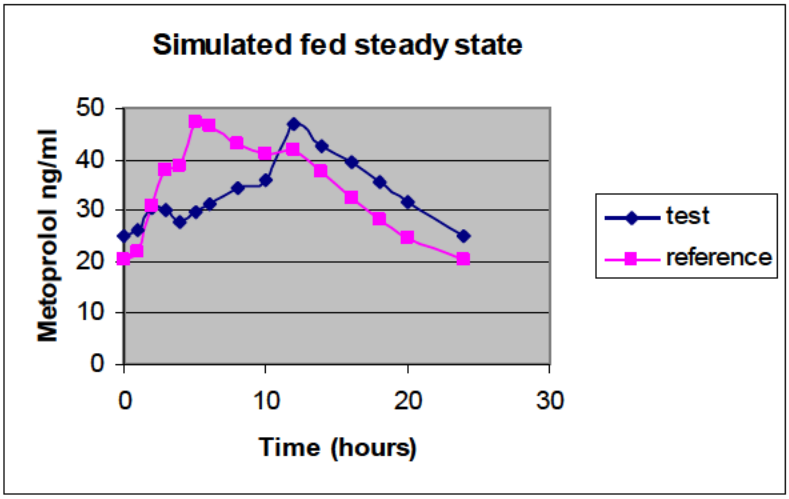
MEDICAL CONSULTATION

To:	**Shriniwas Nerurkar, PhD, DBE, OGD** **Hoainhon Nguyen, PhD, DBE, OGD**
Re:	**ANDA 76-640**
Drug Product:	**Metoprolol Succinate ER tablet** **100 and 200 mg**
Sponsor:	**KV**
RLD:	**Toprol-XL tablet** **AstraZeneca (19-962)**
Date of Review:	**March 16, 2006**
Consultant:	**Nancy Chang, M.D.** **Medical Officer, Office of Generic Drugs**
Through:	**Dena Hixon, M.D.** **Associate Director for Medical Affairs, OGD**

Reason for Consult

This application presented of single dose fasting and single dose fed BE studies of the 200 mg tablet. In both BE studies, Test Tmax is almost twice of the Reference Tmax (fasting: 13.4 versus 7.2 hours; fed: 11.5 versus 6.4 hours, respectively). The simulated steady state profiles show a similar pattern, with Cmin and Cmax approximating 20 ng/ml and 50 ng/ml, respectively. However, LAUC values and LCmax meet 90% C.I./point estimates, so the studies meet the usual criteria for BE. DBE is consulting the clinical team to evaluate for any safety or efficacy implications related to this difference in Tmax.

Figure: Simulation of steady state levels provided by Dr. Hoainhon Nguyen.



Metoprolol pharmacology

Labeling

Toprol-XL (metoprolol succinate) is a beta$_1$-selective adrenergic agent in an extended-release tablet intended for once-daily administration. It is indicated for the treatment of hypertension, the long-term treatment of angina pectoris, and the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. Available dosage strengths are 25, 50, 100, and 200 mg. The following information is derived from the TOPROL-XL labeling.

In healthy volunteers, the same daily doses of TOPROL-XL and immediate release metoprolol provide comparable total beta1-blockade over 24 hours (area under the beta1-blockade versus time curve) in the dose range 100-400 mg. However, at a dose of 50 mg once daily, TOPROL-XL produced significantly higher total beta1-blockade over 24 hours than immediate release metoprolol. The effects at peak/trough (i.e., at 24-hours post-dosing) were: 14/9, 16/10, 24/14, 27/22, and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg TOPROL-XL once a day, respectively. In contrast, immediate release metoprolol given at a dose of 50-100 mg once a day produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Beta$_1$-blocking effects in the range of 30-80% of the maximal effect correspond to metoprolol plasma concentrations from 30-540 nmol/L.

Plasma levels are highly variable after oral administration of TOPROL-XL, and the plasma half-life ranges from approximately 3-7 hours. Elimination is mainly by biotransformation in the liver, and metabolites appear to have no beta-blocking activity.

For treatment of hypertension and angina, when switching from immediate-release metoprolol to Toprol-XL, the same total daily dose should be used. Dosages should be individualized and titration may be needed. The lowest recommended starting doses are 25 mg, 100 mg, and 12.5 mg daily for hypertension, angina pectoris, and heart failure, respectively. For hypertension and angina pectoris, the Dosage and Administration section states that "Dosages above 400 mg per day have not been studied". For heart failure, the highest recommended dose is 200 mg.

In hypertension, the label reports lack of a consistent relationship of antihypertensive activity to drug plasma concentration.

The Lopressor (metoprolol tartrate tablets or injection) label provides some additional information:

Significant beta-blocking effect (reduction in exercise heart rate) occurs within 1 hour of oral administration of Lopressor, and its duration is dose-related. There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels.

Literature

Therapeutic drug concentrations of metoprolol for the treatment of heart failure are thought to be approximately 80-300 nM (Wikstrand et al., 2003 J Cardiovasc Pharmacol 41:151-7). Above 300 nM, there is minimal improved therapeutic effect, and there is a loss of $beta_1$-selectivity. A metoprolol concentration of approximately 89 nM will achieve half of the maximal effect.

Extended release metoprolol formulations are associated with a lower peak-to-trough fluctuation compared to IR formulations, along with a more consistent $beta_1$-blockade (Wikstrand et al., 2003 J Cardiovasc Pharmacol 41:151-7). Thus, with an extended release formulation, less time is spent at both at subtherapeutic levels and at supratherapeutic levels at which $beta_1$-selectivity is lost. A 200 mg daily dose of metoprolol succinate (extended release) has been reported to maintain cardioselectivity throughout the dosing period (Wikstrand 2000 Basic Res Cardiol 95; Suppl 1, 46-51). Unlike immediate-release atenolol (50 mg once a day), a 100 mg daily dose of metoprolol succinate (extended release) is not associated with detectable effects on subjective well-being throughout its dosing period (Dimenas et al., 1990 Eur J Clin Pharmacol 38:571-8). Despite these promising reports, even extended release formulations may exhibit undesirable dose-related pharmacological effects under some conditions. For example, Lofdahl et al. (1988 Eur J Clin Pharmacol 33 (Suppl):S25-S32) reported that after terbutaline infusions, asthmatic subjects on once-daily 200 mg controlled-release metoprolol succinate had significantly lower FEV_1 values compared to placebo, although at the 100 mg dose, no significant difference was found from placebo. This study was not designed to evaluate the extent to which this effect correlated with plasma levels of metoprolol.

The effect-time profiles for beta-blockade for both IR and ER formulations parallel the plasma concentration-time profile of metoprolol (Wikstrand 2000 Basic Res Cardiol 95, Suppl 1:I46-I51;; Sandberg 1988 Eur J Clin Pharmacol 33:S9-S14;;Oosterhuis et al., 1988 Eur J Pharmacol 33(Suppl):S15-8;; Bauman et al. 2004 J Cardiovasc Pharmacol Therapeut 9(2):117-28). Mean percentage peak-trough fluctuations of 79%, 470%, and 225% were reported with the following treatments: metoprolol succinate (ER) 100 mg daily, metoprolol tartrate (IR) 100 mg once daily, and metoprolol tartrate (IR) 50 mg twice daily. Mean Cmax and Cmin with daily administration of 100 mg metoprolol succinate (ER) were 163 nM and 67 nM, respectively (Sandberg 1988 Eur J Clin Pharmacol 33:S9-S14). The hemodynamic effects of metoprolol continue to fluctuate in parallel with plasma levels even after chronic treatment, with a trough to peak ratio in blood pressure reduction of 89% following treatment with 50 mg daily of the extended-release metoprolol succinate (Kukin et al., 1997 Heart 78:444-9;;Kukin et al. 2000 J Am Coll Cardiol 35:45-50).

Treatment with beta blockers, including metoprolol, has been associated with a decrease in myocardial ischemic episodes and an attenuation of the circadian variation in ischemic episodes (Egstrup 1991 Am Heart J 122:648-55;; Mulcahy et al. 1988 Lancet 755-8;;Imperi 1987 Am J Cardiol 60:519-24).

The timing and consistency of beta blockade may be of importance in providing its clinical benefits. For example, the increase in heart rate and risk of cardiac events in the early morning and late afternoon hours may call for particular attention to optimal beta blockade during those times (Hjalmarson and Waagstein 2003 Lancet 363:1077). A study of once daily dosing with 100 mg controlled release metoprolol succinate found that, if clinically relevant $beta_1$-blockade is defined as a reduction in exercise heart rate of >10%, metoprolol succinate is effective over much of the dose interval (23 hours), and that 58% of subjects had effective $beta_1$-blockade at trough, 24 hours after dosing.

Despite the evidence above, the extent and relevance of fluctuations in blood levels to the clinical effect of metoprolol has been downplayed by some authors (Sanderson et al., 2005 Eur J Heart Fail 7:874-7). Sanderson et al. reported that the pattern of heart rate suppression over 24 hours was similar between metoprolol tartrate (IR) 50 mg administered twice a day and carvedilol 25 mg twice a day, even though carvedilol has a half-life twice as long as metoprolol tartrate. Limited data exist comparing the clinical outcomes after treatment with metoprolol tartrate (IR) and metoprolol succinate (ER). A retrospective analysis of post-infarction trials suggests that the clinical outcomes of treatment are similar between the two formulations (Herlitz et al., 1999 Cardiovasc Drugs Ther 13:127-35).

Discussion/Conclusions

Even after chronic administration, the clinical effects of TOPROL-XL fluctuate over the course of the day in parallel with plasma concentrations. While readily detectable, these fluctuations are relatively small in comparison to those observed with the immediate-release metoprolol tartrate formulation, and the clinical relevance of these fluctuations is

unknown. Although there has been some suggestion among experts that the timing of peak pharmacological effect relative to diurnal variations in ischemia may be relevant to the morbidity and mortality benefit of metoprolol treatment, the timing of dose administration is not generally discussed or specified in the labeling or in the literature. In addition, although the timing of peak pharmacological effect may also theoretically affect the timing of adverse events associated with beta blockade, there is no clear evidence to suggest that this is the case, or that patients or physicians manipulate the timing of dose administration to influence the timing of adverse effects.

Therefore, in the context of current clinical use and labeling, sustained release metoprolol succinate products that otherwise meet standard bioequivalence criteria (i.e. for Cmax and AUC) could still be considered therapeutically interchangeable even with a significant difference in Tmax.

Recommendations

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.

CC: Division File
HFD-600/Nancy Chang
HFD-600/Dena Hixon
HFD-650

Saved in:

V:\FIRMSAM\KV\Controls\76640C0705

V:\DIVISION\ClinicalTeam\Drug Files\

Printed in final on:

Endorsements: (final with dates)

HFD-600/Nancy Chang _____ March 16, 2006

HFD-600/Dena Hixon_____ March 16, 2006

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 90-615

APPLICANT: Wockhardt Limited

DRUG PRODUCT: Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg and 200 mg

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

Since your test product, Metoprolol Succinate Extended Release tablets and the reference product, TOPROL-XL tablets are scored and can be divided, please conduct dissolution testing on half tablets of all strengths of the test and reference drug products, using the following USP method:

Apparatus:	USP apparatus II (paddle)
Speed:	50 rpm
Medium:	6.8 phosphate buffer
Volume:	500 mL at 37°C

Please submit the dissolution data in electronic CTD format tables for all strengths of the test and reference products.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.9 Outcome Page

COMPLETED ASSIGNMENT FOR 90615 ID: 7098

Reviewer: Albano, Jennifer **Date Completed:**

Verifier: Stier, Ethan **Date Verified:**

Division: Division of Bioequivalence

Description: Metoprolol Succinate ER Tablets, USP, 25 mg, 50 mg, 100 mg, 200 mg

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Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
7245	5/7/2008	Bioequivalence Study	Fasting Study	1	1
7245	5/7/2008	Bioequivalence Study	Fasting Study	1	1
7245	5/7/2008	Bioequivalence Study	Fed Study	1	1
7245	5/7/2008	Bioequivalence Study	Abbreviated Review	1	1
7245	5/7/2008	Other	Dissolution Waiver	1	1
7245	5/7/2008	Other	Dissolution Waiver	1	1
7245	1/8/2009	Other	Dissolution Amendment	1	1
				Bean Total:	7

PRODUCTIVITY POINTS

ANDA: 90615

Typical BE Study Applications

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*
BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*
BE Study Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fed Study Total	*3*
Abbreviated Review	
BE Fed Study	1
Abbreviated Review Total	*1*
Dissolution Study/ Dissolution Waiver(s)	
Strength 1 (DIW)	0.5
Strength 2 (DIW)	0.5
Dissolution Study/Waiver Total	*2.0*
Study Amendment (s)	
Study Amendment Dissolution data new/resubmitted	1
Study Amendment Total	*1*
TOTAL:	***13.0***

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

/s/

Jennifer Albano
1/16/2009 10:24:36 AM
BIOPHARMACEUTICS

Ethan Stier
1/16/2009 02:57:57 PM
BIOPHARMACEUTICS

Moheb H. Makary
1/17/2009 09:44:16 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-615			
Drug Product Name	Metoprolol Succinate Extended Release Tablets, USP			
Strength(s)	25 mg, 50 mg, 100 mg and 200 mg			
Applicant Name	Wockhardt Limited			
Address	Wockhardt Towers, Bandra-Kurla Complex Bandra (East) Mumbai – 400051, India			
Applicant's Point of Contact	Dr. Brij Khera Wockhardt USA Inc., 135 Route 202/206 Bedminster, NJ 07921			
Contact's Telephone Number	908.234.9761 (973.257.4998)			
Contact's Fax Number	908.234.9748 (973.257.4999)			
Original Submission Date(s)	May 7, 2008			
Submission Date(s) of Amendment(s) Under Review	January 8, 2009 February 6, 2009 (current submission)			
Reviewer	Jennifer N. Albano, Ph.D.			
Study Number (s)	CPB-058-2007	CPB-059-2007	CPB-152-2007	CPB-153-2007
Study Type (s)	Fasting	Fed	Fasting	Fed
Strength (s)	50 mg	50 mg	200 mg	200 mg
Clinical Site	Clinical Pharmacokinetics & Biopharmaceutics Department, Wockhardt Limited			
Clinical Site Address	Mulund-Goregaon Link Road Bhandup (West), Mumbai – 400 078, India			
Analytical Site	Clinical Pharmacokinetics & Biopharmaceutics Department, Wockhardt Limited			
Analytical Site Address	Mulund-Goregaon Link Road Bhandup (West), Mumbai – 400 078, India			
OUTCOME DECISION	**ACCEPTABLE**			

1 EXECUTIVE SUMMARY

This is the review of a **study amendment.**

Wockhardt Limited previously submitted acceptable fasting (50 mg and 200 mg) and fed (200 mg) bioequivalence (BE) studies comparing the test product, Metoprolol Succinate Extended Release Tablets, USP, to the corresponding reference listed drug, Toprol-XL® (Metoprolol Succinate Extended Release Tablets, 50 mg and 200 mg) by AstraZeneca[1]. The firm requested waivers for the 25 mg and 100 mg strengths.

On January 8, 2009, the firm submitted alcohol dose dumping dissolution testing. For the test and reference products, the percentage dissolved at 2 hours in 5%, 20% and 40% ethanol is comparable. Therefore, the DBE concludes that the risk of dose dumping from the test product is the same as for Toprol-XL®.

However, the application was incomplete because the firm had not submitted dissolution testing on half tablets using the current USP method for Metoprolol Succinate Extended Release Tablets. The firm submitted the response to this deficiency on February 6, 2009. The firm's dissolution testing showed that dissolution of the half-tab is comparable to the whole tablet. Therefore, the firm's response to the deficiency is **acceptable**.

The DBE deems the Metoprolol Succinate ER Tablets, the 25 mg and 100 mg bioequivalent to respective strengths of the reference listed drug under 21 CFR § 320.24 (b) (6).

The application is **acceptable**.

[1] Note: The firm submitted a fed study on the 50 mg strength, which is not requested by DBE.

2 TABLE OF CONTENTS

3 REVIEW OF CURREMT SUBMISSION

3.1 DBE Deficiency Comments

Deficiency:

Since your test product, Metoprolol Succinate Extended Release tablets and the reference product, TOPROL-XL tablets are scored and can be divided, please conduct dissolution testing on half tablets of all strengths of the test and reference drug products, using the following USP method:

Apparatus:	USP apparatus II (paddle)
Speed:	50 rpm
Medium:	6.8 phosphate buffer
Volume:	500 mL at 37°C

Please submit the dissolution data in electronic CTD format tables for all strengths of the test and reference products.

Firm's Response:

As requested by the agency, the dissolution testing data on half tablets of Wockhardt's Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg and 200 mg and the reference listed product TOPROL-XL Tablets, 25 mg, 50 mg, 100 mg and 200 mg is provided in **Exhibit-I.**

The dissolution profile data of half tablet of Wockhardt's Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg and 200 mg has been found to be satisfactory and is comparable to that of the reference product TOPROL-XL Tablets, 25 mg, 50 mg, 100 mg and 200 mg respectively. The dissolution profile testing data on half tablet of all the strengths of test product also meets the dissolution acceptance criteria as per the USP monograph of Metoprolol Succinate Extended Release Tablets USP.

Further as required by the agency, the summary of in-vitro dissolution studies performed on half tablet for all the strengths of test and reference products in CTD format tables is enclosed in an electronic format along with this submission (1 CD enclosed). For the ready reference of the agency, these tables are also provided in **Exhibit-II**.

Reviewer's Comment:

The firm has submitted dissolution testing on half tablets of the 25 mg, 50 mg, 100 mg, and 200 mg strengths of the test and reference products using the compendial USP method. The firm's response to the deficiency is acceptable (see data in Appendix below).

3.2 Deficiency Comments

None.

3.3 Recommendations

1. The Division of Bioequivalence (DBE) has previously accepted the fasting BE study (CPB-058-2007) conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 50 mg, Batch #LG10845, comparing it to AstraZeneca's Toprol-XL® (Metoprolol Succinate) ER Tablets, 50 mg, Batch #LT0026.

2. The DBE has previously accepted the fasting BE study (CPB-152-2007) conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 200 mg, Batch #LG10896, comparing it to AstraZeneca's Toprol-XL® (Metoprolol Succinate) Extended Release Tablets, 200 mg, Batch #MA0081.

3. The DBE has previously accepted the fed BE study (CPB-153-2007) conducted by Wockhardt Limited on its Metoprolol Succinate ER Tablets, USP, 200 mg, Batch #LG10896, comparing it to AstraZeneca's Toprol-XL® (Metoprolol Succinate) Extended Release Tablets, 200 mg, Batch #MA0081.

4. Dissolution testing conducted by Wockhardt Limited on half-tablets of Metoprolol Succinate ER Tablets, USP, 50 mg and 25 mg is **acceptable**. The firm has previously submitted acceptable multi-media dissolution testing on whole tablets May 7, 2008 and alcohol dose-dumping dissolution testing on whole tablets January 8, 2009. The formulation for the 25 mg strength is proportionally similar to the 50 mg strength of the test product that underwent bioequivalence testing. Therefore, the DBE deems the 25 mg strength test product to be bioequivalent to the corresponding RLD strength under the Section 21 CFR §320.24 (b) (6).

5. Dissolution testing conducted by Wockhardt Limited on half-tablets of Metoprolol Succinate ER Tablets, USP, 200 mg and 100 mg is **acceptable**. The firm submitted has previously submitted acceptable multi-media dissolution testing on whole tablets May 7, 2008 and alcohol dose-dumping dissolution testing on whole tablets January 8, 2009. The formulation for the 100 mg strength is proportionally similar to the 200 mg strength of the test product that underwent bioequivalence testing. Therefore, the DBE deems the 100 mg strength test product to be bioequivalent to the corresponding RLD strength under the Section 21 CFR §320.24 (b) (6).

6. The application is **acceptable.**

4 APPENDIX

4.1 Dissolution Data on Half-Tablets

Dissolution conditions:	
Apparatus:	USP Apparatus II (Paddle)
Speed of Rotation:	50 RPM
Medium:	pH 6.8 Phosphate Buffer
Volume:	500 mL
Temperature:	37 ± 0.5º C
Firm's Proposed Specifications	1 Hour: Not more than 25% of labeled amount of Metoprolol succinate dissolved 4 Hour: Between 20 and 40% of labeled amount of Metoprolol succinate dissolved 8 Hour: Between 40 and 60% of labeled amount of Metoprolol succinate dissolved 20 Hour: Not less than 80% of labeled amount of Metoprolol succinate dissolved
Site of testing : Wockhardt Limited, D-4, MIDC Area, Aurangabad, Maharashtra, India	

Study Ref No.	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date) Date of Analysis**	**Dosage Form& Strength**	**No. of Dosage Units Tested**		**Collection Times (Hours)**				**Study Report Location**
					1 Hour	**4 Hour**	**8 Hour**	**20 Hour**	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 25 mg /LG10872 Manufacturing Date: Oct. 2007 Date of testing : April 11, 2008	25 mg Tablets	12	Mean	4	23	57	98	Exhibit-I of Bioequivalence Amendment dated February 06, 2009
				Range	(b) (4)				
				%CV	46	11	9	7	
Study Report #:NA	TOPROL-XL ® Tablets, 25mg / PP0025 Expiry Date: June 2011 Date of testing : Feb. 04, 2009	25 mg Tablets	12	Mean	10	29	54	89	
				Range	(b) (4)				
				%CV	20	18	12	4	

Study Ref No.	Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)	Dosage Form& Strength	No. of Dosage Units Tested		Collection Times (Hours)				Study Report Location
					1 Hour	4 Hour	8 Hour	20 Hour	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 50 mg /LG10845 Manufacturing Date: Oct. 2007 Date of testing : April 10, 2008	50 mg Tablets	12	Mean	3	20	52	92	Exhibit-I of Bioequivalence Amendment dated February 06, 2009
				Range	(b) (4)				
				%CV	37	13	8	9	
Study Report #:NA	TOPROL-XL ® Tablets, 50mg / PN0016 Expiry Date: April 2012 Date of testing : Feb. 03, 2009	50 mg Tablets	12	Mean	10	26	49	86	
				Range	(b) (4)				
				%CV	35	18	11	7	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 100 mg /LG10874 Manufacturing Date: Oct. 2007 Date of testing : April 09, 2008	100 mg Tablets	12	Mean	4	21	51	92	Exhibit-I of Bioequivalence Amendment dated February 06, 2009
				Range	(b) (4)				
				%CV	19	10	5	3	
Study Report #:NA	TOPROL-XL ® Tablets, 100 mg PN0019 Expiry Date: May 2012 Date of testing : Feb 02, 2009	100 mg Tablets	12	Mean	10	25	46	83	
				Range	(b) (4)				
				%CV	16	12	8	9	
Study Report #:NA	Metoprolol Succinate Extended Release Tablets USP, 200 mg /LG10896 Manufacturing Date: Oct. 2007 Date of testing : April 07, 2008	200 mg Tablets	12	Mean	3	21	52	94	Exhibit-I of Bioequivalence Amendment dated February 06, 2009
				Range	(b) (4)				
				%CV	17	5	4	4	
Study Report #:NA	TOPROL-XL ® Tablets, 200 mg / PN0149 Expiry Date: May 2012 Date of testing : Jan. 30, 2009	200 mg Tablets	12	Mean	9	27	51	88	
				Range	(b) (4)				
				%CV	17	9	6	3	

4.2 Individual Dissolution Data

DISSOLUTION PROFILE OF *HALF TABLET* OF
Metoprolol Succinate Extended Release Tablets USP, 25mg (Wockhardt Ltd.)

Lot Number : LG10872
Mfg. Date : October, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Date of Analysis : April 11, 2008
Media : pH 6.8 Phosphate buffer
Volume : 500ml
Apparatus : USP Apparatus II (Paddle)
RPM : 50
Temp. : 37± 0.5° C

Tablet No.	% Drug Released			
	1 Hour	4 Hours	8 Hours	20 Hours
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	4	23	57	98
Min.				
Max.				
SD	2	3	5	6
%RSD	46	11	9	7

(b) (4)

DISSOLUTION PROFILE OF *HALF TABLET* OF
Metoprolol Succinate Extended Release Tablets USP, 50mg (Wockhardt Ltd.)

Lot Number : LG10845
Mfg. Date : October, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Date of Analysis : April 10, 2008
Media : pH 6.8 Phosphate buffer
Volume : 500ml
Apparatus : USP Apparatus II (Paddle)
RPM : 50
Temp. : 37± 0.5° C

Tablet No.	% Drug Released			
	1 Hour	4 Hours	8 Hours	20 Hours
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	3	20	52	92
Min.				
Max.				
SD	1	3	4	8
%RSD	37	13	8	9

(b) (4)

DISSOLUTION PROFILE OF *HALF TABLET* OF
Metoprolol Succinate Extended Release Tablets USP, 100mg (Wockhardt Ltd.)

Lot Number : LG10874
Mfg. Date : October, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Date of Analysis : April 9, 2008
Media : pH 6.8 Phosphate buffer
Volume : 500ml
Apparatus : USP Apparatus II (Paddle)
RPM : 50
Temp. : 37± 0.5° C

Tablet No.	% Drug Released			
	1 Hour	4 Hours	8 Hours	20 Hours
1				(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	4	21	51	92
Min.				(b) (4)
Max.				
SD	1	2	3	3
%RSD	19	10	5	3

DISSOLUTION PROFILE OF *HALF TABLET* OF
Metoprolol Succinate Extended Release Tablets USP, 200mg (Wockhardt Ltd.)

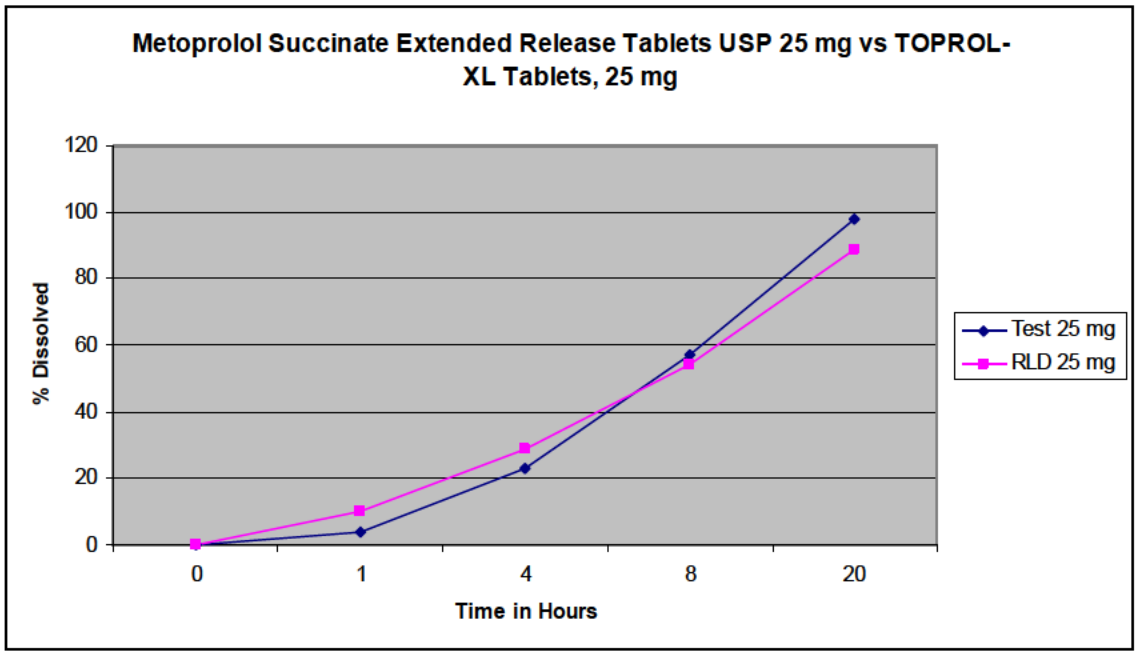
Lot Number : LG10896
Mfg. Date : October, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Date of Analysis : April 7, 2008
Media : pH 6.8 Phosphate buffer
Volume : 500ml
Apparatus : USP Apparatus II (Paddle)
RPM : 50
Temp. : 37± 0.5° C

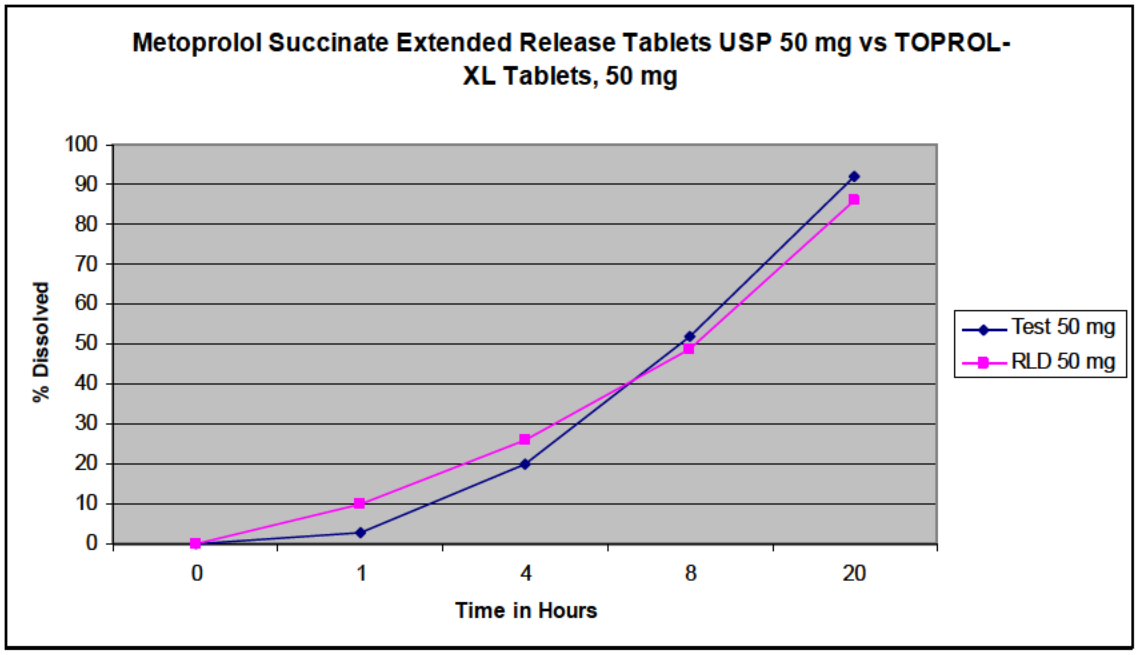
Tablet No.	% Drug Released			
	1 Hour	4 Hours	8 Hours	20 Hours
1				(b) (4)
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	3	21	52	94
Min.				(b) (4)
Max.				
SD	1	1 .	2	4
%RSD	17	5	4	4

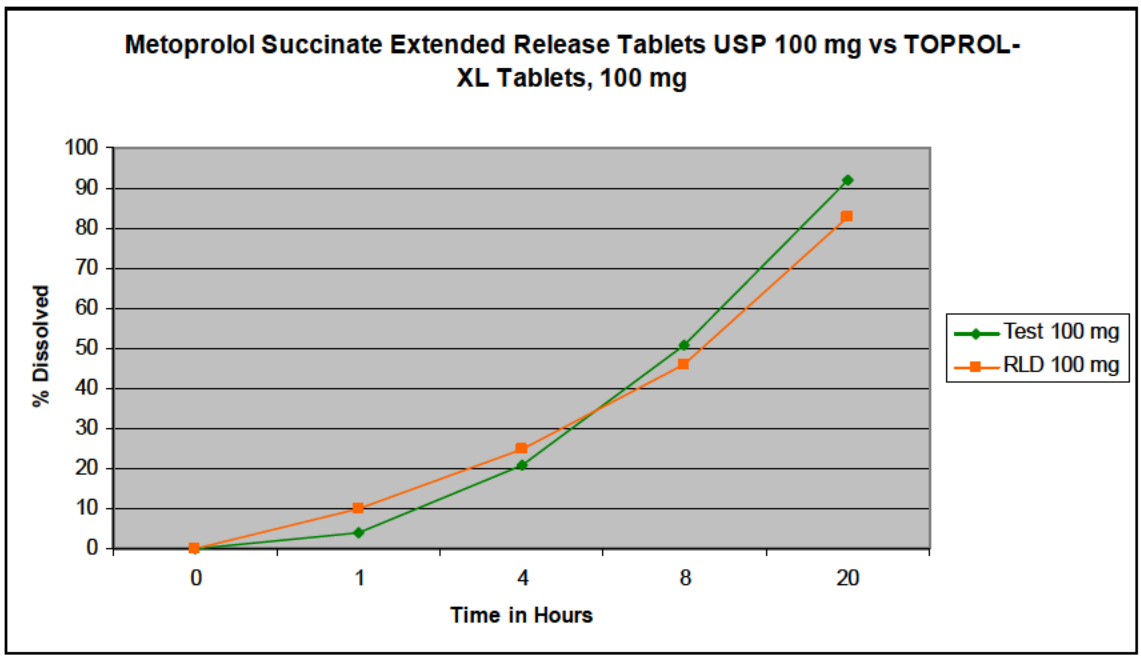
4.3 F2 Metric – Calculated by Reviewer

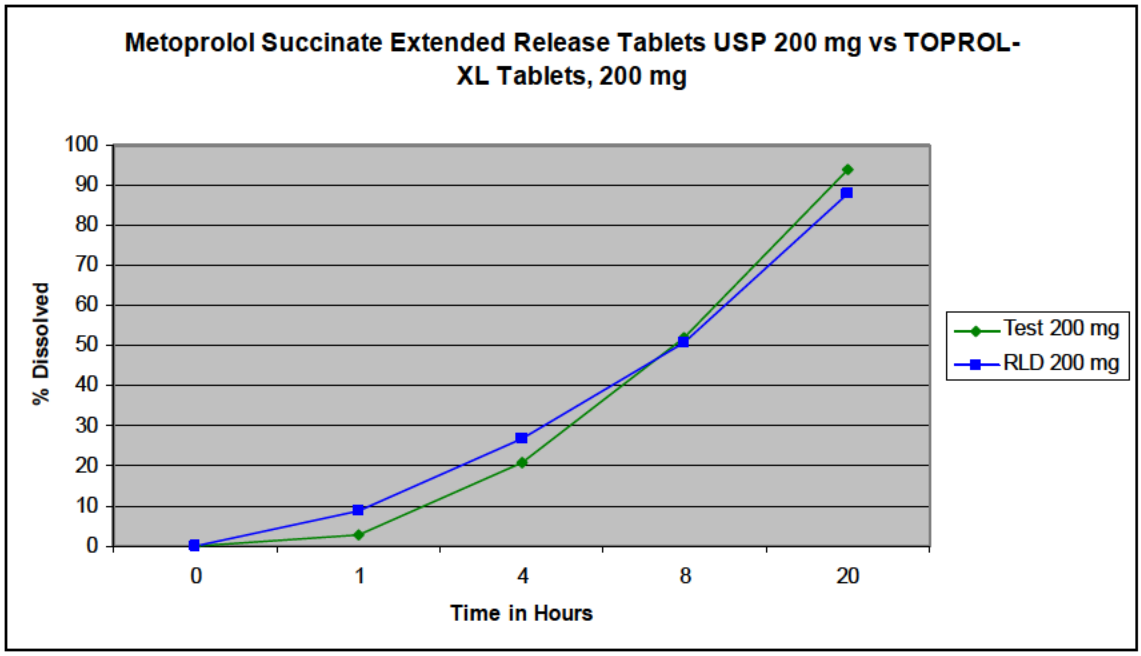
F2 metric calculated by reviewer, biostudy strengths compared to other strengths			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
50 mg	25 mg	78.19	81.89
200 mg	100 mg	94.90	79.68

4.4 Dissolution Profiles




Metoprolol Succinate Extended Release Tablets USP 50 mg vs TOPROL-XL Tablets, 50 mg
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
1
4
8
20
Time in Hours
Test 50 mg
RLD 50 mg


Metoprolol Succinate Extended Release Tablets USP 100 mg vs TOPROL-XL Tablets, 100 mg
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
1
4
8
20
Time in Hours
Test 100 mg
RLD 100 mg


Metoprolol Succinate Extended Release Tablets USP 200 mg vs TOPROL-XL Tablets, 200 mg
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
1
4
8
20
Time in Hours
Test 200 mg
RLD 200 mg

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-615

APPLICANT: Wockhardt Limited

DRUG PRODUCT: Metoprolol Succinate Extended Release Tablets USP, 25 mg, 50 mg, 100 mg and 200 mg

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

The DBE acknowledges that you will conduct future dissolution testing using the USP method and specifications for all strengths.

Medium	pH 6.8 phosphate buffer
Volume (mL)	500
USP Apparatus Type	II (Paddle)
Rotation	50 rpm
Dissolution Specifications	1 Hr: NMT 25 % 4 Hr: 20-40% 8 Hr: 40-60% 20 Hr: NLT 80%

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

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 90615

COMPLETED ASSIGNMENT FOR 90615 ID: 7564

Reviewer: Albano, Jennifer **Date Completed:**

Verifier: Stier, Ethan **Date Verified:**

Division: Division of Bioequivalence

Description: Metoprolol Succinate ER Tablets, USP, 25 mg, 50 mg, 100 mg, 200 mg

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7564	2/6/2009	Other	Study Amendment	1	1
				Bean Total:	1

PRODUCTIVITY POINTS

Study Amendment	
Study Amendment	1
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/

Jennifer Albano
3/5/2009 02:26:25 PM
BIOPHARMACEUTICS

Ethan Stier
3/10/2009 12:22:43 PM
BIOPHARMACEUTICS

Moheb H. Makary
3/10/2009 05:47:54 PM
BIOPHARMACEUTICS
for Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II