CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201089

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	201089	
Drug Product Name	Diclofenac Sodium/Misoprostol Delayed-Release Tablets	
Strength (s)	75 mg/0.2 mg	
Applicant Name	Watson Laboratories, Inc.-Florida	
Address	4955 Orange Drive Ft. Lauderdale, FL 33314	
Applicant's Point of Contact	Radha Goolabsingh, Manager Regulatory Affairs	
Contact's Phone Number	(954) 358-6147	
Contact's Fax Number	(954) 358-6350	
Submission Date(s)	December 23, 2009	
First Generic	No	
Reviewer	Kelly M. Kitchens, Ph.D.	
Study Number (s)	04131/09-10	04132/09-10
Study Type (s)	Fasting	Fed
Strength(s)	75 mg/0.2 mg	75 mg/0.2 mg
Clinical Site	Vimta Labs Ltd.,	
Clinical Site Address	Clinical Research Division 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA	
Analytical Site	Vimta Labs Ltd.	
Analytical Address	Room No's. 131B,140 & 133B Clinical Research Division Central Laboratory 142, IDA, Phase II, Cherlapally Hyderabad-500 051, India	
OUTCOME DECISION	**INADEQUATE**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm did not conduct the dissolution testing using the FDA-recommended method for Diclofenac Sodium/Misoprostol Delayed-Release Tablets. The firm proposed its own dissolution method and specifications:

Medium:	0.1 N HCl for acid stage of Diclofenac **Buffer (pH 6.8)** for buffer stage of Diclofenac Purified Water for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **990 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT Q) Diclofenac dissolved in 45 minutes (buffer stage) NLT Q) Misoprostol dissolved in 45 minutes

[Note: There is a discrepancy in the volume for the buffer stage: 990 mL in module 2.7.1.2 vs. 900 mL in module 3.2.P.2.2.3. The firm will be asked to clarify. It is also not clear how the firm prepared its Buffer (pH 6.8) for buffer stage. In addition, the firm did not submit data using its proposed method.]

The firm's proposed dissolution method is unacceptable. The DBE will request that the firm conduct dissolution testing on 12 dosage units of the 75 mg/0.2 mg strength of the test and reference products using the following FDA-recommended method:

Medium:	0.1 N HCl for acid stage of Diclofenac **750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8)** for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **1000 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Sampling times:	120 minutes for acid stage of Diclofenac 15, 30, 45, and 60 minutes for buffer stage of Diclofenac 10, 20, and 30 minutes for Misoprostol

The DBE will review the fasting and fed bioequivalence studies at a later date.

DSI Status:
There are no pending Division of Scientific Inspection (DSI) inspections for the clinical site. There is a pending DSI inspection for the analytical site for NDA (b) (4).

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	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present 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.					

FDA-recommended method for

Diclofenac/Misoprostol Enteric Coated (Arthrotec)

Dosage Form: Tablet

Medium: Diclofenac: Acid Stage: 0.1 N HCl Buffer Stage: 750ml 0.1N HCL+250ml 0.2M phos.buffer, pH 6.8 (Method A) Misoprostol: Water (deaerated)

Apparatus: II (Paddle) (diclo) II (Paddle) (miso

Speed/RPMs: 100 (diclo) 50 (miso)

Modify Date: 12/15/2005

Sampling Times: Diclo.: 120 (acid) 15, 30, 45 and 60 (Buffer). Miso:10, 20 and 30

Volume: Diclo: Acid: 750 Buffer:1000 Miso: 500

Notes: Specifications added by NT on 5/11/09 (EDR: Annual Report; N020607 Y 013 19-Dec-08)

Specification: Acid stage: NMT (b) (4) Buffer stage: NLT (b) (4)(Q), 45 min (Diclofenac) NLT (b) (4)(Q), 20 min (Misoprostol)

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.8 Phosphate Buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	90	Study Report Location
WSR1751, p.4	12/08/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	47	87	98	99	99	Module 2, Section 2.7.1.2
					Range	(b) (4)					
					%CV	8.6	5.9	1.3	1.3	1.3	
	12/07/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	52	90	100	100	100	
					Range	(b) (4)					
					%CV	8.7	5.6	1.4	1.2	1.2	

Note: Same as Table 5.1 in Module 2.7.1.2.

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	pH 6.0 Phosphate Buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**					**Study Report Location**
						15	**30**	**45**	**60**	**90**	
WSR1672, p.52	12/07/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	54	93	99	100	99	Module 2, Section 2.7.1.2
					Range	(b) (4)					
					%CV	6.7	3.4	1.1	1.1	1.0	
	12/07/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	56	92	99	99	100	
					Range	(b) (4)					
					%CV	7.8	3.6	1.4	1.6	1.6	

Note: Same as Table 5.2 in Module 2.7.1.2

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	Purified Water
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (min)**					**Study Report Location**
						15	**30**	**45**	**60**	**90**	
WSR1461, p.71	12/09/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	69	99	100	100	100	Module 2, Section 2.7.1.2
					Range	(b) (4)					
					%CV	3.7	2.2	1.4	1.2	1.4	
	12/08/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	63	94	99	100	99	
					Range	(b) (4)					
					%CV	8.9	4.1	1.1	1.2	1.0	

Note: Same as Table 5.3 in Module 2.7.1.2.

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (mins)**								**Study Report Location**
						15	**30**	**45**	**60**	**75**	**90**	**105**	**120**	
WSR1751, p.8	12/10/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	0	0	0	0	0	0	0	0	Module 2, Section 2.7.1.2
					Range	0	0	0	0	0	0	0	0	
					%CV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
	12/09/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	0	0	0	0	0	0	0	0	
					Range	0	0	0	0	0	0	0	0	
					%CV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

Note: Same as Table 5.4 in Module 2.7.1.2.

Dissolution Conditions		
	Apparatus:	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	40% Ethanol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (mins) 15	30	45	60	75	90	105	120	Study Report Location
WSR1672, p.59	12/10/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	0	1	1	4	15	20	37	47	Module 2, Section 2.7.1.2
					Range	(b) (4)								
					%CV	233.5	0.0	0.0	226.8	134.0	130.8	79.0	62.3	
	12/09/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	0	1	1	1	8	30	46	59	
					Range	(b) (4)								
					%CV	346.4	88.3	31.5	0.0	189.5	69.6	54.7	33.7	

Note: Same as Table 5.5 in Module 2.7.1.2

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 Phosphate Buffer
	Volume:	500 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes)**					**Study Report Location**
						10	**20**	**30**	**45**	**60**	
WSR1742, p.31, WSR1461, p.83	12/15/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	88	92	92	92	94	Module 2, Section 2.7.1.2
					Range	(b) (4)					
					%CV	4.2	2.9	2.6	2.0	2.8	
	12/14/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	82	90	93	95	96	
					Range	(b) (4)					
					%CV	11.9	9.4	6.3	6.8	4.1	

Note: Same as Table 5.6 in Module 2.7.1.2

Dissolution Conditions		
	Apparatus:	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 SGF
	Volume:	500 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	Study Report Location
WSR1742, p.22, WSR1751, p.11	12/12/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	67	71	71	66	63	Module 2, Section 2.7.1.2
					Range	[redacted] (b) (4)					
					%CV	17.0	3.4	5.3	2.4	2.6	
	12/12/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	70	73	72	69	65	
					Range	[redacted] (b) (4)					
					%CV	7.9	8.3	4.7	4.4	4.9	

Note: Same as Table 5.7 in Module 2.7.1.2.

Dissolution Conditions		
	Apparatus:	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 Acetate Buffer
	Volume:	500 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	Study Report Location
WSR1742, p.27, WSR1751, p.14	12/14/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022A (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	93	95	96	97	98	Module 2, Section 2.7.1.2
					Range	(b) (4)					
					%CV	4.8	2.8	1.9	2.0	2.5	
	12/14/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	82	88	92	94	98	
					Range	(b) (4)					
					%CV	10.6	6.5	4.3	3.4	2.8	

Note: Same as Table 5.8 in Module 2.7.1.2

II. COMMENTS:

1. The firm submitted *in vivo* fasting and fed bioequivalence study reports and summary tables for the 75 mg/0.2 mg strength tablets.

2. The firm did not conduct the dissolution testing using the FDA-recommended method for Diclofenac Sodium/Misoprostol Delayed-Release Tablets. The firm submitted the summary results of dissolution profiles generated in the following media using USP Apparatus II (Paddle) at 100 rpm for Diclofenac Sodium and at 50 rpm for Misoprostol (see Module 2.7.1.2):

    a. 900 mL pH 6.8 Phosphate Buffer (for both Diclofenac Sodium and Misoprostol)
    b. 900 mL pH 6.0 Phosphate Buffer (Diclofenac Sodium only)
    c. 900 mL Purified Water (Diclofenac Sodium only)
    d. 900 mL 0.1N HCl (Diclofenac Sodium only)
    e. 900 mL 40% Alcohol in 0.1N HCl (Diclofenac Sodium only)
    f. SGF pH 1.2 (Misoprostol only)
    g. Acetate Buffer pH 4.5 (Misoprostol only)

3. The firm proposed its own dissolution method and specifications as follows (see Module 2.7.1.2):

    For Diclofenac Sodium:

    USP Apparatus II (Paddle) at 100 rpm
    Acid Stage: 750 mL 0.1N HCl for 2 hours
    Buffer Stage: 990 mL Buffer pH 6.8
    Temperature: 37± 0.5 °C
    Specifications: NMT (b) (4) in 120 minutes (acid stage)
    NLT (b) (4) (Q) in 45 minutes (buffer stage)

    For Misoprostol

    USP Apparatus II (Paddle) at 50 rpm
    Medium (one stage): 500 ml of Purified Water at 37 ± 0.5 °C
    Specification: NLT (b) (4) (Q) Misoprostol dissolved in 45 minutes

    The firm did not submit the dissolution data using its proposed method. It is also not clear how the firm prepared its buffer pH 6.8 solution for the buffer stage. It should also be noted that the volume of buffer stage as stated in Module 2.7.1.2 (990 mL) is different from that stated in Module 3.2.P.2.2.3 (900 mL).

4. The firm submitted electronic SAS transport files (.xpt) in Module 5.3.1.2.25 Individual Subject Data Listing.

5. The DBE summary tables are located in Module 2.7 Clinical Summary.

III. DEFICIENCY COMMENTS:

The firm did not conduct the dissolution testing using the FDA-recommended method for Diclofenac Sodium/Misoprostol Delayed-Release Tablets. The firm proposed its own dissolution method and specifications:

Medium:	0.1 N HCl for acid stage of Diclofenac **Buffer (pH 6.8)** for buffer stage of Diclofenac Purified Water for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **990 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT (Q) Diclofenac dissolved in 45 minutes (buffer stage) NLT (Q) Misoprostol dissolved in 45 minutes

The firm's proposed dissolution method is unacceptable. The DBE will request that the firm conduct dissolution testing on 12 dosage units of the 75 mg/0.2 mg strength of the test and reference products using the following FDA-recommended method:

Medium:	0.1 N HCl for acid stage of Diclofenac **750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8)** for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **1000 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Sampling times:	120 minutes for acid stage of Diclofenac 15, 30, 45, and 60 minutes for buffer stage of Diclofenac 10, 20, and 30 minutes for Misoprostol

IV. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Watson Laboratories, Inc. - Florida on its Diclofenac Sodium/Misoprostol Delayed-Release Tablets, 75 mg/0.2 mg (lot # 0398R0022A), compared to GD Searle's ARTHROTEC® (Diclofenac Sodium/Misoprostol) Delayed-Release Tablets 75 mg/0.2 mg (lot # C081587) is **incomplete** due to the deficiencies cited above.

The firm should be informed of the deficiencies and recommendations.

BIOEQUIVALENCE DEFICIENCIES TO BE COMMUNICATED TO THE FIRM

ANDA: 201089

APPLICANT: Watson Laboratories, Inc. - Florida

DRUG PRODUCT: Diclofenac Sodium/Misoprostol Delayed-Release Tablets
75 mg/0.2 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 studies will be done at a later date.

The following deficiencies have been identified:

You did not conduct the dissolution testing using the FDA-recommended method for Diclofenac Sodium/Misoprostol Delayed-Release Tablets. You proposed the following dissolution methods; however, you did not submit any data using your proposed method for review:

Medium:	0.1 N HCl for acid stage of Diclofenac **Buffer (pH 6.8)** for buffer stage of Diclofenac Purified Water for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **990 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol

There is a discrepancy in the volume of buffer stage as stated in your report. In Module 2.7.1.2, you stated 990 mL of Buffer pH 6.8 for Diclofenac Sodium. However, in Module 3.2.P.2.2.3, a different volume (900 mL) was reported. Please explain. In addition, from your report it is not clear how you prepared Buffer pH 6.8 for the buffer stage testing of Diclofenac Sodium. Please provide the Standard Operating Procedure (SOP) for the dissolution testing which should include detailed information of the buffer preparation procedure.

Your proposed dissolution method will be evaluated in comparison with the current FDA-recommended dissolution method. Please conduct dissolution testing on 12 dosage units of the 75 mg/0.2 mg strength of the test and reference products using the following FDA-recommended method:

Medium:	0.1 N HCl for acid stage of Diclofenac **750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8)** for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **1000 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Sampling times:	120 minutes for acid stage of Diclofenac 15, 30, 45, and 60 minutes for buffer stage of Diclofenac 10, 20, and 30 minutes for Misoprostol

Please submit individual as well as mean dissolution data, with range and percent coefficient of variation (CV%), any relevant SOPs as well as electronic dissolution summary tables for all dissolution testing.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

Completed Assignment for 201089 ID: 11499

Reviewer: Kitchens, Kelly **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Diclofenac Sodium/Misoprostol Delayed-Release Tablets 75 mg/0.2 mg

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11499	12/23/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201089	ORIG-1	WATSON LABORATORIES INC	DICLOFENAC SODIUM AND MISOPROSTOL

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

/s/

KELLY M KITCHENS
06/30/2010

YIH CHAIN HUANG
06/30/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/30/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION AMENDMENT REVIEW

ANDA No.	201089	
Drug Product Name	Diclofenac Sodium/Misoprostol Delayed-Release Tablets	
Strength (s)	75 mg/0.2 mg	
Applicant Name	Watson Laboratories, Inc.-Florida	
Address	4955 Orange Drive Ft. Lauderdale, FL 33314	
Applicant's Point of Contact	Radha Goolabsingh, Manager Regulatory Affairs	
Contact's Phone Number	(954) 358-6147	
Contact's Fax Number	(954) 358-6350	
Submission Date(s)	December 23, 2009 July 30, 2010 (bioequivalence amendment – response to dissolution deficiencies)	
First Generic	No	
Reviewer	Kelly M. Kitchens, Ph.D.	
Study Number (s)	04131/09-10	04132/09-10
Study Type (s)	Fasting	Fed
Strength(s)	75 mg/0.2 mg	75 mg/0.2 mg
Clinical Site	Vimta Labs Ltd.,	
Clinical Site Address	Clinical Research Division 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA	
Analytical Site	Vimta Labs Ltd.	
Analytical Address	Room No's. 131B,140 & 133B Clinical Research Division Central Laboratory 142, IDA, Phase II, Cherlapally Hyderabad-500 051, India	
OUTCOME DECISION	**INADEQUATE**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution amendment.

There is no USP method for the test product Diclofenac Sodium/Misoprostol Delayed-Release Tablets, but there is an FDA-recommended method. In the original submission, Watson Laboratories, Inc.-Florida did not conduct the dissolution testing using the FDA-recommended method for Diclofenac Sodium/Misoprostol Delayed-Release Tablets. The firm proposed its own dissolution method and specifications as follows:

Medium:	0.1 N HCl for acid stage of Diclofenac **Buffer (pH 6.8)** for buffer stage of Diclofenac Purified Water for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **990 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT Q) Diclofenac dissolved in 45 minutes (buffer stage) NLT Q) Misoprostol dissolved in 45 minutes

In a deficiency letter dated July 6, 2010, the Division of Bioequivalence (DBE) requested that the firm conduct dissolution testing on 12 dosage units of the 75 mg/0.2 mg strength of the test and reference products using the following FDA-recommended method:

Medium:	0.1 N HCl for acid stage of Diclofenac **750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8)** for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac **1000 mL** for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Sampling times:	120 minutes for acid stage of Diclofenac 15, 30, 45, and 60 minutes for buffer stage of Diclofenac 10, 20, and 30 minutes for Misoprostol

In the current amendment, the firm submitted dissolution data for its Test product compared to the Reference product using the FDA-recommended method. The firm also revised the Finished Product Specification for the Test product (effective July 30, 2010) based on the dissolution data submitted in the amendment. Per the DBE request, the firm

submitted the Standard Test Method (effective July 30, 2010) that described the test methods used for analysis of the Test product.

The firm proposed the following specifications for its Test product in the Finished Product Specification:

(b) (4)(Q) Misoprostol dissolved in 45 minutes
NMT (b) (4)Diclofenac dissolved in 120 minutes (acid stage)
(b) (4)(Q) Diclofenac dissolved in 45 minutes (buffer stage)

The dissolution testing data are acceptable. However, the firm's proposed specification of NLT (b) (4)(Q) dissolved in 45 minutes for Misoprostol is not acceptable. Therefore, the DBE will request that the firm acknowledge its acceptance of the following FDA-recommended method and specifications:

Medium:	0.1 N HCl for acid stage of Diclofenac 750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8) for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac 1000 mL for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT (Q) Diclofenac dissolved in 45 minutes (buffer stage) NLT (Q) Misoprostol dissolved in 20 minutes

The firm's dissolution testing remains **inadequate** pending the firm's acknowledgement of the DBE-recommended dissolution method and specifications**.**

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	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present 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.					

II. FIRM'S DEFICIENCY LETTER COMMENTS (submitted July 6, 2010)

DBE DEFICIENCY COMMENT:
You did not conduct the dissolution testing using the FDA-recommended method for Diclofenac Sodium/Misoprostol Delayed-Release Tablets. You proposed the following dissolution methods; however, you did not submit any data using your proposed method for review:

Medium:	*0.1 N HCl for acid stage of Diclofenac*
	***Buffer (pH 6.8)** for buffer stage of Diclofenac*
	Purified Water for Misoprostol
Volume:	*750 mL for acid stage of Diclofenac*
	***990 mL** for buffer stage of Diclofenac*
	500 mL for Misoprostol
Temperature:	*37°C ± 0.5°C*
USP Apparatus:	*II (Paddle) for both Diclofenac and Misoprostol*
Rotational Speed:	*100 rpm for Diclofenac*
	50 rpm for Misoprostol

There is a discrepancy in the volume of buffer stage as stated in your report. In Module 2.7.1.2, you stated 990 mL of Buffer pH 6.8 for Diclofenac Sodium. However, in Module 3.2.P.2.2.3, a different volume (900 mL) was reported. Please explain. In addition, from your report it is not clear how you prepared Buffer pH 6.8 for the buffer stage testing of Diclofenac Sodium. Please provide the Standard Operating Procedure (SOP) for the dissolution testing which should include detailed information of the buffer preparation procedure.

Your proposed dissolution method will be evaluated in comparison with the current FDA-recommended dissolution method. Please conduct dissolution testing on 12 dosage units of the 75 mg/0.2 mg strength of the test and reference products using the following FDA-recommended method:

Medium:	*0.1 N HCl for acid stage of Diclofenac*
	***750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8)** for buffer stage of Diclofenac*
	Water (deaerated) for Misoprostol
Volume:	*750 mL for acid stage of Diclofenac*
	***1000 mL** for buffer stage of Diclofenac*
	500 mL for Misoprostol
Temperature:	*37°C ± 0.5°C*
USP Apparatus:	*II (Paddle) for both Diclofenac and Misoprostol*
Rotational Speed:	*100 rpm for Diclofenac*
	50 rpm for Misoprostol
Sampling times:	*120 minutes for acid stage of Diclofenac*
	15, 30, 45, and 60 minutes for buffer stage of Diclofenac
	10, 20, and 30 minutes for Misoprostol

Please submit individual as well as mean dissolution data, with range and percent coefficient of variation (CV%), any relevant SOPs as well as electronic dissolution summary tables for all dissolution testing.

FIRM'S RESPONSE:
Comparative dissolution testing on the test and reference products (12 dosage units each) using the recommended method was conducted, however the data was inadvertently not provided in the ANDA submission. The data which include the individual tablet data as well as the mean, range, % coefficient of variation (CV) at each time point for the 12 tablets tested and dates of dissolution testing, is included in **Module 2.7.1.2** of this amendment. The dissolution testing data summary tables in the DBE-recommended Electronic Common Technical Document (eCTD) format are also included in **Module 2.7.1.2.**

WLF's dissolution method is the same as the FDA-recommended method. The final volume for the buffer stage is 1000 mL (750 mL 0.1N HC1 + 250 mL 0.2M Phosphate Buffer, pH 6.8). All affected documents have been corrected to reflect the intended volume and the revised documents are included in this amendment as follows:

1. Finished product specification in Section **3.2.P.5.1**
2. Standard test method (STM) in Section **3.2.P.5.2**
3. Pharmaceutical Development Report in Section **3.2.P.2**

The dissolution testing procedure, including the buffer preparation is described in the standard test method, STM-AR-FP-0120 (pages 4 thru 14), which is provided in Module 3.2.P.5.2 of this amendment.

Table 5.1 Summary of In Vitro Dissolution Studies – medium of 0.1N HCl for 2 hrs (Acid Stage), and then adjusted to pH 6.8 (Buffer Stage) - Diclofenac Sodium Dissolution Profile

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	750 mL 0.1N HCl for 2 hrs. (Acid Stage), and then add 250 mL of 0.2M Phosphate Buffer adjusted to pH 6.8 (Buffer Stage)
	Volume:	0-2 hrs 750 mL (Acid Stage), after 1000 mL (Buffer Stage)
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hrs)** 2	2.25	2.5	2.75	3	3.5	**Study Report Location**
WSR1459, p.57	09/24/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022 (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	0	28	73	99	99	100	See pages 3 and 4
					Range	(b) (4)						
					%CV	N/A	17.7	12.4	1.5	1.2	1.3	
WSR1459, p.37	08/13/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	0	27	70	94	100	100	
					Range	(b) (4)						
					%CV	N/A	20.2	7.6	3.4	1.4	1.7	

Dissolution Profile for Diclofenac Sodium
STM Conditions

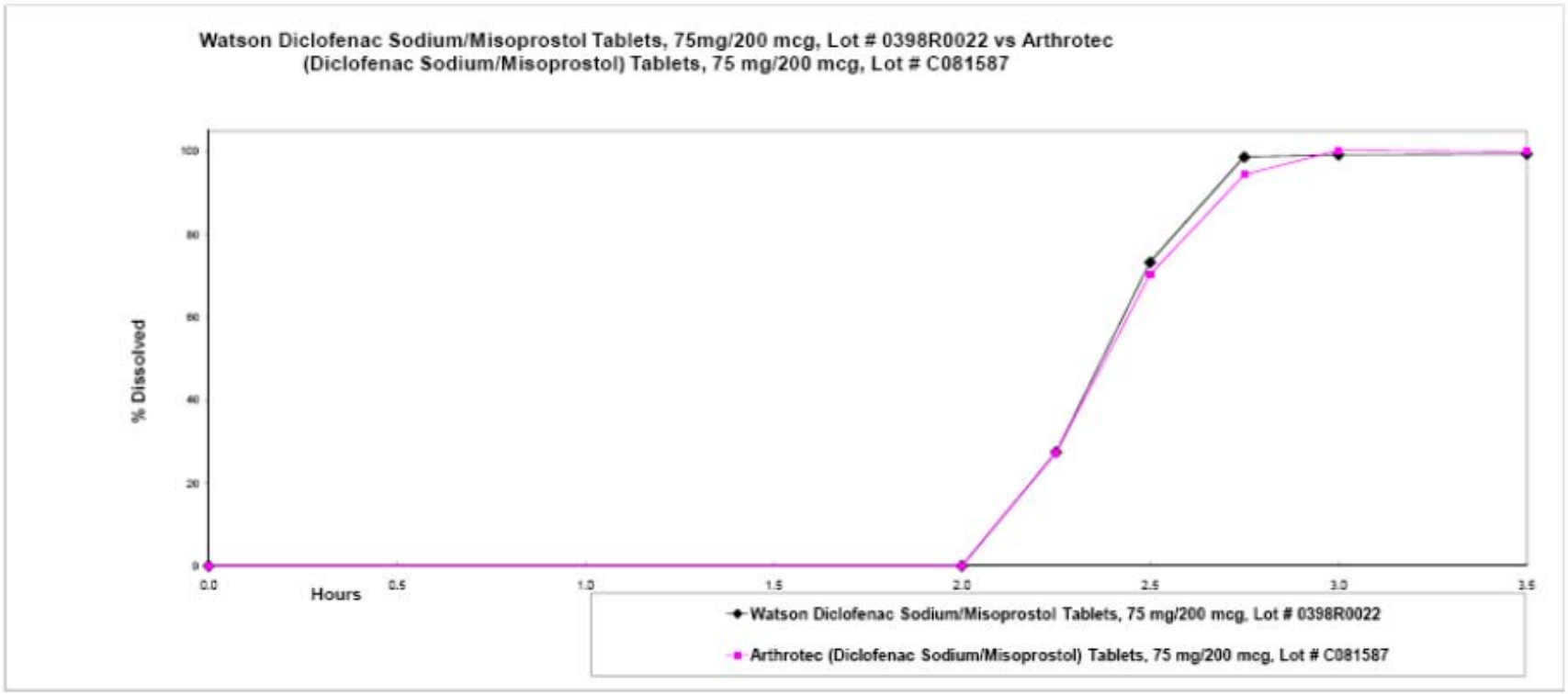
Method: USP Apparatus 2, 100 RPM, 750 mL of 0.1N HCl for 2 hrs then subject to Buffer stage pH 6.8 n=12

Test Product: Watson Diclofenac Sodium/Misoprostol Tablets, 75 mg/200 mcg, Lot # 0398R0022

	Amount (%) Dissolved															
Time (Hours)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD	Min	Max
0												(b) (4)	0	NA		(b) (4)
2													0	NA		
2.25													28	17.7		
2.5													73	12.4		
2.75													99	1.5		
3													99	1.2		
3.5													100	1.3		

Reference Product: Arthrotec (Diclofenac Sodium/Misoprostol) Tablets, 75 mg/200 mcg, Lot # C081587

	Amount (%) Dissolved															
Time (Hours)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD	Min	Max
0												(b) (4)	0	NA		(b) (4)
2													0	NA		
2.25													27	20.2		
2.5													70	7.6		
2.75													94	3.4		
3													100	1.4		
3.5													100	1.7		


Watson Diclofenac Sodium/Misoprostol Tablets, 75mg/200 mcg, Lot # 0398R0022 vs Arthrotec
(Diclofenac Sodium/Misoprostol) Tablets, 75 mg/200 mcg, Lot # C081587
% Dissolved
100
80
60
40
20
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Hours
Watson Diclofenac Sodium/Misoprostol Tablets, 75 mg/200 mcg, Lot # 0398R0022
Arthrotec (Diclofenac Sodium/Misoprostol) Tablets, 75 mg/200 mcg, Lot # C081587

Misoprostol Dissolution Profile

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	Purified Water
	Volume:	500 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	Study Report Location
WSR1672, p.7	09/24/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022 (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	90	93	94	96	98	See pages 6 and 7
					Range	(b) (4)					
					%CV	5.7	3.9	3.5	3.5	3.0	
WSR1458, p.58	08/17/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	90	97	98	99	99	
					Range	(b) (4)					
					%CV	7.3	4.3	2.9	2.0	2.2	

Dissolution Profile for Misoprostol
STM Conditons

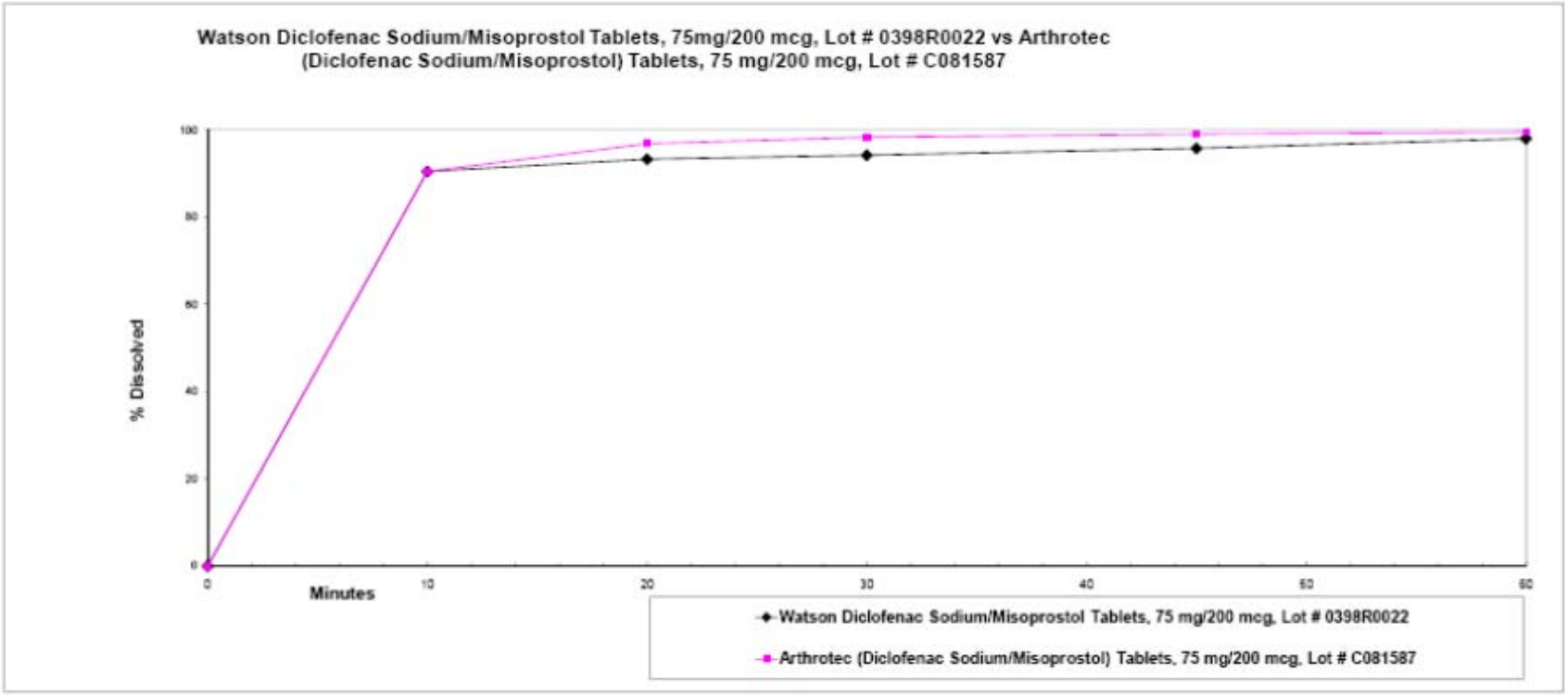
Method: USP Apparatus 2, 50 RPM, 500 mL Water, n=12

Test Product: Watson Diclofenac Sodium/Misoprostol Tablets, 75 mg/200 mcg, Lot # 0398R0022

	Amount (%) Dissolved															
Time (Minutes)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD	Min	Max
0												(b) (4)	0	NA		(b) (4)
10													90	5.7		
20													93	3.9		
30													94	3.5		
45													96	3.5		
60													98	3.0		

Reference Product: Arthrotec (Diclofenac Sodium/Misoprostol) Tablets, 75 mg/200 mcg, Lot # C081587

	Amount (%) Dissolved															
Time (Minutes)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD	Min	Max
0												(b) (4)	0	NA		(b) (4)
10													90	7.3		
20													97	4.3		
30													98	2.9		
45													99	2.0		
60													99	2.2		


Watson Diclofenac Sodium/Misoprostol Tablets, 75mg/200 mcg, Lot # 0398R0022 vs Arthrotec
(Diclofenac Sodium/Misoprostol) Tablets, 75 mg/200 mcg, Lot # C081587
% Dissolved
100
80
60
40
20
0
0
10
20
30
40
50
60
Minutes
Watson Diclofenac Sodium/Misoprostol Tablets, 75 mg/200 mcg, Lot # 0398R0022
Arthrotec (Diclofenac Sodium/Misoprostol) Tablets, 75 mg/200 mcg, Lot # C081587

REVIEWER'S COMMENTS:

- The firm submitted dissolution data for its Test product compared to the Reference product using the FDA-recommended method, including the individual as well as mean dissolution data, with range and percent coefficient of variation (CV%), and relevant SOPs. The testing dates for this data were in August and September 2009. The firm also revised the Finished Product Specification for the Test product (effective July 30, 2010) based on the dissolution data submitted in the amendment. The firm established the following specifications for its Test product in the Finished Product Specification:

  (b) (4) (Q) Misoprostol dissolved in 45 minutes
  NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage)
  (b) (4) (Q) Diclofenac dissolved in 45 minutes (buffer stage)

  The dissolution testing data are acceptable. The firm's proposed specifications are similar to the FDA-recommended specifications, except the FDA-recommended specification for the Misoprostol component of the test product is NLT (b) (4) (Q) dissolved in 20 minutes. Therefore, the DBE will request that the firm acknowledge its acceptance of the following FDA-recommended method and specifications:

Medium:	0.1 N HCl for acid stage of Diclofenac; 750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8) for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac 1000 mL for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT (b) (4) (Q) Diclofenac dissolved in 45 minutes (buffer stage) NLT (b) (4) (Q) Misoprostol dissolved in 20 minutes

- The firm submitted the Standard Test Method (effective July 30, 2010) that described the test methods used for analysis of the Test product. The Standard Test Method included the procedures for the buffer preparation for the buffer stage testing of Diclofenac Sodium:
  - Preparation of 0.025 M Potassium Phosphate Monobasic Buffer pH 6.50 ± 0.05 – Accurately weigh, transfer and dissolve 6.8 g of Potassium

Phosphate Monobasic in 2000 mL of water. Adjust pH to 6.50 ± 0.05 with 1 N NaOH. This preparation may be scaled up or down as needed.

III. DEFICIENCY COMMENTS:

The firm's dissolution testing is acceptable; however, the firm's proposed specification of NLT (b) (4) (Q) in 45 minutes for Misoprostol is not acceptable. The DBE will request that the firm acknowledge its acceptance of the following FDA-recommended method and specifications:

Medium:	0.1 N HCl for acid stage of Diclofenac 750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer (pH 6.8) for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac 1000 mL for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT (Q) Diclofenac dissolved in 45 minutes (buffer stage) NLT (Q) Misoprostol dissolved in 20 minutes

IV. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Watson Laboratories, Inc. - Florida on its Diclofenac Sodium/Misoprostol Delayed-Release Tablets, 75 mg/0.2 mg (lot # 0398R0022A), compared to GD Searle's ARTHROTEC® (Diclofenac Sodium/Misoprostol) Delayed-Release Tablets 75 mg/0.2 mg (lot # C081587) is **incomplete** due to the deficiencies cited above.

The firm should be informed of the deficiencies and recommendations.

BIOEQUIVALENCE DEFICIENCY TO BE COMMUNICATED TO THE FIRM

ANDA: 201089

APPLICANT: Watson Laboratories, Inc. - Florida

DRUG PRODUCT: Diclofenac Sodium/Misoprostol Delayed-Release Tablets 75 mg/0.2 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 studies will be done at a later date.

The following deficiency has been identified:

Your dissolution testing data for both diclofenac and misoprostol are acceptable. However, your proposed specification of NLT (b) (4) Q) in 45 minutes for Misoprostol is not acceptable. Based on the dissolution data submitted for Misoprostol, the DBE recommends a more appropriate specification for this component below. Please acknowledge your acceptance of the following FDA-recommended methods and specifications:

Medium: 0.1 N HCl for acid stage of Diclofenac 750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer pH 6.8 for buffer stage of Diclofenac
Water (deaerated) for Misoprostol

Volume: 750 mL for acid stage of Diclofenac
1000 mL for buffer stage of Diclofenac
500 mL for Misoprostol

Temperature: 37°C ± 0.5°C

USP Apparatus: II (Paddle) for both Diclofenac and Misoprostol

Rotational Speed: 100 rpm for Diclofenac
50 rpm for Misoprostol

Specifications: NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage)
NLT (b) (4) Q) Diclofenac dissolved in 45 minutes(buffer stage)
NLT (b) (4) (Q) Misoprostol dissolved in 20 minutes

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

Completed Assignment for 201089 ID: 12320

Reviewer: Kitchens, Kelly **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Diclofenac Sodium/Misoprostol Delayed-Release Tablets 75 mg/0.2 mg

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
12320	7/30/2010	Other	Dissolution Amendment	1	1
				Bean Total:	1

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

/s/

KELLY M KITCHENS
10/15/2010

YIH CHAIN HUANG
10/15/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/15/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	201089	
Drug Product Name	Diclofenac Sodium/Misoprostol DR Tablets	
Strength(s)	75 mg/0.2 mg	
Applicant Name	Watson Laboratories, Inc. - Florida	
Address	4955 Orange Drive Fort Lauderdale, FL 33314	
Applicant's Point of Contact	Janet Vaughn	
Contact's Telephone Number	954.358.6125	
Contact's Fax Number	954.358.6350	
Original Submission Date(s)	December 24, 2009	
Submission Date(s) of Amendment(s) Under Review	July 30, 2010 November 10, 2010	
Reviewer	Jennifer N. Miller, Ph.D.	
Study Number (s)	04131/09-10	04132/09-10
Study Type (s)	Fasting	Fed
Strength (s)	75 mg/0.2 mg	75 mg/0.2 mg
Clinical Site	Vimta Labs Ltd.,	
Clinical Site Address	Clinical Research Division 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA	
Analytical Site	Vimta Labs Ltd.	
Analytical Site Address	Room No's. 131B,140 & 133B Clinical Research Division Central Laboratory 142, IDA, Phase II, Cherlapally Hyderabad-500 051, India	
OVERALL REVIEW RESULT	**INADEQUATE**	
OSI REPORT RESULT	**INADEQUATE**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #			
1	**FASTING STUDY**	**75 mg/0.2 mg**	**ADEQUATE**
1	**FED STUDY**	**75 mg/0.2 mg**	**ADEQUATE**
1	**DISSOLUTION**	**75 mg/0.2 mg**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Watson Laboratories, Inc.'s Diclofenac Sodium/Misoprostol Delayed Release tablets, 75 mg/0.2 mg, to the corresponding reference product, GD Searle LLC's Arthrotec® 75 DR Tablets, 75 mg/0.2 mg. The fasting and fed BE studies were designed as a single-dose, **4-way fully replicate crossover study** in healthy male subjects.

The firm conducted statistical analysis using scaled as well as non-scaled (traditional) bioequivalence approach as per its protocol. The reference-scaled average bioequivalence (ABE) approach was used to calculate bioequivalence statistics for Cmax for diclofenac and misoprostol acid in the fed study only. The two one-sided tests procedure was used to determine bioequivalence for AUCt and AUCi for diclofenac and misoprostol acid in the fed study and for all parameters in the fasting study. The results are summarized in the tables below.

Fasting BE Study:

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	2403.88	2422.83	0.99	95.93	102.62
AUC∞ (hr *ng/ml)	2481.61	2485.21	1.00	96.60	103.22
Cmax (ng/ml)	1842.75	1677.08	1.10	100.35	120.31

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	192.89	196.19	0.98	94.48	102.30
AUC∞ (hr *pg/ml)	202.38	205.00	0.99	94.89	102.72
Cmax (pg/ml)	326.19	319.41	1.02	93.41	111.65

Fed BE Study:

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fed Bioequivalence Study, Study No. 04132/09-10 (N=40)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.00	94.82	106.08	0.0349613	0.1869793	-0.019709	Unscaled	PASS
LAUCI	1.01	95.68	105.20	0.0290378	0.1704048	-0.016176	Unscaled	PASS
LCMAX	1.17	103.15	132.93	0.1615496	0.4019324	-0.037394	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fed Bioequivalence Study, Study No. 04132/09-10 (N=40)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2108.95	2102.81	1.00	94.82	106.08
AUC∞ (hr *ng/ml)	2202.31	2195.11	1.00	95.68	105.20
Cmax (ng/ml)	1416.08	1209.32	1.17	103.15	132.93

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Misoprostol Acid
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.97	94.14	100.73	0.0210688	0.1451511	-0.010698	Unscaled	PASS
LAUCI	0.98	93.22	103.12	0.0220439	0.1484719	-0.010708	Unscaled	PASS
LCMAX	1.01	91.40	111.39	0.1798378	0.4240729	-0.103926	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Misoprostol Acid
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	286.40	294.10	0.97	94.14	100.73
AUC∞ (hr *pg/ml)	336.99	343.72	0.98	93.22	103.12
Cmax (pg/ml)	162.65	161.19	1.01	91.40	111.39

The 95% Upper confidence bound for Cmax for diclofenac and misoprostol acid in the fed BE study are both negative. Since these values are less than 0, it meets the first condition. Since the point estimates (test/reference geometric mean ratio) for Cmax for diclofenac and misoprostol acid in the fed BE study are within [0.80, 1.25], it meets the second condition.

For AUCt and AUCi in the fed study, since s_{WR} is < 0.294 for both diclofenac and misoprostol, the assessment of bioequivalence was determined using the two one-sided tests procedure. The 90% confidence intervals for log-transformed AUCt and AUCi are within the acceptable range of 80% to 125%.

The fasting and fed studies are adequate.

The firm has conducted acceptable comparative dissolution testing using the FDA-recommended dissolution method, (DARRTS REV-BIOEQ-02(Dissolution Review) Submit Date: 6/30/2010 and 10/15/2010). On November 10, 2010, the firm acknowledged the FDA-recommended dissolution method and specifications.

A routine OSI inspection was requested for the clinical site regarding this ANDA on 08/12/2011 and is pending. No OSI inspection is necessary for the analytical site.

The application is **inadequate**, due to a pending OSI inspection of the clinical site.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Diclofenac Sodium/Misoprostol Delayed Release Tablets, 75 mg/0.2 mg
Reference Product	Arthrotec® Delayed Release Tablets, 75 mg/0.2 mg
RLD Manufacturer	GD Searle LLC
NDA No.	020607
RLD Approval Date	December 24, 1997
Indication	Arthrotec® is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. Arthrotec® is **contraindicated** in pregnant women.

3.2 PK/PD Information

Bioavailability	**Diclofenac:** Diclofenac sodium is completely absorbed from the GI tract following oral administration but only 50% of the absorbed dose is systemically available due to first pass metabolism. **Misoprostol:** Orally administered misoprostol is rapidly and extensively absorbed. There is high variability in plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose of misoprostol over the range of 200 to 400 mcg.
Food Effect	**Diclofenac:** Administration with food delays the rate, but not the extent, of absorption. Food can delay peak concentrations up to 12 hours in some patients. **Misoprostol:** Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food.
Tmax	**Diclofenac:** 2 hours (1-4 hours) **Misoprostol acid:** 20-40 minutes
Metabolism	**Diclofenac:** Extensive and rapid hydroxylation and conjugation occur in the liver via cytochrome P450 2C9 and 3A4. Five diclofenac metabolites have been identified in human plasma and urine. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac. **Misoprostol:** Undergoes rapid metabolism to its biologically active metabolite, misoprostol acid.
Excretion	**Diclofenac:** About 65% of a dose is excreted in the urine and about 35% in the bile. Less than 1% of diclofenac is excreted in the urine unchanged, with the remainder as metabolites or conjugates of the drug. **Misoprostol:** Less than 1% of a dose is excreted in the urine as unchanged drug. Approximately 15% of a dose is excreted in the feces, with 74% being excreted in the urine within 7 days.

Half-life	**Diclofenac:** 2 hours **Misoprostol acid:** 30 minutes
Dosage and Administration	
Drug Specific Issues (if any)	**CONTRAINDICATIONS AND WARNINGS** ARTHROTEC® CONTAINS DICLOFENAC SODIUM AND MISOPROSTOL. ADMINISTRATION OF MISOPROSTOL TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY. ARTHROTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN. PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.ARTHROTEC should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID. In such patients, ARTHROTEC may be prescribed if the patient: • has had a negative serum pregnancy test within 2 weeks prior to beginning therapy. • is capable of complying with effective contraceptive measures. • has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake. • will begin ARTHROTEC only on the second or third day of the next normal menstrual period. **Cardiovascular Risk** NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. ARTHROTEC is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. **Gastrointestinal Risk** NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

3.3

OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	75 mg/0.2 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Applicant may consider using a reference scaled average bioequivalence approach for diclofenac and misoprostol. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	75 mg/0.2 mg
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	Please see comments above

Analytes to measure (in plasma/serum/blood):	Diclofenac and misoprostol's active metabolite, misoprostol acid
Bioequivalence based on:	90% CI on diclofenac and misoprostol acid
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Individual Draft Guidance on Diclofenac Sodium/Misoprostol Delayed Release Tablets: http://www.fda.gov/cder/guidance/bioequivalence/default.htm

Summary of OGD or DBE History (for details, see Appendix 4.4):	The Office of Generic Drugs has received the following **ANDAs:** (b) (4) **Protocols:** 07-068 (b) (4) 09-031 **Control Documents:** 01-504 (b) (4) 02-270 (Watson) 03-621 (Watson) 04-654 (b) (4) 05-0009 (b) (4) 05-0454 05-0584 05-0970 05-1504 06-0214 06-1178 07-0040 07-0500 07-0625 09-0394

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state		
In vitro dissolution	Yes	1
Waiver requests		
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendments	Yes	2

3.5

Pre-Study Bioanalytical Method Validation

Analyte	Diclofenac	Misoprostol Acid
Report Location	**Appendix: 16.6**	**Appendix: 16.6**
Internal standard (ISTD)	(b) (4)	(b) (4)
Method description	Extraction method: Refer Method Validation Report No:23/MVR/290/01 page No.23 of 61,Analytical Method:LC-MS/MS	Refer Method Validation Report No. 23/MVR/292, Page No.22 of 54, Analytical Method: LC-MS/MS
Limit of quantitation	30.050 ng/mL	9.000 pg/mL
Average recovery of drug (%)	LQC: 65.40 MQC: 55.11 HQC: 52.93 Mean: 57.81	LQC: 61.61 MQC: 52.72 HQC: 65.40 Mean: 59.91
Average recovery of ISTD (%)	58.88	76.22
Standard curve concentrations	29.950, 59.950, 149.850, 449.550, 999.000, 1998.000, 2997.000 and 3996.050 ng/mL	9.000, 18.000, 45.000, 90.000, 225.000, 450.000, 675.000 and 900.000 pg/mL
QC concentrations	LQC = 90.100 ng/mL GMQC = 380.400 ng/mL MQC = 1601.650 ng/mL HQC = 3203.350 ng/mL	LQC= 27.000 pg/mL GMQC= 99.000 pg/mL MQC= 360.000 pg/mL HQC= 720.000 pg/mL
QC Intra batch precision range (%)	0.90 to 2.96	0.40 to 12.83
QC Intra batch accuracy range (%)	89.87 to 100.41	89.54 to 106.94
QC Inter batch precision (%)	1.45 to 3.45	2.82 to 7.77
QC Inter batch accuracy (%)	93.99 to 100.04	95.00 to 105.32
Bench-top stability (hrs)	13 hours @ ambient temperature	7.00 hours @ ambient temperature
Stock stability (hrs)	7 hours @ room temperature	7.00 hours @ room temperature
Processed stability (hrs)	a) Auto sampler stability : 19.00 hours @ 10°C b) Wet extract stability : 18.00 hours @ ambient temperature c) Dry extract stability : 18.00 hours @ ambient temperature	**a) Auto Injector stability** : 24.00 hours @ 10°C **b) Wet extract stability** : 24.00 hours @ ambient temperature
Freeze-thaw stability (cycles)	02 cycles @ -20^{0}C 03 cycles @ -60^{0}C	03 cycles @ -60°C
Long-term storage stability (days)	179 days @ -60^{0}C	92 days @ -60°C %
Long-term Stock stability (days)	41 days @ 2-8^{0}C	36 days @ -20°C
Dilution Integrity	1/2 dilution	1/2 and 1/4 dilution
Selectivity	No interference peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples

Partial Method Validation:

Analyte	Diclofenac	Misoprostol free acid
Report Location	**Appendix: 16.6**	**Appendix: 16.6**

Internal standard (ISTD)	(b) (4)	(b) (4)
Method description	Refer Method Validation Report No. 23/PMVR/DICLOFENAC/290/08, Page No.12 of 23, Analytical Method: LC-MS/MS	Refer Method Validation Report No. 23/PMVR/MISOPROSTOL FREE ACID/292/03, Page No.12&13 of 34, Analytical Method: LC-MS/MS
Limit of quantitation	30.100 ng/mL	10.000 pg/mL
Average recovery of drug (%)	N/A	LQC: 84.68 MQC: 66.79 HQC: 63.79 Mean: 71.66
Average recovery of ISTD (%)	N/A	69.22
Standard curve concentrations	30.050, 60.050, 150.200, 450.550, 1001.250, 2002.450, 3003.700, 4004.950 ng/mL	10.000, 20.000, 50.000, 99.950, 249.900, 499.800, 749.700, 999.600 pg/mL
QC concentrations (ng/mL)	LLOQ= 30.100 ng/mL LQC= 90.300 ng/mL GMQC= 381.150 ng/mL MQC= 1604.950 ng/mL HQC= 3209.850 ng/mL	LLOQ= 10.000 pg/mL LQC= 30.000 pg/mL GMQC= 110.000 pg/mL MQC= 400.000 pg/mL HQC= 800.000 pg/mL
QC Intra batch precision range (%)	1.21 to 4.75	1.04 to 9.32
QC Intra batch accuracy range (%)	92.45 to 106.70	95.38 to 108.36
QC Inter batch precision (%)	1.85 to 3.70	2.85 to 7.91
QC Inter batch accuracy (%)	94.02 to 105.64	98.25 to 101.84

SOPs submitted	No	Firm did not submit SOP No. 23/14 but did submit the Analytical Method Validation Procedure for Diclofenac and Misoprostol Acid
Bioanalytical method is acceptable	Yes	

Comments on the Pre-Study Method Validation:

The pre-study method validation is **adequate**. Human plasma containing K_3EDTA was used for preparation of calibration standards and quality control samples.

The firm conducted an acceptable partial validation to change the sample storage temperature from -20ºC to -60ºC and to check the interference at Diclofenac's retention time due to the presence of Misoprostol free acid. The firm also conducted an acceptable partial validation to check for the effect of instrument variation, change in sample processing procedure, and the effect of Misoprostol free acid in the presence of Diclofenac and in hemolytic plasma.

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)
04131/09-10	An Open labeled, randomized, two treatment, four period, two sequence, single dose fully replicate crossover design using a scaled bioequivalence approach of Diclofenac sodium/ Misoprostol 75mg/0.2mg Tablets (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of Watson Laboratories Inc, USA against Arthrotec® (Diclofenac sodium/ Misoprostol) Tablet (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of G. D. Searle LLC (Division of Pfizer Inc), USA in healthy human, adult subjects under fasting condition using a reference-scaled average bioequivalence approach	An Open labeled, randomized, two treatment, four period, two sequence, single dose, fully replicate, crossover using a scaled bioequivalence approach.	**Test** Diclofenac sodium/ Misoprostol, 75mg/0.2mg 1 tablet orally administered with 240mL of water at ambient temperature. Bulk Lot No.: 0398R0022 **Reference** Arthrotec® 75 1 tablet orally administered with 240mL of water at ambient temperature. Lot No.: C081587	48 healthy male subjects Mean age: 27.90 Years Range: 18-39

Study Ref. No.	Formulation	C_{max} (ng/mL)	T_{max} hr	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	$t_{1/2}$ (hr)	K_{el} (hr^{-1})	Study report location
04131/09-10 **Diclofenac**	Treatment T (Replicate-1)	2093.599 (29.20)	1.47 (61.28)	2496.543 (22.35)	2567.616 (22.04)	1.158 (27.68)	0.639 (24.58)	Table 14.2.2-1 to 14.2.2-4
	Treatment T (Replicate-2)	1915.855 (45.89)	1.49 (74.40)	2477.212 (25.69)	2562.122 (25.09)	1.289 (51.13)	0.628 (36.57)	
	Treatment R (Replicate-1)	1743.467 (29.70)	1.33 (48.96)	2452.120 (19.86)	2515.078 (19.59)	1.039 (22.59)	0.704 (25.15)	
	Treatment R (Replicate-2)	1842.634 (38.74)	1.52 (62.01)	2528.773 (21.96)	2592.409 (22.02)	1.069 (31.41)	0.712 (30.72)	

	Formulation	Cmax	Tmax	AUC0-t	AUC0-∞	t1/2	Kel	
		(pg/mL)	hr	(pg*hr/mL)	(pg*hr/mL)	(hr)	(hr-1)	
04131/09-10 **Misoprostol Acid**	Treatment T (Replicate-1)	363.904 (37.05)	0.29 (35.09)	203.677 (33.04)	212.344 (32.41)	0.465 (38.96)	1.727 (38.73)	
	Treatment T (Replicate-2)	353.376 (48.92)	0.33 (51.77)	207.893 (36.43)	218.962 (36.91)	0.542 (65.07)	1.508 (31.67)	
	Treatment R (Replicate-1)	360.061 (45.58)	0.32 (54.48)	204.173 (33.38)	211.623 (32.42)	0.410 (34.76)	1.851 (27.68)	
	Treatment R (Replicate-2)	355.254 (52.29)	0.34 (35.38)	218.588 (39.13)	228.367 (37.92)	0.504 (46.37)	1.575 (34.45)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)
04132/09-10	An Open labeled, randomized, two treatment, four period, two sequence, single dose fully replicate crossover design using a scaled bioequivalence approach of Diclofenac sodium/ Misoprostol 75mg/0.2mg Tablets (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of Watson Laboratories Inc, USA against Arthrotec® (Diclofenac sodium/ Misoprostol) Tablet (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of G. D. Searle LLC (Division of Pfizer Inc), USA in healthy human, adult subjects under fed condition using a reference-scaled average bioequivalence approach.	An Open labeled, randomized, two treatment, four period, two sequence, single dose fully replicate crossover design using a scaled bioequivalence approach.	**Test** Diclofenac sodium/ Misoprostol, 75mg/0.2mg 1 tablet orally administered with 240mL of water at ambient temperature. Bulk Lot No.: 0398R0022 **Reference** Arthrotec® 75 1 tablet orally administered with 240mL of water at ambient temperature. Lot No.: C081587	48 healthy male subjects Mean age: 26.60 Years Range: 18-41

Study Ref. No.	Formulation	C_{max} (ng/mL)	T_{max} hr	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	$t_{1/2}$ (hr)	K_{el} (hr^{-1})	Study report location
04132/09-10 **Diclofenac**	Treatment T (Replicate-1)	1613.205 (52.92)	3.51 (37.92)	2274.976 (37.87)	2348.611 (36.68)	0.964 (48.57)	0.833 (35.40)	Table 14.2.2-1 to 14.2.2-4
	Treatment T (Replicate-2)	1626.783 (56.07)	3.60 (46.56)	2133.605 (25.96)	2228.023 (24.58)	0.938 (58.27)	0.866 (32.11)	
	Treatment R (Replicate-1)	1455.652 (50.62)	3.44 (38.28)	2207.135 (25.86)	2293.357 (24.65)	1.032 (70.26)	0.846 (38.02)	
	Treatment R (Replicate-2)	1283.981 (48.51)	3.94 (37.51)	2139.096 (25.63)	2226.550 (24.51)	0.892 (48.11)	0.906 (34.62)	
	Formulation	**Cmax**	**Tmax**	**AUC0-t**	**AUC0-∞**	**t1/2**	**Kel**	
04132/09-10 **Misoprostol Acid**		**(pg/mL)**	**hr**	**(pg*hr/mL)**	**(pg*hr/mL)**	**(hr)**	**(hr-1)**	
	Treatment T (Replicate-1)	181.356 (53.51)	1.52 (111.40)	307.250 (33.92)	367.415 (37.45)	1.897 (158.27)	0.652 (56.49)	
	Treatment T (Replicate-2)	188.448 (56.42)	1.52 (98.58)	297.805 (32.39)	347.034 (34.00)	1.319 (60.79)	0.756 (62.29)	
	Treatment R (Replicate-1)	182.263 (61.67)	0.98 (99.13)	307.713 (32.39)	351.680 (31.68)	1.220 (56.34)	0.722 (48.37)	
	Treatment R (Replicate-2)	181.849 (50.18)	1.05 (131.34)	312.236 (32.65)	367.555 (33.52)	1.511 (66.54)	0.622 (51.07)	

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

Fasting BE Study:

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Scaled and Unscaled Data								
Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.99	95.93	102.62	0.0130749	0.1143455	-0.007203	Unscaled	PASS
LAUCI	1.00	96.60	103.22	0.0124079	0.1113906	-0.006992	Unscaled	PASS
LCMAX	1.10	100.35	120.31	0.0845979	0.2908572	-0.027567	Unscaled	PASS

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2403.88	2422.83	0.99	95.93	102.62
AUC∞ (hr *ng/ml)	2481.61	2485.21	1.00	96.60	103.22
Cmax (ng/ml)	1842.75	1677.08	1.10	100.35	120.31

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Scaled and Unscaled Data								
Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.98	94.48	102.30	0.0202397	0.1422661	-0.010721	Unscaled	PASS
LAUCI	0.99	94.89	102.72	0.0187469	0.1369193	-0.010124	Unscaled	PASS
LCMAX	1.02	93.41	111.65	0.068066	0.2608947	-0.035698	Unscaled	PASS

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	192.89	196.19	0.98	94.48	102.30
AUC∞ (hr *pg/ml)	202.38	205.00	0.99	94.89	102.72
Cmax (pg/ml)	326.19	319.41	1.02	93.41	111.65

Fed BE Study:

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Scaled and Unscaled Data								
Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.00	94.82	106.08	0.0349613	0.1869793	-0.019709	Unscaled	PASS
LAUCI	1.01	95.68	105.20	0.0290378	0.1704048	-0.016176	Unscaled	PASS
LCMAX	1.17	103.15	132.93	0.1615496	0.4019324	-0.037394	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2108.95	2102.81	1.00	94.82	106.08
AUC∞ (hr *ng/ml)	2202.31	2195.11	1.00	95.68	105.20
Cmax (ng/ml)	1416.08	1209.32	1.17	103.15	132.93

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Scaled and Unscaled Data								
Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.97	94.14	100.73	0.0210688	0.1451511	-0.010698	Unscaled	PASS
LAUCI	0.98	93.22	103.12	0.0220439	0.1484719	-0.010708	Unscaled	PASS
LCMAX	1.01	91.40	111.39	0.1798378	0.4240729	-0.103926	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	286.40	294.10	0.97	94.14	100.73
AUC∞ (hr *pg/ml)	336.99	343.72	0.98	93.22	103.12
Cmax (pg/ml)	162.65	161.19	1.01	91.40	111.39

Table 3. Reanalysis of Study Samples

Study No. 04131/09-10 Diclofenac Location in final report: Bio-analytical Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual number		%of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Extraction/processing error	31	30	2.35	2.27	31	30	2.35	2.27
Unacceptable Calibration Curve	30	30	2.27	2.27	30	30	2.27	2.27
Anomalous Value	1	2	0.08	0.15	0	0	0.00	0.00
Total	**62**	**62**	**4.70**	**4.70**	**61**	**60**	**4.62**	**4.55**

Study No. 04131/09-10 Misoprostol Acid Location in final report: Bio-analytical Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual number		%of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Unacceptable Calibration Curve	26	26	2.27	2.27	26	26	2.27	2.27
ISTD area variation	9	19	0.79	1.66	9	19	0.79	1.66
Concentration of a subject sample is more than the highest CC Point	1	1	0.09	0.09	1	1	0.09	0.09
Extraction/processing error	0	2	0.00	0.17	0	2	0.00	0.17
Total	**36**	**48**	**3.15**	**4.20**	**36**	**48**	**3.15**	**4.20**

Study No. 04132/09-10 Diclofenac Location in final report: Bio-analytical Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual number		%of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Anomalous Value	1	0	0.08	0.00	1	0	0.08	0.00
Concentration of a subject sample is more than the highest CC point	2	0	0.16	0.00	2	0	0.16	0.00
ISTD area variation	1	2	0.08	0.16	1	2	0.08	0.16
Unacceptable Calibration Curve	30	30	2.33	2.33	30	30	2.33	2.33
Total	**34**	**32**	**2.64**	**2.48**	**34**	**32**	**2.64**	**2.48**

Study No. 04132/09-10 Misoprostol Acid Location in final report: Bio-analytical Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual number		%of total assays	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Unacceptable Calibration Curve	90	90	6.98	6.98	90	90	6.98	6.98
ISTD area variation	22	40	1.71	3.10	22	40	1.71	3.10
Extraction/processing error	0	1	0.00	0.08	0	1	0.00	0.08
Pre-dose sample(0.00hrs+ISTD) concentration, if any more than the 5% if Cmax from the same period	0	1	0.00	0.08	0	1	0.00	0.08
Anomalous Value	1	0	0.08	0.00	1	0	0.08	0.00
BLQ in middle of the profile	1	2	0.08	0.16	1	2	0.08	0.16
Poor Chromatography	1	0	0.08	0.00	1	0	0.08	0.00
Total	**115**	**134**	**8.91**	**10.39**	**115**	**134**	**8.91**	**10.39**

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

For the fasting study, the firm reanalyzed 3 diclofenac samples as "anomalous values," which the reviewer considers a pharmacokinetic repeats. However, the firm used the original values for all 3 samples in the statistical analysis.

For the fed study, the firm reanalyzed 1 diclofenac and 1 misoprostol acid sample as "anomalous values." The reviewer conducted statistical analysis using both original and repeat values for both diclofenac and misoprostol acid. The use of the original values did not change the study outcome.

Reanalysis of samples were performed according to SOP 23/13 "Repeat Analysis of Samples & Reintegration of Chromatograms."

3.7 Formulation

Location in appendix	Section 4.2, Page 57
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS REV-BIOEQ-02(Dissolution Review) Submit Date: 6/30/2010 and 10/15/2010
Source of Method (USP, FDA or Firm)	FDA
Medium	**Diclofenac:** 0.1 N HCl for acid stage; + 0.2 M Phosphate Buffer (pH 6.8) for buffer stage **Misoprostol:** Water (deaerated)
Volume (mL)	**Diclofenac:** 750 mL for acid stage + 250 mL (1000 mL total) for buffer stage **Misoprostol:** 500 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	**Diclofenac:** 100 rpm **Misoprostol:** 50 rpm
DBE-recommended specifications	**Diclofenac:** NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT (b) (4) (Q) Diclofenac dissolved in 45 minutes (buffer stage) **Misoprostol:** NLT (b) (4) (Q) Misoprostol dissolved in 20 minutes
If a modified-release tablet, was testing done on ½ tablets?	Not needed as they are not scored
F2 metric calculated?	No
If no, reason why F2 not calculated	Only one strength
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

3.9 Deficiency Comments

None.

3.10 Recommendations

1. The Division of Bioequivalence II (DB II) accepts the fasting BE study (No.04131/09-10) conducted by Watson Laboratories, Inc. on its Diclofenac Sodium/Misoprostol Delayed Release Tablets, 75 mg/0.2 mg (Lot #0398R0022A), comparing it to GD Searle LLC's Arthrotec® Delayed Release Tablets, 75 mg/0.2 mg (Lot #C081587).

2. The DB II accepts the fed BE study (No.04132/09-10) conducted by Watson Laboratories, Inc. on its Diclofenac Sodium/Misoprostol Delayed Release Tablets, 75 mg/0.2 mg (Lot #0398R0022A), comparing it to GD Searle LLC's Arthrotec® Delayed Release Tablets, 75 mg/0.2 mg (Lot #C081587).

3. The firm's *in vitro* dissolution testing is adequate. The dissolution testing should be conducted using the following FDA-recommended dissolution method and specification:

Medium:	0.1 N HCl for acid stage of Diclofenac 750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer pH 6.8 for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac 1000 mL for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotational Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol

Specifications:

NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage)
NLT (Q) Diclofenac dissolved in 45 minutes (buffer stage)
NLT (Q) Misoprostol dissolved in 20 minutes

The application is **inadequate,** due to a pending OSI inspection of the clinical site.

3.11 Comments for Other OGD Disciplines

Discipline	Comment
ALL	A routine OSI inspection was requested for the clinical site regarding this ANDA on 08/12/2011.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	04131/09-10
Study Title	An Open labeled, randomized, two treatment, four period, two sequence, single dose fully replicate crossover design using a scaled bioequivalence approach of Diclofenac sodium/ Misoprostol 75mg/0.2mg Tablets (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of Watson Laboratories Inc, USA against Arthrotec® (Diclofenac sodium/ Misoprostol) Tablet (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of G. D. Searle LLC (Division of Pfizer Inc), USA in healthy human, adult subjects under fasting condition using a reference-scaled average bioequivalence approach
Clinical Site (Name & Address)	Clinical Research Division Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA
Principal Investigator	Dr. Manoj K Bose, MD
Dosing Dates	Period-I: 09 Oct 2009 Period-II: 16 Oct 2009 Period-III: 23 Oct 2009 Period-IV: 30 Oct 2009
Analytical Site (Name & Address)	Room No's. 131B,140 & 133B Clinical Research Division Central Laboratory Vimta Labs Ltd. 142, IDA, Phase II, Cherlapally Hyderabad-500 051, India
Analysis Dates	Analysis Started: 09 Nov 2009 (Diclofenac) Analysis Completed: 21 Nov 2009 (Diclofenac including ISR) Analysis Started: 12 Nov 2009 (Misoprostol free acid) Analysis Completed: 23 Nov 2009 (Misoprostol free acid including ISR)
Analytical Director	(b) (6) Bio analytical.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	44 days (Diclofenac) 46 days (Misoprostol free acid)

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Diclofenac Sodium/Misoprostol Tablets	Arthrotec™ (Diclofenac Sodium/Misoprostol Tablets)
Manufacturer	Watson Laboratories, Inc.-FL	G.D. Searle, LLC, a division of Pfizer, Inc.
Batch/Lot No.	0398R0022A	C081587
Manufacture Date	02/27/09	N/A
Expiration Date	N/A	08/2012
Strength	75 mg/0.2 mg	75 mg/ 0.2 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	Misoprostol: 102.9% Diclofenac Sodium: 97.4%	Misoprostol: 101.4% Diclofenac Sodium: 98.7%
Content Uniformity (mean, %CV)	Misoprostol: 104.1%. (%CV: 0.8%; AV: 4.5) Diclofenac Sodium: 99.4%, (%CV: 1.2%; AV: 2.9)	Misoprostol: 103.5%, (%CV:1.8%; AV: 6.3) Diclofenac Sodium: 98.9%, (%CV: 0.9%; AV: 2.2)
Dose Administered	1 x 75 mg/0.2 mg	1 x 75 mg/0.2 mg
Route of Administration	Oral	Oral

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

Number of Subjects	**Enrolled:** 48 **Dosed:** 44 **Completed:** 44 **Analyzed and included in statistical analysis:** 44
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**TRTR:** 2, 3, 4, 7, 8, 9, 13, 14, 17, 21, 23, 24, 25, 26, 29, 32, 35, 36, 37, 38, 39, 43, 46, 48 **RTRT:** 1, 5, 6, 10, 11, 12, 15, 16, 18, 19, 20, 22, 27, 28, 30, 31, 33, 34, 40, 41, 42, 44, 45, 47
Blood Sampling Times	Pre-dose and 0.08, 0.17, 0.25, 0.42, 0.5, 0.67, 0.75, 1, 1.33, 1.5, 1.67, 2, 2.33, 2.5, 2.67, 3, 3.5, 4, 5, 6, 8, and 10 hours post-dose in each period.
Blood Volume Collected/Sample	1 x 3-6 mL in tubes containing K3 EDTA

Blood Sample Processing/Storage	The blood samples were collected into K3 EDTA vacutainer. All blood samples were centrifuged within 30 minutes of collection. Centrifugation was performed with centrifuge set for about 10 minutes at 3800 rpm at 10ºC. After centrifugation the supernatant plasma was transferred directly into two prelabelled vials and the vials were immediately stored in a deep freezer below -60ºC. Plasma samples were transferred to Bio-analytical department after completion of each period of study where the samples were stored below -60ºC until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Overnight fast of at least 10 hours.
Length of Confinement	From 10 hours prior to dosing until 12 hours post dose in each period.
Safety Monitoring	Safety assessments of all subjects were carried out at the time of screening, during the course of study and at the end of the study by conducting medical examination, monitoring of vital parameters and pathological testing. Medical examinations of subjects were carried out during screening, pre-study examination of each period of the study, at the time of adverse event, if any and during post study examination. In each period, vital parameters of each subject were monitored during check-in, before administration of investigational products and at 2.25, 5.25 hrs post dose and at check-out.

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

Study No. 04131/09-10 **Location in final report: Section**-14.1.2-2		
	Treatment Groups	
	Test Product **N = 44**	**Reference Product** **N = 44**
Age (Years)		
Mean ± SD	28.59 ± 5.222	28.59 ± 5.222
Range	20 – 39	20 – 39
Groups		
< 18	Nil	Nil
18 – 40	44 (100%)	44 (100%)
41 – 64	Nil	Nil
65 – 75	Nil	Nil
> 75	Nil	Nil
Sex		
Female	Nil	Nil
Male	44 (100%)	44 (100%)
Race		
Asian	44 (100%)	44 (100%)
Black	Nil	Nil
Caucasian	Nil	Nil
Hispanic	Nil	Nil
Other	Nil	Nil
BMI		
Mean ± SD	21.98 ± 1.776	21.98 ± 1.776
Range	19 – 25	19 – 25
Other Factors	Nil	Nil

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 04131/09-10 **Location in final report:; Section**-10.1						
Subject No.	**Reason for Dropout/Replacement**			**Period**	**Replaced**	**Replaced with**
	Time (Hr:Min)	**Treatment**	**Reasons**			
10	-	-	Participant had not presented himself for study participation on period III admission day due to personal reasons	III	No	Nil
11	-	-	Participant had not presented himself for study participation on period III admission day due to personal reasons	III	No	Nil
27	-	-	Detected positive in urine for recent abuse of drugs prior to period II admission.	II	No	Nil
28	-	-	Detected positive in urine for recent abuse of drugs prior to period II admission.	II	No	Nil

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body system/Adverse Event	Reported Incidence by Treatment Groups Fasted Bioequivalence Study No.: 04131/09-10	
	Test	Reference
Body as a whole N (%)	Nil	Nil
Nervous System N (%)		
Vascular disorders N (%)		
Skin and sub cutaneous tissue disorders N (%)		
Gastrointestinal N (%)		
Haemopoetic system*		
Serum bilirubin increased N (%)	1 (4.17%)	1 (2.08%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 04131/09-10 **Location in final report: Section-16.2.2**		
Type	**Subject No. (Test)**	**Subject No. (Reference)**
In Period II, III & IV, listed participants were admitted late into the CPU due to administrative reasons	**Period II** 30 **Period III** 14,26,32 and 48 **Period IV** 20 and 42	**Period II** Nil **Period III** 12,15,18,34,40 and 42 **Period IV** 35,37 and 43
After blood collection, blood samples vacutainers were not kept in box Containing dry ice for all the samples before centrifugation through out the study		

Comments on Dropouts/Adverse Events/Protocol Deviations:

There were no serious adverse events during the study. Subjects 10 and 11 were withdrawn from the study due to personal reasons prior to Period III check-in. Subjects 27 and 28 tested positive for drugs of abuse prior to Period II check-in. These subjects were not replaced. Protocol deviations did not affect the study outcome.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No.: 04131/09-10 Analyte Name: Diclofenac								
Parameter	**Standard Curve Samples**							
CC Level →	**CC1**	**CC2**	**CC3**	**CC4**	**CC5**	**CC6**	**CC7**	**CC8**
Concentration (ng/mL)	30.050	60.050	150.150	450.450	1001.050	2002.100	3003.150	4004.200
Inter day Precision (%CV)	4.08	4.17	3.53	4.73	3.08	5.11	3.59	4.36
Inter day Accuracy (%Actual)	98.74	101.29	102.79	100.60	103.20	98.33	97.20	97.88
Linearity (r)	0.995737 to 0.999881							
Linearity Range (ng/mL)	30.050 to 4004.200 ng/mL							
Sensitivity(ng/mL)	30.050 ng/mL							

Bioequivalence Study No.: 04131/09-10 Analyte Name: Diclofenac				
Parameter	**Quality Control Samples**			
QC ID →	**LQC**	**GMQC**	**MQC**	**HQC**
Concentration (ng/mL)	90.300	381.250	1605.250	3210.450
Inter day Precision (%CV)	6.41	5.30	5.74	4.80
Inter day Accuracy (%Actual)	104.16	102.91	102.97	98.98

Bioequivalence Study No.:04131/09-10 Analyte Name: Misoprostol Acid								
Parameter	**Standard Curve Samples**							
CC Level →	**CC1**	**CC2**	**CC3**	**CC4**	**CC5**	**CC6**	**CC7**	**CC8**
Concentration (pg/mL)	10.000	20.000	50.000	99.950	249.900	499.800	749.700	999.600
Inter day Precision (%CV)	6.48	7.05	5.07	4.61	3.40	3.51	3.66	3.23
Inter day Accuracy (%Actual)	101.07	97.34	101.46	99.16	102.97	96.91	100.84	100.08
Linearity (r)	0.9941 to 0.9995							
Linearity Range (pg/mL)	10.000 to 999.600 pg/mL							
Sensitivity(pg/mL)	10.000 pg/mL							

Bioequivalence Study No.: 04131/09-10 Analyte Name: Misoprostol Acid				
Parameter	**Quality Control Samples**			
QC ID →	**LQC**	**GMQC**	**MQC**	**HQC**
Concentration (pg/mL)	30.000	110.000	400.000	800.000
Inter day Precision (%CV)	7.35	6.27	4.94	3.86
Inter day Accuracy (%Actual)	102.85	107.30	101.22	106.56

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. SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
23/13	2008-04-30	Repeat Analysis of Samples & Reintegration of Chromatograms

Table 13. 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?	N/A
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

Diclofenac (n=44):
REPLICATE 1 (PERIODS 1 AND 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2496.543	22.35	1345.73	3708.60	2452.120	19.86	1549.05	3464.41	1.02
AUCINF	ng hr/mL	2567.616	22.04	1400.07	3794.11	2515.078	19.59	1608.41	3522.59	1.02
CMAX	ng/mL	2093.599	29.20	727.16	3593.16	1743.467	29.70	934.98	3259.89	1.20
TMAX	hr	1.500	.	0.50	5.00	1.500	.	0.25	4.00	1.00
KEL	hr-1	0.639	24.58	0.31	0.97	0.704	25.15	0.46	1.27	0.91
THALF	hr	1.158	27.68	0.72	2.23	1.039	22.59	0.55	1.52	1.11

REPLICATE 2 (PERIODS 3 AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2477.212	25.69	1501.50	4544.45	2528.773	21.96	1585.74	3811.53	0.98
AUCINF	ng hr/mL	2562.122	25.09	1533.24	4623.63	2592.409	22.02	1686.40	3884.14	0.99
CMAX	ng/mL	1915.855	45.89	466.60	3945.39	1842.634	38.74	732.35	3692.98	1.04
TMAX	hr	1.000	.	0.50	5.00	1.500	.	0.50	6.00	0.67
KEL	hr-1	0.628	36.57	0.17	1.26	0.712	30.72	0.37	1.25	0.88
THALF	hr	1.289	51.13	0.55	4.05	1.069	31.41	0.55	1.85	1.21

ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2486.877	23.93	1345.73	4544.45	2490.446	20.91	1549.05	3811.53	1.00
AUCINF	ng hr/mL	2564.869	23.48	1400.07	4623.63	2553.299	20.80	1608.41	3884.14	1.00
CMAX	ng/mL	2004.727	37.82	466.60	3945.39	1793.050	34.69	732.35	3692.98	1.12
TMAX	hr	1.000	.	0.50	5.00	1.500	.	0.25	6.00	0.67
KEL	hr-1	0.634	30.89	0.17	1.26	0.708	27.91	0.37	1.27	0.89
THALF	hr	1.223	42.45	0.55	4.05	1.054	27.31	0.55	1.85	1.16

Misoprostol Acid (n=44):
REPLICATE 1 (PERIODS 1 AND 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	203.677	33.04	90.51	351.35	204.173	33.38	101.28	375.65	1.00
AUCINF	pg hr/mL	212.344	32.41	98.75	363.06	211.623	32.42	106.91	382.58	1.00
CMAX	pg/mL	363.904	37.05	74.53	680.52	360.061	45.58	135.54	823.39	1.01

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
TMAX	hr	0.250	.	0.08	0.42	0.250	.	0.17	1.00	1.00
KEL	hr-1	1.727	38.73	0.70	3.27	1.851	27.68	0.73	2.88	0.93
THALF	hr	0.465	38.96	0.21	0.99	0.410	34.77	0.24	0.95	1.13

REPLICATE 2 (PERIODS 3 AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	207.893	36.43	96.04	442.06	218.588	39.13	97.78	443.84	0.95
AUCINF	pg hr/mL	218.962	36.91	101.94	457.44	228.367	37.92	108.74	452.81	0.96
CMAX	pg/mL	353.376	48.92	117.42	928.69	355.254	52.29	90.66	878.50	0.99
TMAX	hr	0.250	.	0.17	1.00	0.420	.	0.17	0.67	0.60
KEL	hr-1	1.508	31.67	0.27	2.39	1.575	34.45	0.43	3.60	0.96
THALF	hr	0.542	65.07	0.29	2.54	0.504	46.37	0.19	1.60	1.08

ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	205.785	34.63	90.51	442.06	211.380	36.53	97.78	443.84	0.97
AUCINF	pg hr/mL	215.653	34.64	98.75	457.44	219.995	35.51	106.91	452.81	0.98
CMAX	pg/mL	358.640	43.00	74.53	928.69	357.657	48.73	90.66	878.50	1.00
TMAX	hr	0.250	.	0.08	1.00	0.250	.	0.17	1.00	1.00
KEL	hr-1	1.617	36.36	0.27	3.27	1.713	31.68	0.43	3.60	0.94
THALF	hr	0.503	55.90	0.21	2.54	0.457	43.36	0.19	1.60	1.10

* Tmax values are presented as median, range

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

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 04131/09-10				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	2403.8764	2422.8264	99.22	95.93 – 102.62
AUC∞ (hr *ng/ml)	2481.6107	2485.2143	99.85	96.60 – 103.22
Cmax (ng/ml)	1842.7528	1677.0832	109.88	100.35 – 120.31
Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 04131/09-10				

Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *pg/ml)	192.8889	196.1945	98.32	94.48 – 102.30
AUC∞ (hr *pg/ml)	202.3826	204.9951	98.73	94.89 – 102.72
Cmax (pg/ml)	326.1861	319.4056	102.12	93.41 – 111.65

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

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.99	95.93	102.62	0.0130749	0.1143455	-0.007203	Unscaled	PASS
LAUCI	1.00	96.60	103.22	0.0124079	0.1113906	-0.006992	Unscaled	PASS
LCMAX	1.10	100.35	120.31	0.0845979	0.2908572	-0.027567	Unscaled	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2403.88	2422.83	0.99	95.93	102.62
AUC∞ (hr *ng/ml)	2481.61	2485.21	1.00	96.60	103.22
Cmax (ng/ml)	1842.75	1677.08	1.10	100.35	120.31

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Misoprostol Acid
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.98	94.48	102.30	0.0202397	0.1422661	-0.010721	Unscaled	PASS
LAUCI	0.99	94.89	102.72	0.0187469	0.1369193	-0.010124	Unscaled	PASS
LCMAX	1.02	93.41	111.65	0.068066	0.2608947	-0.035698	Unscaled	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Misoprostol Acid
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. 04131/09-10 (N=44)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	192.89	196.19	0.98	94.48	102.30
AUC∞ (hr *pg/ml)	202.38	205.00	0.99	94.89	102.72
Cmax (pg/ml)	326.19	319.41	1.02	93.41	111.65

Table 17. Additional Study Information, Fasting Study No. 04131/09-10

	Diclofenac		Misoprostol Acid	
Root mean square error, AUC0-t	0.1143		0.1423	
Root mean square error, AUC∞	0.1114		0.1369	
Root mean square error, Cmax	0.2909		0.2609	
	Test		Reference	
	Diclofenac	Misoprostol Acid	Diclofenac	Misoprostol Acid
Kel and AUC∞ determined for how many subjects?	44	44	44*	44
Do you agree or disagree with firm's decision?	Agree	Agree	Agree	Agree
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0	1	0	0
first point as Cmax	0	2**	1**	0
first measurable drug concentration as Cmax	5	0	7	0
Were the subjects dosed as more than one group?	No	No	No	No

*Kel and AUCinf were not calculated for Subject 25 P4 (R).
***Note:** Dropping all subjects with first point Cmax does not affect the study outcome.

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test				
Diclofenac	44	0.97	0.89	0.98
Misoprostol Acid	44	0.95	0.90	0.98
Reference				
Diclofenac	44	0.97	0.95	0.99
Misoprostol Acid	44	0.96	0.91	0.98

Comments on Pharmacokinetic and Statistical Analysis:

1. The firm proposed to use the reference-scaled average bioequivalence approach in the study protocol. The current approach calls for using the reference-scaled average BE approach with a point estimate constraint, if s_{WR} (the estimated within-subject standard deviation on the log scale for the RLD) is greater than or equal to 0.294 (meaning that s^2_{WR} is greater than or equal to 0.086436). This was not true for any parameters in this study for both analytes, diclofenac and misoprostol acid. Therefore, the reviewer performed the statistical analysis by using the two one-sided tests procedure to determine bioequivalence for diclofenac and misoprostol acid.

2. One subject had a pre-dose concentration above the LLOQ. This pre-dose value was < 5% Cmax; therefore, this subject was not dropped from the statistical analysis.

3. The pharmacokinetic measures (AUCt, AUCi, Cmax, Tmax, KE and t1/2) and confidence intervals of AUCt, AUCi, and Cmax for diclofenac and misoprostol acid as calculated by the reviewer were in agreement with the values reported by the firm.

4. The 90% confidence intervals for diclofenac and misoprostol acid of ln-transformed AUCt, AUCi, and Cmax ratios are within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting *in vivo* bioequivalence study is **adequate.**

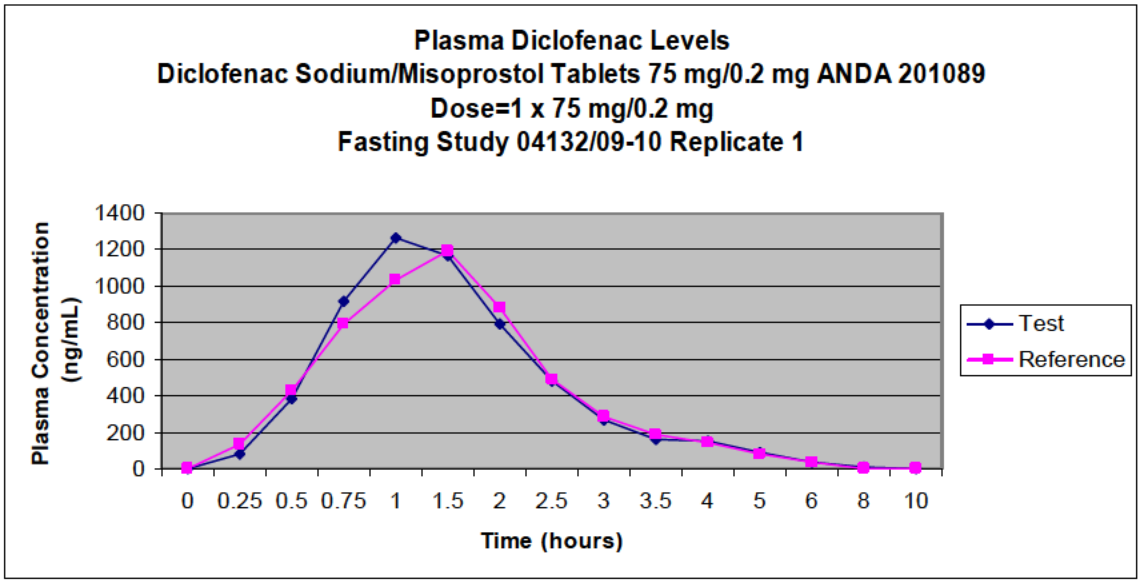
Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

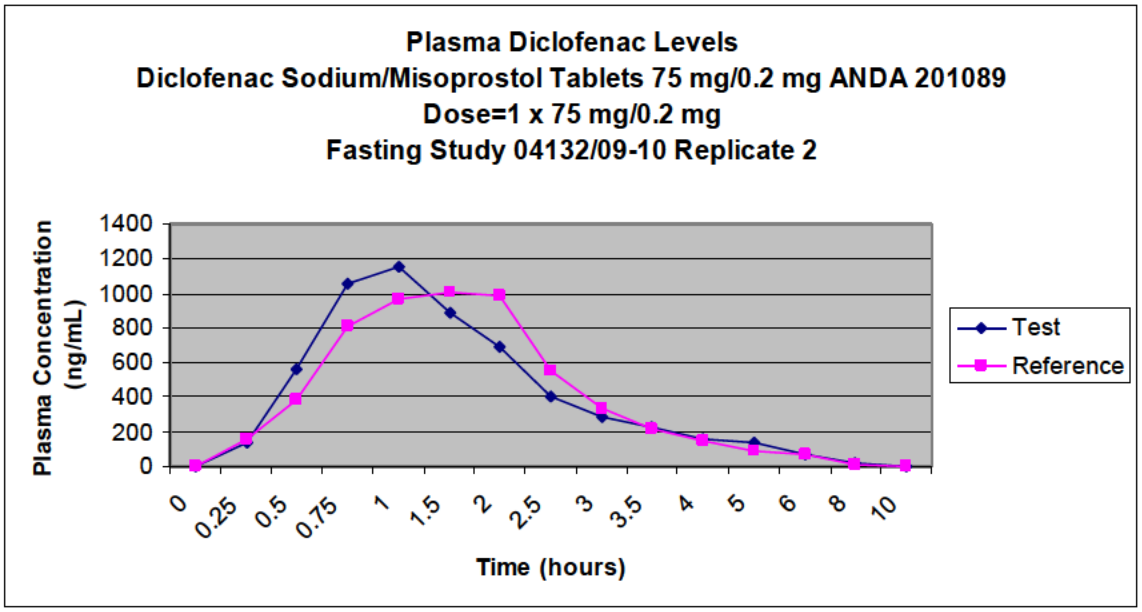
Diclofenac					
Time (hr)	Test (n= 44)		Reference (n=44)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0	--	0	--	-
0.25	108.88	274.15	146.19	252.98	0.74
0.5	472.09	166.44	406.19	150.86	1.16
0.75	988.56	104.27	801.48	102.99	1.23
1.0	1210.44	85.89	996.88	77.56	1.21
1.5	1028.93	72.34	1099.89	59.56	0.94
2.0	740.61	91.62	937.07	65.33	0.79
2.5	445.75	78.95	522.85	70.05	0.85
3.0	273.54	74.47	308.97	58.27	0.89
3.5	190.69	96.25	204.33	69.84	0.93
4.0	154.86	136.23	143.82	81.96	1.08
5.0	112.92	183.08	84.89	112.95	1.33
6.0	51.39	161.66	52.13	290.94	0.99
8.0	12.69	319.62	4.22	339.14	3.01
10.0	2.54	425.51	0	--	-

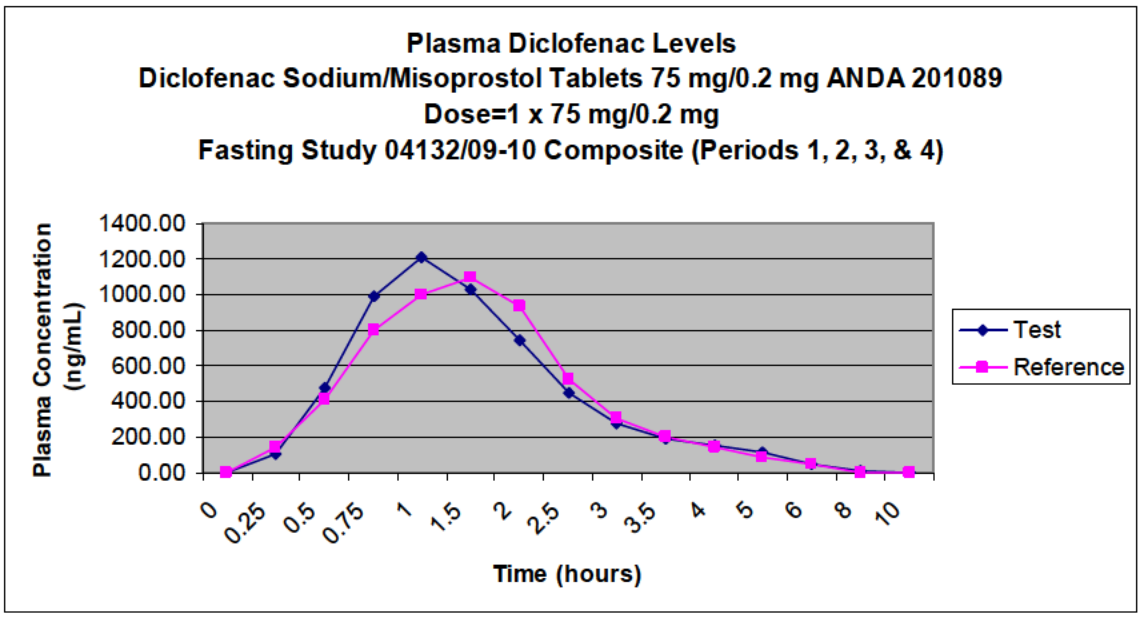
Misoprostol Acid					
Time (hr)	Test (n= 44)		Reference (n=44)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0	0.13	938.08	0.00	--	--
0.08	115.71	109.45	67.50	121.46	1.71
0.17	231.85	72.00	220.57	87.70	1.05
0.25	300.20	54.96	300.06	62.37	1.00
0.42	254.13	43.40	258.28	37.79	0.98
0.67	138.15	48.41	144.95	44.39	0.95
1.0	66.24	53.52	77.78	55.92	0.85
1.33	35.94	53.84	40.70	69.64	0.88
1.67	20.63	58.93	23.87	84.57	0.86
2.0	11.51	94.47	13.80	105.35	0.83
2.33	5.53	147.07	5.94	137.83	0.93
2.67	2.27	238.55	2.87	200.789	0.79
3.0	0.90	381.55	1.50	287.81	0.60

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

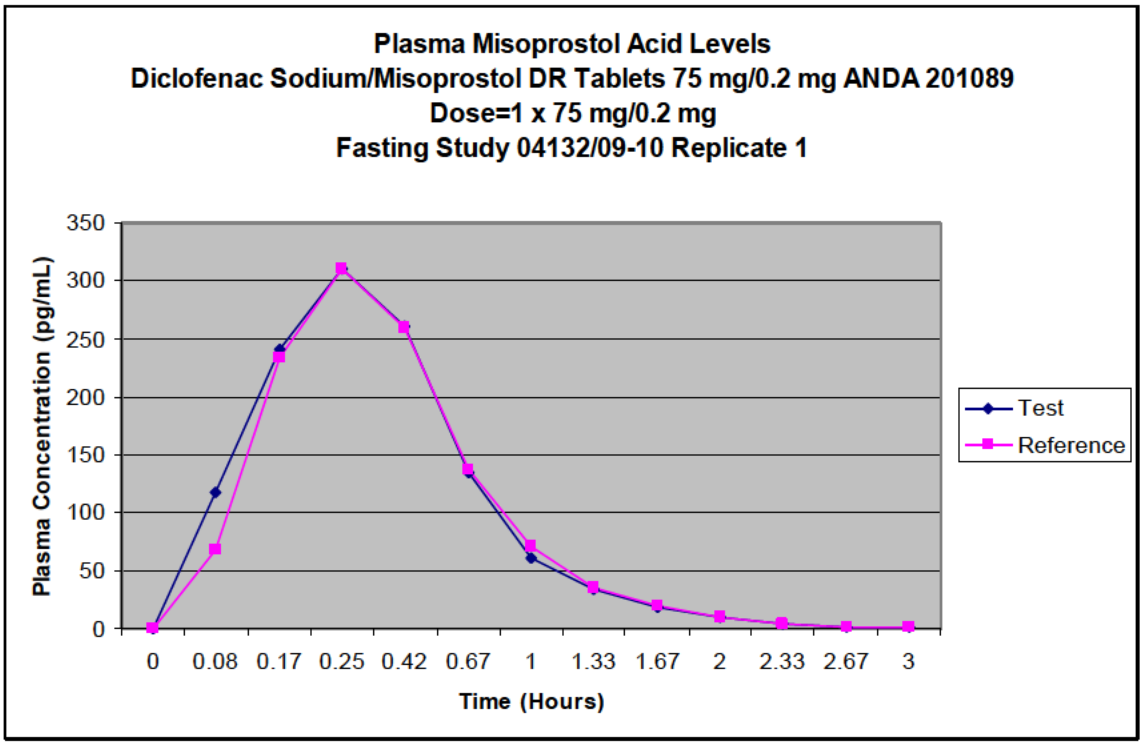
Diclofenac:

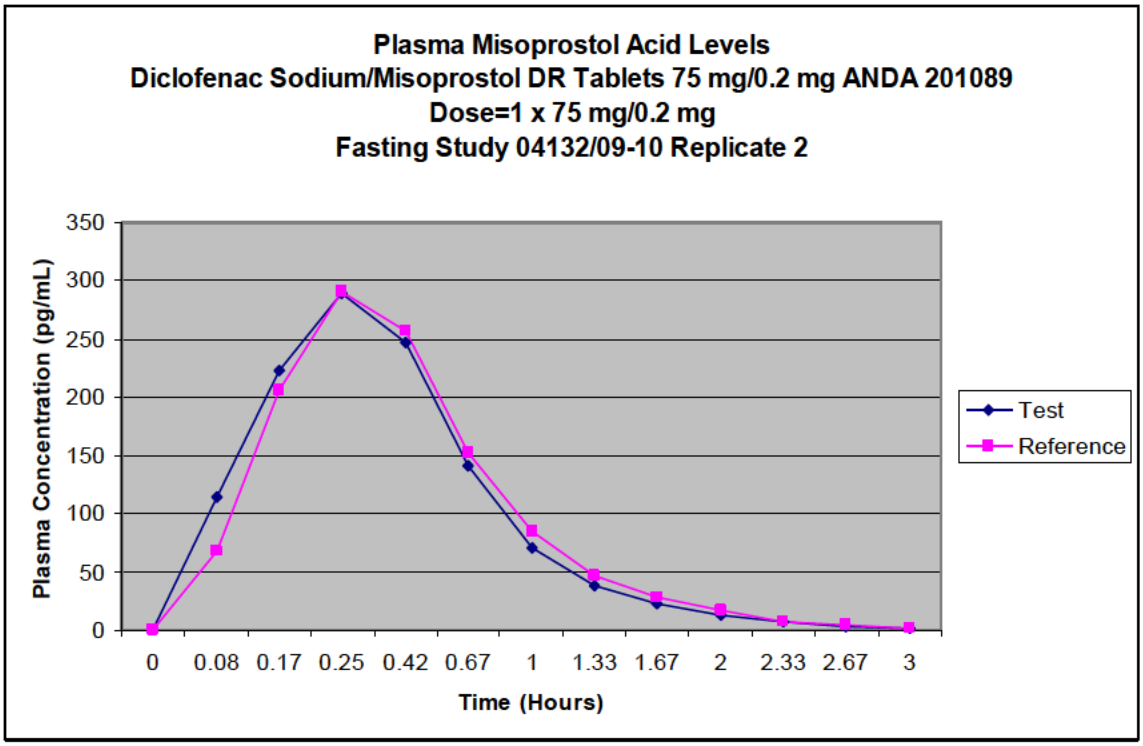


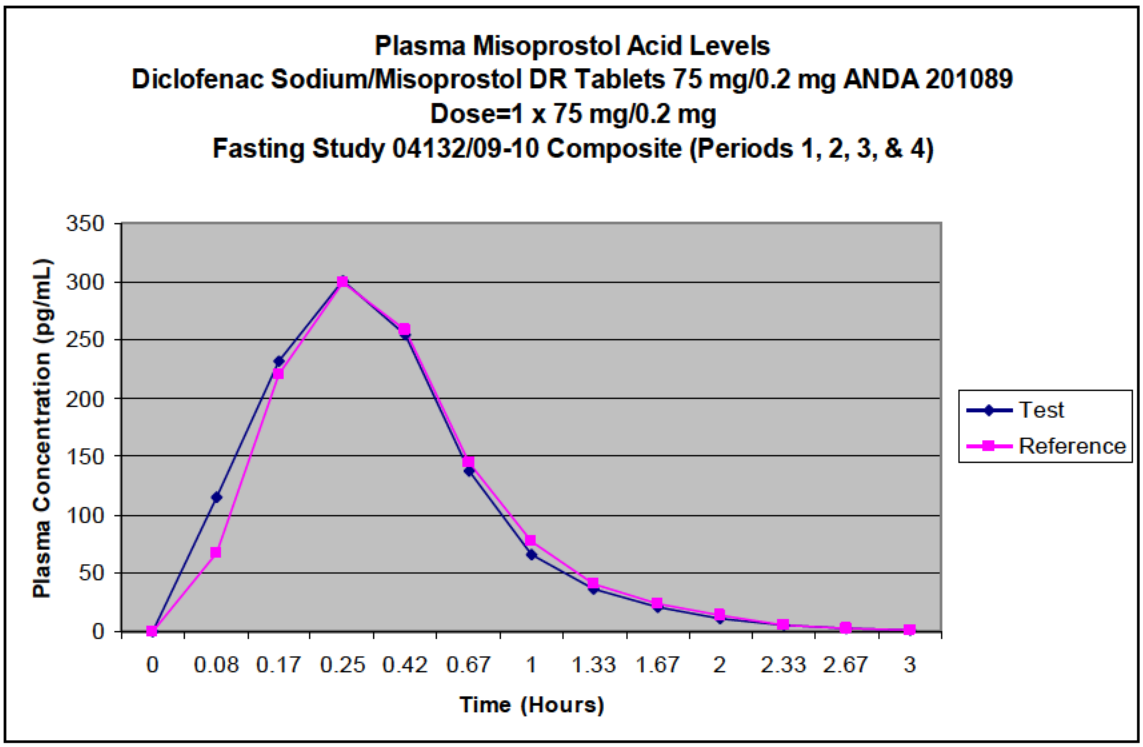




Misoprostol Acid:




Plasma Misoprostol Acid Levels
Diclofenac Sodium/Misoprostol DR Tablets 75 mg/0.2 mg ANDA 201089
Dose=1 x 75 mg/0.2 mg
Fasting Study 04132/09-10 Replicate 2
Plasma Concentration (pg/mL)
350
300
250
200
150
100
50
0
0 0.08 0.17 0.25 0.42 0.67 1 1.33 1.67 2 2.33 2.67 3
Time (Hours)
Test
Reference


Plasma Misoprostol Acid Levels
Diclofenac Sodium/Misoprostol DR Tablets 75 mg/0.2 mg ANDA 201089
Dose=1 x 75 mg/0.2 mg
Fasting Study 04132/09-10 Composite (Periods 1, 2, 3, & 4)
Plasma Concentration (pg/mL)
350
300
250
200
150
100
50
0
0 0.08 0.17 0.25 0.42 0.67 1 1.33 1.67 2 2.33 2.67 3
Time (Hours)
Test
Reference

4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	04132/09-10
Study Title	An Open labeled, randomized, two treatment, four period, two sequence, single dose fully replicate crossover design using a scaled bioequivalence approach of Diclofenac sodium/ Misoprostol 75mg/0.2mg Tablets (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of Watson Laboratories Inc, USA against Arthrotec® (Diclofenac sodium/ Misoprostol) Tablet (each tablet containing Diclofenac sodium 75mg and Misoprostol 0.2mg) of G. D. Searle LLC (Division of Pfizer Inc), USA in healthy human, adult subjects under fed condition using a reference-scaled average bioequivalence approach
Clinical Site (Name & Address)	Clinical Research Division Vimta Labs Ltd., 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA
Principal Investigator	Dr. Manoj K Bose, MD
Dosing Dates	Period-I: 15 Oct 2009 Period-II: 22 Oct 2009 Period-III: 29 Oct 2009 Period-IV: 05 Nov 2009
Analytical Site (Name & Address)	Room No's. 131B,140 & 133B Clinical Research Division Central Laboratory Vimta Labs Ltd. 142, IDA, Phase II, Cherlapally Hyderabad-500 051, India
Analysis Dates	Analysis Started: 24 Nov 2009 (Diclofenac) Analysis Completed: 08 Dec 2009 (Diclofenac including ISR) Analysis Started: 26 Nov 2009 (Misoprostol free acid) Analysis Completed: 09 Dec 2009 (Misoprostol free acid including ISR)
Analytical Director	(b) (6) Bio analytical.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	55 days (Diclofenac) 56 days (Misoprostol free acid)

Table 20. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Diclofenac Sodium/Misoprostol Tablets	Arthrotec™ (Diclofenac Sodium/Misoprostol Tablets)
Manufacturer	Watson Laboratories, Inc.-FL	G.D. Searle, LLC, a division of

		Pfizer, Inc.
Batch/Lot No.	0398R0022A	C081587
Manufacture Date	02/27/09	N/A
Expiration Date	N/A	08/2012
Strength	75 mg/0.2 mg	75 mg/ 0.2 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (Assay)	Misoprostol: 102.9% Diclofenac Sodium: 97.4%	Misoprostol: 101.4% Diclofenac Sodium: 98.7%
Content Uniformity (mean, %CV)	Misoprostol: 104.1%. (%CV: 0.8%; AV: 4.5) Diclofenac Sodium: 99.4%, (%CV: 1.2%; AV: 2.9)	Misoprostol: 103.5%, (%CV:1.8%; AV: 6.3) Diclofenac Sodium: 98.9%, (%CV: 0.9%; AV: 2.2)
Dose Administered	1 x 75 mg/0.2 mg	1 x 75 mg/0.2 mg
Route of Administration	Oral	Oral

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

No. of Subjects	**Enrolled:** 48 **Dosed:** 48 **Completed:** 43 **Analyzed: 43** **Included in statistical analysis:** 40 for diclofenac and 43 for misoprostol acid*
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**TRTR:** 4, 5, 6, 8, 9, 12, 13, 16, 18, 20, 21, 24, 25, 29, 30, 31, 35, 36, 37, 38, 42, 44, 45, 46 **RTRT:** 1, 2, 3, 7, 10, 11, 14, 15, 17, 19, 22, 23, 26, 27, 28, 32, 33, 34, 39, 40, 41, 43, 47, 48
Blood Sampling Times	Pre-dose and 0.08, 0.17, 0.33, 0.5, 0.67, 1, 1.33, 1.5, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours post-dose
Blood Volume Collected/Sample	1 x 3-6 mL in tubes containing K3 EDTA
Blood Sample Processing/Storage	The blood samples were collected into K3 EDTA vacutainer. All blood samples were centrifuged within 30 minutes of collection. Centrifugation was performed with centrifuge set for about 10 minutes at 3800 rpm at 10ºC. After centrifugation the supernatant plasma was transferred directly into two prelabelled vials and the vials were immediately stored in a deep freezer below -60ºC. Plasma samples were transferred to Bio-analytical department after completion of each period of study where the samples were stored below -60ºC until analysis.
IRB Approval	Yes

Informed Consent	Yes
Length of Fasting Before Meal	Overnight fast of at least 10 hours followed by a high-fat high-calorie breakfast 30 minutes prior to dosing.
Length of Confinement	From 10 hours prior to dosing until 12 hours post dose in each period.
Safety Monitoring	Safety assessments of all subjects were carried out at the time of screening, during the course of study and at the end of the study by conducting medical examination, monitoring of vital parameters and pathological testing. Medical examinations of subjects were carried out during screening, pre-study examination of each period of the study, at the time of adverse event, if any and during post study examination. In each period, vital parameters of each subject were monitored during check-in, before administration of investigational products and at 2.25, 5.25 hrs post dose and at check-out.

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	57.25	537.84
Carbohydrate	29.89	280.76
Protein	12.86	120.8
Total	**100.00**	**939.4**

***Note:** The firm states:

"Subjects 15, 29 & 37 were not used for pharmacokinetic and statistical analysis of Diclofenac, because after bioanalysis for period I only at one time point the drug concentration was detected for participant 15, for period III only at two time points the drug concentration were detected for participant 29 and for period II no drug concentration was detected at any of the time point for participant 37."

S.No	Menu	Quantity
1	Bread-sliced, with 20 grams butter	2 slices
2	Chicken tikka (bacon replacement)	75 grams
3	Egg-omlette	20 grams
4	Hash brown potatoes with 5 grams butter	85+5 = 90 grams
5	Whole milk	240 mL

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

Study No. 04132/09-10 **Location in final report: Section**-14.1.2-2		
	Treatment Groups	
	Test Product **N = 43**	**Reference Product** **N = 43**
Age (Years)		
Mean ± SD	26.84 ± 5.765	26.84 ± 5.765
Range	18 – 41	18 – 41
Groups		
< 18	Nil	Nil
18 – 40	42 (97.67%)	42 (97.67%)
41 – 64	1 (2.33%)	1 (2.33%)
65 – 75	Nil	Nil
> 75	Nil	Nil
Sex		
Female	Nil	Nil
Male	43 (100%)	43 (100%)
Race		
Asian	43 (100%)	43 (100%)
Black	Nil	Nil
Caucasian	Nil	Nil
Hispanic	Nil	Nil
Other	Nil	Nil
BMI		
Mean ± SD	22.48 ± 1.746	22.48 ± 1.746
Range	19 – 25	19 – 25
Other Factors	Nil	Nil

Table 23. Dropout Information, Fed Bioequivalence Study

Study No. 04132/09-10 **Location in final report:; Section**-10.1						
Subject No.	**Reason for Dropout/Replacement**			**Period**	**Replaced**	**Replaced with**
	Time (Hr:Min)	**Treatment**	**Reasons**			
20	-	-	Participant had not presented himself for study participation on period II admission day due to personal reasons	II	No	Nil
31	-	-	Participant had not presented himself for study participation on period III admission day due to personal reasons	III	No	Nil
47	-	-	Participant had not presented himself for study participation on period III admission day due to personal reasons	III	No	Nil
44	0824	R	Subject was withdrawn from the study in period II after dosing due	II	No	Nil

			to AE (Vomiting).			
41	-	-	Detected positive in urine for recent abuse of drugs prior to period II admission.	II	No	Nil

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body system/Adverse Event	Reported Incidence by Treatment Groups Fed Bioequivalence Study No.: 04132/09-10	
	Test	Reference
Body as a whole N (%)	Nil	Nil
Nervous System N (%)		
Vascular disorders N (%)		
Skin and sub cutaneous tissue disorders N (%)		
Gastrointestinal N (%)		
Vomiting N (%)		1 (2.32%)
Haemopoetic system*		
ALT increased N (%)	1 (2.32%)	

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No. 04132/09-10 **Location in final report: Section-16.2.2**		
Type	**Subject No. (Test)**	**Subject No. (Reference)**
In period II, few of the participants admission was done beyond the allowable limit of 10 hours prior to dosing	**Period II** 01,02,07,11,14,15,17, 19,22,23,26,28,32,33 34,39,40,41,47 and 48	**Period II** 06,08,13,18,21,24,25, 31,42,44,45 and 46
In period I, III and IV, few participants blood samples were collected out of the specified time due to cannula block	**Period I** 29 **Period II** Nil **Period III** 35 **Period IV** 15	**Period I** Nil **Period II** Nil **Period III** 33 **Period IV** 29 and 35
In period IV, for participant 32 vitals were measured prior to the scheduled allowable limit due to inadequacy in logistic reasons	**Period IV** 32	**Period IV** Nil
After blood collection, blood samples vacutainers were not kept in box containing dry ice for all the samples before centrifugation throughout the study		

Comments on Adverse Events/Protocol Deviations:

There were no serious adverse events during the study. Subject 20 withdrawn from the study due to personal reasons prior to Period II check-in. Subjects 31 and 47 withdrew from the study due to personal reasons prior to Period III check-in. Subject 41 tested positive for drugs of abuse prior to Period II check-in. Per the firm's protocol, Subject 44 was dropped from the study as emesis occurred within the housing period after dosing. A summary is provided below:

Subject	T/R	Time of Drug Dosing	Date/Time Emesis Onset	Days/Hours Post Dose
41	T	10/22/09 @ 08:08	10/22/09 @ 8:24	16 minutes

Protocol deviations did not affect the study outcome.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No.: 04132/09-10 Analyte Name: Diclofenac								
Parameter	**Standard Curve Samples**							
CC Level →	**CC1**	**CC2**	**CC3**	**CC4**	**CC5**	**CC6**	**CC7**	**CC8**
Concentration (ng/mL)	**30.050**	**60.100**	**150.300**	**450.900**	**1001.950**	**2003.950**	**3005.900**	**4007.900**
Inter day Precision (%CV)	3.56	3.47	3.30	4.54	3.98	4.95	3.54	4.44
Inter day Accuracy (%Actual)	97.58	102.21	106.08	103.96	97.73	98.00	97.36	97.29
Linearity (r)	0.995120 to 0.999664							
Linearity Range (ng/mL)	30.050 to 4007.900 ng/mL							
Sensitivity(ng/mL)	30.050 ng/mL							

Bioequivalence Study No.: 04132/09-10 Analyte Name: Diclofenac				
Parameter	**Quality Control Samples**			
QC ID →	**LQC**	**GMQC**	**MQC**	**HQC**
Concentration (ng/mL)	**90.250**	**381.100**	**1604.650**	**3209.300**
Inter day Precision (%CV)	5.87	5.55	6.71	5.88
Inter day Accuracy (%Actual)	102.02	102.26	96.46	94.94

Bioequivalence Study No.:04132/09-10 Analyte Name: Misoprostol Acid								
Parameter	**Standard Curve Samples**							
CC Level →	**CC1**	**CC2**	**CC3**	**CC4**	**CC5**	**CC6**	**CC7**	**CC8**
Concentration (pg/mL)	**10.000**	**20.000**	**50.000**	**99.950**	**249.900**	**499.750**	**749.650**	**999.500**
Inter day Precision (%CV)	9.93	8.02	6.25	4.86	3.69	3.54	3.41	3.37
Inter day Accuracy (%Actual)	99.65	98.60	103.37	102.10	102.79	96.70	97.80	98.73
Linearity (r)	0.9940 to 0.9988							
Linearity Range (pg/mL)	10.000 to 999.500 pg/mL							
Sensitivity(pg/mL)	10.000 pg/mL							

Bioequivalence Study No.: 04132/09-10 Analyte Name: Misoprostol Acid				
Parameter	**Quality Control Samples**			
QC ID →	**LQC**	**GMQC**	**MQC**	**HQC**

Concentration (pg/mL)	30.000	110.000	400.000	800.000
Inter day Precision (%CV)	12.39	5.50	5.28	4.72
Inter day Accuracy (%Actual)	97.14	101.12	105.78	106.49

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. SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
23/13	2008-04-30	Repeat Analysis of Samples & Reintegration of Chromatograms

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 33 and Figure 2

Diclofenac (n=40):

REPLICATE 1 (PERIODS 1 AND 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2274.976	37.87	1083.02	6186.42	2207.135	25.86	1251.08	3530.88	1.03
AUCINF	ng hr/mL	2348.611	36.68	1243.17	6226.41	2293.357	24.65	1313.61	3680.18	1.02
CMAX	ng/mL	1613.205	52.92	544.46	3957.89	1455.652	50.62	324.10	3806.05	1.11
TMAX	hr	3.265	.	1.50	6.00	3.500	.	1.50	6.00	0.93
KEL	hr-1	0.833	35.41	0.22	1.56	0.846	38.02	0.16	1.58	0.98
THALF	hr	0.964	48.57	0.44	3.16	1.032	70.26	0.44	4.34	0.93

REPLICATE 2 (PERIODS 3 AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2133.605	25.96	1206.76	3685.16	2139.096	25.63	1071.44	3701.88	1.00
AUCINF	ng hr/mL	2228.023	24.58	1236.80	3724.36	2226.550	24.51	1121.55	3798.82	1.00
CMAX	ng/mL	1626.783	56.07	230.40	3941.74	1283.981	48.51	426.31	3117.00	1.27
TMAX	hr	3.500	.	1.50	10.00	3.500	.	1.50	8.00	1.00
KEL	hr-1	0.866	32.11	0.19	1.31	0.906	34.62	0.27	1.57	0.96
THALF	hr	0.938	58.27	0.53	3.67	0.892	48.11	0.44	2.54	1.05

ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	2204.291	32.81	1083.02	6186.42	2173.116	25.64	1071.44	3701.88	1.01
AUCINF	ng hr/mL	2289.100	31.52	1236.80	6226.41	2260.377	24.47	1121.55	3798.82	1.01
CMAX	ng/mL	1619.994	54.19	230.40	3957.89	1369.817	49.89	324.10	3806.05	1.18
TMAX	hr	3.500	.	1.50	10.00	3.500	.	1.50	8.00	1.00
KEL	hr-1	0.850	33.60	0.19	1.56	0.876	36.22	0.16	1.58	0.97
THALF	hr	0.951	53.11	0.44	3.67	0.963	62.11	0.44	4.34	0.99

Misoprostol Acid (n=43):

REPLICATE 1 (PERIODS 1 AND 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	307.250	33.92	141.72	658.84	307.713	32.39	125.64	645.47	1.00
AUCINF	pg hr/mL	367.415	37.45	169.20	767.37	351.680	31.68	157.17	701.55	1.04
CMAX	pg/mL	181.356	53.51	58.17	603.78	182.263	61.67	57.42	704.62	1.00
TMAX	hr	0.330	.	0.17	5.00	0.330	.	0.17	3.50	1.00
KEL	hr-1	0.652	56.49	0.04	1.94	0.722	48.38	0.21	2.03	0.90
THALF	hr	1.897	158.27	0.36	18.38	1.220	56.34	0.34	3.26	1.56

REPLICATE 2 (PERIODS 3 AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	297.805	32.39	135.64	545.82	312.236	32.65	129.20	585.07	0.95
AUCINF	pg hr/mL	347.034	34.00	169.35	676.79	367.555	33.52	154.07	657.81	0.94
CMAX	pg/mL	188.448	56.42	60.19	555.45	181.849	50.18	59.08	577.01	1.04
TMAX	hr	1.330	.	0.17	5.00	0.330	.	0.17	6.00	4.03
KEL	hr-1	0.756	62.29	0.20	2.24	0.622	51.07	0.12	1.29	1.22
THALF	hr	1.319	60.79	0.31	3.40	1.511	66.54	0.54	5.57	0.87

ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	302.527	33.03	135.64	658.84	309.974	32.34	125.64	645.47	0.98
AUCINF	pg hr/mL	356.963	35.72	169.20	767.37	359.522	32.52	154.07	701.55	0.99
CMAX	pg/mL	184.902	54.76	58.17	603.78	182.056	55.90	57.42	704.62	1.02
TMAX	hr	0.500	.	0.17	5.00	0.330	.	0.17	6.00	1.52
KEL	hr-1	0.705	60.19	0.04	2.24	0.673	49.93	0.12	2.03	1.05
THALF	hr	1.601	136.03	0.31	18.38	1.364	63.54	0.34	5.57	1.17

* Tmax values are presented as median, range

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

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 04132/09-10				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	2108.9473	2102.8124	100.29	94.82 – 106.08
AUC∞ (hr *ng/ml)	2202.3074	2195.1089	100.33	95.68 – 105.20
Cmax (ng/ml)	1416.0843	1209.3234	117.10	Not applicable

Study No.: 04132/09-10 Analyte: Diclofenac Least Squares Geometric Means, Ratio of the Means and 90% Confidence Intervals							
Parameter (Diclofenac)	**Test (μT)**	**Reference (μR)**	**$(\mu T - \mu R)^2$**	**Theta (θ)**	**Intra-Subject Reference Variability (σ^2_{WR}) (%CV)**	**RSABE***	**95% Upper Confidence Bound for RSABE**
Ln C_{max}	7.2492	7.0951	0.0238	0.7967	40.2	-0.1049	-0.0384

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Misoprostol Acid 1 x 75 mg/0.2 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. 04132/09-10				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *pg/ml)	286.3963	294.1037	97.38	94.14 – 100.73
AUC∞ (hr *pg/ml)	336.9898	343.7177	98.04	93.22 – 103.12
Cmax (pg/ml)	162.6472	161.1933	100.90	Not applicable

Study No.: 04132/09-10 Analyte: Misoprostol Least Squares Geometric Means, Ratio of the Means and 90% Confidence Intervals							
Parameter (Misoprostol)	**Test (μT)**	**Reference (μR)**	**$(\mu T - \mu R)^2$**	**Theta (θ)**	**Intra-Subject Reference Variability (σ^2_{WR}) (%CV)**	**RSABE***	**95% Upper Confidence Bound for RSABE**
Ln C_{max}	5.0945	5.0826	0.00014	0.7967	42.4	-0.1431	-0.1012

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

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fed Bioequivalence Study, Study No. 04132/09-10 (N=40)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.00	94.82	106.08	0.0349613	0.1869793	-0.019709	Unscaled	PASS
LAUCI	1.01	95.68	105.20	0.0290378	0.1704048	-0.016176	Unscaled	PASS
LCMAX	1.17	103.15	132.93	0.1615496	0.4019324	-0.037394	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fed Bioequivalence Study, Study No. 04132/09-10 (N=40)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2108.95	2102.81	1.00	94.82	106.08
AUC∞ (hr *ng/ml)	2202.31	2195.11	1.00	95.68	105.20
Cmax (ng/ml)	1416.08	1209.32	1.17	103.15	132.93

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Misoprostol Acid
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.97	94.14	100.73	0.0210688	0.1451511	-0.010698	Unscaled	PASS
LAUCI	0.98	93.22	103.12	0.0220439	0.1484719	-0.010708	Unscaled	PASS
LCMAX	1.01	91.40	111.39	0.1798378	0.4240729	-0.103926	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Misoprostol Acid
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	286.40	294.10	0.97	94.14	100.73
AUC∞ (hr *pg/ml)	336.99	343.72	0.98	93.22	103.12
Cmax (pg/ml)	162.65	161.19	1.01	91.40	111.39

Table 32. Additional Study Information, Fed Study No. 04132/09-10

	Diclofenac		Misoprostol Acid	
Root mean square error, AUC0-t	0.1870		0.1452	
Root mean square error, AUC∞	0.1704		0.1485	
Root mean square error, Cmax	0.4019		0.4247	
	Test		**Reference**	
	Diclofenac	**Misoprostol Acid**	**Diclofenac**	**Misoprostol Acid**
Kel and AUC∞ determined for how many subjects?	39	41	40	43
Do you agree or disagree with firm's decision?	Agree	Agree	Agree	Agree
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0	0	0	0
first point as Cmax	0	0	0	0
first measurable drug concentration as Cmax	21	1	17	1
Were the subjects dosed as more than one group?	No	No	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test				
Diclofenac	39*	0.97	0.89	0.99
Misoprostol Acid	41**	0.86	0.58	0.97
Reference				
Diclofenac	40	0.96	0.80	0.99
Misoprostol Acid	43	0.87	0.69	0.96

*Kel and AUCi were not calculated for both Test periods for Subject 9.
**Kel and AUCi were not calculated for both Test periods for Subjects 1 and 4.

Comments on Pharmacokinetic and Statistical Analysis:

1. The reviewer conducted statistical analysis using the original and repeat values. All analysis conducted by the reviewer presented in this review used the repeat plasma concentration data for all anomalous values. No significant difference was observed by using the repeat values for LAUCt, LAUCi, and LCmax for diclofenac or misoprostol acid.

2. In the clinical report, the firm stated the following:

> *"Subjects 15, 29 & 37 were not used for pharmacokinetic and statistical analysis of Diclofenac, because after bioanalysis for period I only at one time point the drug concentration was detected for participant 15, for period III only at two time points*

the drug concentration were detected for participant 29 and for period II no drug concentration was detected at any of the time point for participant 37."

The reviewer noted that for Subject 11, drug concentration for diclofenac was detected at only two time points for period 4. It is unclear why the firm chose to include this subject, while not including Subjects 15, 29, and 37. The reviewer conducted the statistical analysis excluding Subject 11, which did not change the outcome of the study. The results are below:

(Excluding Subject 11)

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fed Bioequivalence Study, Study No. 04132/09-10 (N=39)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.01	95.60	106.89	0.0336162	0.1833473	-0.018269	Unscaled	PASS
LAUCI	1.01	95.86	105.65	0.0273736	0.1654496	-0.015127	Unscaled	PASS
LCMAX	1.19	104.45	134.87	0.1631075	0.4038657	-0.03038	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Unscaled Data
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Fed Bioequivalence Study, Study No. 04132/09-10 (N=39)

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	2116.41	2093.66	1.01	95.60	106.89
AUC∞ (hr *ng/ml)	2200.58	2186.74	1.01	95.86	105.65
Cmax (ng/ml)	1427.74	1202.93	1.19	104.45	134.87

The reviewer also conducted the statistical analysis including Subjects 15, 29, and 37, which also did not change the outcome of the study. The results are below:

(Including Subjects 15, 29, and 37):

Diclofenac Sodium/Misoprostol DR Tablets
Analyte: Diclofenac
1 x 75 mg/0.2 mg
Summary of Statistical Analysis – Scaled and Unscaled Data

Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.99	92.20	104.55	0.0504801	0.2246778	-0.028616	Unscaled	PASS
LAUCI	1.01	95.00	106.17	0.0458615	0.214153	-0.026123	Unscaled	PASS
LCMAX	1.14	99.53	128.23	0.2071458	0.4551328	-0.083242	Scaled/PE	PASS

Diclofenac Sodium/Misoprostol DR Tablets Analyte: Diclofenac 1 x 75 mg/0.2 mg Summary of Statistical Analysis – Unscaled Data Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 04132/09-10 (N=43)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	2052.34	2090.35	0.98	92.20	104.55
AUC∞ (hr *ng/ml)	2197.63	2188.16	1.00	95.00	106.17
Cmax (ng/ml)	1352.51	1197.22	1.13	99.53	128.23

3. The pharmacokinetic measures (AUCt, AUCi, Cmax, Tmax, KE and t1/2) and confidence intervals of AUCt, AUCi, and Cmax for diclofenac and misoprostol acid as calculated by the reviewer were in agreement with the values reported by the firm.

4. The 90% confidence intervals for diclofenac and misoprostol acid of ln-transformed AUCt, AUCi, and Cmax ratios are within the acceptable limits of 80-125%.

Comments on Reference-Scaled Statistical Analysis:

The firm proposed to use the reference-scaled average bioequivalence approach in the study protocol.

The current approach calls for using the reference-scaled average BE approach with a point estimate constraint, if s_{WR} (the estimated within-subject standard deviation on the log scale for the RLD) is greater than or equal to 0.294 (meaning that s^2_{WR} is greater than or equal to 0.086436). This was true for Cmax only for both diclofenac and misoprostol acid in this study. Therefore, the reviewer performed the statistical analysis by using the reference-scaled approach for establishing bioequivalence.

The method used for calculating the reference-scaled average BE for Cmax in the fed study is as follows[1]:

In the analysis of a bioequivalence study, the measurements of both Cmax and AUC are subject to the following procedure. The measurement for each subject is log-transformed and the averages, μT and μR, of the test and reference products are calculated. The within subject variability (σ^2_{WR} or s^2_{WR}) of the reference product is also calculated.

There are two parts to the proposed bioequivalence criteria, a scaled average bioequivalence evaluation and a point estimate constraint. In order to demonstrate bioequivalence both parts must pass. Reference-Scaled average bioequivalence for Cmax are evaluated by testing the following null hypothesis:

[1] S. H. Haidar, B. Davit, M. L. Chen, et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products. *Pharm. Res.* **25**:237-41 (2008)

$$H_0 : \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} > \theta$$

(for given $\theta > 0$) versus the alternative hypothesis

$$H_1 : \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta \ ,$$

where μT and μR are the averages of the log-transformed measure (Cmax) for the test and reference products, respectively; usually testing is done at level $\alpha = 0.05$; and θ is the scaled average BE limit. Furthermore,

$$\theta = \frac{(\ln \Delta)^2}{\sigma_{W0}^2}$$

where Δ is 1.25, the usual average BE upper limit for the untransformed Test/Reference ratio of geometric means, and $\sigma_{W0} = 0.25$. Note that rejection of the null hypothesis H_0 supports the conclusion of equivalence.

A 95% upper confidence bound for $\frac{(\bar{Y}_T - \bar{Y}_R)^2}{s_{WR}^2}$ determined in a BE study must be must be $\leq \theta$, or equivalently, a 95% upper confidence bound for $(\bar{Y}_T - \bar{Y}_R)^2 - \theta s_{WR}^2$ must be ≤ 0, where S_{WR} is within reference standard deviation determined in the BE study.

Additionally, the point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

In order to be considered bioequivalent to the RLD, the test drug must pass the following two conditions:

1. A 95% upper confidence bound (calculated as explained in the above equations) must be must be less than or equal to 0.

2. The point estimate (test/reference geometric mean ratio) must fall within [0.80, 1.25].

The 95% upper confidence bounds for $(\bar{Y}_T - \bar{Y}_R)^2 - \theta s_{WR}^2$ for Cmax in the fed BE study was negative for diclofenac (-0.037394) and misoprostol acid (-0.103926). Since these values are

less than 0, they meet the first condition. In firm's report, the 95% upper confidence bounds for $\left(\overline{Y}_T - \overline{Y}_R\right)^2 - \theta s_{WR}^2$ for Cmax was also less than 0.

The point estimate (test/reference geometric mean ratio) for Cmax in the fed BE study is 1.17 for diclofenac and 1.01 for misoprostol acid. Since these values are within [0.80, 1.25], they meet the second condition.

The two one-sided tests procedure was used to determine bioequivalence for AUCt and AUCi for diclofenac and misoprostol acid in the fed study.

Hence, Diclofenac Sodium/Misoprostol Delayed Release Tablets by Watson Laboratories, Inc. are bioequivalent to GD Searle LLC's Arthrotec® Delayed Release Tablets under fed conditions.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The fed *in vivo* bioequivalence study is **adequate.**

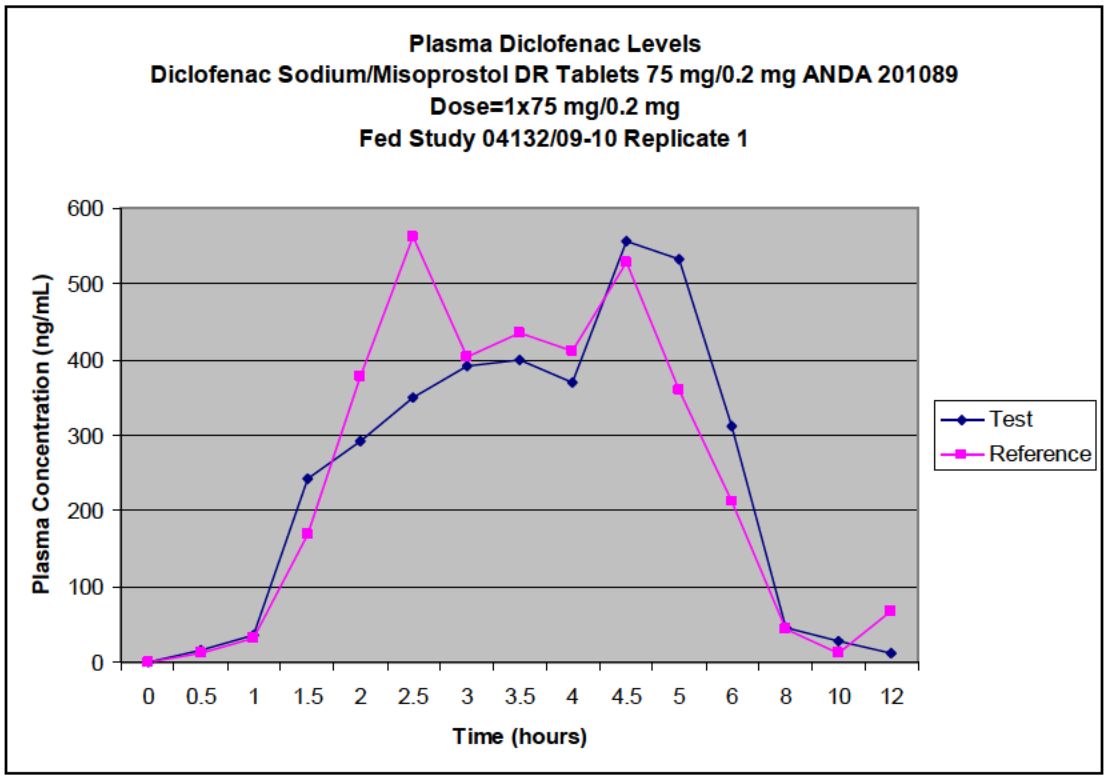
Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

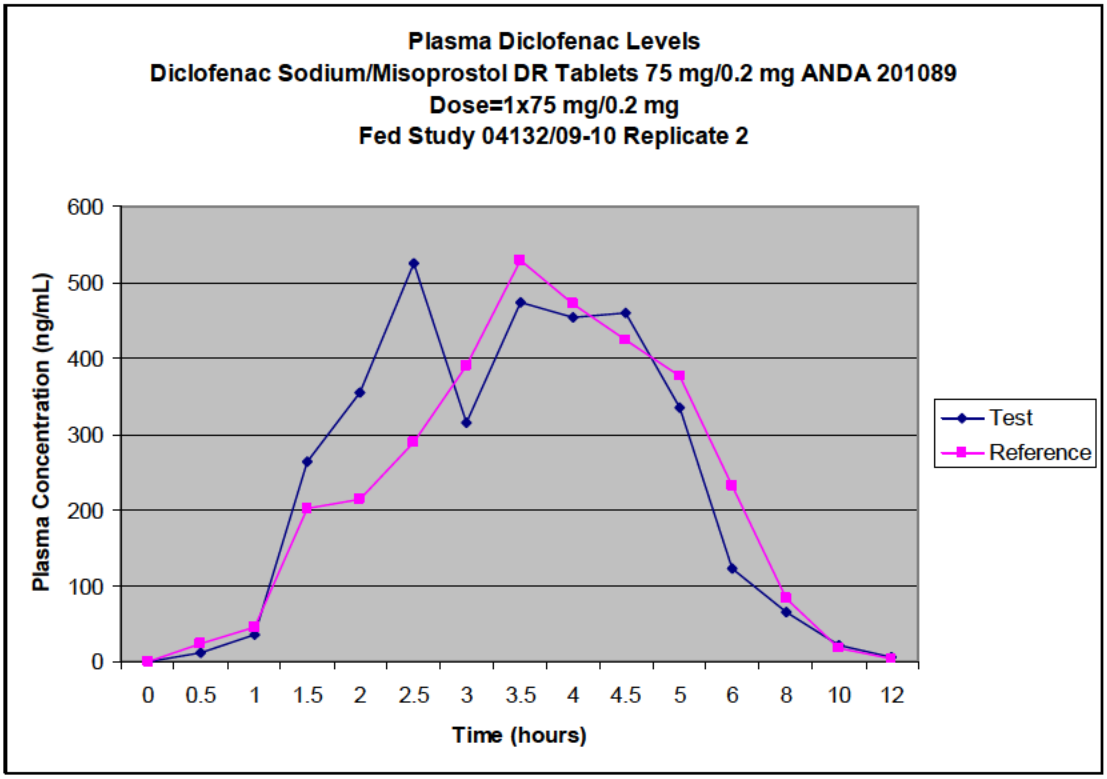
Diclofenac					
Time (hr)	Test (n=40)		Reference (n=40)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0	0	--	0	--	--
0.5	13.97	320.66	17.52	337.27	0.80
1.0	35.78	296.10	38.72	216.94	0.92
1.5	253.19	275.78	185.88	220.45	1.36
2.0	323.16	170.09	296.03	176.35	1.09
2.5	437.53	161.52	424.84	141.42	1.03
3.0	353.99	120.76	396.45	101.01	0.89
.3.5	437.04	117.54	481.92	108.46	0.91
4	411.6	131.92	441.52	95.71	0.93
4.5	507.73	134325	475.75	133.24	1.07
5.0	433.81	127.43	368.50	137.71	1.18
6.0	217.27	223.34	222.57	159.13	0.98
8.0	55.58	190.29	63.01	178.34	0.88
10.0	24.77	367.55	14.65	222.93	1.69
12.0	8.83	458.17	36.40	800.44	0.24

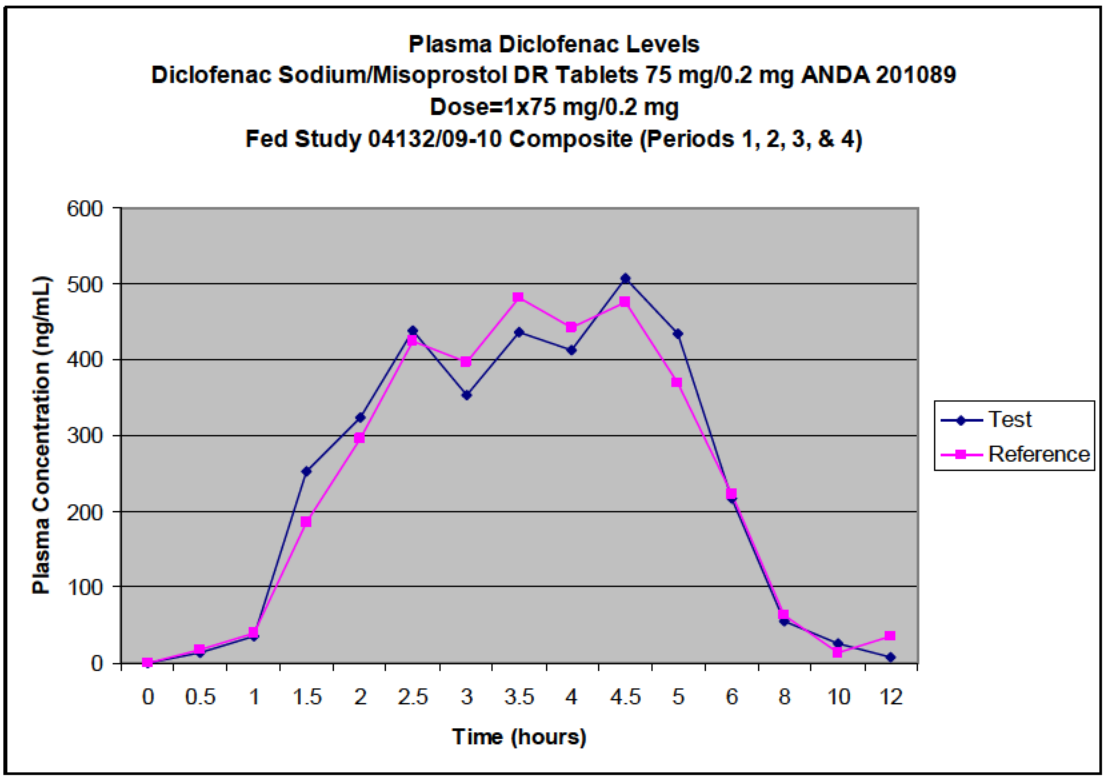
Misoprostol Acid					
Time (hr)	Test (n= 43)		Reference (n=43)		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
0	0.0	--	0.0	--	--
0.08	47.62	135.60	26.33	187.40	1.81
0.17	115.32	110.03	102.745	114.83	1.12
0.33	138.67	62.93	129.43	71.13	1.07
0.67	75.76	64.64	92.98	63.00	0.81
1.0	54.61	63.16	74.04	50.30	0.74
1.3	52.70	68.99	74.39	58.377	0.71
1.67	62.42	79.66	82.14	46.49	0.76
2	50.19	84.01	70.35	50.19	0.71
2.5	36.20	102.84	60.80	54.92	0.60
3.0	38.44	100.78	55.33	64.39	0.69
3.5	31.72	95.53	48.04	91.98	0.66
4	22.94	237.59	37.34	90.20	0.61
5	16.84	282.59	21.28	131.56	0.79
6	3.58	410.61	6.02	243.93	0.59

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

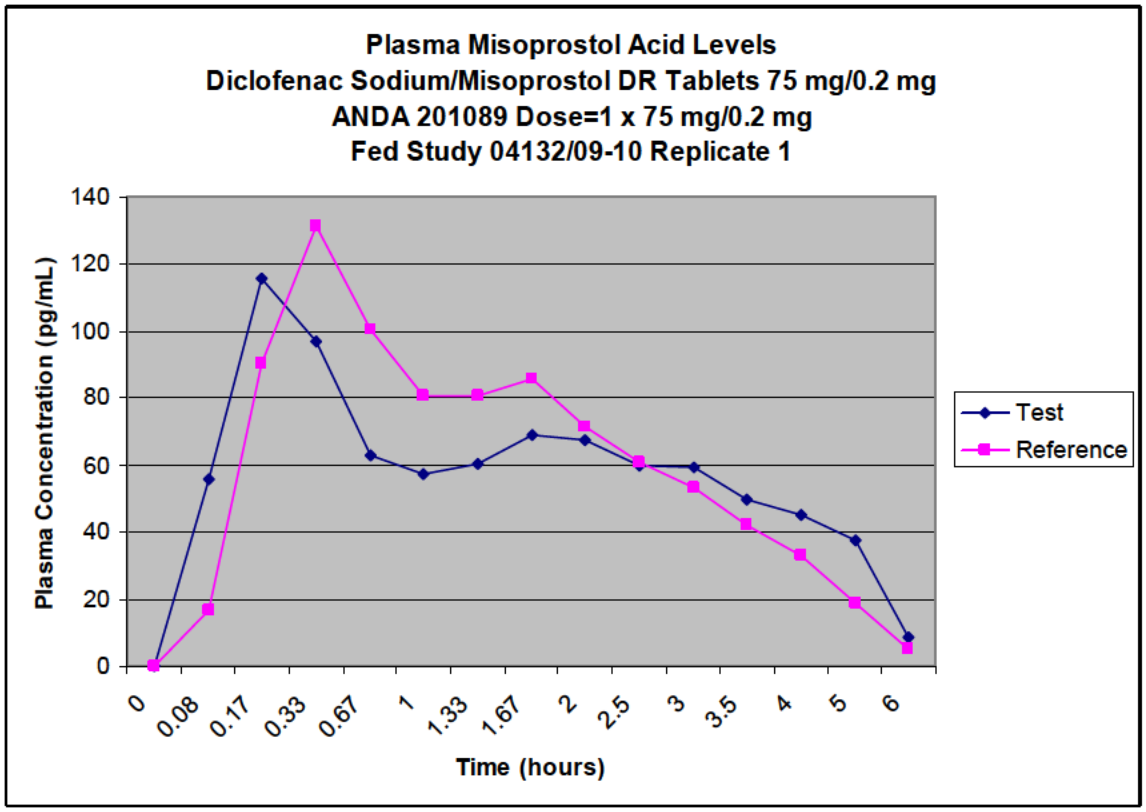
Diclofenac:

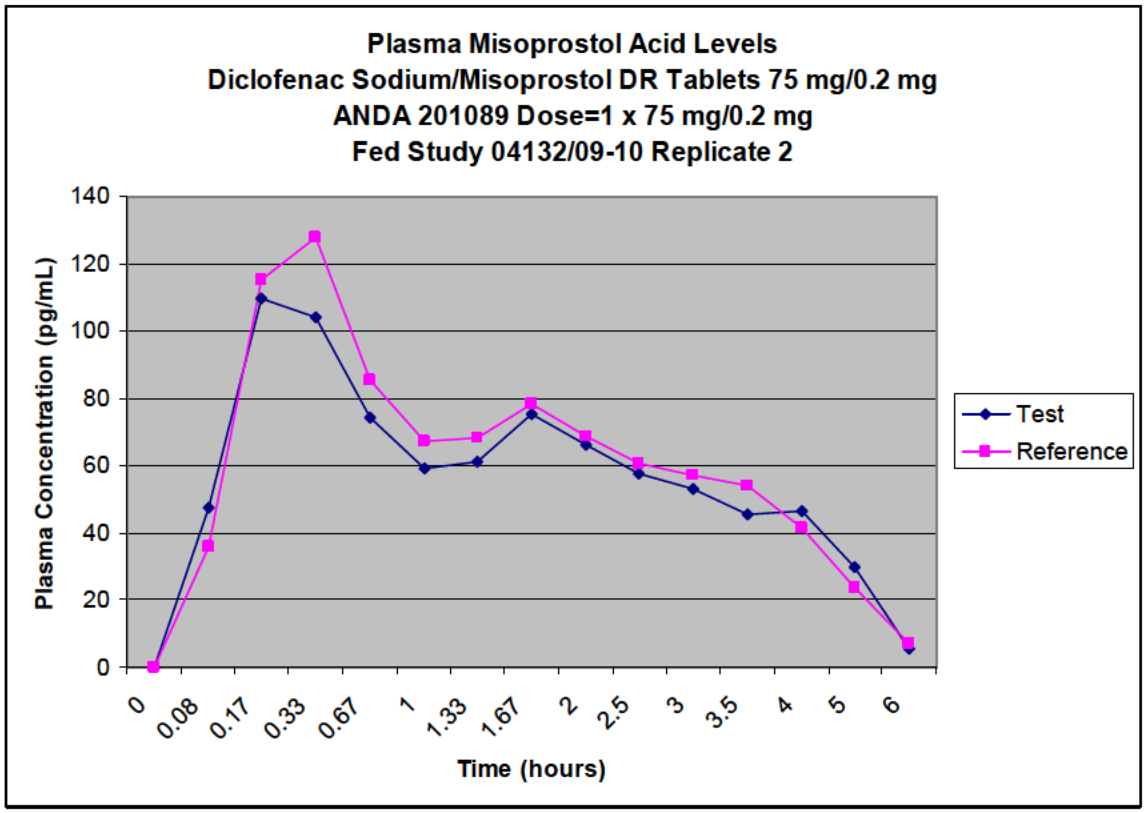


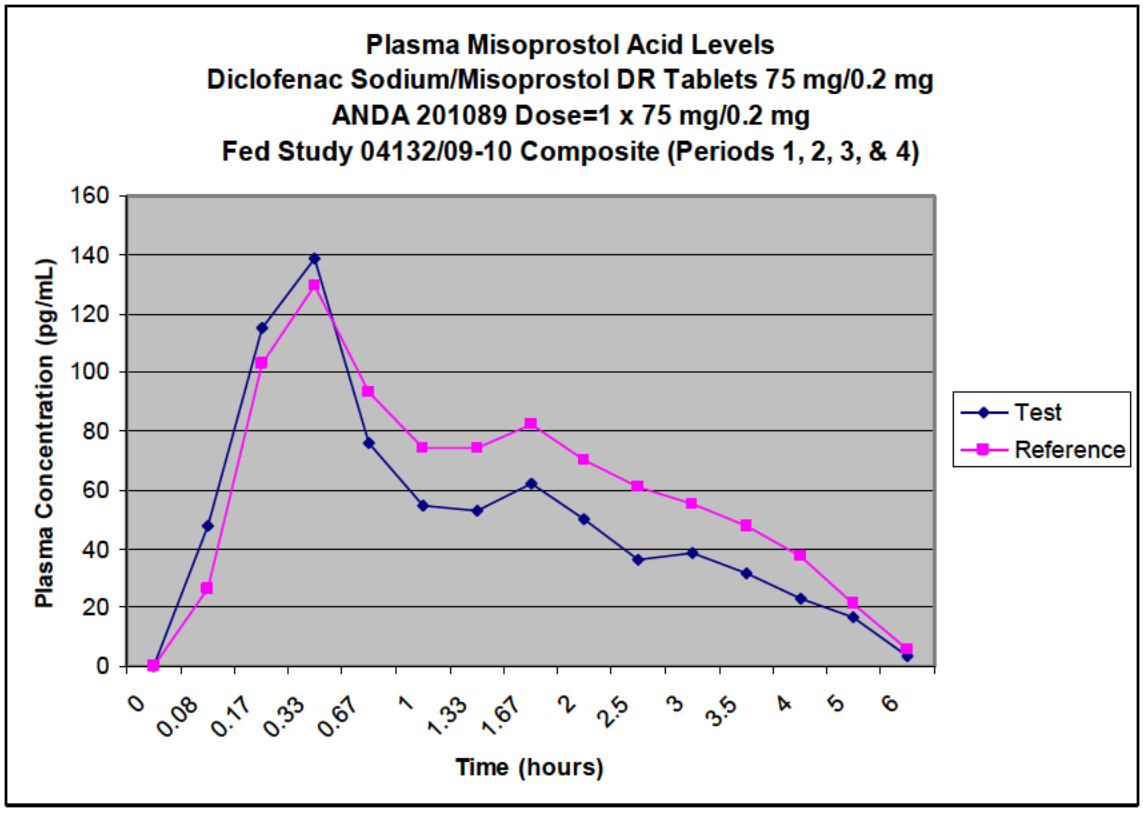




Misoprostol Acid:







4.2 Formulation Data

Composition of Diclofenac Sodium/Misoprostol Tablets, 75mg/0.2 mg

Ingredients/Grade	Function	mg/tab	% w/w (per tablet)	IID Max Level
(b) (4)				

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:	The inactive ingredients are within the acceptable IIG limits based on the MDD of 150 mg/0.4 mg for Arthrotec® 75.

4.3 Dissolution Data

Dissolution Review Path	DARRTS REV-BIOEQ-02(Dissolution Review) Submit Dates: 6/30/2010 and 10/15/2010

Table 34. Dissolution Data

Table 5.1 Summary of In Vitro Dissolution Studies – medium of 0.1N HCl for 2 hrs (Acid Stage), and then adjusted to pH 6.8 (Buffer Stage) - Diclofenac Sodium Dissolution Profile

Dissolution Conditions		
	Apparatus:	II (Paddle)
	Speed of Rotation:	100 rpm
	Medium:	750 mL 0.1N HCl for 2 hrs. (Acid Stage), and then add 250 mL of 0.2M Phosphate Buffer adjusted to pH 6.8 (Buffer Stage)
	Volume:	0-2 hrs 750 mL (Acid Stage), after 1000 mL (Buffer Stage)
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)		Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hrs) 2	2.25	2.5	2.75	3	3.5	Study Report Location
WSR1459, p.57	09/24/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022 (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	0	28	73	99	99	100	See pages 3 and 4
					Range						(b) (4)	
					%CV	N/A	17.7	12.4	1.5	1.2	1.3	
WSR1459, p.37	08/13/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	0	27	70	94	100	100	
					Range						(b) (4)	
					%CV	N/A	20.2	7.6	3.4	1.4	1.7	

Misoprostol Dissolution Profile

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	Purified Water
	Volume:	500 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Watson Laboratories, Inc.– Florida 2945 West Corporate Lakes Blvd., Suite B, Weston Fl, 33331	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	45	60	Study Report Location
WSR1672, p.7	09/24/09	Test Product Diclofenac Sodium/Misoprostol Tablets Lot # 0398R0022 (Mfg. 08/2009)	75 mg/200 mcg Tablet	12	Mean	90	93	94	96	98	See pages 6 and 7
					Range	(b) (4)					
					%CV	5.7	3.9	3.5	3.5	3.0	
WSR1458, p.58	08/17/09	Reference Product Arthrotec™ Lot # C081587 (Exp.08/2012)	75 mg/200 mcg Tablet	12	Mean	90	97	98	99	99	
					Range	(b) (4)					
					%CV	7.3	4.3	2.9	2.0	2.2	

Reviewer's Comment:

Per the "Dissolution Only" review, the firm's dissolution testing data with the FDA-recommended dissolution method are acceptable; however, the firm's proposed specification [NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage); (b) (4) (Q) Diclofenac dissolved in 45 minutes (buffer stage); (b) (4) (Q) Misoprostol dissolved in 45 minutes] was not acceptable. Based on the submitted data, the DBE recommended the following specification: NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage); NLT (b) (4) (Q) Diclofenac dissolved in 45 minutes (buffer stage); NLT (b) (4) (Q) Misoprostol dissolved in 20 minutes. On November 10, 2010 the firm accepted the FDA-recommended method and specification.

4.4 Detailed Regulatory History (If Applicable)

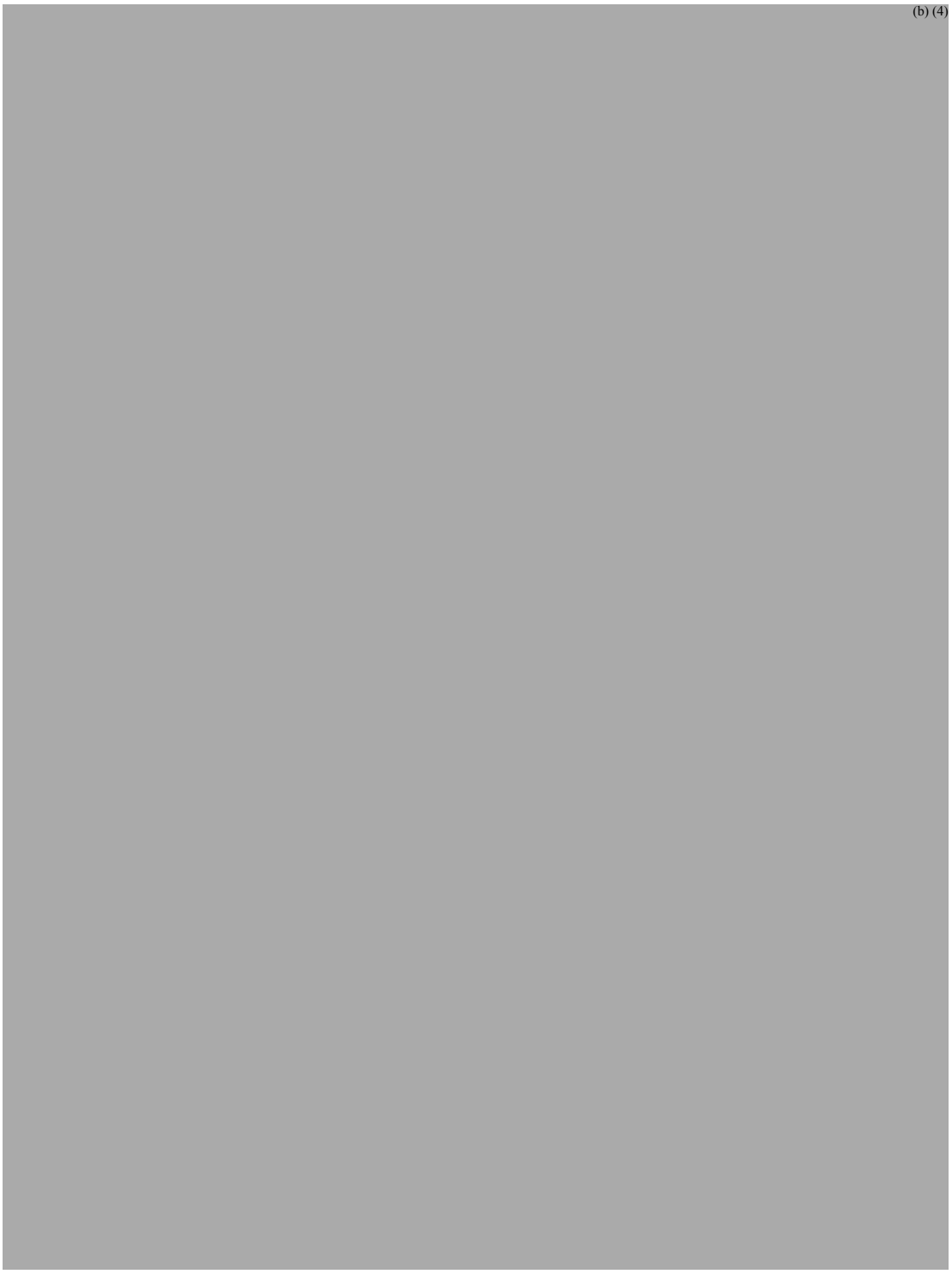
4.5 Consult Review

4.6 SAS Output

4.6.1 Fasting Study Data (Diclofenac)

(b) (4)

Following this page, 144 pages withheld in full (b)(4)- SAS Output



4.7 Additional Attachments

N/A

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT – **ONLY AFTER AN ACCEPTABLE OSI INSPECTION**

ANDA: 201089

APPLICANT: Watson Laboratories, Inc.- Florida

DRUG PRODUCT: Diclofenac Sodium/Misoprostol Delayed Release Tablets, 75 mg/0.2 mg

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

The DB II acknowledges that you will conduct future dissolution testing of your test product using the following FDA-recommended method and specifications:

Medium:	0.1 N HCl for acid stage of Diclofenac 750 mL 0.1 N HCl + 250 mL 0.2 M Phosphate Buffer pH 6.8 for buffer stage of Diclofenac Water (deaerated) for Misoprostol
Volume:	750 mL for acid stage of Diclofenac 1000 mL for buffer stage of Diclofenac 500 mL for Misoprostol
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle) for both Diclofenac and Misoprostol
Rotation Speed:	100 rpm for Diclofenac 50 rpm for Misoprostol
Specifications:	NMT (b) (4) Diclofenac dissolved in 120 minutes (acid stage) NLT (b) (4) (Q) Diclofenac dissolved in 45 minutes(buffer stage) NLT (b) (4) (Q) Misoprostol dissolved in 20 minutes

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

4.8 Outcome Page

COMPLETED ASSIGNMENT FOR 201089 ID: 15040

Reviewer: Miller, Jennifer **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Diclofenac Sodium/Misoprostol Delayed Release Tablets, 75 mg/0.2 mg

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15040	12/24/2009	Bioequivalence Study	Fasting Study	1	1
15040	12/24/2009	Bioequivalence Study	Fed Study	1	1
15040	7/30/2010	Other	Study Amendment Without Credit (WC)	0	0
15040	11/10/2010	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	2

COMPLEXITY POINTS
ANDA: 201089

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Bioanalytical (API 2)	1
Statistical Analysis (API 2)	1
Fasting Study Total	*5*
BE Study Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Bioanalytical (API 2)	1
Statistical Analysis (API 2)	1

Fasting Study Total	*5*
Study Amendments	
Study Amendment without credit	0
Study Amendment without credit	0
Study Amendment Total	*0*
Total	***10***

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/s/

JENNIFER N MILLER
09/28/2011

KULDEEP R DHARIWAL
09/28/2011

BARBARA M DAVIT
09/30/2011

DIVISION OF BIOEQUIVALENCE
ACCEPTABLE OSI INSPECTION REPORT REVIEW

ANDA No.	201089
Drug Product Name	Diclofenac Sodium / Misoprostol DR Tablets
Strength(s)	75 mg/0.2 mg
Applicant Name	Watson Laboratories, Inc. - Florida
Original Submission Date(s)	December 24, 2009
Date of Report	September 23, 2011
Reviewer	Scott Vehovic, R.Ph.
Clinical Site/Address	Vimta Labs Ltd. Clinical Research Division 142, IDA, Phase II, Cherlapally, Hyderabad – 500 051, India
Analytical Site/Address	Vimta Labs Ltd. Room No's. 131B, 140, & 133B Clinical Research Division Central Laboratory 142, IDA, Phase II, Cherlapally, Hyderabad – 500 051, India
OUTCOME DECISION	**ADEQUATE**

EXECUTIVE SUMMARY

The Office of Scientific Investigations (OSI) inspection report of the clinical site, Vimta Labs Ltd., Clinical Research Division, 142, IDA, Phase II, Cherlapally, Hyderabad – 500 051, India, was received by the Division of Bioequivalence and found acceptable. The clinical site inspection was requested for ANDA 201089. The following application contained studies conducted at this site. Given the acceptable inspection of the site, the bioequivalence section of the application is now adequate.

ANDA	Firm	Drug Product
201089	Watson Laboratories, Inc. - Florida	Diclofenac Sodium / Misoprostol DR Tablets

COMMENTS:

From: Miller, Jennifer
Sent: Thursday, October 13, 2011 10:03 AM
To: Vehovic, Scott
Subject: Clinical Inspection regarding ANDA 201089 Diclofenac/Misoprostol

Scott -

Based on the OSI report for the clinical site (Clinical Research Division, 142, IDA, Phase II, Cherlapally, Hyderabad-500 051, INDIA) under ANDA (b) (4) the OSI status for ANDA 201089 is adequate. There will be no effect on the outcome of the fasting and fed BE studies for Dliclofenac Sodium/Misoprostol DR Tablets.

Thanks,

Jennifer

Jennifer N. Miller, Ph.D.
Division of Bioequivalence II
Office of Generic Drugs
MPN 1 Room 1323
Office: 240.276.8762

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

The Office of Scientific Investigation (OSI) inspection report of the clinical site, Vimta Labs Ltd., Clinical Research Division, 142, IDA, Phase II, Cherlapally, Hyderabad – 500 051, India, was received by the Division of Bioequivalence on September 23, 2011 and found acceptable.

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

I. Completed Assignment for 201089 ID: 15281

Reviewer: Vehovic, Scott **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Adequate OSI / BE Review – ANDA 201089

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15281	9/23/2011	Other	DSI Inspection Report PMs	1	1
				Bean Total:	1

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/s/

DAVID S VEHOVIC
10/21/2011

AARON W SIGLER
10/24/2011