

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 202103

Name: Dasatinib Tablets

Sponsor: Apotex Inc

Approval Date: June 10, 2016

Indication: Dasatinib is Kinase inhibitor for the treatment of:

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (1, 14)
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (1, 14)
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)

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APPLICATION NUMBER:
ANDA 202103Orig1s000
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APPLICATION NUMBER:
ANDA 202103

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202103		
Drug Product Name	Dasatinib Tablets		
Strength(s)	20 mg, 50 mg, 70 mg and 100 mg		
Applicant Name	Apotex Inc.		
Applicant Address	150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
US Agent Name and the mailing address	Kiran Krishnan, Vice President, US Regulatory Affairs Apotex Corp. 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326		
Applicant's Telephone Number	954-384-3986		
Applicant's Fax Number	866-392-1774		
Applicant's Email Address	kkrishna1@apotex.com		
Original Submission Date(s)	06/27/2010		
Submission Date(s) of Amendment(s) Under Review	August 16, 2012, July 23, 2013 and 08/27/2015 (CURRENT Submission of a new fasting PK study (#DASA-IMTB-05SB11-4FA))		
Reviewer	Vipra Kundoor, Ph.D.		
Study Number (s)	DASA-IMTB-05SB01-2FA (DD6366)	DASA-IMTB-05SB02-2FE (DD6367)	DASA-IMTB-05SB03-2FA
Study Type (s)	Fasting	Fed	Fasting (re-dosing)
Strength (s)	100 mg	100 mg	100 mg
Clinical Site	Anapharm	Anapharm	Anapharm
Clinical Site Address	2500, rue Einstein Quebec (Quebec), Canada, G1P 0A2	5160, boul. Decarie, Suite 800, Montreal (Quebec) Canada, H3X 2H9	2500, rue Einstein Québec (Québec), Canada G1P 0A2
Analytical Site	Apotex Inc.	Apotex Inc.	Apotex Inc.
Analytical Site Address	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario
Study Number (s)	DASA-IMTB-05SB11-4FA		
Study Type (s)	Fasting (Repeat BE study)		
Strength (s)	100 mg		
Clinical Site	Apotex Inc., BioClinical Development		
Clinical Site Address	Clinical Operations Department 465 Garyray Drive Toronto, Ontario		

	Canada M9L 1P9		
Analytical Site	Apotex Inc., BioClinical Development		
Analytical Site Address	Bioanalytical Laboratory 440 Garyray Drive Toronto, Ontario Canada M9L 1P7		
OSIS Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> <input type="checkbox"/> Pending <input checked="" type="checkbox"/> Complete		<u>Year 3 ANDAs</u> x To Be Determined by OSIS <input type="checkbox"/> Pending For Cause Inspection
OVERALL REVIEW RESULT	ADEQUATE		
REVISED/NEW DRAFT GUIDANCE INCLUDED	NO		
COMMUNICATION	<input type="checkbox"/> ECD <input type="checkbox"/> IR <input checked="" type="checkbox"/> NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
20	Fasting Study (DASA-IMTB-05SB11-4FA)	100 mg	ADEQUATE
1, 13, 14	Fed Study (DASA-IMTB-05SB02-2FE)	100 mg	ADEQUATE
1, 7,	Bio Waiver	20 mg, 50 mg and 70 mg	ADEQUATE

1 EXECUTIVE SUMMARY

On June 27, 2010, Apotex, submitted the original application for Dasatinib Tablets, 100 mg. The firm’s fasting and fed BE studies were incomplete due to bioanalytical deficiencies. For the fasting study: (DASA-IMTB-05SB01-2FA (DD6366)), the firm identified Subjects – (b) (6) as being suspected of having “aberrant” plasma concentrations. The firm identified (b) (6) as outliers after performing the Lund’s outlier test. The reviewer could not confirm Subjects – (b) (6) as outliers because the firm did not submit the concentration vs. time data for the identified Subjects (b) (6). The firm did not mention about re-dosing study in the study protocol a priori. However, the firm conducted the re-dosing study with the above mentioned 3 subjects and included five additional control subjects. The acceptability of the decision to re-dose and the acceptability of dropping the subjects in question from the statistical analysis of the original fasting biostudy was pending the submission of the data requested above. The application was found **inadequate** as stated in DBI review of this application dated 6/27/2012. A deficiency letter was issued to the firm on 07/12/2012.

On August 16, 2012, Apotex, submitted its responses to the deficiency letter issued from DBI on July 12, 2012 due to several clinical and analytical deficiencies. Based on the firm’s responses, the fasting study was **unacceptable**, the fasting re-dosing study was **adequate**, and the fed study was **inadequate**. The application was **inadequate** with deficiencies as stated in DBI review of this application dated 06/25/2013. A complete response letter was sent to the firm on 07/09/2013.

On July 23, 2013, the firm submitted its responses to the complete response letter issued from DBI on July 09, 2013. Based on the firm’s responses, the fasting study was still **unacceptable**, the fasting re-dosing study was **adequate**, and the fed study was **adequate**. Another complete response letter was sent to the firm on 09/10/2014.

On August 27, 2015, the firm submitted the current amendment to the complete response letter issued on 09/10/2014. In the current amendment, the firm submitted a new fasting study (# DASA-IMTB-05SB11-4FA) comparing a test product, Dasatinib Tablets, 100 mg to the corresponding reference product, Sprycel® (dasatinib) Tablets, 100 mg. The fasting study was designed as a single-dose, randomized, two-treatment, four-period fully replicated crossover design. The fasting study is adequate. The results are summarized in the tables below:

Reviewer Calculated Results:

ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng hr/mL	419.064	71.79	48.17	1644.60	422.752	77.82	30.99	2085.50	0.99
AUCINF	ng hr/mL	453.558	66.19	128.84	1663.20	453.079	72.82	90.24	2112.80	1.00

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
CMAX	ng/mL	108.761	45.28	14.66	215.44	109.249	54.46	3.13	250.90	1.00
TMAX	hr	0.750	.	0.50	3.00	1.250	.	0.50	4.00	0.60
THALF	hr	5.431	31.65	3.36	11.31	5.935	29.37	3.29	11.13	0.92
KEL	hr-1	0.138	25.91	0.06	0.21	0.126	28.71	0.06	0.21	1.09

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - 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	447.737	91.22	57.02	2242.10	457.944	87.73	19.07	2061.70	0.98
AUCINF	ng hr/mL	470.367	87.75	124.38	2264.00	505.835	79.59	133.81	2076.30	0.93
CMAX	ng/mL	109.491	48.72	10.07	240.86	117.105	49.17	2.85	225.30	0.93
TMAX	hr	1.000	.	0.33	3.00	1.000	.	0.33	3.00	1.00
THALF	hr	6.089	32.15	3.40	9.93	5.979	34.03	3.37	12.72	1.02
KEL	hr-1	0.126	31.90	0.07	0.20	0.128	30.46	0.05	0.21	0.98

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - 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	432.097	81.39	48.17	2242.10	438.995	82.54	19.07	2085.50	0.98
AUCINF	ng hr/mL	461.387	76.85	124.38	2264.00	476.928	76.09	90.24	2112.80	0.97
CMAX	ng/mL	109.093	46.58	10.07	240.86	112.875	51.71	2.85	250.90	0.97
TMAX	hr	0.750	.	0.33	3.00	1.000	.	0.33	4.00	0.75
THALF	hr	5.737	32.25	3.36	11.31	5.955	31.35	3.29	12.72	0.96
KEL	hr-1	0.132	28.78	0.06	0.21	0.127	29.32	0.05	0.21	1.04

* Tmax values are presented as median, range.

SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Parameter	Geometric Means		T/R Ratio	90% CI	
	Test	Reference		Lower CI	Upper CI
LAUCT	345.94	335.69	1.03	92.79	114.45
LAUCI	384.54	388.87	0.99	90.17	108.45
LCMAX	95.31	89.20	1.07	92.26	123.74

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.03	92.79	114.45	0.2402595	0.4901627	-0.130164	Scaled/PE	PASS
LAUCI	0.96	90.17	108.45	0.062097	0.2491927	-0.023679	Unscaled	PASS
LCMAX	1.06	92.26	123.74	0.4601613	0.6783519	-0.242525	Scaled/PE	PASS

The dissolution data are adequate with respect to supporting waiver request(s) of the lower strength(s) (20 mg, 50 mg and 70 mg).

Office of Scientific Investigation and Surveillance (OSIS) Report:

The OSIS inspection for the clinical and analytical sites for the fed study (#DASA-IMTB-05SB02-2FE) was previously found adequate¹. With respect to the repeat fasting study (#DASA-IMTB-05SB11-4FA) subject to the current amendment: A routine inspection of the Clinical Site, Apotex Inc., BioClinical Development, Clinical Operations Department, 465 Garyray Drive, Toronto, Ontario, Canada M9L 1P9 was completed between [REDACTED] (b) (4)

A routine inspection of the Analytical Site, Apotex Inc., BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive, Toronto, Ontario, Canada M9L 1P7 was completed between [REDACTED] (b) (4)

The OSIS report for the current ANDA is, therefore, deemed complete.

The DB grants the waiver request(s) for in vivo BE study requirements for the following strengths (20 mg, 50 mg and 70 mg) based on criteria set forth in 21 CFR § 320.22 (d) (2)

The application is acceptable with no deficiencies.

¹ DARRTS, ANDA 202103, REV-BIOEQ-21 (Primary Review), 06/25/2013

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3 SUBMISSION SUMMARY

3.1 Drug Product Information, PK/PD Information and Relevant DB History

Original review: DARRTS, ANDA: 202103 - PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive.

Amendment 1: DARRTS, ANDA: 202103 -PABBA, SANTHOSH K 06/25/2013 N/A 06/25/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive.

Amendment 2: DARRTS, ANDA: 202103 -PABBA, SANTHOSH K 08/18/2014 N/A 08/18/2014 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive.

3.2 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	16.6 (within Section 5.3.1.4 pg. 1 to 241)
Analyte	Dasatinib (DD)
Internal standard (IS)	Dasatinib-D8 (IS)
Method description	Protein Precipitation extraction with HPLC and Tandem Mass Spectrometry detection
Limit of quantitation	0.200 ng/mL
Average recovery of drug (%)	88.25 %
Average recovery of IS (%)	91.24 %
Standard curve concentrations (units/mL)	0.200 to 200.000 ng/mL
QC concentrations (units/mL)	QC A: 0.600 ng/mL QC B: 60.000 ng/mL QC C: 150.000 ng/mL QC E: 5.000 ng/mL
QC Intraday precision range (%)	QC A: 1.7 to 6.3 % QC B: 1.3 to 3.6 % QC C: 1.1 to 2.4 % QC E: 2.0 to 2.8 %
QC Intraday accuracy range (%)	QC A: -4.3 to 3.0 % QC B: -3.9 to 2.7 % QC C: -2.8 to 2.3 % QC E: -3.8 to 0.9 %
QC Interday precision range (%)	2.4 to 4.2 %
QC Interday accuracy range (%)	-1.8 to 0.3 %
Bench-top stability (hrs)	19.7 hours @ room temperature
Stock stability (days)	29 days @ refrigerated conditions for dasatinib 29 days @ refrigerated conditions for dasatinib-D8
Processed stability (hrs)	49.1 hours @ room temperature 197.5 hours @ refrigerated conditions
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	94 days @ -30°C set point freezer

Dilution integrity	300 ng/mL Concentration diluted 2 fold and 4 fold 2 fold Dilution: %CV: 6.7 Accuracy: 96.27% 4 fold Dilution: %CV: 1.9 Accuracy: 98.55%
Selectivity	Known metabolites, endogenous plasma components, common drug / metabolites or commonly used female contraceptives do not significantly interfere with the analytical assay

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates	Yes

Comments on the Pre-Study Method Validation:

1. K₂-EDTA anti-coagulant was used in the bioanalytical method validation and pivotal fasting BE study.
2. The method validation conducted by the firm is **adequate**.

3.3 In Vivo Studies

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments: Dose, Dosage Form, Route, Product ID	Subjects ¹ No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters ²						Study Report Location
					Median (Range) for T _{max}						
					C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (ng·h/mL)	AUC _{0-inf} (ng·h/mL)	T _{1/2} (h)	Kel (1/h)	
Sponsor Protocol # DASA-IMTB-05SB11-4FA-(0)	To determine the relative bioavailability of Dasatinib Tablets (Apotex Inc.) and Sprycel Tablets (Bristol Myers Squibb), (USA) under fasting conditions	Randomized, 2-treatment, 4-period fully-replicated crossover study under fasting conditions	Test: Dasatinib Tablets, 100 mg; Oral; Lot No. FD150-215	42 (42/0) Completing Healthy Volunteers 35.5 years (21- 54 years)	104.299 (46.82%)	0.75 (0.33-3.00)	348.107 (42.15%)	373.162 (36.56%)	5.46 (29.06%)	0.1369 (26.31%)	Table 14.2.1.35 and 14.2.1.36
			Reference: Sprycel Tablets, 100 mg; Oral; Lot No. 4H69158B		107.023 (50.64%)	1.00 (0.33-4.00)	353.161 (42.91%)	385.843 (34.04%)	5.60 (24.93%)	0.1319 (26.26%)	

¹Subjects used in final statistical results

²The number of subjects utilized to calculate mean values for the parameters are presented in Tables 14.2.1.35 and 14.2.1.36 within the clinical study.

Table 2. Reanalysis of Study Samples

Study No. DASA-IMTB-05SB11-4FA								
Additional information in Volume(s), Page(s): Module 5/ Section 5.3.1.4/ Bioanalytical Report for the Assay of Dasatinib under Fasting Conditions/ Subsection 5.3 (Page 24)/Table 6 (Page. 37)								
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	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
F: Outside Range	6	3	0.20	0.10	6	3	0.20	0.10
H: Anomalous IS Response	1	0	0.03	0.00	1	0	0.03	0.00
Total	7	3	0.23	0.10	7	3	0.23	0.10

Table 3. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ABM-BL-0167	July 07, 2014	Sample Coding and Reporting Final Concentrations

Is there any other particular concern that should be investigated further?	No
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Comments from the Reviewer:

The repeat analysis conducted by the firm is adequate.

3.4 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable ²	20 mg, 50 mg and 70 mg
Waiver regulation cited?	Yes
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Acceptable
Waivers granted?	WAIVERS GRANTED
If not then why?	N/A

3.5 Deficiency Comments

None

3.6 Comments for Other OGD Disciplines

Discipline	Comment
N/A	N/A

² For Modified Release Dosage Forms, please note waiver is not applicable

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	DASA-IMTB-05SB11-4FA
Study Title	Comparative, Randomized, 4-way Crossover Bioavailability Study of Dasatinib Tablets (Apotex) And Sprycel Tablets (Bristol Myers Squibb) (USA) under Fasting Conditions
Clinical Site (Name & Address)	Apotex Inc., BioClinical Development Clinical Operations Department 465 Garyray Drive Toronto, Ontario Canada M9L 1P9
Principal Investigator	Gurinder Rai, MD
Dosing Dates	Period 1: March 03, 2015 Period 2: March 10, 2015 Period 3: March 17, 2015 Period 4: March 24, 2015
Analytical Site (Name & Address)	Apotex Inc., BioClinical Development Bioanalytical Laboratory 440 Garyray Drive Toronto, Ontario Canada M9L 1P7
Analysis Dates	April 06, 2015- April 27, 2015
Analytical Director	Laura Coppola, B.Sc
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	55 days @ -30°C

Table 5. Product information

Product	Test	Reference
Treatment ID	Test	Reference
Product Name	Dasatinib Tablets	Sprycel [®] (dasatinib) Tablets
Manufacturer	Apotex Inc.	Bristol-Myers Squibb Company
Batch/Lot No.	FD150-215	4H69158B
Manufacture Date	January 5, 2015	
Expiration Date		July 2017
Strength	100 mg	100 mg

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Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	101.1 %	98.2 %
Content Uniformity (expressed as mean, %CV or per USP)	100.3%, 1.4	
Dose Administered	1 x 100 mg	1 x 100 mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	N/A
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*NOTE: (b) (4)

The CMC review [HAN, SULENE X 07/25/2012 N/A 07/25/2012 REV-QUALITY-03(General Review) Original-1 (Not Applicable) Archive] found this to be unacceptable. A deficiency was sent to the firm. In an amendment dated 07/23/2013, the firm provided its response to the deficiency. However, the firm's response was still found to be inadequate³ and another deficiency was sent to the firm on 09/10/2014. In the current amendment dated 08/27/2015, the firm again responded to the deficiency and the firm's response is now found to be adequate by the chemistry reviewer⁴. Therefore, the production batch size provided by the firm is **acceptable**.

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

Number of Subjects	Enrolled: 51 Dosed: 42 Completed: 31 (All 4 Periods) Samples Analyzed: 39 Data Analyzed: 39
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	T1R1T2R2 R1T1R2T2
Blood Sampling Times	Blood samples were collected using 4 mL lavender cap vacuum tubes containing K ₂ EDTA at the following time-points: 0.00 (x1) (5-45 minutes prior to dosing) followed by 0.25, 0.3333, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 7, 9, 12, 16, 20, and 24 hours post-dosing.

³ DARRTS, ANDA REV-QUALITY-21 (Primary Review), 10/08/2013

⁴ Panorama Database, ANDA 202103, Project # ANDA-202103-ORIG-1-AMEND-20, Drug Product Primary Review, Document # 202103_R4_Amendment.docx, Author: Murali Divi, Updated: 10/16/2015

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Blood Sample Processing & Storage (include storage temperature)	Blood samples were centrifuged and the plasma was transferred into an appropriate labelled storage tubes and stored in a – 30°C set point freezer within 1 hour of sample collection pending assay.
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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. DASA-IMTB-05SB11-4FA-(0)			
		Treatment Groups	
		Test Product N=31	Reference Product N =31
Age (years)	Mean ± SD	36.1 ± 9.6	36.1 ± 9.6
	Range	21 - 53	21 - 53
Age Groups	< 18	0.0 (0.0%)	0.0 (0.0%)
	18 – 40	20.0 (64.5%)	20.0 (64.5%)
	41 – 64	11.0 (35.5%)	11.0 (35.5%)
	65 – 75	0.0 (0.0%)	0.0 (0.0%)
	> 75	0.0 (0.0%)	0.0 (0.0%)
Sex	Male	31.0 (100.0%)	31.0 (100.0%)
	Female	0.0 (0.0%)	0.0 (0.0%)
Race	Asian	2.0 (6.5%)	2.0 (6.5%)
	Black	10.0 (32.3%)	10.0 (32.3%)
	Caucasian	13.0 (41.9%)	13.0 (41.9%)
	Multi-racial	1.0 (3.2%)	1.0 (3.2%)
	Native Hawaiian	0.0 (0.0%)	0.0 (0.0%)
	Aboriginal	5.0 (16.1%)	5.0 (16.1%)
Ethnicity	Hispanic or Latino	7.0 (22.6%)	7.0 (22.6%)
	Not Hispanic or Latino	24.0 (77.4%)	24.0 (77.4%)
BMI	Mean ± SD	26.2 ± 2.6	26.2 ± 2.6
	Range	20.2 – 29.9	20.2 – 29.9
Other Factors			

Table 8. Dropout Information, Fasting Bioequivalence Study

Protocol No. DASA-IMTB-05SB11-4FA-(0) Amendment No: 1 Study No. DD8860				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
(b) (6)	Withdrawn due to adverse event (blood pressure out of spec) on 03/24/15 at 06:30 Test product (Dose Code B)	Period 4 dosing morning (subject not dosed)	No	NAP
	Voluntary withdrawal on 03/16/15 at 10:07 Test product (Dose Code A)	Period 3 check in night	No	NAP
	Withdrawn due to adverse event (blood pressure out of spec) on 03/24/15 at 06:33 Reference product (Dose Code D)	Period 4 dosing morning (subject not dosed)	No	NAP
	Withdrawn due to non-compliance (positive nicotine) on 03/16/15 at 20:03 Reference product (Dose Code C)	Period 3 check in night	No	NAP
	Withdrawn due to non-compliance on 03/23/15 at 21:35 Reference product (Dose Code D)	Period 4 check in night	No	NAP
	Withdrawn due to adverse event (ECG- ECG T wave abnormality in limb leads) on 03/17/25 at 06:09 Reference product (Dose Code C)	Period 3 dosing morning (subject not dosed)**	No	NAP
	Voluntary withdrawal on 03/09/15 at 14:11 Reference product (Dose Code C)	Period 2 check in night	No	NAP
	Withdrawn due to adverse event (ECG- Prolonged QTc) on 03/23/15 at 21:20 Test product (Dose Code B)	Period 4 check in night	No	NAP
	Withdrawn due to adverse event (blood pressure out of spec) on 03/17/15 at 06:37 and withdrawn due to adverse event (blood pressure out of spec and heart rate out of spec on 03/24/15 at 06:36 Reference product (Dose Code C)	Period 3 dosing morning (subject not dosed) and Period 4 dosing morning (subject not dosed)	No	NAP
	Withdrawn due to non-compliance (positive drug screen) on 03/16/15 at 19:51 Reference product (Dose Code C)	Period 3 check in night	No	NAP
	Withdrawn due to non-compliance (positive drug screen) on 03/09/15 at 19:41 Reference product (Dose Code C)	Period 2 check in night	No	NAP
	Withdrawn due to adverse event (ECG – 1 st degree AV block) on 03/09/15 at 20:10 Reference product (Dose code C)	Period 2 check in night	No	NAP

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups			
	Fasted/Fed Bioequivalence Study Protocol No. DASA-IMTB-05SB11-4FA-(0) Amendment No: 1 Study No. DD8860			
	Test (Dose Code A) N= 39	Test (Dose Code B) N= 32	Reference (Dose Code C) N= 42	Reference (Dose Code D) N= 33
Skin and subcutaneous tissue disorders				
Laceration	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Respiratory thoracic and mediastinal disorders				
Cough	0 (0.00%)	1 (3.12%)	0 (0.00%)	0 (0.00%)
Dry throat	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Dyspnoea	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Sinus congestion	0 (0.00%)	1 (3.12%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Dizziness	1 (2.56%)	0 (0.00%)	2 (4.76%)	1 (3.03%)
Headache	9 (23.07%)	6 (18.75%)	8 (19.04%)	4 (12.12%)
Presyncope	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Somnolence	1 (2.56%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Arthralgia	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.03%)
Myalgia	0 (0.00%)	1 (3.12%)	0 (0.00%)	2 (6.06%)
Pain in extremity	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Metabolism and nutrition disorders				
Decreased appetite	0 (0.00%)	0 (0.00%)	2 (4.76%)	0 (0.00%)
Investigations				
Aspartate aminotransferase increased	1 (2.56%)	0 (0.00%)	0 (0.00%)	1 (3.03%)
Blood creatine phosphokinase increased	1 (2.56%)	1 (3.12%)	0 (0.0%)	1 (3.03%)
Blood pressure increased	3 (7.69%)	5 (15.62%)	6 (14.28%)	3 (9.09%)
Body temperature increased	0 (0.00%)	1 (3.12%)	0 (0.0%)	0 (0.00%)
Electrocardiogram QT prolonged	10 (25.64%)	7 (21.87%)	11 (26.19%)	5 (15.15%)
Electrocardiogram T wave abnormal	1 (2.56%)	1 (3.12%)	3 (7.14%)	3 (9.09%)
Glomerular filtration rate decreased	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Heart rate decreased	8 (20.51%)	10 (31.25%)	14 (33.33%)	10 (30.30%)
Heart rate increased	2 (5.12%)	1 (3.12%)	3 (7.14%)	2 (6.06%)

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Body System / Adverse Event	Reported Incidence by Treatment Groups			
	Fasted/Fed Bioequivalence Study Protocol No. DASA-IMTB-05SB11-4FA-(0) Amendment No: 1 Study No. DD8860			
	Test (Dose Code A) N= 39	Test (Dose Code B) N= 32	Reference (Dose Code C) N= 42	Reference (Dose Code D) N= 33
Neutrophil count decreased	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
QRS axis abnormal	0 (0.00%)	0 (0.00%)	1 (2.38%)	1 (3.03%)
White blood cell count decreased	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
Viral infection	0 (0.00%)	1 (3.12%)	0 (0.00%)	0 (0.00%)
General disorders administration site conditions				
Catheter site erythema	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site pain	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Catheter site swelling	1 (2.56%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest pain	0 (0.00%)	0 (0.00%)	2 (4.76%)	1 (3.03%)
Fatigue	1 (2.56%)	1 (3.12%)	0 (0.00%)	0 (0.00%)
Feeling hot	0 (0.00%)	0 (0.00%)	2 (4.76%)	0 (0.00%)
Rigors	0 (0.00%)	1 (3.12%)	1 (2.38%)	0 (0.00%)
Weakness	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Gastrointestinal disorders				
Abdominal distension	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.03%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.03%)
Lip dry	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)
Nausea	0 (0.00%)	0 (0.00%)	3 (7.14%)	1 (3.03%)
Vomiting	0 (0.00%)	1 (3.12%)	1 (2.38%)	0 (0.00%)
Eye disorders				
Lacrimation increased	0 (0.00%)	1 (3.12%)	0 (0.00%)	1 (3.03%)
Cardiac disorders				
Atrioventricular block first degree	0 (0.00%)	0 (0.00%)	1 (2.38%)	1 (3.03%)
Sinus bradycardia	13 (33.33%)	7 (21.87%)	10 (23.80%)	8 (24.24%)
Total	31 (79.48%)	21(65.62%)	33 (78.57%)	21 (63.63%)

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Duration Between Dosing and Emesis (hrs)
(b) (6)	Reference	II	10 hours

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(b) (6)	Test	III	11.78 hours
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Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Yes

Are there any serious adverse events or death? If so, are they reported to the OGD Safety Committee? No

Are there any other safety concerns based on the adverse event profile? No

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Protocol No. DASA-IMTB-05SB11-4FA-(0) Amendment No: 1 Study No. DD8860		
Type	Subject #s (Test – Dose Codes A and B)	Subject #s (Ref. – Dose Codes C and D)
Safety	NAP	Upon post study review on 04/06/15 it was determined that (b) (6)'s period 2, 6:00 hour ECG (conducted on 03/10/15 at 13:35) was misinterpreted , therefore was not to be summarized due to lead misplacement.
Technical	During Period 3 on 03/17/15, (b) (6) 0.15 hour sample was not stored into a -30°C set point freezer within 1 hour of sample collection. Sample was stored 1 hour and 12 minutes into the freezer from sample collection.	NAP

Comments:

- There were 12 dropouts in the fasting study. The following are the reasons for the dropouts:
 1. Subject (b) (6) was withdrawn period 4 dosing morning (subject not dosed) due to adverse event (blood pressure out of spec) – subject was dosed with test product in period 3.
 2. Subject (b) (6) voluntarily withdrew period 3 check-in night.
 3. Subject (b) (6) was withdrawn period 4 dosing morning (subject not dosed) due to adverse event (blood pressure out of spec) – subject was dosed with reference product in period 3.
 4. Subject (b) (6) was withdrawn period 3 check-in night due to non-compliance (positive nicotine).
 5. Subject (b) (6) was withdrawn period 4 check-in night due to non-compliance.

6. Subject (b) (6) was withdrawn period 3 dosing morning (subject not dosed) due to adverse event (ECG- T wave abnormality (limb leads)) – subject was dosed with reference product in period 2.
 7. Subject (b) (6) voluntarily withdrew period 2 check in night
 8. Subject (b) (6) was withdrawn period 4 check in night due to adverse event (ECG – prolonged QTc) – subject was dosed with test product in period 3.
 9. Subject (b) (6) was withdrawn period 3 dosing morning (subject not dosed) due to adverse event (blood pressure out of spec) and was withdrawn period 4 dosing morning (subject not dosed) due to adverse events (blood pressure and heart rate out of spec) – subject was dosed with reference product in period 2.
 10. Subject (b) (6) was withdrawn period 3 check in night due to non-compliance (positive drug screen).
 11. Subject (b) (6) was withdrawn period 2 check in night due to non-compliance (positive drug screen).
 12. Subject (b) (6) was withdrawn period 2 check in night due to adverse event (ECG – 1st degree AV block) – subject was dosed with reference product in period 1.
- As per the firm’s pre-established protocol (# DASA-IMTB-05SB11-4FA, effective date: 02/23/2015), data from subjects who completed at least two periods of the study will be included in the statistical analysis. Therefore, as per their protocol, the data of 39 subjects (excluding subject (b) (6)) were included in statistical analysis as these subjects completed at least two periods of the study.
 - The firm’s dropouts are acceptable.
 - Two subjects (b) (6) experienced vomiting. As per the firm’s pre-established protocol ((# DASA-IMTB-05SB11-4FA, effective date: 02/23/2015), if a subject experiences emesis (vomiting) within 2 hours following drug administration (based on 2 times reported median Tmax of dasatinib), the subject will be withdrawn from the respective period. Since subject (b) (6) did not experience emesis within 2 hours of dosing, the data of these subjects were included in statistical analysis. However, as per the RLD labeling, the Tmax of dasatinib is from 0.5 – 6 hours⁵. Therefore, based on the maximum value of 6 hours, the data of these subjects from their respective periods should not have been included in the statistical analysis. Therefore, the reviewer excluded this data and re-ran the statistical analysis and the study still passed. Please see results below:

Subject Number	Test/Reference	Period	Duration Between Dosing and Emesis (hrs)
(b) (6)	Reference	II	10 hours

⁵ Drugs@fda database, link: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021986s7s8lbl.pdf, search term: Sprycel®.

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(b) (6)	Test	III	11.78 hours
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Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.06	94.60	116.38	0.2428917	0.4928405	-0.126435	Scaled/PE	PASS
LAUCI	0.99	91.91	109.28	0.0616386	0.2482713	-0.029872	Unscaled	PASS
LCMAX	1.10	94.23	125.47	0.4668316	0.6832508	-0.234299	Scaled/PE	PASS

- There was one protocol deviation where the sample was stored 12 minutes late in the freezer. However, this should not impact the study results as the firm conducted adequate bench top stability for 19 hours and 37 minutes.
- There were no deaths or serious adverse events reported in the fasting BE study and the adverse event profiles of the test and reference products were comparable.
- There were few blood draw deviations; however, the firm used actual sampling time points in their statistical analysis. Therefore, this should not have an impact on the study outcome.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control

Bioequivalence Study No. DASA-IMTB-05SB11-4FA Analyte Name: Dasatinib										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	0.200	0.400	1.000	4.000	20.000	40.000	80.000	120.000	160.000	200.000
Inter day Precision (%CV)	2.0	4.0	2.2	2.2	1.6	1.7	1.7	1.7	1.5	1.4
Inter day Accuracy (%Actual)	-0.5	1.0	-0.1	-0.4	0.4	0.2	-0.7	-0.4	0.0	0.4
Linearity	0.9975 – 0.9999									
Linearity Range (ng/mL)	0.200 – 200.000									
Sensitivity/LOQ (ng/mL)	0.200									

Bioequivalence Study No. DASA-IMTB-05SB11-4FA Analyte Name: Dasatinib				
Parameter	Quality Control Samples			
Concentration (ng/mL)	0.600	5.000	60.000	150.000
Inter day Precision (%CV)	4.5	4.1	2.5	2.2
Inter day Accuracy (%Actual)	1.0	-0.3	-1.6	-1.0

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?	Yes
Did the firm provide 100% numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log) in the instrument printout format?	Yes

Table 12. SOP's Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
ABM-BL-0167	July 07, 2014	Sample Coding and Reporting Final Concentrations

Comments:

- Two hundred and fifty six (256) out of the 3003 study samples were analyzed as part of the incurred sample reanalysis (ISR). As per the firm's SOP, incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of $\leq 20\%$. Relative percent difference calculations (reported as "% Difference of Repeat Assay Relative to Original Assay") were performed. 100% of the samples repeated for incurred samples reproducibility were acceptable. The data meets the FDA criteria for ISR mentioned in the Guidance for Industry: Bioanalytical Method Validation, effective September 2013.
- The study validation assay is **adequate**.

4.1.1.4 Pharmacokinetic Results

Is there a Tmax difference between T and R	Yes
Are any CIs marginal?	No
Were the subjects dosed in groups?	No
Is the study design replicate and/or reference-scaled?	Yes Single-dose, randomized, two-treatment, four-period fully replicated crossover design
Is sampling time adequate?	Yes

Reviewer Calculated Results:

ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng hr/mL	419.064	71.79	48.17	1644.60	422.752	77.82	30.99	2085.50	0.99
AUCINF	ng hr/mL	453.558	66.19	128.84	1663.20	453.079	72.82	90.24	2112.80	1.00
C _{MAX}	ng/mL	108.761	45.28	14.66	215.44	109.249	54.46	3.13	250.90	1.00
T _{MAX}	hr	0.750	.	0.50	3.00	1.250	.	0.50	4.00	0.60
THALF	hr	5.431	31.65	3.36	11.31	5.935	29.37	3.29	11.13	0.92
KEL	hr-1	0.138	25.91	0.06	0.21	0.126	28.71	0.06	0.21	1.09

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng hr/mL	447.737	91.22	57.02	2242.10	457.944	87.73	19.07	2061.70	0.98
AUCINF	ng hr/mL	470.367	87.75	124.38	2264.00	505.835	79.59	133.81	2076.30	0.93
C _{MAX}	ng/mL	109.491	48.72	10.07	240.86	117.105	49.17	2.85	225.30	0.93
T _{MAX}	hr	1.000	.	0.33	3.00	1.000	.	0.33	3.00	1.00
THALF	hr	6.089	32.15	3.40	9.93	5.979	34.03	3.37	12.72	1.02
KEL	hr-1	0.126	31.90	0.07	0.20	0.128	30.46	0.05	0.21	0.98

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	ng hr/mL	432.097	81.39	48.17	2242.10	438.995	82.54	19.07	2085.50	0.98
AUCINF	ng hr/mL	461.387	76.85	124.38	2264.00	476.928	76.09	90.24	2112.80	0.97
C _{MAX}	ng/mL	109.093	46.58	10.07	240.86	112.875	51.71	2.85	250.90	0.97
T _{MAX}	hr	0.750	.	0.33	3.00	1.000	.	0.33	4.00	0.75
THALF	hr	5.737	32.25	3.36	11.31	5.955	31.35	3.29	12.72	0.96
KEL	hr-1	0.132	28.78	0.06	0.21	0.127	29.32	0.05	0.21	1.04

* Tmax values are presented as median, range.

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SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Parameter	Geometric Means		T/R Ratio	90% CI	
	Test	Reference		Lower CI	Upper CI
LAUCT	345.94	335.69	1.03	92.79	114.45
LAUCI	384.54	388.87	0.99	90.17	108.45
LCMAX	95.31	89.20	1.07	92.26	123.74

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.03	92.79	114.45	0.2402595	0.4901627	-0.130164	Scaled/PE	PASS
LAUCI	0.96	90.17	108.45	0.062097	0.2491927	-0.023679	Unscaled	PASS
LCMAX	1.06	92.26	123.74	0.4601613	0.6783519	-0.242525	Scaled/PE	PASS

The median Tmax (range) of the test product is 0.75 hr (0.33-3.0 hr) and that for the reference is 1 hr (0.33-4.0 hr). Per the RLD label, the Tmax range under fasting conditions in healthy volunteers is 0.50 to 3 hours⁶. Please see table below:

100 mg dose (2 x 50 mg) of Dasatinib	Fasting (n=49)	Fed (n=47)
AUCinf (ng*h/mL) Geometric Mean (CV)	304.24 (47)	355.27 (32)
Cmax (ng/mL) Geometric Mean (CV)	92.09 (50)	71.03 (40)
Tmax (hours) Median (range)	1.00 (0.50 - 3.00)	2.00 (0.50 - 6.00)
Thalf (hours) Mean (SD)	4.84 (2.16)	4.77 (1.34)

The median Tmax and range of the test product is within the range specified in the RLD label. Therefore, based on the above information, the Tmax of the test product, 0.75 hr (0.33-3.0 hr) is acceptable.

Summary table of Cmax values calculated by the reviewer

	Test	Reference
Mean Cmax (ng/mL)	109.86	111.78
Minimum Cmax (ng/mL)	10.07	2.84
Maximum Cmax (ng/mL)	240.86	250.9

In their clinical study report, the firm mentioned the following:

“During the blinded review of the dasatinib concentration-time data for all analyzed subjects, it was discovered that Subject (b) (6) and Subject (b) (6) had very low concentration time-profiles in Period 3 and Period 2, respectively, relative to the concentration-time profile in the other three periods for these subjects. Apotex Inc. conducted an

⁶ Drugs@fda database, link: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021986s7s8lbl.pdf, search term: Sprycel®.

investigation regarding these concentration-time profiles for Subject (b) (6) (Period 3) and Subject (b) (6) (Period 2) and found no analytical or clinical causes for the unexpected subject profiles. To test if these subjects were outliers, outlier tests for the ln-transformed parameters AUC_t, AUC_{inf} and C_{max} were performed for all subjects. The analysis concluded that Subject (b) (6) (Period 3) and Subject (b) (6) (Period 2) were outliers because their studentized residuals for both ln-transformed AUC_t and C_{max} were greater than 3. **Since the exclusion of outliers was not indicated a priori with regards to the statistical analysis of this study, the primary analysis included these outlying profiles. Nonetheless, inclusion of the outlying profiles demonstrated that bioequivalence criteria were met.** For information purposes only, a supplementary analysis was conducted that excluded Subject (b) (6) (Period 3) and Subject (b) (6) (Period 2). The supplementary analysis determined that bioequivalence criteria were still met.”

It should be noted that the reviewer included all the data (including data from subject #s (b) (6) in the statistical analysis and the study still passed.

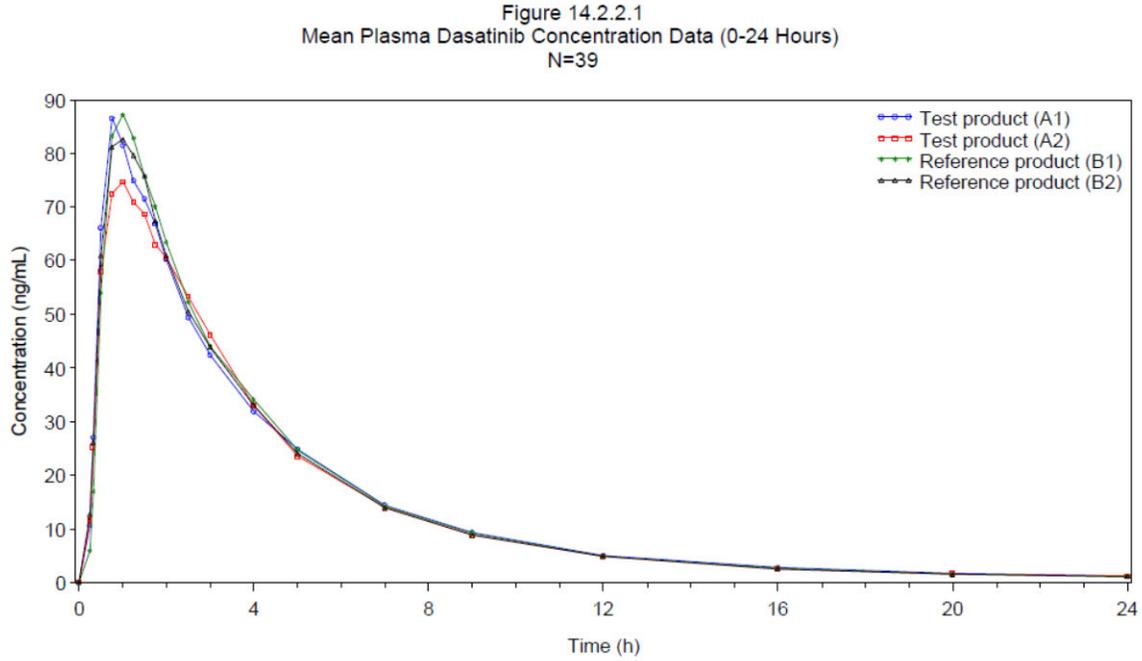
Overall Comment:

The statistical analysis conducted by the firm is acceptable.

**Table 13. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
(Firm-Submitted Data in Firm's Format)**

Please refer to the appendix section of the current review.

**Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
(Firm-Submitted Plot)**



Test product: 100 mg Dasatinib Tablets (Apotex Inc.)
Reference product: 100 mg Sprycel Tablets (Bristol Myers Squibb)

4.2 Formulation Data

Ingredient	Amount (mg) / Tablet				Amount (%) / Tablet
	20 mg	50 mg	70 mg	100 mg	20 mg, 50 mg, 70 mg 100 mg
Core					
Dasatinib*	20.0	50.0	70.0	100	24.3
Lactose monohydrate (b) (4) NF*	(b) (4)				
Microcrystalline Cellulose (b) (4) NF					
Croscarmellose Sodium NF					
Magnesium Stearate NF					
Colloidal Silicon Dioxide NF					
Film-coating					
Hypromellose (b) (4) USP	(b) (4)				
Hydroxypropyl Cellulose (b) (4) NF					
Triethyl Citrate (b) (4) NF					
Titanium Dioxide NF					
(b) (4)					
	--		--	--	-
TOTAL	(b) (4)				100

Reviewer Comments

The formulation was previously reviewed and was found acceptable⁷. The same formulation was used in the new fasting study (#DASA-IMTB-05SB11-4FA) submitted in the current amendment.

⁷ DARRTS, ANDA 202103, REV-BIOEQ-01 (General Review), 06/27/2012

4.3 Dissolution Data (Applicable if there are waiver requests)

Dissolution Review Path	DARRTS, ANDA 202103, REV-BIOEQ-02 (Dissolution Review), 01/28/2011
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Table 24. Dissolution Data

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	
						5	10	15	20	30	45		
dasa_imtb_10 0mg_sg_u_cd r_01		01/31/2015	Dasatinib Tablets Batch No.: FD150-215 Manufacture date: January 5, 2015	100 mg Film-coated Tablets	12	Mean	41	72	85	91	96	98	Section 2.7
						Range	(b) (4)						
						%RSD	19	8	4	3	2	1	
		01/31/2015	Sprycel® Tablets Batch No.: 4H69158B Expiration date: July 2017	100 mg Film-coated Tablets	12	Mean	40	68	81	87	92	95	
						Range	(b) (4)						
				%RSD	16	8	4	2	2	1			

Please comment on whether dissolution data are adequate to support waiver requests.

YES

Overall Comment:

- The firm previously conducted acceptable dissolution testing using the following FDA-recommended method^{8,9}:

Apparatus: USP Apparatus 2

Rotation Speed: 60 rpm

Medium: pH 4.0 Acetate buffer with 1.0% (v/v) Triton X-100

Volume: 1000 mL

Temperature: 37°C ± 0.5°C

Specification: NLT $\frac{(b)}{(4)}\%$ (Q) of dasatinib dissolved in $\frac{(b)}{(4)}$ minutes

- In the current amendment, the firm conducted an additional fasting study (#DASA-IMTB-05SB11-4FA) using new test lot (# FD150-215) and RLD lot (# 4H69158B) of the 100 mg strength. Therefore, the firm conducted additional dissolution testing using the above mentioned FDA-recommended method comparing the test product, 100 mg (lot # FD150-215) and reference product, 100 mg (lot # 4H69158B). The dissolution data of the test and reference products are comparable.
- The dissolution testing conducted by the firm is adequate.

⁸ DARRTS, ANDA 202103, REV-BIOEQ-02 (Dissolution Review), 01/28/2011

⁹ DARRTS, ANDA 202103, REV-BIOEQ-01 (General Review), 06/27/2012

4.4 OSIS Information

The OSIS inspection for the clinical and analytical sites was previously found adequate¹⁰. The new fasting study (#DASA-IMTB-05SB11-4FA) submitted in the current ANDA was conducted with the following time frame, clinical study dates 4/3/2015 to 3/24/2015, and analytical studies during the period of 4/6/2015 to 4/27/2015. For another (b) (4) an OSIS inspection of the clinical site, Apotex Inc., Clinical Operations Department, 465 Garyray Drive, Toronto, Ontario, (b) (4). (b) (4). The OSIS inspection for the analytical site Apotex Inc. 440 Garyray Drive, Toronto, Ontario, Canada M9L 1P7 for the current study was also conducted for (b) (4). Please see the tables below. The OSIS report for this ANDA is deemed complete.

OSI INSPECTION STATUS

According to OSI Search Database, GDRP, and DARRTS, the OSI inspection history for clinical and analytical sites under ANDA 202103

Clinical Site 1:

Summarization of the OSI Inspection of Clinical Site										
Site Name		Anapharm								
Site Address		5160, boul. Decarie, Suite 800, Montreal (Quebec), Canada, H3X 2H9								
Application	Inspected BE Study Type (In Vivo, In Vitro)	Inspection Type (Routine or For Cause)	OSI EIR Review Date	Inspection Outcome (NAI, VAI, OAI)*	Dates of Clinical portion of inspected studies		Current ANDA Clinical dates		Were the Current ANDA studies conducted within 3.5 years of the studies under/pending the OSI inspection?	Conclusion (Relevant, Irrelevant)
					Start	End	Start	End		
ANDA 204844	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

Clinical Site 2:

Summarization of the OSI Inspection of Clinical Site									
Site Name		Anapharm							
Site Address		2500, rue Einstein, Québec (Québec), Canada, G1P 0A2							
Application	Inspected BE Study	Inspection Type	OSI EIR Review	Inspection Outcome	Dates of Clinical portion of inspected studies	Current ANDA Clinical dates	Were the Current ANDA	Conclusion (Relevant,	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	

¹⁰ DARRTS, ANDA 202103, REV-BIOEQ-21 (Primary Review), 06/25/2013

	Type (In Vivo, In Vitro)	(Routine or For Cause)	Date	(NAI, VAI, OAI)*	Start	End	Start	End	studies conducted within 3.5 years of the studies under/pending the OSI inspection?	Irrelevant)
ANDA 204844	(b) (4)									

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

Clinical Site 3:

Summarization of the OSI Inspection of Clinical Site										
Site Name		Apotex Inc.								
Site Address		Clinical Operations Department, 465 Garyray Drive, Toronto, Ontario, Canada M9L 1P9								
Application	Inspected BE Study Type (In Vivo, In Vitro)	Inspection Type (Routine or For Cause)	OSI EIR Review Date	Inspection Outcome (NAI, VAI, OAI)*	Dates of Clinical portion of inspected studies		Current ANDA Clinical dates		Were the Current ANDA studies conducted within 3.5 years of the studies under/pending the OSI inspection?	Conclusion (Relevant, Irrelevant)
					Start	End	Start	End		
(b) (4)										

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

Analytical Site 1:

Summarization of the OSI Inspection of Analytical Site										
Site Name		Apotex Inc.								
Site Address		440 Garyray Drive, Toronto, Ontario, Canada M9L 1P7								
Application	Inspected BE Study Type (In Vivo, In Vitro)	Inspection Type (Routine or For Cause)	OSI EIR Review Date	Inspection Outcome (NAI, VAI, OAI)*	Dates of Clinical portion of inspected studies		Current ANDA Clinical dates		Were the Current ANDA studies conducted within 3.5 years of the studies under/pending the OSI inspection?	Conclusion (Relevant, Irrelevant)
					Start	End	Start	End		
(b) (4)										

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated

Analytical Site 2:

Summarization of the OSI Inspection of Analytical Site									
Site Name		Apotex Inc.							
Site Address		440 Garyray Drive, Toronto, Ontario, Canada M9L 1P7							

Application	Inspected BE Study Type (In Vivo, In Vitro)	Inspection Type (Routine or For Cause)	OSI EIR Review Date	Inspection Outcome (NAI, VAI, OAI)*	Dates of Clinical portion of inspected studies		Current ANDA Clinical dates		Were the Current ANDA studies conducted within 3.5 years of the studies under/pending the OSI inspection?	Conclusion (Relevant, Irrelevant)
					Start	End	Start	End		
(b) (4)										
*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action Indicated										

4.5 Appendix

Table 14.2.1.1
Individual Plasma Concentration Data - Test Product A1'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	0.00 h	0.25 h	0.3333 h	0.50 h	0.75 h	1.00 h	1.25 h	1.50 h	1.75 h	2.00 h
%CV	.	130.32	102.51	57.75	50.38	55.45	62.26	67.64	69.03	62.76
Median	0.000	4.646	20.709	61.014	82.111	74.983	56.661	55.686	52.523	53.615
Min	0.000	0.000	0.493	4.882	14.161	11.880	8.338	6.410	5.355	4.528
Max	0.000	59.357	102.232	150.800	195.272	191.120	176.506	210.067	215.437	175.449

Table 14.2.1.1
Individual Plasma Concentration Data - Test Product A1'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	2.50 h	3.00 h	4.00 h	5.00 h	7.00 h	9.00 h	12.00 h	16.00 h	20.00 h	24.00 h
%CV	53.69	47.25	45.99	45.15	46.36	44.95	41.43	43.59	38.14	36.09
Median	48.915	44.564	32.445	25.523	14.269	9.609	5.035	2.508	1.584	1.151
Min	3.874	3.200	2.437	2.218	1.977	1.587	1.036	0.603	0.507	0.333
Max	110.983	84.109	66.529	52.669	26.363	19.095	9.930	5.996	3.148	2.098

Table 14.2.1.2
Individual Plasma Concentration Data - Test Product A2'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	0.00 h	0.25 h	0.3333 h	0.50 h	0.75 h	1.00 h	1.25 h	1.50 h	1.75 h	2.00 h
Mean	0.000	11.648	25.248	58.045	72.559	74.781	71.022	68.779	63.118	60.551
SD	0.000	17.960	28.638	42.084	44.314	50.016	48.842	45.497	38.163	36.131
%CV	.	154.19	113.43	72.50	61.07	66.88	68.77	66.15	60.46	59.67
Median	0.000	1.452	11.208	52.184	69.190	66.020	59.013	59.343	56.356	52.513
Min	0.000	0.000	0.000	0.000	0.000	0.000	6.961	8.194	7.326	6.160
Max	0.000	70.908	97.143	133.668	186.911	222.532	240.860	234.720	198.131	176.085

Table 14.2.1.2
Individual Plasma Concentration Data - Test Product A2'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	2.50 h	3.00 h	4.00 h	5.00 h	7.00 h	9.00 h	12.00 h	16.00 h	20.00 h	24.00 h
Mean	53.349	46.133	33.048	23.466	13.992	8.792	4.840	2.539	1.582	1.158
SD	32.245	30.526	16.639	11.089	6.755	3.933	2.102	1.033	0.614	0.450
%CV	60.44	66.17	50.35	47.26	48.28	44.73	43.42	40.68	38.83	38.88
Median	48.363	41.420	31.412	21.836	12.978	8.239	4.576	2.596	1.542	1.092
Min	5.702	5.349	5.647	4.775	3.015	1.951	1.505	0.950	0.577	0.355
Max	133.864	156.821	84.582	47.437	26.126	17.105	9.416	5.103	3.340	2.475

Table 14.2.1.3
Individual Plasma Concentration Data - Reference Product B1'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	0.00 h	0.25 h	0.3333 h	0.50 h	0.75 h	1.00 h	1.25 h	1.50 h	1.75 h	2.00 h
%CV	.	198.11	134.84	83.25	64.30	62.08	60.86	58.06	57.49	52.09
Median	0.000	1.608	8.213	46.697	70.211	78.819	78.929	77.278	70.224	64.951
Min	0.000	0.000	0.207	0.937	1.185	1.064	2.204	2.834	3.127	3.133
Max	0.000	61.778	90.564	170.066	203.325	196.532	183.643	172.256	181.049	133.759

Table 14.2.1.3
Individual Plasma Concentration Data - Reference Product B1'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	2.50 h	3.00 h	4.00 h	5.00 h	7.00 h	9.00 h	12.00 h	16.00 h	20.00 h	24.00 h
%CV	49.32	41.82	47.41	45.76	44.26	43.64	43.97	45.36	44.21	46.05
Median	55.996	45.647	36.232	24.917	13.926	9.063	4.841	2.498	1.449	1.061
Min	2.638	2.345	2.372	1.831	1.227	0.908	0.579	0.354	0.311	0.277
Max	110.688	76.744	85.759	46.124	24.177	16.213	9.920	6.336	3.745	2.650

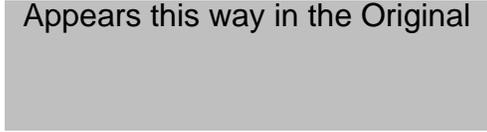
Table 14.2.1.4
Individual Plasma Concentration Data - Reference Product B2'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	0.00 h	0.25 h	0.3333 h	0.50 h	0.75 h	1.00 h	1.25 h	1.50 h	1.75 h	2.00 h
Mean	0.000	12.804	26.109	60.916	81.210	82.730	79.733	75.867	67.455	60.911
SD	0.000	23.510	36.063	42.296	47.452	48.078	52.278	53.190	45.286	35.713
%CV	.	183.62	138.12	69.43	58.43	58.11	65.57	70.11	67.14	58.63
Median	0.000	2.437	11.670	62.703	74.082	79.459	62.576	61.217	59.546	52.491
Min	0.000	0.000	0.539	1.456	1.926	2.625	2.848	2.390	2.207	1.767
Max	0.000	90.549	149.871	139.367	176.080	198.171	199.999	213.960	194.698	139.914

Table 14.2.1.4
Individual Plasma Concentration Data - Reference Product B2'
Dasatinib
LLOQ=0.200 ng/mL

Subject Sequence ² Period	2.50 h	3.00 h	4.00 h	5.00 h	7.00 h	9.00 h	12.00 h	16.00 h	20.00 h	24.00 h
Mean	50.568	43.847	33.096	23.936	13.799	8.785	4.855	2.553	1.551	1.128
SD	26.652	22.578	15.347	11.691	6.794	4.269	2.314	1.157	0.636	0.420
%CV	52.71	51.49	46.37	48.84	49.24	48.60	47.66	45.34	41.01	37.26
Median	49.603	42.948	34.746	24.477	14.359	8.425	4.843	2.560	1.519	1.061
Min	1.540	1.315	1.056	0.855	0.709	0.633	0.613	0.501	0.462	0.499
Max	104.969	82.697	57.889	45.131	27.609	17.950	10.088	5.104	3.054	2.125

Appears this way in the Original



BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202103

APPLICANT: Apotex Inc.

DRUG PRODUCT: Dasatinib Tablets, 20 mg, 50 mg, 70 mg and 100 mg

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

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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 }

Bing V. Li, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202103		
Drug Product Name	Dasatinib Tablets		
Strength(s)	20 mg, 50 mg, 70 mg and 100 mg		
Applicant Name	Apotex Inc.		
Applicant Address	150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
US Agent Name and the mailing address*	Kiran Krishnan, Vice President, US Regulatory Affairs Apotex Corp. 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326		
US agent's Telephone Number	954-384-3986		
US Agent's Fax Number	866-392-1774		
Original Submission Date(s)	06/27/2010		
Submission Date(s) of Amendment(s) Under Review	07/23/2013		
Reviewer	Santhosh K. Pabba, Ph.D., R.Ph.		
Study Number (s)	DASA-IMTB-05SB01-2FA (DD6366)	DASA-IMTB-05SB02-2FE (DD6367)	DASA-IMTB-05SB03-2FA
Study Type (s)	Fasting	Fed	Fasting (re-dosing)
Strength (s)	100 mg	100 mg	100 mg
Clinical Site	Anapharm	Anapharm	Anapharm
Clinical Site Address	2500, rue Einstein Quebec (Quebec), Canada, G1P 0A2	5160, boul. Decarie, Suite 800, Montreal (Quebec) Canada, H3X 2H9	2500, rue Einstein Québec (Québec), Canada G1P 0A2
Analytical Site	Apotex Inc.	Apotex Inc.	Apotex Inc.
Analytical Site Address	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario
OSI Status	Adequate		
OVERALL REVIEW RESULT	Inadequate		
REVISED/NEW DRAFT GUIDANCE INCLUDED	NO		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 13, 14	Fasting study	100 mg	Unacceptable
1, 13, 14	Fasting (redosing)	100 mg	Adequate

	study		
1, 13, 14	Fed study	100 mg	Adequate
1, 7	Dissolution	20 mg, 50 mg, 70 mg and 100 mg	Adequate

* As per the 356h form dated 05/30/2014

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

On July 23, 2013, Apotex submitted the current amendment to the Complete Response (CR) letter issued on July 09, 2013. Based on the firm's responses, the fasting study is still **unacceptable**, the fasting redosing study is **adequate**, and the fed study is **adequate**.

In the earlier review [DARRTS, ANDA: 202103 -PABBA, SANTHOSH K 06/25/2013 N/A 06/25/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive], for the fasting study, the results of the re-dosing study # DASA-IMTB-05SB03-2FA confirmed that Subject - (b) (6) was an "extreme" subject whose test-to-reference (T/R) ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other subjects from the original and re-dosing studies. The T/R ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject - (b) (6) were "aberrant" in the original fasting BE study. For this reason, the Subject - (b) (6) was not excluded from the final statistical analysis of the original fasting BE study. With the inclusion of Subject - (b) (6) the fasting BE study did not meet bioequivalence criteria. As a result, the firm was informed that the original fasting study was **unacceptable**.

In the current amendment, the firm's response to deficiency comment # 2 and 3 is acceptable. However, the firm's response to deficiency comment # 1 is incomplete. The Division of Bioequivalence I (DBI) does not agree with the firm's explanation for why Subject - (b) (6) should be excluded from the final statistical analysis of the original fasting BE study. DBI still considers the fasting study as **unacceptable**.

The test product formulations of the lower strengths (20 mg, 50 mg and 70 mg) are proportional to the test product formulation of the bio-strength (100 mg). The dissolution data of the lower strengths (20 mg, 50 mg and 70 mg) are comparable to the dissolution data of the biostrength (100 mg). Please note that all the strengths of the test product are (b) (4). However, DBI does not grant the waiver requests for in vivo BE study requirements at this time due to the unacceptable fasting BE study.

No Office of Scientific Investigations (OSI) inspection is pending or necessary at this time.

The application is **inadequate**.

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3 BACKGROUND

1. On June 27, 2010, Apotex, submitted the original application for Dasatinib Tablets, 100 mg.

This application contained the results of fasting and fed bioequivalence (BE) studies comparing a test product, Dasatinib Tablets, 100 mg to the corresponding reference product, Sprycel® (dasatinib) Tablets, 100 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The results are summarized in the tables below.

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fasting Bioequivalence Study [Study No. DASA-IMTB-05SB01-2FA (DD6366), N=44 (Male=37 and Female=7)]					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	332.25	317.11	1.05	95.79	114.60
AUC _∞ (ng·hr/mL)	355.27	339.82	1.05	95.66	114.26
C _{max} (ng/mL)	104.59	96.71	1.08	97.26	120.24

Note: The reviewer performed data analysis using the SAS code: Calcke.

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fed Bioequivalence Study, Study No. DASA-IMTB-05SB02-2FE (DD6367), N=52 (Male=47 and Female=5)]					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	405.94	379.43	1.07	99.32	115.25
AUC _∞ (ng·hr/mL)	423.02	395.67	1.07	100.04	114.26
C _{max} (ng/mL)	88.99	81.41	1.09	98.88	120.82

Note: The reviewer performed data analysis using the SAS code: Calcke.

The firm's fasting and fed BE studies were incomplete due to bioanalytical deficiencies. For the fasting study: (DASA-IMTB-05SB01-2FA (DD6366)), the firm identified Subjects – (b) (6) as being suspected of having “aberrant” plasma concentrations. The firm identified (b) (6) as outliers after performing the Lund’s outlier test. The reviewer could not confirm Subjects - (b) (6) as outliers because the firm did not submit the concentration vs. time data for the identified Subjects - (b) (6). The firm did not mention about redosing

study in the study protocol a priori. However, the firm conducted the redosing study with the above mentioned 3 subjects and included five additional control subjects. The acceptability of the decision to redose and the acceptability of dropping the subjects in question from the statistical analysis of the original fasting biostudy was pending the submission of the data requested above.

The application was found **inadequate** as stated in DBI review of this application dated 6/27/2012.

2. On August 16, 2012, Apotex, submitted its responses to the deficiency letter issued from DBI on July 12, 2012¹ due to several clinical and analytical deficiencies. Based on the firm’s responses, the fasting study was **unacceptable**, the fasting redosing study was **adequate**, and the fed study was **inadequate**.

Regarding the fasting study, the results of the re-dosing study # DASA-IMTB-05SB03-2FA confirm that Subject - (b) (6) was an “extreme” Subject whose test-to-reference (T/R) ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other subjects from the original and re-dosing studies, even though the T/R ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject - (b) (6) were “aberrant” in the original fasting BE study. For this reason, the reviewer included the data from Subject – (b) (6) in the final statistical analysis of the original fasting BE study. With the inclusion of Subject - (b) (6) the fasting BE study did not meet bioequivalence criteria (please see the table below). Please note that the T/R ratios (Cmax and AUCt) of Subjects (b) (6) in the redosing study fall within the range of T/R ratios (Cmax and AUCt) of subjects in the original study (i.e., all subjects in the original study except the suspected aberrant subjects).

Geometric Means and 90% Confidence Intervals - Reviewer Calculated – with Original values for Code: I (reported in the current amendment) and repeat values for Codes F and B

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fasting Bioequivalence Study [Study No. DASA-IMTB-05SB01-2FA (DD6366), N=42 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	336.19	293.91	1.14	96.68	135.34
AUC _∞ (ng·hr/mL)	359.41	343.01	1.05	95.89	114.50

¹ DARRTS, ANDA # 202103, SOLANA-SODEINDE, DIANA A
07/12/2012 FAX 07/12/2012 COR-ANDADE-01(Bio Incomplete Deficiencies) Original-1 (Not Applicable) Archive

Cmax (ng/mL)	105.14	88.27	1.19	98.23	144.45
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Note: The reviewer performed data analysis using the SAS code: Calcke. N=42 (including Subject - (b) (6) for AUCt and Cmax, N=41 for AUCi (test) and N =40 for AUCi (reference) - for Subject (b) (6) for both test and reference treatments and for Subject (b) (6) (reference), Kel could not be calculated

As a result, the original fasting study was unacceptable.

The application was **inadequate** with deficiencies.

3. On July 23, 2013, the firm submitted the current amendment to the Complete Response (CR) letter issued on July 09, 2013.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

Original review: DARRTS, ANDA: 202103 - PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive.

Amendment 1: DARRTS, ANDA: 202103 -PABBA, SANTHOSH K 06/25/2013 N/A 06/25/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive

4.2 Contents of Submission

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

4.3 Review of Submission – Amendment dated – July 23, 2013

Deficiency 1:

The results of the re-dosing study # DASA-IMTB-05SB03-2FA confirmed that Subject - (b) (6) was an “extreme” Subject, with highly variable pharmacokinetic (PK) responses

and test-to-reference (T/R) ratios of PK parameters consistently outside the PK ratio range of other Subjects from the original (# DASA-IMTB-05SB01-2FA) and re-dosing studies, even though the (T/R) ratios for this Subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject (b) (6) were “aberrant” in the original fasting BE study. For this reason, the Subject should not be excluded from the final statistical analysis of the original fasting BE study. With the inclusion of Subject (b) (6) the fasting BE study does not meet bioequivalence criteria. Specifically, the 90% Confidence Interval of lnAUCt is 96.68 to 135.34 and the 90% Confidence Interval of lnCmax is 98.23 to 144.45. As a result, the original fasting BE study is unacceptable.

Firm’s Response:

The original study (DASA-IMTB-05SB01-2FA) identified three (3) statistical outliers, Subject (b) (6) with extreme Test/Reference (T/R) ratios falling outside the observed range compared to the other Subjects in the study. A re-dosing study (DASA-IMTB-05SB03-2FA) was subsequently conducted, which demonstrated Subject (b) (6) to have T/R ratios within the range of the control Subjects, thus supporting the findings that Subject (b) (6) were statistical outliers in the original study. On the other hand, data from Subject (b) (6) in the original study (DASA-IMTB-05SB01-2FA) and the re-dosing study (DASA-IMTB-05SB03-2FA) both demonstrated “extreme” results in period 1, with highly variable pharmacokinetic responses leading to Test/Reference (T/R) ratios falling outside the observed range of other Subjects. We believe that the data from the re-dosing study supports that the T/R ratio obtained from Subject (b) (6) in the original study was outlying because the drug levels were extremely low in period 1 of the original and re-dosing studies while they were normal in period 2, despite dosing sequences being the opposite between the original (RT) and the re-dosing studies (TR). That is, the Subject is outlying with respect to the period of dosing. More importantly, the re-dosing data indicates that the observed differences in pharmacokinetic (PK) parameters between the Test and Reference products in the original study for this Subject are not a reflection of true differences between products. Consequently, inclusion of the original study data from this Subject would result in significant bias on the comparison of the two products and thus, it should be acceptable to exclude the data from this Subject.

While the cause of the extreme differences between periods in Subject (b) (6) is not known, it should be noted that dasatinib exposure is characterized by large inter- and intra-individual variability (Takahashi N et al, 2011) ranging from 32% to 118% (van Erp NP et al, 2009). In addition to this, variability has been reported to be due mainly to intra-individual (inter-occasion) variability (Dai G et al, 2008). As dasatinib primarily undergoes CYP3A4 metabolism which is inducible by a number of xenobiotics, the potential for a number of drug-drug interactions that ultimately affect dasatinib plasma concentrations is great (Raucy JL, 2003) (Refer to Appendix 7). More importantly, due to the considerable role that CYP3A4 plays in the metabolism of a large number of xenobiotics, coupled with their variable CYP3A4 induction potency and

duration, any number of these xenobiotics could have an impact on dasatinib plasma concentration. Therefore non-compliance to study restrictions or intake of drug or over-the-counter (OTC) products could contribute to the “extreme” plasma profiles observed with dasatinib administration. Furthermore, in addition to dasatinib being characterized as a low solubility/high permeability [Biopharmaceutics Classification System (BCS II)] compound for which solubility can potentially be rate-limiting for absorption (Dasatinib Scientific Discussion, EMA 2006), dasatinib solubility is also pH dependent (Sprycel® FDA Prescribing Information), therefore dasatinib absorption can also be impacted by acid levels within the gastrointestinal tract. Accordingly, marked decreases in dasatinib levels have been observed with co-administration of OTC antacids in addition to H₂ antagonists and proton-pump inhibitors (Dasatinib Clinical Pharmacology and Biopharmaceutics Review) (**Refer to Appendix 8**). Additional simulation and modeling performed by Apotex on the original and re-dosing studies using GastroPlus Software (**Refer to Appendix 9**) revealed an important detail that could explain the low plasma concentrations observed in Subject ^{(b) (6)} for the Reference and Test product in the original and re-dosing studies, respectively. Whereas dasatinib was almost completely absorbed upon oral administration, which is in agreement with literature information, the simulation revealed that in Subject ^{(b) (6)}, the absorption was incomplete for both Reference and the Test products in the original study and re-dosing study, respectively. The reason for incomplete absorption is believed to be most likely a failure of the dosage form to disintegrate and dissolve due to reduced exposure to highly acidic stomach environment. By simulating a short exposure to an acidic stomach environment in conjunction with a large particle size (occurring in absence of complete tablet disintegration), we demonstrated that once the practically undisintegrated/undissolved tablet reaches the intestine (characterized by a relatively higher pH than in the stomach), dissolution of dasatinib which is pH dependent becomes limited, resulting in a low bioavailability reflected in both C_{max} and AUC parameters. Given the intrinsic properties of the drug (low solubility and pH dependency) in addition to the potential for drug-drug interactions with dasatinib, it is not surprising that in one of the clinical trials submitted by the Brand company of Sprycel® (Dasatinib) (NDA 21-986 & 22-072), Study CA180020 also identified a Subject outlier whereby no measurable concentrations were noted following a single evening dose of Dasatinib 50 mg treatment. Consequently, pharmacokinetic parameters from that outlying Subject were excluded from the statistical analysis for the evening dosing, further demonstrating the fact that extreme pharmacokinetic profiles are not uncommon for this drug (**Refer to Appendix 10**).

Moreover, the results of the re-dosing study for Subject ^{(b) (6)} did demonstrate that the anomalous results in the original study cannot be attributed to a product-specific mal-absorption (Subject by product interaction), considering that the extremely low absorption was observed for one product (Reference) in the original study and for the other product (Test) in the re-dosing study. Because the results of this Subject cannot be attributed to a specific interaction between this Subject and either one of the drug products (but instead is observed to be period-specific), the results obtained for this Subject do not provide any valid information or added value in the assessment of bioequivalence of the two products.

Therefore the submitted results from the original study (Analysis #1) should be considered justified:

Analysis 1:

<i>Study Number</i>	<i>lnAUCt Ratio (and 90% CI) (%)</i>	<i>lnCmax Ratio (and 90% CI) (%)</i>
DASA-IMTB-O5SBO1-2FA	104.94 (95.95 – 114.77)	108.14 (97.26 – 120.24)

Nevertheless, should the agency believe that the data from Subject (b) (6) is valid in the original study, then it should also be accepted that the data for this Subject in the re-dosing study (Subject (b) (6) is considered equally valid by virtue that the extreme profiles occurred for this Subject in both studies which were conducted in the same manner, and that these extreme profiles were not associated with a particular product only. Since both products were affected similarly, it is unfair to discriminate the two occurrences by simply considering one T/R ratio to be acceptable (original result) over the other (re-dosing result). Therefore, in the presence of two “valid” estimations on pharmacokinetic parameters, (in essence, data which has been replicated), it should be accepted that the average of each of the two Test and Reference Cmax and AUC values be taken in determining the T/R value of this Subject for the overall bioequivalence assessment. This concept is consistent with the common practice in bio-analysis of Subject PK samples that when the repeat values do not support the original assay value of a sample, either a missing value or the average (or in some cases, the median) of the original and repeat values is reported for the final value of that sample. The statistical analysis (Analysis #2) including the average pharmacokinetic values from Subject (b) (6) from the original and re-dosing studies was conducted and results of the bioequivalence assessment are presented below:

Analysis 2:

<i>Study Number</i>	<i>lnAUCt Ratio (and 90% CI) (%)</i>	<i>lnCmax Ratio (and 90% CI) (%)</i>
DASA-IMTB-O5SBO1-2FA including average PK parameters from Subject (b) (6) (original and re-dosing study)	105.07 (96.29 – 114.65)	108.27 (97.64 – 120.06)

Further to the rationale for conducting Analysis #2, since data from the re-dosing study for the other Subject outliers (Subject (b) (6) are considered valid in the re-dosing study (as the re-dosing study confirmed that the original results for these Subjects were indeed anomalous), an additional bioequivalence assessment including the average pharmacokinetic data from Subject (b) (6) along with the pharmacokinetic data of Subject (b) (6) obtained from the re-dosing study are presented below (Analysis #3):

Analysis 3:

<i>Study Number</i>	<i>lnAUCt Ratio (and 90% CI) (%)</i>	<i>lnCmax Ratio (and 90% CI) (%)</i>
DASA-IMTB-O5SBO1-2FA including	105.84 (97.35 – 115.07)	109.08 (98.81 – 120.42)

average PK parameters from Subject (b) (6) (original and re-dosing study) and PK parameters from Subject (b) (6) (re-dosing study)		
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Finally, taking this concept further, since data from the re-dosing study for the control Subjects are also equally valid, an additional bioequivalence assessment (Analysis #4) including the average pharmacokinetic data from Subject (b) (6) along with the average pharmacokinetic data from the control Subjects (Subject (b) (6) and pharmacokinetic data for Subject (b) (6) from the re-dosing study was also conducted and these results are presented below:

Analysis 4:

Study Number	lnAUCt Ratio (and 90% CI) (%)	lnCmax Ratio (and 90% CI) (%)
DASA-IMTB-05SBO1-2FA including average PK parameters from Subject (b) (6) (original and re-dosing study) and PK parameters from Subject (b) (6) (re-dosing study)	107.26 (99.59 – 115.53)	111.17 (101.62 – 121.60)

In conclusion, we believe that the exclusion of the data from Subject (b) (6) is justified for the bioequivalence assessment of the Test and Reference products. Nevertheless, the bioequivalence results presented above using multiple scenarios of “valid” data all demonstrate the same finding that the 90% CI of the AUC and Cmax T/R ratios are within the 80 – 125% bioequivalence limits. Consequently, the Apotex product Dasatinib 100 mg Tablets should indeed be deemed bioequivalent to the Reference product, Sprycel® Tablets 100 mg (Bristol-Myers Squibb Company), (USA), under fasting conditions.

Reviewer note: Please see Section: 8 – Attachments for Appendices – 7, 8, 9, 10 and list of references provided by the firm in the above deficiency response.

Reviewer’s Comments:

- Earlier in the reviews², DBI excluded Subjects (b) (6) from the statistical analysis of the original fasting BE study based on the DB practice^{3,4} that removal of a subject from the statistical analysis is acceptable only when all the three following criteria are met: a) the subject qualifies as “having aberrant PK results” (and therefore can be excluded from the statistical analysis of the original study) on the basis of an “a priori” statistical test, and b) the Subject’s T/R ratios in the redosing study fall within the range of T/R ratios of Subjects in the original study

² DARRTS, ANDA: 202103 - PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) and DARRTS, ANDA: 202103 -PABBA, SANTHOSH K 06/25/2013 N/A 06/25/2013 REV-BIOEQ-21(Primary Review)

³ Please refer to ANDA #'s – 91608, 205302 and (b) (4)

⁴ Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (January 2001)

(i.e., all Subjects in the original study except the suspected aberrant subject) **and** c) the T/R ratios of the control Subjects in the redosing study fall within the range of T/R ratios of subjects in the original study (i.e., all Subjects in the original study except the suspected aberrant Subject), i.e. the redosing study is valid.

- It was confirmed based on the results from the redosing study (# DASA-IMTB-05SB03-2FA) that Subjects (b) (6) had aberrant results in the original fasting study (#DASA-IMTB-05SB01-2FA (DD6366)). The results of the re-dosing study confirm that only Subject - (b) (6) was an “extreme” Subject whose test-to-reference ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other Subjects from the original and re-dosing studies, even though the test-to-reference ratios for this Subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject (b) (6) were “aberrant” in the original fasting BE study. For this reason, DBI considered that Subject (b) (6) should not be excluded from the final statistical analysis of the original fasting BE study (please refer to the above mentioned reviews for complete details).
- In the firm’s response of the current amendment, the firm did not provide conclusive evidence with supporting data to demonstrate the reason for the extreme differences in the pharmacokinetic responses following the test treatment in Period I (original fasting BE study) and Period II (redosing study) for Subject – (b) (6). The firm explains that *‘dasatinib exposure is characterized by large inter- and intra-individual variability, considerable role played by CYP3A4 in the metabolism of a large number of xenobiotics, coupled with their variable CYP3A4 induction potency and duration. Dasatinib is characterized as a low solubility/high permeability [Biopharmaceutics Classification System (BCS II)] compound for which solubility can potentially be rate-limiting for absorption (Dasatinib Scientific Discussion, EMA 2006), dasatinib solubility is also pH dependent (Sprycel® FDA Prescribing Information), therefore dasatinib absorption can also be impacted by acid levels within the gastrointestinal tract’*. The reviewer considers the firm’s response to deficiency # 1 is incomplete and the fasting BE study is still considered unacceptable for the following reasons:
 - The reviewer understands that dasatinib exposure is characterized by large inter- and intra-individual variability, therefore the firm should have powered the study adequately to address the data variability often observed for this drug and/or should have used reference replicate study design during the conduct of the BE studies.
 - The reviewer understands that dasatinib is characterized as a low solubility/high permeability [Biopharmaceutics Classification System (BCS II)] compound, dasatinib solubility is pH dependent and dasatinib absorption can also be impacted by acid levels within the gastrointestinal tract. The firm clearly mentioned in its exclusion criteria of the study protocol that subjects to whom any

of the following applies (the list below does not include all the exclusion criteria) will be excluded from the study: *‘Use of any drugs known to induce or inhibit hepatic drug metabolism (examples of inducers: barbiturates, carbamazepine, phenytoin, glucocorticoids, omeprazole; examples of inhibitors: antidepressants (SSRI), cimetidine, diltiazem, macrolides, imidazoles, neuroleptics, verapamil, fluoroquinolones, antihistamines) within 30 days prior to administration of the study medication. Use of an investigational drug or participation in an investigational study within 30 days prior to dosing. Clinically significant history or presence of any gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of the drug. Use of prescription medication within 14 days prior to the first administration of study medication or over-the-counter products (including natural health products, e.g. food supplements, vitamins, herbal supplements) within 7 days prior to the first administration of study medication, except for topical products without significant systemic absorption. Use of any tobacco products in the 3 months preceding the screening visit or positive cotinine test at screening. History of significant alcohol or drug abuse within one year prior to the screening visit. Regular use of alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).* Since the fasting BE study was a well controlled study in healthy subjects, the variability in dasatinib metabolism due to enzyme induction and drug-drug interaction is unlikely to contribute to the extreme plasma profile of Subject (b) (6)

- Please note that no protocol deviations were reported for Subject - (b) (6) [the reviewer has verified the case report form (CRF), in the submission dated: June 28, 2010, location: module – 5.3.1.2, file name: supportive documents (meals) part 3, pages – 636-654]. The firm mentioned that Subject - (b) (6) met the inclusion/exclusion criteria and complied with the study restrictions. The firm did not demonstrate evidence that Subject - (b) (6) was on CYP3A4 enzyme inducing/inhibiting agents prior to enrollment into the fasting BE study. Also the firm did not demonstrate evidence if Subject - (b) (6) has gastrointestinal (GI) physiological/anatomical abnormalities leading to shorter gastric residence/transit time which could have influenced dasatinib absorption. If indeed Subject - (b) (6) had any of the aforementioned issues, the Subject - (b) (6) should not have been included in the fasting BE study. Therefore the reviewer does not agree with the firm’s explanation that drug-drug/drug-food interactions, non-compliance to study restrictions, gastric pH and other reasons (please see the firm’s response) could have played a role in the aberrant dasatinib plasma concentrations for Subject - (b) (6)
- The firm also explains that: *“the results of the re-dosing study for Subject - (b) (6) demonstrate that the anomalous results in the original study cannot be attributed to a product-specific mal-absorption (Subject by product interaction), considering*

that the extremely low absorption was observed for one product (Reference) in the original study and for the other product (Test) in the re-dosing study. Because the results of this Subject cannot be attributed to a specific interaction between this Subject and either one of the drug products (but instead is observed to be period-specific), the results obtained for this Subject do not provide any valid information or added value in the assessment of bioequivalence of the two products”.

- Based on the Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (posted January 2001), the reviewer does not consider the firm’s explanation valid. *‘A subject-by-formulation interaction could occur when an individual is representative of subjects present in the general population in low numbers, for whom the relative BA of the two products is markedly different than for the majority of the population, and for whom the two products are not bioequivalent, even though they might be bioequivalent in the majority of the population. In the case of product failure, the unusual response could be present for either the T or R product. However, in the case of a subpopulation, even if the unusual response is observed on the R product, there could still be concern for lack of interchangeability of the two products. For these reasons, deletion of outlier values is generally discouraged, particularly for nonreplicated designs. With replicated crossover designs, the retest character of these designs should indicate whether to delete an outlier value or not’.*
- In addition, the results of the re-dosing study # DASA-IMTB-05SB03-2FA confirm that Subject - (b) (6) was an “extreme” subject whose test-to-reference ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other subjects from the original and re-dosing studies, even though the test-to-reference ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject - (b) (6) were “aberrant” in the original fasting BE study. For this reason, the subject should not be excluded from the final statistical analysis of the original fasting BE study⁵.
- The firm also explains that *‘in one of the clinical trials submitted by the Brand company of Sprycel® (Dasatinib) (NDA 21-986 & 22-072), Study CA180020 also identified a Subject outlier whereby no measurable concentrations were noted following a single evening dose of Dasatinib 50 mg treatment. Consequently, pharmacokinetic parameters from that outlying Subject were excluded from the statistical analysis for the evening dosing, further demonstrating the fact that extreme pharmacokinetic profiles are not uncommon for this drug’.* The reviewer does not agree with the firm’s explanation. Study # CA180020 (for the NDA # 21-986) is a ‘Gastric acid pH modulators interaction’ study and is not a

⁵ The preceding language in the bullet point was obtained from the review - DARRTS, ANDA # 091608, DEHAVEN, WAYNE I 03/24/2011 N/A 03/24/2011 REV-BIOEQ-01(General Review) Original-1 Archive

bioequivalence study and outlier test was not performed and complete details regarding the study and the OCP reviewer's evaluation for excluding Subject with no measurable concentrations is not known. Two different studies conducted at different times, conditions and different study objectives cannot be compared. Since large inter- and intra-individual variability and extreme pharmacokinetic profiles have been reported for this drug, the firm should have powered the study adequately to address the data variability often observed for this drug and/or should have used reference replicate study design during the conduct of the BE studies.

- The reviewer does not agree with the firm's explanation that *'should the agency believe that the data from Subject - (b) (6) is valid in the original study, then it should also be accepted that the data for this Subject in the re-dosing study (Subject (b) (6) is considered equally valid by virtue that the extreme profiles occurred for this Subject in both studies which were conducted in the same manner, and that these extreme profiles were not associated with a particular product only. Since both products were affected similarly, it is unfair to discriminate the two occurrences by simply considering one T/R ratio to be acceptable (original result) over the other (re-dosing result). Therefore, in the presence of two "valid" estimations on pharmacokinetic parameters, (in essence, data which has been replicated), it should be accepted that the average of each of the two Test and Reference Cmax and AUC values be taken in determining the T/R value of this Subject for the overall bioequivalence assessment'*. The firm's explanation that average of each of the two Test and Reference Cmax and AUC values from the original and redosing fasting studies should be taken in determining the T/R value of this Subject for the overall bioequivalence assessment is not acceptable. The DB does not combine data from two different studies to conclude bioequivalence.
- Based on the above mentioned information, the reviewer still considers the fasting study as **unacceptable**.

Deficiency 2:

For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), you did not submit the assay failure investigation report for rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats). Please submit the assay failure investigation reports for the said run.

Firm's Response:

As requested, please refer to Appendix 11 for the Assay failure investigation report for 21DD6367.

Reviewer Comments:

- The firm has submitted the assay failure investigation report for rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats), please see Section: 8 – Attachments for the report. The reviewer has verified the raw data and the assay failure investigation report [2 out of 3 QC-A samples failed to meet the acceptance criteria (>15% deviation) due to analytical instrument malfunction. After instrument maintenance, the reinjected run met the run acceptance criteria]. Upon verification, the reviewer considers that the run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats) was rejected as per the SOP: ABM-BL-0154 rev 6 Routine Batch Sample Analysis for assay acceptance criteria.
- The firm's response is acceptable.

Deficiency 3:

For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), you have submitted whole blood stability validation data for 2 hours on ice in the current amendment to address the protocol deviation pertaining to centrifugation of post-dose fed BE study samples as much as 72 minutes after blood collection. However, you did not provide the nominal concentrations of the quality control (QC) samples used in this validation study. Please provide these nominal concentrations. If the measured values of the QC samples are greater than 15% from nominal, then please repeat the validation study.

Firm's Response:

The whole blood stability test samples were left on ice for two hours and reference blood test samples were prepared after the 2 hours test condition had elapsed. Both test and reference samples were spun down at the same time to obtain plasma. These stability samples were extracted along with a plasma standard curve and plasma QCs as per the analytical method DD-AM rev 1. The spun down blood samples were labeled as QCA test, QCC test, QCA ref or QCC ref. The plasma QCs extracted along with the stability samples met specification and therefore the run was deemed acceptable. Refer to the Watson results attached in file "Blood Stability Run".

The blood test and reference samples were spiked with the same amount of Dasatinib as the method plasma QC preparation (QC A = Low = 3 ng/mL and QC C = High = 150 ng/mL). Due to the blood/plasma partitioning in these blood samples not all the Dasatinib is recovered into the plasma sample. Therefore, we expected the spun down blood samples to have a lower Dasatinib concentration in plasma than what was spiked into the whole blood so a comparison to the nominal (spiked) concentration was not possible. For the blood stability test we compared the ratio of the extracted test concentrations to the extracted reference concentrations. If the ratio of these two concentrations was within 15% the stability test was acceptable. Both test and reference blood samples were spun down at the same time and extracted at the same so this isolated the test condition of 2 hours on ice as this was the only difference between the handling of the samples. The plasma QCs used in the run demonstrated that the extraction was accurate and precise and were used for the run acceptance.

Therefore, the blood stability test is valid and will not be repeated.

Reviewer Comments:

- The firm mentioned the nominal concentration for QC-A (Low) - 3 ng/mL and QC-C (High) - 150 ng/mL. The measured values of the QC samples (mentioned below) are greater than 15% from nominal. Still, the reviewer agrees with the firm that due to the blood/plasma partitioning in these blood samples not all the Dasatinib is recovered into the plasma sample. The reviewer has verified and found the difference between the extracted test and extracted reference samples (both at LQC and HQC) was <15%. The reviewer agrees with the firm's explanation and therefore, considers the firm's response as acceptable.

(b) (4)

5 DEFICIENCY COMMENTS

The firm explains that while the cause of the extreme differences between periods in Subject - (b) (6) is not known, the observed differences in pharmacokinetic (PK) parameters between the Test and Reference products in the original study for this Subject are not a reflection of true differences between products. Therefore, it should be acceptable to exclude the data for this subject from the statistical analysis of the original fasting BE study.

The firm explains that:

- Dasatinib exposure is characterized by large inter- and intra-individual variability.
- Simulation performed on the original and re-dosing studies using GastroPlus Software revealed that in Subject - (b) (6), the absorption was incomplete for both Reference and the Test products in the original study and re-dosing study, respectively. Given the intrinsic properties of the drug (low solubility and pH

- dependency) the firm attributed the cause for the incomplete absorption to a failure of the dosage form to disintegrate and dissolve due to reduced exposure to highly acidic stomach environment.
- The average of each of the two Test and Reference Cmax and AUC values from the original and redosing fasting studies should be taken in determining the T/R ratio of Subject - (b) (6) for the overall bioequivalence assessment.

DBI does not agree with the firm's explanations for the following reasons:

- DBI understands that dasatinib exposure is characterized by large inter- and intra-individual variability, therefore the firm should have powered the study adequately to address the data variability often observed for this drug and/or should have used reference replicate study design during the conduct of the BE studies.
- DBI understands that dasatinib is characterized as a low solubility/high permeability [Biopharmaceutics Classification System (BCS II)] compound, dasatinib solubility is pH dependent and dasatinib absorption can be impacted by acid levels within the gastrointestinal tract. However, for the fasting study, there are no protocol deviations reported for Subject - (b) (6). The firm mentioned that Subject - (b) (6) met the inclusion/exclusion criteria and complied with the study restrictions. The firm did not demonstrate evidence that Subject - (b) (6) was on CYP3A4 enzyme inducing/inhibiting agents prior to enrollment into the fasting BE study. Also the firm did not demonstrate evidence if Subject - (b) (6) has shorter gastric residence/transit time or gastrointestinal (GI) physiological/anatomical abnormalities which could have influenced dasatinib absorption. If indeed the Subject - (b) (6) had any of the aforementioned issues, the Subject - (b) (6) should not have been included in the fasting BE study. The reviewer notes that, *clinically significant history or presence of any gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of the drug is an exclusion criteria*. Therefore DBI does not agree with the firm's explanation that drug-drug/drug-food interactions, non-compliance to study restrictions, gastric pH and other reasons) could have played a role in the aberrant dasatinib plasma concentrations for Subject - (b) (6).
- DBI does not agree with the firm's explanation with regards to the clinical trials submitted by the Brand company of Sprycel® (Dasatinib) (NDA 21-986 & 22-072). The study # CA180020 (for the NDA # 21-986) is a 'Gastric acid pH modulators interaction' study and is not a bioequivalence study. From the OCP review, it is unclear whether the outlier test was performed. Complete details regarding the study are not available. OCP reviewer's evaluation for excluding the subject with no measurable concentrations is not known. Two different studies conducted at different times, conditions and evaluated for different objectives cannot be compared. Since large inter- and intra-individual variability and extreme pharmacokinetic profiles have been reported for this drug, the firm should have powered the study adequately to address the data variability often

observed for this drug and/or should have used reference replicate study design during the conduct of the BE studies.

- DBI does not agree with the firm's explanation that average of each of the two Test and Reference C_{max} and AUC values from the original and redosing fasting studies should be taken in determining the T/R ratio of Subject - (b) (6) for the overall bioequivalence assessment. The DB does not combine data from two different studies conducted at different times. Also, as per the CDER Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (January 2001) and the Divisions of Bioequivalence current practice, dropping of an "outlier" subject data from BE studies solely based on a statistical test is not acceptable.
- Based on the above mentioned information, DBI still considers the fasting study as **unacceptable**.

6 RECOMMENDATIONS

1. The Division of Bioequivalence finds the fasting BE study (DASA-IMTB-05SB01-2FA (DD6366)) **unacceptable** due to the deficiencies mentioned above. The firm, Apotex Inc., conducted the fasting BE study on its Dasatinib Tablets, 100 mg (lot # FD150-31) comparing it to Bristol Myers Squibb's Sprycel® (dasatinib) Tablets, 100 mg (lot # 9L6029B).
2. The Division of Bioequivalence **accepts** the fasting (re-dosing) BE study (DASA-IMTB-05SB03-2FA). The firm, Apotex Inc., conducted the fasting (re-dosing) BE study on its Dasatinib Tablets, 100 mg (lot # FD150-31) comparing it to Bristol Myers Squibb's Sprycel® (dasatinib) Tablets, 100 mg (lot # 9L6029B).
3. The Division of Bioequivalence **accepts** the fed BE study (DASA-IMTB-05SB02-2FE). The firm, Apotex Inc., conducted the fasting BE study on its Dasatinib Tablets, 100 mg (lot # FD150-31) comparing it to Bristol Myers Squibb's Sprycel® (dasatinib) Tablets, 100 mg (lot # 9L6029B).
4. The dissolution testing conducted by Apotex Inc., on its test product Dasatinib Tablets, 20 mg (Batch # FD150-32), 50 mg (Batch # FD150-33), 70 mg (Batch # FD150-34) and 100 mg (Batch # FD150-31) is **acceptable**. The dissolution testing data for the lower strengths of the test product Dasatinib Tablets, 20 mg (Batch # FD150-32), 50 mg (Batch # FD150-33), 70 mg (Batch # FD150-34), using the FDA recommended method are comparable to the dissolution data of the bio-strength, Dasatinib Tablets, 100 mg (lot # FD150-31). The formulation of Dasatinib Tablets, 20 mg, 50 mg and 70 mg are proportionally similar to the Dasatinib Tablets, 100 mg which underwent bioequivalence testing. The DB does not grant the waivers of in vivo bioequivalence study requirements for Dasatinib Tablets, 20 mg, 50 mg and 70 mg due to the deficiency comments listed above.

7 COMMENT FOR OTHER OGD DISCIPLINES

Discipline	Comment
None	.

8 ATTACHMENTS:

Appendix 7: Dasatinib plasma levels are reduced in the presence of CYP3A4 inducers.

Human CYP3A4 metabolizes a majority of clinically important substrates at variable rates. Consequently, CYP3A4 is responsible for approximately 60% of P450-mediated metabolism of drugs in therapeutic use today implicating this enzyme as important with respect to the action, duration, and disposition of drugs and their metabolites. Wide variation in tissue concentrations of this enzyme has been found among individuals that ultimately affects drug disposition, often making disposition difficult to predict. Variability in CYP3A4 expression can result from a variety of factors and is partially explained by the ability of various xenobiotics to increase the expression of this P450. The inducibility of CYP3A4 gene expression, coupled with the remarkable versatility of CYP3A4 catalytic activities, creates the potential for drug-drug interactions. (Raucy JL, 2003) Dasatinib is extensively metabolized by CYP3A4. (Sprycel® FDA Prescribing Information) In fact, the Sprycel® Prescribing Information recommends dose modification when dasatinib is concomitantly administered with strong CYP3A4 inducers, as these compounds have been shown to decrease dasatinib plasma concentrations respectively. (Sprycel® FDA Prescribing Information) Furthermore, CYP3A4 is inducible not only by therapeutic agents but also by a number of natural products (Raucy JL, 2003) and cigarette smoke components. (Kumagai T et al, 2012) This potentially leads to a large variability in the induction effects observed for CYP3A4 activity as the de-induction of hepatic enzymes are likely to also depend on the elimination of the inducing agent itself. (Horn JR and Hansten PD, 2011) For instance, rifampin is known to induce multiple enzymes responsible for metabolism including CYP3A4. A recent report noted that it takes 2 – 4 weeks for rifampin-induced midazolam clearance to return to baseline values with a de-induction half-life of 7.7 days. (Horn JR and Hansten PD, 2011) On the other hand, recovery time of CYP3A4 after enzyme induction by St. John's Wort administration takes approximately 1 week to return to basal levels. (Imai H et al, 2008) Taken together, this suggests that due to the considerable role that CYP3A4 plays in the metabolism of a large number of xenobiotics, coupled with their variable CYP3A4 induction potency and duration, any number of these xenobiotics could have an impact on dasatinib plasma concentration. Therefore, non-compliance to study restrictions on intake of drug or OTC products could contribute to the "extreme" plasma profiles observed with dasatinib administration.

Appendix 8: Dasatinib absorption is pH dependent and is reduced when gastric acid secretion is suppressed.

Another potential cause of variable bioavailability could be a change in the absorption profile of dasatinib. Following oral administration, drugs typically must be dissolved in order to be absorbed from the gastrointestinal tract. Notably, the solubility of dasatinib is pH-dependent, with the highest solubility in gastric pH. Hence, if the drug does not dissolve promptly in the stomach or the proximal region of the small intestine, the absorption of the drug could be greatly reduced. Therefore, any alteration of the pH in the gastrointestinal tract could significantly change dasatinib exposure. Consistent with this notion, it is not surprising that dasatinib absorption is reportedly altered by gastric acid suppressants, resulting in reduced bioavailability. (Takahashi N et al, 2011) In fact, long-term suppression of gastric acid secretion by H₂ antagonists or proton pump inhibitors (e.g. famotidine and omeprazole, respectively) reduces dasatinib exposure by approximately 60% and approximately 40%, respectively (Sprycel® FDA Prescribing Information), while simultaneous administration of dasatinib with antacids, led to a 55% and 58% reduction in dasatinib AUC and C_{max}. (Eley T et al, 2009). For these reasons, use of H₂ antagonists and proton pump inhibitors are contraindicated as per the Sprycel® Prescribing Information and administration of over-the-counter antacids at least 2 hours prior to or 2 hours after dasatinib administration is recommended. (Sprycel® FDA Prescribing Information)

Appendix 9: Simulation and modeling of data from original study (DASA-IMTB-05SB03-2FA) and re-dosing study (DASA-IMTB-05SB03-2FA)

A simulation analysis was performed for Subject (b)(6) whose Test/Reference (T/R) ratios were consistently outside the range in the original (# DASA-IMTB-05SB01-2FA) and re-dosing study (# DASA-IMTB-05SB03-2FA) to ascertain the root cause of the low concentrations observed. To conduct the analysis, GastroPlus software tool (version 8, SimulationsPlus Inc) was employed to predict the PK profile for Dasatinib upon oral administration of a 100 mg dose formulated as an immediate release tablet. The following information was used as an input:

- Molecular formula: C₂₂H₂₆CIN₇O₂S
- Molecular weight: 488.01
- pKa (base) = 3.1; 6.8; 10.9

(b)(4)

- Particle size (b)(4)
(b)(4) (default GastroPlus parameter)

(b)(4)

(b)(4) (i.e. default GastroPlus parameter of (b)(4))

Results

(A) Simulation and Modeling Using Default Particle Size and Stomach Transit Time Values

(b) (6)

(b) (4)

(b) (4)

(b) (6)

(b) (4)

(b) (4)

(b) (6)

Figure 3: Observed (empty squares) PK profile of Dasatinib administered as Sprycel 100 mg tablets to healthy volunteers (mean, study # DASA-IMTB-05SB01-2FA) versus predicted (line) PK profile for the same drug not completely dissolved in gastric media.

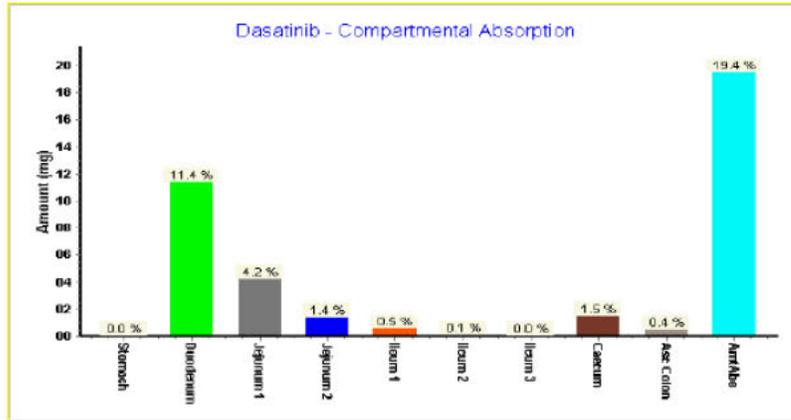


Figure 4: Gastro-intestinal compartmental absorption of Dasatinib administered to healthy volunteers with very fast stomach transit time under fasting conditions

Discussion

The results of modeling and simulation obtained using default values show that Dasatinib is almost completely absorbed upon oral administration. The results are in agreement with the observations from Apotex study # DASA-IMTB-05SB01-2FA and the literature information: i.e. Dasatinib is described by the innovator as well absorbed and is categorized as BCS II drug (low solubility/high permeability).

(b) (4)
(u) (4)

(b) (4)

In Subject (b) (6) identified as an outlier, the absorption was incomplete for both Reference and the Test product in the original study (DASA-IMTB-05SB01-2FA) and re-dosing study (DASA-

The reason for incomplete absorption is most likely failure of dosage form to disintegrate and/or dissolve due to reduced exposure to highly acidic stomach environment. Once the practically undesintegrated/undissolved tablet reaches the intestine, dissolution of dasatinib which is pH dependent becomes limited, resulting in a low bioavailability reflected in both Cmax and AUC parameters. By simulating a short exposure to an acidic stomach environment in conjunction with a large particle size (occurring in absence of complete tablet disintegration), we demonstrated that the low Cmax and AUC are due to undesintegrated/undissolved drug. For Subject (b) (6) this effect was observed in the original study for reference (R) and in the re-dosing study for test (T) product (in both cases the dosing was in Period 1).

Conclusion

For Subject (b) (6) the likelihood for undisintegrated/undissolved drug to reach the intestine was equal for both T and R product among the two studies (original and re-dosing). In both cases it was observed for the drug dosed in period 1. Therefore, the T/R ratios of PK parameters for Subject (b) (6) consistently falling outside the PK ratio range is unlikely to be product-related, and as such the subject should be excluded from the final statistical analysis.

Appendix 10: Extreme plasma profiles associated with Dasatinib drug administration are not uncommon

The occurrence of outliers in dasatinib pharmacokinetic measures is not limited to the data obtained in the original submitted Apotex study (DASA-IMTB-O5SBO1-2FA – (b) (6) (b) (6)). In fact, during a Phase I study included in the Sprycel® (Dasatinib) NDA submission (NDA 21-986 & 22-072), Study CA180020 also identified a subject outlier which was ultimately excluded from the statistical analysis. Subjects in that study received either 2 doses of the control dose (dasatinib 50 mg) separated by 12 hours starting with an evening dose (Treatment A) or dasatinib 50 mg dose in the presence of gastric pH modifiers (Treatments B and C). Out of the twenty-two (22) healthy subjects that were to be included in the pharmacokinetic and statistical analysis, one subject had no quantifiable concentrations of dasatinib following the evening dose of Treatment A and was therefore excluded from the evening dose statistical comparison. No further investigations or discussions were included in the available documents to determine the cause. (Dasatinib Clinical Pharmacology and Biopharmaceutics Review; Eley T et al, 2009) In the original study (DASA-IMTB-O5SBO1-2FA), three statistical outliers were identified out of forty-four (44) subjects completing the study, leading to a prevalence of approximately 6.8% in observing an outlier, while in Study CA180020, one subject outlier out of twenty-two (22) subjects led to the prevalence approximately 4.5% in observing an outlier. Taken together, the occurrence of outliers in addition to the prevalence of statistical outlier occurrences (4.5 – 6.8%) within these dasatinib studies is quite consistent, providing further evidence that extreme pharmacokinetic profiles are associated with this drug.

Given that dasatinib has pharmacokinetics with known high variability due to its low and pH-dependent solubility and its high potential for drug-drug interactions, this makes this drug particularly prone to observing statistical outliers especially when observations are made on a single occasion.

References:

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BIOEQUIVALENCE DEFICIENCY TO BE COMMUNICATED TO THE APPLICANT

ANDA: 202103

APPLICANT: Apotex Inc.

DRUG PRODUCT: Dasatinib Tablets, 20 mg, 50 mg, 70 mg and 100 mg

The Division of Bioequivalence I (DBI) has completed its review and identified the following deficiency:

Based on the data submitted in the original submission and amendment dated July 23, 2013, we conclude that subject- (b) (6) in the fasting bioequivalence study (DASA-IMTB-05SB01-2FA) did not have aberrant response. You explain that while the cause of the extreme differences between periods in Subject (b) (6) is not known, the observed differences in pharmacokinetic (PK) parameters between the Test and Reference products in the original study for this Subject are not a reflection of true differences between products. Therefore, it should be acceptable to exclude the data for this subject from the statistical analysis of the original fasting BE study.

You explain that:

- Dasatinib exposure is characterized by large inter- and intra-individual variability.
- Simulation performed on the original and re-dosing studies using GastroPlus Software revealed that for Subject (b) (6) the absorption was incomplete for both Reference and the Test products in the original study and re-dosing study, respectively. Given the intrinsic properties of the drug (low solubility and pH dependency), you attributed the reason for incomplete absorption to a failure of the dosage form to disintegrate and dissolve due to reduced exposure to highly acidic stomach environment.
- The average of each of the two Test and Reference Cmax and AUC values from the original and redosing fasting studies should be taken in determining the test/reference (T/R) ratio of Subject (b) (6) for the overall bioequivalence assessment.

DBI does not agree with your explanations for the following reasons:

- DBI understands that dasatinib exposure is characterized by large inter- and intra-individual variability; therefore, you should have powered the study adequately to address the data variability often observed for this drug product, or should have used reference replicate study design during the conduct of the BE studies.
- DBI understands that dasatinib is characterized as a low solubility/high permeability [Biopharmaceutics Classification System (BCS II)] drug substance; dasatinib solubility is pH dependent and dasatinib absorption can be impacted by acid levels within the gastrointestinal tract. You attributed the reason for incomplete absorption of the drug in Subject (b) (6) to a failure of the dosage

form to disintegrate and dissolve due to reduced exposure to highly acidic stomach environment. However, for the fasting study, DBI notes that you did not report any protocol deviations for Subject (b) (6). You mentioned that Subject - (b) (6) met the inclusion/exclusion criteria and complied with the study restrictions. You did not demonstrate evidence that Subject (b) (6) was on CYP3A4 enzyme inducing/inhibiting agents prior to enrollment into the fasting BE study. Also you did not demonstrate evidence if Subject (b) (6) has shorter gastric residence/transit time or gastrointestinal (GI) physiological/anatomical abnormalities which could have influenced dasatinib absorption. If indeed Subject - (b) (6) had any of the aforementioned issues, Subject (b) (6) should not have been included in the fasting BE study. DBI notes that, *clinically significant history or presence of any gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of the drug* is an exclusion criteria. Therefore, DBI does not agree with your explanation that drug-drug/drug-food interactions, non-compliance to study restrictions, gastric pH and other reasons could have played a role in the aberrant dasatinib plasma concentrations for Subject (b) (6).

- DBI does not agree with your explanation with regards to the outlier identified in clinical trials submitted by the Brand company of Sprycel® (Dasatinib) (NDA 21-986 & 22-072). Study # CA180020 (for the NDA # 21-986) is a ‘*Gastric acid pH modulators interaction*’ study and is not a bioequivalence study. Two studies with different objectives, conducted at different times and under different conditions cannot be compared.
- DBI does not agree with your explanation that an average of each of the two Test and Reference Cmax and AUC values from the original and redosing fasting studies should be taken in determining the T/R ratio of Subject (b) (6) for the overall bioequivalence assessment. DBI does not combine data from two different studies conducted at different times. Also, as per the CDER Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (January 2001) and the Divisions of Bioequivalence current practice, dropping of an “outlier” subject data from BE studies solely based on a statistical test is not acceptable.
- Based on the above mentioned information, DBI still considers the fasting study as **unacceptable**.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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}

Wayne DeHaven, Ph.D.
Acting Director,
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

9 OUTCOME PAGE

ANDA: 202103

Reviewer: Pabba, Santhosh

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description:

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
23033	7/23/2013	Other (REGULAR)	Study Amendment	1	1
				Total:	1

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

/s/

SANTHOSH K PABBA
08/11/2014

NILUFER M TAMPAL
08/11/2014

WAYNE I DEHAVEN
08/18/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202103		
Drug Product Name	Dasatinib Tablets		
Strength(s)	20 mg, 50 mg, 70 mg and 100 mg		
Applicant Name	Apotex Inc.		
Address	150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
Applicant's Point of Contact	Bernice Tao 150 Signet Drive, Toronto, Ontario, Canada, M9L 1T9		
Contact's Telephone Number	1- 416- 401-7889		
Contact's Fax Number	1- 416- 401-3809		
Original Submission Date(s)	06/27/2010		
Submission Date(s) of Amendment(s) Under Review	August 16, 2012 (Supporting document #13)		
Reviewer	Santhosh K. Pabba		
Study Number (s)	DASA-IMTB-05SB01-2FA (DD6366)	DASA-IMTB-05SB02-2FE (DD6367)	DASA-IMTB-05SB03-2FA
Study Type (s)	Fasting	Fed	Fasting (re-dosing)
Strength (s)	100 mg	100 mg	100 mg
Clinical Site	Anapharm	Anapharm	Anapharm
Clinical Site Address	2500, rue Einstein Quebec (Quebec), Canada, G1P 0A2	5160, boul. Decarie, Suite 800, Montreal (Quebec) Canada, H3X 2H9	2500, rue Einstein Québec (Québec), Canada G1P 0A2
Analytical Site	Apotex Inc.	Apotex Inc.	Apotex Inc.
Analytical Site Address	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario
OVERALL REVIEW RESULT	Inadequate		
OSI REVIEW RESULT	Adequate		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 13	Fasting study	100 mg	Unacceptable
1, 13	Fasting (redosing) study	100 mg	Adequate
1, 13	Fed study	100 mg	Inadequate
1, 7	Dissolution	20 mg, 50 mg, 70 mg and 100 mg	Adequate

REVIEW OF AN AMENDMENT

Reviewer Note: The (b) (4) and 202103 are (b) (4) from Apotex Inc. The current (b) (4)
The ANDA # 202103 addresses Dasatinib Tablets, 20 mg, 50 mg, 70 mg and 100 mg.

1 EXECUTIVE SUMMARY

On August 16, 2012, Apotex, submitted its responses to the deficiency letter issued from the Division of Bioequivalence I (DBI) on July 12, 2012¹ due to several clinical and analytical deficiencies. Based on the firm's responses, the fasting study is **unacceptable**, the fasting redosing study is **adequate**, and the fed study is **inadequate**.

Regarding the fasting study, the results of the re-dosing study # DASA-IMTB-05SB03-2FA confirm that Subject (b) (6) was an "extreme" subject whose test-to-reference (T/R) ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other subjects from the original and re-dosing studies, even though the T/R ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject (b) (6) were "aberrant" in the original fasting BE study (please refer to Section: 4.3 – Review of Submission for details). For this reason, the subject (b) (6) should not be excluded from the final statistical analysis of the original fasting BE study. With the inclusion of subject (b) (6) the fasting BE study does not meet bioequivalence criteria (please see the table below).

Geometric Means and 90% Confidence Intervals - Reviewer Calculated – with Original values for Code: I (reported in the current amendment) and repeat values for Codes F and B

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fasting Bioequivalence Study [Study No. DASA-IMTB-05SB01-2FA (DD6366), N=42 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	336.19	293.91	1.14	96.68	135.34
AUC _∞ (ng·hr/mL)	359.41	343.01	1.05	95.89	114.50
C _{max} (ng/mL)	105.14	88.27	1.19	98.23	144.45

¹ DARRTS, ANDA # 202103, SOLANA-SODEINDE, DIANA A
07/12/2012 FAX 07/12/2012 COR-ANDE-01(Bio Incomplete Deficiencies) Original-1 (Not Applicable) Archive

Note: The reviewer performed data analysis using the SAS code: CalcKe. N=42 (including subject (b) (6) for AUCt and Cmax, N=41 for AUCi (test) and N =40 for AUCi (reference) - for subject (b) (6) for both test and reference treatments and for subject (b) (6) (reference), Kel could not be calculated

As a result, the original fasting study is unacceptable.

Earlier, the firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method, (refer DARRTS – ANDA # 202103, SHRIVASTAVA, SURENDRA P 01/28/2011 N/A 01/28/2011 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive). On February 22, 2011, the firm has acknowledged the FDA-recommended dissolution method and specification.

Medium:	Acetate buffer at pH 4.0 with 1% Triton X-100 at 37 ⁰ C
Volume:	1000 mL
USP Apparatus:	II (Paddle) at 60 rpm
Specification:	NLT (b) (4) % (Q) in (b) (4) minutes

The DB does not grant the waiver requests for in vivo BE study requirements at this time due to the unacceptable fasting BE study.

No Office of Scientific Investigations (OSI) inspection is pending or necessary at this time.

The application is **inadequate** with deficiencies.

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3 BACKGROUND

1. On June 27, 2010, Apotex, submitted the original application for Dasatinib Tablets, 100 mg.

This application contained the results of (fasting and fed) bioequivalence (BE) studies comparing a test product, Dasatinib Tablets, 100 mg to the corresponding reference product, Sprycel® (dasatinib) Tablets, 100 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The results are summarized in the tables below.

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fasting Bioequivalence Study [Study No. DASA-IMTB-05SB01-2FA (DD6366), N=44 (Male=37 and Female=7)]					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	332.25	317.11	1.05	95.79	114.60
AUC _∞ (ng·hr/mL)	355.27	339.82	1.05	95.66	114.26
C _{max} (ng/mL)	104.59	96.71	1.08	97.26	120.24

Note: The reviewer performed data analysis using the SAS code: Calcke.

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fed Bioequivalence Study, Study No. DASA-IMTB-05SB02-2FE (DD6367), N=52 (Male=47 and Female=5)]					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	405.94	379.43	1.07	99.32	115.25
AUC _∞ (ng·hr/mL)	423.02	395.67	1.07	100.04	114.26
C _{max} (ng/mL)	88.99	81.41	1.09	98.88	120.82

Note: The reviewer performed data analysis using the SAS code: Calcke.

The firm’s fasting and fed BE studies were incomplete due to bioanalytical deficiencies. For the fasting study: (DASA-IMTB-05SB01-2FA (DD6366)), the firm identified subjects – (b) (6) as being suspected of having “aberrant” plasma concentrations. The firm classified (b) (6) as outliers after performing outlier detection through Lund’s test. The reviewer could not confirm subjects (b) (6)

(b) (6) as outliers because the firm did not submit the concentration vs. time data for the identified subjects (b) (6). The firm did not mention about redosing study in the study protocol a priori. However, the firm conducted the redosing study with the above mentioned 3 subjects and included five additional control subjects. The acceptability of the decision to redose and the acceptability of dropping the subjects in question from the statistical analysis of the original fasting biostudy was pending the submission of the data requested above.

Earlier, the firm conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method, (refer DARRTS – ANDA # 202103, SHRIVASTAVA, SURENDRA P 01/28/2011 N/A 01/28/2011 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive). On February 22, 2011, the firm acknowledged the FDA-recommended dissolution method and specification.

Medium:	Acetate buffer at pH 4.0 with 1% Triton X-100 at 37 ⁰ C
Volume:	1000 mL
USP Apparatus:	II (Paddle) at 60 rpm
Specification:	NLT (b) (4) % (Q) in (b) (4) minutes

The DB did not grant the waiver requests for in vivo BE study requirements pending additional information.

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

The application was found **inadequate** as stated in the DBI review of this application dated 6/27/2012.

2. On August 16, 2012, the firm submitted the current amendment to the deficiency letter issued from the Division of Bioequivalence I (DBI) on July 12, 2012.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

DARRTS, ANDA: 202103 - PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive.

Note: There is no change in the labeling² and the individual product BE recommendations for the current drug product³ from the time of the original review dated 6/27/2012.

² http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021986s7s8lbl.pdf

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM224205.pdf>

4.2 Contents of Submission

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

4.3 Review of Submission – Amendment dated – August 16, 2012

Deficiency 1:

For the fasting study (DASA-IMTB-05SB01-2FA (DD6366)), you identified the subjects (b) (6) as being suspected of having “aberrant” plasma concentrations. You classified these subjects (b) (6) as outliers after performing the Lund’s statistical outlier test. In order for the DBI to verify these subjects (b) (6) as statistical outliers, please submit the individual concentration vs. time data and individual pharmacokinetic data for the identified subjects (b) (6) in SAS Transport format.

Firm’s Response:

As requested please find attached data in SAS format. The following files are provided as attachments:

- [APODD6366_1_outlier.dat.xpt](#)
- [APODD6366_1_outlier.pkv.xpt](#)
- [APODD6366_1_outlier.inf.pdf](#)

Reviewer’s Comments: The firm’s response to deficiency # 1 is **incomplete**.

- The subjects classified by the firm as having aberrant PK results - Subjects (b) (6) exhibited very low dasatinib concentrations-time profiles for the test, test and reference drug products, respectively, when compared to other subjects. Consequently, the firm performed statistical analysis after excluding subjects – (b) (6)

- The firm suspected Subject (b) (6) as a subject with “aberrant PK values” because of the high T/R ratio of the PK parameters (AUCt: T/R-36.7, Cmax: T/R-61.4) of this subject. The firm suspected Subjects (b) (6) as subjects with “aberrant PK values” because of the very low T/R ratio of the PK parameters (AUCt: T/R-0.02, Cmax: T/R-0.01) for the subject (b) (6) and very low T/R ratio of the PK parameters (AUCt: T/R-0.13, AUCi: T/R-0.16, Cmax: T/R-0.08) for the subject – (b) (6). The firm performed Lund’s test and classified the subjects (b) (6) as statistical outliers. Therefore, the firm performed redosing study for subjects (b) (6)
- In the first full review of this application, the reviewer could not confirm the firm’s findings as the firm did not submit the individual concentration vs. time data and pharmacokinetic parameters for subjects (b) (6) in SAS transport format. The firm has provided the requested information in the current amendment.
- In the reviewer’s evaluation of the firm’s decision to remove Subjects (b) (6) from the statistical analysis, the reviewer calculated all three PK parameters (based on original sample values, where appropriate) for the original and redosing studies and then used the obtained values to run the Lund’s test and to compare T to R ratios.
- It is DBI’s current practice that removal of a subject from the statistical analysis is acceptable when a) the subject qualifies as “having aberrant PK results” (and therefore can be excluded from the statistical analysis of the original study) on the basis of an “a priori” statistical test, and b) the subject’s T/R ratios in the redosing study fall within the range of T/R ratios of subjects in the original study (i.e., all subjects in the original study except the suspected aberrant subject) **and** c) the T/R ratios of the control subjects in the redosing study fall within the range of T/R ratios of subjects in the original study (i.e., all subjects in the original study except the suspected aberrant subject). In regard to these criteria, the reviewer notes the following:
 - a) The firm did not mention about redosing study in the study protocol *a priori*. However, the firm conducted redosing study with the above mentioned 3 subjects and included five additional control subjects. The reviewer confirmed subjects (b) (6) as outliers after performing Lund’s test with the reviewer calculated PK parameters (using SAS code: Calcke). The critical value for studentized residuals of 3.109 and 3.460 was applied to test for outliers, based on a sample size of n=44, at a significance level of $\alpha=0.05$ and $\alpha=0.01$, respectively⁴. Based on these critical values, subjects (b) (6) were identified to be statistical outliers. Specifically, Subjects (b) (6) were

⁴ Rotondi M and Koval J. (2007). Extension of Lund’s Tables for an approximate test for outliers in linear models

above the critical values with respect to AUCt and Cmax, while Subject (b) (6) was above the critical values for AUCi. No other subjects were identified as outliers. Please see Appendix section: 8.2 for the detailed results of Lund's test.

- b) The T/R ratios (Cmax and AUCt) of Subject (b) (6) in the redosing study falls within the range of T/R ratios (Cmax and AUCt) of subjects in the original study (i.e., all subjects in the original study except the suspected aberrant subjects) – please see the table below. The T/R ratio (AUCi) of Subject (b) (6) in the redosing study falls within the range of T/R ratios (AUCi) of subjects in the original study (i.e., all subjects in the original study except the suspected aberrant subjects) – please see the table below (please note that AUCi could not be calculated for subject # (b) (6) in the original study). The T/R ratios of subject – (b) (6) (Cmax and AUCt) in the redosing study does **not** fall within the range of T/R ratios of subjects in the original study-please see table below.
- c) The T/R ratios (Cmax, AUCt and AUCi) of the control subjects (b) (6) in the redosing study fall within the range of T/R ratios (Cmax, AUCt and AUCi) of subjects in the original study (i.e., all subjects in the original study except the suspected aberrant subject) – please see the table below.

Test-to-Reference Ratios for Cmax and AUCt in the Original and Redosing Studies.

Study No	Subject No		Cmax			AUCt		
	Original	Redosing	Test	Ref	T/R Ratio	Test	Ref	T/R Ratio
(Redosing Study# DASA-IMTB-05SB03-2FA)	(b) (6)		5.09	134.37	0.04	19.256	451.78	0.04
		79	102.78	0.77	290.91	303.37	0.96	
		156.43	79.11	1.98	448.5	265.59	1.69	
		169.76	166.91	1.02	504.46	545.46	0.92	
		79.2	68.6	1.15	323.6	322.9	1.00	
		80.18	66.43	1.21	254.23	224.13	1.13	
		153.62	114.08	1.35	511.29	380.65	1.34	
		83.03	51.95	1.60	233.99	218.75	1.07	
(Original fasting study # DASA-IMTB-05SB01-2FA)	(b) (6)		147.38	2.4	61.41	476.97	12.999	36.69
		100.89	91.3	1.11	350.34	259.98	1.35	
		66.16	166.63	0.40	195.03	382.02	0.51	
		118.82	157.17	0.76	294.18	521.55	0.56	
		69.53	63.17	1.10	292.71	248.48	1.18	
		1.85	122.24	0.02	11.838	504.78	0.02	
		8.94	105.44	0.08	34.261	256.33	0.13	
		106.1	65.63	1.62	372.5	270.76	1.38	
				Redosing Study (T/R) (n=5, all subjects except (b) (6))			Redosing Study (T/R) (n=5, all subjects except (b) (6))	
				Cmax			AUCt	
			Min	0.77		Min	0.96	
			Max	1.98		Max	1.69	

					Original Study (T/R)			Original Study (T/R)
					Cmax (n=41)			AUCt (n=41)
				Min	0.40		Min	0.44
				Max	2.55		Max	1.96

Study No	Subject No		AUCi		T/R Ratio
	Original	Redosing (b) (6)	Test	Ref	
(Redosing Study# DASA-IMTB-05SB03-2FA)				460.4	Not calculable
			304.76	313.81	0.97
			458.02	273.11	1.68
			518.75	558.2	0.93
			332.86	332.25	1.00
			262.39	232.14	1.13
			521.68	388.87	1.34
			239.95	225.39	1.06
(Original fasting study # DASA-IMTB-05SB01-2FA)			489.72		Not calculable
			357.16	266.29	1.34
			202.66	391.85	0.52
			311.9	538.8	0.58
			298.94	254.68	1.17
				518.12	Not calculable
			42.608	263.13	0.16
			377.45	282.27	1.34
				Redosing Study (T/R) (n=5, all subjects except (b) (6))	
				AUCi	
			Min	0.93	
			Max	1.68	
				Original Study (T/R)	
				Cmax (n=41)	
			Min	0.44	
			Max	1.94	

Note: Subject – (b) (6) is highlighted green and subjects – (b) (6) are highlighted yellow in the above table.

Reviewer Comments:

- Based on the above, only Subject (b) (6) from the redosing study can be considered as aberrant, while Subject (b) (6) cannot. Based on this conclusion, the reviewer has rerun the statistical analysis excluding Subject (b) (6) but including Subject (b) (6) in the final dataset. The results are as follows. The results indicate that the fasting study is **unacceptable**.

Geometric Means and 90% Confidence Intervals - Reviewer Calculated – with Original values for Code: I (reported in the current amendment) and repeat values for Codes F and B

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fasting Bioequivalence Study [Study No. DASA-IMTB-05SB01-2FA (DD6366), N=42 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	336.19	293.91	1.14	96.68	135.34
AUC _∞ (ng·hr/mL)	359.41	343.01	1.05	95.89	114.50
C _{max} (ng/mL)	105.14	88.27	1.19	98.23	144.45

Note: The reviewer performed data analysis using the SAS code: Calcke. N=42 (including subject ^(b)₍₆₎) for AUC_t and C_{max}, N=41 for AUC_i (test) and N =40 for AUC_i (reference) - for subject # ^(b)₍₆₎ for both test and reference treatments and for subject ^(b)₍₆₎ (reference), Kel could not be calculated because of erratic concentration vs. time profile (rather than the concentration decreasing, the concentration was increasing) in the elimination portion – please refer to DARRTS, ANDA # 202103, PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive for details). The reviewer to sponsor ratios of the PK parameter C_{max} is 1 is for all the subjects and the PK parameter AUC_t, the reviewer to sponsor ratios are close to unity. The slight differences are because the reviewer used nominal time points and firm used actual blood sampling times. The reviewer to sponsor ratios for the PK parameter AUC_i are not close to unity for some subjects because of the SAS code: Calcke used by the reviewer, sampling time point deviations and different time points used for the calculation of Kel and subsequently AUC_i by the reviewer.

- Please note for the fasting study, the reviewer used original values for the study samples identified as Code: I for the statistical analysis. The reviewer confirmed that these were the original values based on the raw data submitted in the current amendment (please also refer to the reviewer comments for the deficiency comment # 2). In addition, the decision to repeat the fasting BE study samples for the codes F and B (shown below) was justified based on the pre-established SOP (please refer to the original review - DARRTS, ANDA # 202103, PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive for details). Furthermore, the reported values were selected consistent with the pre-established and effective SOP: [ABM-BL-0154](#) for the (codes F and B).

Study No. : DASA-IMTB-05SB01-2FA								
Additional information in Volume(s), Page(s): Table 16.5.1.8.6								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
F : Outside Range	5	0	0.27	0.0	5	0	0.27	0.0
B: Analysis Incomplete-system error	1	0	0.05	0.0	1	0	0.05	0.0
I : Not Updated	2	1	0.11	0.05	2	1	0.11	0.05
Total	8	1	0.43	0.05	8	1	0.43	0.05

- For subject (b) (6) in the original study (b) (6) in this study), the AUCt and Cmax T/R ratios were 36.69 and 61.41 (please see the reviewer calculated table above), respectively, and thus considerably higher than the ratios obtained for other subjects in the remaining dataset. Upon re-dosing, both AUCt and Cmax T/R ratios were 0.04, and thus considerably lower than the ratios obtained for other subjects in the remaining dataset of the original and re-dosing studies. Based on these results, the firm argues that Subject (b) (6) should be excluded from the statistical analysis of the original study. Specifically, the firm states that: *“Since the abnormally low dasatinib concentrations were not product-specific, they do not provide added value in the assessment of bioequivalence between the two drug products. Furthermore, the fact that in both studies “normal” concentrations were observed for both test and reference in one of the study periods indicates that there is no anomalous absorption of dasatinib as a drug substance in this subject, therefore indicating that this subject is not a representative of a sub-population that experiences an extremely low bioavailability of dasatinib. Therefore, this lack of consistency supports the exclusion of subject (b) (6)’s data from the statistical analysis in the original bioequivalence study.”*
- The reviewer does not consider the firm’s explanation valid. The results of the re-dosing study # DASA-IMTB-05SB03-2FA confirm that Subject (b) (6) was an “extreme” subject whose test-to-reference ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other subjects from the original and re-dosing studies, even though the test-to-reference ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject (b) (6) were “aberrant” in the original fasting BE study. For this reason, the subject should not be excluded from the final statistical analysis of the original

fasting BE study⁵. This explanation as to why Subject (b) (6) cannot be excluded will be conveyed to the firm.

- The fasting study is **unacceptable**.

Deficiency 2:

For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), you repeated two samples under “Code D - Suspected Results” and for the fasting BE study [Study No. DASA-IMTB-05SB01-2FA (DD6366)], you repeated three samples under “Code I - Not Updated”. Per your SOP: ABM-BL-0158 – Analytical run analysis and documentation procedures, effective date: 03/24/10, the criteria for Code D and I were stated respectively as follows: “Code D: Suspected Results – Identified subject samples with valid results that are suspected. (SOP ABM-BL-0160)”, and “Code I: Not Updated – Identifies data that is not to be included in summary tables. This is used to ignore any injection that is made in the place of a subject time-point not provided by the clinic, samples analyzed for confirmation purposes only, investigational analysis (as directed by management), and any subject time point result that cannot be accepted due to test failure (e.g. dilution integrity). Code-I can also be used for gross transposition (analytical) errors, where a sample ID cannot be verified to the data (approval for this use of Code I is required). This applicable to any standard or sample analyzed, when intention of the injection was not to use the results”. These criteria are not considered objective. Therefore, the reassay values for these samples are not accepted by the DBI. Please provide the raw numerical and chromatographic data, as well as corresponding calculated original assay values of these samples for further evaluation. The samples for the Fed BE study are:

<i>Subject</i>	<i>Period</i>	<i>Time</i>	<i>Reason for Reassay</i>
(b) (6)	2	0.33 hrs	Code D – Suspected Results
	2	1 hr	Code D – Suspected Results

The samples for the Fasting BE study are:

<i>Subject</i>	<i>Period</i>	<i>Time</i>	<i>Reason for Reassay</i>
(b) (6)	2	1 hr	Code I – Not Updated
	2	1.25 hr	Code I – Not Updated
	2	2 hrs	Code I – Not Updated

⁵ The preceding language in the bullet point was obtained from the review - DARRTS, ANDA # 091608, DEHAVEN, WAYNE I 03/24/2011 N/A 03/24/2011 REV-BIOEQ-01(General Review) Original-1 Archive

Firm's Response:

In assay 07DD6367, subject (b) (6), 1 hr, period 2 sample was identified as out of trend since the concentration was very low relative to adjacent samples. An investigation was initiated as per SOP ABM-BL-0160 rev 1 Event Resolution and it was hypothesized that a sample transposition could have been made between the (b) (6), 1 hr, period 2 sample and the (b) (6), 0.33 hr, period 2 sample during sample analysis. This hypothesis could not be conclusively proven without additional testing as part of the investigation. Therefore, both samples were coded (b) (6) as suspected samples since transposition was suspected. These samples were repeated in duplicate in assay 28DD6367 to confirm the suspected transposition. The duplicate repeat results confirmed the original assay values indicating that no transposition had occurred during sample analysis. The final concentration selection was made using the original value and the two repeat values as dictated by SOP ABM-BL-0154 Rev 6 Routine Batch Sample Analysis (attached). The reported concentration was presented in Table 16.5.1.8.6.2 Summary of Assay Repeats in the Study report. The concentration data is also tabulated below:

(b) (6) time-point and period	Original result (ng/mL)	Repeat result(s) (ng/mL)	Reported Value ng/mL
1h P2	15.41	15.45, 15.41	15.41 (median value selected)
0.3333h P2	127.13	122.26, 120.48	122.26 (median value selected)

Please see the attached file "07DD6367" for absolute responses and concentration data for the original assay (07DD6367 = Watson run 7) and individual chromatograms for (b) (6) 1 h, p2 and (b) (6) 0.3333h, p2.

Please see attached file "28DD6367" for absolute responses and concentration data for the repeat assay (28DD6367 = Watson run 27) and individual chromatograms for (b) (6) ,1 h, p2 and (b) (6) 0.3333h, p2.

In the fasting study DD6366, the clinic provided information on May 10, 2010 concerning a protocol deviation indicating that samples (b) (6), 1.0 hr, period 2, (b) (6), 1.25 hr period 2 and (b) (6) 2.00hr, period 2 all contained clots during processing. The clinic indicated that the sample matrix could not be confirmed as either plasma or serum. This deviation was reported in Section 10.2 of the clinic report. The sample analysis had already commenced prior to the receipt of the deviation information from the clinic. (b) (6) samples were analyzed on May 6, 2010 and (b) (6) sample was analyzed on May 10, 2010. Since the sample matrix could not be confirmed due to the processing error, and the impact to sample concentrations could not be determined, it was concluded that the samples should not have been analyzed. Since the concentration data was already generated, these samples had to be coded so the data would not be transferred to Pharmacokinetics for Bioequivalence assessment. The most appropriate code determined at the time was I: Not updated. Since the definition of this code is

“Identifies data that is not to be included in summary tables.” This code was relevant in this case although the examples given in the SOP did not cover this exact scenario, this code was used and documented. In addition, the analytical method, DD- AM rev 1, was validated for Dasatinib in plasma only and the validation could not support the stability and extraction of samples from serum, further justifying the removal of these concentrations from the reported data. Please refer to the attached memo “DD6366 memo”.

The concentration for the three samples coded “I” were considered invalid and the original data was not reported. The samples were not repeated. See below for the original concentrations obtained for these samples:

<i>Subject</i>	<i>Period</i>	<i>Time</i>	<i>Original concentration</i>	<i>Assay ID</i>
(b) (6)	2	1 hr	135.97 ng/mL	05DD6366 Run 2
(b) (6)	2	1.25 hr	112.76 ng/mL	07DD6366 Run 4
(b) (6)	2	2 hr	101.61 ng/mL	15DD6366 Run 12

Please see attached files 05DD6366, 07DD6366 and 15DD6366 for absolute responses and concentration data for each assay in which the above samples were assayed in addition to the individual chromatograms of the samples.

Reviewer Comments:

The firm has submitted the explanation; the reviewer still considers the following repeats for the codes D and I as deemed PK repeats. Therefore, the reviewer has performed the statistical analysis with the original values for the said PK repeats.

The samples for the Fasting BE study are:

<i>Subject</i>	<i>Period</i>	<i>Time</i>	<i>Original concentration</i>	<i>Reason for Reassay</i>
(b) (6)	2	1 hr	135.97 ng/mL	Code I – Not Updated
(b) (6)	2	1.25 hr	112.76 ng/mL	Code I – Not Updated
(b) (6)	2	2 hrs	101.61 ng/mL	Code I – Not Updated

- For the fasting study: The reviewer used original values for the study samples identified as Code: I for the statistical analysis. The reviewer confirmed that these were the original values based on the raw data submitted in the current amendment. The reviewer verified the analytical report and found no repeat study samples for the subjects – (b) (6). In addition, the decision to repeat the samples (codes F and B) was justified based on the pre-established SOP (please

refer to the original review - DARRTS, ANDA # 202103, PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive for details). Furthermore, the reported values were selected consistent with the pre-established and effective SOP: [ABM-BL-0154](#) for the (codes F and B).

- Please refer to the reviewer comments of deficiency comment # 1 for the 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC0-inf and LnCmax.

The samples for the Fed BE study are:

Subject	Period	Time	Original result (ng/mL)	Reason for Reassay
(b) (6)	2	0.33 hrs	15.41	Code D – Suspected Results
(b) (6)	2	1 hr	127.13	Code D – Suspected Results

- For the fed study: The reviewer used original values (Code: D) for the statistical analysis. The reviewer confirmed that these were the original values based on the raw data submitted in the current amendment. In addition, the decision to repeat the samples (codes F and H) was justified based on the pre-established SOP (please refer to the original review - DARRTS, ANDA # 202103, PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive for details). Furthermore, the reported values were selected consistent with the pre-established and effective SOP: [ABM-BL-0154](#) for the (codes F and H).
- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC0-inf and LnCmax, with the original values for the said subjects are still within the acceptable BE limits of 80.00-125.00% for BE.

Geometric Means and 90% Confidence Intervals - Firm Calculated

DASATINIB TABLETS				
Dose (1 x 100 mg)				
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. DASA-IMTB-05SB02-2FE (DD6367)				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	406.12	379.53	107.0	99.4 – 115.2
AUC∞ (hr *ng/ml)	424.86	410.78	103.4	98.9 – 108.2
Cmax (ng/ml)	88.99	81.41	109.3	98.9 – 120.8

Note: N=52 for AUCt and Cmax. N=52 (AUCi –test) and N=51 (AUCi-reference)

Geometric Means and 90% Confidence Intervals - Reviewer Calculated – with Original values for Code: D (reported in the current amendment) and repeat values for Codes F and H

DASATINIB TABLETS					
Dose (1 x 100 mg)					
Fed Bioequivalence Study, Study No. DASA-IMTB-05SB02-2FE (DD6367)					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng·hr/mL)	405.96	379.43	1.07	99.32	115.25
AUC _∞ (ng·hr/mL)	423.04	395.67	1.07	100.04	114.26
Cmax (ng/mL)	88.99	81.41	1.09	98.88	120.82

Note: The reviewer performed data analysis using the SAS code: Continu2. N=52 for AUCt and Cmax. N=52 (AUCi –test) and N=51 (AUCi-reference). The Kel could not be calculated for subject ^{(b) (6)} (reference treatment) because of erratic terminal conc. vs. time profile (the reviewer agrees with the firm). The reviewer to sponsor ratios of the PK parameter Cmax is 1 for all the subjects and the PK parameters AUCt and AUCi, the reviewer to sponsor ratios are close to unity. The slight differences are because the reviewer used nominal time points and firm used actual blood sampling times. The Ke estimated by the reviewer included use of original values where appropriate.

Deficiency 3:

For the fasting BE study [Study No. DASA-IMTB-05SB01-2FA (DD6366)], you did not submit raw data and complete details about the 2 rejected runs – Run Nos. 9 and 15. Please submit the complete raw data and reasons for rejection of Run Nos. 9 and 15. In addition, please submit the pre-established SOP governing run acceptance/rejection.

Firm’s Response:

As requested we are herby providing raw data for incomplete runs (Watson run #9 - 12DD6366 and Watson run#15 - 18DD6366) which are attached with this response as file DD6366 run 9 and 15 raw data

For run 9 (12DD6366) the run stopped, at injection #36 due to an auto-sampler error “low sample pressure error”. The system was reset and checked with no apparent issues and the run was re-started as per ABM-BL-0158 Rev 9 Analytical Run Analysis and Documentation Procedures appendix B, scenario 2, The run stopped again, at injection #41 and then again at injection #43. Service was called and maintenance performed, (refer to attached service report). The run was deemed incomplete as defined in ABM-BL-0155 Rev 2 Assay Failure Investigation as insufficient QCs (3/9) were analyzed to meet the run acceptance criteria as defined in ABM-BL-0154 Rev 6. Routine Batch Sample Analysis. This entire run was re-injected as run 25DD6366 as per ABM-BL-0158 Rev 9 Analytical Run Analysis and Documentation Procedures appendix B, scenario 3.

For run 15 (18DD6366) the run paused during the night (off-shift) due to a computer communication error. As there was insufficient mobile phase to complete the run, it was aborted as per ABM-BL-0158 Rev 9 Analytical Run Analysis and Documentation Procedures appendix B, scenario 3. This run was also considered incomplete as defined in ABM-BL-0155 rev 2 Assay Failure Investigation as insufficient QCs (0/9) were analyzed to meet the run Acceptance criteria. This entire run was re-injected as run 29DD6366 as per ABM-BL-0158 Rev 9 Analytical Run Analysis and Documentation Procedures appendix B, scenario 3.

Please also refer to SOP ABM-BL-0154 rev 6 Routine Batch Sample Analysis for the acceptance criteria for each assay.

Reviewer Comments:

- The firm has submitted raw data and complete details about the two rejected runs ID # 9 and 15 for the fasting BE study [Study No. DASA-IMTB-05SB01-2FA (DD6366)].
- The raw data convinced the reviewer that the run ID # 9 was rejected because of auto-sampler error “low sample pressure error”. The firm has submitted supporting documentation with the service report.
- The raw data convinced the reviewer that the run ID # 15 was stopped due to a computer communication error.
- For both the rejected runs – Run Nos. 9 and 15, the reasons for stopping the run and steps to be taken after stopping the run are pre-established in the SOP: ABM-BL-0158 rev 9 - Analytical Run Analysis and Documentation Procedures with an effective date of effective date: March 24, 2010. The mentioned SOP is effective at the time of fasting BE study sample analysis from May 6, 2010 to May 17, 2010. The rejected run ID # 15 was investigated as per the pre-established SOP: ABM-BL-0155 rev 2 Assay Failure Investigation and system performance.
- The pre-established SOP allows the firm to reinject samples for the issues that the firm has described. The firm has established a processed stability duration of 24 hours @ room temperature and 58 days @ refrigerated conditions (4°C) during the pre-study validation.
- The reinjection of the runs was performed within the said established processed stability duration and the reinjected runs were accepted as per the SOP: ABM-BL-0154 (Routine Batch Sample Analysis). In addition, for all the accepted (including the reinjected) runs the acceptance of the runs was based on the said pre-established SOP. As per the fasting BE study analytical report there are no other reinjections.
- The firm’s response is acceptable.

Deficiency 4:

For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), you did not submit raw data and complete details about the rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats) and incomplete assay run ID # 13 (Run description 13DD6367- (b) (6) - Incomplete Assay). Please submit the complete raw data and reasons for rejection of the run and incomplete assay. In addition, please submit the pre-established SOP governing run acceptance/rejection.

Firm's Response:

As requested we are providing raw data for incomplete run (Watson run #13 - 13DD6367) and failed assay (Watson run#20 - 21DD6367) which are attached as file [DD6367 run13 and 20 raw data](#)

For Watson run 13 – 13DD6367 the run stopped due to a computer communication error. As per ABM-BL-0158 rev 9 Analytical Run Analysis and Documentation Procedures appendix B, scenario 2 a new pre-assay calibration check was performed and combined with the original pre-assay data. This combined pre-assay failed specifications. Therefore as per the same procedural reference the run was deemed incomplete as per ABM-BL-0155 rev 2 Assay Failure Investigation and the complete batch of samples in the set were re-injected as run 23DD6367.

For Watson run 20 – 21DD6367 two QC A samples were outside of specifications and therefore as per ABM-BL-0154 rev 6 Routine Batch Sample Analysis section 5 B the assay failed. The assay was investigated as per ABM-BL-0155 rev 2 Assay Failure Investigation and system performance was deemed the cause of the failure. The Mass spectrometer sample cone was cleaned and the assay was reinjected as run 28DD6367.

See attached [ABM-BL-0154 rev 6 Routine Batch Sample Analysis](#) for assay acceptance criteria.

Reviewer Comments:

- The firm has submitted raw data about the rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats) and incomplete assay run ID # 13 (Run description 13DD6367 (b) (6) - Incomplete Assay). However, the firm did not submit the assay failure investigation report for rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats) and incomplete assay run ID # 13 (Run description 13DD6367- (b) (6) - Incomplete Assay). The firm will be requested to submit assay failure investigation reports for the said runs. Upon submission of additional documentation mentioned above, the reviewer will evaluate if the rejection of the said rejected runs was as per the pre-established SOPs. Please note that based on the submitted data, the

reviewer agrees that all the other acceptable runs were accepted as per the pre-established SOPs.

- The firm's response is incomplete.

Deficiency 5:

For fasting re-dosing BE study # DASA-IMTB-05SB03-2FA, please provide the pre-established SOP governing run acceptance/rejection.

Firm's Response:

For the fasting re-dosing BE study # DASA-IMTB-055B03-2FA, run acceptance criteria were defined in SOP ABM-BL-0154 rev 7 Routine Batch Sample Analysis. The procedure for restarting stopped assays was defined in SOP ABM-BL-0158 rev 9 Analytical Run Analysis and Documentation Procedures and the assay failure investigation process was defined in SOP ABM-BL-0155 rev 3 Assay Failure Investigation. All the SOPs are provided with this response.

There were no failed, incomplete assays or analytical repeats in the DASA-IMTB-05SB03-2FA (DD6577) study.

Reviewer Comments:

- The firm submitted the relevant pre-established standard operating procedure (SOP: ABM-BL-0154 rev 7 - Routine Batch Sample Analysis, effective date: August 25, 2010) with run acceptance/rejection criteria. The fasting (re-dosing) study sample analysis was performed from October 12-14, 2010. The content of the SOPs are acceptable. The SOP is effective at the time of sample analysis.
- The firm accepted runs based on the pre-established SOP's that they have submitted. As per the analytical report there are no other reinjections.
- The firm's response is acceptable.

Deficiency 6:

Concerning the fed BE study (Study No. DASA-IMTB-05SB02-2FE): For Subject Nos. (b) (6) with the test treatment and Subject (b) (6) with the reference treatment, you mentioned that the 2.00-hour post-dose blood samples were centrifuged as much as 72 minutes after blood collection in Period 1. However, you did not submit additional validation data to support the sample stability. Please provide these data.

Firm's Response:

Additional validation work was conducted, (whole blood stability for 2 hours on ice) to support the deviation noted. This additional data was not added to the validation report as at that time whole blood stability was not included as a validation activity.

Low and high QC levels were spiked into whole blood and the test samples were kept on ice for 2 hours. After 2 hours, reference low and high QCs were spiked into whole blood and both test and reference samples were spun down to obtain plasma and the samples were extracted along with a standard curve and QCs. Please see table in attached file ‘Blood Stability’ representing the results.

Reviewer Comments:

- As requested the firm submitted additional stability data for 2 hours on ice with low and high QC’s. The blood stability data as submitted by the firm is presented below and also in the Section 9: Attachments.
- As per the information below, there is no mention of the nominal concentration values for LQC and HQC. As per the DB summary table for pre-study method validation, the nominal concentration values for LQC and HQC are 3 ng/mL and 150 ng/mL. However, the firm did not provide the nominal concentrations of the quality control (QC) samples used in this validation study. The firm will be requested to provide these nominal concentrations. If the measured values of the QC samples are greater than 15% from nominal, then the firm will be requested to repeat the validation study.

(b) (4)

The firm’s response is incomplete.

Deficiency 7:

You did not submit the Certificate of Analysis (COA) for the reference bio-lot # 9L6029B. Please submit the COA along with the potency testing dates for the reference bio-lot # 9L6029B.

Firm's Response:

As requested [Certificate of Analysis](#) for the reference biolot # 9L6029B mentioning the potency testing date is being provided under section 5.3.1.3. In vitro-In vivo Correlation Study Reports. The date of potency testing for the reference biolot is 03/29/2010.

Reviewer Comments:

The firm submitted the COA along with the content uniformity and potency testing dates for the reference bio-lot # 9L6029B in the Module – 5.3.1.3 (File name: In vitro-In vivo Correlation Study Reports). The content uniformity is 98.2% (%CV – 2.6) and the potency is 97.8%. The date of potency testing for the reference biolot is 03/29/2010. As per the Certificate of Analysis (COA), the date of manufacture is March 11, 2010.

Please note for the test product biolot # FD150-31, the content uniformity (Mean: 99.8%, %CV: 1.1) and potency tests (Results: 100.1%) are conducted in April 2010 and the dissolution studies are performed in May 2010. The fasting and fed biostudies are conducted from April 24, 2010 to May 16, 2010. Please note that the fasting re-dosing study was conducted with the dosing dates - Period 1: 09/18/2010 and Period 2: 09/25/2010.

The firm's response is acceptable.

Deficiency 8:

In the DB summary table for Product Information, you have mentioned the Production Batch Size as 'Pilot'. Please clarify the production batch size by providing the exact number of tablets manufactured for this particular batch, as well as the batch size that you intend to manufacture for commercial batches.

Firm's Response:

We acknowledge your comments. We would like to clarify that the in the summary table 11 Product Information, the Batch Size for the biolot is already specified as (b) (4) tablets. The Table 11 has been further revised to include the commercial production batch size. The revised Table 11 as well as All Tables in one file are provided in this response.

Reviewer Comments:

The revised DB summary table for product information is shown below. The firm clarified the commercial production batch size. The firm's response is acceptable.

Table 11 Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Dasatinib Tablets	SPRYCEL [®] Tablets
Manufacturer	Apotex Inc.	Bristol Myers Squibb
Batch/Lot No.	FD150-31	9L6029B
Manufacture Date	March 2010	NA
Expiration Date	(b) (4)	(b) (4)
Strength	100 mg	100 mg
Dosage Form	Film coated tablets	Film coated tablets
Bio-batch Size	(b) (4) tablets	NA
Production Batch Size	(b) (4) tablets	NA
Potency	100.1%	97.8%
Content Uniformity (mean, %CV)	NA	NA
Dose Administered	1 x 100 mg	1 x 100 mg
Route of Administration	Oral	Oral

Reviewer's note:

(b) (4)
 The CMC review [HAN, SULENE X 07/25/2012 N/A 07/25/2012 REV-QUALITY-03(General Review) Original-1 (Not Applicable) Archive] found this to be unacceptable.

Deficiency 9:

For the fasting BE study (Study No. DASA-IMTB-05SB01-2FA (DD6366)), fasting re-dosing study (DASA-IMTB-05SB01-2FA (DD6366) and fed BE study (Study No. DASA-IMTB-05SB02-2FE), you did not submit case report forms (CRF) and the actual blood sampling times. Please submit the CRFs of all the subjects, as well as actual blood sampling times in SAS Transport format, for all the above mentioned studies.

Firm's Response:

Regarding the case report forms (CRF) for the above studies; as per protocols section 9.9, "All clinical data will be recorded on site by the clinical staff on raw data and/or recorded electronically using validated software. Case report Forms will be completed only for subjects who are withdrawn from the study due to adverse event; otherwise source documents will replace case report forms."

No subjects were withdrawn due to adverse events in any of the 3 studies. Source documents for the three projects, containing all applicable information, can be found in section 16.4 of the final reports.

Blood sampling times for the studies are provided with this response as below.

Study No. DASA-IMTB-05SB01-2FA (DD6366):

- [APODD6366_1_revised.dat.xpt](#)
- [APODD6366_1_revised.pkv.xpt](#)
- [APODD6366_1_revised.inf.pdf](#)

Study No. DASA-IMTB-05SB02—2FE (DD6367):

- [APODD6367_1_revised.dat.xpt](#)
- [APODD6367_1_revised.pkv.xpt](#)
- [APODD6367_1_revised.inf.pdf](#)

Study No. DASA-IMTB-05SB03-2FA (DD6577):

- [APODD6577_1_revised.dat.xpt](#)
- [APODD6577_1_revised.pkv.xpt](#)
- [APODD6577_1_revised.inf.pdf](#)

Reviewer Comments:

- The reason the reviewer requested the firm to submit CRFs to ensure that the firm submitted a complete application. The firm has submitted the source documents for all the BE studies. The firm clarified that the subject information is located in the source documents for each BE study. The firm has also submitted the actual blood sampling times in SAS Transport format, for all the above mentioned studies. There were some blood sampling deviations during the fasting and fed BE studies. The firm used the actual collection time points and the reviewer used nominal time points for the calculation of PK parameters. However, these sampling time deviations were minor deviations (less than 5% of the nominal time point). So, the sampling time deviations were considered to be insignificant. The sample time deviations did not compromise the outcome of the BE studies (please refer to the original review - DARRTS, ANDA # 202103, PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive for details).
- The firm's response is acceptable.

Deficiency 10:

During the inspections from August 22, 2011 to February 08, 2012, for another application, the Office of Scientific Investigations (OSI) identified the following violations involving the analytical site, Apotex Inc., Bio-Clinical Development, Bioanalytical Laboratory, 440 Garyray Drive Toronto, Ontario, which may potentially affect the integrity of the fasting BE study # DASA-IMTB-05SB01-2FA (DD6366), fasting re-dosing BE study # DASA-IMTB-05SB03-2FA and fed BE study # DASA-IMTB-05SB02-2FE (DD6367) of the current ANDA.

The findings call into question the reliability of source data generated in the BE studies of the current ANDA. For considering the impact of similar study conduct and site practices by the same analytical facility on the aforementioned BE studies of the current ANDA, please address the OSI findings below. Please provide documentation as appropriate to support your response.

a) Investigate reassays done in all the studies due to "incomplete analysis," and if the reassays were justified.

b) Investigate the high internal standard (IS) peak variability. Specifically, examine why these peak areas for IS in the subject samples showed considerable variability, whereas, the IS peak areas for the calibration standards and QCs were consistent with a mean response.

Firm's Response:

Please note, the analytical site at Apotex Inc., Bio-Clinical Development was inspected from August 22-26, 2011, not Aug 22-Feb 8, 2012 as stated in the deficiency letter from July 2012. Since the inspection, an Establishment Inspection Report (EIR) was received concluding the inspection was closed. In addition, approval of the ANDA 90960 Quetiapine Fumarate Tablets inspected in Aug 2011 was received from the agency in March 27, 2012.

With respect to the current ANDA under review:

In study DD6366, one sample - Sample (b) (6), 5hr, P1 - was coded "B: Analysis Incomplete-system error". The system paused at this injection due to a communication error and there was no data collected for this sample. A single reassay was done for this sample, as directed by SOP ABM-BL-0154 rev 6 Appendix A Routine Batch Sample Analysis and the reassay value was reported as per Appendix B of the same SOP.

In studies DD6367 or DD6577, there were no samples coded "incomplete analysis" (code (b) (6))

As per SOP ABM -BL-0156 Chromatography Acceptance (rev 5 for DD6366 and DD6367 and rev 6 for DD6577) the mean IS response (area) is calculated for each run

using a validated spreadsheet. The absolute IS peak areas for each standard and sample in the run are compared individually to the run mean.

The specification for IS response used was: “IS response for individual samples should fall within 50-180% of the mean IS response for quantifiable extracted samples from within the run, excluding SYS samples. Samples coded A, B, C, or I are not included in the mean IS response calculation.”

Any samples outside of this specification are coded H.

There were no H coded samples in DD6366 or DD6577. There was only one H code in DD6367 – (b) (6) 0hr, p1. This sample had an IS response 3% of the mean for the run.

Please see the copies of the original calculations done at the time of the studies for each of DD6366, DD6367 and DD6577 which are provided as attached files [DD6366 IS Response](#); [DD6367 IS Response](#) and [DD6577 IS Response](#). The data show each sample compared to the mean of the run. These worksheets demonstrate that the subject samples did not have higher variability in IS peak areas than the calibration standards and QCs. Therefore, the concern regarding IS variability does not apply to these studies.

Reviewer Comments:

- In the fasting BE study # DD6366, one sample - Sample (b) (6) 5hr, P1 - was coded (b) (6) “Analysis Incomplete-system error”. The firm mentioned that the system was paused at this injection due to a communication error and there was no data collected for this sample. The firm mentioned that a single reassay was done for this sample, as directed by SOP ABM-BL-0154 rev 6 Appendix A Routine Batch Sample Analysis and the reassay value was reported as per Appendix B of the same SOP. In the original review, the reviewer has found the decision to repeat the sample (code (b) (6)) was justified based on the said pre-established SOP. Furthermore, the reported values were selected consistent with the SOP (please refer to the original review - DARRTS, ANDA # 202103, PABBA, SANTHOSH K 06/27/2012 N/A 06/27/2012 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive for details).
- In the studies DD6367 (fed) or DD6577 (fasting redosing), there were no samples coded “incomplete analysis” (code (b) (6)).
- For the fed study, the decision to repeat the sample (code H - Anomalous IS Response) was justified based on the pre-established SOP. The reviewer has verified the mean internal standard response for the run # 5 (subject (b) (6), P1, 0h, PLM-1), the said sample has very low internal standard response (3% of the mean internal standard response for the run # 5). Therefore, the reviewer agrees with the firm for repeating the said sample. Furthermore, the reported values were selected consistent with the SOP: ABM –BL-0156 (the said SOP is effective during the

conduct of the BE studies). In the studies DD6366 (fasting) or DD6577 (fasting - redosing), there were no samples for code H.

- Finally, please note that the IS variability of the subject samples for all three BE and the IS variability of the CC and QC samples used in all the three BE studies is similar and within the acceptable limits of 50-180% of the mean IS response as specified in the SOP: ABM –BL-0156 Chromatography Acceptance.
- The firm’s response is acceptable.

5 DEFICIENCY COMMENTS

1. The results of the re-dosing study # DASA-IMTB-05SB03-2FA confirm that Subject (b) (6) was an “extreme” subject whose test-to-reference (T/R) ratios of pharmacokinetic (PK) parameters were consistently outside the PK ratio range of other subjects from the original and re-dosing studies, even though the (T/R) ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject (b) (6) were “aberrant” in the original fasting BE study. For this reason, the subject should not be excluded from the final statistical analysis of the original fasting BE study. With the inclusion of subject (b) (6), the fasting BE study does not meet bioequivalence criteria (lnAUCt confidence intervals are 96.68 to 135.34 and lnCmax confidence intervals are 98.23 to 144.45) and the fasting BE study is **unacceptable**.
2. For the fed BE study (Study No. DASA-IMTB-05SB02-2FE): The firm did not submit the assay failure investigation report for rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats) and incomplete assay run ID # 13 (Run description 13DD6367- (b) (6) - Incomplete Assay). The firm will be requested to submit assay failure investigation reports for the said runs.
3. For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), the firm submitted whole blood stability validation data for 2 hours on ice in the current amendment to address the protocol deviation pertaining to centrifugation of post-dose fed BE study samples as much as 72 minutes after blood collection. However, the firm did not provide the nominal concentrations of the quality control (QC) samples used in this validation study. The firm will be requested to provide these nominal concentrations. If the measured values of the QC samples are greater than 15% from nominal, then the firm should repeat the validation study.

6 RECOMMENDATIONS

1. The Division of Bioequivalence finds the fasting BE study (DASA-IMTB-05SB01-2FA (DD6366)) **unacceptable** due to the deficiencies mentioned above. The firm, Apotex Inc., conducted the fasting BE study on its Dasatinib Tablets, 100

mg (lot # FD150-31) comparing it to Bristol Myers Squibb's Sprycel® (dasatinib) Tablets, 100 mg (lot # 9L6029B).

2. The Division of Bioequivalence **accepts** the fasting (re-dosing) BE study (DASA-IMTB-05SB03-2FA). The firm, Apotex Inc., conducted the fasting (re-dosing) BE study on its Dasatinib Tablets, 100 mg (lot # FD150-31) comparing it to Bristol Myers Squibb's Sprycel® (dasatinib) Tablets, 100 mg (lot # 9L6029B).

3. The Division of Bioequivalence finds the fed BE study (DASA-IMTB-05SB02-2FE) **inadequate** due to the deficiencies mentioned above. The firm, Apotex Inc., conducted the fasting BE study on its Dasatinib Tablets, 100 mg (lot # FD150-31) comparing it to Bristol Myers Squibb's Sprycel® (dasatinib) Tablets, 100 mg (lot # 9L6029B).

4. The firm's in vitro dissolution testing is **acceptable**. The dissolution testing should be conducted in 1000 mL of acetate buffer at pH 4.0 with 1% Triton X-100 at 37°C ± 0.5°C) using USP apparatus II (paddle) at 60 rpm. The test product should meet the following specification:

NLT ^(b)₍₄₎% (Q) of dasatinib is dissolved in ^(b)₍₄₎ minutes.

5. The dissolution testing conducted by Apotex Inc., on its test product Dasatinib Tablets, 20 mg (Batch # FD150-32), 50 mg (Batch # FD150-33), 70 mg (Batch # FD150-34) and 100 mg (Batch # FD150-31) is **acceptable**. The formulation of Dasatinib Tablets, 20 mg, 50 mg and 70 mg are proportionally similar to the Dasatinib Tablets, 100 mg which underwent bioequivalence testing. The DB grants the waivers of in vivo bioequivalence study requirements for Dasatinib Tablets, 20 mg, 50 mg and 70 mg.

7 COMMENT FOR OTHER OGD DISCIPLINES

Discipline	Comment
None	.

8 APPENDIX

8.1 SAS Output

8.1.1 Fasting Study Data with Original values for Code: I (reported in the current amendment) and repeat values for Codes F and B

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	(b) (6)	1	1	1	A	0	7.92	22.67	48.96	73.09	52.52	40.20	34.70	44.34	61.24	72.45	56.94	41.63	34.70	16.46
2		1	2	1	B	0	0.00	0.00	8.03	67.05	65.84	45.18	51.50	56.47	57.91	51.37	56.94	40.77	37.79	18.17
3		2	1	1	B	0	4.21	18.77	68.92	113.93	105.06	81.69	78.81	89.53	92.36	66.77	53.04	32.96	27.17	14.34
4		2	2	1	A	0	9.08	32.90	114.53	158.47	144.35	135.83	112.89	100.33	132.57	131.51	100.90	65.72	53.63	30.52
5		2	1	1	B	0	1.31	4.25	69.02	104.52	66.13	46.95	43.02	46.06	45.74	57.25	54.84	35.78	21.17	14.56
6		2	2	1	A	0	0.00	1.77	19.14	110.40	84.28	56.30	50.40	49.46	47.36	59.28	56.27	39.90	23.31	13.16
7		2	1	1	B	0	0.00	1.29	15.70	77.23	128.30	162.00	142.86	158.78	127.09	102.76	72.53	46.14	34.50	19.50
8		2	2	1	A	0	1.83	16.91	63.02	111.00	135.97	127.33	120.22	151.20	111.24	81.66	56.15	39.69	29.31	16.77
9		2	1	1	B	0	0.00	0.00	5.93	47.37	98.03	103.35	152.20	120.00	105.27	75.18	59.93	41.40	30.46	15.61
10		2	2	1	A	0	17.05	69.58	85.76	84.58	133.10	125.93	104.58	84.92	62.77	46.71	39.19	27.54	23.24	13.32
11		1	1	1	A	0	11.02	22.34	38.10	57.43	77.06	86.54	71.78	67.70	53.44	41.99	32.21	26.52	18.47	9.89
12		1	2	1	B	0	5.93	37.00	83.83	75.29	55.24	46.56	41.97	34.14	30.71	28.11	26.04	18.16	30.04	13.50
13		1	1	1	A	0	4.30	12.00	32.33	65.69	66.16	51.01	62.35	52.00	42.48	26.91	21.25	13.65	10.67	6.43
14		1	2	1	B	0	2.88	6.81	45.87	120.64	166.63	158.97	114.62	85.68	65.01	46.45	37.34	25.05	19.86	12.25
15		1	1	1	A	0	5.81	21.03	125.78	101.70	69.00	54.35	62.58	87.31	115.35	91.95	65.06	43.90	29.85	17.87
16		1	2	1	B	0	2.62	9.96	80.58	147.55	118.27	112.76	108.99	110.18	107.44	74.52	58.81	40.40	36.91	18.63
17		2	1	1	B	0	16.99	54.66	85.31	62.04	50.46	39.24	32.67	31.13	25.43	22.66	19.50	14.45	10.13	5.35
18		2	2	1	A	0	22.06	63.92	104.30	60.72	36.23	32.83	30.80	29.52	25.57	20.58	26.49	22.02	16.93	9.72

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
19	(b) (6)	1	1	1	A	0	0.00	3.00	52.27	154.05	108.41	71.49	66.08	70.40	66.26	47.79	35.99	28.81	24.27	13.82
20		1	2	1	B	0	0.00	0.00	9.94	70.03	101.49	71.13	47.38	38.31	31.03	28.10	25.21	23.97	25.55	12.72
21		2	1	1	B	0	7.54	24.50	66.52	72.96	51.66	52.50	108.75	172.88	152.19	88.68	58.59	38.38	28.27	16.61
22		2	2	1	A	0	12.74	56.09	127.80	159.87	151.34	118.51	97.78	77.78	63.75	48.21	37.07	29.57	20.97	14.59
23		2	1	1	B	0	1.49	6.81	18.67	45.49	120.71	113.75	90.19	77.27	64.73	52.75	38.50	30.12	24.47	13.51
24		2	2	1	A	0	0.00	1.47	18.16	84.46	157.92	169.83	148.36	126.63	99.01	67.82	63.19	42.81	32.36	17.70
25		1	1	1	A	0	11.78	62.01	118.82	93.06	71.54	55.25	57.77	48.73	43.89	36.10	30.00	22.12	16.93	10.36
26		1	2	1	B	0	0.00	6.41	59.13	113.33	133.99	157.17	136.57	122.37	108.97	77.09	58.19	44.61	31.57	18.70
27		1	1	1	A	0	3.34	12.44	40.01	91.18	124.96	103.79	91.64	76.93	64.42	47.60	37.11	28.00	20.03	9.90
28		1	2	1	B	0	1.81	5.97	26.89	64.02	103.23	76.39	62.37	47.96	43.70	32.02	31.41	31.24	17.85	10.13
29		2	1	1	B	0	0.00	3.43	72.54	151.07	132.71	109.89	93.41	79.18	65.89	49.76	42.25	30.98	22.69	13.46
30		2	2	1	A	0	0.00	0.00	21.66	73.01	57.35	44.47	35.87	31.98	29.28	22.47	17.07	12.46	10.15	6.49
31		2	1	1	B	0	0.00	1.46	1.90	2.40	2.23	1.95	1.94	1.77	1.68	1.39	1.18	1.01	1.34	0.00
32		2	2	1	A	0	15.45	47.33	110.02	131.06	122.22	126.95	147.38	124.73	100.98	68.08	47.37	33.01	24.46	14.15
33		1	1	1	A	0	37.18	70.15	97.61	100.89	93.85	83.11	76.22	65.61	60.11	51.53	41.11	29.40	23.33	11.53
34		1	2	1	B	0	14.64	31.08	73.30	91.30	70.63	58.69	53.39	52.31	45.99	34.44	25.12	22.94	16.99	9.70
35		2	1	1	B	0	7.63	20.90	121.71	80.12	53.21	36.14	32.08	30.41	31.10	25.02	25.02	22.21	15.45	8.97
36		2	2	1	A	0	0.00	1.50	9.44	23.66	39.10	69.65	66.60	58.26	50.03	42.34	38.29	23.27	15.93	8.47
37		1	1	1	A	0	0.00	0.00	54.81	105.84	81.76	59.67	52.44	44.05	35.85	37.75	35.20	44.57	26.33	14.12
38		1	2	1	B	0	16.89	34.00	74.09	142.34	101.70	73.91	60.41	51.53	43.61	33.92	35.37	35.39	20.36	11.23
39		2	1	1	B	0	18.33	47.83	138.99	157.32	128.16	84.49	75.76	72.73	68.17	42.64	34.46	24.69	17.39	10.32
40		2	2	1	A	0	7.95	32.03	119.51	133.78	120.66	106.19	94.79	79.12	58.91	46.00	35.59	26.79	17.79	10.15
41		2	1	1	B	0	3.43	16.97	65.32	112.63	103.21	81.40	69.87	80.03	97.83	76.57	51.40	32.50	24.76	13.75
42		2	2	1	A	0	12.53	60.22	178.35	238.91	229.67	166.76	110.58	79.81	67.72	52.75	43.94	30.65	21.52	13.14
43		1	1	1	A	0	3.07	9.99	27.98	112.63	161.13	141.18	114.16	89.20	73.01	53.37	44.82	39.80	27.92	13.16
44		1	2	1	B	0	0.00	2.61	39.06	91.80	125.56	123.38	107.64	93.70	85.80	67.90	59.17	38.06	24.43	14.45

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
45	(b) (6)	2	1	1	B	0	0.00	1.21	11.92	45.96	76.93	140.84	141.66	125.02	128.97	91.14	76.07	57.23	48.11	22.17
46		2	2	1	A	0	4.39	14.14	28.54	75.53	103.71	117.30	117.97	114.60	101.61	92.30	81.17	49.71	38.81	20.09
47		1	1	1	A	0	29.15	51.09	60.55	60.33	49.85	49.13	41.13	70.18	106.10	73.11	58.81	37.58	30.16	14.99
48		1	2	1	B	0	16.38	28.31	45.94	40.62	31.42	27.99	38.98	62.69	65.63	54.60	41.64	23.22	21.07	10.48
49		1	1	1	A	0	4.74	37.67	101.04	99.58	92.79	73.23	66.42	64.64	61.82	47.92	43.31	25.55	18.60	9.53
50		1	2	1	B	0	2.81	11.97	50.04	96.98	88.29	88.75	75.26	72.96	74.31	55.12	46.55	35.50	26.10	12.74
51		2	1	1	B	0	21.12	63.95	117.61	116.71	94.78	70.61	61.15	51.81	44.99	30.07	24.18	17.56	13.65	7.69
52		2	2	1	A	0	64.42	100.20	161.62	127.78	92.71	73.10	65.52	63.15	50.53	39.50	30.82	22.26	16.92	9.82
53		1	1	1	A	0	2.37	21.06	99.84	97.81	81.03	74.21	97.55	131.78	168.93	142.16	109.22	71.47	54.71	28.55
54		1	2	1	B	0	1.76	14.61	57.06	58.15	45.15	40.26	55.26	80.43	92.56	86.54	66.16	38.47	30.86	17.75
55		2	1	1	B	0	16.40	49.69	78.29	75.65	59.63	52.24	65.56	79.46	86.20	68.78	49.34	46.07	39.52	26.15
56		2	2	1	A	0	6.00	12.56	55.14	51.78	40.08	36.78	32.77	27.90	25.18	26.42	24.61	20.98	14.82	9.13
57		1	1	1	A	0	7.52	27.20	80.57	86.94	72.86	67.13	68.14	78.35	92.90	108.04	98.60	83.60	56.43	25.02
58		1	2	1	B	0	1.68	12.03	64.27	72.11	58.34	66.89	50.79	69.27	85.34	94.59	86.56	77.46	61.63	33.10
59		2	1	1	B	0	2.71	13.73	76.07	115.79	87.30	68.72	66.06	60.22	59.25	50.00	42.81	33.25	25.54	14.16
60		2	2	1	A	0	10.30	39.13	86.19	70.69	54.27	42.99	44.81	43.30	40.71	43.85	35.84	25.30	21.79	13.12
61		1	1	1	A	0	11.71	31.06	78.44	141.66	116.57	89.58	77.01	80.87	78.45	67.52	69.27	46.73	35.73	19.61
62		1	2	1	B	0	24.72	42.54	77.49	92.63	74.35	70.27	97.64	113.18	109.21	86.45	58.33	39.62	32.44	19.14
63		2	1	1	B	0	6.46	21.54	66.85	52.57	34.68	27.72	33.06	40.59	37.65	29.85	23.25	15.83	12.36	6.37
64		2	2	1	A	0	33.75	58.56	90.80	87.67	64.17	50.20	60.21	74.20	63.55	42.79	34.38	21.09	15.42	7.90
65		1	1	1	A	0	5.70	21.44	69.14	112.38	114.11	100.10	101.28	83.71	77.06	48.94	40.64	33.15	28.35	19.52
66		1	2	1	B	0	2.63	11.32	53.51	111.83	132.66	125.21	90.19	82.62	78.32	58.62	41.79	30.86	22.25	11.81
67		1	1	1	A	0	44.00	75.50	92.68	73.63	64.65	58.52	60.44	71.29	75.42	65.26	53.79	33.79	22.79	15.60
68		1	2	1	B	0	12.11	34.90	65.44	75.49	74.56	60.94	58.87	47.38	40.58	35.43	31.17	19.96	14.40	9.68
69		2	1	1	B	0	30.20	49.45	67.33	42.21	33.25	25.71	22.73	32.64	37.54	29.83	39.41	27.17	31.51	16.35
70		2	2	1	A	0	0.00	2.38	12.65	56.13	107.81	118.10	108.23	77.70	71.91	47.85	37.23	26.67	21.67	11.85

Obs	sub (b) (6)	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
71		1	1	1	A	0	0.00	0.00	0.00	1.21	1.66	1.84	2.25	2.13	2.04	1.83	1.51	2.45	2.58	2.17
72		1	2	1	B	0	0.00	0.00	1.87	2.81	2.51	2.45	2.61	2.65	2.34	2.26	4.84	3.60	2.81	2.06
73		1	1	1	A	0	0.00	2.17	31.99	69.53	53.04	55.10	51.00	54.72	55.07	47.52	52.54	33.23	23.74	12.23
74		1	2	1	B	0	3.14	15.51	60.17	63.17	46.95	38.53	42.49	53.60	53.11	41.39	41.78	21.93	16.19	9.20
75		2	1	1	B	0	25.74	61.67	101.68	100.24	86.22	59.65	48.98	41.64	41.45	61.90	50.55	35.46	23.36	13.23
76		2	2	1	A	0	0.00	7.42	55.76	170.74	230.86	246.19	202.87	187.55	145.86	109.52	89.72	56.26	40.78	20.62
77		2	1	1	B	0	2.19	8.55	72.38	86.65	72.14	51.45	39.40	32.88	28.88	25.95	22.67	19.24	13.59	7.97
78		2	2	1	A	0	3.50	25.38	46.32	76.91	68.51	48.66	38.71	36.24	33.96	33.69	28.63	25.40	14.45	8.34
79		1	1	1	A	0	4.85	32.94	96.60	80.35	56.68	39.58	35.78	32.23	24.09	17.03	13.47	8.68	6.25	4.19
80		1	2	1	B	0	0.00	8.63	30.60	37.86	36.52	34.63	29.05	21.17	15.86	11.71	9.63	6.62	5.06	3.21
81		2	1	1	B	0	0.00	1.32	43.12	62.54	54.98	42.35	41.11	47.60	66.75	78.66	68.31	51.58	32.27	16.42
82		2	2	1	A	0	0.00	2.48	29.29	92.74	82.18	60.41	57.80	54.14	51.40	37.17	30.72	21.99	16.58	10.24
83		1	1	1	A	0	1.92	8.44	58.86	76.31	63.66	120.48	139.10	115.49	96.14	66.52	51.58	36.79	27.64	15.04
84		1	2	1	B	0	1.74	21.75	75.68	60.96	42.33	42.24	67.31	76.65	91.86	62.29	39.14	27.68	17.60	11.57

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
1	11.00	5.99	3.26	1.96	1.52	17	20	1	20
2	11.63	6.23	2.80	1.73	1.26	16	19	2	20
3	10.02	5.58	3.27	2.10	1.69	17	20	2	20
4	16.35	9.22	4.67	2.73	1.94	17	20	1	20
5	8.88	3.86	1.73	1.02	0.00	16	19	2	20
6	10.19	5.26	2.27	1.32	0.00	17	20	1	20
7	12.76	6.23	2.63	1.43	1.10	16	19	2	20
8	9.76	6.38	3.00	1.71	1.44	17	19	1	20
9	10.12	4.88	2.21	1.04	0.00	16	19	2	20
10	8.24	3.95	1.66	0.00	0.00	16	18	1	20
11	6.90	3.16	1.63	1.01	0.00	15	19	1	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
12	8.27	4.11	2.26	1.32	1.18	16	19	2	20
13	4.99	2.44	1.44	0.00	0.00	13	18	1	20
14	9.01	4.37	2.22	1.38	1.12	16	19	2	20
15	11.48	6.06	3.14	1.83	1.33	17	20	1	20
16	13.03	6.90	3.67	2.09	1.55	17	20	2	20
17	3.60	1.86	0.00	0.00	0.00	14	17	2	20
18	5.84	2.98	1.63	1.06	0.00	16	19	1	20
19	8.93	4.04	1.99	1.10	0.00	15	19	1	20
20	7.57	4.27	2.28	1.35	1.13	16	19	2	20
21	9.01	5.61	3.11	1.90	1.60	16	19	2	20
22	8.85	4.87	2.70	1.64	1.23	17	20	1	20
23	8.57	4.02	1.49	0.00	0.00	14	18	2	20
24	11.61	5.16	2.38	1.35	0.00	15	19	1	20
25	7.57	3.85	2.71	1.62	1.49	16	19	1	20
26	14.34	7.18	3.92	2.39	1.92	16	19	2	20
27	6.45	3.24	1.62	1.04	0.00	15	19	1	20
28	6.91	3.44	1.59	1.06	0.00	15	18	2	20
29	10.26	5.58	3.17	1.76	1.63	16	19	2	20
30	4.80	2.87	1.95	1.43	1.81	16	19	1	20
31	1.21	1.06	0.00	0.00	0.00	.	.	2	20
32	10.75	7.45	3.11	2.07	1.60	16	19	1	20
33	7.72	3.91	2.01	1.20	0.00	15	19	1	20
34	6.32	3.04	1.75	1.07	0.00	16	19	2	20
35	6.26	3.18	1.69	1.08	0.00	16	19	2	20
36	5.69	3.55	1.56	0.00	0.00	15	18	1	20
37	9.47	4.98	2.94	1.84	1.33	17	20	1	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
38	7.23	4.18	2.35	1.44	0.00	16	19	2	20
39	6.88	3.23	1.46	0.00	0.00	14	18	2	20
40	6.06	2.96	1.37	0.00	0.00	14	18	1	20
41	10.90	4.94	2.59	1.52	1.14	16	19	2	20
42	9.73	5.43	2.44	1.52	0.00	16	19	1	20
43	7.26	3.55	1.65	0.00	0.00	15	18	1	20
44	8.04	4.41	1.95	0.00	0.00	15	18	2	20
45	13.75	7.35	3.14	1.90	1.11	17	20	2	20
46	12.35	7.23	3.64	2.21	1.58	17	20	1	20
47	10.12	3.89	1.72	1.05	0.00	15	19	1	20
48	7.11	3.28	2.27	1.24	1.11	15	19	2	20
49	6.39	3.61	2.07	1.25	1.14	16	19	1	20
50	8.79	4.38	2.37	1.44	1.13	16	19	2	20
51	5.41	2.68	1.37	0.00	0.00	14	18	2	20
52	6.32	3.18	1.61	0.00	0.00	14	18	1	20
53	22.31	10.26	5.01	3.00	1.81	17	20	1	20
54	13.98	7.81	4.03	2.30	1.66	16	19	2	20
55	16.52	8.00	3.73	2.58	2.02	16	19	2	20
56	5.36	3.68	1.94	1.23	1.07	16	19	1	20
57	16.52	8.22	3.84	2.35	1.84	17	20	1	20
58	18.57	9.60	4.77	3.01	2.71	16	19	2	20
59	8.19	4.41	2.35	1.46	1.21	16	19	2	20
60	7.87	4.46	2.21	1.33	1.30	16	19	1	20
61	12.94	6.18	3.79	2.21	2.08	16	19	1	20
62	12.62	6.97	3.47	2.05	1.80	16	19	2	20
63	3.88	1.98	0.00	0.00	0.00	13	17	2	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
64	5.13	2.70	1.21	0.00	0.00	15	18	1	20
65	10.51	5.39	2.25	1.49	1.54	16	19	1	20
66	7.18	4.13	2.12	1.44	1.18	16	19	2	20
67	9.86	6.25	3.35	2.37	1.78	17	20	1	20
68	6.66	4.07	2.48	1.63	1.48	16	19	2	20
69	9.22	5.05	2.26	1.48	1.11	18	20	2	20
70	7.66	3.74	1.77	0.00	0.00	14	18	1	20
71	3.00	3.16	2.93	2.93	3.55	.	.	1	20
72	2.32	1.77	1.54	1.83	3.24	.	.	2	20
73	6.94	3.35	1.64	1.06	0.00	16	19	1	20
74	6.17	3.41	1.53	1.06	0.00	16	19	2	20
75	8.07	4.90	2.47	1.53	1.22	16	19	2	20
76	13.23	7.39	3.75	2.16	1.51	17	20	1	20
77	4.41	2.11	1.21	0.00	0.00	15	18	2	20
78	4.78	2.66	1.22	0.00	0.00	14	18	1	20
79	2.39	1.35	0.00	0.00	0.00	13	17	1	20
80	2.16	1.31	0.00	0.00	0.00	13	17	2	20
81	10.03	5.89	3.26	1.85	1.13	16	20	2	20
82	6.36	3.87	1.98	1.17	0.00	15	19	1	20
83	9.92	5.98	3.32	2.15	1.84	16	19	1	20
84	7.77	4.73	2.76	1.66	1.39	16	19	2	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
1	11.00	5.99	3.26	1.96	1.52	17	20	1	20
2	11.63	6.23	2.80	1.73	1.26	16	19	2	20
3	10.02	5.58	3.27	2.10	1.69	17	20	2	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
4	16.35	9.22	4.67	2.73	1.94	17	20	1	20
5	8.88	3.86	1.73	1.02	0.00	16	19	2	20
6	10.19	5.26	2.27	1.32	0.00	17	20	1	20
7	12.76	6.23	2.63	1.43	1.10	16	19	2	20
8	9.76	6.38	3.00	1.71	1.44	17	19	1	20
9	10.12	4.88	2.21	1.04	0.00	16	19	2	20
10	8.24	3.95	1.66	0.00	0.00	16	18	1	20
11	6.90	3.16	1.63	1.01	0.00	15	19	1	20
12	8.27	4.11	2.26	1.32	1.18	16	19	2	20
13	4.99	2.44	1.44	0.00	0.00	13	18	1	20
14	9.01	4.37	2.22	1.38	1.12	16	19	2	20
15	11.48	6.06	3.14	1.83	1.33	17	20	1	20
16	13.03	6.90	3.67	2.09	1.55	17	20	2	20
17	3.60	1.86	0.00	0.00	0.00	14	17	2	20
18	5.84	2.98	1.63	1.06	0.00	16	19	1	20
19	8.93	4.04	1.99	1.10	0.00	15	19	1	20
20	7.57	4.27	2.28	1.35	1.13	16	19	2	20
21	9.01	5.61	3.11	1.90	1.60	16	19	2	20
22	8.85	4.87	2.70	1.64	1.23	17	20	1	20
23	8.57	4.02	1.49	0.00	0.00	14	18	2	20
24	11.61	5.16	2.38	1.35	0.00	15	19	1	20
25	7.57	3.85	2.71	1.62	1.49	16	19	1	20
26	14.34	7.18	3.92	2.39	1.92	16	19	2	20
27	6.45	3.24	1.62	1.04	0.00	15	19	1	20
28	6.91	3.44	1.59	1.06	0.00	15	18	2	20
29	10.26	5.58	3.17	1.76	1.63	16	19	2	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
30	4.80	2.87	1.95	1.43	1.81	16	19	1	20
31	1.21	1.06	0.00	0.00	0.00	.	.	2	20
32	10.75	7.45	3.11	2.07	1.60	16	19	1	20
33	7.72	3.91	2.01	1.20	0.00	15	19	1	20
34	6.32	3.04	1.75	1.07	0.00	16	19	2	20
35	6.26	3.18	1.69	1.08	0.00	16	19	2	20
36	5.69	3.55	1.56	0.00	0.00	15	18	1	20
37	9.47	4.98	2.94	1.84	1.33	17	20	1	20
38	7.23	4.18	2.35	1.44	0.00	16	19	2	20
39	6.88	3.23	1.46	0.00	0.00	14	18	2	20
40	6.06	2.96	1.37	0.00	0.00	14	18	1	20
41	10.90	4.94	2.59	1.52	1.14	16	19	2	20
42	9.73	5.43	2.44	1.52	0.00	16	19	1	20
43	7.26	3.55	1.65	0.00	0.00	15	18	1	20
44	8.04	4.41	1.95	0.00	0.00	15	18	2	20
45	13.75	7.35	3.14	1.90	1.11	17	20	2	20
46	12.35	7.23	3.64	2.21	1.58	17	20	1	20
47	10.12	3.89	1.72	1.05	0.00	15	19	1	20
48	7.11	3.28	2.27	1.24	1.11	15	19	2	20
49	6.39	3.61	2.07	1.25	1.14	16	19	1	20
50	8.79	4.38	2.37	1.44	1.13	16	19	2	20
51	5.41	2.68	1.37	0.00	0.00	14	18	2	20
52	6.32	3.18	1.61	0.00	0.00	14	18	1	20
53	22.31	10.26	5.01	3.00	1.81	17	20	1	20
54	13.98	7.81	4.03	2.30	1.66	16	19	2	20
55	16.52	8.00	3.73	2.58	2.02	16	19	2	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
56	5.36	3.68	1.94	1.23	1.07	16	19	1	20
57	16.52	8.22	3.84	2.35	1.84	17	20	1	20
58	18.57	9.60	4.77	3.01	2.71	16	19	2	20
59	8.19	4.41	2.35	1.46	1.21	16	19	2	20
60	7.87	4.46	2.21	1.33	1.30	16	19	1	20
61	12.94	6.18	3.79	2.21	2.08	16	19	1	20
62	12.62	6.97	3.47	2.05	1.80	16	19	2	20
63	3.88	1.98	0.00	0.00	0.00	13	17	2	20
64	5.13	2.70	1.21	0.00	0.00	15	18	1	20
65	10.51	5.39	2.25	1.49	1.54	16	19	1	20
66	7.18	4.13	2.12	1.44	1.18	16	19	2	20
67	9.86	6.25	3.35	2.37	1.78	17	20	1	20
68	6.66	4.07	2.48	1.63	1.48	16	19	2	20
69	9.22	5.05	2.26	1.48	1.11	18	20	2	20
70	7.66	3.74	1.77	0.00	0.00	14	18	1	20
71	3.00	3.16	2.93	2.93	3.55	.	.	1	20
72	2.32	1.77	1.54	1.83	3.24	.	.	2	20
73	6.94	3.35	1.64	1.06	0.00	16	19	1	20
74	6.17	3.41	1.53	1.06	0.00	16	19	2	20
75	8.07	4.90	2.47	1.53	1.22	16	19	2	20
76	13.23	7.39	3.75	2.16	1.51	17	20	1	20
77	4.41	2.11	1.21	0.00	0.00	15	18	2	20
78	4.78	2.66	1.22	0.00	0.00	14	18	1	20
79	2.39	1.35	0.00	0.00	0.00	13	17	1	20
80	2.16	1.31	0.00	0.00	0.00	13	17	2	20
81	10.03	5.89	3.26	1.85	1.13	16	20	2	20

Obs	c16	c17	c18	c19	c20	KE_FIRST	KE_LAST	trt	i
82	6.36	3.87	1.98	1.17	0.00	15	19	1	20
83	9.92	5.98	3.32	2.15	1.84	16	19	1	20
84	7.77	4.73	2.76	1.66	1.39	16	19	2	20

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	42	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	84
Number of Observations Used	84

Data for Analysis of AUCI LAUCI	
Number of Observations Read	84
Number of Observations Used	81

Data for Analysis of AUCI LAUCI		
Class Level Information		
Class	Levels	Values
sub	42	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LC MAX	
Number of Observations Read	84
Number of Observations Used	84

Data for Analysis of AUCI LAUCI	
Number of Observations Read	84
Number of Observations Used	81

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	43	18.49912856	0.43021229	2.05	0.0118
Error	40	8.38302450	0.20957561		
Corrected Total	83	26.88215306			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.688157	7.960976	0.457794	5.750479

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00013547	0.00013547	0.00	0.9798
sub(seq)	40	18.06540527	0.45163513	2.15	0.0086
per	1	0.05418122	0.05418122	0.26	0.6139
trt	1	0.37940659	0.37940659	1.81	0.1860

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00013547	0.00013547	0.00	0.9798
sub(seq)	40	18.06540527	0.45163513	2.15	0.0086
per	1	0.05418122	0.05418122	0.26	0.6139
trt	1	0.37940659	0.37940659	1.81	0.1860

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00013547	0.00013547	0.00	0.9863

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.13441347	0.09989890	1.35	0.1860

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	43	32.68163115	0.76003793	2.76	0.0008

Error	40	11.01574173	0.27539354		
Corrected Total	83	43.69737288			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.747908	11.48863	0.524780	4.567818

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.66077832	0.66077832	2.40	0.1293
sub(seq)	40	31.25856196	0.78146405	2.84	0.0007
per	1	0.11960873	0.11960873	0.43	0.5137
trt	1	0.64268214	0.64268214	2.33	0.1345

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.66077832	0.66077832	2.40	0.1293
sub(seq)	40	31.25856196	0.78146405	2.84	0.0007
per	1	0.11960873	0.11960873	0.43	0.5137
trt	1	0.64268214	0.64268214	2.33	0.1345

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.66077832	0.66077832	0.85	0.3633

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.17493974	0.11451628	1.53	0.1345

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	42	8.05486651	0.19178254	3.46	<.0001
Error	38	2.10432163	0.05537689		
Corrected Total	80	10.15918815			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.792865	4.017589	0.235323	5.857317

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00037597	0.00037597	0.01	0.9348
sub(seq)	39	7.99249448	0.20493576	3.70	<.0001
per	1	0.01836827	0.01836827	0.33	0.5681
trt	1	0.04362779	0.04362779	0.79	0.3803

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00020956	0.00020956	0.00	0.9513
sub(seq)	39	7.98451020	0.20473103	3.70	<.0001
per	1	0.01836827	0.01836827	0.33	0.5681
trt	1	0.04362779	0.04362779	0.79	0.3803

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00020956	0.00020956	0.00	0.9746

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.04670535	0.05261981	0.89	0.3803

Fasting BE study – Reviewer calculated PK dataset

Obs	sub	trt	seq	per	GRP	auct	auci	C _{MAX}	T _{MAX}	THALFR	KEL
1	(b) (6)	1	1	1	1	376.515	386.132	73.09	0.75	4.38562	0.15805
2		2	1	2	1	368.618	375.622	67.05	0.75	3.85324	0.17989
3		1	2	2	1	697.603	707.995	158.47	0.75	3.71297	0.18668
4		2	2	1	1	414.404	423.443	113.93	0.75	3.70731	0.18697
5		1	2	2	1	338.343	345.969	110.40	0.75	4.00423	0.17310
6		2	2	1	1	320.144	326.208	104.52	0.75	4.12066	0.16821
7		1	2	2	1	487.382	495.011	151.20	1.75	3.67213	0.18876
8		2	2	1	1	533.222	539.043	162.00	1.25	3.66798	0.18897
9		1	2	2	1	365.869	372.330	133.10	1.00	2.69800	0.25691
10		2	2	1	1	425.107	429.632	152.20	1.50	3.01586	0.22983
11		1	1	1	1	278.787	283.249	86.54	1.25	3.06263	0.22632
12		2	1	2	1	273.569	279.915	83.83	0.50	3.72766	0.18595
13		1	1	1	1	195.034	201.438	66.16	1.00	3.08270	0.22485
14		2	1	2	1	382.003	387.625	166.63	1.00	3.47958	0.19920
15		1	1	1	1	458.627	465.758	125.78	0.50	3.71613	0.18652
16		2	1	2	1	505.584	514.631	147.55	0.75	4.04561	0.17133

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
17	(b) (6)	1	2	2	1	221.329	226.051	104.30	0.50	3.08757	0.22450
18		2	2	1	1	169.062	175.374	85.31	0.50	2.35233	0.29466
19		1	1	1	1	344.174	349.300	154.05	0.75	3.23017	0.21459
20		2	1	2	1	267.151	272.733	101.49	1.00	3.42378	0.20245
21		1	2	2	1	412.280	417.474	159.87	0.75	2.92674	0.23683
22		2	2	1	1	457.722	465.925	172.88	1.75	3.55384	0.19504
23		1	2	2	1	480.284	487.732	169.83	1.25	3.82435	0.18125
24		2	2	1	1	328.714	339.094	120.71	1.00	4.82853	0.14355
25		1	1	1	1	294.178	301.008	118.82	0.50	3.17733	0.21815
26		2	1	2	1	521.552	530.995	157.17	1.25	3.40884	0.20334
27		1	1	1	1	322.293	327.080	124.96	1.00	3.19039	0.21726
28		2	1	2	1	267.209	273.838	103.23	1.00	4.33473	0.15991
29		1	2	2	1	180.086	188.221	73.01	0.75	3.11541	0.22249
30		2	2	1	1	398.598	406.491	151.07	0.75	3.35615	0.20653
31		1	2	2	1	476.960	484.073	147.38	1.50	3.08152	0.22494
32		2	2	1	1	12.999	.	2.40	0.75	.	.
33		1	1	1	1	350.340	354.740	100.89	0.75	2.54108	0.27278
34		2	1	2	1	259.985	264.587	91.30	0.75	2.98110	0.23251
35		1	2	2	1	229.011	238.904	69.65	1.25	4.39560	0.15769
36		2	2	1	1	229.383	234.573	121.71	0.50	3.33100	0.20809
37		1	1	1	1	331.359	337.512	105.84	0.75	3.20696	0.21614
38		2	1	2	1	323.285	329.718	142.34	0.75	3.09655	0.22384
39		1	2	2	1	337.856	342.797	133.78	0.75	2.49975	0.27729

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
40	(b) (6)	2	2	1	1	343.375	348.401	157.32	0.75	2.38643	0.29045
41		1	2	2	1	483.546	489.519	238.91	0.75	2.72399	0.25446
42		2	2	1	1	402.111	408.026	112.63	0.75	3.59672	0.19272
43		1	1	1	1	391.760	399.929	161.13	1.00	3.43198	0.20197
44		2	1	2	1	397.591	406.496	125.56	1.00	3.16533	0.21898
45		1	2	2	1	516.739	526.361	117.97	1.50	4.22102	0.16421
46		2	2	1	1	542.458	549.549	141.66	1.50	4.42775	0.15655
47		1	1	1	1	372.712	377.549	106.10	2.00	3.19356	0.21704
48		2	1	2	1	270.755	276.247	65.63	2.00	3.42972	0.20210
49		1	1	1	1	322.179	327.183	101.04	0.50	3.04245	0.22783
50		2	1	2	1	363.302	369.312	96.98	0.75	3.68652	0.18802
51		1	2	2	1	321.903	326.967	161.62	0.50	2.18022	0.31792
52		2	2	1	1	264.043	268.572	117.61	0.50	2.29139	0.30250
53		1	1	1	1	698.909	711.536	168.93	2.00	4.83551	0.14335
54		2	1	2	1	422.697	435.749	92.56	2.00	5.45024	0.12718
55		1	2	2	1	205.147	211.201	55.14	0.50	3.92164	0.17675
56		2	2	1	1	468.443	480.247	86.20	2.00	4.05049	0.17113
57		1	1	1	1	594.518	605.773	108.04	2.50	4.23995	0.16348
58		2	1	2	1	591.515	616.126	94.59	2.50	6.29472	0.11012
59		1	2	2	1	289.047	295.569	86.19	0.50	3.47741	0.19933
60		2	2	1	1	350.437	356.837	115.79	0.75	3.66631	0.18906
61		1	1	1	1	485.526	496.305	141.66	0.75	3.59225	0.19296
62		2	1	2	1	473.798	482.690	113.18	1.75	3.42419	0.20243

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
63	(b) (6)	1	2	2	1	271.795	275.854	90.80	0.50	2.32477	0.29816
64		2	2	1	1	171.213	179.374	66.85	0.50	2.85691	0.24262
65		1	1	1	1	407.777	415.356	114.11	1.00	3.41100	0.20321
66		2	1	2	1	375.596	381.280	132.66	1.00	3.33856	0.20762
67		1	1	1	1	391.688	400.070	92.68	0.50	3.26423	0.21235
68		2	1	2	1	266.938	274.008	75.49	0.75	3.31131	0.20933
69		1	2	2	1	317.415	326.418	118.10	1.25	3.52567	0.19660
70		2	2	1	1	288.029	294.220	67.33	0.50	3.86616	0.17929
71		1	1	1	1	64.845	.	3.55	24.00	.	.
72		2	1	2	1	53.178	.	4.84	3.00	.	.
73		1	1	1	1	292.708	297.959	69.53	0.75	3.43397	0.20185
74		2	1	2	1	248.439	253.764	63.17	0.75	3.48196	0.19907
75		1	2	2	1	693.207	699.711	246.19	1.25	2.98537	0.23218
76		2	2	1	1	354.622	360.092	101.68	0.50	3.10764	0.22305
77		1	2	2	1	219.242	224.806	76.91	0.75	3.16085	0.21929
78		2	2	1	1	204.462	210.038	86.65	0.75	3.19423	0.21700
79		1	1	1	1	148.445	152.758	96.60	0.50	2.21471	0.31297
80		2	1	2	1	94.332	98.884	37.86	0.75	2.40854	0.28779
81		1	2	2	1	261.223	267.002	92.74	0.75	3.42335	0.20248
82		2	2	1	1	388.174	395.725	78.66	2.50	4.63162	0.14966
83		1	1	1	1	430.110	441.209	139.10	1.50	4.18125	0.16578
84		2	1	2	1	319.879	327.890	91.86	2.00	3.99520	0.17350

Fasting BE study – Firm to reviewer ratios

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	1	1	1	376.515	386.132	73.09	A	376.670	389.82	73.09	1.00041	1.00955	1
2		1	2	1	2	368.618	375.622	67.05	B	369.070	378.59	67.05	1.00123	1.00790	1
3		2	1	1	2	414.404	423.443	113.93	B	414.400	431.19	113.93	0.99999	1.01830	1
4		2	2	1	1	697.603	707.995	158.47	A	697.600	712.49	158.47	1.00000	1.00635	1
5		2	1	1	2	320.144	326.208	104.52	B	320.140	325.37	104.52	0.99999	0.99743	1
6		2	2	1	1	338.343	345.969	110.40	A	338.340	345.49	110.40	0.99999	0.99862	1
7		2	1	1	2	533.222	539.043	162.00	B	534.030	541.60	162.00	1.00152	1.00474	1
8		2	2	1	1	487.382	495.011	151.20	A	483.180	494.64	151.20	0.99138	0.99925	1
9		2	1	1	2	425.107	429.632	152.20	B	425.110	430.08	152.20	1.00001	1.00104	1
10		2	2	1	1	365.869	372.330	133.10	A	361.810	368.55	133.10	0.98891	0.98985	1
11		1	1	1	1	278.787	283.249	86.54	A	278.790	284.41	86.54	1.00001	1.00410	1
12		1	2	1	2	273.569	279.915	83.83	B	273.570	284.59	83.83	1.00000	1.01670	1
13		1	1	1	1	195.034	201.438	66.16	A	195.030	202.66	66.16	0.99998	1.00607	1
14		1	2	1	2	382.003	387.625	166.63	B	382.020	391.85	166.63	1.00004	1.01090	1
15		1	1	1	1	458.627	465.758	125.78	A	458.900	469.36	125.78	1.00059	1.00773	1
16		1	2	1	2	505.584	514.631	147.55	B	506.220	518.52	147.55	1.00126	1.00756	1
17		2	1	1	2	169.062	175.374	85.31	B	169.060	175.74	85.31	0.99999	1.00208	1
18		2	2	1	1	221.329	226.051	104.30	A	221.490	228.41	104.30	1.00073	1.01044	1
19		1	1	1	1	344.174	349.300	154.05	A	344.650	350.24	154.05	1.00138	1.00269	1
20		1	2	1	2	267.151	272.733	101.49	B	267.140	277.15	101.49	0.99996	1.01620	1
21		2	1	1	2	457.722	465.925	172.88	B	458.010	473.05	172.88	1.00063	1.01529	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
22	(b) (6)	2	2	1	1	412.280	417.474	159.87	A	412.280	422.91	159.87	1.00000	1.01302	1
23		2	1	1	2	328.714	339.094	120.71	B	328.890	334.83	120.71	1.00054	0.98743	1
24		2	2	1	1	480.284	487.732	169.83	A	480.380	487.09	169.83	1.00020	0.99868	1
25		1	1	1	1	294.178	301.008	118.82	A	294.180	311.90	118.82	1.00001	1.03618	1
26		1	2	1	2	521.552	530.995	157.17	B	521.550	538.80	157.17	1.00000	1.01470	1
27		1	1	1	1	322.293	327.080	124.96	A	322.290	328.20	124.96	0.99999	1.00342	1
28		1	2	1	2	267.209	273.838	103.23	B	267.250	273.16	103.23	1.00015	0.99752	1
29		2	1	1	2	398.598	406.491	151.07	B	399.060	414.32	151.07	1.00116	1.01926	1
30		2	2	1	1	180.086	188.221	73.01	A	180.090	.	73.01	1.00002	.	1
31		2	1	1	2	12.999	.	2.40	B	12.999	.	2.40	1.00000	.	1
32		2	2	1	1	476.960	484.073	147.38	A	476.970	489.72	147.38	1.00002	1.01167	1
33		1	1	1	1	350.340	354.740	100.89	A	350.340	357.16	100.89	1.00000	1.00682	1
34		1	2	1	2	259.985	264.587	91.30	B	259.980	266.29	91.30	0.99998	1.00644	1
35		2	1	1	2	229.383	234.573	121.71	B	229.380	235.89	121.71	0.99999	1.00561	1
36		2	2	1	1	229.011	238.904	69.65	A	229.010	237.42	69.65	0.99999	0.99379	1
37		1	1	1	1	331.359	337.512	105.84	A	331.440	343.43	105.84	1.00024	1.01753	1
38		1	2	1	2	323.285	329.718	142.34	B	323.280	333.17	142.34	0.99999	1.01047	1
39		2	1	1	2	343.375	348.401	157.32	B	343.900	350.38	157.32	1.00153	1.00568	1
40		2	2	1	1	337.856	342.797	133.78	A	338.050	343.93	133.78	1.00057	1.00330	1
41		2	1	1	2	402.111	408.026	112.63	B	402.160	411.40	112.63	1.00012	1.00827	1
42		2	2	1	1	483.546	489.519	238.91	A	483.660	492.49	238.91	1.00024	1.00607	1
43		1	1	1	1	391.760	399.929	161.13	A	392.540	399.77	161.13	1.00199	0.99960	1
44		1	2	1	2	397.591	406.496	125.56	B	397.890	406.43	125.56	1.00075	0.99984	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
45	(b) (6)	2	1	1	2	542.458	549.549	141.66	B	542.460	549.65	141.66	1.00000	1.00018	1
46		2	2	1	1	516.739	526.361	117.97	A	517.280	529.76	117.97	1.00105	1.00646	1
47		1	1	1	1	372.712	377.549	106.10	A	372.500	377.45	106.10	0.99943	0.99974	1
48		1	2	1	2	270.755	276.247	65.63	B	270.760	282.27	65.63	1.00002	1.02180	1
49		1	1	1	1	322.179	327.183	101.04	A	322.180	333.69	101.04	1.00000	1.01989	1
50		1	2	1	2	363.302	369.312	96.98	B	363.300	373.21	96.98	0.99999	1.01055	1
51		2	1	1	2	264.043	268.572	117.61	B	264.270	270.71	117.61	1.00086	1.00796	1
52		2	2	1	1	321.903	326.967	161.62	A	321.900	329.21	161.62	0.99999	1.00686	1
53		1	1	1	1	698.909	711.536	168.93	A	698.910	711.57	168.93	1.00000	1.00005	1
54		1	2	1	2	422.697	435.749	92.56	B	423.020	435.77	92.56	1.00076	1.00005	1
55		2	1	1	2	468.443	480.247	86.20	B	468.440	486.41	86.20	0.99999	1.01283	1
56		2	2	1	1	205.147	211.201	55.14	A	205.150	214.61	55.14	1.00002	1.01614	1
57		1	1	1	1	594.518	605.773	108.04	A	595.120	609.89	108.04	1.00101	1.00680	1
58		1	2	1	2	591.515	616.126	94.59	B	591.520	616.99	94.59	1.00001	1.00140	1
59		2	1	1	2	350.437	356.837	115.79	B	350.570	361.78	115.79	1.00038	1.01385	1
60		2	2	1	1	289.047	295.569	86.19	A	289.070	301.43	86.19	1.00008	1.01983	1
61		1	1	1	1	485.526	496.305	141.66	A	485.530	507.38	141.66	1.00001	1.02231	1
62		1	2	1	2	473.798	482.690	113.18	B	473.800	489.49	113.18	1.00000	1.01409	1
63		2	1	1	2	171.213	179.374	66.85	B	171.210	178.73	66.85	0.99998	0.99641	1
64		2	2	1	1	271.795	275.854	90.80	A	271.800	277.60	90.80	1.00002	1.00633	1
65		1	1	1	1	407.777	415.356	114.11	A	407.780	422.55	114.11	1.00001	1.01732	1
66		1	2	1	2	375.596	381.280	132.66	B	375.790	387.17	132.66	1.00052	1.01545	1
67		1	1	1	1	391.688	400.070	92.68	A	391.690	408.99	92.68	1.00001	1.02230	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
68	(b) (6)	1	2	1	2	266.938	274.008	75.49	B	267.000	284.11	75.49	1.00023	1.03687	1
69		2	1	1	2	288.029	294.220	67.33	B	288.050	300.58	67.33	1.00007	1.02162	1
70		2	2	1	1	317.415	326.418	118.10	A	317.470	325.01	118.10	1.00017	0.99569	1
71		1	1	1	1	64.845	.	3.55	A	64.848	.	3.55	1.00005	.	1
72		1	2	1	2	53.178	.	4.84	B	53.178	.	4.84	1.00001	.	1
73		1	1	1	1	292.708	297.959	69.53	A	292.710	298.94	69.53	1.00001	1.00329	1
74		1	2	1	2	248.439	253.764	63.17	B	248.480	254.68	63.17	1.00017	1.00361	1
75		2	1	1	2	354.622	360.092	101.68	B	354.620	365.12	101.68	0.99999	1.01396	1
76		2	2	1	1	693.207	699.711	246.19	A	693.470	704.80	246.19	1.00038	1.00727	1
77		2	1	1	2	204.462	210.038	86.65	B	204.570	209.99	86.65	1.00053	0.99977	1
78		2	2	1	1	219.242	224.806	76.91	A	217.900	223.39	76.91	0.99388	0.99370	1
79		1	1	1	1	148.445	152.758	96.60	A	148.450	154.27	96.60	1.00003	1.00989	1
80		1	2	1	2	94.332	98.884	37.86	B	94.367	100.88	37.86	1.00037	1.02018	1
81		2	1	1	2	388.174	395.725	78.66	B	388.400	396.19	78.66	1.00058	1.00118	1
82		2	2	1	1	261.223	267.002	92.74	A	261.220	268.31	92.74	0.99999	1.00490	1
83		1	1	1	1	430.110	441.209	139.10	A	430.290	448.82	139.10	1.00042	1.01725	1
84		1	2	1	2	319.879	327.890	91.86	B	320.090	333.37	91.86	1.00066	1.01671	1

8.1.2 Fed Study Data with Original values for Code: D (reported in the current amendment) and repeat values for Codes F and H

Fed CONCENTRATION DATASET

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
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Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	(b) (6)	1	1	1	0	8.37	48.00	91.11	121.70	115.22	93.52	79.57	61.82	50.42	43.26	35.39	33.04	27.47	21.28	18.75
2		1	2	1	0	22.90	117.41	178.82	148.44	108.39	77.30	56.98	41.05	35.56	29.45	24.60	24.91	21.83	14.66	12.07
3		2	1	1	0	3.34	11.81	31.03	45.74	41.18	49.52	58.40	60.14	57.54	53.71	48.22	46.36	37.04	26.06	19.00
4		2	2	1	0	0.00	0.00	1.22	4.16	13.66	26.43	30.41	35.73	43.88	64.15	68.84	77.90	62.56	50.48	28.12
5		1	1	1	0	0.00	0.00	0.00	0.00	5.49	22.75	32.43	36.02	45.52	60.58	77.76	68.10	64.39	63.96	40.74
6		1	2	1	0	0.00	0.00	1.17	1.81	4.24	7.90	10.35	22.60	37.21	62.10	46.20	49.46	45.72	55.81	46.39
7		2	1	1	0	20.96	93.58	123.44	85.15	61.52	43.79	39.12	33.55	29.90	29.50	27.74	25.98	20.76	14.44	10.68
8		2	2	1	0	2.20	4.75	9.28	21.26	46.82	81.90	76.27	57.17	56.74	47.37	38.40	33.71	27.28	23.41	21.61
9		2	1	1	0	2.95	15.61	43.15	70.47	116.05	108.94	85.12	80.33	98.39	80.45	74.31	60.56	44.24	29.33	22.53
10		2	2	1	0	2.31	9.62	32.47	60.51	69.85	112.78	112.93	98.34	85.42	69.68	58.73	52.32	41.34	26.46	18.06
11		1	1	1	0	0.00	1.84	47.11	112.43	102.12	95.41	101.06	116.91	101.96	84.99	66.82	69.23	58.44	43.54	32.03
12		1	2	1	0	0.00	0.00	2.13	5.93	12.21	25.75	30.41	27.54	27.10	30.80	40.86	47.79	50.86	43.82	30.51
13		1	1	1	0	51.17	162.21	165.24	125.56	95.08	75.78	59.91	39.37	31.62	26.30	21.94	18.92	16.43	12.15	9.34
14		1	2	1	0	4.75	26.58	74.93	101.43	94.40	87.84	76.72	59.55	45.92	38.02	30.98	27.73	21.79	15.95	12.17
15		2	1	1	0	2.60	10.56	30.67	68.56	94.64	90.96	94.38	100.17	63.16	52.18	38.70	30.50	22.59	17.40	12.97
16		2	2	1	0	8.07	40.14	62.66	81.09	69.63	76.04	110.00	77.82	66.91	51.75	46.39	33.41	28.79	18.34	12.56
17		1	1	1	0	0.00	1.02	5.26	17.74	35.48	46.94	51.65	48.23	55.34	41.28	35.51	33.09	31.85	27.32	19.39
18		1	2	1	0	0.00	4.26	16.90	28.16	41.03	53.70	63.97	51.87	58.30	49.72	45.03	34.48	30.10	22.50	14.39
19		2	1	1	0	0.00	0.00	0.00	3.12	15.37	28.98	35.11	36.02	35.57	48.19	42.50	43.84	32.61	31.03	23.50
20		2	2	1	0	0.00	0.00	3.58	25.38	43.86	51.54	47.93	47.78	49.67	46.58	56.78	57.00	41.08	36.17	26.26
21		2	1	1	0	24.75	39.22	46.00	45.08	39.77	39.87	34.85	29.35	31.16	30.64	28.41	23.62	19.33	15.47	11.55
22		2	2	1	0	0.00	4.29	23.39	55.79	91.87	66.59	46.72	49.07	51.16	42.08	33.70	28.29	23.88	17.68	10.77
23		1	1	1	0	7.82	27.34	44.73	56.20	57.23	57.72	54.96	48.27	49.49	43.71	40.85	42.22	35.36	22.51	19.26
24		1	2	1	0	1.70	6.54	16.45	31.23	44.80	64.85	71.32	68.95	61.32	51.61	45.39	41.28	32.58	24.01	22.49
25		1	1	1	0	0.00	0.00	4.88	18.93	37.58	49.30	54.68	48.22	43.12	41.17	34.78	42.63	33.62	33.71	18.84
26		1	2	1	0	5.40	24.90	86.95	93.32	84.00	70.56	59.29	48.62	45.95	44.57	38.58	38.11	27.72	19.19	14.23

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
27	(b) (6)	2	1	1	0	0.00	5.64	62.60	136.06	122.09	92.61	94.32	89.50	84.72	61.91	49.48	46.08	34.53	26.92	19.83
28		2	2	1	0	127.13	203.16	173.55	15.41	115.93	103.03	85.48	60.40	47.46	37.32	30.54	26.68	23.16	17.34	14.88
29		2	1	1	0	2.17	5.83	10.22	12.58	12.39	24.69	27.94	29.66	26.34	25.96	31.45	38.23	34.18	33.54	28.19
30		2	2	1	0	2.28	4.83	9.85	17.58	20.59	22.05	23.14	20.80	18.50	20.61	32.27	34.82	30.54	31.15	25.76
31		2	1	1	0	3.78	6.93	21.68	46.61	70.35	80.23	66.64	51.02	42.20	39.98	41.47	35.17	28.16	20.91	15.18
32		2	2	1	0	25.03	70.13	102.44	80.70	58.87	59.80	65.29	57.24	45.64	40.57	31.99	28.06	22.50	17.96	13.77
33		1	1	1	0	0.00	0.00	4.77	25.53	62.00	94.75	92.61	65.00	55.46	50.24	45.36	38.28	28.19	20.84	15.79
34		1	2	1	0	35.35	106.05	114.34	92.06	70.42	52.50	46.66	37.86	31.31	25.87	22.97	18.68	16.42	11.01	8.73
35		1	1	1	0	25.86	94.06	215.30	194.66	165.18	119.78	112.27	111.47	107.62	101.31	105.08	99.50	81.84	50.46	38.41
36		1	2	1	0	9.92	36.50	45.86	52.51	68.81	83.19	88.56	80.79	75.02	107.09	99.58	86.97	67.04	59.74	56.40
37		2	1	1	0	1.19	4.42	13.67	50.03	65.28	76.08	74.93	59.31	51.59	41.32	36.71	37.36	30.16	21.79	15.94
38		2	2	1	0	13.72	41.67	56.13	52.73	38.27	33.90	27.86	22.15	19.40	16.56	15.42	14.99	12.12	9.85	7.19
39		2	1	1	0	41.06	140.96	181.79	161.95	107.78	91.10	92.17	60.73	49.21	38.17	35.67	31.50	25.02	21.75	17.81
40		2	2	1	0	0.00	3.61	42.46	96.32	134.67	135.95	109.17	91.64	69.94	62.51	53.66	46.04	35.63	24.84	19.26
41		2	1	1	0	0.00	1.46	4.82	7.77	20.87	49.79	72.24	70.09	53.78	40.61	40.82	36.24	39.72	28.05	24.62
42		2	2	1	0	6.35	17.63	51.86	73.71	81.98	59.27	42.73	45.39	38.15	38.18	36.26	36.20	25.64	17.18	12.37
43		1	1	1	0	32.37	98.93	118.37	120.12	95.99	85.28	76.07	62.49	63.71	56.60	49.24	45.09	36.32	23.16	17.54
44		1	2	1	0	0.00	0.00	0.00	1.35	17.53	35.50	55.63	70.02	78.16	93.22	105.05	74.59	55.42	34.61	25.50
45		1	1	1	0	1.57	6.10	14.01	34.43	58.17	61.96	48.20	38.66	35.13	32.01	28.39	28.27	22.05	17.11	13.08
46		1	2	1	0	0.00	2.25	3.92	11.08	37.77	62.82	63.06	50.90	54.97	48.11	41.20	37.01	34.20	26.11	19.95
47		1	1	1	0	0.00	1.96	6.55	11.99	38.57	61.69	62.15	52.06	58.70	50.64	55.21	56.42	36.20	17.75	13.16
48		1	2	1	0	0.00	2.01	10.29	29.24	52.46	106.44	84.64	59.14	62.70	56.36	52.47	41.11	23.12	15.59	11.72
49		1	1	1	0	1.88	21.44	79.02	103.26	130.22	114.87	102.63	71.06	65.65	55.81	54.77	48.61	36.75	28.04	19.55
50		1	2	1	0	0.00	1.11	5.70	17.63	42.62	85.65	98.04	106.09	117.86	102.88	88.30	78.09	54.41	37.78	26.22
51		2	1	1	0	0.00	0.00	0.00	2.68	10.67	50.28	68.59	60.99	46.86	40.71	31.26	34.60	40.67	42.51	23.57
52		2	2	1	0	0.00	10.50	57.70	89.24	82.12	65.11	48.47	44.83	38.91	45.91	36.29	34.35	36.17	22.53	16.27

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
53	(b) (6)	2	1	1	0	2.39	10.55	61.38	109.58	125.02	123.78	94.93	56.71	47.92	41.75	34.97	36.59	33.58	22.66	16.43
54		2	2	1	0	11.50	27.72	38.57	57.85	76.80	89.71	79.29	71.29	57.38	48.20	35.89	32.98	29.47	22.42	15.59
55		2	1	1	0	1.05	5.50	20.16	30.05	33.53	56.73	50.64	49.72	42.13	34.66	30.28	30.59	28.39	19.15	13.47
56		2	2	1	0	61.80	93.70	69.24	47.16	36.54	35.52	35.19	32.20	31.43	27.68	23.73	17.41	15.60	11.09	8.60
57		1	1	1	0	19.69	72.45	118.28	136.04	162.91	137.93	123.56	121.31	100.18	82.32	78.26	70.92	52.25	44.22	33.48
58		1	2	1	0	0.00	2.53	5.76	9.34	14.82	36.04	50.71	63.68	78.18	67.06	71.59	77.30	68.95	49.44	38.62
59		1	1	1	0	36.06	69.23	79.16	63.41	53.92	53.36	52.72	46.75	40.37	33.78	31.17	30.67	25.44	17.15	15.98
60		1	2	1	0	0.00	0.00	4.01	33.61	55.63	65.81	54.96	36.52	31.18	40.38	40.51	51.96	43.33	25.31	18.74
61		2	1	1	0	0.00	4.44	30.70	67.32	63.89	61.55	67.05	53.14	48.50	42.59	38.68	33.20	28.55	25.61	19.39
62		2	2	1	0	0.00	1.60	3.04	6.93	16.12	33.12	37.56	45.45	67.92	81.09	70.09	61.20	52.62	32.95	23.81
63		2	1	1	0	80.99	99.59	148.35	151.11	149.73	142.31	116.23	81.27	69.35	55.58	48.00	43.86	35.78	29.12	25.92
64		2	2	1	0	39.64	115.10	144.33	158.57	155.04	132.37	110.24	87.06	65.59	54.98	47.88	43.53	35.89	32.37	23.00
65		2	1	1	0	11.93	25.64	28.26	21.39	20.90	23.50	19.77	19.25	15.70	12.76	11.05	9.77	7.80	6.27	4.65
66		2	2	1	0	0.00	0.00	3.39	18.88	41.37	47.07	52.40	52.32	51.85	53.81	44.83	49.52	39.24	34.01	19.86
67		1	1	1	0	0.00	0.00	0.00	1.46	6.03	18.28	20.83	20.13	22.59	27.72	26.58	33.50	27.01	19.26	15.11
68		1	2	1	0	1.59	18.06	55.64	74.28	62.26	57.88	45.63	39.77	37.29	31.26	34.43	30.64	24.99	17.63	11.53
69		1	1	1	0	0.00	0.00	1.80	13.59	23.87	60.27	67.13	76.53	72.79	48.24	44.24	37.53	35.29	32.77	26.65
70		1	2	1	0	0.00	0.00	0.00	0.00	1.21	9.50	21.21	68.48	81.45	89.28	64.60	55.91	38.47	33.88	41.88
71		2	1	1	0	8.53	52.59	135.36	149.43	122.28	132.41	147.01	123.81	105.96	86.31	71.40	60.45	51.69	37.28	31.34
72		2	2	1	0	14.53	83.94	281.72	260.06	193.49	149.91	139.16	107.67	89.58	73.67	59.65	55.00	44.30	36.02	29.96
73	1	1	1	0	0.00	0.00	0.00	2.50	11.49	18.41	31.92	27.72	63.58	68.59	70.78	96.26	65.94	47.46	33.53	
74	1	2	1	0	0.00	0.00	0.00	0.00	20.99	33.52	46.43	64.10	78.27	94.01	72.51	81.07	67.76	38.46	28.75	
75	2	1	1	0	0.00	0.00	6.47	64.50	81.98	83.40	72.21	63.93	47.13	38.85	35.21	30.52	21.40	17.88	16.38	
76	2	2	1	0	0.00	0.00	1.16	9.21	85.56	131.30	111.31	91.00	75.73	86.70	60.63	39.37	30.75	23.86	19.53	
77	2	1	1	0	0.00	0.00	4.52	10.12	18.98	57.72	61.57	44.12	33.91	28.44	26.95	40.82	34.20	23.44	15.43	
78	2	2	1	0	6.43	23.19	43.42	85.35	75.94	69.02	59.89	61.07	45.46	42.35	35.96	30.70	26.69	18.68	13.23	

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
79	(b) (6)	1	1	1	0	5.32	13.31	19.29	22.36	30.59	41.47	40.49	32.83	33.69	31.62	37.58	41.42	50.74	46.46	36.00
80		1	2	1	0	0.00	3.23	8.11	13.74	34.51	57.77	96.52	98.70	83.93	80.13	74.67	63.56	47.59	33.46	23.93
81		1	1	1	0	1.86	20.95	129.27	153.06	86.22	75.34	74.85	52.12	42.13	32.23	27.20	22.24	18.01	14.85	10.68
82		1	2	1	0	1.13	4.07	11.22	31.26	54.95	54.74	60.00	61.78	64.92	48.99	39.15	34.47	25.52	18.50	13.77
83		2	1	1	0	23.83	59.34	96.23	141.08	126.53	146.70	146.62	140.01	128.15	112.61	110.76	102.37	81.10	66.57	49.03
84		2	2	1	0	74.62	138.09	169.14	169.34	133.56	116.70	98.20	79.10	64.32	55.94	52.18	42.61	39.06	29.87	21.54
85		1	1	1	0	0.00	3.28	13.91	28.79	50.52	64.24	65.98	51.50	45.07	41.20	39.89	42.13	40.96	29.83	22.58
86		1	2	1	0	3.59	12.04	39.85	73.95	79.19	77.63	58.96	43.57	38.85	31.72	32.17	28.22	24.95	18.79	14.93
87		2	1	1	0	2.80	57.08	146.73	144.46	98.39	79.18	68.12	58.10	52.66	46.54	39.90	38.50	29.09	23.02	18.25
88		2	2	1	0	0.00	0.00	0.00	1.02	1.81	2.92	3.17	6.36	41.57	55.23	111.93	134.48	81.93	68.92	38.54
89		1	1	1	0	0.00	0.00	1.07	5.16	18.71	59.25	77.46	67.62	70.18	62.14	47.62	48.73	37.75	27.07	20.04
90		1	2	1	0	14.38	60.77	88.60	139.79	90.91	78.42	76.37	76.37	67.70	54.98	41.42	36.06	30.10	19.15	16.53
91		1	1	1	0	0.00	0.00	0.00	3.92	13.40	29.46	47.50	47.33	43.81	42.75	44.25	45.82	42.78	43.53	37.65
92		1	2	1	0	0.00	1.31	9.81	33.68	74.83	79.27	63.82	53.38	56.10	73.49	65.17	61.01	53.54	57.98	42.85
93		2	1	1	0	13.76	36.01	55.20	51.72	50.55	55.41	54.49	56.12	49.04	49.81	45.32	40.21	40.36	26.16	20.88
94		2	2	1	0	2.77	4.38	8.79	19.41	38.77	42.45	38.42	35.81	42.99	53.40	53.25	52.50	46.28	31.97	30.01
95		2	1	1	0	5.94	18.65	33.00	42.69	41.45	43.15	45.81	54.63	59.01	50.76	47.69	48.82	43.42	40.73	32.32
96		2	2	1	0	3.19	7.36	28.64	79.92	76.90	71.48	71.97	73.08	68.36	65.07	56.30	57.69	53.60	41.82	33.88
97		1	1	1	0	11.83	25.26	48.26	57.04	64.59	57.37	48.10	35.50	32.95	30.91	28.17	34.35	22.77	15.44	12.17
98		1	2	1	0	0.00	0.00	0.00	3.75	14.30	74.43	96.43	69.13	51.83	43.13	34.57	41.33	36.06	23.59	15.33
99		2	1	1	0	2.15	6.33	20.51	27.23	24.21	49.97	59.59	49.13	41.27	36.86	33.01	36.64	33.02	23.40	17.67
100		2	2	1	0	1.89	7.02	14.84	25.86	82.92	96.90	83.43	65.57	58.96	51.37	47.55	51.74	49.11	31.32	24.80
101		2	1	1	0	10.71	18.50	24.92	20.96	13.09	11.41	9.13	7.28	6.44	5.61	4.77	4.55	3.90	3.44	3.17
102		2	2	1	0	0.00	0.00	1.31	4.92	18.08	65.61	96.10	83.69	73.45	69.50	62.29	72.06	54.80	41.19	26.44
103		1	1	1	0	0.00	0.00	0.00	1.44	4.24	5.12	8.81	13.53	20.68	50.54	60.79	62.72	48.77	38.79	29.11
104		1	2	1	0	4.12	17.98	32.45	42.90	35.19	32.23	34.19	48.08	52.06	51.51	48.17	48.61	42.29	32.44	23.76

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
1	12.15	6.56	3.67	1.96	1.31	17	21	1
2	8.57	5.17	3.54	1.98	1.92	17	20	2
3	11.45	6.33	3.27	1.84	1.59	17	20	2
4	18.56	10.74	5.02	2.44	2.31	17	20	1
5	22.19	11.65	4.78	2.65	1.81	18	21	1
6	28.77	13.71	5.56	2.88	2.17	18	21	2
7	6.17	3.20	1.64	0.00	0.00	16	19	2
8	12.07	5.25	2.39	1.48	1.08	18	21	1
9	14.84	8.03	3.56	2.12	1.64	18	21	2
10	12.74	5.70	2.79	1.63	1.24	18	21	1
11	20.37	12.90	7.15	4.45	2.91	17	21	1
12	24.42	14.51	6.23	3.83	3.32	17	20	2
13	6.75	4.19	2.24	1.42	1.08	17	20	1
14	8.27	5.18	2.89	2.19	1.93	17	20	2
15	8.19	3.81	1.95	1.18	0.00	17	20	2
16	9.37	4.68	2.11	1.14	1.02	17	20	1
17	12.21	5.78	3.50	1.89	1.30	18	21	1
18	10.71	6.25	2.46	1.53	1.07	18	21	2
19	16.96	8.06	3.15	1.62	1.30	17	20	2
20	15.41	7.17	3.16	2.05	1.35	18	21	1
21	7.55	3.46	1.62	1.03	0.00	17	20	2
22	7.90	4.20	1.89	1.02	0.00	17	20	1
23	11.12	5.52	2.79	1.60	1.33	17	20	1
24	12.16	6.00	3.42	1.85	1.47	18	21	2
25	11.11	5.60	2.46	1.56	1.10	18	21	1
26	8.83	4.90	2.60	1.74	1.67	17	20	2

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
27	15.59	7.84	3.37	2.21	1.59	18	21	2
28	9.80	5.19	3.09	1.77	1.43	18	21	1
29	26.02	16.82	7.33	4.12	3.56	17	20	2
30	30.30	21.98	8.31	4.93	4.09	18	21	1
31	10.07	6.32	3.32	2.26	1.79	18	21	2
32	9.04	5.94	3.29	2.38	1.90	17	20	1
33	10.26	5.26	2.90	2.02	1.61	18	21	1
34	6.39	3.69	2.30	1.85	1.84	18	21	2
35	26.48	11.51	6.50	4.20	3.93	18	21	1
36	30.09	15.07	7.99	4.51	3.98	17	20	2
37	9.73	5.38	2.88	2.12	1.52	18	21	2
38	6.08	3.97	3.03	1.83	1.83	17	21	1
39	13.85	8.04	4.54	3.19	2.72	18	21	2
40	13.14	8.46	4.42	3.24	2.59	18	21	1
41	12.18	5.99	2.57	1.63	0.00	17	20	2
42	8.77	5.22	2.52	1.55	1.17	18	21	1
43	11.52	7.19	3.84	2.53	1.90	18	21	1
44	17.58	8.96	4.20	2.96	2.10	18	21	2
45	10.48	7.18	4.78	3.37	3.08	18	21	1
46	11.95	7.23	4.37	3.04	2.58	18	21	2
47	7.80	4.63	2.72	2.01	1.62	18	21	1
48	7.08	4.12	2.08	1.46	1.28	17	20	2
49	13.74	8.56	4.97	2.79	2.04	17	21	1
50	16.21	10.35	5.13	2.93	2.41	18	21	2
51	11.60	5.89	2.60	1.46	1.02	18	21	2
52	9.08	5.26	2.41	1.48	1.60	17	20	1

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
53	9.46	5.53	2.34	1.42	1.04	18	21	2
54	9.03	4.91	2.55	1.43	1.17	17	20	1
55	8.42	4.15	2.34	1.42	1.31	17	20	2
56	6.88	3.84	2.41	1.86	1.80	18	21	1
57	20.86	12.77	6.66	3.75	2.71	17	21	1
58	23.05	12.10	5.65	3.54	3.38	17	20	2
59	10.50	6.55	3.21	2.31	2.10	17	20	1
60	11.71	6.73	3.38	2.43	2.80	17	20	2
61	11.56	7.90	3.28	2.09	1.50	18	21	2
62	13.55	7.19	3.82	2.38	1.95	18	21	1
63	16.57	7.86	3.78	2.12	1.58	17	20	2
64	13.53	8.76	4.25	2.69	2.10	18	21	1
65	3.34	2.81	2.09	2.04	1.82	16	19	2
66	12.41	7.71	4.22	3.02	2.00	17	20	1
67	15.09	7.18	3.65	2.21	1.49	18	21	1
68	7.76	4.65	1.98	1.26	1.10	17	20	2
69	13.26	6.14	3.30	1.87	1.52	18	21	1
70	14.22	7.15	3.46	2.09	1.41	18	21	2
71	21.99	14.14	7.10	4.39	3.58	18	21	2
72	23.84	14.70	8.63	5.57	3.78	18	21	1
73	30.40	12.94	5.95	3.52	2.47	18	21	1
74	17.73	11.20	5.43	2.83	2.18	17	21	2
75	9.76	7.05	4.02	2.86	2.84	17	20	2
76	11.30	7.97	4.23	2.43	2.35	17	20	1
77	9.26	6.08	2.70	1.82	2.07	17	20	2
78	8.57	4.98	2.29	1.74	1.37	18	21	1

Obs	c17	c18	c19	c20	c21	KE_FIRST	KE_LAST	trt
79	22.50	9.74	4.72	2.83	2.35	18	21	1
80	14.92	7.59	3.66	2.54	1.85	18	21	2
81	6.18	3.47	1.69	1.16	0.00	17	20	1
82	7.48	4.15	2.05	1.31	1.12	17	20	2
83	28.61	19.57	9.38	7.21	6.88	17	20	2
84	16.34	12.38	8.13	6.54	8.24	17	20	1
85	12.89	6.74	3.39	2.37	1.72	18	21	1
86	8.36	4.83	2.85	1.71	1.58	17	20	2
87	12.85	8.00	3.85	2.13	1.65	17	20	2
88	24.20	14.36	6.03	3.16	1.93	17	21	1
89	10.90	6.20	3.17	1.73	1.31	17	20	1
90	11.58	6.11	3.30	2.39	2.13	17	20	2
91	25.64	14.38	7.43	4.77	3.59	18	21	1
92	27.00	14.46	8.37	4.57	2.92	18	21	2
93	12.16	7.01	4.05	2.45	1.92	18	21	2
94	15.54	8.81	5.18	3.17	2.20	18	21	1
95	14.87	9.13	4.83	2.72	2.21	17	21	2
96	22.94	10.70	5.42	3.41	2.79	17	20	1
97	7.62	5.07	3.15	2.24	1.78	18	21	1
98	8.68	6.18	2.87	2.03	2.02	17	20	2
99	10.76	6.55	3.63	2.55	2.19	17	20	2
100	14.62	8.35	4.14	2.91	2.50	18	21	1
101	2.41	1.91	1.45	1.27	1.74	16	19	2
102	14.82	7.74	3.76	2.25	1.94	17	20	1
103	17.70	8.12	3.62	2.03	1.29	18	21	1
104	14.37	7.18	3.16	1.88	1.36	18	21	2

Fed STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	52	(b) (6)
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	104
Number of Observations Used	104

Data for Analysis of AUCI LAUCI	
Number of Observations Read	104
Number of Observations Used	103

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	53	9.12844380	0.17223479	3.37	<.0001
Error	50	2.55554472	0.05111089		

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Corrected Total	103	11.68398851			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.781278	3.785820	0.226077	5.971683

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.04271199	0.04271199	0.84	0.3650
sub(seq)	50	8.83794849	0.17675897	3.46	<.0001
per	1	0.12925063	0.12925063	2.53	0.1181
trt	1	0.11853269	0.11853269	2.32	0.1341

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.04271199	0.04271199	0.84	0.3650
sub(seq)	50	8.83794849	0.17675897	3.46	<.0001
per	1	0.11972061	0.11972061	2.34	0.1322
trt	1	0.11853269	0.11853269	2.32	0.1341

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.04271199	0.04271199	0.24	0.6252

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.06756999	0.04437021	1.52	0.1341

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	53	7.90428058	0.14913737	8.10	<.0001
Error	49	0.90182015	0.01840449		
Corrected Total	102	8.80610073			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.897591	2.248349	0.135663	6.033902

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00117165	0.00117165	0.06	0.8019
sub(seq)	50	7.83376923	0.15667538	8.51	<.0001
per	1	0.04090364	0.04090364	2.22	0.1424
trt	1	0.02843606	0.02843606	1.55	0.2198

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00074665	0.00074665	0.04	0.8412
sub(seq)	50	7.82429235	0.15648585	8.50	<.0001
per	1	0.03956166	0.03956166	2.15	0.1490
trt	1	0.02843606	0.02843606	1.55	0.2198

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00074665	0.00074665	0.00	0.9452

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.03340013	0.02687047	1.24	0.2198

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	53	15.62710187	0.29485098	3.18	<.0001
Error	50	4.63883946	0.09277679		
Corrected Total	103	20.26594133			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.771102	6.853568	0.304593	4.444296

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00629713	0.00629713	0.07	0.7955
sub(seq)	50	14.99811375	0.29996227	3.23	<.0001
per	1	0.41719555	0.41719555	4.50	0.0389
trt	1	0.20549544	0.20549544	2.21	0.1430

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00629713	0.00629713	0.07	0.7955

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sub(seq)	50	14.99811375	0.29996227	3.23	<.0001
per	1	0.39437598	0.39437598	4.25	0.0444
trt	1	0.20549544	0.20549544	2.21	0.1430

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00629713	0.00629713	0.02	0.8854

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.08896842	0.05977980	1.49	0.1430

Ratio of Sponsor/Reviewer calculated parameters

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
1	(b) (6)	1	1	1	1.00	1.00	1	1.00
2		2	2	1	1.00	1.00	1	1.00
3		1	1	1	1.00	1.00	1	1.00
4		2	2	1	1.00	1.00	1	1.00
5		2	2	1	1.00	1.00	1	1.00
6		1	1	1	1.00	1.00	1	1.00
7		1	1	1	1.00	1.00	1	1.00
8		2	2	1	1.00	1.00	1	1.00
9		1	1	1	1.00	1.00	1	1.00
10		2	2	1	1.00	1.00	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
11	(b) (6)	2	2	1	1.00	1.00	1	1.00
12		1	1	1	1.00	1.00	1	1.00
13		1	1	1	1.00	1.00	1	1.00
14		2	2	1	1.00	1.00	1	1.00
15		2	2	1	1.00	1.00	1	1.00
16		2	2	1	1.00	1.00	1	1.00
17		1	1	1	1.00	1.00	1	1.00
18		1	1	1	1.00	1.00	1	1.00
19		2	2	1	1.00	1.00	1	1.00
20		2	2	1	1.00	1.00	1	1.00
21		2	2	1	1.00	1.00	1	1.00
22		1	1	1	1.00	1.00	1	1.00
23		1	1	1	1.00	1.00	1	1.00
24		1	1	1	1.00	1.00	1	1.00
25		1	1	1	1.00	1.00	1	1.00
26		2	2	1	1.00	1.00	1	1.00
27		2	2	1	1.00	1.00	1	1.00
28		2	2	1	1.00	1.00	1	1.00
29		1	1	1	1.00	1.00	1	1.02
30		1	1	1	1.00	1.00	1	1.00
31		2	2	1	1.00	1.00	1	1.00
32		2	2	1	1.00	1.00	1	1.00
33		2	2	1	1.00	1.00	1	1.00
34		1	1	1	1.00	1.00	1	1.00
35		1	1	1	1.00	1.00	1	1.00
36		2	2	1	1.00	1.00	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
37	(b) (6)	1	1	1	1.00	1.00	1	1.00
38		2	2	1	1.00	1.00	1	1.00
39		2	2	1	1.00	1.00	1	1.00
40		1	1	1	1.00	1.00	1	1.00
41		1	1	1	1.00	1.00	1	1.00
42		2	2	1	1.00	1.00	1	1.00
43		1	1	1	1.00	1.00	1	1.00
44		2	2	1	1.00	1.00	1	1.00
45		1	1	1	1.00	1.00	1	1.00
46		1	1	1	1.00	1.00	1	1.00
47		2	2	1	1.00	1.00	1	1.00
48		2	2	1	1.00	1.00	1	1.00
49		1	1	1	1.00	1.00	1	1.00
50		2	2	1	1.00	1.00	1	1.00
51		2	2	1	1.00	1.00	1	1.00
52		1	1	1	1.00	1.00	1	1.00
53		1	2	2	1.00	1.00	1	1.00
54		2	1	2	1.00	1.00	1	1.00
55		1	2	2	1.00	1.00	1	1.00
56		2	1	2	1.00	1.00	1	1.00
57		2	1	2	1.00	1.00	1	1.00
58		1	2	2	1.00	1.00	1	1.00
59		1	2	2	1.00	1.00	1	1.00
60		2	1	2	1.00	1.00	1	1.00
61		1	2	2	1.00	1.00	1	1.00
62		2	1	2	1.00	1.00	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
63	(b) (6)	2	1	2	1.00	1.00	1	1.00
64		1	2	2	1.00	1.00	1	1.00
65		1	2	2	1.00	1.00	1	1.00
66		2	1	2	1.00	1.00	1	1.00
67		2	1	2	1.00	1.00	1	1.00
68		2	1	2	1.00	1.00	1	1.00
69		1	2	2	1.00	1.00	1	1.00
70		1	2	2	1.00	1.00	1	1.00
71		2	1	2	1.00	1.00	1	1.00
72		2	1	2	1.00	1.00	1	1.00
73		2	1	2	1.00	1.00	1	1.00
74		1	2	2	1.00	1.00	1	1.00
75		1	2	2	1.00	1.00	1	1.00
76		1	2	2	1.00	1.00	1	1.00
77		1	2	2	1.00	1.00	1	1.00
78		2	1	2	1.00	1.00	1	1.00
79		2	1	2	1.00	1.00	1	1.02
80		2	1	2	1.00	1.00	1	1.00
81		1	2	2	1.00	1.00	1	1.00
82		1	2	2	1.00	1.00	1	1.00
83		2	1	2	1.00	1.00	1	1.00
84		2	1	2	0.99	0.99	1	1.00
85		2	1	2	1.00	1.00	1	1.00
86		1	2	2	1.00	1.00	1	1.00
87		1	2	2	1.00	1.00	1	1.00
88		2	1	2	1.00	1.00	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMA XO_N	TMAXO_N
89	(b) (6)	1	2	2	1.00	1.00	1	1.00
90		2	1	2	1.00	1.00	1	1.00
91		2	1	2	1.00	1.00	1	1.00
92		1	2	2	1.00	1.00	1	1.00
93		1	2	2	1.00	1.00	1	1.00
94		2	1	2	1.00	1.00	1	1.00
95		1	2	2	1.00	1.00	1	1.00
96		2	1	2	1.01	1.01	1	1.00
97		1	2	2	0.99	0.99	1	1.00
98		1	2	2	1.00	1.00	1	1.00
99		2	1	2	1.00	1.00	1	1.00
100		2	1	2	1.00	1.00	1	1.00
101		1	2	2	0.99	0.99	1	1.00
102		2	1	2	1.00	1.00	1	1.00
103		2	1	2	1.01		1	1.00
104		1	2	2	1.00	1.00	1	1.01

8.2 Results of Lund's test

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Obs	SUBJECT	SEQUENCE	PERIOD	FORM	CMA X	AUCOT	AUCINF
1	(b) (6)	1	1	A	73.09	376.52	386.13
2		2	2	A	158.47	697.60	708.00

3	(b) (6)	2	2	A	110.40	338.34	345.97
4	(b) (6)	2	2	A	151.20	487.38	495.01
5	(b) (6)	2	2	A	133.10	365.87	372.33
6	(b) (6)	1	1	A	86.54	278.79	283.25
7	(b) (6)	1	1	A	66.16	195.03	201.44
8	(b) (6)	1	1	A	125.78	458.63	465.76
9	(b) (6)	2	2	A	104.30	221.33	226.05
10	(b) (6)	1	1	A	154.05	344.17	349.30
11	(b) (6)	2	2	A	159.87	412.28	417.47
12	(b) (6)	2	2	A	169.83	480.28	487.73
13	(b) (6)	1	1	A	118.82	294.18	301.01
14	(b) (6)	1	1	A	124.96	322.29	327.08
15	(b) (6)	2	2	A	73.01	180.09	188.22
16	(b) (6)	2	2	A	147.38	476.96	484.07
17	(b) (6)	1	1	A	100.89	350.34	354.74
18	(b) (6)	2	2	A	69.65	229.01	238.90
19	(b) (6)	1	1	A	105.84	331.36	337.51
20	(b) (6)	2	2	A	133.78	337.86	342.80
21	(b) (6)	2	2	A	238.91	483.55	489.52
22	(b) (6)	1	1	A	161.13	391.76	399.93
23	(b) (6)	2	2	A	117.97	516.74	526.36
24	(b) (6)	1	1	A	106.10	372.71	377.55
25	(b) (6)	1	1	A	101.04	322.18	327.18
26	(b) (6)	2	2	A	161.62	321.90	326.97
27	(b) (6)	1	1	A	168.93	616.84	629.37
28	(b) (6)	2	2	A	55.14	205.15	211.20

Obs	lauct	laucinf	lcmax	stlauct	stlauci	stlcmax
1	5.93097	5.95617	4.29169	0.04279	0.11506	0.09995
2	6.54765	6.56244	5.06557	0.57173	1.15594	0.27188
3	5.82405	5.84635	4.70411	0.05452	0.10327	0.00599
4	6.18904	6.20458	5.01860	-0.10678	-0.22977	-0.11354
5	5.90228	5.91978	4.89110	-0.17364	-0.36374	-0.17643
6	5.63046	5.64633	4.46061	0.04023	0.07863	0.04736
7	5.27315	5.30549	4.19208	-0.72768	-1.46042	-0.87568
8	6.12824	6.14367	4.83453	-0.08905	-0.17912	-0.13758
9	5.39965	5.42076	4.64727	0.29240	0.55431	0.14726

10	5.84114	5.85593	5.03728	0.30068	0.62282	0.41977
11	6.02170	6.03421	5.07436	-0.12307	-0.28669	-0.12247
12	6.17437	6.18976	5.13480	0.41439	0.80784	0.28292
13	5.68419	5.70714	4.77761	-0.61696	-1.25962	-0.25358
14	5.77545	5.79020	4.82799	0.22746	0.46164	0.20117
15	5.19346	5.23761	4.29060	-0.88962	-1.81319	-0.74933
16	6.16743	6.18223	4.99301	3.99555	.	3.93076
17	5.85890	5.87139	4.61403	0.35061	0.72849	0.11312
18	5.43377	5.47605	4.24348	-0.00870	0.00957	-0.58608
19	5.80321	5.82160	4.66193	0.04662	0.10525	-0.26959
20	5.82263	5.83715	4.89620	-0.02491	-0.07020	-0.20347
21	6.18115	6.19343	5.47609	0.19800	0.38833	0.67954
22	5.97065	5.99129	5.08221	0.00282	0.01369	0.25758
23	6.24754	6.26599	4.77043	-0.06088	-0.13243	-0.22367
24	5.92080	5.93370	4.66438	0.37428	0.77282	0.48066
25	5.77511	5.79051	4.61552	-0.11423	-0.22843	0.05625
26	5.77424	5.78987	5.08525	0.21323	0.42226	0.26019
27	6.42461	6.44472	5.12948	0.43914	0.90043	0.59782
28	5.32374	5.35281	4.00988	-0.92425	-1.93240	-0.47850

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Obs	SUBJECT	SEQUENCE	PERIOD	FORM	CMAx	AUCOT	AUCINF
29	(b) (6)	1	1	A	108.04	594.52	605.77
30	(b) (6)	2	2	A	86.19	289.05	295.57
31	(b) (6)	1	1	A	141.66	485.53	496.31
32	(b) (6)	2	2	A	90.80	271.80	275.85
33	(b) (6)	2	2	A	1.85	11.84	.
34	(b) (6)	1	1	A	114.11	407.78	415.36
35	(b) (6)	1	1	A	92.68	391.69	400.07
36	(b) (6)	2	2	A	118.10	317.42	326.42
37	(b) (6)	1	1	A	3.55	64.85	.
38	(b) (6)	1	1	A	69.53	292.71	297.96
39	(b) (6)	2	2	A	246.19	693.21	699.71
40	(b) (6)	1	1	A	8.94	34.28	41.60
41	(b) (6)	2	2	A	76.91	219.24	224.81
42	(b) (6)	1	1	A	96.60	148.45	152.76
43	(b) (6)	2	2	A	92.74	261.22	267.00
44	(b) (6)	1	1	A	139.10	430.11	441.21
45	(b) (6)	1	2	B	67.05	368.62	375.62
46	(b) (6)	2	1	B	113.93	414.40	423.44
47	(b) (6)	2	1	B	104.52	320.14	326.21
48	(b) (6)	2	1	B	162.00	533.22	539.04
49	(b) (6)	2	1	B	152.20	425.11	429.63
50	(b) (6)	1	2	B	83.83	273.57	279.92
51	(b) (6)	1	2	B	166.63	382.00	387.63
52	(b) (6)	1	2	B	147.55	505.58	514.63
53	(b) (6)	2	1	B	85.31	169.06	175.37
54	(b) (6)	1	2	B	101.49	267.15	272.73
55	(b) (6)	2	1	B	172.88	457.72	465.93
56	(b) (6)	2	1	B	120.71	328.71	339.09

Obs	lauct	laucinf	lcmax	stlauct	stlauci	stlcmax
29	6.38775	6.40650	4.68250	0.02485	0.01216	0.14506

30	5.66660	5.68891	4.45655	-0.22088	-0.46835	-0.33208
31	6.18524	6.20720	4.95343	0.04640	0.11559	0.23345
32	5.60507	5.61986	4.50866	0.50658	0.96256	0.24892
33	2.47148	.	0.61519	-4.17620	.	-4.09530
34	6.01073	6.02915	4.73716	0.11056	0.24905	-0.12888
35	5.97047	5.99164	4.52915	0.44525	0.92543	0.21481
36	5.76023	5.78818	4.77153	0.10104	0.20744	0.49595
37	4.17208	.	1.26695	0.23965	.	-0.28281
38	5.67918	5.69696	4.24176	0.20142	0.42217	0.10930
39	6.54133	6.55067	5.50610	0.73780	1.50346	0.80734
40	3.53456	3.72810	2.19054	-2.21605	-4.18839	-2.36713
41	5.39017	5.41526	4.34264	0.07064	0.12442	-0.16208
42	5.00025	5.02887	4.57058	0.52302	1.05589	0.92149
43	5.56536	5.58725	4.52980	-0.44696	-0.94264	0.11218
44	6.06404	6.08952	4.93519	0.34820	0.73689	0.41746
45	5.90977	5.92858	4.20544	-0.04279	-0.11506	-0.09995
46	6.02683	6.04841	4.73558	-0.57173	-1.15594	-0.27188
47	5.76876	5.78754	4.64938	-0.05452	-0.10327	-0.00599
48	6.27893	6.28979	5.08760	0.10678	0.22977	0.11354
49	6.05235	6.06292	5.02520	0.17364	0.36374	0.17643
50	5.61156	5.63450	4.42879	-0.04023	-0.07863	-0.04736
51	5.94542	5.96005	5.11578	0.72768	1.46042	0.87568
52	6.22571	6.24345	4.99417	0.08905	0.17912	0.13758
53	5.13025	5.16690	4.44629	-0.29240	-0.55431	-0.14726
54	5.58781	5.60848	4.61996	-0.30068	-0.62282	-0.41977
55	6.12626	6.14404	5.15260	0.12307	0.28669	0.12247
56	5.79518	5.82627	4.79339	-0.41439	-0.80784	-0.28292

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Obs	SUBJECT	SEQUENCE	PERIOD	FORM	CMAX	AUC0T	AUCINF
	(b) (6)						
57		1	2	B	157.17	521.55	531.00
58		1	2	B	103.23	267.21	273.84
59		2	1	B	151.07	398.60	406.49
60		2	1	B	2.40	13.00	.
61		1	2	B	91.30	259.99	264.59
62		2	1	B	121.71	229.38	234.57
63		1	2	B	142.34	323.29	329.72
64		2	1	B	157.32	343.38	348.40
65		2	1	B	112.63	402.11	408.03
66		1	2	B	125.56	397.59	406.50
67		2	1	B	141.66	542.46	549.55
68		1	2	B	65.63	270.76	276.25
69		1	2	B	96.98	363.30	369.31
70		2	1	B	117.61	264.04	268.57
71		1	2	B	92.56	422.70	435.75
72		2	1	B	86.20	468.44	480.25
73		1	2	B	94.59	591.52	616.13
74		2	1	B	115.79	350.44	356.84
75		1	2	B	113.18	473.80	482.69
76		2	1	B	66.85	171.21	179.37
77		2	1	B	122.24	504.78	512.41
78		1	2	B	132.66	375.60	381.28
79		1	2	B	75.49	266.94	274.01
80		2	1	B	67.33	288.03	294.22
81		1	2	B	4.84	53.18	.
82		1	2	B	63.17	248.44	253.76
83		2	1	B	101.68	354.62	360.09
84		1	2	B	105.44	256.33	260.82

Obs	lauct	laucinf	lcmax	stlauct	stlauci	stlcmax
57	6.25681	6.27476	5.05733	0.61696	1.25962	0.25358

58	5.58803	5.61254	4.63696	-0.22746	-0.46164	-0.20117
59	5.98796	6.00756	5.01774	0.88962	1.81319	0.74933
60	2.56495	.	0.87547	-3.99555	.	-3.93076
61	5.56064	5.57818	4.51415	-0.35061	-0.72849	-0.11312
62	5.43538	5.45775	4.80164	0.00870	-0.00957	0.58608
63	5.77855	5.79824	4.95822	-0.04662	-0.10525	0.26959
64	5.83884	5.85335	5.05828	0.02491	0.07020	0.20347
65	5.99673	6.01134	4.72411	-0.19800	-0.38833	-0.67954
66	5.98542	6.00758	4.83278	-0.00282	-0.01369	-0.25758
67	6.29611	6.30910	4.95343	0.06088	0.13243	0.22367
68	5.60123	5.62131	4.18403	-0.37428	-0.77282	-0.48066
69	5.89523	5.91164	4.57450	0.11423	0.22843	-0.05625
70	5.57610	5.59311	4.76737	-0.21323	-0.42226	-0.26019
71	6.04666	6.07707	4.52786	-0.43914	-0.90043	-0.59782
72	6.14941	6.17431	4.45667	0.92425	1.93240	0.47850
73	6.38270	6.42346	4.54955	-0.02485	-0.01216	-0.14506
74	5.85919	5.87729	4.75178	0.22088	0.46835	0.33208
75	6.16079	6.17937	4.72898	-0.04640	-0.11559	-0.23345
76	5.14289	5.18945	4.20245	-0.50658	-0.96256	-0.24892
77	6.22412	6.23913	4.80599	4.17620	.	4.09530
78	5.92852	5.94353	4.88779	-0.11056	-0.24905	0.12888
79	5.58702	5.61316	4.32400	-0.44525	-0.92543	-0.21481
80	5.66306	5.68433	4.20961	-0.10104	-0.20744	-0.49595
81	3.97368	.	1.57691	-0.23965	.	0.28281
82	5.51520	5.53639	4.14583	-0.20142	-0.42217	-0.10930
83	5.87105	5.88635	4.62183	-0.73780	-1.50346	-0.80734
84	5.54647	5.56383	4.65814	2.21605	4.18839	2.36713

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Obs	SUBJECT	SEQUENCE	PERIOD	FORM	C _{MAX}	AUC _{0T}	AUC _{INF}
85	(b) (6)	2	1	B	86.65	204.46	210.04
86	(b) (6)	1	2	B	37.86	94.33	98.88
87	(b) (6)	2	1	B	78.66	388.17	395.73
88	(b) (6)	1	2	B	91.86	319.88	327.89

Obs	lauct	laucinf	lcmax	stlauct	stlauci	stlcmax
85	5.32037	5.34730	4.46188	-0.07064	-0.12442	0.16208
86	4.54680	4.59391	3.63390	-0.52302	-1.05589	-0.92149
87	5.96144	5.98073	4.36513	0.44696	0.94264	-0.11218
88	5.76795	5.79268	4.52027	-0.34820	-0.73689	-0.41746

DSTDRES data set

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Obs	SUBJECT	SEQUENCE	dstdat	dstdai	dstdcm
1	(b) (6)	1	0.04279	0.11506	0.09995
2	(b) (6)	2	0.57173	1.15594	0.27188
3	(b) (6)	2	0.05452	0.10327	0.00599
4	(b) (6)	2	-0.10678	-0.22977	-0.11354
5	(b) (6)	2	-0.17364	-0.36374	-0.17643
6	(b) (6)	1	0.04023	0.07863	0.04736
7	(b) (6)	1	-0.72768	-1.46042	-0.87568
8	(b) (6)	1	-0.08905	-0.17912	-0.13758
9	(b) (6)	2	0.29240	0.55431	0.14726
10	(b) (6)	1	0.30068	0.62282	0.41977
11	(b) (6)	2	-0.12307	-0.28669	-0.12247
12	(b) (6)	2	0.41439	0.80784	0.28292
13	(b) (6)	1	-0.61696	-1.25962	-0.25358
14	(b) (6)	1	0.22746	0.46164	0.20117
15	(b) (6)	2	-0.88962	-1.81319	-0.74933
16	(b) (6)	2	3.99555	.	3.93076
17	(b) (6)	1	0.35061	0.72849	0.11312
18	(b) (6)	2	-0.00870	0.00957	-0.58608
19	(b) (6)	1	0.04662	0.10525	-0.26959
20	(b) (6)	2	-0.02491	-0.07020	-0.20347
21	(b) (6)	2	0.19800	0.38833	0.67954
22	(b) (6)	1	0.00282	0.01369	0.25758
23	(b) (6)	2	-0.06088	-0.13243	-0.22367
24	(b) (6)	1	0.37428	0.77282	0.48066
25	(b) (6)	1	-0.11423	-0.22843	0.05625
26	(b) (6)	2	0.21323	0.42226	0.26019
27	(b) (6)	1	0.43914	0.90043	0.59782
28	(b) (6)	2	-0.92425	-1.93240	-0.47850
29	(b) (6)	1	0.02485	0.01216	0.14506
30	(b) (6)	2	-0.22088	-0.46835	-0.33208
31	(b) (6)	1	0.04640	0.11559	0.23345
32	(b) (6)	2	0.50658	0.96256	0.24892
33	(b) (6)	2	-4.17620	.	-4.09530

34	(b) (6)	1	0.11056	0.24905	-0.12888
35		1	0.44525	0.92543	0.21481
36		2	0.10104	0.20744	0.49595
37		1	0.23965	.	-0.28281
38		1	0.20142	0.42217	0.10930
39		2	0.73780	1.50346	0.80734
40		1	-2.21605	-4.18839	-2.36713
41		2	0.07064	0.12442	-0.16208
42		1	0.52302	1.05589	0.92149
43		2	-0.44696	-0.94264	0.11218
44		1	0.34820	0.73689	0.41746

9 ATTACHMENTS:

(b) (4)



BIOEQUIVALENCE DEFICIENCIES TO BE COMMUNICATED TO THE APPLICANT

ANDA: 202103

APPLICANT: Apotex Inc.

DRUG PRODUCT: Dasatinib Tablets, 20 mg, 50 mg, 70 mg and 100 mg

The Division of Bioequivalence I (DBI) has completed its review and identified the following deficiencies:

1. The results of the re-dosing study # DASA-IMTB-05SB03-2FA confirmed that Subject - (b) (6) was an “extreme” subject, with highly variable pharmacokinetic (PK) responses and test-to-reference (T/R) ratios of PK parameters consistently outside the PK ratio range of other subjects from the original (# DASA-IMTB-05SB01-2FA) and re-dosing studies, even though the (T/R) ratios for this subject were found to be on the low extreme in the redosing study, compared with the high extreme observed in the original fasting BE study. In other words, the redosing study did not demonstrate conclusively that the PK ratio values for Subject - (b) (6) were “aberrant” in the original fasting BE study. For this reason, the subject should not be excluded from the final statistical analysis of the original fasting BE study. With the inclusion of subject - (b) (6) the fasting BE study does not meet bioequivalence criteria. Specifically, the 90% Confidence Interval of lnAUC_t is 96.68 to 135.34 and the 90% Confidence Interval of lnC_{max} is 98.23 to 144.45. As a result, the original fasting BE study is **unacceptable**.
2. For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), you did not submit the assay failure investigation report for rejected run ID # 20 (Run description 21DD6367 - (b) (6) & Repeats). Please submit the assay failure investigation reports for the said run.
3. For the fed BE study (Study No. DASA-IMTB-05SB02-2FE), you have submitted whole blood stability validation data for 2 hours on ice in the current amendment to address the protocol deviation pertaining to centrifugation of post-dose fed BE study samples as much as 72 minutes after blood collection. However, you did not provide the nominal concentrations of the quality control (QC) samples used in this validation study. Please provide these nominal concentrations. If the measured values of the QC samples are greater than 15% from nominal, then please repeat the validation study.

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

APPEARS THIS WAY ON
THE ORIGINAL

10 OUTCOME PAGE

ANDA: 202103

Reviewer: Pabba, Santhosh

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description:

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
19409	8/16/2012	Other (REGULAR)	Study Amendment	1	1
19409	6/27/2010	Other (REGULAR)	OSI Inspection Review Report (Clinical)	1	1
19409	6/27/2010	Other (REGULAR)	OSI Inspection Review Report (Analytical)	1	1
				Total:	3

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

/s/

SANTHOSH K PABBA
06/12/2013

UTPAL M MUNSHI
06/13/2013

HOAINHON N CARAMENICO
06/14/2013

DALE P CONNER
06/25/2013

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202103		
Drug Product Name	Dasatinib Tablet		
Strength (s)	20, 50, 70 and 100 mg		
Applicant Name	Apotex Inc.		
Address	150 Signet Drive Toronto, Ontario M9L 1T9 CANADA		
US Agent	Apotex Corp, 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326		
Applicant's Point of Contact	Kiran Krishnan, Director, Regulatory Affairs		
Contact's Phone Number	(954) 384-3986		
Contact's Fax Number	(866) 392-1774		
Submission Date(s)	June 27, 2010		
First Generic Reviewer	S. P. Shrivastava, Ph.D.		
Study Number (s)	DASA-IMTB-05SB01-2FA (DD6366)	DASA-IMTB-05SB02-2FE (DD6367)	DASA-IMTB-05SB03-2FA (DD6577)
Study Type (s)	Fasting	Fed	Fasting Re-dosing Study
Strength(s)	100 mg	100 mg	100 mg
Clinical Site	Anapharm		
Clinical Site Address	2500, rue Einstein, Quebec (Quebec), Canada, G1P 0A2		
Analytical Site	Apotex Inc.		
Analytical Address	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive , Toronto, Ontario		
OUTCOME DECISION	INADEQUATE		

1. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The product references Sprycel® Tablet, 20, 50, 70 and 100 mg (Bio-study strength) [Bristol Myers Squibb, NDA 021986; Approved, 20, 50, 70 mg tablets – 6/28/2006, 100 mg tablets - 5/30/2008, and 80 and 140 mg tablets (RLD) -10/28/2010].

There is no USP method for this product, but there is an FDA-recommended method [1000 mL acetate buffer at pH 4.0 with 1% Triton X-100 at 37°C, using Paddle at 60 rpm]. The firm's dissolution testing data with the FDA-recommended method are

acceptable (at S1 level). However, the firm's proposed specification [NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes] is not acceptable. The firm should acknowledge the acceptance of FDA-recommended method and specification as follows:

Medium: Acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C
 Volume: 1000 mL
 USP Apparatus: II (Paddle) at 60 rpm
 Specification: NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes

The DBE will review the BE studies and waiver request at a later date.

The firm has provided the eCTD Summary Tables.

Table 1: SUBMISSION CONTENT CHECKLIST

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

*LTSS submitted for 81 days at -30⁰C and 46 days at -80⁰C. Sample storage period = 36 days. Stability data is for adequate period.

2. IN VITRO DISSOLUTION

Location of DBE Dissolution Review	See below
Source of Method (USP, FDA or Firm) ^{1,2}	FDA
Medium	Acetate buffer at pH 4.0 with 1% Triton-X 100 at 37 ⁰ C
Volume (mL)	1000 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	60 rpm
Firm's specification	NLT (b) ₍₄₎ % (Q) in (b) ₍₄₎ minutes
FDA-Recommended Specification	NLT (b) ₍₄₎ % (Q) in (b) ₍₄₎ minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	INCOMPLETE
If not then why?	Pending the acceptance of FDA's dissolution specification by the firm

Comments:

- There is no USP method for this product, but there is an FDA-recommended method [1000 mL acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C, using Paddle at 60 rpm]. The summary results of *in vitro* dissolution testing by FDA-recommended method are given in Tables 2-5. The similarity Factor, F2 Values, is provided in Tables 6 and 7. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). However, the firm's proposed specification [NLT (b)₍₄₎% (Q) in (b)₍₄₎ minutes] is not acceptable. The firm should acknowledge the acceptance of FDA-recommended method and specification as follows:

Medium: Acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C
Volume: 1000 mL
USP Apparatus: II (Paddle) at 60 rpm
Specification: NLT (b)₍₄₎% (Q) in (b)₍₄₎ minutes

- The firm has also conducted dissolution in two other media, phosphate buffer at pH 6.8 with 1% Triton X-100 and 0.1 N HCl with 1% Triton X-100, using the above dissolution conditions. Data are provided in Tables 8-19. Among the three media used by the firm, the acetate buffer at pH 4.0 (FDA method) appears to be most appropriate, because it is discriminatory and provides (b)₍₄₎% dissolution within the test period (see Figs. 1-3).

¹ OGD External Dissolution Database, http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

² OGD Internal Dissolution Database, <http://cdsogd1/bio/DissGrid.ASP>

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA – FDA Method, 20 mg

Dissolution Conditions		Apparatus:	USP#2									
		Speed of Rotation:	60 rpm									
Firm's Proposed Specifications		Medium:	Acetate buffer pH4.0 with 1.0% Triton X-100									
		Volume:	1000 mL									
		Temperature:	37°C ±5									
Dissolution Testing Site (Name, Address)		Q = $\frac{(b)}{(4)}$ % in $\frac{(b)}{(4)}$ minutes Apotex Inc 150 Signet Drive Toronto, ON M9L 1T9 Canada										
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 or hours)						Study Report Location	
					Dasatinib							
					5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01	May 2010	Dasatinib Tablets (FD150-32) March 2010	20 mg Tablets	12	Mean	45	84	93	96	98	99	5.3.1.2
					Range	(b) (4)						
					%RSD	8	2	1	1	1	1	
		SPRYCEL [®] Tablets (9G4704E) Exp: 07/2011	20 mg Tablets	12	Mean	42	77	89	94	97	98	
					Range	(b) (4)						
					%RSD	14	6	3	2	1	1	

Table 3: SUMMARY OF IN VITRO DISSOLUTION DATA – FDA Method, 50 mg

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 or hours)						Study Report Location	
						Dasatinib							
						5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01	May 2010	Dasatinib Tablets (FD150-33) March 2010	50 mg Tablets	12	Mean	44	74	88	93	97	97	5.3.1.2	
					Range	(b) (4)							
					%RSD	7	4	3	2	2	2		
		SPRYCEL [®] Tablets (9J6013G) Exp: 09/2011	50 mg Tablets	12	Mean	47	76	88	93	97	99		
					Range	(b) (4)							
					%RSD	15	7	4	2	2	1		

Table 4: SUMMARY OF IN VITRO DISSOLUTION DATA – FDA Method, 70 mg

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 or hours)						Study Report Location	
						Dasatinib							
						5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01		May 2010	Dasatinib Tablets (FD150-34) March 2010	70 mg Tablets	12	Mean	31	72	86	92	95	96	5.3.1.2
						Range	(b) (4)						
						%RSD	13	3	2	1	1	1	
			SPRYCEL® Tablets (9G4728C) Exp: 07/2011	70 mg Tablets	12	Mean	30	66	82	88	93	95	
						Range	(b) (4)						
						%RSD	17	6	4	3	2	1	

Table 5: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 100 mg

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 or hours)						Study Report Location	
						Dasatinib							
						5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01	May 2010	Dasatinib Tablets (FD150-31) March 2010	100 mg Tablets	12	Mean	42	73	86	92	96	97	5.3.1.2	
					Range	(b) (4)							
					%RSD	10	4	3	2	2	2		
		SPRYCEL [®] Tablets (9L6029B) Exp: Nov 2012	100 mg Tablets	12	Mean	48	75	85	91	95	96		
					Range	(b) (4)							
					%RSD	9	4	3	2	2	1		

Table 6: F2 Metric – Biobatch Strength vs. Other Strengths

F2 metric, biostudy strengths compared to other strength(s)*				
Medium	Biostudy Strength	Other Strength	F2 metric for test	F2 metric for RLD
FDA Method: Acetate Buffer at pH 4.0 with 1% Triton-X 100	100 mg	20 mg	57.86	69.08
		50 mg	86.40	83.08
		70 mg	62.54	49.29

*Used data for 5, 10, 15, and 20 minutes time points.

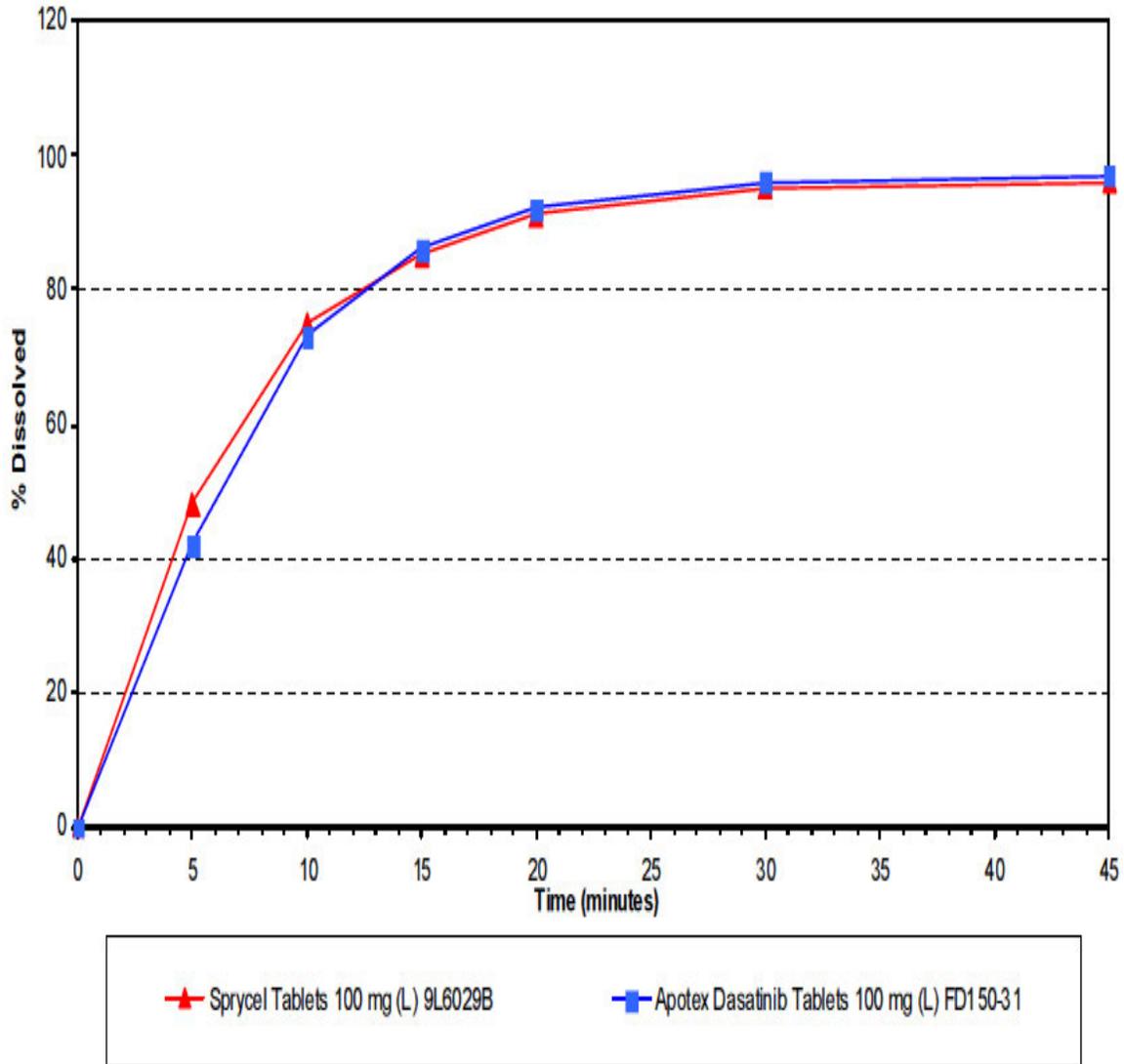
Table 7: F2 Metric – Test vs. Reference

F2 metric, Test vs. Reference*		
Medium	Strength	F2 Value
FDA Method: Acetate Buffer at pH 4.0 with 1% Triton-X 100	20 mg	67.21
	50 mg	84.29
	70 mg	68.47
	100 mg	73.48

*Used data for 5, 10, 15, and 20 minutes time points.

**Figure 1. Comparative Dissolution of 100 mg Test and Reference Dasatinib Tablets
FDA Method**

Apotex Dasatinib Tablets 100 mg vs Sprycel Tablets 100 mg

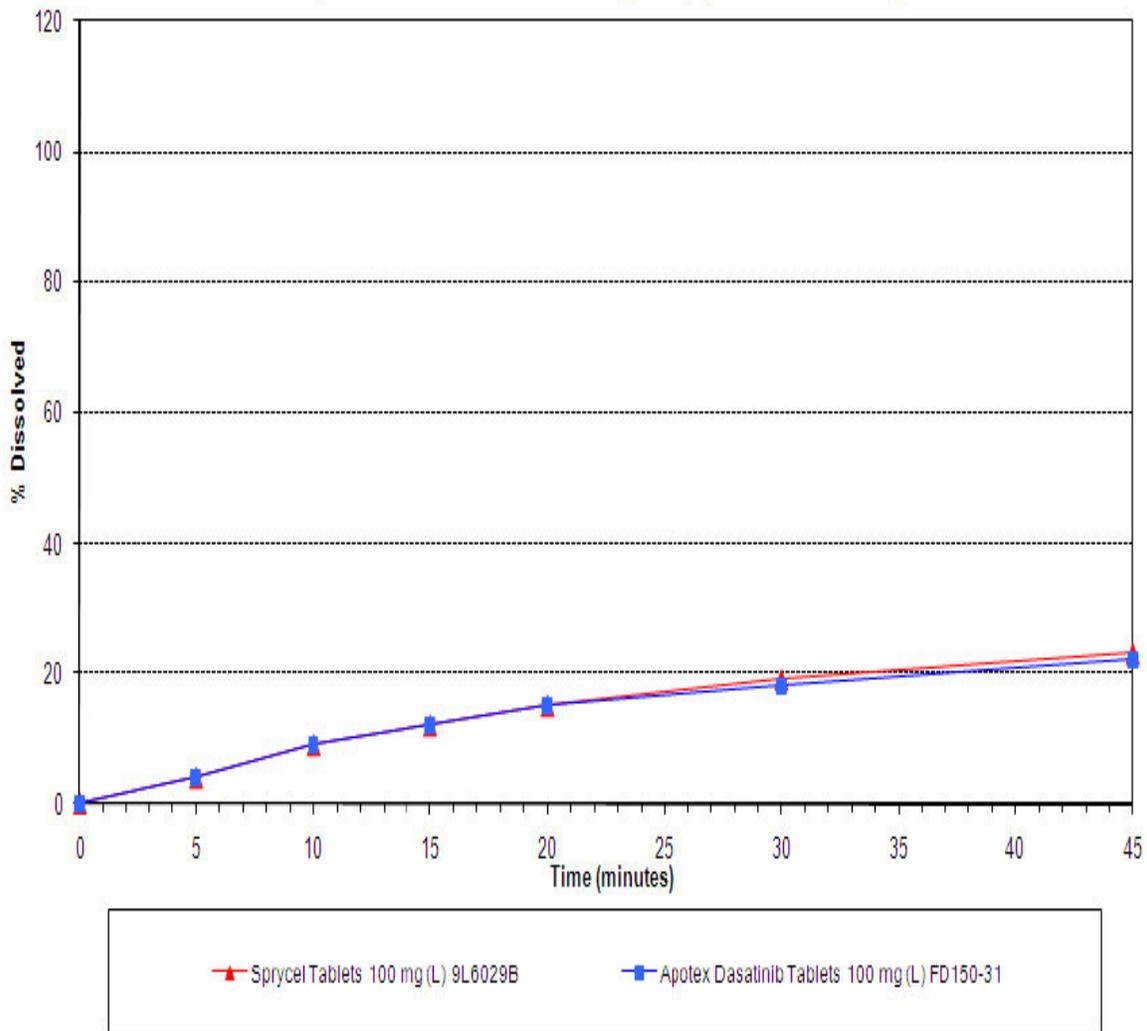


Method: USP#2, 60 rpm

Medium: 1000 mL, Acetate Buffer pH 4.0 with 1.0% Triton X-100

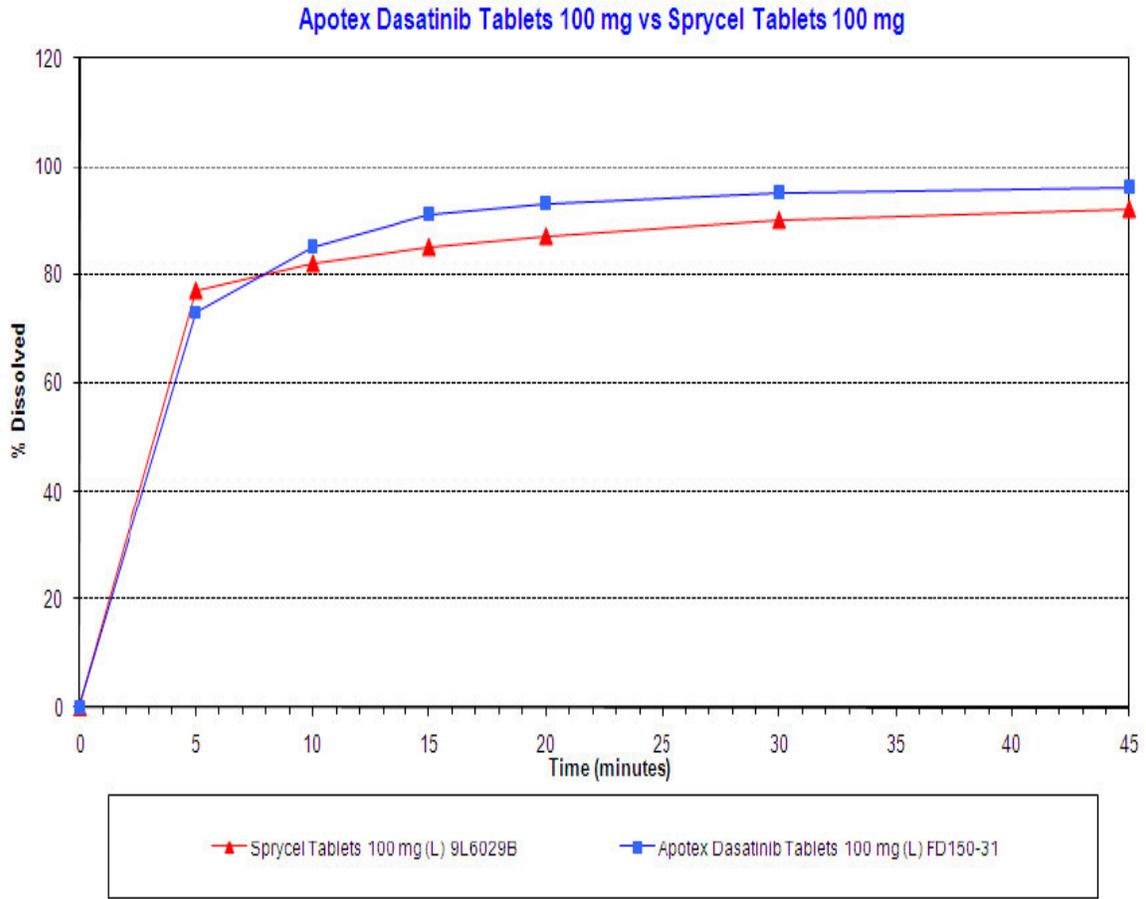
**Figure 2. Comparative Dissolution of 100 mg Test and Reference Dasatinib Tablets
Phosphate Buffer at pH 6.8 with 1% Triton-X 100**

Apotex Dasatinib Tablets 100 mg vs Sprycel Tablets 100 mg



Method: USP#2, 60 rpm
Medium: 1000 mL, Phosphate Buffer pH 6.8 with 1.0% Triton X-100

**Figure 3. Comparative Dissolution of 100 mg Test and Reference Dasatinib Tablets
0.1 N HCl with 1% Triton-X 100**



3. DEFICIENCY/COMMENTS

1. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). However, the firm's proposed specification [NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes] is not acceptable. The firm should acknowledge the acceptance of FDA-recommended method and specification as follows:

Medium:	Acetate buffer at pH 4.0 with 1% Triton X-100 at 37 ⁰ C
Volume:	1000 mL
USP Apparatus:	II (Paddle) at 60 rpm
Specification:	NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes

4. RECOMMENDATIONS:

1. The in vitro dissolution testing conducted by the firm on its test and reference products is **incomplete** due to the deficiency/comment #1 cited above.

The firm should be informed of the deficiency and recommendation.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

5. APPENDIX

5.1. Additional Dissolution Data

Table 8: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 20 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 20 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 20 mg, (L) FD150-32¹¹⁷, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	45	8
10	(b) (4)													84	2
15	(b) (4)													93	1
20	(b) (4)													96	1
30	(b) (4)													98	1
45	(b) (4)													99	1

Reference: MVRC032761 and MVRC032763. Data were from initial time point stability study.
 Tested on Mar.31, 2010 and Apr. 01, 2010.

Table 2: SPRYCEL® Tablets 20 mg (L) 9G4704E, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	42	14
10	(b) (4)													77	6
15	(b) (4)													89	3
20	(b) (4)													94	2
30	(b) (4)													97	1
45	(b) (4)													98	1

Reference: MVRC027524 and MVRC027525.
 Tested on May 08, 2010.

Table 9: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer, pH 6.8, 20 mg

Table 3: Dasatinib Tablets 20 mg, (L) FD150-32, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	5	14
10													12	8	
15													17	5	
20													21	4	
30													28	4	
45													36	3	

Reference: MVRC027510 and MVRC027511.

Tested on: May 07, 2010.

Table 4: SPRYCEL® Tablets 20 mg (L) 9G4704E, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	4	20
10													10	12	
15													15	9	
20													19	8	
30													26	6	
45													34	4	

Reference: MVRC027508 and MVRC027509.

Tested on May 07, 2010.

Table 10: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 20 mg

Table 5: Dasatinib Tablets 20 mg, (L) FD150-32, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5													(b) (4)	55	40
10													84	27	
15													87	24	
20													90	22	
30													94	17	
45													96	9	

Reference: MVRC027504 and MVRC027505.

Tested on May 06, 2010.

Table 6: SPRYCEL® Tablets 20 mg (L) 9G4704E, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5													(b) (4)	81	9
10													86	7	
15													88	7	
20													90	6	
30													94	5	
45													97	2	

Reference: MVRC027506 and MVRC027507.

Tested on May 07, 2010.

Table 11: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 50 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 50 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 50 mg, (L) FD150-33⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	44	7
10	(b) (4)													74	4
15	(b) (4)													88	3
20	(b) (4)													93	2
30	(b) (4)													97	2
45	(b) (4)													97	2

Reference: MVRC032762 and MVRC032764. ⁽¹⁾ Data were from initial time point stability study.
 Tested on Mar.31, 2010 and Apr. 01, 2010.

Table 2: SPRYCEL® Tablets 50 mg (L) 9J6013G, Bristol-Myers Squibb, US, Expiry Date 09/2011 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	47	15
10	(b) (4)													76	7
15	(b) (4)													88	4
20	(b) (4)													93	2
30	(b) (4)													97	2
45	(b) (4)													99	1

Reference: MVRC027532 and MVRC027533.
 Tested on May 12, 2010.

Table 12: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer at pH 6.8 , 50 mg

Table 3: Dasatinib Tablets 50 mg, (L) FD150-33, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	6	9
10													11	5	
15													14	3	
20													18	3	
30													23	2	
45													29	2	

Reference: MVRC027514 and MVRC027515.

Table 4: SPRYCEL® Tablets 50 mg (L) 9J6013G, Bristol-Myers Squibb, US, Expiry Date 09/2011 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	4	22
10													9	10	
15													13	8	
20													16	6	
30													21	4	
45													27	2	

Reference: MVRC027516.

Table 13: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 50 mg

Table 5: Dasatinib Tablets 50 mg, (L) FD150-33, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	83	8
10													(b) (4)	87	6
15													(b) (4)	89	6
20													(b) (4)	91	5
30													(b) (4)	94	5
45													(b) (4)	97	3

Reference: MVRC027530 and MVRC027531.

Tested on May 11, 2010.

Table 6: SPRYCEL® Tablets 50 mg (L) 9J6013G, Bristol-Myers Squibb, US, Expiry Date 09/2011 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	87	11
10													(b) (4)	91	7
15													(b) (4)	92	6
20													(b) (4)	94	5
30													(b) (4)	96	4
45													(b) (4)	97	3

Reference: MVRC 027557 and MVRC 027558.

Tested on May 17, 2010.

Table 14: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 70 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 70 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 70 mg, (L) FD150-34⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	31	13
10	(b) (4)													72	3
15	(b) (4)													86	2
20	(b) (4)													92	1
30	(b) (4)													95	1
45	(b) (4)													96	1

Reference: MVRC032768 and MVRC032778 (1) Data were from initial time point stability study.

Tested on Apr. 01, 2010.

Table 2: SPRYCEL® Tablets 70 mg (L) 9G4728C, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	30	17
10	(b) (4)													66	6
15	(b) (4)													82	4
20	(b) (4)													88	3
30	(b) (4)													93	2
45	(b) (4)													95	1

Reference: MVRC027534 and MVRC027535.

Tested on May 12, 2010.

Table 15: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer at pH 6.8 , 70 mg

Table 3: Dasatinib Tablets 70 mg, (L) FD150-34, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												4	21	
10													9	7	
15													13	5	
20													16	3	
30													20	3	
45													25	2	

Reference: MVRC027560 and MVRC027562.

Tested on: May 17, 2010.

Table 4: SPRYCEL® Tablets 70 mg (L) 9G4728C, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												3	26	
10													9	8	
15													13	6	
20													16	5	
30													21	3	
45													26	3	

Reference: MVRC027517 and MVRC027518.

Tested on May 10, 2010.

Table 16: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 70 mg

Table 5: Dasatinib Tablets 70 mg, (L) FD150-34, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	51	24
10													(b) (4)	89	6
15													(b) (4)	91	5
20													(b) (4)	92	5
30													(b) (4)	95	3
45													(b) (4)	98	3

Reference: MVRC027550 and MVRC027551.

Table 6: SPRYCEL® Tablets 70 mg (L) 9G4728C, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	67	31
10													(b) (4)	78	25
15													(b) (4)	80	23
20													(b) (4)	82	21
30													(b) (4)	87	15
45													(b) (4)	90	12

Reference: MVRC027544 and MVRC027545.

Tested on May 13, 2010.

Table 17: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 100 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 100 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 100 mg, (L) FD150-31⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	42	10
10	(b) (4)													73	4
15	(b) (4)													86	3
20	(b) (4)													92	2
30	(b) (4)													96	2
45	(b) (4)													97	2

Reference: MVRC 032760, MVRC 032765. (b) (4) Data were from initial time point stability study.
 Tested on March 31, 2010.

Table 2: SPRYCEL® Tablets 100 mg (L) 9L6029B, Bristol-Myers Squibb, US, Expiry Date 11/2012 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	48	9
10	(b) (4)													75	4
15	(b) (4)													85	3
20	(b) (4)													91	2
30	(b) (4)													95	2
45	(b) (4)													96	1

Reference: MVRC 032766, MVRC 032767.
 Tested on April 01, 2010.

Table 18: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer at pH 6.8 , 100 mg

Table 3: Dasatinib Tablets 100 mg, (L) FD150-31, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time</u> <u>(minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)													4	20
10													9	10	
15													12	8	
20													15	6	
30													18	4	
45													22	4	

Reference: MVRC027520 and MVRC027559.

Tested on: May 15, 2010 and May 17, 2010.

Table 4: SPRYCEL® Tablets 100 mg (L) 9L6029B, Bristol-Myers Squibb, US, Expiry Date 11/2012 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time</u> <u>(minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)													4	20
10													9	6	
15													12	4	
20													15	3	
30													19	3	
45													23	2	

Reference: MVRC 027523 and MVRC 027554.

Tested on May 15, 2010.

Table 19: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 100 mg

Table 5: Dasatinib Tablets 100 mg, (L) FD150-31, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	73	10
10													(b) (4)	85	7
15													(b) (4)	91	3
20													(b) (4)	93	3
30													(b) (4)	95	3
45													(b) (4)	96	2

Reference: MVRC 027526 and MVRC 027527.

Tested on May 08, 2010.

Table 6: SPRYCEL® Tablets 100 mg (L) 9L6029B, Bristol-Myers Squibb, US, Expiry Date 11/2012 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	77	19
10													(b) (4)	82	14
15													(b) (4)	85	13
20													(b) (4)	87	11
30													(b) (4)	90	9
45													(b) (4)	92	8

Reference: MVRC 027555 and MVRC 027556.

Tested on May 15, 2010.

BIOEQUIVALENCE DEFICIENCY

ANDA:	202103
APPLICANT:	Apotex Inc.
DRUG PRODUCT:	Dasatinib Tablet 20, 50, 70 and 100 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 and waiver requests will be conducted later. The following deficiency has been identified:

Your dissolution testing data with the FDA method are acceptable. However, your proposed specification [NLT 80% (Q) in 30 minutes] is not acceptable for the test product. Based on the dissolution data submitted for the test product, the DBE recommends a more appropriate specification below. Please acknowledge your acceptance of the FDA-recommended method and specification as follows:

Medium: Acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C
Volume: 1000 mL
USP Apparatus: II (Paddle) at 60 rpm
Specification: NLT (b) (4) (Q) in (b) (4) minutes

Sincerely yours,

{See appended electronic signature page}

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

6. OUTCOME

CC: ANDA 202103

7. Completed Assignment for 202103 ID: 13051

Reviewer: Shrivastava, Surendra **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Dasatinib Tablets

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
13051	6/27/2010	Dissolution Data	Dissolution Review	1	1	Edit	Delete
				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/

SURENDRA P SHRIVASTAVA
01/27/2011

YIH CHAIN HUANG
01/27/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
01/28/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202103		
Drug Product Name	Dasatinib Tablet		
Strength (s)	20, 50, 70 and 100 mg		
Applicant Name	Apotex Inc.		
Address	150 Signet Drive Toronto, Ontario M9L 1T9 CANADA		
US Agent	Apotex Corp, 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326		
Applicant's Point of Contact	Kiran Krishnan, Director, Regulatory Affairs		
Contact's Phone Number	(954) 384-3986		
Contact's Fax Number	(866) 392-1774		
Submission Date(s)	June 27, 2010		
First Generic Reviewer	S. P. Shrivastava, Ph.D.		
Study Number (s)	DASA-IMTB-05SB01-2FA (DD6366)	DASA-IMTB-05SB02-2FE (DD6367)	DASA-IMTB-05SB03-2FA (DD6577)
Study Type (s)	Fasting	Fed	Fasting Re-dosing Study
Strength(s)	100 mg	100 mg	100 mg
Clinical Site	Anapharm		
Clinical Site Address	2500, rue Einstein, Quebec (Quebec), Canada, G1P 0A2		
Analytical Site	Apotex Inc.		
Analytical Address	BioClinical Development, Bioanalytical Laboratory, 440 Garyray Drive , Toronto, Ontario		
OUTCOME DECISION	INADEQUATE		

1. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The product references Sprycel® Tablet, 20, 50, 70 and 100 mg (Bio-study strength) [Bristol Myers Squibb, NDA 021986; Approved, 20, 50, 70 mg tablets – 6/28/2006, 100 mg tablets - 5/30/2008, and 80 and 140 mg tablets (RLD) -10/28/2010].

There is no USP method for this product, but there is an FDA-recommended method [1000 mL acetate buffer at pH 4.0 with 1% Triton X-100 at 37°C, using Paddle at 60 rpm]. The firm's dissolution testing data with the FDA-recommended method are

acceptable (at S1 level). However, the firm's proposed specification [NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes] is not acceptable. The firm should acknowledge the acceptance of FDA-recommended method and specification as follows:

Medium: Acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C
 Volume: 1000 mL
 USP Apparatus: II (Paddle) at 60 rpm
 Specification: NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes

The DBE will review the BE studies and waiver request at a later date.

The firm has provided the eCTD Summary Tables.

Table 1: SUBMISSION CONTENT CHECKLIST

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

*LTSS submitted for 81 days at -30⁰C and 46 days at -80⁰C. Sample storage period = 36 days. Stability data is for adequate period.

2. IN VITRO DISSOLUTION

Location of DBE Dissolution Review	See below
Source of Method (USP, FDA or Firm) ^{1,2}	FDA
Medium	Acetate buffer at pH 4.0 with 1% Triton-X 100 at 37 ⁰ C
Volume (mL)	1000 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	60 rpm
Firm's specification	NLT (b) ₍₄₎ % (Q) in (b) ₍₄₎ minutes
FDA-Recommended Specification	NLT (b) ₍₄₎ % (Q) in (b) ₍₄₎ minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	INCOMPLETE
If not then why?	Pending the acceptance of FDA's dissolution specification by the firm

Comments:

- There is no USP method for this product, but there is an FDA-recommended method [1000 mL acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C, using Paddle at 60 rpm]. The summary results of *in vitro* dissolution testing by FDA-recommended method are given in Tables 2-5. The similarity Factor, F2 Values, is provided in Tables 6 and 7. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). However, the firm's proposed specification [NLT (b)₍₄₎% (Q) in (b)₍₄₎ minutes] is not acceptable. The firm should acknowledge the acceptance of FDA-recommended method and specification as follows:

Medium: Acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C
Volume: 1000 mL
USP Apparatus: II (Paddle) at 60 rpm
Specification: NLT (b)₍₄₎% (Q) in (b)₍₄₎ minutes

- The firm has also conducted dissolution in two other media, phosphate buffer at pH 6.8 with 1% Triton X-100 and 0.1 N HCl with 1% Triton X-100, using the above dissolution conditions. Data are provided in Tables 8-19. Among the three media used by the firm, the acetate buffer at pH 4.0 (FDA method) appears to be most appropriate, because it is discriminatory and provides (b)₍₄₎% dissolution within the test period (see Figs. 1-3).

¹ OGD External Dissolution Database, http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

² OGD Internal Dissolution Database, <http://cdsogd1/bio/DissGrid.ASP>

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA – FDA Method, 20 mg

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 or hours)						Study Report Location	
						Dasatinib							
						5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01		May 2010	Dasatinib Tablets (FD150-32) March 2010	20 mg Tablets	12	Mean	45	84	93	96	98	99	5.3.1.2
						Range	(b) (4)						
						%RSD	8	2	1	1	1	1	
			SPRYCEL [®] Tablets (9G4704E) Exp: 07/2011	20 mg Tablets	12	Mean	42	77	89	94	97	98	
						Range	(b) (4)						
						%RSD	14	6	3	2	1	1	

Table 3: SUMMARY OF IN VITRO DISSOLUTION DATA – FDA Method, 50 mg

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 or hours)						Study Report Location	
					Dasatinib							
					5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01	May 2010	Dasatinib Tablets (FD150-33) March 2010	50 mg Tablets	12	Mean	44	74	88	93	97	97	5.3.1.2
					Range	(b) (4)						
					%RSD	7	4	3	2	2	2	
		SPRYCEL [®] Tablets (9J6013G) Exp: 09/2011	50 mg Tablets	12	Mean	47	76	88	93	97	99	
					Range	(b) (4)						
					%RSD	15	7	4	2	2	1	

Table 4: SUMMARY OF IN VITRO DISSOLUTION DATA – FDA Method, 70 mg

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 or hours)						Study Report Location	
						Dasatinib							
						5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01		May 2010	Dasatinib Tablets (FD150-34) March 2010	70 mg Tablets	12	Mean	31	72	86	92	95	96	5.3.1.2
						Range	(b) (4)						
						%RSD	13	3	2	1	1	1	
			SPRYCEL® Tablets (9G4728C) Exp: 07/2011	70 mg Tablets	12	Mean	30	66	82	88	93	95	
						Range	(b) (4)						
						%RSD	17	6	4	3	2	1	

Table 5: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 100 mg

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 or hours)						Study Report Location	
						Dasatinib							
						5 min	10 min	15 min	20 min	30 min	45 min		
Comparative Dissolution Report dasa_imtb_02_u_cdr_01	May 2010	Dasatinib Tablets (FD150-31) March 2010	100 mg Tablets	12	Mean	42	73	86	92	96	97	5.3.1.2	
					Range	(b) (4)							
					%RSD	10	4	3	2	2	2		
		SPRYCEL® Tablets (9L6029B) Exp: Nov 2012	100 mg Tablets	12	Mean	48	75	85	91	95	96		
					Range	(b) (4)							
					%RSD	9	4	3	2	2	1		

Table 6: F2 Metric – Biobatch Strength vs. Other Strengths

F2 metric, biostudy strengths compared to other strength(s)*				
Medium	Biostudy Strength	Other Strength	F2 metric for test	F2 metric for RLD
FDA Method: Acetate Buffer at pH 4.0 with 1% Triton-X 100	100 mg	20 mg	57.86	69.08
		50 mg	86.40	83.08
		70 mg	62.54	49.29

*Used data for 5, 10, 15, and 20 minutes time points.

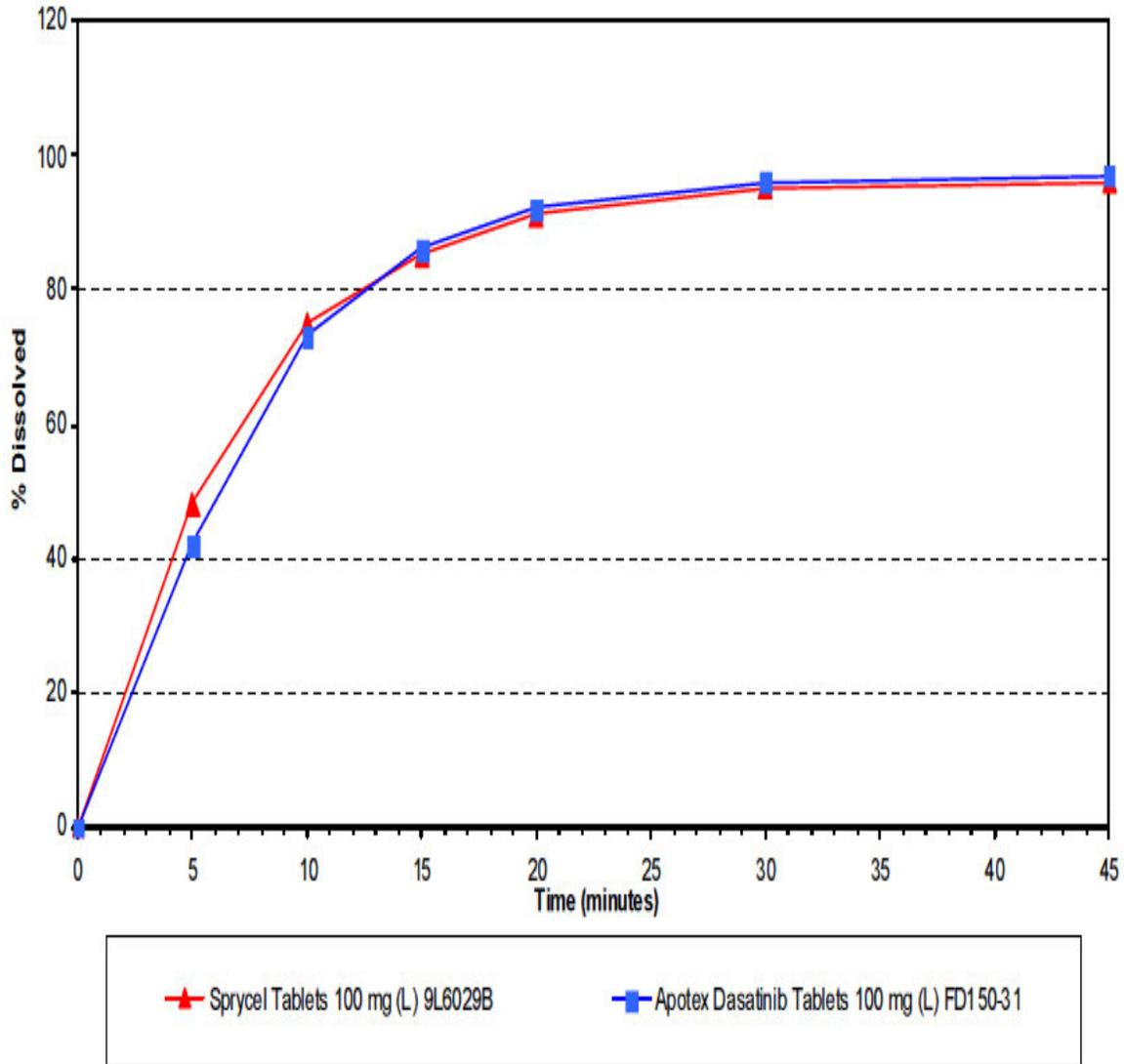
Table 7: F2 Metric – Test vs. Reference

F2 metric, Test vs. Reference*		
Medium	Strength	F2 Value
FDA Method: Acetate Buffer at pH 4.0 with 1% Triton-X 100	20 mg	67.21
	50 mg	84.29
	70 mg	68.47
	100 mg	73.48

*Used data for 5, 10, 15, and 20 minutes time points.

**Figure 1. Comparative Dissolution of 100 mg Test and Reference Dasatinib Tablets
FDA Method**

Apotex Dasatinib Tablets 100 mg vs Sprycel Tablets 100 mg

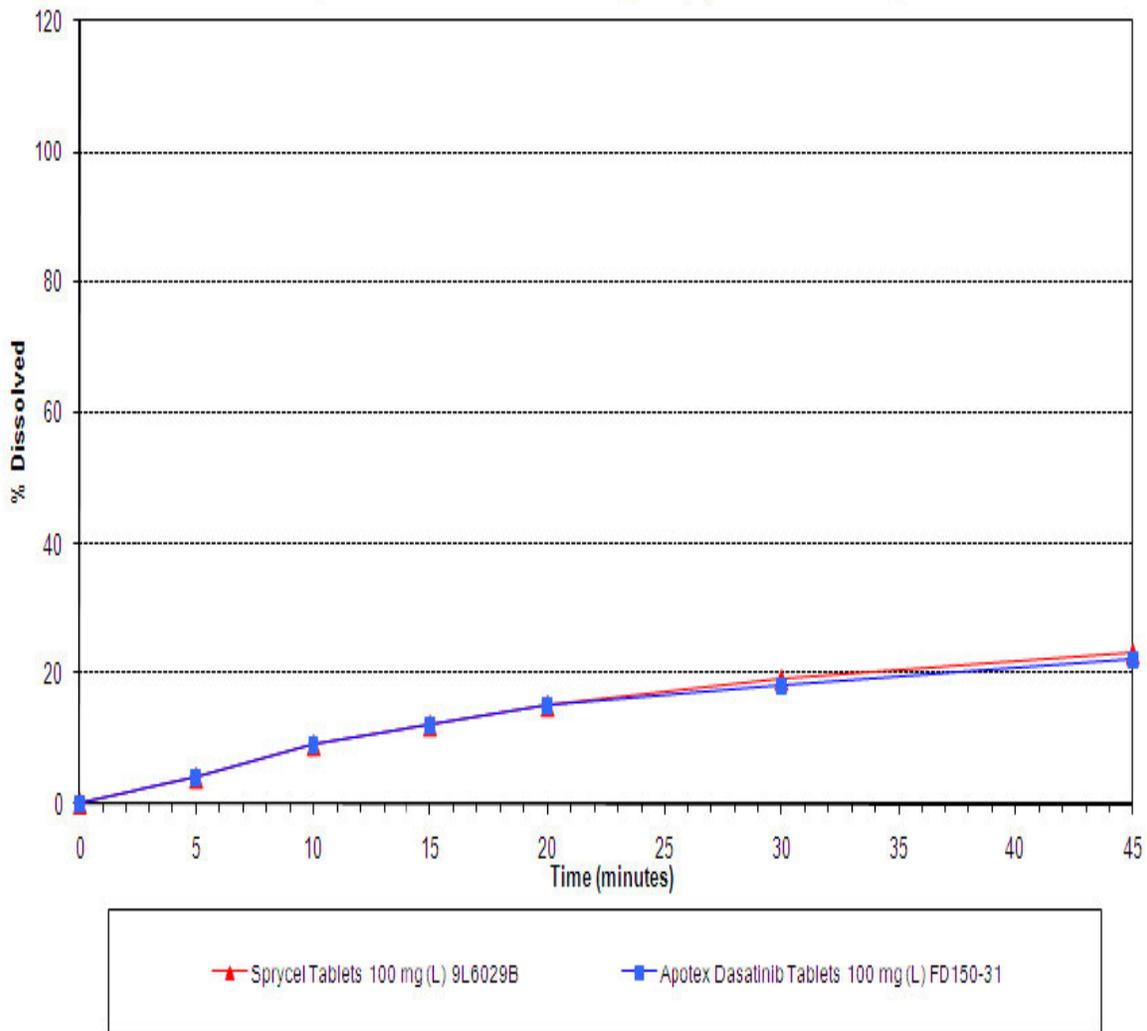


Method: USP#2, 60 rpm

Medium: 1000 mL, Acetate Buffer pH 4.0 with 1.0% Triton X-100

**Figure 2. Comparative Dissolution of 100 mg Test and Reference Dasatinib Tablets
Phosphate Buffer at pH 6.8 with 1% Triton-X 100**

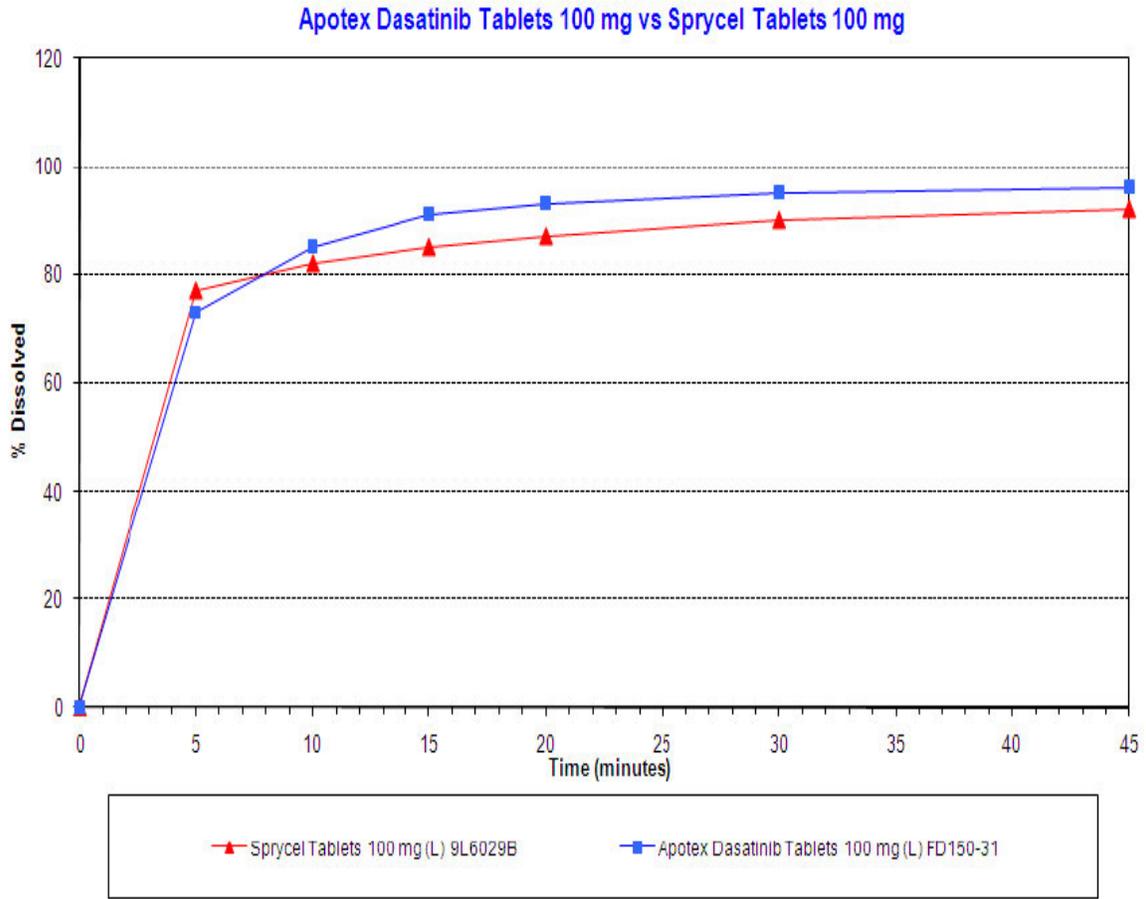
Apotex Dasatinib Tablets 100 mg vs Sprycel Tablets 100 mg



Method: USP#2, 60 rpm

Medium: 1000 mL, Phosphate Buffer pH 6.8 with 1.0% Triton X-100

**Figure 3. Comparative Dissolution of 100 mg Test and Reference Dasatinib Tablets
0.1 N HCl with 1% Triton-X 100**



3. DEFICIENCY/COMMENTS

1. The firm's dissolution testing data with the FDA-recommended method are acceptable (at S1 level). However, the firm's proposed specification [NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes] is not acceptable. The firm should acknowledge the acceptance of FDA-recommended method and specification as follows:

Medium:	Acetate buffer at pH 4.0 with 1% Triton X-100 at 37 ⁰ C
Volume:	1000 mL
USP Apparatus:	II (Paddle) at 60 rpm
Specification:	NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes

4. RECOMMENDATIONS:

1. The in vitro dissolution testing conducted by the firm on its test and reference products is **incomplete** due to the deficiency/comment #1 cited above.

The firm should be informed of the deficiency and recommendation.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

5. APPENDIX

5.1. Additional Dissolution Data

Table 8: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 20 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 20 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 20 mg, (L) FD150-32⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	45	8
10	(b) (4)												(b) (4)	84	2
15	(b) (4)												(b) (4)	93	1
20	(b) (4)												(b) (4)	96	1
30	(b) (4)												(b) (4)	98	1
45	(b) (4)												(b) (4)	99	1

Reference: MVRC052761 and MVRC052765. (b) (4) Data were from initial time point stability study.
 Tested on Mar.31, 2010 and Apr. 01, 2010.

Table 2: SPRYCEL® Tablets 20 mg (L) 9G4704E, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	42	14
10	(b) (4)												(b) (4)	77	6
15	(b) (4)												(b) (4)	89	3
20	(b) (4)												(b) (4)	94	2
30	(b) (4)												(b) (4)	97	1
45	(b) (4)												(b) (4)	98	1

Reference: MVRC027524 and MVRC027525.
 Tested on May 08, 2010.

Table 9: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer, pH 6.8, 20 mg

Table 3: Dasatinib Tablets 20 mg, (L) FD150-32, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)													5	14
10														12	8
15														17	5
20														21	4
30														28	4
45														36	3

Reference: MVRC027510 and MVRC027511.

Tested on: May 07, 2010.

Table 4: SPRYCEL® Tablets 20 mg (L) 9G4704E, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)													4	20
10														10	12
15														15	9
20														19	8
30														26	6
45														34	4

Reference: MVRC027508 and MVRC027509.

Tested on May 07, 2010.

Table 10: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 20 mg

Table 5: Dasatinib Tablets 20 mg, (L) FD150-32, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)													55	40
10													84	27	
15													87	24	
20													90	22	
30													94	17	
45													96	9	

Reference: MVRC027504 and MVRC027505.

Tested on May 06, 2010.

Table 6: SPRYCEL® Tablets 20 mg (L) 9G4704E, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

Time (minutes)	<u>% Dissolved</u>												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)													81	9
10													86	7	
15													88	7	
20													90	6	
30													94	5	
45													97	2	

Reference: MVRC027506 and MVRC027507.

Tested on May 07, 2010.

Table 11: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 50 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 50 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 50 mg, (L) FD150-33⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	44	7
10	(b) (4)													74	4
15	(b) (4)													88	3
20	(b) (4)													93	2
30	(b) (4)													97	2
45	(b) (4)													97	2

Reference: MVRC032762 and MVRC032764. Data were from initial time point stability study.
 Tested on Mar.31, 2010 and Apr. 01, 2010.

Table 2: SPRYCEL® Tablets 50 mg (L) 9J6013G, Bristol-Myers Squibb, US, Expiry Date 09/2011 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	47	15
10	(b) (4)													76	7
15	(b) (4)													88	4
20	(b) (4)													93	2
30	(b) (4)													97	2
45	(b) (4)													99	1

Reference: MVRC027532 and MVRC027533.
 Tested on May 12, 2010.

Table 12: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer at pH 6.8 , 50 mg

Table 3: Dasatinib Tablets 50 mg, (L) FD150-33, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	6	9
10													11	5	
15													14	3	
20													18	3	
30													23	2	
45													29	2	

Reference: MVRC027514 and MVRC027515.

Table 4: SPRYCEL® Tablets 50 mg (L) 9J6013G, Bristol-Myers Squibb, US, Expiry Date 09/2011 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	4	22
10													9	10	
15													13	8	
20													16	6	
30													21	4	
45													27	2	

Reference: MVRC027516.

Table 13: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 50 mg

Table 5: Dasatinib Tablets 50 mg, (L) FD150-33, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	83	8
10													(b) (4)	87	6
15													(b) (4)	89	6
20													(b) (4)	91	5
30													(b) (4)	94	5
45													(b) (4)	97	3

Reference: MVRC027530 and MVRC027531.

Tested on May 11, 2010.

Table 6: SPRYCEL® Tablets 50 mg (L) 9J6013G, Bristol-Myers Squibb, US, Expiry Date 09/2011 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	87	11
10													(b) (4)	91	7
15													(b) (4)	92	6
20													(b) (4)	94	5
30													(b) (4)	96	4
45													(b) (4)	97	3

Reference: MVRC 027557 and MVRC 027558.

Tested on May 17, 2010.

Table 14: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 70 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 70 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 70 mg, (L) FD150-34⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	31	13
10	(b) (4)													72	3
15	(b) (4)													86	2
20	(b) (4)													92	1
30	(b) (4)													95	1
45	(b) (4)													96	1

Reference: MVRC032768 and MVRC032778 ⁽¹⁾ Data were from initial time point stability study.

Tested on Apr. 01, 2010.

Table 2: SPRYCEL® Tablets 70 mg (L) 9G4728C, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	30	17
10	(b) (4)													66	6
15	(b) (4)													82	4
20	(b) (4)													88	3
30	(b) (4)													93	2
45	(b) (4)													95	1

Reference: MVRC027534 and MVRC027535.

Tested on May 12, 2010.

Table 15: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer at pH 6.8 , 70 mg

Table 3: Dasatinib Tablets 70 mg, (L) FD150-34, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												4	21	
10													9	7	
15													13	5	
20													16	3	
30													20	3	
45													25	2	

Reference: MVRC027560 and MVRC027562.

Tested on: May 17, 2010.

Table 4: SPRYCEL® Tablets 70 mg (L) 9G4728C, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												3	26	
10													9	8	
15													13	6	
20													16	5	
30													21	3	
45													26	3	

Reference: MVRC027517 and MVRC027518.

Tested on May 10, 2010.

Table 16: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 70 mg

Table 5: Dasatinib Tablets 70 mg, (L) FD150-34, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)													51	24
10														89	6
15														91	5
20														92	5
30														95	3
45														98	3

Reference: MVRC027550 and MVRC027551.

Table 6: SPRYCEL® Tablets 70 mg (L) 9G4728C, Bristol-Myers Squibb, US, Expiry Date 07/2011 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)													67	31
10														78	25
15														80	23
20														82	21
30														87	15
45														90	12

Reference: MVRC027544 and MVRC027545.

Tested on May 13, 2010.

Table 17: SUMMARY OF IN VITRO DISSOLUTION DATA - FDA Method, 100 mg

Preamble:

An investigation was initiated to study the effect of pH on the rate of drug release of Apotex Dasatinib Tablets 100 mg by running independent dissolutions at various pH ranging from about 1 to 6.8.

Method:

Method No.: DASA-IMTB-40-SG
 Medium: As indicated under each condition below.
 Apparatus: USP 2.
 Stirring Speed: 60 rpm.
 Quantitation: (b) (4)

Table 1: Dasatinib Tablets 100 mg, (L) FD150-31⁽¹⁾, Apotex Inc. - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	42	10
10	(b) (4)													73	4
15	(b) (4)													86	3
20	(b) (4)													92	2
30	(b) (4)													96	2
45	(b) (4)													97	2

Reference: MVRC 032760, MVRC 032765.

⁽¹⁾ Data were from initial time point stability study.

Tested on March 31, 2010.

Table 2: SPRYCEL® Tablets 100 mg (L) 9L6029B, Bristol-Myers Squibb, US, Expiry Date 11/2012 - Dissolution Medium: Acetate Buffer pH 4.0 with 1.0% (v/v) Triton X-100 (as per method).

Time (minutes)	% Dissolved												Range	Mean	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12			
5	(b) (4)												(b) (4)	48	9
10	(b) (4)													75	4
15	(b) (4)													85	3
20	(b) (4)													91	2
30	(b) (4)													95	2
45	(b) (4)													96	1

Reference: MVRC 032766, MVRC 032767.

Tested on April 01, 2010.

Table 18: SUMMARY OF IN VITRO DISSOLUTION DATA – Buffer at pH 6.8 , 100 mg

Table 3: Dasatinib Tablets 100 mg, (L) FD150-31, Apotex Inc. - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time</u> <u>(minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	4	20
10													9	10	
15													12	8	
20													15	6	
30													18	4	
45													22	4	

Reference: MVRC027520 and MVRC027559.

Tested on: May 15, 2010 and May 17, 2010.

Table 4: SPRYCEL® Tablets 100 mg (L) 9L6029B, Bristol-Myers Squibb, US, Expiry Date 11/2012 - Dissolution Medium: Phosphate Buffer pH 6.8 with 1.0% (v/v) Triton X-100.

<u>Time</u> <u>(minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)												(b) (4)	4	20
10													9	6	
15													12	4	
20													15	3	
30													19	3	
45													23	2	

Reference: MVRC 027523 and MVRC 027554.

Tested on May 15, 2010.

Table 19: SUMMARY OF IN VITRO DISSOLUTION DATA – 0.1 N HCl, 100 mg

Table 5: Dasatinib Tablets 100 mg, (L) FD150-31, Apotex Inc. - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)													73	10
10														85	7
15														91	3
20														93	3
30														95	3
45														96	2

Reference: MVRC 027526 and MVRC 027527.

Tested on May 08, 2010.

Table 6: SPRYCEL® Tablets 100 mg (L) 9L6029B, Bristol-Myers Squibb, US, Expiry Date 11/2012 - Dissolution Medium: 0.1N HCl with 1.0% (v/v) Triton X-100.

<u>Time (minutes)</u>	<u>% Dissolved</u>												<u>Range</u>	<u>Mean</u>	<u>%RSD</u>
	<u>V1</u>	<u>V2</u>	<u>V3</u>	<u>V4</u>	<u>V5</u>	<u>V6</u>	<u>V7</u>	<u>V8</u>	<u>V9</u>	<u>V10</u>	<u>V11</u>	<u>V12</u>			
5	(b) (4)													77	19
10														82	14
15														85	13
20														87	11
30														90	9
45														92	8

Reference: MVRC 027555 and MVRC 027556.

Tested on May 15, 2010.

BIOEQUIVALENCE DEFICIENCY

ANDA:	202103
APPLICANT:	Apotex Inc.
DRUG PRODUCT:	Dasatinib Tablet 20, 50, 70 and 100 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 and waiver requests will be conducted later. The following deficiency has been identified:

Your dissolution testing data with the FDA method are acceptable. However, your proposed specification [NLT 80% (Q) in 30 minutes] is not acceptable for the test product. Based on the dissolution data submitted for the test product, the DBE recommends a more appropriate specification below. Please acknowledge your acceptance of the FDA-recommended method and specification as follows:

Medium: Acetate buffer at pH 4.0 with 1% Triton X-100 at 37⁰C
Volume: 1000 mL
USP Apparatus: II (Paddle) at 60 rpm
Specification: NLT (b)(4)% (Q) in (b)(4) minutes

Sincerely yours,

{See appended electronic signature page}

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

6. OUTCOME

CC: ANDA 202103

7. Completed Assignment for 202103 ID: 13051

Reviewer: Shrivastava, Surendra **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Dasatinib Tablets

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
13051	6/27/2010	Dissolution Data	Dissolution Review	1	1	Edit	Delete
				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/

SURENDRA P SHRIVASTAVA
01/27/2011

YIH CHAIN HUANG
01/27/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
01/28/2011