CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 200484

Name: Niacin Extended-Release Tablets USP, 500 mg and 1000 mg

Sponsor: Sun Pharma Global FZE

Approval Date: April 23, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	**X**
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200484

Caraco Pharmaceutical Laboratories, Ltd.
U.S. Agent for: Sun Pharma Global FZE
Attention: Kalpana R. Vanam
Vice President, Regulatory Affairs
270 Prospect Plains Road
Cranbury, NJ 08512

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 29, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Niacin Extended-release Tablets USP, 500 mg and 1000 mg.

Reference is also made to the Tentative Approval letter issued on June 10, 2013, and to your amendments dated March 21, and April 2, 2014

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Niacin Extended-release Tablets USP, 500 mg and 1000 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Niaspan Extended-release Tablets 500 mg and 1000 mg, respectively, of AbbVie Inc. (AbbVie).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in:

Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C

USP Apparatus: I (Basket)
Rotational Speed: 100 rpm

"Interim" Specifications:

Time (Hours)	Percent Dissolved
1	NMT (b) (4)
3	(b) (4)
6	
9	
12	
20	NLT (b) (4)

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, AbbVie's Niaspan Extended-release Tablets, 500 mg and 1000 mg, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,080,428 (the '428 patent) and 6,469,035 (the '035 patent) are scheduled to expire on May 27, 2017, and March 15, 2018, respectively.

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Niacin Extended-release Tablets USP, 500 mg and 1000 mg, under this ANDA. You have notified the agency that Sun Pharma Global FZE (Sun) complied with the requirements of section 505(j)(2)(B) of the Act, that litigation was initiated against Sun for infringement of the both patents within the statutory 45-day period in the United States District Court for the District of Delaware [AbbVie Inc. and AbbVie Respiratory LLC v. Sun Pharmaceutical Industries LTD. and Sun Pharma Global FZE, Civil Action No. 10-112], and that the case was dismissed.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. You should advise the Office of Generic Drugs of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA)(Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in

prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

04/23/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200484

Caraco Pharmaceutical Laboratories Ltd.
U.S. Agent for Sun Pharma Global FZE
Attention: Kalpana R. Vanam
Vice President, Regulatory Affairs
Cranbury, NJ 08512

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 29, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Niacin Extended-Release Tablets USP, 500 mg and 1000 mg.

Reference is made to your amendments dated January 4, January 13, April 20, April 27, May 26, and September 6, 2010; January 11, February 17, September 6, September 20, September 27, September 30, October 8, October 21, October 22, November 21, and December 20, 2011; May 8 , May 26, and September 5, 2012; and January 12, March 6, April 3, and May 8, 2013.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Niaspan Extended-release Tablets of Abbvie Inc. is subject to periods of patent protection. The following patents and

their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
6,129,930 (the '930 patent)	September 20, 2013
6,406,715 (the '715 patent)	September 20, 2013
6,676,967 (the '967 patent)	September 20, 2013
6,746,691 (the '691 patent)	September 20, 2013
6,818,229 (the '229 patent)	September 20, 2013
7,011,848 (the '848 patent)	September 20, 2013
7,998,506 (the '506 patent)	September 20, 2013
6,080,428 (the '428 patent)	May 27, 2017
6,469,035 (the '035 patent)	March 15, 2018

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Niacin Extended-Release Tablets USP, 500 mg and 1000 mg, under this ANDA. You have notified the agency that Sun Pharma Global FZE (Sun) complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '930, '715, '967, '691, '229, '848, '428 and '035 patents was brought against Sun within the statutory 45-day period in the United States District Court for the District of Delaware [Abbott Laboratories and Abbott Respiratory LLC v. Sun Pharma Global FZE, Civil Action No. 1:10-CV-00112].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period (pertaining to the '930, '715, '967, '691, '229, and '848 patents) provided for in section 505(j)(5)(B)(iii),

   b. the date the court decides[1] that the '930, '715, '967, '691, '229, and '848 patents are invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

   c. the '930, '715, '967, '691, '229, and '848 patents have expired, and

[1] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

2. The agency is assured there is no new information that would affect whether final approval should be granted.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMP are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under

section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Dat Doan, Project Manager, at (240) 276-9336.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

06/10/2013

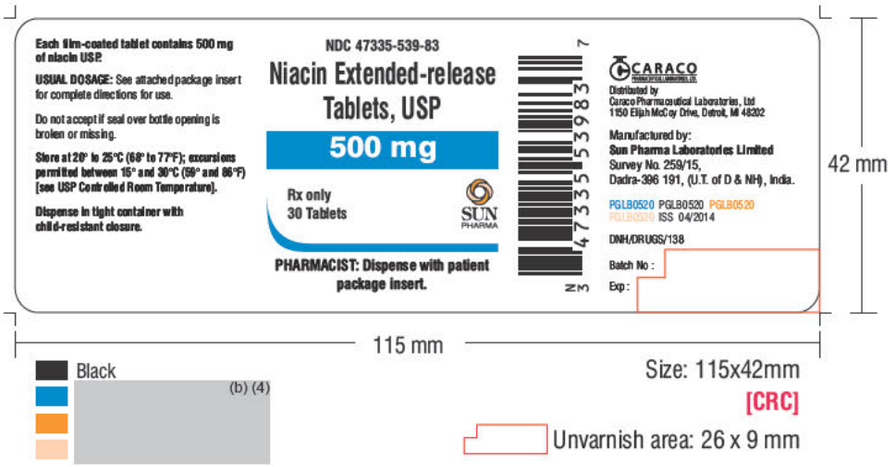
Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

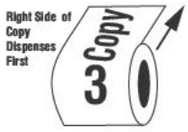
APPLICATION NUMBER:

ANDA 200484

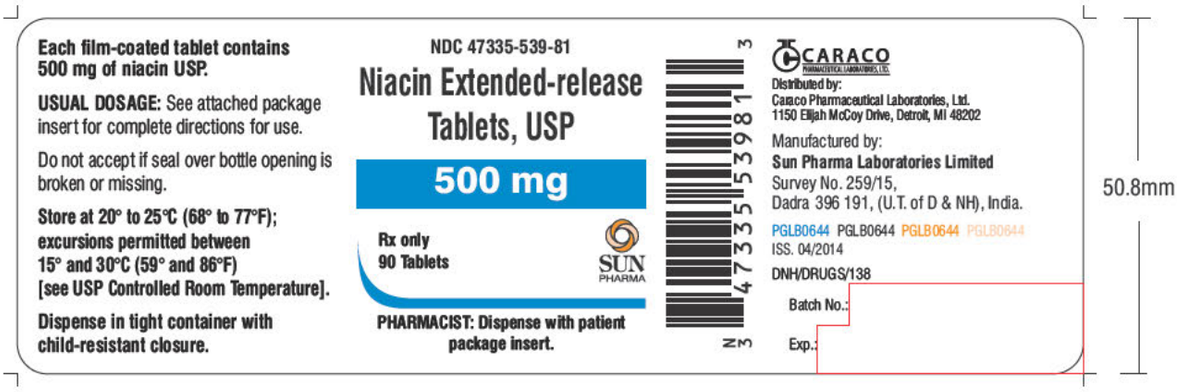
LABELING



Name of Product: Niacin ER Tabs-500mg-US-30T		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0520	Void artwork Code No:		CD-	
Actual Size	115x42mm	Reason :		REMARKS:	
Unvarnished Area	26x9mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				



Reference ID: 3487614



Black

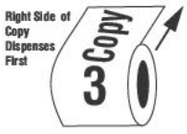
(b) (4)

Size: 152.4x50.8mm

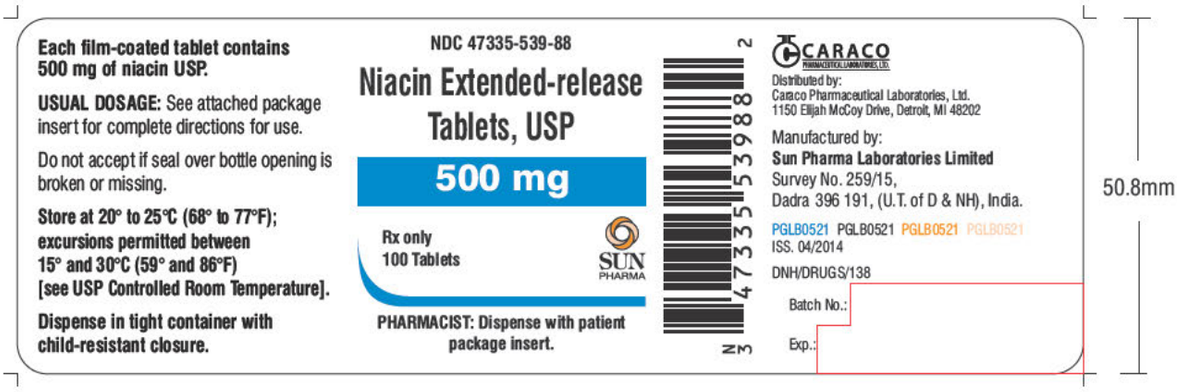
[CRC]

Unvarnish area: 38x13mm

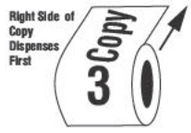
Name of Product: Niacin ER Tabs-500mg-US-90T		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0644	Void artwork Code No:		CD-	
Actual Size	152.4x50.8 mm	Reason :		REMARKS:	
Unvarnished Area	38x13mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -				
	Aqueous YES	APPROVAL HISTORY ATTACHED			



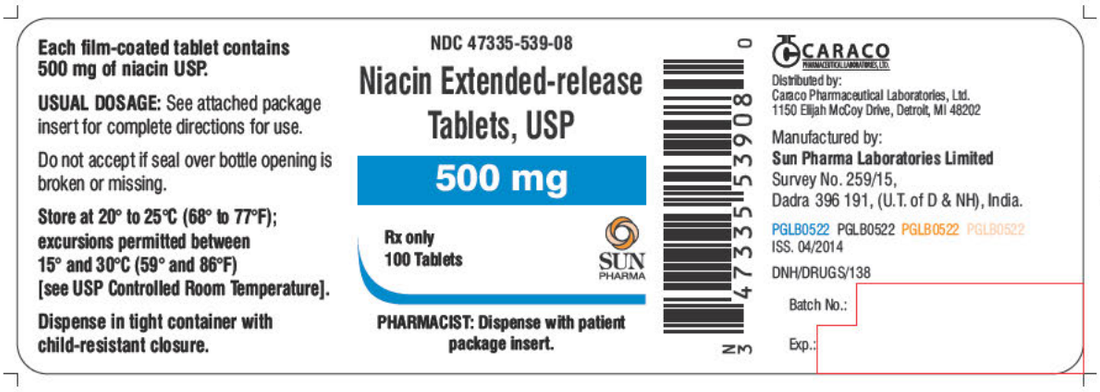
Reference ID: 3487614



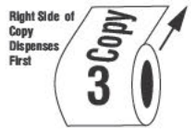
Name of Product: Niacin ER Tabs-500mg-US-100T CRC		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0521	Void artwork Code No:		CD-	
Actual Size	152.4x50.8 mm	Reason :		REMARKS:	
Unvarnished Area	38x13mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black, (b) (4)			
Sticker Label Roll Form				Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				



Reference ID: 3487614



Name of Product: Niacin ER Tabs-500mg-US-100T NCRC		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0522	Void artwork Code No:		CD-	
Actual Size	152.4x50.8 mm	Reason :		REMARKS:	
Unvarnished Area	38x13mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				



Reference ID: 3487614

Each film-coated tablet contains 500 mg of niacin USP.

USUAL DOSAGE: See attached package insert for complete directions for use.

Do not accept if seal over bottle opening is broken or missing.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in tight container with child-resistant closure.

NDC 47335-539-18

Niacin Extended-release Tablets, USP

500 mg

Rx only
1000 Tablets

SUN PHARMA

PHARMACIST: Dispense with patient package insert.

CARACO PHARMACEUTICAL LABORATORIES, LTD.

Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191, (U.T. of D & NH), India.

PGLB0523 PGLB0523 PGLB0523 PGLB0523
ISS. 04/2014

DNH/DRUGS/138

Batch No.:

Exp.:

N 3 47335 53918 9

250 mm

Black

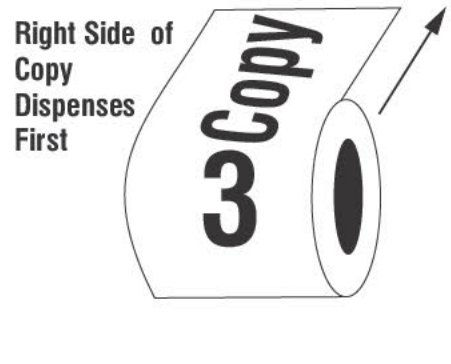
(b) (4)

Size: 250x90mm

[NCRC]

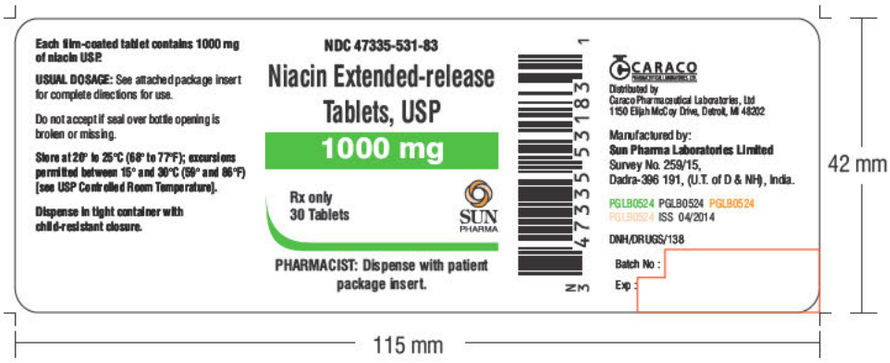
Unvarnish area: 65x17mm

Name of Product: Niacin ER Tabs-500mg-US-1000T		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0523	Void artwork Code No:		CD-	
Actual Size	250X90 MM	Reason :		REMARKS:	
Unvarnished Area	65x17mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				



100 95 75 25 5 0

Reference ID: 3487614



Black

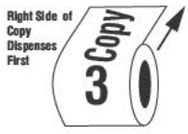
(b) (4)

Size: 115x42mm

[CRC]

Unvarnish area: 26 x 9 mm

Name of Product: Niacin ER Tabs-1000mg-30T		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0524	Void artwork Code No:		CD-	
Actual Size	115x42mm	Reason :		REMARKS:	
Unvarnished Area	26x9mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				



Reference ID: 3487614

Each film-coated tablet contains 1000 mg of niacin USP.

USUAL DOSAGE: See attached package insert for complete directions for use.

Do not accept if seal over bottle opening is broken or missing.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in tight container with child-resistant closure.

NDC 47335-531-81

Niacin Extended-release Tablets, USP

1000 mg

Rx only
90 Tablets

PHARMACIST: Dispense with patient package insert.

CARACO PHARMACEUTICAL LABORATORIES, LTD.
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191, (U.T. of D & NH),
India.

PGLB0646 PGLB0646 PGLB0646
PGLB0646 ISS. 04/2014

DNH/DRUGS/138

Batch No.:

Exp.:

161.9 mm

Black
(b) (4)

Size: 161.9x76.2 mm
[CRC]
Unvarnish area: 48 x 16 mm

Name of Product: Niacin ER Tabs-1000mg-US-90T		AWS TYPE: Labels	Country: ANDA-US	Language: English	Location: Dadra
Code	PGLB0646	Void artwork Code No:		CD-	
Actual Size	161.9x76.2 mm	Reason :		REMARKS:	
Unvarnished Area	48x16mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black, (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				

Right Side of Copy Dispenses First
3 Copy

Reference ID: 3487614

Each film-coated tablet contains 1000 mg of niacin USP.

USUAL DOSAGE: See attached package insert for complete directions for use.

Do not accept if seal over bottle opening is broken or missing.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in tight container with child-resistant closure.

NDC 47335-531-88

Niacin Extended-release Tablets, USP

1000 mg

Rx only
100 Tablets

SUN PHARMA

PHARMACIST: Dispense with patient package insert.

CARACO PHARMACEUTICAL LABORATORIES, LTD.
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191, (U.T. of D & NH),
India.

PGLB0525 PGLB0525 PGLB0525
PGLB0525 ISS. 04/2014

DNH/DRUGS/138

Batch No.:

Exp.:

161.9 mm

Black

(b) (4)

Size: 161.9x76.2 mm

[CRC]

Unvarnish area: 48 x 16 mm

Name of Product: Niacin ER Tabs-1000mg-US-100T CRC		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0525	Void artwork Code No:		CD-	
Actual Size	161.9x76.2 mm	Reason :		REMARKS:	
Unvarnished Area	48x16mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				

Right Side of Copy Dispenses First

3 Copy

Reference ID: 3487614

Each film-coated tablet contains 1000 mg of niacin USP.

USUAL DOSAGE: See attached package insert for complete directions for use.

Do not accept if seal over bottle opening is broken or missing.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in tight container with child-resistant closure.

NDC 47335-531-08

Niacin Extended-release Tablets, USP

1000 mg

Rx only
100 Tablets

SUN PHARMA

PHARMACIST: Dispense with patient package insert.

CARACO PHARMACEUTICAL LABORATORIES, LTD.
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191, (U.T. of D & NH),
India.

PGLB0526 PGLB0526 PGLB0526
PGLB0526 ISS. 04/2014

DNH/DRUGS/138

4 47335 53108 3

Batch No.:

Exp.:

161.9 mm

Black

(b) (4)

Size: 161.9x76.2 mm

[NCRC]

Unvarnish area: 48 x 16 mm

Name of Product: Niacin ER Tabs-1000mg-US-100T NCRC			AWS TYPE: Labels	Country: ANDA-US	Language: English / Location: Dadra
Code	PGLB0526		Void artwork Code No:		CD-
Actual Size	161.9x76.2 mm		Reason :		REMARKS:
Unvarnished Area	48x16mm		No. of Colors : 4		
Specification / Type of Paper			Color codes: Black, (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish		Prepared by	Checked by	Approved by / Approved by (b) (6)
	U.V.	-	APPROVAL HISTORY ATTACHED		
	Aqueous	YES			

Right Side of Copy Dispenses First

3 Copy

Reference ID: 3487614

Each film-coated tablet contains 1000 mg of niacin USP.

USUAL DOSAGE: See attached package insert for complete directions for use.

Do not accept if seal over bottle opening is broken or missing.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in tight container with child-resistant closure.

NDC 47335-531-18

Niacin Extended-release Tablets, USP

1000 mg

Rx only
1000 Tablets

SUN PHARMA

PHARMACIST: Dispense with patient package insert.

CARACO PHARMACEUTICAL LABORATORIES, LTD.

Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191, (U.T. of D & NH),
India.

PGLB0527 PGLB0527 PGLB0527
PGLB0527 ISS. 04/2014

DNH/DRUGS/138

Batch No.:

Exp.:

N 3 47335 53118 3

250 mm

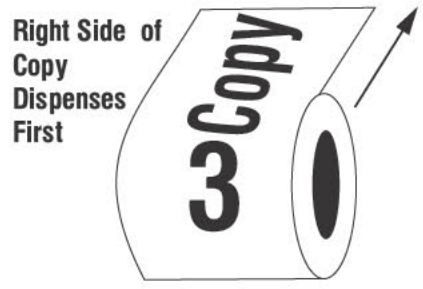
Black

(b) (4)

Size: 250x90mm
[NCRC]

Unvarnish area: 65x17mm

Name of Product: Niacin ER Tabs-1000mg-US-1000T		AWS TYPE	Country	Language	Location
		Labels	ANDA-US	English	Dadra
Code	PGLB0527	Void artwork Code No:		CD-	
Actual Size	250x90 mm	Reason :		REMARKS:	
Unvarnished Area	65x17mm	No. of Colors : 4			
Specification / Type of Paper		Color codes: Black (b) (4)		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
Sticker Label Roll Form					
(b) (4)					
Lamination	Varnish	Prepared by	Checked by	Approved by	Approved by (b) (6)
	U.V. -	APPROVAL HISTORY ATTACHED			
	Aqueous YES				



100 95 75 25 5 0

Reference ID: 3487614

47335PGPI0294

Niacin Extended-Release Tablets, USP 500 mg and 1000 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NIACIN extended-release safely and effectively. See full prescribing information for NIACIN extended-release tablets.

NIACIN extended-release tablets, USP, film-coated, extended-release for oral use

Initial U.S. Approval: 1997

--RECENT MAJOR CHANGES--

Indications and Usage: Limitations of Use (1) 02/2013
Warnings and Precautions, Mortality and Coronary Heart Disease Morbidity (5.1) 02/2013

--INDICATIONS AND USAGE--

Niacin extended-release tablets, USP contain extended-release niacin (nicotinic acid), and are indicated:

- To reduce elevated TC, LDL-C, Apo B and TG, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.(1)
- *In combination with simvastatin or lovastatin:* to treat primary hyperlipidemia and mixed dyslipidemia when treatment with niacin extended-release tablets, simvastatin, or lovastatin monotherapy is considered inadequate. (1)
- To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia.(1)
- *In combination with a bile acid binding resin:*
  - Slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hyperlipidemia. (1)
  - As an adjunct to diet to reduce elevated TC and LDL-C in adult patients with primary hyperlipidemia. (1)
- To reduce TG in adult patients with severe hypertriglyceridemia. (1)

Limitations of use:
No incremental benefit of niacin extended-release coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin and lovastatin monotherapy, has been established.

Niacin extended-release, at doses of 1,500 to 2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline LDL-C levels of 74 mg per deciliter (5.1).

---------------------------------------DOSAGE AND ADMINISTRATION---------------------------------------

- Niacin extended-release tablets, USP should be taken at bedtime with a low-fat snack. (2)
- Dose range: 500 mg to 2000 mg once daily. (2)
- Therapy with niacin extended-release tablets, USP must be initiated at 500 mg at bedtime in order to reduce the incidence and severity of side effects which may occur during early therapy and should not be increased by more than 500 mg in any four week period. (2)
- Maintenance dose: 1000 mg to 2000 mg once daily. (2)
- Doses greater than 2000 mg daily are not recommended. (2)
- Concomitant therapy with lovastatin: Initial dose of lovastatin is 20 mg once a day; combination therapy with niacin extended-release tablets, USP and lovastatin should not exceed doses of 2000 mg and 40 mg daily, respectively. (2)
- Concomitant therapy with simvastatin: Initial dose of simvastatin is 20 mg once a day; combination therapy with niacin extended-release tablets, USP and simvastatin should not exceed doses of 2000 mg and 40 mg daily, respectively. (2)

--------------------------------------DOSAGE FORMS AND STRENGTHS--------------------------------------

Unscored film-coated tablets for oral administration: 500 mg and 1000 mg niacin extended-release. (3)

---CONTRAINDICATIONS---

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. (4, 5.3)
- Active peptic ulcer disease. (4)
- Arterial bleeding. (4)
- Known hypersensitivity to product components. (4, 6.1)

-------------------------------------WARNINGS AND PRECAUTIONS-------------------------------------

- Severe hepatic toxicity has occurred in patients substituting sustained-release niacin for immediate-release niacin at equivalent doses. (5.3)
- Myopathy has been reported in patients taking niacin extended-release tablets. The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with niacin extended-release, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism. (5.2)
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (5.3)
- Use with caution in patients with unstable angina or in the acute phase of an MI. (5)
- Niacin extended-release can increase serum glucose levels. Glucose levels should be closely monitored in diabetic or potentially diabetic patients particularly during the first few months of use or dose adjustment. (5.4)

--ADVERSE REACTIONS--

Most common adverse reactions (incidence >5% and greater than placebo) are flushing, diarrhea, nausea, vomiting, increased cough, and pruritus. (6.1)

Flushing of the skin may be reduced in frequency or severity by pretreatment with aspirin (up to the recommended dose of 325 mg taken 30 minutes prior to niacin extended-release dose).(2)

To report SUSPECTED ADVERSE REACTIONS, contact CARACO Pharmaceutical Laboratories Ltd. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--DRUG INTERACTIONS--

- Statins: Caution should be used when prescribing niacin with statins as these agents can increase risk of myopathy/rhabdomyolysis. (5.2, 7.1)
- Bile Acid Sequestrants: Bile acid sequestrants have a high niacin-binding capacity and should be taken at least 4 to 6 hours before niacin extended-release administration. (7.2)

---------------------------------------USE IN SPECIFIC POPULATIONS---------------------------------------

- Renal impairment: Niacin extended-release tablets should be used with caution in patients with renal impairment. (5, 8.6)
- Hepatic impairment: Niacin extended-release tablets are contraindicated in active liver disease or significant or unexplained hepatic dysfunction or unexplained elevations of serum transaminases. (4, 5, 5.3, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hyperlipidemia. Niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

1. Niacin extended-release tablets, USP are indicated to reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.
2. Niacin extended-release in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with niacin extended-release, simvastatin, or lovastatin monotherapy is considered inadequate.
3. In patients with a history of myocardial infarction and hyperlipidemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
4. In patients with a history of coronary artery disease (CAD) and hyperlipidemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.
5. Niacin extended-release in combination with a bile acid binding resin is indicated to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia.
6. Niacin is also indicated as adjunctive therapy for treatment of adult patients with severe hypertriglyceridemia who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.

Limitations of Use
No incremental benefit of niacin extended-release coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin, or lovastatin monotherapy has been established.

Niacin extended-release, at doses of 1,500 to 2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline LDL-C levels of 74 mg per deciliter *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

Niacin extended-release tablets, USP should be taken at bedtime, after a low-fat snack, and doses should be individualized according to patient response. Therapy with niacin extended-release tablets, USP must be initiated at 500 mg at bedtime in order to reduce the incidence and severity of side effects which may occur during early therapy. The recommended dose escalation is shown in Table 1 below.

Table 1. Recommended Dosing

	Week(s)	Daily dose	Niacin Extended-Release Dosage
INITIAL TITRATION SCHEDULE	1 to 4	500 mg	1 niacin extended-release 500 mg tablet at bedtime
	5 to 8	1000 mg	1 niacin extended-release 1000 mg tablet or 2 niacin extended-release 500 mg tablets at bedtime
	*	1500 mg	2 niacin extended-release 750 mg tablets or 3 niacin extended-release 500 mg tablets at bedtime
	*	2000 mg	2 niacin extended-release 1000 mg tablets or 4 niacin extended-release 500 mg tablets at bedtime

* After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended. Women may respond at lower doses than men.

Maintenance Dose
The daily dosage of niacin extended-release tablets, USP should not be increased by more than 500 mg in any 4-week period. The recommended maintenance dose is 1000 mg (two 500 mg tablets or one 1000 mg tablet) to 2000 mg (two 1000 mg tablets or four 500 mg tablets) once daily at bedtime. Doses greater than 2000 mg daily are not recommended. Women may respond at lower niacin extended-release tablets, USP doses than men *[see Clinical Studies (14.2)]*.

Single-dose bioavailability studies have demonstrated that two of the 500 mg and one of the 1000 mg tablet strengths are interchangeable but three of the 500 mg and two of the 750 mg tablet strengths are not interchangeable.

If lipid response to niacin extended-release tablets, USP alone is insufficient or if higher doses of niacin extended-release tablets, USP are not well tolerated, some patients may benefit from combination therapy with a bile acid binding resin or statin *[see Drug Interactions (7.3), Concomitant Therapy below and Clinical Studies (14.3, 14.4)]*.

Flushing of the skin *[see Adverse Reactions (6.1)]* may be reduced in frequency or severity by pretreatment with aspirin (up to the recommended dose of 325 mg taken 30 minutes prior to niacin extended-release tablets, USP dose). Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach. Concomitant alcoholic, hot drinks or spicy foods may increase the side effects of flushing and pruritus and should be avoided around the time of niacin extended-release tablets, USP ingestion.

Equivalent doses of niacin extended-release tablets, USP should not be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin *[see Warnings and Precautions (5)]*. Patients previously receiving other niacin products should be started with the recommended niacin extended-release tablets, USP titration schedule (see Table 1), and the dose should subsequently be individualized based on patient response.

If niacin extended-release tablets, USP therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see Table 1).

Niacin extended-release tablets, USP should be taken whole and should not be broken, crushed or chewed before swallowing.

Concomitant Therapy
Concomitant Therapy with Lovastatin or Simvastatin
Patients already receiving a stable dose of lovastatin or simvastatin who require further TG-lowering or HDL-raising (e.g., to achieve NCEP non-HDL-C goals), may receive concomitant dosage titration with niacin extended-release tablets, USP per niacin extended-release tablets, USP recommended initial titration schedule *[see Dosage and Administration (2)]*. For patients already receiving a stable dose of niacin extended-release tablets, USP who require further LDL-lowering (e.g., to achieve NCEP LDL-C goals), the usual recommended starting dose of lovastatin and simvastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with niacin extended-release tablets, USP and lovastatin or niacin extended-release tablets, USP and simvastatin should not exceed doses of 2000 mg niacin extended-release tablets, USP and 40 mg lovastatin or simvastatin daily.

Dosage in Patients with Renal or Hepatic Impairment
Use of niacin extended-release tablets, USP in patients with renal or hepatic impairment has not been studied. Niacin extended-release tablets, USP are contraindicated in patients with significant or unexplained hepatic dysfunction. Niacin extended-release tablets, USP should be used with caution in patients with renal impairment *[see Warnings and Precautions (5)]*.

3 DOSAGE FORMS AND STRENGTHS

- 500 mg unscored, pink, film-coated, capsule-shaped tablets
- 1000 mg unscored, pink, film-coated, capsule-shaped tablets

4 CONTRAINDICATIONS

Niacin extended-release tablets are contraindicated in the following conditions:

- Active liver disease or unexplained persistent elevations in hepatic *transaminases [see Warnings and Precautions (5.3)]*
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Hypersensitivity to niacin or any component of this medication *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

Niacin extended-release tablets preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to niacin extended-release tablets, therapy with niacin extended-release tablets should be initiated with low doses (i.e., 500 mg at bedtime) and the niacin extended-release tablets dose should then be titrated to the desired therapeutic response *[see Dosage and Administration (2)]*.

Caution should also be used when niacin extended-release is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. Niacin extended-release is contraindicated in patients with significant or unexplained hepatic impairment *[see Contraindications (4) and Warnings and Precautions (5.3)]* and should be used with caution in patients with renal impairment. Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during niacin extended-release therapy.

5.1 Mortality and Coronary Heart Disease Morbidity

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was a randomized placebo-controlled trial of 3414 patients with stable, previously diagnosed cardiovascular disease. Mean baseline lipid levels were LDL-C 74 mg/dL, HDL-C 35 mg/dL, non-HDL-C 111 mg/dL and median triglyceride level of 163 to 177 mg/dL. Ninety-four percent of patients were on background statin therapy prior to entering the trial. All participants received simvastatin, 40 to 80 mg per day, plus ezetimibe 10 mg per day if needed, to maintain an LDL-C level of 40 to 80 mg/dL, and were randomized to receive niacin extended-release 1,500 to 2,000 mg/day (n=1718) or matching placebo (IR Niacin, 100 to 150 mg, n=1696). On-treatment lipid changes at two years for LDL-C were -12% for the simvastatin plus niacin extended-release group and -5.5% for the simvastatin plus placebo group. HDL-C increased by 25% to 42 mg/dL in the simvastatin plus niacin extended-release group and by 9.8% to 38 mg/dL in the simvastatin plus placebo group (P<0.001). Triglyceride levels decreased by 28.6% in the simvastatin plus niacin extended-release group and by 8.1% in the simvastatin plus placebo group. The primary outcome was an ITT composite of the first study occurrence of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization procedures. The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. The primary outcome occurred in 282 patients in the simvastatin plus niacin extended-release group (16.4%) and in 274 patients in the simvastatin plus placebo group (16.2%) (HR 1.02 [95% CI, 0.87 to 1.21], P=0.79. In an ITT analysis, there were 42 cases of first occurrence of ischemic stroke reported, 27 (1.6%) in the simvastatin plus niacin extended-release group and 15 (0.9%) in the simvastatin plus placebo group, a non-statistically significant result (HR 1.79, [95%CI = 0.95 to 3.36], p=0.071). The on-treatment ischemic stroke events were 19 for the simvastatin plus niacin extended-release group and 15 for the simvastatin plus placebo group *[see Adverse Reactions (6.1)]*.

5.2 Skeletal Muscle

Cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and statins. Physicians contemplating combined therapy with statins and niacin extended-release should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with niacin extended-release, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism.

5.3 Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

Niacin extended-release should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of niacin extended-release.

Niacin preparations have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily niacin extended-release doses ranging from 500 mg to 3000 mg, 245 patients received niacin extended-release for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with niacin extended-release. In these studies, fewer than 1% (2/245) of niacin extended-release patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of niacin extended-release and lovastatin involving titration to final daily doses (expressed as mg of niacin/mg of lovastatin) 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1%) experienced reversible elevations in AST/ALT to more than 3 times the ULN. Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

Niacin extended-release and simvastatin can cause abnormal liver tests. In a simvastatin-controlled, 24 week study with a fixed dose combination of niacin extended-release and simvastatin in 641 patients, there were no persistent increases (more than 3x the ULN) in serum transaminases. In three placebo-controlled clinical studies of extended-release niacin there were no patients with normal serum transaminase levels at baseline who experienced elevations to more than 3x the ULN. Persistent increases (more than 3x the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminases levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of niacin extended-release.

Liver function tests should be performed on all patients during therapy with niacin extended-release. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

5.4 Laboratory Abnormalities

Increase in Blood Glucose:
Niacin treatment can increase fasting blood glucose. Frequent monitoring of blood glucose should be performed to ascertain that the drug is producing no adverse effects. Diabetic patients may experience a dose-related increase in glucose intolerance. Diabetic or potentially diabetic patients should be observed closely during treatment with niacin extended-release, particularly during the first few months of use or dose adjustment; adjustment of diet and/or hypoglycemic therapy may be necessary.

Reduction in platelet count:
Niacin extended-release has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). Caution should be observed when niacin extended-release is administered concomitantly with anticoagulants; platelet counts should be monitored closely in such patients.

Increase in Prothrombin Time (PT):
Niacin extended-release has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when niacin extended-release is administered concomitantly with anticoagulants; prothrombin time should be monitored closely in such patients.

Increase in Uric Acid:
Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

Decrease in Phosphorus:
In placebo-controlled trials, niacin extended-release has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000 mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience

In the placebo-controlled clinical trials database of 402 patients (age range 21 to 75 years, 33% women, 89% Caucasians, 7% Blacks, 3% Hispanics, 1% Asians) with a median treatment duration of 16 weeks, 16% of patients on niacin extended-release and 4% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with niacin extended-release that led to treatment discontinuation and occurred at a rate greater than placebo were flushing (6% vs. 0%), rash (2% vs. 0%), diarrhea (2% vs. 0%), nausea (1% vs. 0%), and vomiting (1% vs. 0%). The most commonly reported adverse reactions (incidence >5% and greater than placebo) in the niacin extended-release controlled clinical trial database of 402 patients were flushing, diarrhea, nausea, vomiting, increased cough and pruritus.

In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse reactions (reported by as many as 88% of patients) for niacin extended-release. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, burning sensation/skin burning sensation, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, 6% (14/245) of niacin extended-release patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and niacin extended-release tablets, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received niacin extended-release tablets. Following 4 weeks of maintenance therapy at daily doses of 1500 mg, the incidence of flushing over the 4-week period averaged 8.6 events per patient for IR niacin versus 1.9 following niacin extended-release tablets.

Other adverse reactions occurring in ≥5% of patients treated with niacin extended-release tablets and at an incidence greater than placebo are shown in Table 2 below.

Table 2. Treatment-Emergent Adverse Reactions by Dose Level in ≥ 5% of Patients and at an Incidence Greater than Placebo; Regardless of Causality Assessment in Placebo-Controlled Clinical Trials

	Placebo-Controlled Studies Niacin Extended-Release Tablets Treatment@		Recommended Daily Maintenance Doses†		
	Placebo (n = 157) %	500 mg‡ (n = 87) %	1000 mg (n = 110) %	1500 mg (n = 136) %	2000 mg (n = 95) %
Gastrointestinal Disorders					
Diarrhea	13	7	10	10	14
Nausea	7	5	6	4	11
Vomiting	4	0	2	4	9
Respiratory					
Cough, Increased	6	3	2	< 2	8
Skin and Subcutaneous Tissue Disorders					
Pruritus	2	8	0	3	0
Rash	0	5	5	5	0
Vascular Disorders					
Flushing&	19	68	69	63	55

Note: Percentages are calculated from the total number of patients in each column.
† Adverse reactions are reported at the initial dose where they occur.
@ Pooled results from placebo-controlled studies; for niacin extended-release tablets, n = 245 and median treatment duration = 16 weeks. Number of niacin extended-release tablets patients (n) are not additive across doses.
‡ The 500 mg/day dose is outside the recommended daily maintenance dosing range *[see Dosage and Administration (2)]*.
& 10 patients discontinued before receiving 500 mg, therefore they were not included.

In general, the incidence of adverse events was higher in women compared to men.

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)
In AIM-HIGH involving 3,414 patients (mean age of 64 years, 15% women, 92% Caucasians, 34% with diabetes mellitus) with stable, previously diagnosed cardiovascular disease, all patients received simvastatin, 40 to 80 mg per day, plus ezetimibe 10 mg per day if needed, to maintain an LDL-C level of 40 to 80 mg/dL, and were randomized to receive niacin extended-release 1,500 to 2,000 mg/day (n=1718) or matching placebo (IR Niacin, 100 mg to 150 mg, n=1696). The incidence of the adverse reactions of "blood glucose increased" (6.4% vs. 4.5%) and "diabetes mellitus" (3.6% vs. 2.2%) was significantly higher in the simvastatin plus niacin extended-release group as compared to the simvastatin plus placebo group. There were 5 cases of rhabdomyolysis reported, 4 (0.2%) in the simvastatin plus niacin extended-release group and one (<0.1%) in the simvastatin plus placebo group *[see Warnings and Precautions (5.1)]*.

6.2 Postmarketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of niacin extended-release tablets:

Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash; maculopapular rash; dry skin; tachycardia; palpitations; atrial fibrillation; other cardiac arrhythmias; syncope; hypotension; postural hypotension; blurred vision; macular edema; peptic ulcers; eructation; flatulence; hepatitis; jaundice; decreased glucose tolerance; gout; myalgia; myopathy; dizziness; insomnia; asthenia; nervousness; paresthesia; dyspnea; sweating; burning sensation/skin burning sensation; skin discoloration, and migraine.

Clinical Laboratory Abnormalities
Chemistry: Elevations in serum transaminases *[see Warnings and Precautions (5.3)]*, LDH, fasting glucose, uric acid, total bilirubin, amylase and creatine kinase, and reduction in phosphorus.

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time *[see Warnings and Precautions (5.4)]*.

7 DRUG INTERACTIONS

7.1 Statins

Caution should be used when prescribing niacin (≥1 gm/day) with statins as these drugs can increase risk of myopathy/rhabdomyolysis. Combination therapy with niacin extended-release and lovastatin or niacin extended-release and simvastatin should not exceed doses of 2000 mg niacin extended-release and 40 mg lovastatin or simvastatin daily. *[see Warnings and Precautions (5) and Clinical Pharmacology (12.3)]*.

7.2 Bile Acid Sequestrants

An *in vitro* study results suggest that the bile acid-binding resins have high niacin binding capacity. Therefore, 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of niacin extended-release *[see Clinical Pharmacology (12.3)]*.

7.3 Aspirin

Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

7.4 Antihypertensive Therapy

Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

7.5 Other

Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of niacin extended-release.

7.6 Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.
Animal reproduction studies have not been conducted with niacin or with niacin extended-release tablets. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hyperlipidemia becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

All statins are contraindicated in pregnant and nursing women. When niacin extended-release is administered with a statin in a woman of childbearing potential, refer to the pregnancy category and product labeling for the statin.

8.3 Nursing Mothers

Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. No studies have been conducted with niacin extended-release tablets in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) have not been established.

8.5 Geriatric Use

Of 979 patients in clinical studies of niacin extended-release, 21% of the patients were age 65 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No studies have been performed in this population. Niacin extended-release should be used with caution in patients with renal impairment *[see Warnings and Precautions (5)]*.

8.7 Hepatic Impairment

No studies have been performed in this population. Niacin extended-release should be used with caution in patients with a past history of liver disease and/or who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations and significant or unexplained hepatic dysfunction are contraindications to the use of niacin extended-release *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

8.8 Gender

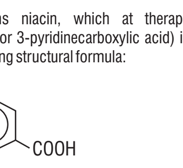
Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin extended-release.

10 OVERDOSAGE

Supportive measures should be undertaken in the event of an overdose.

11 DESCRIPTION

Niacin extended-release tablet, USP contains niacin, which at therapeutic doses is an antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, sparingly soluble in water, with the following structural formula:



$C_6H_5NO_2$ M.W. = 123.11

Niacin extended-release tablets, USP are unscored, pink, film-coated tablets for oral administration and are available in two tablet strengths containing 500 mg, and 1000 mg niacin USP. Niacin extended-release tablets, USP also contain the inactive ingredients hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

USP Dissolution Test Pending

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which niacin alters lipid profiles has not been well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

12.2 Pharmacodynamics

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C). The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL-C particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk. In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/proteins on cardiovascular morbidity or mortality in individuals without preexisting coronary disease has not been established.

A variety of clinical studies have demonstrated that elevated levels of TC, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C, and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

Absorption
Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Time to reach the maximum niacin plasma concentrations was about 5 hours following niacin extended-release tablets. To reduce the risk of gastrointestinal (GI) upset, administration of niacin extended-release tablets with a low-fat meal or snack is recommended.

Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent.

Metabolism
The pharmacokinetic profile of niacin is complicated due to extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose niacin extended-release tablets administration.

Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Elimination
Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as niacin extended-release tablets was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Pediatric Use
No pharmacokinetic studies have been performed in this population (≤16 years) *[see Use in Specific Populations (8.4)]*.

Geriatric Use
No pharmacokinetic studies have been performed in this population (> 65 years) [see Use in Specific Populations (8.5)].

Renal Impairment
No pharmacokinetic studies have been performed in this population. Niacin extended-release tablets should be used with caution in patients with renal disease *[see Warnings and Precautions (5)]*.

Hepatic Impairment
No pharmacokinetic studies have been performed in this population. Active liver disease, unexplained transaminase elevations and significant or unexplained hepatic dysfunction are contraindications to the use of niacin extended-release tablets *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Gender
Steady-state plasma concentrations of niacin and metabolites after administration of niacin extended-release tablets are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. This gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders *[see Gender (8.8)]*.

Drug interactions
Fluvastatin
Niacin did not affect fluvastatin pharmacokinetics *[see Drug Interactions (7.1)]*.

Lovastatin
When niacin extended-release 2000 mg and lovastatin 40 mg were co-administered, niacin extended-release increased lovastatin Cmax and AUC by 2% and 14%, respectively, and decreased lovastatin acid Cmax and AUC by 22% and 2%, respectively. Lovastatin reduced niacin extended-release bioavailability by 2 to 3% *[see Drug Interactions (7.1)]*.

Simvastatin
When niacin extended-release 2000 mg and simvastatin 40 mg were co-administered, niacin extended-release increased simvastatin Cmax and AUC by 1% and 9%, respectively, and simvastatin acid Cmax and AUC by 2% and 18%, respectively. Simvastatin reduced niacin extended-release bioavailability by 2% *[see Drug Interactions (7.1)]*.

Bile Acid Sequestrants
An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

Niacin administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3,000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed. No studies have been conducted with niacin extended-release regarding carcinogenesis, mutagenesis, or impairment of fertility.

14 CLINICAL STUDIES

14.1 Niacin Clinical Studies

The role of LDL-C in atherogenesis is supported by pathological observations, clinical studies, and many animal experiments. Observational epidemiological studies have clearly established that high TC or LDL-C and low HDL-C are risk factors for CHD. Additionally, elevated levels of Lp(a) have been shown to be independently associated with CHD risk.

Niacin's ability to reduce mortality and the risk of definite, nonfatal myocardial infarction (MI) has been assessed in long-term studies. The Coronary Drug Project, completed in 1975, was designed to assess the safety and efficacy of niacin and other lipid-altering drugs in men 30 to 64 years old with a history of MI. Over an observation period of 5 years, niacin treatment was associated with a statistically significant reduction in nonfatal, recurrent MI. The incidence of definite, nonfatal MI was 8.9% for the 1,119 patients randomized to nicotinic acid versus 12.2% for the 2,789 patients who received placebo (*p*<0.004). Total mortality was similar in the two groups at 5 years (24.4% with nicotinic acid versus 25.4% with placebo; *p*=N.S.). At the time of a 15-year follow-up, there were 11% (69) fewer deaths in the niacin group compared to the placebo cohort (52% versus 58.2%; *p*=0.0004). However, mortality at 15 years was not an original endpoint of the Coronary Drug Project. In addition, patients had not received niacin for approximately 9 years, and confounding variables such as concomitant medication use and medical or surgical treatments were not controlled.

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing combined colestipol and niacin therapy in 162 non-smoking males with previous coronary bypass surgery. The primary, per-subject cardiac endpoint was global coronary artery change score. After 2 years, 61% of patients in the placebo cohort showed disease progression by global change score (n=82), compared with only 38.8% of drug-treated subjects (n=80), when both native arteries and grafts were considered (*p*<0.005); disease regression also occurred more frequently in the drug-treated group (16.2% versus 2.4%; *p*=0.002). In a follow-up to this trial in a subgroup of 103 patients treated for 4 years, again, significantly fewer patients in the drug-treated group demonstrated progression than in the placebo cohort (48% versus 85%, respectively; *p*<0.0001).

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with Apo B levels ≥125 mg/dL, established coronary artery disease, and family histories of vascular disease, assessed change in severity of disease in the proximal coronary arteries by quantitative arteriography. Patients were given dietary counseling and randomized to treatment with either conventional therapy with double placebo (or placebo plus colestipol if the LDL-C was elevated); lovastatin plus colestipol; or niacin plus colestipol. In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least one of nine proximal coronary segments; regression was the only change in 11%. In contrast, progression (as the only change) was seen in only 25% in the niacin plus colestipol group, while regression was observed in 39%. Though not an original endpoint of the trial, clinical events (death, MI, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 who received niacin plus colestipol.

The Harvard Atherosclerosis Reversibility Project (HARP) was a randomized placebo-controlled, 2.5-year study of the effect of a stepped-care antihyperlipidemic drug regimen on 91 patients (80 men and 11 women) with CHD and average baseline TC levels less than 250 mg/dL and ratios of TC to HDL-C greater than 4. Drug treatment consisted of an HMG-CoA reductase inhibitor administered alone as initial therapy followed by addition of varying dosages of either a slow-release nicotinic acid, cholestyramine, or gemfibrozil. Addition of nicotinic acid to the HMG-CoA reductase inhibitor resulted in further statistically significant mean reductions in TC, LDL-C, and TG, as well as a further increase in HDL-C in a majority of patients (40 of 44 patients). The ratios of TC to HDL-C and LDL-C to HDL-C were also significantly reduced by this combination drug regimen *[see Warnings and Precautions (5.2)]*.

14.2 Niacin Extended-Release Tablets Clinical Studies

Placebo-Controlled Clinical Studies in Patients with Primary Hyperlipidemia and Mixed Dyslipidemia: In two randomized, double-blind, parallel, multi-center, placebo-controlled trials, niacin extended-release tablets dosed at 1000 mg, 1500 mg or 2000 mg daily at bedtime with a low-fat snack for 16 weeks (including 4 weeks of dose escalation) favorably altered lipid profiles compared to placebo (Table 3). Women appeared to have a greater response than men at each niacin extended-release tablets dose level (*see Gender Effect,* below).

Table 3. Lipid Response to Niacin Extended-Release Tablets Therapy

	Mean Percent Change from Baseline to Week 16*								
Treatment	**n**	**TC**	**LDL-C**	**HDL-C**	**TC/HDL-C**	**TG**	**Lp(a)**	**Apo B**	**Apo A-I**
Niacin extended-release tablets 1000 mg at bedtime	41	-3	-5	+18	-17	-21	-13	-6	+9
Niacin extended-release tablets 2000 mg at bedtime	41	-10	-14	+22	-25	-28	-27	-16	+8
Placebo	40	0	-1	+4	-3	0	0	+1	+3
Niacin extended-release tablets 1500 mg at bedtime	76	-8	-12	+20	-20	-13	-15	-12	+8
Placebo	73	+2	+1	+2	+1	+12	+2	+1	+2

n = number of patients at baseline;
* Mean percent change from baseline for all niacin extended-release tablets doses was significantly different ($p < 0.05$) from placebo for all lipid parameters shown except Apo A-I at 2000 mg.

In a double-blind, multi-center, forced dose-escalation study, monthly 500 mg increases in niacin extended-release tablets dose resulted in incremental reductions of approximately 5% in LDL-C and Apo B levels in the daily dose range of 500 mg through 2000 mg (Table 4). Women again tended to have a greater response to niacin extended-release tablets than men (*see Gender Effect*, below).

Table 4. Lipid Response in Dose-Escalation Study

		Mean Percent Change from Baseline*							
Treatment	**n**	**TC**	**LDL-C**	**HDL-C**	**TC/HDL-C**	**TG**	**Lp(a)**	**Apo B**	**Apo A-I**
Placebo‡	44	-2	-1	+5	-7	-6	-5	-2	+4
Niacin extended-release tablets	87								
500 mg at bedtime		-2	-3	+10	-10	-5	-3	-2	+5
1000 mg at bedtime		-5	-9	+15	-17	-11	-12	-7	+8
1500 mg at bedtime		-11	-14	+22	-26	-28	-20	-15	+10
2000 mg at bedtime		-12	-17	+26	-29	-35	-24	-16	+12

n = number of patients enrolled;
‡ Placebo data shown are after 24 weeks of placebo treatment.
* For all niacin extended-release tablets doses except 500 mg, mean percent change from baseline was significantly different ($p < 0.05$) from placebo for all lipid parameters shown except Lp(a) and Apo A-I which were significantly different from placebo starting with 1500 mg and 2000 mg, respectively.

Pooled results for major lipids from these three placebo-controlled studies are shown below (Table 5).

Table 5. Selected Lipid Response to Niacin Extended-Release Tablets in Placebo-Controlled Clinical Studies*

		Mean Baseline and Median Percent Change from Baseline (25th, 75th Percentiles)		
Niacin Extended-Release Tablets Dose	**n**	**LDL-C**	**HDL-C**	**TG**
1000 mg at bedtime	104			
Baseline (mg/dL)		218	45	172
Percent Change		-7 (-15, 0)	+14 (+7, +23)	-16 (-34, +3)
1500 mg at bedtime	120			
Baseline (mg/dL)		212	46	171
Percent Change		-13 (-21, -4)	+19 (+9, +31)	-25 (-45, -2)
2000 mg at bedtime	85			
Baseline (mg/dL)		220	44	160
Percent Change		-16 (-26, -7)	+22 (+15, +34)	-38 (-52, -14)

* Represents pooled analyses of results; minimum duration on therapy at each dose was 4 weeks.

Gender Effect:
Combined data from the three placebo-controlled niacin extended-release tablets studies in patients with primary hyperlipidemia and mixed dyslipidemia suggest that, at each niacin extended-release tablets dose level studied, changes in lipid concentrations are greater for women than for men (Table 6).

Table 6. Effect of Gender on Niacin Extended-Release Tablets Dose Response

Niacin Extended-Release Tablets	n	Mean Percent Change from Baseline							
		LDL-C		HDL-C		TG		Apo B	
Dose	(M/F)	M	F	M	F	M	F	M	F
500 mg at bedtime	50/37	-2	-5	+11	+8	-3	-9	-1	-5
1000 mg at bedtime	76/52	-6*	-11*	+14	+20	-10	-20	-5*	-10*
1500 mg at bedtime	104/59	-12	-16	+19	+24	-17	-28	-13	-15
2000 mg at bedtime	75/53	-15	-18	+23	+26	-30	-36	-16	-16

n = number of male/female patients enrolled.
* Percent change significantly different between genders ($p < 0.05$).

Other Patient Populations:
In a double-blind, multi-center, 19-week study the lipid-altering effects of niacin extended-release tablets (forced titration to 2000 mg at bedtime) were compared to baseline in patients whose primary lipid abnormality was a low level of HDL-C (HDL-C ≤40 mg/dL, TG ≤400 mg/dL, and LDL-C ≤160, or <130 mg/dL in the presence of CHD). Results are shown below (Table 7).

Table 7. Lipid Response to Niacin Extended-Release Tablets in Patients with Low HDL-C

	Mean Baseline and Mean Percent Change from Baseline*									
	n	**TC**	**LDL-C**	**HDL-C**	**TC/HDL-C**	**TG**	**Lp(a)†**	**Apo B†**	**Apo A-I†**	**Lp A-I††**
Baseline (mg/dL)	88	190	120	31	6	194	8	106	105	32
Week 19 (% Change)	71	-3	0	+26	-22	-30	-20	-9	+11	+20

n = number of patients
* Mean percent change from baseline was significantly different ($p < 0.05$) for all lipid parameters shown except LDL-C.
† n = 72 at baseline and 69 at week 19.
†† n = 30 at baseline and week 19.

At niacin extended-release tablets 2000 mg/day, median changes from baseline (25th, 75th percentiles) for LDL-C, HDL-C, and TG were -3% (-14, +12%), +27% (+13, +38%), and -33% (-50, -19%), respectively.

14.3 Niacin Extended-Release and Lovastatin Clinical Studies

Combination niacin extended-release and Lovastatin Study: In a multi-center, randomized, double-blind, parallel, 28-week study, a combination tablet of niacin extended-release and lovastatin was compared to each individual component in patients with Type IIa and IIb hyperlipidemia. Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with the combination tablet of niacin extended-release and lovastatin initially received 500 mg/20 mg (expressed as mg of niacin/mg of lovastatin) once daily before bedtime. The dose was increased by 500 mg at 4-week intervals (based on the niacin extended-release component) to a maximum dose of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The niacin extended-release monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks. Up to a third of the patients randomized to the combination tablet of niacin extended-release and lovastatin or niacin extended-release monotherapy discontinued prior to Week 28. Results from this study showed that combination therapy decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (Tables 8, 9, 10, and 11). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1. LDL-lowering with the combination tablet of niacin extended-release and lovastatin was significantly greater than that achieved with lovastatin 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg ($p<0.0001$)
2. The combination tablet of niacin extended-release and lovastatin at doses of 1000 mg/20 mg or higher achieved greater LDL-lowering than niacin extended-release ($p<0.0001$)

The LDL-C results are summarized in Table 8.

Table 8. LDL-C mean percent change from baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release			Lovastatin		
	n*	Dose (mg/mg)	LDL	n*	Dose (mg)	LDL	n*	Dose (mg)	LDL
Baseline	57	–	190.9 mg/dL	61	–	189.7 mg/dL	61	–	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1500/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

* n = number of patients remaining in trial at each time point

Combination therapy achieved significantly greater HDL-raising compared to lovastatin and niacin extended-release monotherapy at all doses (Table 9).

Folding
430--4 Zigzag--40 mm
570--14 Zigzag--40 mm

430 mm

Size: 430x570 mm

Name of Product: Niacin ER Tabs-Outsert-US-430x570mm (WO 750 mg)	AWS TYPE	Country	Language	Location
	Outsert	ANDA-US	English	Dadra
Code: PGPI0294	Void artwork Code No:		CD-	
Actual Size: 430x570mm	Reason:		REMARKS:	
	No. of Colors : 1			
Specification / Type of paper	Color codes: Black		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
(b) (4)				
Folding 430--4 Zigzag--40 mm 570--14 Zigzag--40 mm	Prepared by	Checked by	Approved by	Approved by (b) (6)
	APPROVAL HISTORY ATTACHED			

100 95 75 25 5 0

Table 9. HDL-C mean percent change from baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release			Lovastatin		
	n*	Dose (mg/mg)	HDL	n*	Dose (mg)	HDL	n*	Dose (mg)	HDL
Baseline	57	–	45 mg/dL	61	–	47 mg/dL	61	–	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

* n = number of patients remaining in trial at each time point

In addition, combination therapy achieved significantly greater TG lowering at doses of 1000 mg/20mg or greater compared to lovastatin and niacin extended-release monotherapy (Table 10).

Table 10. TG median percent change from baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release			Lovastatin		
	n*	Dose (mg/mg)	TG	n*	Dose (mg)	TG	n*	Dose (mg)	TG
Baseline	57	–	174 mg/dL	61	–	186	61 mg/dL	–	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

* n = number of patients remaining in trial at each time point

The Lp(a)-lowering effects of combination therapy and niacin extended-release monotherapy were similar, and both were superior to lovastatin (Table 11). The independent effect of lowering Lp(a) with niacin extended-release or combination therapy on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Table 11. Lp(a) median percent change from baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release			Lovastatin		
	n*	Dose (mg/mg)	Lp(a)	n*	Dose (mg)	Lp(a)	n*	Dose (mg)	Lp(a)
Baseline	57	–	34 mg/dL	61	–	41 mg/dL	60	–	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

* n = number of patients remaining in trial at each time point

14.4 Niacin Extended-Release and Simvastatin Clinical Studies
In a double-blind, randomized, multicenter, multi-national, active-controlled, 24-week study, the lipid effects of a combination tablet of niacin extended-release and simvastatin were compared to simvastatin 20 mg and 80 mg in 641 patients with type II hyperlipidemia or mixed dyslipidemia. Following a lipid qualification phase, patients were eligible to enter one of two treatment groups. In Group A, patients on simvastatin 20 mg monotherapy, with elevated non-HDL levels and LDL-C levels at goal per the NCEP guidelines, were randomized to one of three treatment arms: combination tablet of niacin extended-release and simvastatin 1000/20 mg, combination tablet of niacin extended-release and simvastatin 2000/20 mg, or simvastatin 20 mg. In Group B, patients on simvastatin 40 mg monotherapy, with elevated non-HDL levels per the NCEP guidelines regardless of attainment of LDL-C goals, were randomized to one of three treatment arms: combination tablet of niacin extended-release and simvastatin 1000/40 mg, combination tablet of niacin extended-release and simvastatin 2000/40 mg, or simvastatin 80 mg. Therapy was initiated at the 500 mg dose of combination tablet of niacin extended-release and simvastatin and increased by 500 mg every four weeks. Thus patients were titrated to the 1000 mg dose of combination tablet of niacin extended-release and simvastatin after four weeks and to the 2000 mg dose of combination tablet of niacin extended-release and simvastatin after 12 weeks. All patients randomized to simvastatin monotherapy received 50 mg immediate-release niacin daily in an attempt to keep the study from becoming unblinded due to flushing in the combination tablet of niacin extended-release and simvastatin groups. Patients were instructed to take one 325 mg aspirin or 200 mg ibuprofen 30 minutes prior to taking the double-blind medication to help minimize flushing effects.

In Group A, the primary efficacy analysis was a comparison of the mean percent change in non-HDL levels between the combination tablet of niacin extended-release and simvastatin 2000/20 mg and simvastatin 20 mg groups, and if statistically significant, then a comparison was conducted between the combination tablet of niacin extended-release and simvastatin 1000/20 mg and simvastatin 20 mg groups. In Group B, the primary efficacy analysis was a determination of whether the mean percent change in non-HDL in the combination tablet of niacin extended-release and simvastatin 2000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group, and if so, whether the mean percent change in non-HDL in the combination tablet of niacin extended-release and simvastatin 1000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group.

In Group A, the non-HDL-C lowering with combination tablet of niacin extended-release and simvastatin 2000/20 and combination tablet of niacin extended-release and simvastatin 1000/20 was statistically significantly greater than that achieved with simvastatin 20 mg after 24 weeks ($p < 0.05$; Table 12). The completion rate after 24 weeks was 72% for the combination tablet of niacin extended-release and simvastatin arms and 88% for the simvastatin 20 mg arm. In Group B, the non-HDL-C lowering with combination tablet of niacin extended-release and simvastatin 2000/40 and combination tablet of niacin extended-release and simvastatin 1000/40 was non-inferior to that achieved with simvastatin 80 mg after 24 weeks (Table 13). The completion rate after 24 weeks was 78% for the combination tablet of niacin extended-release and simvastatin arms and 80% for the simvastatin 80 mg arm.

The combination tablet of niacin extended-release and simvastatin was not superior to simvastatin in lowering LDL-C in either Group A or Group B. However, the combination tablet of niacin extended-release and simvastatin was superior to simvastatin in both groups in lowering TG and raising HDL (Tables 14 and 15).

Table 12. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20 mg Treated Baseline

Group A	Combination Tablet of Niacin Extended-Release and Simvastatin 2000/20			Combination Tablet of Niacin Extended-Release and Simvastatin 1000/20			Simvastatin 20		
Week	n*	Dose (mg/mg)	Non-HDL[b]	n*	Dose (mg/mg)	Non-HDL[b]	n*	Dose (mg/mg)	Non-HDL[b]
Baseline	56	–	163.1 mg/dL	108	–	164.8 mg/dL	102	–	163.7 mg/dL
4	52	500/20	-12.9%	86	500/20	-12.8%	91	20	-8.3%
8	46	1000/20	-17.5%	91	1000/20	-15.5%	95	20	-8.3%
12	46	1500/20	-18.9%	90	1000/20	-14.8%	96	20	-6.4%
24	40	2000/20	-19.5%[†]	78	1000/20	-13.6%[†]	90	20	-5%
Dropouts by week 24:	28.6%			27.8%			11.8%		

* n=number of subjects with values in the analysis window at each timepoint
[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.
† significant vs. simvastatin 20 mg at the primary endpoint (Week 24), $p < 0.05$

Table 13. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 40 mg Treated Baseline

Group B	Combination Tablet of Niacin Extended-Release and Simvastatin 2000/40			Combination Tablet of Niacin Extended-Release and Simvastatin 1000/40			Simvastatin 80		
Week	n*	Dose (mg/mg)	Non-HDL[b]	n*	Dose (mg/mg)	Non-HDL[b]	n*	Dose (mg/mg)	Non-HDL[b]
Baseline	98	–	144.4 mg/dL	111	–	141.2 mg/dL	113	–	134.5 mg/dL
4	96	500/40	-6%	108	500/40	-5.9%	110	80	-11.3%
8	93	1000/40	-15.5%	100	1000/40	-16.2%	104	80	-13.7%
12	90	1500/40	-18.4%	97	1000/40	-12.6%	100	80	-9.5%
24	80	2000/40	-7.6%[‡]	82	1000/40	-6.7%[ǂ]	90	80	-6%
Dropouts by week 24:	18.4%			26.1%			20.4%		

* n=number of subjects with values in the analysis window at each timepoint
[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.
[c] non-inferior to simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for the combination tablet of niacin extended-release and simvastatin 2000/40 vs. simvastatin 80 is (-7.7%, 4.5%)
[d] non-inferior to simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for combination tablet of niacin extended-release and simvastatin 1000/40 vs. combination tablet of niacin extended-release and simvastatin 80 is (-6.6%, 5.3%)

Table 14. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

Treatment Group A

TREATMENT	N	LDL-C	Total-C	HDL-C	TG*	Apo B
Baseline (mg/dL)*	266	120	207	43	209	102
Simvastatin 20 mg	102	-6.7%	-4.5%	7.8%	-15.3%	-5.6%
Combination Tablet of Niacin Extended-Release and Simvastatin 1000/20	108	-11.9%	-8.8%	20.7%	-26.5%	-13.2%
Combination Tablet of Niacin Extended-Release and Simvastatin 2000/20	56	-14.3%	-11.1%	29%	-38%	-18.5%

* either treatment naïve or after receiving simvastatin 20 mg
* medians are reported for TG

Table 15. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

Treatment Group B

TREATMENT	N	LDL-C	Total-C	HDL-C	TG*	Apo B
Baseline (mg/dL)*	322	108	187	47	145	93
Simvastatin 80 mg	113	-11.4%	-6.2%	0.1%	0.3%	-7.5%
Combination Tablet of Niacin Extended-Release and Simvastatin 1000/40	111	-7.1%	-3.1%	15.4%	-22.8%	-7.7%
Combination Tablet of Niacin Extended-Release and Simvastatin 2000/40	98	-5.1	-1.6%	24.4%	-31.8%	-10.5%

* after receiving simvastatin 40 mg
* medians are reported for TG

16 HOW SUPPLIED/STORAGE AND HANDLING
Niacin extended-release tablets, USP are supplied as unscored, pink, film-coated, capsule-shaped tablets containing 500 mg or 1000 mg of niacin USP in an extended-release formulation. Tablets are debossed 'S' on one side and the tablet strength (500 or 1000) on the other side.
Tablets are supplied as follows:

500 mg tablets:
Bottles of 30's with Child Resistant Cap.....NDC 47335-539-83
Bottles of 90's with Child Resistant Cap.....NDC 47335-539-81
Bottles of 100's with Child Resistant Cap.....NDC 47335-539-88
Bottles of 100's with Non Child Resistant Cap.....NDC 47335-539-08
Bottles of 1000's with Non Child Resistant Cap.....NDC 47335-539-18

1000 mg tablets
Bottles of 30's with Child Resistant Cap.....NDC 47335-531-83
Bottles of 90's with Child Resistant Cap.....NDC 47335-531-81
Bottles of 100's with Child Resistant Cap.....NDC 47335-531-88
Bottles of 100's with Non Child Resistant Cap.....NDC 47335-531-08
Bottles of 1000's with Non Child Resistant Cap.....NDC 47335-531-18

Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in a tight container with child-resistant closure.

17 PATIENT COUNSELING INFORMATION

17.1 Patient Counseling

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP) recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised to inform other healthcare professionals prescribing a new medication that they are taking niacin extended-release tablets.

The patient should be informed of the following:

Dosing Time
Niacin extended-release tablets should be taken at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.

Tablet Integrity
Niacin extended-release tablets should not be broken, crushed or chewed, but should be swallowed whole.

Dosing Interruption
If dosing is interrupted for any length of time, their physician should be contacted prior to restarting therapy; re-titration is recommended.

Muscle Pain
Notify their physician of any unexplained muscle pain, tenderness, or weakness promptly. They should discuss all medication, both prescription and over the counter, with their physician.

Flushing
Flushing (warmth, redness, itching and/or tingling of the skin) is a common side effect of niacin therapy that may subside after several weeks of consistent niacin extended-release tablets use. Flushing may vary in severity and is more likely to occur with initiation of therapy, or during dose increases. By dosing at bedtime, flushing will most likely occur during sleep. However, if awakened by flushing at night, the patient should get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications. Advise patients of the symptoms of flushing and how they differ from the symptoms of a myocardial infarction.

Use of Aspirin Medication
Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes before dosing can minimize flushing.

Diet
Avoid ingestion of alcohol, hot beverages and spicy foods around the time of taking niacin extended-release tablets to minimize flushing.

Supplements
Notify their physician if they are taking vitamins or other nutritional supplements containing niacin or nicotinamide.

Dizziness
Notify their physician if symptoms of dizziness occur.

Diabetics
If diabetic, to notify their physician of changes in blood glucose.

Pregnancy
Discuss future pregnancy plans with your patients, and discuss when to stop niacin extended-release tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking niacin extended-release tablets and call their healthcare professional.

Breastfeeding
Women who are breastfeeding should be advised to not use niacin extended-release tablets. Patients, who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

PATIENT INFORMATION

Niacin (nahy-uh-sin) Extended-Release Tablets, USP

Read this information carefully before you start taking niacin extended-release tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are niacin extended-release tablets?
Niacin extended-release tablets are prescription medicines used with diet and exercise to increase the good cholesterol (HDL) and lower the bad cholesterol (LDL) and fats (triglycerides) in your blood.
- Niacin extended-release tablets can be used by itself or with other cholesterol-lowering medicines
- Niacin extended-release tablets are also used to lower the risk of heart attack in people who have had a heart attack and have high cholesterol.
- In people with coronary artery disease and high cholesterol, niacin extended-release tablets, when used with a bile acid-binding resin (another cholesterol medicine) can slow down or lessen the build-up of plaque (fatty deposits) in your arteries
- In people with heart problems and well-controlled cholesterol, taking niacin extended-release tablets with another cholesterol-lowering medicine (simvastatin) has not been shown to reduce heart attacks or strokes more than taking simvastatin alone.

It is not known if niacin extended-release tablets are safe and effective in children 16 years of age and under.

Who should not take niacin extended-release tablets?

Do not take niacin extended-release tablets if you have:
- liver problems
- a stomach ulcer
- bleeding problems
- an allergy to niacin or any of the ingredients in niacin extended-release tablets. See the end of this leaflet for a complete list of ingredients in niacin extended-release tablets.

What should I tell my doctor before taking niacin extended-release tablets?

Before you take niacin extended-release tablets, tell your doctor, if you:
- have diabetes. Tell your doctor if your blood sugar levels change after you take niacin extended-release tablets.
- have gout
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if niacin extended-release tablets will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant while taking niacin extended-release tablets.
- are breastfeeding or plan to breastfeed. Niacin can pass into your breast milk. You and your doctor should decide if you will take niacin extended-release tablets or breastfeed. You should not do both. Talk to your doctor about the best way to feed your baby if you take niacin extended-release tablets.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, herbal supplements or other nutritional supplements containing niacin or nicotinamide. Niacin extended-release tablets and other medicines may affect each other causing side effects. Niacin extended-release tablets may affect the way other medicines work, and other medicines may affect how niacin extended-release tablets work.

Especially tell your doctor if you take:
- other medicines to lower cholesterol or triglycerides
- aspirin
- blood pressure medicines
- blood thinner medicines
- large amounts of alcohol

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take niacin extended-release tablets?
- Take niacin extended-release tablets exactly as your doctor tells you to take it.
- Take niacin extended-release tablets whole. Do not break, crush or chew niacin extended-release tablets before swallowing.
- Take niacin extended-release tablets 1 time a day at bedtime after a low-fat snack. Niacin extended-release tablets should not be taken on an empty stomach.
- All forms of niacin are not the same as niacin extended-release tablets. Do not switch between forms of niacin without first talking to your doctor as severe liver damage can occur.
- Do not change your dose or stop taking niacin extended-release tablets unless your doctor tells you to.
- If you need to stop taking niacin extended-release tablets, call your doctor before you start taking niacin extended-release tablets again. Your doctor may need to lower your dose of niacin extended-release tablets.
- If you forget to take a dose of niacin extended-release tablets, take it as soon as you remember.
- If you take too many niacin extended-release tablets, call your doctor right away.
- Medicines used to lower your cholesterol called bile acid resins, such as colestipol and cholestyramine, should not be taken at the same time of day as niacin extended-release tablets. You should take niacin extended-release tablets and the bile acid resin medicine at least 4 to 6 hours apart.
- Your doctor may do blood tests before you start taking niacin extended-release tablets and during your treatment. You should see your doctor regularly to check your cholesterol and triglyceride levels and to check for side effects.

What are the possible side effects of niacin extended-release tablets?

Niacin extended-release tablets may cause serious side effects, including:
- **severe liver problems. Signs of liver problems include:**
  - increased tiredness
  - dark colored urine (tea-colored)
  - loss of appetite
  - light colored stools
  - nausea
  - right upper stomach (abdomen) pain
  - yellowing of your skin or whites of your eye
  - itchy skin
- **unexplained muscle pain, tenderness or weakness**
- **high blood sugar level (glucose)**

Call your doctor right away if you have any of the side effects listed above.

The most common side effects of niacin extended-release tablets include:
- flushing
- diarrhea
- nausea
- vomiting
- increased cough
- rash

Flushing is the most common side effect of niacin extended-release tablets. Flushing happens when tiny blood vessels near the surface of the skin (especially on the face, neck, chest and/or back) open wider. Symptoms of flushing may include any or all of the following:
- warmth
- redness
- itching
- tingling of the skin

Flushing does not always happen. If it does, it is usually within 2 to 4 hours after taking a dose of niacin extended-release tablets. Flushing may last for a few hours. Flushing is more likely to happen when you first start taking niacin extended-release tablets or when your dose of niacin extended-release tablets is increased. Flushing may get better after several weeks.

If you wake up at night because of flushing, get up slowly, especially if you:
- feel dizzy or faint
- take blood pressure medicines

To lower your chance of flushing:
- Ask your doctor if you can take aspirin to help lower the flushing side effect from niacin extended-release tablets. You can take aspirin (up to the recommended dose of 325 mg) about 30 minutes before you take niacin extended-release tablets to help lower the flushing side effect.
- Do not drink hot beverages (including coffee), alcohol, or eat spicy foods around the time you take niacin extended-release tablets.
- Take niacin extended-release tablets with a low-fat snack to lessen upset stomach.

People with high cholesterol and heart disease are at risk for a heart attack. Symptoms of a heart attack may be different from a flushing reaction from niacin extended-release tablets. **The following may be symptoms of a heart attack due to heart disease and not a flushing reaction:**
- chest pain
- pain in other areas of your upper body such as one or both arms, back, neck, jaw or stomach
- shortness of breath
- sweating
- nausea
- lightheadedness

The chest pain you have with a heart attack may feel like uncomfortable pressure, squeezing, fullness or pain that lasts more than a few minutes, or that goes away and comes back. Heart attacks may be sudden and intense, but often start slowly, with mild pain or discomfort.

Call your doctor right away if you have any symptoms of a heart attack.

Tell your doctor if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of niacin extended-release tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store niacin extended-release tablets?
- Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F).

Keep niacin extended-release tablets and all medicines out of the reach of children.

General information about the safe and effective use of niacin extended-release tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use niacin extended-release tablets for a condition for which it was not prescribed. Do not give niacin extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about niacin extended-release tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about niacin extended-release tablets that is written for health professionals.

For more information, call 1-800-818-4555.

What are the ingredients in niacin extended-release tablets?
Active ingredient:
niacin
Inactive Ingredients:
hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

This Patient Information has been approved by the U.S. Food and Drug Administration.

CARACO PHARMACEUTICAL LABORATORIES, LTD.
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Supplier logo here

SUN PHARMA
Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191 (U.T. of D & NH), India.

ISS. 04/2014
PGP0294

Folding
430--5 Zigzag--43 mm
570--7 Zigzag--40.71 mm

430 mm

Size: 430x570 mm

Reference ID: 3487614

47335PGPI0237

PATIENT INFORMATION

Niacin (nahy-uh-sin) Extended-Release Tablets, USP

Read this information carefully before you start taking niacin extended-release tablets and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are niacin extended-release tablets?
Niacin extended-release tablets are prescription medicines used with diet and exercise to increase the good cholesterol (HDL) and lower the bad cholesterol (LDL) and fats (triglycerides) in your blood.

- Niacin extended-release tablets can be used by itself or with other cholesterol-lowering medicines
- Niacin extended-release tablets are also used to lower the risk of heart attack in people who have had a heart attack and have high cholesterol.
- In people with coronary artery disease and high cholesterol, niacin extended-release tablets, when used with a bile acid-binding resin (another cholesterol medicine) can slow down or lessen the build-up of plaque (fatty deposits) in your arteries
- In people with heart problems and well-controlled cholesterol, taking niacin extended-release tablets with another cholesterol-lowering medicine (simvastatin) has not been shown to reduce heart attacks or strokes more than taking simvastatin alone.

It is not known if niacin extended-release tablets are safe and effective in children 16 years of age and under.

Who should not take niacin extended-release tablets?

Do not take niacin extended-release tablets if you have:

- liver problems
- a stomach ulcer
- bleeding problems
- an allergy to niacin or any of the ingredients in niacin extended-release tablets. See the end of this leaflet for a complete list of ingredients in niacin extended-release tablets.

What should I tell my doctor before taking niacin extended-release tablets?

Before you take niacin extended-release tablets, tell your doctor, if you:

- have diabetes. Tell your doctor if your blood sugar levels change after you take niacin extended-release tablets.
- have gout
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if niacin extended-release tablets will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant while taking niacin extended-release tablets.
- are breastfeeding or plan to breastfeed. Niacin can pass into your breast milk. You and your doctor should decide if you will take niacin extended-release tablets or breastfeed. You should not do both. Talk to your doctor about the best way to feed your baby if you take niacin extended-release tablets.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, herbal supplements or other nutritional supplements containing niacin or nicotinamide. Niacin extended-release tablets and other medicines may affect each other causing side effects. Niacin extended-release tablets may affect the way other medicines work, and other medicines may affect how niacin extended-release tablets work.

Especially tell your doctor if you take:

- other medicines to lower cholesterol or triglycerides
- aspirin
- blood pressure medicines
- blood thinner medicines
- large amounts of alcohol

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take niacin extended-release tablets?

- Take niacin extended-release tablets exactly as your doctor tells you to take it.
- Take niacin extended-release tablets whole. Do not break, crush or chew niacin extended-release tablets before swallowing.
- Take niacin extended-release tablets 1 time a day at bedtime after a low-fat snack. Niacin extended-release tablets should not be taken on an empty stomach.
- All forms of niacin are not the same as niacin extended-release tablets. Do not switch between forms of niacin without first talking to your doctor as severe liver damage can occur.
- Do not change your dose or stop taking niacin extended-release tablets unless your doctor tells you to.
- If you need to stop taking niacin extended-release tablets, call your doctor before you start taking niacin extended-release tablets again. Your doctor may need to lower your dose of niacin extended-release tablets.
- If you forget to take a dose of niacin extended-release tablets, take it as soon as you remember.
- If you take too many niacin extended-release tablets, call your doctor right away.
- Medicines used to lower your cholesterol called bile acid resins, such as colestipol and cholestyramine, should not be taken at the same time of day as niacin extended-release tablets. You should take niacin extended-release tablets and the bile acid resin medicine at least 4 to 6 hours apart.
- Your doctor may do blood tests before you start taking niacin extended-release tablets and during your treatment. You should see your doctor regularly to check your cholesterol and triglyceride levels and to check for side effects.

What are the possible side effects of niacin extended-release tablets?

Niacin extended-release tablets may cause serious side effects, including:

- **severe liver problems. Signs of liver problems include:**
  - increased tiredness
  - dark colored urine (tea-colored)
  - loss of appetite
  - light colored stools
  - nausea
  - right upper stomach (abdomen) pain
  - yellowing of your skin or whites of your eye
  - itchy skin
- **unexplained muscle pain, tenderness or weakness**
- **high blood sugar level (glucose)**

Call your doctor right away if you have any of the side effects listed above.

The most common side effects of niacin extended-release tablets include:

- flushing
- diarrhea
- nausea
- vomiting
- increased cough
- rash

Flushing is the most common side effect of niacin extended-release tablets. Flushing happens when tiny blood vessels near the surface of the skin (especially on the face, neck, chest and/or back) open wider. Symptoms of flushing may include any or all of the following:

- warmth
- redness
- itching
- tingling of the skin

Flushing does not always happen. If it does, it is usually within 2 to 4 hours after taking a dose of niacin extended-release tablets. Flushing may last for a few hours. Flushing is more likely to happen when you first start taking niacin extended-release tablets or when your dose of niacin extended-release tablets is increased. Flushing may get better after several weeks.

If you wake up at night because of flushing, get up slowly, especially if you:

- feel dizzy or faint
- take blood pressure medicines

To lower your chance of flushing:

- Ask your doctor if you can take aspirin to help lower the flushing side effect from niacin extended-release tablets. You can take aspirin (up to the recommended dose of 325 mg) about 30 minutes before you take niacin extended-release tablets to help lower the flushing side effect.

30 pages pad
365--2--91.25 mm
198--0--198 mm
Glueing on 198 mm side

365 mm

Size: 365x198 mm

Name of Product: Niacin ER Tabs-Outsert-US-430x570mm		AWS TYPE	Country	Language	Location
		PIL	ANDA-US	English	Dadra
Code	PGPI0237	Void artwork Code No:		CD-	
Actual Size	365X198mm	Reason:		REMARKS:	
		No. of Colors : 1			
Specification / Type of paper		Color codes: Black		Artwork Prepared by : Sun Pharmaceutical Industries Limited Packaging Development Department [PDD] SPIL - Vadodara	
(b) (4)					
30 pages pad 365--2--91.25 mm 198--0--198 mm Glueing on 198 mm side		Prepared by	Checked by	Approved by	Approved by (b) (6)
		APPROVAL HISTORY ATTACHED			

Reference ID: 3487614

- Do not drink hot beverages (including coffee), alcohol, or eat spicy foods around the time you take niacin extended-release tablets.
- Take niacin extended-release tablets with a low-fat snack to lessen upset stomach.

People with high cholesterol and heart disease are at risk for a heart attack. Symptoms of a heart attack may be different from a flushing reaction from niacin extended-release tablets. **The following may be symptoms of a heart attack due to heart disease and not a flushing reaction:**
- chest pain
- pain in other areas of your upper body such as one or both arms, back, neck, jaw or stomach
- shortness of breath
- sweating
- nausea
- lightheadedness

The chest pain you have with a heart attack may feel like uncomfortable pressure, squeezing, fullness or pain that lasts more than a few minutes, or that goes away and comes back. Heart attacks may be sudden and intense, but often start slowly, with mild pain or discomfort.

Call your doctor right away if you have any symptoms of a heart attack.

Tell your doctor if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of niacin extended-release tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store niacin extended-release tablets?
- Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F)

Keep niacin extended-release tablets and all medicines out of the reach of children.

General information about the safe and effective use of niacin extended-release tablets
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use niacin extended-release tablets for a condition for which it was not prescribed. Do not give niacin extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about niacin extended-release tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about niacin extended-release tablets that is written for health professionals.

For more information, call 1-800-818-4555.

What are the ingredients in niacin extended-release tablets?
Active ingredient:
niacin
Inactive Ingredients:
hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

This Patient Information has been approved by the U.S. Food and Drug Administration.

CARACO PHARMACEUTICAL LABORATORIES, LTD.
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

SS 03/2014
PGP 0237

Supplier logo here

SUN PHARMA
Manufactured by:
Sun Pharma Laboratories Limited
Survey No. 259/15,
Dadra-396 191 (U.T. of D & NH), India.

30 pages pad
365--2--91.25 mm
198--0--198 mm
Glueing on 198 mm side

365 mm

Size: 365x198 mm

Reference ID: 3487614

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

LABELING REVIEWS

APPROVAL SUMMARY #2

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (6th cycle)

ANDA Number:	200484
Date of Submission:	April 2, 2014
Applicant:	Sun Pharma Global FZE
Established Name and Strength:	Niacin Extended-release Tablets USP, 500 mg and 1000 mg
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments (Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated April 2, 2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

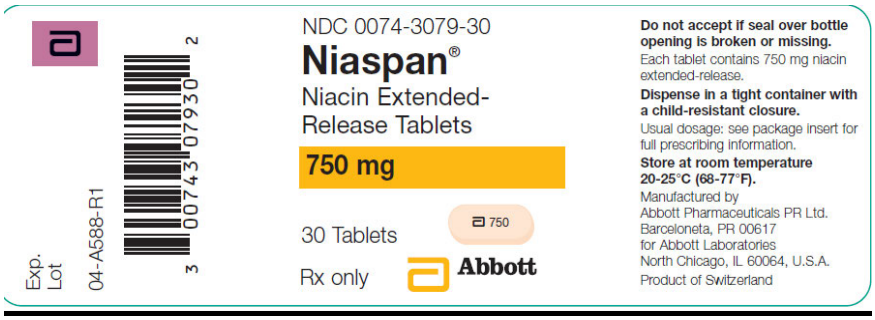
Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 30s, 90s, 100s, 1000s	4/2/2014	Final	Acceptable for approval
INSERT	4/2/2014	Final	Acceptable for approval
PATIENT INFORMATION LEAFLET	3/21/2014	Final	Acceptable for approval

FOR THE RECORD: Please note the first three review cycles were completed by labeling reviewer Thuyanh Vu.

Please note: The firm provided a combined insert with the 750 mg strength tablets (filed under ANDA 201273). The insert for ANDA 200484 has only the 500 mg and 1000 mg strengths and may be approved before or at the same time as ANDA 201273.

1. **MODEL LABELING:** This review is based on the labeling Niaspan® (niacin extended-release) Tablets (NDA 020381/S-048), approved February 21, 2013. This labeling supplement provided for revisions to the PI and PPI to include information from the clinical trial "Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)".



MedWatch –(checked March 25, 2014)

Niaspan (niacin extended-release) tablets
Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – February 2013
Revisions were made to the WARNINGS AND PRECAUTIONS, Mortality and Coronary

Heart Disease Morbidity and ADVERSE REACTIONS, Clinical Studies Experience sections. The Safety Labeling Changes are in the last approved labeling for the RLD.

2. **USP -36: (checked March 25, 2014)**

Niacin Extended-Release Tablets
Packaging and Storage: Preserve in tight containers.

***Easily Correctable Deficiency Labeling submitted* 4/2/2014**

Response-1
Please note that Sun's proposed drug product does not meet the USP dissolution test hence the disclaimer "USP Dissolution Test Pending" has been added to the end of the description section of Sun's package insert.

Chemistry review dated 6/6/2013:

With this amendment, Sun's drug product now complies with current USP monograph criteria, except dissolution test. Dissolution test specifications are per DBE recommendations. Upon approval of ANDA 200484, Sun shall submit a petition to USP for inclusion of Sun's dissolution method in the monograph.

3. **PATENT AND EXCLUSIVITY** (checked March 25, 2014)

Patent Data – NDA 20381

No	Expiration	Use Code	Use	How filed	Labeling Impact
6080428	May 27, 2017	U-1138 U-1139 U-1140 U-1141 U-331	Refer to definition below	PIV	None
6459035	Mar 15, 2018	U-1142 U-1143 U-1144 U-1145 U-768	Refer to definition below	PIV	None

Firm submitted cert IV to all patents in original submission.

From Cover letter in amendment dated 3/21/2014

Sun's ANDA shall be eligible for final approval on the expiration of 180 day's exclusivity period of the first filer on 20 March, 2014. Consequently we hereby request you to grant us final approval for this ANDA.

Patent and Exclusivity:

The court order dismissing the suit filed by Abbvie Inc. and Abbvie Respiratory LLC against Sun in connection with Sun's above mentioned ANDA has already been submitted to FDA dated 6 March, 2013.

As requested by agency, information on patent/ exclusivity for Sun's Niacin Extended-Release Tablets, 750 mg (ANDA # 201273), the following information has also been provided for subject ANDA:

- Sun's Civil Actions (Delaware cases - C.A. No. 10-488, & C.A. No. 11-1190) were consolidated into C.A.No. 10-112. The complaint copy of C.A. No. 10-488, & C.A. No. 11-1190 and also copy of consolidation orders have been provided herewith for your ready reference in section ***1.3.5.2***.
- Sun's ANDA #200484 (500mg, 1000mg) for Niacin extended release tablets was filed with a paragraph IV certification to the '035 patent on September 30, 2009. Notice letter to that effect was sent to the patentee/NDA holder on January 04, 2010. On September 27, 2011, Sun submitted claim-by-claim split certification to the '035 patent for this ANDA, i.e. Sun certified that it maintained its paragraph IV certification with respect to some claims of the '035 patent, while converting certification to claims 2-5 and 11-30 of the '035 patent to sec viii. This amendment was accompanied by labeling amendment that carvedout uses covered by claims 2-5 and 11-30 of the '035 patent from Sun's label in the ANDA. However, FDA communication dated November 30, 2011 informed Sun that such carve-out was not permissible, as the patent use-code did not support such carve-out. In response, Sun amended back the certification to the '035 patent to a paragraph IV on December 20, 2011.

Sun believes that the original 2010 notice letter sent on the '035 patent meet the statutory requirements, as the later-filed split certification was withdrawn and replaced with the original paragraph IV certification. To the extent this reconversion back to paragraph IV certification requires a fresh notice letter, we believe that, that is moot in view of the fact that Sun now has a license from the patent holder on the '035 patent. As communicated earlier to FDA, this license agreement ended the litigation, and therefore, the 30-month stay on approval of the Sun ANDA.

***Code Definition**

U-331 METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

U-1138 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1139 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1140 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1141 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1142 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

U-1143 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR A T NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1144 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1145 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

Exclusivity Data– There is no unexpired exclusivity for this product.

4. **INACTIVE INGREDIENTS [2.3.P.1-original submission]**

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

The inactive ingredients are: hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

5. **MANUFACTURING FACILITY[2.3.P.3-original submission]**

Sun Pharma Laboratories Limited-Dadra
Survey No. 259/15,
Dadra-396 191
UT of Dadra & Nagar Haveli,
India

6. **FINISHED PRODUCT DESCRIPTION**

The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). YES [2.3.P.1-original submission]

RLD: Unscored, medium orange, film-coated, capsuleshaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side

ANDA: unscored, pink colored, capsule shaped, film coated tablets with "500" or "1000" debossed on one side and "S" on other side.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store at room temperature (20 to 25°C or 68 to 77°F). Dispense in a tight container with child-resistant closure.

ANDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°and 30°C (59° and 86°F). [see USP Controlled Room Temperature]. Dispense in a tight container with child-resistant closure.

8. **PRODUCT LINE**

RLD: bottles of 100s

ANDA: bottles of 30s, 90s, 100s and 1000s (both strengths)

Bottles of 30s, 90s and 100s- CRC

Bottles of 100s, 1000s- non CRC

9. **CONTAINER/CLOSURE**

Module 3.2.P.7.

Strength	Count	Packaging component		(b) (4)
		White round HDPE Bottles	Polypropylene closures	
500 mg	30's	60 cc	33 mm CRC	
	100's	120 cc	38 mm CRC	
	100's	120 cc	38 mm NCRC	
	1000's	950 cc	53 mm NCRC	
1000 mg	30's	75 cc	33 mm CRC	
	100's	300 cc	53 mm CRC	
	100's	300 cc	53 mm NCRC	
	1000's	1500 cc	89 mm NCRC	

CRC : Child resistant closure
NCRC : Non Child resistant closure

In AF dated 4/20/10, firm added 90s count size.

- Additional count of 90's is also proposed for all three strengths. Packaging configuration for this count is given below:

Counts	*Strength*	*Bottle Size*	*Cap Size*	(b) (4)
90's CRC	500 mg	120 cc	38 mm	
	1000 mg	300 cc	53 mm	
Supplier Name	(b) (4)			

10. BIOAVAILABILITY/BIOEQUIVALENCE

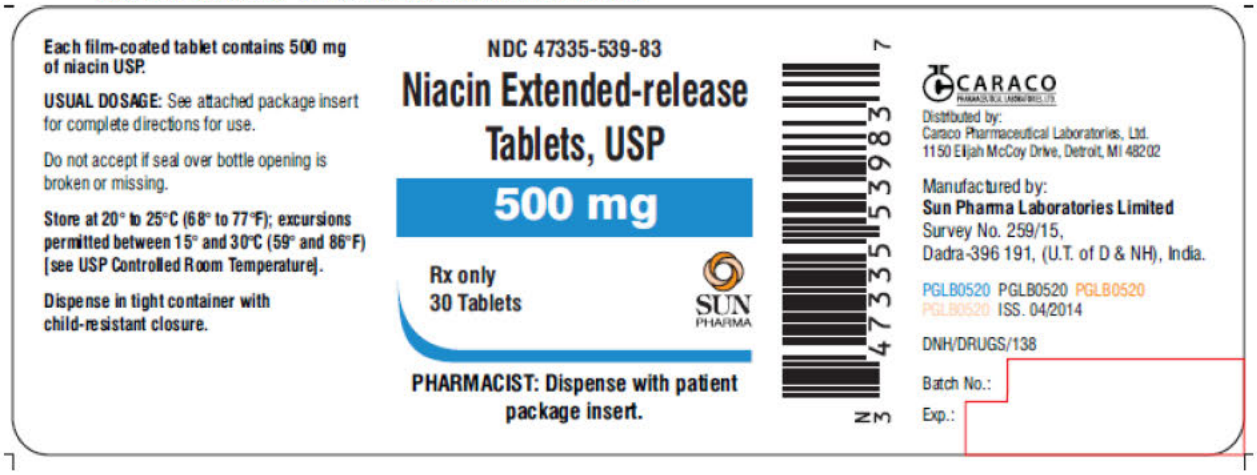
Bio results adequate as of review dated 10/17/2011.

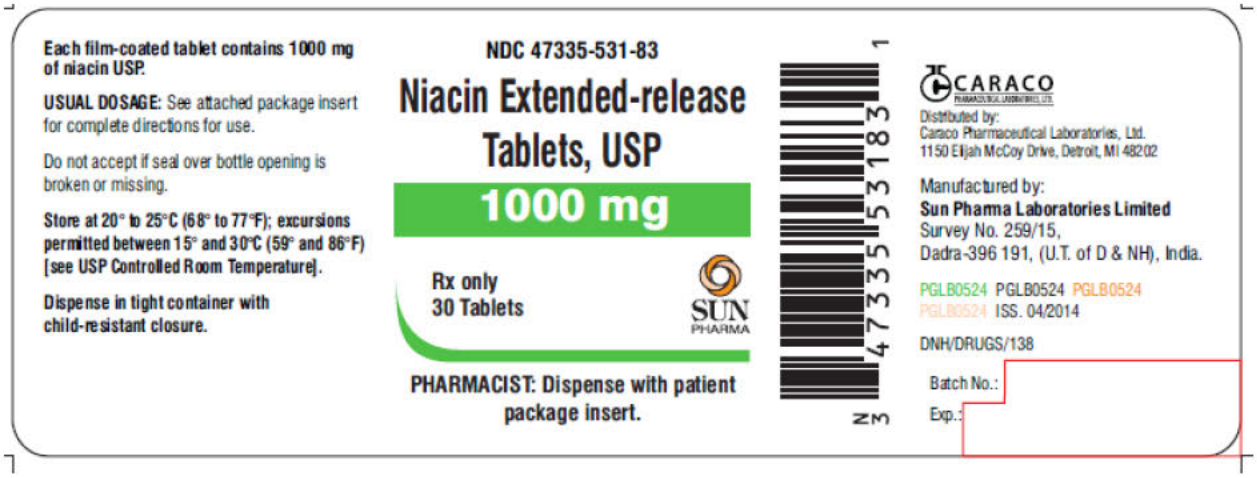
The dissolution testing on all strengths using the FDA-recommended method previously found acceptable.

11. RELATED APPLICATIONS

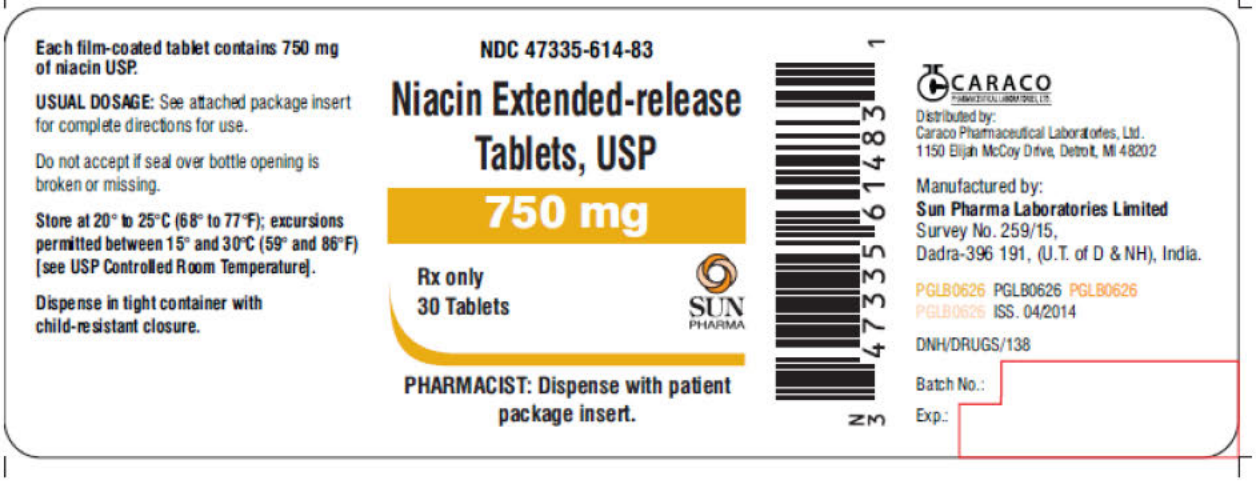
This review- ANDA 200484 Niacin Extended-release Tablets (Pending) submitted 4/2/2014

- In the amendment dated 4/2/2014, the firm revised the container labels by using lower case "r" in "release" in the established name.
- In the amendment date 3/21/2014, the firm revised the container label so that the colors do not conflict with the colors of the RLD.





ANDA 201273 Niacin Extended-release Tablets 750 mg (Pending) submitted 4/2/2014



12. **SPL DATA ELEMENTS (submitted 3/21/2014)**

ANDA

500 mg: Size = 17 mm

1000 mg: Size = 19 mm

RLD:

500 mg: Size = 17 mm

1000 mg: Size = 19 mm

13. **AMENDMENT dated 3/21/2014**

Labeling comment:

c. 12.3 Pharmacokinetics, Absorption
Upon further review, please revise the second paragraph to read as follows.
"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent."

Under section 12.3 Pharmacokinetics, Absorption: The firm revised the second paragraph to be the same as the reference listed drug and it read as follows:

Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent.

The information in the emails below supports the decision for the firm to follow the RLD in section 12.3 of the insert labeling.

The firm revised the insert in section 12.3 as request by labeling reviewer in an email correspondence dated 7/20/11 to read (b) (4) This is in the 12.3 Pharmacokinetics, Absorption section.

From:
Sent: Friday, December 21, 2012 1:03 PM
To:
Subject: FW: Question on niacin ER Tab

The firm was asked to revise to (b) (4) However, per Agency's email, firm did not really need to revise. Sun decided to revise anyway per my instructions. At this point in time, we could approve with the statement as it stands but firm could revise back to the original statement post approval.

From:
Sent: Friday, January 13, 2012 7:35 AM
To:
Subject: RE: Question on niacin ER Tab

If the firm has this statement:

"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are
dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent

Then, it's acceptable. Don't ask the firm to revise to (b) (4)

Most firms would have the first statement b/c that statement follows the RLD. Hope this clears it up.

From:
Sent: Thursday, January 12, 2012 3:52 PM
To:
Subject: RE: Question on niacin ER Tab

So, just to be clear - I don't have to ask any firms to add the sentence "in their labeling?

I read the other email you sent, but I am a little confused still.

From:
Sent: Thursday, January 12, 2012 3:38 PM
To:
Subject: RE: Question on niacin ER Tab

Don't worry about the statement. There's a guidance from the Bio group that chemistry wasn't aware of. I'll forward you the email.

From:
Sent: Thursday, January 12, 2012 3:36 PM
To:
Subject: Question on niacin ER Tab

In reference to the email chain in darrts:

<< File: Pharmacokinetics email chain.pdf >>

Do I need to ask all firms to include the following statement in the labeling or is it on a case by case basis?

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

Date of Review:	April 4, 2014
Primary Reviewer:	Betty Turner
Acting Team Leader:	Angela Payne

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

/s/

BETTY B TURNER
04/11/2014

ANGELA M PAYNE
04/11/2014
ATL

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (5th cycle)

ANDA Number:	200484
Date of Submission:	March 21, 2014
Applicant:	Sun Pharma Global FZE
Established Name and Strength:	Niacin Extended-release Tablets USP, 500 mg and 1000 mg
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☒ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on March 26, 2014, based on your submission dated March 21, 2014.

1. GENERAL COMMENT:

   Does your product meet the USP dissolution test? If your product does not meet the USP dissolution test, please add the disclaimer "USP Dissolution Test Pending" to the end of the DESCRIPTION section in your insert labeling.

2. CONTAINER:

   a. We note that the labels submitted in the amendment dated March 21, 2014, contains a logo for the distributor and a logo for the manufacturer. The labels submitted November 21, 2011, contained only the manufacturer's logo. Please comment.

   b. We encourage you to revise the established name to read "Niacin Extended-release Tablets, USP" [use lower case "r" in "release"]. Please note that this deficiency is annual reportable.

3. INSERT:

   a. WARNINGS AND PRECAUTIONS, Mortality and Coronary Heart Disease Morbidity: Replace "niacin" with "niacin extended-release" except in the section of the sentence as follows. "…or matching placebo (IR Niacin, 100 to 150 mg, n = 1696)."

   b. ADVERSE REACTIONS, Clinical Studies Experience: In the last paragraph that begins with "In AIM-HIGH involving 3, 414 patients…" replace "niacin" with "niacin extended-release" except in the section of the sentence as follows. "…or matching

placebo (IR Niacin, 100 mg to 150 mg, n = 1696)."

c. Please refer to container comment 2(a).

4. PATIENT INFORMATION LEAFLET:

Please refer to container comment 2(a).

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

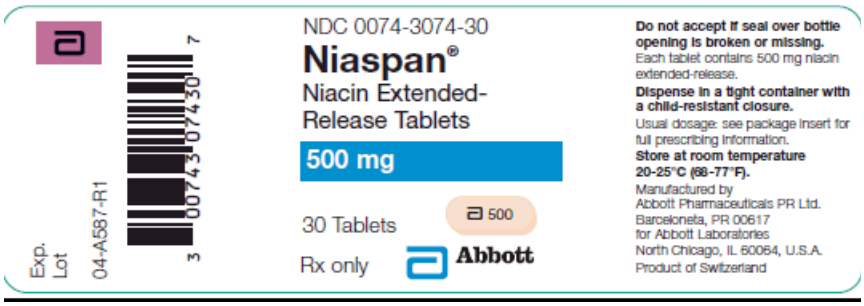
Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 30s, 90s, 100s, 1000s	3/21/2014	Final	Revisions requested
INSERT	3/21/2014	Final	Revisions requested
PATIENT INFORMATION	3/21/2014	Final	Revisions requested

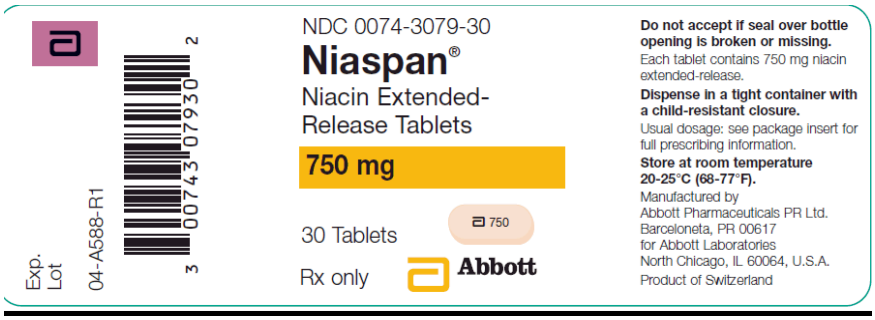
FOR THE RECORD: Please note the first three review cycles were completed by labeling reviewer Thuyanh Vu.

Please note: The firm provided a combined insert with the 750 mg strength tablets (filed under ANDA 201273). ANDA 200484 must be approved after or at the same time as ANDA 201273.

1. **MODEL LABELING:** This review is based on the labeling Niaspan® (niacin extended-release) Tablets (NDA 020381/S-048), approved February 21, 2013. This labeling

supplement provided for revisions to the PI and PPI to include information from the clinical trial "Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)".





MedWatch –(checked March 25, 2014)

Niaspan (niacin extended-release) tablets
Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – February 2013
Revisions were made to the WARNINGS AND PRECAUTIONS, Mortality and Coronary Heart Disease Morbidity and ADVERSE REACTIONS, Clinical Studies Experience sections.

2. **USP -36: (checked March 25, 2014)**

Niacin Extended-Release Tablets
Packaging and Storage: Preserve in tight containers.

Chemistry review dated 6/6/2013:

Revised October 2013

With this amendment, Sun's drug product now complies with current USP monograph criteria, except dissolution test. Dissolution test specifications are per DBE recommendations. Upon approval of ANDA 200484, Sun shall submit a petition to USP for inclusion of Sun's dissolution method in the monograph.

3. **PATENT AND EXCLUSIVITY** (checked March 25, 2014)

Patent Data – NDA 20381

No	Expiration	Use Code	Use	How filed	Labeling Impact
6080428	May 27, 2017	U-1138 U-1139 U-1140 U-1141 U-331	Refer to definition below	PIV	None
6459035	Mar 15, 2018	U-1142 U-1143 U-1144 U-1145 U-768	Refer to definition below	PIV	None

Firm submitted cert IV to all patents in original submission.

From Cover letter in amendment dated 3/21/2014

Sun's ANDA shall be eligible for final approval on the expiration of 180 day's exclusivity period of the first filer on 20 March, 2014. Consequently we hereby request you to grant us final approval for this ANDA.

Patent and Exclusivity:

The court order dismissing the suit filed by Abbvie Inc. and Abbvie Respiratory LLC against Sun in connection with Sun's above mentioned ANDA has already been submitted to FDA dated 6 March, 2013.

As requested by agency, information on patent/ exclusivity for Sun's Niacin Extended-Release Tablets, 750 mg (ANDA # 201273), the following information has also been provided for subject ANDA:

- Sun's Civil Actions (Delaware cases - C.A. No. 10-488, & C.A. No. 11-1190) were consolidated into C.A.No. 10-112. The complaint copy of C.A. No. 10-488, & C.A. No. 11-1190 and also copy of consolidation orders have been provided herewith for your ready reference in section ***1.3.5.2***.
- Sun's ANDA #200484 (500mg, 1000mg) for Niacin extended release tablets was filed with a paragraph IV certification to the '035 patent on September 30, 2009. Notice letter to that effect was sent to the patentee/NDA holder on January 04, 2010. On September 27, 2011, Sun submitted claim-by-claim split certification to the '035 patent for this ANDA, i.e. Sun certified that it maintained its paragraph IV certification with respect to some claims of the '035 patent, while converting certification to claims 2-5 and 11-30 of the '035 patent to sec viii. This amendment was accompanied by labeling amendment that carvedout uses covered by claims 2-5 and 11-30 of the '035 patent from Sun's label in the ANDA. However, FDA communication dated November 30, 2011 informed Sun that such carve-out was not permissible, as the patent use-code did not support such carve-out. In response, Sun amended back the certification to the '035 patent to a paragraph IV on December 20, 2011.

Sun believes that the original 2010 notice letter sent on the '035 patent meet the statutory requirements, as the later-filed split certification was withdrawn and replaced with the original paragraph IV certification. To the extent this reconversion back to paragraph IV certification requires a fresh notice letter, we believe that, that is moot in view of the fact that Sun now has a license from the patent holder on the '035 patent. As communicated earlier to FDA, this license agreement ended the litigation, and therefore, the 30-month stay on approval of the Sun ANDA.

***Code Definition**

U-331 METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

U-1138 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1139 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1140 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1141 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1142 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

U-1143 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR A T NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1144 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1145 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

Exclusivity Data– There is no unexpired exclusivity for this product.

Revised October 2013

4. **INACTIVE INGREDIENTS [2.3.P.1-original submission]**

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

The inactive ingredients are: hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

5. **MANUFACTURING FACILITY[2.3.P.3-original submission]**

Sun Pharmaceutical Industries- Dadra
Survey No. 259/15,
Dadra-396 191
UT of Dadra & Nagar Haveli,
India

6. **FINISHED PRODUCT DESCRIPTION**

The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). YES [2.3.P.1-original submission]

RLD: Unscored, medium orange, film-coated, capsuleshaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side

ANDA: unscored, pink colored, capsule shaped, film coated tablets with "1000" debossed on one side and "S" on other side.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store at room temperature (20 to 25°C or 68 to 77°F). Dispense in a tight container with child-resistant closure.

ANDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°and 30°C (59° and 86°F). [see USP Controlled Room Temperature]. Dispense in a tight container with child-resistant closure.

8. **PRODUCT LINE**

RLD: bottles of 100s

ANDA: bottles of 30s, 90s, 100s and 1000s (both strengths)

9. **CONTAINER/CLOSURE**

Module 3.2.P.7.

Strength	Count	Packaging component		(b) (4)
		White round HDPE Bottles	Polypropylene closures	
500 mg	30's	60 cc	33 mm CRC	
	100's	120 cc	38 mm CRC	
	100's	120 cc	38 mm NCRC	
	1000's	950 cc	53 mm NCRC	
1000 mg	30's	75 cc	33 mm CRC	
	100's	300 cc	53 mm CRC	
	100's	300 cc	53 mm NCRC	
	1000's	1500 cc	89 mm NCRC	

CRC : Child resistant closure
NCRC : Non Child resistant closure

In AF dated 4/20/10, firm added 90s count size.

- Additional count of 90's is also proposed for all three strengths. Packaging configuration for this count is given below:

Counts	*Strength*	*Bottle Size*	*Cap Size*	(b) (4)
90's CRC	500 mg	120 cc	38 mm	
	1000 mg	300 cc	53 mm	
Supplier Name		(b) (4)		

10. **BIOAVAILABILITY/BIOEQUIVALENCE**

Bio results adequate as of review dated 10/17/2011.

The dissolution testing on all strengths using the FDA-recommended method was previously found acceptable.

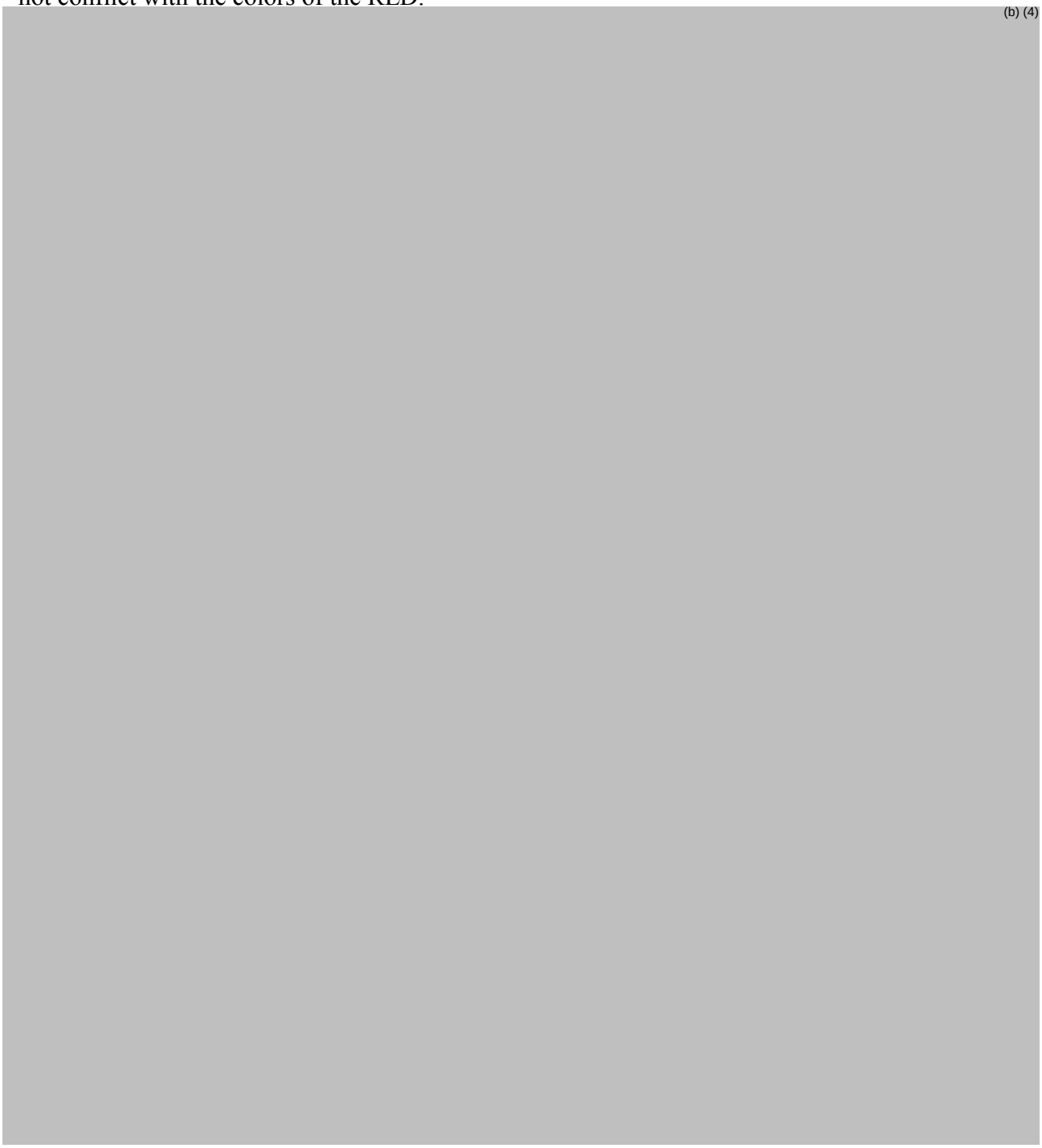
Revised October 2013

11. **RELATED APPLICATIONS**

This review- ANDA 200484 Niacin Extended-release Tablets (Pending) submitted 3/21/2014

In the amendment date 3/21/2014, the firm revised the container label so that the colors do not conflict with the colors of the RLD.

(b) (4)



12. **SPL DATA ELEMENTS (submitted 3/21/2014)**

ANDA

Revised October 2013

500 mg

Color	**PINK**	**Score**	**no score**
Shape	**CAPSULE**	**Size**	**17mm**
Flavor		**Imprint Code**	**S;500**

1000 mg:

Color	**PINK**	**Score**	**no score**
Shape	**CAPSULE**	**Size**	**19mm**
Flavor		**Imprint Code**	**S;1000**

RLD:

500 mg

Color	**ORANGE (MEDIUM ORANGE)**	**Score**	**no score**
Shape	**OVAL (OVAL)**	**Size**	**17mm**
Flavor		**Imprint Code**	**A;500**

1000 mg

Color	**ORANGE (MEDIUM ORANGE)**	**Score**	**no score**
Shape	**OVAL (OVAL)**	**Size**	**19mm**
Flavor		**Imprint Code**	**A;750**

13. **FIRMS Response to labeling deficiencies:**

In the amendment dated 3/21/2014, the firm used the telephone number and the contact number for Caraco in the HIGHLIGHTS section "To report SUSPECTED ADVERSE REACTIONS, contact CARACO…"

Note that for the final inserts for 79020 and 90931: Sun had the telephone number for Caraco as the contact number for the AR section.

Labeling comment:
b. HIGHLIGHTS, ADVERSE EVENTS – Please revise the statement "To report SUSPECTED ADVERSE REACTIONS…" to include the manufacturer's name and phone number to be in accord with 21 CFR 201.57(a)(11)(ii).

Revised October 2013

Response:
b. In the HIGHLIGHTS, ADVERSE REACTIONS, the company name and phone number have been added in the statement as follows:
To report SUSPECTED ADVERSE REACTIONS, contact CARACO Pharmaceutical Laboratories Ltd. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

14. **AMENDMENT dated 3/21/2014**

Labeling comment:

c. 12.3 Pharmacokinetics, Absorption
Upon further review, please revise the second paragraph to read as follows.
"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent."

Under section 12.3 Pharmacokinetics, Absorption: The firm revised the second paragraph to be the same as the reference listed drug and it read as follows:

Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent.

The information in the emails below supports the decision for the firm to follow the RLD in section 12.3 of the insert labeling.

The firm revised the insert in section 12.3 as request by labeling reviewer in an email correspondence dated 7/20/11 to read (b) (4) This is in the 12.3 Pharmacokinetics, Absorption section.

From:
Sent: Friday, December 21, 2012 1:03 PM
To:
Subject: FW: Question on niacin ER Tab

The firm was asked to revise to (b) (4) However, per Agency's email, firm did not really need to revise. Sun decided to revise anyway per my instructions. At this point in time, we could approve with the statement as it stands but firm could revise back to the original statement post approval.

From:
Sent: Friday, January 13, 2012 7:35 AM
To:
Subject: RE: Question on niacin ER Tab

If the firm has this statement:

Revised October 2013

"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are
dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent

Then, it's acceptable. Don't ask the firm to revise to (b) (4)

Most firms would have the first statement b/c that statement follows the RLD. Hope this clears it up.

From:
Sent: Thursday, January 12, 2012 3:52 PM
To:
Subject: RE: Question on niacin ER Tab

So, just to be clear - I don't have to ask any firms to add the sentence "in their labeling?

I read the other email you sent, but I am a little confused still.

From:
Sent: Thursday, January 12, 2012 3:38 PM
To:
Subject: RE: Question on niacin ER Tab

Don't worry about the statement. There's a guidance from the Bio group that chemistry wasn't aware of. I'll forward you the email.

From:
Sent: Thursday, January 12, 2012 3:36 PM
To:
Subject: Question on niacin ER Tab

In reference to the email chain in darrts:

<< File: Pharmacokinetics email chain.pdf >>

Do I need to ask all firms to include the following statement in the labeling or is it on a case by case basis?

(b) (4)

(b) (4)

(b) (4)

[redacted]

Date of Review:	March 26, 2014
Primary Reviewer:	Betty Turner
Team Leader:	Chi-Ann Wu

Revised October 2013

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

/s/

BETTY B TURNER
03/27/2014

CHI-ANN Y WU
03/27/2014
For Wm. Peter Rickman

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200484

Date of Submission: May 8, 2012

Applicant's Name: Sun Pharma Global FZE

Established Name and Strength: Niacin Extended-Release Tablets USP, 500 mg and 1000 mg

---

Labeling Comments below are considered:

☒ No Comments **(**Labeling Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated May 8, 2012.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☒ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

	Date submitted	Final or Draft	Recommendation
CONTAINER Bottles of 30s, 90s, 100s, 1000s	11/21/2011	Final	Acceptable for approval
INSERT	5/8/2012	Final	Acceptable for approval
PATIENT INFORMATION	11/21/2011	Final	Acceptable
SPL (DLDE)	9/29/2009		Acceptable

REVISIONS NEEDED POST APPROVAL? Yes

Labeling comments determined on 12/20/2012 based on your submission dated 5/8/2012:

1. GENERAL COMMENT
   Please note this product is the subject of a USP monograph. We encourage you to add "USP" to your established name in the container and insert labeling.

2. CONTAINER
   Please note that the RLD uses the following colors for their product; 500 mg (blue); 750 mg (orange) and 1000 mg (green). We notice that you proposed the following colors for your product; (b) (4)

3. INSERT
   a. We encourage you to add "USP" in the Title, Dosage and Administration, Description and How Supplied sections.
   b. HIGHLIGHTS, ADVERSE EVENTS – Please revise the statement "To report SUSPECTED ADVERSE REACTIONS…" to include the manufacturer's name and phone number to be in accord with 21 CFR 201.57(a)(11)(ii).

   c. 12.3 Pharmacokinetics, Absorption

Upon further review, please revise the second paragraph to read as follows.

"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent."

The above post approval comments will be email to the firm to Robert Kurkiewicz at Robert.Kurkiewicz@sunpharmausa.com.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

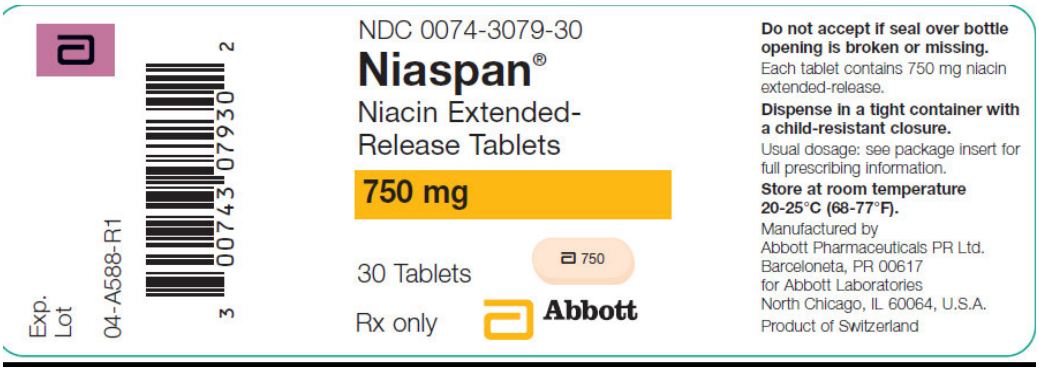
FOR THE RECORD: Please note the previous review cycles were completed by labeling reviewer Thuyanh Vu. Portions of this review were taken from the review dated 11/30/2011 in DARRTS.

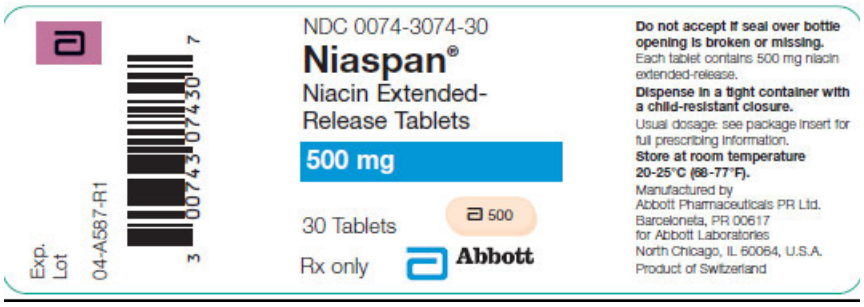
1. **MODEL LABELING**
   This review was based on the labeling Niaspan™ (niacin extended-release) Tablet (NDA 020381/S-043), approved 11/9/2010. S-043 provides for a PPI and also removes the "Fredrickson Type" descriptions of the various dyslipidemias.

   The S-042 provided for the addition of "burning sensation/skin burning sensation" in the postmarketing adverse event section.

   The S-032 approved 5/29/08 provided for changes in the labels.

   Note that tables 14 and 15 of S-042, last column (ApoB) the numbers are positive, when they should be negative per S-039 and S-041. I sent an FYI email to Kati Johnson (OND PM).





2. **USP-35:** (checked December 19, 2012)
   Niacin Extended-Release Tablets
   Packaging and Storage: Preserve in tight containers.
   - **USP Reference Standards** 〈11〉

   PF: (checked December 19, 2012)
   37(4) In-Process Revision: Niacin Extended-Release Tablets

3. **PATENT AND EXCLUSIVITY**
   Patent Data – NDA 020381

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**
6080428	May 27, 2017	U-1138		PIV	NONE
		U-1139			
		U-1140			
		U-1141			
		U-331			
6129930	Sep 20, 2013	U-1138		**PIV**	NONE
		U-1139			
		U-1140			
		U-1141			

		U-354			
6406715	Sep 20, 2013	U-450		**PIV**	NONE
6469035	Mar 15, 2018	U-1142		**PIV**	NONE
		U-1143			
		U-1144			
		U-1145			
		U-768			
6676967	Sep 20, 2013	U-1138		**PIV**	NONE
		U-1139			
		U-1140			
		U-1146			
		U-548			
6746691	Sep 20, 2013	U-586		**PIV**	NONE
6818229	Sep 20, 2013			**PIV**	NONE
7011848	Sep 20, 2013	U-1140		**PIV**	NONE
		U-1141			
		U-1147			
		U-1148			
		U-712			
7998506	Sep 20, 2013	U-1138		**PIV**	NONE
		U-1139			
		U-1140			
		U-1141			

Firm submitted cert IV to all patents in original submission.

Code Definition

U-331 METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-450 INTERMEDIATE REL NICOTINIC ACID FORMULATIONS HAVING UNIQUE URINARY METAB PROFILES RESULTING FROM ABSORPTION PROFILES OF NICOTINIC ACID FROM THE INTERMEDIATE NICOTINIC ACID FORMULATIONS,SUITABLE FOR TX HYPERLIPIDEMIA FOLLOWING QD DOSING

U-354 METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

U-548 A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED

FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER

U-586 AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH

U-712 A METHOD OF USING A NICOTINIC ACID FORMULATION TO REDUCE ELEVATED TC, LDL-C AND TG LEVELS, AND RAISE HDL-C LEVELS IN PATIENTS WITH HYPERLIPIDEMIA

U-1138 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1139 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1140 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1141 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1142 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

U-1143 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR A T NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1144 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1145 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

U-1146 REDUCTION IN TG WITH REDUCED FLUSHING BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1147 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, THROUGH REDUCTION OF LDL-C, TC, TG, LP(A), AND INCREASE OF HDL-C

U-1148 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, THROUGH REDUCTINO OF LDL- C, TC, TG, LP(A), AND INCREASE OF HDL-C

No remaining exclusivities.

In XP dated 4/27/10, Abbott sued Sun. Abbott sued Sun for patent infringement of '428 and '035 patents (Case 1:10-cv-00112-UNA filed in the U.S. District Court of Delaware). As of November 29, 2011, the case is still pending.

XP dated 1/10/2011: Sun patent cert IV for '428 and '035 patent, patent cert III for '930, '715, '967, '691, '229, '848, and '506

XP dated 9/16/2011: Sun filed patent cert IV for '428 and '035 patents, changed back to patent cert IV for '930, '715, '967, '691, '229, '848, and '506

XP dated 9/27/2011: Sun filed patent cer IV for '428 and split cert IV for '035 and viii for claims 2-5 and 11-30. To read about the claims, need to look at PTO website. Not sure if Sun could do a split for the '035 patent b/c this patent is one of the patents that is involved in the pending lawsuit. Furthermore, OGD could only acknowledge use codes that are in the electronic OB. Unfortunately, the firm "carved out" the use in combination with simvastatin or lovastatin (the claims 2-5 and 11-30 pertain to simvastatin and lovastatin use combination with niacin).

XP dated 12/20/2011: Sun filed a P IV certification for 6080428 patent.
SUN PHARMA GLOBAL FZE hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,080,428 which as per the expiration date listed in the Orange Book for this patent will expire on May 27, 2017 is *invalid, unenforceable or will not be infringed* by the manufacture, use or sale of SUN PHARMA GLOBAL FZE's Niacin Extended-Release Tablets, 500 mg, 1000 mg.

4. **INACTIVE INGREDIENTS [2.3.P.1-original submission]**
The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

The inactive ingredients are: hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

(b) (4)

5. **MANUFACTURING FACILITY [2.3.P.3 original submission]**
Sun Pharmaceutical Industries- Dadra
Survey No. 259/15,
Dadra-396 191
UT of Dadra & Nagar Haveli,
India

6. **FINISHED PRODUCT DESCRIPTION**
The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). YES [2.3.P.1-original submission]

RLD: Unscored, medium orange, film-coated, capsuleshaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side

ANDA:
500 mg: unscored, pink colored, capsule shaped, film coated tablets with "500" debossed on one side and "S" on other side.

1000 mg: unscored, pink colored, capsule shaped, film coated tablets with "1000" debossed on one side and "S" on other side.

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store at room temperature (20 to 25°C or 68 to 77°F).
Dispense in a tight container with child-resistant closure.

ANDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°and 30°C (59° and 86°F). [see USP Controlled Room Temperature]. Dispense in a tight container with child-resistant closure.

8. **PRODUCT LINE**

RLD: bottle of 100s

ANDA: both strengths: 30s, 90s, 100s and 1000s

9. **CONTAINER/CLOSURE**

Module 3.2.P.7.

Strength	Count	Packaging component		(b) (4)
		White round HDPE Bottles	Polypropylene closures	
500 mg	30's	60 cc	33 mm CRC	
	100's	120 cc	38 mm CRC	
	100's	120 cc	38 mm NCRC	
	1000's	950 cc	53 mm NCRC	
1000 mg	30's	75 cc	33 mm CRC	
	100's	300 cc	53 mm CRC	
	100's	300 cc	53 mm NCRC	
	1000's	1500 cc	89 mm NCRC	

CRC : Child resistant closure
NCRC : Non Child resistant closure

In AF dated 4/20/10, firm added 90s count size.

- Additional count of 90's is also proposed for all three strengths. Packaging configuration for this count is given below:

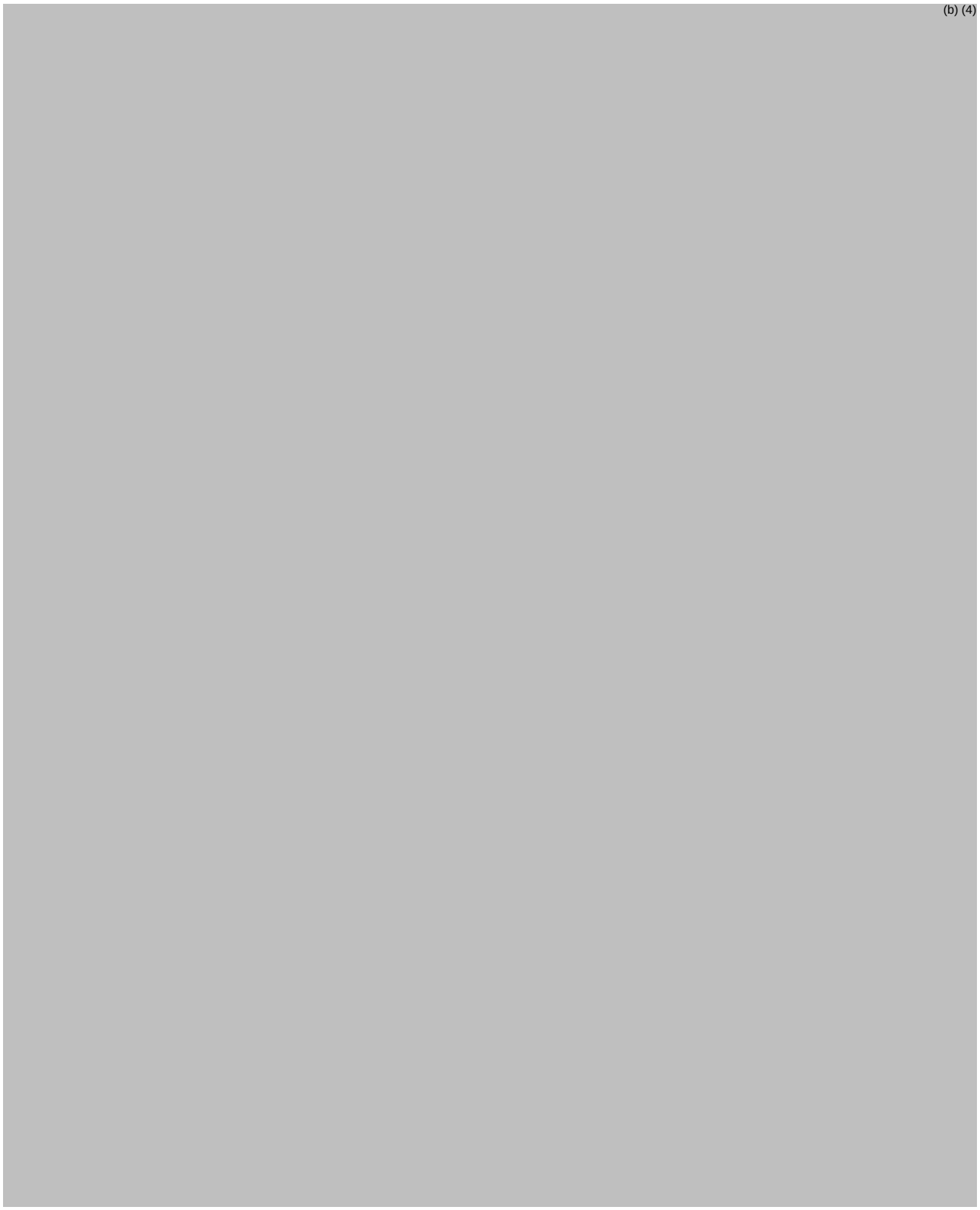
Counts	*Strength*	*Bottle Size*	*Cap Size*	(b) (4)
90's CRC	500 mg	120 cc	38 mm	
	1000 mg	300 cc	53 mm	
Supplier Name		(b) (4)		

10. **BIOAVAILABILITY/BIOEQUIVALENCE**

Bio results adequate as of review dated 10/17/2011.
The dissolution testing on all strengths using the FDA-recommended method was previously found acceptable.

11. **RELATED APPLICATIONS:**

This review- ANDA 200484 Niacin Extended-release Tablets (Pending)



12. **SPL DATA ELEMENTS**
Acceptable 9/29/2009

13. FIRMS Response to labeling Amendment;

In AF dated 5/8/12, the firm provided the following response to labeling comments dated 11/30/11.

PACKAGE INSERT
You may not "carve out" the indication "in combination with simvastatin and lovastatin ... ". According to the electronic Orange Book, the '035 patent does not have the use code associated with this indication. You may only fIle a "viii" to the use codes listed in the Orange Book. Please contact the Regulatory Support Staff for further information about patent certifications.

Please revise your labeling accordingly.

Response-2
Please note that information related to use of proposed drug product in combination therapy with simvastatin or lovastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia has been added in Sun's labeling. The Patent Amendment had already been submitted to FDA dated 20 December, 2011 for changing the sec VIII to Para IV for OB Patent 6469035.

14. In the submission dated 11/21/2011, the firm revised the insert in section 12.3 as request by labeling reviewer in an email correspondence dated 7/20/11 to read (b) (4) [redacted]. This is in the 12.3 Pharmacokinetics, Absorption section.

Based on the emails below the position of the office regarding the statement above is clarified. The firm will be asked to revise the 12.3 Pharmacokinetics, Absorption section of the insert labeling post approval.

From: Vu, Thuyanh (Ann)
Sent: Friday, December 21, 2012 1:03 PM
To: Turner, Betty
Subject: FW: Question on niacin ER Tab

FYI

I asked Ms. Toland to revise to (b) (4) [redacted] However, per Lizzie Sanchez' s email, firm did not really need to revise. Sun decided to revise anyway per my instructions. At this point in time, we could approve with the statement as it stands but firm could revise back to the original statement post approval.

Ann

From: Vu, Thuyanh (Ann)
Sent: Friday, January 13, 2012 7:35 AM
To: Kwok, Lisa
Subject: RE: Question on niacin ER Tab

Lisa,

If the firm has this statement:

"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent

Then, it's acceptable. Don't ask the firm to revise to (b) (4)

Most firms would have the first statement b/c that statement follows the RLD. Hope this clears it up.

Ann

From: Kwok, Lisa
Sent: Thursday, January 12, 2012 3:52 PM
To: Vu, Thuyanh (Ann)
Subject: RE: Question on niacin ER Tab

So, just to be clear - I don't have to ask any firms to add the sentence "in their labeling?

I read the other email you sent, but I am a little confused still.

Thanks,
Lisa

From: Vu, Thuyanh (Ann)
Sent: Thursday, January 12, 2012 3:38 PM
To: Kwok, Lisa
Subject: RE: Question on niacin ER Tab

Don't worry about the statement. There's a guidance from the Bio group that chemistry wasn't aware of. I'll forward you the email.

Ann

From: Kwok, Lisa
Sent: Thursday, January 12, 2012 3:36 PM
To: Vu, Thuyanh (Ann)
Subject: Question on niacin ER Tab

Hi Ann,

In reference to the email chain in darrts:

<< File: Pharmacokinetics email chain.pdf >>

Do I need to ask all firms to include the following statement in the labeling or is it on a case by case basis?

(b) (4)

Thanks,
Lisa

From: Sanchez, Aida L
Sent: Friday, August 05, 2011 1:42 PM
To: Sayeed, Vilayat A; Vu, Thuyanh (Ann)
Cc: Grace, John F; Vaithiyalingam, Sivakumar; Patankar, Suhas; Nagavelli, Laxma; Gill, Devinder; Ahmed,

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)

Date of Review: December 19, 2012

Primary Reviewer: Betty Turner

Team Leader: Chi-Ann Y Wu

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

/s/

BETTY B TURNER
12/22/2012

CHI-ANN Y WU
12/29/2012
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200484 Date of Submission: November 21, 2011

Applicant's Name: Sun Pharma Global FZE

Established Name: Niacin Extended-Release Tablets 500 mg and 1000 mg

---

Labeling Deficiencies:

1. **CONTAINER** (30s, 90s, 100s and 1000s)

   We encourage you to add “Pharmacist: dispense with patient package insert” to the principal display panel.

2. **PACKAGE INSERT**

   You may not “carve out” the indication “In combination with simvastatin and lovastatin...”. According to the electronic Orange Book, the ‘035 patent does not have the use code associated with this indication. You may only file a “viii” to the use codes listed in the Orange Book. Please contact the Regulatory Support Staff for further information about patent certifications.

   Please revise your labeling accordingly.

Submit labels and labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last labeling submission with all differences annotated and explained.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No

Container Labels (30s, 90s, 100s, and 1000s): Final Printed Labels submitted in e-submission 4/20/10

Professional Package Insert Labeling: Not acceptable.

SPL: DLDE is acceptable in 9/29/09 e-submission

Revisions needed post-approval: Make sure the 750 mg stength and 90s count are reflected in the DLDE

section of the SPL

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Niaspan
NDA Number: 20-381
NDA Drug Name: Niacor (Niacin Tablets)
NDA Firm: Upsher Smith
Date of Approval of NDA Insert and supplement #: S-042, approved 2/24/10
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review was based on the labeling Niaspan (20-381/S-043, approved 11/9/2010) S-043 provides for a PPI and also removes the "Fredrickson Type" descriptions of the various dyslipidemias . The S-042 provided for the addition of "burning sensation/skin burning sensation" in the postmarketing adverse event section. The S-032 approved 5/29/08 provided for changes in the labels

   Note that tables 14 and 15 of S-042, last column (ApoB) the numbers are positive, when they should be negative per S-039 and S-041. I sent an FYI email to Kati Johnson (OND PM).

   This ANDA shared the same insert as the sister application ANDA 201273 (750 mg).

2. PATENTS/EXCLUSIVITIES: for 20-381

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020381	002	6080428	May 27, 2017			U - 1138	
N020381	002	6080428	May 27, 2017			U - 1139	
N020381	002	6080428	May 27, 2017			U - 1140	
N020381	002	6080428	May 27, 2017			U - 1141	
N020381	002	6080428	May 27, 2017			U - 331	
N020381	002	6129930	Sep 20, 2013		Y	U - 1138	
N020381	002	6129930	Sep 20, 2013		Y	U - 1139	
N020381	002	6129930	Sep 20, 2013		Y	U - 1140	
N020381	002	6129930	Sep 20, 2013		Y	U - 1141	
N020381	002	6129930	Sep 20, 2013		Y	U - 354	

N020381	002	6406715	Sep 20, 2013	Y	U - 450	
N020381	002	6469035	Mar 15, 2018		U - 1142	
N020381	002	6469035	Mar 15, 2018		U - 1143	
N020381	002	6469035	Mar 15, 2018		U - 1144	
N020381	002	6469035	Mar 15, 2018		U - 1145	
N020381	002	6469035	Mar 15, 2018		U - 768	
N020381	002	6676967	Sep 20, 2013		U - 1138	
N020381	002	6676967	Sep 20, 2013		U - 1139	
N020381	002	6676967	Sep 20, 2013		U - 1140	
N020381	002	6676967	Sep 20, 2013		U - 1146	
N020381	002	6676967	Sep 20, 2013		U - 548	
N020381	002	6746691	Sep 20, 2013	Y	U - 586	
N020381	002	6818229	Sep 20, 2013	Y		
N020381	002	7011848	Sep 20, 2013		U - 1140	
N020381	002	7011848	Sep 20, 2013		U - 1141	
N020381	002	7011848	Sep 20, 2013		U - 1147	
N020381	002	7011848	Sep 20, 2013		U - 1148	
N020381	002	7011848	Sep 20, 2013		U - 712	
N020381	002	7998506	Sep 20, 2013		U - 1138	
N020381	002	7998506	Sep 20, 2013		U - 1139	
N020381	002	7998506	Sep 20, 2013		U - 1140	
N020381	002	7998506	Sep 20, 2013		U - 1141	

Firm submitted cert IV to all patents in original submission.

Code	Definition
U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-450	INTERMEDIATE REL NICOTINIC ACID FORMULATIONS HAVING UNIQUE URINARY METAB PROFILES RESULTING FROM ABSORPTION PROFILES OF NICOTINIC ACID FROM THE INTERMEDIATE NICOTINIC ACID FORMULATIONS,SUITABLE FOR TX HYPERLIPIDEMIA FOLLOWING QD DOSING
U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-768	A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC

ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

U-548 A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER

U-586 AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH

U-712 A METHOD OF USING A NICOTINIC ACID FORMULATION TO REDUCE ELEVATED TC, LDL-C AND TG LEVELS, AND RAISE HDL-C LEVELS IN PATIENTS WITH HYPERLIPIDEMIA

U-1138 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1139 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1140 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1141 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1142 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

U-1143 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR A T NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1144 REDUCTION IN ELEVATED TC AND LDL-C BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITIN AGENT SUCH AS ASPIRIN

U-1145 REDUCTION IN TG BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, WITH PRETREATMENT WITH A FLUSH INHIBITING AGENT SUCH AS ASPIRIN

U-1146 REDUCTION IN TG WITH REDUCED FLUSHING BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-1147 TREATMENT OF PRIMARY AND MIXED DYSLIPIDEMIA BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, THROUGH REDUCTION OF LDL-C, TC, TG, LP(A), AND INCREASE OF HDL-C

U-1148 REDUCTION IN RISK OF RECURRENT NONFATAL MYOCARDIAL INFARCTION BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT, THROUGH REDUCTINO OF LDL-C, TC, TG, LP(A), AND INCREASE OF HDL-C

No remaining exclusivities.

In XP dated 4/27/10, Abbott sued Sun. Abbott sued Sun for patent infringement of '428 and '035 patents (Case 1:10-cv-00112-UNA filed in the U.S. District Court of Delaware). As of November 29, 2011, the case is still pending.

XP dated 1/10/2011: Sun patent cert IV for '428 and '035 patent, patent cert III for '930, '715, '967, '691, '229, '848, and '506

XP dated 9/16/2011: Sun filed patent cert IV for '428 and '035 patents, changed back to patent cert IV for '930, '715, '967, '691, '229, '848, and '506

XP dated 9/27/2011: Sun filed patent cer IV for '428 and split cert IV for '035 and viii for claims 2-5 and 11-30. To read about the claims, need to look at PTO website. Not sure if Sun could do a split for the '035 patent b/c this patent is one of the patents that is involved in the pending lawsuit. Furthermore, OGD could only acknowledge use codes that are in the electronic OB. Unfortunately, the firm "carved out" the use in combination with simvastatin or lovastatin (the claims 2-5 and 11-30 pertain to simvastatin and lovastatin use combination with niacin).

3. INACTIVE INGREDIENTS [2.3.P.1-original submission]

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

The inactive ingredients are: hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

(b) (4)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE [2.3.P.3 original submission]

   Sun Pharmaceutical Industries- Dadra
   Survey No. 259/15,
   Dadra- 396 191,
   UT of Dadra & Nagar Haveli,
   India.

5. The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). YES [2.3.P.1-original submission]

   NDA: Unscored, medium orange, film-coated, capsuleshaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side.

   ANDA:

   500 mg: pink colored, capsule shaped, film coated tablets with “500” debossed on one side and “S” on othe side.

   1000 mg: pink colored, capsule shaped, film coated tablets with “1000” debossed on one side and “S” on othe side.

6. CONTAINER/CLOSURE [3.2.P.7-original submission]

Module 3.2.P.7.

Strength	Count	Packaging component		(b) (4)
		White round HDPE Bottles	Polypropylene closures	
500 mg	30's	60 cc	33 mm CRC	
	100's	120 cc	38 mm CRC	
	100's	120 cc	38 mm NCRC	
	1000's	950 cc	53 mm NCRC	
1000 mg	30's	75 cc	33 mm CRC	
	100's	300 cc	53 mm CRC	
	100's	300 cc	53 mm NCRC	
	1000's	1500 cc	89 mm NCRC	

CRC : Child resistant closure
NCRC : Non Child resistant closure

In AF dated 4/20/10, firm added 90s count size.

- Additional count of 90's is also proposed for all three strengths. Packaging configuration for this count is given below:

Counts	*Strength*	*Bottle Size*	*Cap Size*	(b) (4)
90's CRC	500 mg	120 cc	38 mm	
	1000 mg	300 cc	53 mm	
Supplier Name		(b) (4)		

7. PACKAGING CONFIGURATIONS

RLD: bottle of 100s

ANDA: both strengths: 30s, 90s, 100s, and 1000s.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at room temperature (20 to 25°C or 68 to 77°F).

ANDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°and 30°C (59° and 86°F). [see USP Controlled Room Temperature].

9. DISPENSING STATEMENTS COMPARISON

USP: Preserve in well-closed containers [the extended release tablet is NOT USP, only the regular release one]. Checked PF on October 15, 2010 and there I did not find any information relating to niacin extended release tablet.

RLD: Dispense in a tight container with child-resistant closure.

ANDA: Dispense in a tight container with child-resistant closure.

10. BIOAVAILABILITY/BIOEQUIVALENCE: Bio pending as of October 15, 2010.

11. Scoring:

NDA – not scored
ANDA – not scored

12. In this submission firm revised: to [redacted] (b) (4) This is in the 12.3 Pharmacokinetics, Absorption section.

Date of Review: November 29, 2011 Date of Submission: November 21, 2011

Primary Reviewer: T. Vu

Team Leader: John Grace

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

/s/

THUYANH VU
11/29/2011

JOHN F GRACE
11/30/2011
for Wm Peter Rickman

LABELING APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200484 Date of Submission: April 20, 2010

Applicant's Name: Sun Pharma Global FZE

Established Name: Niacin Extended-Release Tablets 500 mg and 1000 mg

---

BASIS OF APPROVAL:

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No

Container Labels (30s, 90s, 100s, and 1000s): Final Printed Labels submitted in e-submission 4/20/10

Professional Package Insert Labeling: Final Printed Labels submitted in e-submission 4/20/10

SPL: DLDE is acceptable in 9/29/09 e-submission

Revisions needed post-approval: Make sure the 750 mg stength and 90s count are reflected in the DLDE section of the SPL

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Niaspan
NDA Number: 20-381
NDA Drug Name: Niacor (Niacin Tablets)
NDA Firm: Upsher Smith
Date of Approval of NDA Insert and supplement #: S-042, approved 2/24/10
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review was based on the labeling Niaspan (20-381/S-042, approved 2/24/2010. The S-042 provided for the addition of "burning sensation/skin burning sensation" in the postmarketing adverse event section. The S-032 approved 5/29/08 provided for changes in the labels

   Note that tables 14 and 15 of S-042, last column (ApoB) the numbers are positive, when they should be negative per S-039 and S-041. I sent an FYI email to Kati Johnson (OND PM).

   This ANDA shared the same insert as the sister application ANDA 201273 (750 mg).

2. PATENTS/EXCLUSIVITIES: for 20-381

Patent Data

Patent No	Patent Expiration	Firm Filed	Patent Use Code	Impact on Labeling
6080428	May 27, 2017	IV	U-331	No impact
6129930	Sep 20, 2013	IV	U-354	No impact
6406715	Sep 20, 2013	IV	U-450	No impact
6469035	Mar 15, 2018	IV	U-768	"Carve out"
6676967	Sep 20, 2013	IV	U-548	No impact
6746691	Sep 20, 2013	IV	U-586	No impact
6818229	Feb 15, 2014	**IV**		No impact
7011848	Sep 20, 2013	IV	U-712	No impact

Firm submitted cert IV to all patents in original submission.

Code	Definition
U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-450	INTERMEDIATE REL NICOTINIC ACID FORMULATIONS HAVING UNIQUE URINARY METAB PROFILES RESULTING FROM ABSORPTION PROFILES OF NICOTINIC ACID FROM THE INTERMEDIATE NICOTINIC ACID FORMULATIONS,SUITABLE FOR TX HYPERLIPIDEMIA FOLLOWING QD DOSING
U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-768	A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID
U-548	A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED FOR A

LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER

U-586 AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH

U-712 A METHOD OF USING A NICOTINIC ACID FORMULATION TO REDUCE ELEVATED TC, LDL-C AND TG LEVELS, AND RAISE HDL-C LEVELS IN PATIENTS WITH HYPERLIPIDEMIA

No remaining exclusivities.

In XP dated 4/27/10, Abbott sued Sun. Abbott sued Sun for patent infringement of '428 and '035 patents (Case 1:10-cv-00112-UNA filed in the U.S. District Court of Delaware)

3. INACTIVE INGREDIENTS [2.3.P.1-original submission]

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

The inactive ingredients are: hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

(b) (4)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE [2.3.P.3 original submission]

Sun Pharmaceutical Industries- Dadra
Survey No. 259/15,

Dadra- 396 191,
UT of Dadra & Nagar Haveli,
India.

5. The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). YES [2.3.P.1-original submission]

NDA: Unscored, medium orange, film-coated, capsuleshaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side.

ANDA:

500 mg: pink colored, capsule shaped, film coated tablets with "500" debossed on one side and "S" on othe side.

1000 mg: pink colored, capsule shaped, film coated tablets with "1000" debossed on one side and "S" on othe side.

6. CONTAINER/CLOSURE [3.2.P.7-original submission]

Module 3.2.P.7.

Strength	Count	Packaging component		(b) (4)
		White round HDPE Bottles	Polypropylene closures	
500 mg	30's	60 cc	33 mm CRC	
	100's	120 cc	38 mm CRC	
	100's	120 cc	38 mm NCRC	
	1000's	950 cc	53 mm NCRC	
1000 mg	30's	75 cc	33 mm CRC	
	100's	300 cc	53 mm CRC	
	100's	300 cc	53 mm NCRC	
	1000's	1500 cc	89 mm NCRC	

CRC : Child resistant closure
NCRC : Non Child resistant closure

In AF dated 4/20/10, firm added 90s count size.

- Additional count of 90's is also proposed for all three strengths. Packaging configuration for this count is given below:

Counts	*Strength*	*Bottle Size*	*Cap Size*	(b) (4)
90's CRC	500 mg	120 cc	38 mm	
	1000 mg	300 cc	53 mm	
Supplier Name			(b) (4)	

7. PACKAGING CONFIGURATIONS

RLD: bottle of 100s

ANDA: both strengths: 30s, 90s, 100s, and 1000s.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at room temperature (20 to 25°C or 68 to 77°F).

ANDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°and 30°C (59° and 86°F). [see USP Controlled Room Temperature].

9. DISPENSING STATEMENTS COMPARISON

USP: Preserve in well-closed containers [the extended release tablet is NOT USP, only the regular release one]. Checked PF on October 15, 2010 and there I did not find any information relating to niacin extended release tablet.

RLD: Dispense in a tight container with child-resistant closure.

ANDA: Dispense in a tight container with child-resistant closure.

10. BIOAVAILABILITY/BIOEQUIVALENCE: Bio pending as of October 15, 2010.

11. Scoring:

NDA – not scored
ANDA – not scored

Date of Review: October 15, 2010 Date of Submission: April 20, 2010

Primary Reviewer: T. Vu

Team Leader: John Grace

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

/s/

THUYANH VU
10/15/2010

JOHN F GRACE
10/19/2010

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200-484 Date of Submission: September 29, 2009

Applicant's Name: Sun Pharma Global FZE

Established Name: Niacin Extended-Release Tablets 500 mg and 1000 mg

---

Labeling Deficiencies:

1. **CONTAINER** (30s, 100s and 1000s)

(b) (4)

2. **PACKAGE INSERT**

   a. GENERAL COMMENT

      Please note that the established name is "niacin extended release". There are many instances in the insert that you replaced "Niaspan" with "niacin" instead of "niacin extended release". This is especially glaring in the section 14.4 where the insert specified a combination tablet of niacin extended release and simvastatin. Please revise accordingly.

   b. HIGHLIGHTS, ADVERSE REACTIONS:

      We note that you did not state your contact number for patients to report adverse reactions. Please provide your contact number.

   c. 6.1 Clinical Studies Experience

      Second paragraph, second sentence, add "burning sensation/skin burning sensation" between "sweating" and "chills".

   d. 6.2 Postmarketing Experience

      Third paragraph, add "burning sensation/skin burning sensation" between "sweating" and "skin discoloration"

Submit labels and labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last labeling submission with all differences annotated and explained.

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review was based on the labeling Niaspan (20-381/S-042, approved 2/24/2010. The s-042 provided for the addition of "burning sensation/skin burning sensation" in the postmarketing adverse event section. The S-032 approved 5/29/08 provided for changes in the labels

   Note that tables 14 and 15 of S-042, last column (ApoB) the numbers are positive, when they should be negative per S-039 and S-041. I sent an FYI email to Kati Johnson (OND PM).

2. PATENTS/EXCLUSIVITIES: for 20-381

Patent Data

Patent No	Patent Expiration	Firm Filed	Patent Use Code	Impact on Labeling
6080428	May 27, 2017	IV	U-331	No impact
6129930	Sep 20, 2013	IV	U-354	No impact
6406715	Sep 20, 2013	IV	U-450	No impact
6469035	Mar 15, 2018	IV	U-768	"Carve out"
6676967	Sep 20, 2013	IV	U-548	No impact
6746691	Sep 20, 2013	IV	U-586	No impact
6818229	Feb 15, 2014	**IV**		No impact
7011848	Sep 20, 2013	IV	U-712	No impact

Firm submitted cert IV to all patents in original submission.

Code	Definition
U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-450	INTERMEDIATE REL NICOTINIC ACID FORMULATIONS HAVING UNIQUE URINARY METAB PROFILES RESULTING FROM ABSORPTION PROFILES OF NICOTINIC ACID FROM THE INTERMEDIATE NICOTINIC ACID FORMULATIONS,SUITABLE FOR TX HYPERLIPIDEMIA FOLLOWING QD DOSING
U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

U-548 A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER

U-586 AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH

U-712 A METHOD OF USING A NICOTINIC ACID FORMULATION TO REDUCE ELEVATED TC, LDL-C AND TG LEVELS, AND RAISE HDL-C LEVELS IN PATIENTS WITH HYPERLIPIDEMIA

No remaining exclusivities.

3. INACTIVE INGREDIENTS [2.3.P.1-original submission]

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

The inactive ingredients are: hypromellose, hydrogenated vegetable oil Type I, glyceryl behenate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol-partially hydrolyzed, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow.

(b) (4)

[redacted]

4. MANUFACTURING FACILITY OF FINISHED DOSAGE [2.3.P.3 original submission]

Sun Pharmaceutical Industries- Dadra
Survey No. 259/15,
Dadra- 396 191,
UT of Dadra & Nagar Haveli,
India.

5. The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). YES [2.3.P.1-original submission]

NDA: Unscored, medium orange, film-coated, capsuleshaped tablets containing 500, 750 or 1000mg of niacin in an extended-release formulation. Tablets are debossed KOS on one side and the tablet strength (500, 750 or 1000) on the other side.

ANDA:

500 mg: pink colored, capsule shaped, film coated tablets with "500" debossed on one side and "S" on othe side.

1000 mg: pink colored, capsule shaped, film coated tablets with "1000" debossed on one side and "S" on othe side.

6. CONTAINER/CLOSURE [3.2.P.7-original submission]

Module 3.2.P.7.

Strength	Count	Packaging component		(b) (4)
		White round HDPE Bottles	Polypropylene closures	
500 mg	30's	60 cc	33 mm CRC	
	100's	120 cc	38 mm CRC	
	100's	120 cc	38 mm NCRC	
	1000's	950 cc	53 mm NCRC	
1000 mg	30's	75 cc	33 mm CRC	
	100's	300 cc	53 mm CRC	
	100's	300 cc	53 mm NCRC	
	1000's	1500 cc	89 mm NCRC	

CRC : Child resistant closure
NCRC : Non Child resistant closure

7. PACKAGING CONFIGURATIONS

RLD: bottle of 100s

ANDA: both strengths: 30s, 100s, and 1000s.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at room temperature (20 to 25°C or 68 to 77°F).

ANDA: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°and 30°C (59° and 86°F). [see USP Controlled Room Temperature].

9. DISPENSING STATEMENTS COMPARISON

USP: Preserve in well-closed containers [the extended release tablet is NOT USP, only the regular release one]

RLD: Dispense in a tight container with dhild-resistant closure.

ANDA: Dispense in a tight container with dhild-resistant closure.

10. BIOAVAILABILITY/BIOEQUIVALENCE: Bio pending as of March 23, 2010.

11. Scoring:

NDA – not scored
ANDA – not scored

Date of Review: March 23, 2010 Date of Submission: September 29, 2009

Primary Reviewer: T. Vu

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

THUYANH VU
03/23/2010

JOHN F GRACE
03/25/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

CHEMISTRY REVIEWS

APPROVAL - **No further Chemistry questions at this time.**

Addendum #1 to

ANDA 200484

Niacin Extended Release Tablets USP, 500 mg and 1000 mg

Sun Pharmaceutical Industries, Inc.

Weiqin Jiang, PhD
Office of Generic Drugs
Division of Chemistry IV

Review of Apr. 3, 2013 gratuitous amendment.

Reviewer's note: ANDA 200484CR#3 was found approvable for CMC as of 9/25/2012. API DMF (b) (4) is adequate as of 8/28/2012. GDUFA DMF (b) (4) completeness assessment checklist is provided by D. Skanchy on 1/8/2013.

This amendment is submitted with respect to TL's communication dated 22-Mar-2013 with Mr. Robert Kurkiewicz, informing Sun to submit a gratuitous amendment indicating that drug product complies with the newly official USP monograph and to demonstrate that the in-house methods for assay (b) (4) are equivalent to USP monograph method.

With this amendment, Sun's drug product now complies with current USP monograph criteria, except dissolution test. Dissolution test specifications are per DBE recommendations. Upon approval of ANDA 200484, Sun shall submit a petition to USP for inclusion of Sun's dissolution method in the monograph.

The labeling reviewer has informed the applicant to include the word "USP" in the label as the monograph is now official. This may be done post-approval.

An equivalency report of current in-house assay, dissolution (b) (4) method with USP monograph methods are provided. The USP methods are adopted for assay (b) (4) (b) (4) since Dec. 01, 2012.

For Dissolution test, Sun's in-house validated method shall be used.

(b) (4)

Following this page, 5 Pages Withheld in Full as (b)(4)

Endorsement Block

HFD-630 / W. Jiang/5/28/2013
HFD-630 / S. Zuk/5/29/2013
HFD-617 / M. Gonitzke /6/3/2013

Bob 6/3/2013

TYPE OF LETTER: Approval

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

/s/

WEIQIN JIANG
06/04/2013

MARK A GONITZKE
06/04/2013

ERIN M KIM on behalf of SUSAN ZUK
06/05/2013
Signing on behalf of S. Zuk

ROBERT L ISER
06/06/2013

ANDA 200484

Niacin Extended-release Tablets, 500 mg and 1000 mg

Sun Pharmaceutical Industries, Inc.

Weiqin Jiang, Ph. D.
Division of Chemistry IV
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200484

2. REVIEW #: 3

3. REVIEW DATE: 8/22/2012

4. REVIEWER: Weiqin Jiang

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original submission	Sep. 29, 2009
Acceptable for Filing	Sep. 30, 2009 (letter date Dec. 16, 2009)
Amendment (1) Bio AM	May 26, 2010
CMC Rev.#1-NA	Jan. 18, 2011
Amendment	Sep. 30, 2011
CMC Rev. #2-NA	Feb. 10, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	May 26, 2012
Telephone amendment	September 5, 2012 (response to TL tecon)

7. NAME & ADDRESS OF APPLICANT:

ANDA holder:

Name & Address:	Sun Pharmaceutical Industries Ltd.
	Office #43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U. A. E. Authorized Rep.: Mr. Alok Gandhi; Manager, Sun Pharm. Global Tel.: 917-50-7882483; Fax: 917-43-597674
U.S. Representative:	Sun Pharmaceutical Industries, Ltd. (C/O Caraco) 1150 Elijah McCoy Drive, Detriot, MI 48202 Email: Robert.Kurkiewicz@Caraco.com
Telephone:	313-556-4105
Fax:	248-926-0231

Updated in Sep. 30, 2011 AM

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A

Non-Proprietary Name (USAN): Niacin Extended-release tablets, 500 mg and 1000 mg

9. LEGAL BASIS FOR SUBMISSION:

RLD, Niaspan® Tablets, in NDA 20381 manufactured by Abbott Laboratories approved on Jul 28, 1997, Niacin extended release for oral tablet, 500 mg, 750 mg and 1 g.

Patent Certification (314.94(a)(12)): Pursuant to 21 USC 355(J)(2)(A)(vii), Sun's statement of Certification, for all patents which claim the RLD Niaspan® (niacin extended-release tablets), referred to in this application or which claim a use of the listed drug have been provided in this section.

Statement of Exclusivity (314.94(a)(3):

Pursuant to 21CFR314.94(a)(3)(ii), Sun certified that according to the information published in the list, the reference listed drug NIASPAN® (niacin extended-release tablets) referred to in this application is not entitled for marketing exclusivity under section 505(j)(4)(D) and 505(c)(3)(D)(II) of the Federal Food, Drug and Cosmetic Act.

The applicant filed a paragraph IV patent certification. In XP dated 4/27/10, Abbott sued Sun for patent infringement of '428 and '035 patents (Case 1:10-cv-00112-UNA filed in the U.S. District Court of Delaware).

Patents listed for the RLD in the electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations are as follows:

Patent No	Patent Expiration
6080428	May 27, 2017
6129930	September 20, 2013
6406715	September 20, 2013
6469035	March 15, 2018
6676967	September 20, 2013
6746691	September 20, 2013
6818229	February 15, 2014
7011848	September 20, 2013

b.

NPP (New Patient Population)

The Labeling review indicates that use patent code **U-768** 6469035 Mar 15, 2018, is a "Carve Out" from the labeling.

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

10. PHARMACOL. CATEGORY: Lipid Regulating Agent

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg and 1000 mg

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
Not a SPOTS product

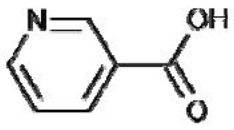
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Nicotinic acid, 3-pyridinecarboxylic acid, pyridine-β-carboxylic acid, Pyridine-3-carboxylic acid

Molecular formula: $C_6H_5NO_2$

Molecular Weight: 123.11

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	adequate	8/21/2012	by W. Jiang
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Chemistry Review Data Sheet

(b) (4)		(b) (4)				
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	IV		4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Sun also submitted an ANDA for the 750 mg strength in ANDA 201273.

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	201273	750 mg strength

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2/10/12	A. Inyard
Methods Validation	N/A		
Labeling	Deficient	11/30/11	T. Vu
Bioequivalence	Adequate	10/17/11	B. Lerman
EA	N/A		
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

Chemistry Review Data Sheet

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

RLD is NIASPAN® (niacin extended-release tablets), 500 mg, and 1000 mg; NDA # 020381 manufactured by Abbott Laboratories, approved on July 28, 1997.

USP status: DS is USP and EP compendial. DS meets USP monograph. There is an official Niacin Tablet USP monograph for the IR product, but not for the extended release product. There is currently a proposed monograph for extended release tablets in PF 37(4). This will become official in USP 35 supplement 2 on 12/1/2012.

Drug Substance: API is Niacin, USP, supplied by (b) (4). It is called nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is "White crystals or crystalline powder, is odorless, or has a slight odor. Melts at about 235 ºC, freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; sparingly soluble in water; practically insoluble in ether"-quoted from USP. (b) (4)

Drug Product: It is an Extended-Release tablets (ER), matrix controlled, oral, solid dosage form and proposed in strengths 500 mg and 1000 mg. Inactive ingredients: Hypropmellose, Hydrogenated vegetable oil Type I, Glyceryl behenate, Colloidal silicon dioxide, Magnesium stearate and (b) (4) Pink, (b) (4) Polyvinyl alcohol-partially hydrolyzed, Titanium dioxide, Polyethylene glycol, Talc, Iron oxide red, Iron oxide yellow.

DP and Strength: It is an ER, matrix-controlled, oral, solid dosage form and in strengths 500 mg and 1000 mg.

DP Manufacturing Process: The DP is manufactured by (b) (4)

Chemistry Review Data Sheet

Indication and Packaging: Indicated for lipid regulation and thus appropriately packaged in 30's CRC, 100's CRC, 100's NCRC and 1000's NCRC in HPDE bottles.

Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Expiration: The proposed expiration dating period is 24 months, which is supported by 3-month ACC stability data and 24-month CRT stability data (5/12/12 AM).

C. Description of How the Drug Product is intended to be used

Proposed Indication: Indicated to reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia (b) (4) (b) (4) and mixed dyslipidemia (b) (4)

For the treatment of primary hyperlipidemia (b) (4) and mixed dyslipidemia (b) (4) in combination with simvastatin or lovastatin.

To reduce the risk of recurrent nonfatal myocardial infarction.

To slow progression or promote regression of atherosclerotic disease & to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia (b) (4) in combination with a bile acid binding resin.

(b) (4) for treatment of adult patients with severe hypertriglyceridemia (b) (4)

Dose and Packaging: Four configurations are used. See above. Administration: There is no special instruction for administration since the DP is designed for oral administration and needs to be swallowed as is. The MDD is 2000 mg.

Thresholds for Impurities:

ICH	IT	QT
Q3A	(b) (4)	
Q3B		

D. Basis for Approvability or Not-Approval Recommendation

The application is approvable.

Following this page, 46 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

A APPENDICES: N/A

R REGIONAL INFORMATION-

R.1	**Executed Batch Records**	Provided and Adequate
R.2	**Comparability Protocols:**	None
R.3	**Methods Validation Package**	Provided

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The firm provided in label: chemical structure, chemical name, description, ingredients and CCS; which are the same as what are in CMC.

The solubility for RLD and ANDA are slightly different. The comparison follows.

RLD "very soluble in water",
ANDA 200484 "sparingly soluble in water"

(b) (4)

[redacted]

The generic sponsor's description as sparingly soluble is accurate based on ANDA data.

Conclusion: Label part related to CMC is adequate.

B. Environmental Assessment Or Claim Of Categorical Exclusion Provided

Chemistry Review Data Sheet

III. **List of Deficiencies to Be Communicated: None**

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

Endorsements:

HFD-630/W. Jiang – CR/ 8/22/2012
HFD-630/S. Zuk – TL/9/20/2012
HFD-617/M. Gonitzke- PM/9/21/2012

V:\Chemistry Division IV\Team 43\Final Version for DARRTS Folder\200484.R03.AP.doc

TYPE OF LETTER: APPROVAL

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

/s/

WEIQIN JIANG
09/24/2012

SUSAN ZUK
09/25/2012

MARK A GONITZKE
09/25/2012

ANDA 200484

Niacin Extended-release Tablets, 500 mg and 1000 mg

Sun Pharmaceutical Industries, Inc.

Weiqin Jiang, Ph. D.
Division of Chemistry IV
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200484

2. REVIEW #: 2

3. REVIEW DATE: 11/21/2011

4. REVIEWER: Weiqin Jiang

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original submission	Sep. 29, 2009
Acceptable for Filing	Sep. 30, 2009 (letter date Dec. 16, 2009)
Amendment (1) Bio AM	May 26, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	Sep. 30, 2011

7. NAME & ADDRESS OF APPLICANT:

ANDA holder:

Name & Address:	Sun Pharmaceutical Industries Ltd. Office #43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U. A. E. Authorized Rep.: Mr. Alok Gandhi; Manager, Sun Pharm. Global Tel.: 917-50-7882483; Fax: 917-43-597674
U.S. Representative:	Sun Pharmaceutical Industries, Ltd. (C/O Caraco) 1150 Elijah McCoy Drive, Detriot, MI 48202 Email: Robert.Kurkiewicz@Caraco.com
Telephone:	313-556-4105
Fax:	248-926-0231

Updated in Sep. 30, 2011 AM

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A

Non-Proprietary Name (USAN): Niacin Extended-release tablets, 500 mg and 1000 mg

9. LEGAL BASIS FOR SUBMISSION:

The basis for Sun's proposed ANDA for Niacin Extended-release tablets, 500 mg and 1000 mg is the approved, referenced listed drug, Niaspan® Tablets, subject of NDA 20381 manufactured by Abbott Laboratories.

a.

Patent Certification (§ 314.94(a)(12))

Pursuant to 21 U.S.C. 355(j)(2)(A)(vii), Sun Pharma Global FZE's Statement of Certification, for all patents which claim the listed drug, NIASPAN® (niacin extended-release tablets), referred to in this application or which claim a use of the listed drug have been provided in this section.

Statement of Exclusivity (§ 314.94(a)(3))

Pursuant to 21 CFR § 314.94(a)(3)(ii), Sun Pharma Global FZE hereby certifies that according to the information published in the list, the reference listed drug NIASPAN® (niacin extended-release tablets) referred to in this application is not entitled for marketing exclusivity under section 505(j)(4)(D) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act.

The applicant filed a paragraph IV patent certification. In XP dated 4/27/10, Abbott sued Sun. Abbott sued Sun for patent infringement of '428 and '035 patents (Case 1:10-cv-00112-UNA filed in the U.S. District Court of Delaware).

Patents listed for the RLD in the electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations are as follows:

Patent No	Patent Expiration
6080428	May 27, 2017
6129930	September 20, 2013
6406715	September 20, 2013
6469035	March 15, 2018
6676967	September 20, 2013
6746691	September 20, 2013
6818229	February 15, 2014
7011848	September 20, 2013

b.

NPP (New Patient Population)

The Labeling review indicates that use patent code **U-768** 6469035 Mar 15, 2018, is a "Carve Out" from the labeling.

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

10. PHARMACOL. CATEGORY: Lipid Regulating Agent

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg and 1000 mg

Chemistry Review Data Sheet

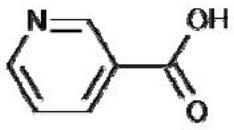
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Nicotinic acid, 3-pyridinecarboxylic acid, pyridine-β-carboxylic acid, Pyridine-3-carboxylic acid
Molecular formula: $C_6H_5NO_2$
Molecular Weight: 123.11
Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	11/16/11	R2 by W. Jiang
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)	III	(b) (4)	4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	IV		4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Sun also submitted an ANDA for the 750 mg strength in ANDA 201273.

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	201273	750 mg strength

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2/10/12	A. Inyard
Methods Validation	N/A		
Labeling	Deficient	11/30/11	T. Vu
Bioequivalence	Adequate	10/17/11	B. Lerman
EA	N/A		
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

Chemistry Review Data Sheet

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug is NIASPAN® (niacin extended-release tablets), 500 mg, and 1000 mg. NDA # 020381 manufactured by Abbott Laboratories.

USP status: DS is USP and EP compendial. DS meets USP monograph. There is an official Niacin Tablet USP monograph for the IR product, but not for the extended release product. There is currently a proposed monograph for extended release tablets in PF 37(4).

Drug Substance: API is Niacin, USP, supplied by (b) (4) It is called nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is "White crystals or crystalline powder, is odorless, or has a slight odor. Melts at about 235 °C, freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; sparingly soluble in water; practically insoluble in ether"-quoted from USP. (b) (4)

Drug Product: It is an Extended-Release tablets (ER), matrix controlled, oral, solid dosage form and proposed in strengths 500 mg and 1000 mg. Indication and Packaging: Indicated for lipid regulation and thus appropriately packaged in 30's CRC, 100's CRC, 100's NCRC and 1000's NCRC in HPDE bottles. Inactive ingredients: Hypropmellose, Hydrogenated vegetable oil Type I, Glyceryl behenate, Colloidal silicon dioxide, Magnesium stearate and (b) (4) Pink, (b) (4) Polyvinyl alcohol-partially hydrolyzed, Titanium dioxide, Polyethylene glycol, Talc, Iron oxide red, Iron oxide yellow.

DP and Strength: It is an ER, matrix-controlled, oral, solid dosage form and in strengths 500 mg and 1000 mg.
Tablets are supplied as follows:
500 mg tablets: Bottles of 30's and 100's with Child Resistant Cap; Bottles of 100's and 1000's with Non Child Resistant Cap
1000 mg tablets: Bottles of 30's and 100's with Child Resistant Cap; Bottles of 100's and 1000's with Non Child Resistant Cap

Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in a tight container with child-resistant closure.

Expiration: The proposed expiration dating period is 24 months, which is supported by 3-month ACC stability data and18-month CRT stability data.

DP Manufacturing Process: The DP is manufactured by (b) (4)

B. Description of How the Drug Product is intended to be used

Dose and Packaging: Four configurations are used. See above. Administration: There is no special instruction for administration since the DP is designed for oral administration and needs to be swallowed as is. Thresholds for Impurities: The MDD is 2000 mg. The IT and QT for impurities in DS is (b) (4) respectively. The IT and QT for the degradative products in DP is (b) (4) respectively.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable.

III. Administrative

TYPE OF LETTER: Deficiency Minor

Following this page, 46 Pages Withheld in Full as (b)(4)

A APPENDICES: N/A

R REGIONAL INFORMATION-

R.1	**Executed Batch Records**	Provided and Adequate
R.2	**Comparability Protocols:**	None
R.3	**Methods Validation Package**	Provided

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The firm provided in label: chemical structure, chemical name, description, ingredients and CCS; which are the same as what are in CMC.

The solubility for RLD and ANDA are slightly different. The comparison follows.

RLD "very soluble in water",
ANDA 200484 "sparingly soluble in water"

(b) (4)

The generic sponsor's description as sparingly soluble is accurate based on ANDA data.

Conclusion: Label part related to CMC is adequate.

B. Environmental Assessment Or Claim Of Categorical Exclusion Provided

III. List of Deficiencies to Be Communicated: See Deficiency letter

CHEMISTRY REVIEW

Chemistry Review Data Sheet

LIST OF DEFICIENCIES TO BE COMMUNICATED TO THE APPLICANT

ANDA: 200848 **APPLICANT: Sun Pharmaceutical Industries, Inc.**

DRUG PRODUCT: Niacin Extended-release Tablets, 500 mg and 1000 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The Drug Master File# (b) (4) is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies. Please also make any applicable changes to the drug substance specifications based on consultation with DMF holder and provide the revised specifications and certificate of analysis.

2. Please provide updated long-term stability data if available.

Sincerely yours,

{See appended electronic signature page}

Robert Iser
Acting Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Review Data Sheet

Endorsements:

HFD-630/W. Jiang – CR/ 11/21/2011
HFD-630/S. Zuk – TL/2/8/2012
HFD-617/M. Gonitzke/2/10/2012

V:\Chemistry Division IV\Team 43\Final Version for DARRTS Folder\200484.R02.NA.doc

TYPE OF LETTER: Deficiency Letter - Minor

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

/s/

WEIQIN JIANG
02/10/2012

MARK A GONITZKE
02/10/2012

SUSAN ZUK
02/10/2012

ANDA 200484

Niacin Extended-release Tablets, 500 mg and 1000 mg

Sun Pharmaceutical Industries, Inc.

Weiqin Jiang, Ph. D.
Division of Chemistry IV
Office of Generic Drugs
OPS/CDER/FDA

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200484

2. REVIEW #: 1

3. REVIEW DATE: Aug. 16, 2010, revised on Jan. 19, 2011.

4. REVIEWER: Weiqin Jiang

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	Sep. 29, 2009
Acceptable for Filing	Sep. 30, 2009 (letter date Dec. 16, 2009)
Amendment (1) Bio AM	May 26, 2010

7. NAME & ADDRESS OF APPLICANT:

ANDA holder:

Name & Address:	Sun Pharm Office #43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U. A. E. Authorized Rep.: Mr. Alok Gandhi; Manager, Sun Pharm. Global Tel.: 917-50-7882483; Fax: 917-43-597674
U.S. Representative:	Ann Toland Sun Pharmaceutical Industries, Inc. 270 Prospect Plains Rd. Cranbury, NJ 08512 Email: (b) (6)
Telephone:	609-495-2823, (b) (6)
Fax:	609-495-2711,

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A

Non-Proprietary Name (USAN): Niacin Extended-release tablets, 500 mg and 1000 mg

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

The basis for Sun's proposed ANDA for Niacin Extended-release tablets, 500 mg and 1000 mg is the approved, referenced listed drug, Niaspan® Tablets, subject of NDA 20381 manufactured by Abbott Laboratories.

a.

Patent Certification (§ 314.94(a)(12))

Pursuant to 21 U.S.C. 355(j)(2)(A)(vii), Sun Pharma Global FZE's Statement of Certification, for all patents which claim the listed drug, NIASPAN® (niacin extended-release tablets), referred to in this application or which claim a use of the listed drug have been provided in this section.

Statement of Exclusivity (§ 314.94(a)(3))

Pursuant to 21 CFR § 314.94(a)(3)(ii), Sun Pharma Global FZE hereby certifies that according to the information published in the list, the reference listed drug NIASPAN® (niacin extended-release tablets) referred to in this application is not entitled for marketing exclusivity under section 505(j)(4)(D) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act.

The applicant filed a paragraph IV patent certification. In XP dated 4/27/10, Abbott sued Sun. Abbott sued Sun for patent infringement of '428 and '035 patents (Case 1:10-cv-00112-UNA filed in the U.S. District Court of Delaware).

Patents listed for the RLD in the electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations are as follows:

Patent No	Patent Expiration
6080428	May 27, 2017
6129930	September 20, 2013
6406715	September 20, 2013
6469035	March 15, 2018
6676967	September 20, 2013
6746691	September 20, 2013
6818229	February 15, 2014
7011848	September 20, 2013

b.

NPP (New Patient Population)

The Labeling review indicates that use patent code **U-768** 6469035 Mar 15, 2018, is a "Carve Out" from the labeling.

U-768 A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID

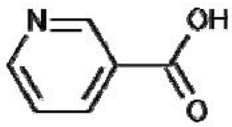
10. PHARMACOL. CATEGORY: Lipid Regulating Agent
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 500 mg and 1000 mg
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Nicotinic acid, 3-pyridinecarboxylic acid, pyridine-β-carboxylic acid, Pyridine-3-carboxylic acid
Molecular formula: $C_6H_5NO_2$
Molecular Weight: 123.11
Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	NA	AUG. 15, 2010; updated 1/17/2011	By W. Jiang
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)		(b) (4)				
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	IV		4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Sun also submitted an ANDA for the 750 mg strength 201273.

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	201273	750 mg strength

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/20/09	A. Inyard
Methods Validation	N/A		
Labeling	Acceptable	10/19/10	T. Vu
Bioequivalence	Deficient	11/13/10	B. Lerman
EA	N/A		
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NOT Approvable. (Review #1)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug is NIASPAN® (niacin extended-release tablets), 500 mg, and 1000 mg. NDA # 020381 manufactured by Abbott Laboratories.

USP status: DS is USP compendial. DS is also EP compendial. DS meets USP monograph. There is a Niacin Tablet USP monograph, but there is no USP or PF for extended release tablet.

Drug Substance: API is Niacin, USP, supplied by [redacted] (b) (4) It is called nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is "White crystals or crystalline powder, is odorless, or has a slight odor. Melts at about 235 ºC, freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; sparingly soluble in water; practically insoluble in ether"-quoted from USP. [redacted] (b) (4)

Drug Product: It is an Extended-Release tablets (ER), matrix controlled, oral, solid dosage form and proposed in strengths 500 mg and 1000 mg. Indication and Packaging: Indicated for lipid regulation and thus appropriately packaged in 30's CRC, 100's CRC, 100's NCRC and 1000's NCRC in HPDE bottles. Inactive ingredients: Hypropmellose, Hydrogenated vegetable oil Type I, Glyceryl behenate, Colloidal silicon dioxide, Magnesium stearate and [redacted] (b) (4) Pink, [redacted] (b) (4) Polyvinyl alcohol-partially hydrolyzed, Titanium dioxide, Polyethylene glycol, Talc, Iron oxide red, Iron oxide yellow.

DP and Strength: It is an ER, matrix controlled, oral, solid dosage form and in strengths 500 mg and 1000 mg. Tablets are supplied as follows:
500 mg tablets: Bottles of 30's and 100's with Child Resistant Cap; Bottles of 100's and 1000's with Non Child Resistant Cap
1000 mg tablets: Bottles of 30's and 100's with Child Resistant Cap; Bottles of 100's and 1000's with Non Child Resistant Cap
Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Dispense in a tight container with child-resistant closure.

Expiration: The proposed expiration dating period is 24 months, which is supported by 3-month ACC stability data. 3-month CRT stability data are currently available.

DP Manufacturing Process: The DP is manufactured by (b) (4)

B. Description of How the Drug Product is intended to be used

Dose and Packaging: Four configurations are used. See below. Administration: There is no special instruction for administration since the DP is designed for oral administration and needs to be swallowed as is. Thresholds for Impurities: The MDD is 2000 mg. The IT and QT for impurities in DS is (b) (4) respectively. The IT and QT for the degradative products in DP is (b) (4) respectively.

C. Basis for Approvability or Not-Approval Recommendation

CMC is not approvable based on deficiencies related to drug substance specification and drug product excipients and manufacturing related questions. Other disciplines are pending.

III. Administrative

TYPE OF LETTER: Minor Deficiency Letter

Following this page, 48 Pages Withheld in Full as (b)(4)

A APPENDICES: N/A

R REGIONAL INFORMATION

R.1	**Executed Batch Records**	Provided and Adequate
R.2	**Comparability Protocols:**	None
R.3	**Methods Validation Package**	Provided

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The firm provided in label: chemical structure, chemical name, description, ingredients and CCS; which are the same as what are in CMC.

The solubility for RLD and ANDA are slightly different. The comparison follows.

RLD "very soluble in water",
ANDA 200484 "sparingly soluble in water"

(b) (4)

The generic sponsor's description as sparingly soluble is accurate based on ANDA data.

Conclusion: Label part related to CMC is adequate.

B. Environmental Assessment Or Claim Of Categorical Exclusion Provided

III. List of Deficiencies to Be Communicated

See the letter

CHEMISTRY REVIEW

Chemistry Review Data Sheet

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **200484**
APPLICANT: **Sun Pharmaceutical Industries Ltd.**
DRUG PRODUCT: **Niacin Extended-release Tablets, 500 mg and 1000 mg**

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The Drug Master File (b) (4) is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies. Please also make any applicable changes to the drug substance specifications based on consultation with DMF holder and provide the revised specifications and certificate of analysis.

2. Please provide all available long-term stability data.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Review Data Sheet

Endorsements (Draft and Final with Dates):

HFD-630/W. Jiang – CR/ 16-Aug-2010, revised on 19-JAN-2011
HFD-630/S. Zuk – TL/1/19/2011
HFD-617/M. Gonitzke/1/20/2011

V:\Chemistry Division IV\Team 43\Final Version for DARRTS Folder\200484.R01.NA.doc

TYPE OF LETTER: Minor Deficiency Letter

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

/s/

WEIQIN JIANG
01/20/2011

MARK A GONITZKE
01/20/2011

SUSAN ZUK
01/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200484		
Drug Product Name	Niacin Tablet, film coated, extended release		
Strength(s)	500 and 1000 mg		
Applicant Name	Sun Pharma Global FZE.		
Address	1150 Elijah MCoy Dr. Detroit, MI 48202		
Applicant's Point of Contact	Robert Kurkiewicz		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	609-495-2711		
Original Submission Date(s)	09/30/2009		
Submission Date(s) of Amendment(s) Under Review	2/17/2011 – Amendment 2/25/2011 – OSI Investigational Report – Clinical Site 9/6/2011 – Telephone Amendment 9/20/2011 – Telephone Amendment 10/11/2011 – Telephone Amendment		
Reviewer	Dr. Bruce Lerman		
Study Number (s)	PKD_09_277	PKD_09_278	
Study Type (s)	Fasting	Fed	
Strength (s)	1000 mg	1000 mg	
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Tandalja Vadodara – 390 020, India		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalja Vadodara – 390 020, India.		
OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
OSI INSPECTION	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1,9,15	**Fasted**	**1000 mg**	**ADEQUATE**
1,9,15	**Fed**	**1000 mg**	**ADEQUATE**
1,7	**Dissolution**	**1000 and 500 mg**	**ADEQUATE**

REVIEW OF AN AMENDMENT AND THE OFFICE OF SCIENTIFIC INVESTIGATION (OSI) INSPECTION REPORT FINDINGS

1 EXECUTIVE SUMMARY

This submission is an amendment to an application which contains the results of fasting (#PKD_09_277) and fed (#PKD_09_278) bioequivalence (BE) studies comparing a test product, Niacin film coated, extended release, Tablet, 1000 mg, to the corresponding reference product, Niaspan (niacin tablet, film coated, extended release), 1000 mg.

This application was previously reviewed and found to have bioanalytical deficiencies related to study repeat analysis and batch run acceptance criteria[4]. In the current amendment, the firm provided: 1) their explanation as to how repeat analysis was performed and; 2) and provided more detail for why certain batch runs were rejected. In most cases the firm was able to address the deficiencies raised by the Division of Bioequivalence. However, because the firm was unable to explain inconsistencies in performance of sample repeat analysis, the reviewer determined bioequivalence of the test to reference drug product based on the original (non-reassayed data). Based on this analysis, the pharmacokinetic (PK) parameters were still within BE acceptance criteria of 80.00% to 125.00%.

The firm's fasting and fed BE studies are now acceptable. The results are summarized in the tables below.

Niacin (Nicotinuric Acid – Original Values) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	1991.3835	1990.5726	1	91.554	109.314
AUC∞ (hr*ng/ml)	2117.2652	2092.5795	1.01	92.397	110.797
Cmax (ng/mL)	757.80504	692.93177	1.09	101.532	117.796

Niacin (Nicotinuric Acid – Original Values) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	9643.8458	10554.786	0.91	84.348	98.976
AUC∞ (hr*ng/ml)	9398.9533	9904.2544	0.95	87.878	102.479
Cmax (ng/mL)	2874.9324	2956.788	0.97	88.529	106.789

The dissolution testing on all strengths using the FDA-recommended method was previously found acceptable.

The Division of Bioequivalence (DB) now grants the waiver request for in vivo BE study requirements for the 500 mg strength tablet of the firm's test drug product based on criteria set forth in 21 CFR § 320.24 (b) (6).

No Office of Scientific Investigations inspections are pending or necessary.

At the request of the Division of Bioequivalence (DB), the Office of Scientific Investigations (OSI) audited clinical portions of the fasting (PKD_09-277) and fed (PKD_09_278) bioequivalence studies. Inspection of clinical portions was conducted at Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara 390 020, India. Following the inspection (October 25-29th, 2010), no Form-483 was issued and no significant findings were uncovered during the inspection. The final classification of the inspection resulted in no action indicated (NAI)[1].

For the analytical site (Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara - 390020, Gujarat, India) there were routine inspections completed for the following ANDAs:

- ANDA #078271 (6/29/2009 result: voluntary action indicated (VAI). The OSI report for ANDA #078271 has been reviewed by DB and found to be incomplete[2]. However, all unaddressed deficiencies related to OSI inspection were specific to issues related to nasal product study design and analysis and does not have an impact on the current ANDA submission.
- ANDA #090362 (6/17/2010 result VAI)[9] and ANDA #090178 (6/8/2010 result VAI)[3]. Both ANDA 090362 and ANDA 090178 were covered in the same OSI inspection. Some of the OSI findings were found to be significant and flagged as having possible impact on other ANDAs. These concerns are reviewed in Section 8 of this review. It was determined that none of the OSI findings would impact the current ANDA submission.

The application is **acceptable** with no deficiencies.

[1] DARRTS: ANDA #200484 CONSULT REV-BIOEQ-01(General Consult Review) Submit Date: 2/25/2011
[2] DARRTS: #078271 (REV-BIOEQ-01(General Review) Submit Date: 7/134/2009.
[3] DARRTS: ANDA #090178 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Submit Date: 6/8/2010.

2 TABLE OF CONTENTS

3 BACKGROUND ON SUBMISSION

On 9/30/2009[4]: the firm submitted an Abbreviated New Drug Application (ANDA) for Niacin Tablet, film coated, extended release, 1000 mg. The Draft guidance for Niacin (date recommended: 12/2009) can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188541.pdf

In the fasting (#PKD_09_277) and fed (#PKD_09_278) BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, nicotinuric acid, were within the CI acceptance criteria. Therefore, based solely on the data of the metabolite, the studies were acceptable. However, the application was found incomplete due to several analytical deficiencies related to repeat analysis and batch rejection criteria, and due to a pending OSI inspection of the clinical site for the current ANDA. The results of niacin are presented for information only. (Some of the point estimates of niacin PK parameters exceeded the limits of [0.80 to 1.25] and the CI of these PK parameters exceeded the limits of [80.00 to 125.00]).

The study result analysis from the original review is follows:

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	1982.1479	1977.8473	1	91.977	109.196
AUC∞ (hr*ng/ml)	2080.5507	2064.3542	1.01	92.972	109.254
Cmax (ng/mL)	754.7901	691.48968	1.09	101.694	117.161

[4] DARRTS: ANDA #200484 REV-BIOEQ-01(General Review) Submit Date: 11/13/2010

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	456.93653	353.76094	1.29	101.497	164.377
AUC∞ (hr*ng/ml)	603.42166	553.58912	1.09	91.046	130.498
Cmax (ng/mL)	569.76371	418.09805	1.36	101.987	182.091

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	9404.3334	10066.42	0.93	87.046	100.267
AUC∞ (hr*ng/ml)	9664.8362	10616.574	0.91	84.634	97.921
Cmax (ng/mL)	2825.005	2916.1819	0.97	89.181	105.230

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	454.83744	472.21568	0.96	76.536	121.217
AUC∞ (hr*ng/ml)	876.82085	760.17914	1.15	97.920	135.868
Cmax (ng/mL)	439.84306	430.26045	1.02	78.309	133.451

The firm's dissolution testing data with the FDA-recommended method was previously deemed acceptable. On 5/26/2010, the firm acknowledged the FDA-recommended dissolution method and specifications.

However, the biowaiver for the lower strength (500 mg) was denied at the time of the original review.

4 REVIEW OF CURRENT AMENDMENT

On 2/17/2011, the firm responded to the deficiencies raised by the Division of Bioequivalence[5]:

FDA's Deficiency #1

1. **For the fasted Study, No. PKD-09-277, sample reanalysis was conducted for Niacin and Nicotinuric Acid for all samples pertaining to subject 16. You indicated that the sample reanalysis was conducted due to suspected "sample mix up" (Code J). Please provide an adequate and detailed explanation as to why you believed the samples were mixed up. In addition, please provide a summary table listing the original assayed values, the reassayed values and the reported values for this subject.**

Firm's Reponses #1

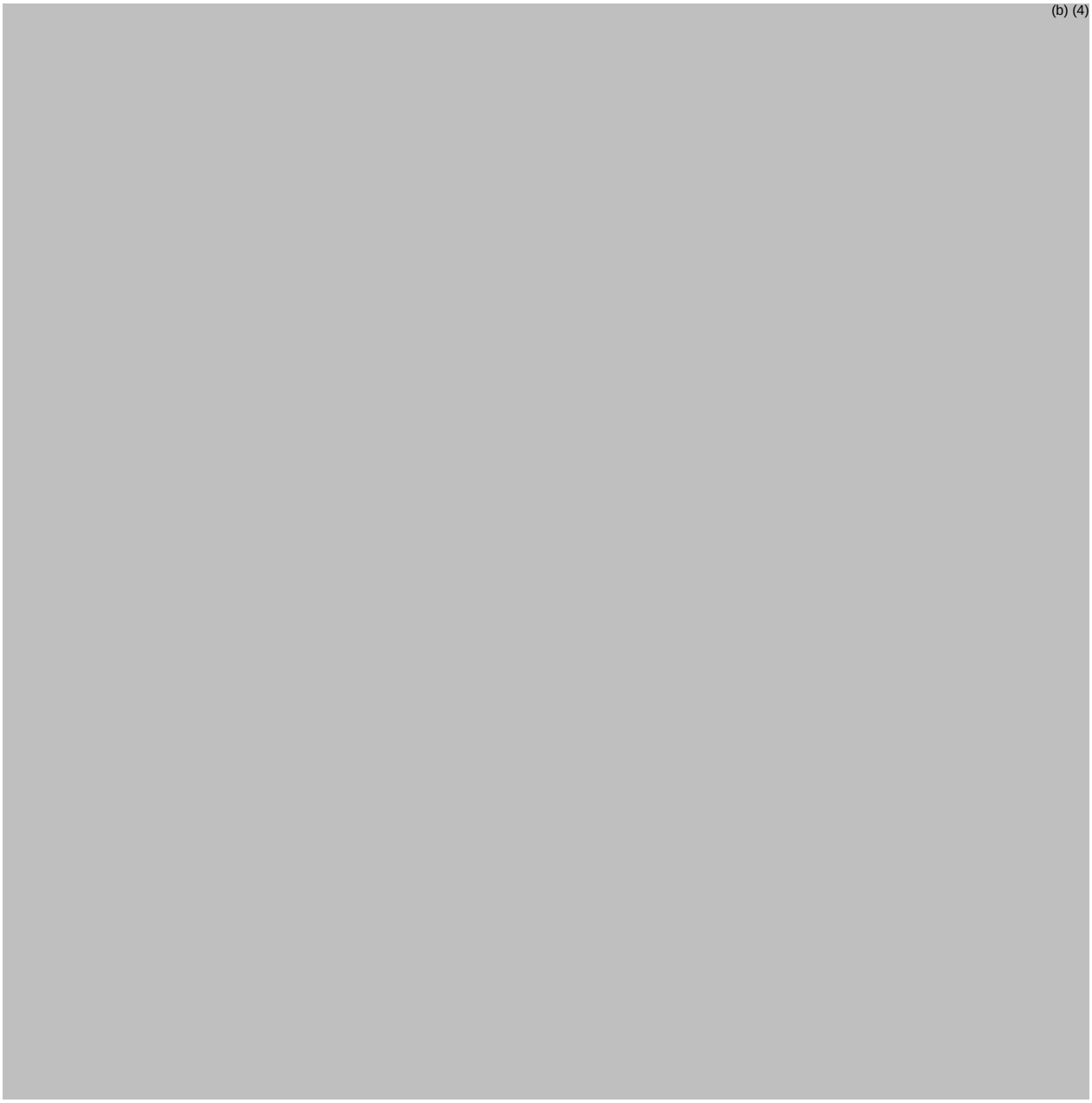
Please note that subject 16 samples were repeated as sample mix-up occurred during processing which resulted into failure of analytical batch as more than 67% of batch QC's were not meeting acceptance criteria. Data analysis with reference to known concentration, revealed that for HQC_01, LQC-A_02, LQC-B_02 and MQC-A_02 QCs, the expected concentrations were observed in the next study sample of that sequence. Hence the sequence was discontinued.

By rearranging the concentration obtained, to expected vial position, these QC concentrations falls within range. This is also confirmed by values obtained for pre dose sample (0.0 hr) and pre dose with internal standard samples (0.00 with IS). Please refer below table for the original values and rearrangement values.

Please also note that following data have been provided herewith in ***Section 5.3.1.4,*** for this subject.

1. Copy of Analytical Run Rejection form
2. Evaluation of subject 16 (rejected) run concentration (corrected vial position)
3. Summary table representing initial, repeat value, reported value of subject 16 for nicotinuric acid (PKD_09_277)
4. Summary table representing initial, repeat value, reported value of subject 16 for niacin (PKD_09_277)
5. Result sheet of Subject 16_200809 of both niacin and nicotinuric acid
6. Result sheet of Subject 16_REP_280809 of both niacin and nicotinuric acid

[5] EDR: ANDA #200484 Section 1 Cover Letter and Bioequivalence Response Submit Date: 2/17/2011



* For QC, in column titled ‘Repeat analysis concentration’ nominal value is mentioned.

Reviewer’s Comments #1

After reviewing the referenced documentation, the reviewer finds that the repeat analysis performed for Subject 16 is valid. As demonstrated in the chart above, expected quality control (QC) sample concentrations can be seen in the next study sample of the sample sequence. Therefore, it is likely that sample loading leading up to LC-MS/MS analysis was in fact done incorrectly.

Deficiency #1 has been adequately addressed by the firm.

FDA's Deficiency #2

For the fasted study, study no. PKD_09_277, all samples for subjects 8, 16, 17 and 22 were reassayed for Niacin and Nicotinuric Acid due to "rejected analytical run" (code J) . In addition, for Fed Study, study no. PKD_09_278, the entire subject samples for 28 (Niacin and Nicotinuric acid samples) and subject 13 (Nicotinuric acid samples) were reanalyzed due to "rejected analytical run"(code J) .

There are several criteria outlined in section 7.1.9 of the Standard Operating Procedure (SOP) PKD/S/019 Revision 03, entitled Sample Reanalysis and Reporting of Final concentrations detailing how samples can be classified as "rejected analytical runs." As required in, section 7.1.9.3 of this SOP, for each subject reanalysis please submit documentation of the "investigated and detailed justification of the reanalysis of the batch (form attachment-3)".

In addition, please submit in tabular format, a complete list of original assay values, repeat assay values and reported values of these subjects for evaluation. For each subject clearly justify why the original or reassayed value was reported.

Firm's Response #2

Details of runs rejected for study number PKD_09_277 and PKD_09_278 are as below.

Study Number : PKD_09_277 Analyte: Nicotinuric acid

Run ID rejected	**Remark**
180809\SUBJECT_08	Both LQC-A were not meeting acceptance criteria. Therefore 50% QCs at each level are not within acceptance.
200809\SUBJECT_16	Sample Mix up suspected as HQC_01, LQC-A_02, LQC-B_02 and MQC-A_02 QCs concentrations were observed in their next study samples. Therefore More than 67% of Batch QC's were not meeting acceptance criteria.
210809\SUBJECT_17	All CCs except CS6 were not meeting acceptance criteria. Therefore Calibration curve is not with in acceptance (More than 75% of CC's were not meeting acceptance criteria).
220809\SUBJECT_22	Both MQC-A were not meeting acceptance criteria. Therefore 50% QCs at each level are not within acceptance.

Study Number: PKD 09 277 Analyte: Niacin

Run ID rejected	Remark
180809\SUBJECT_08	Both LQC-A were not meeting acceptance criteria. Therefore 50% QCs at each level are not within acceptance.
200809\SUBJECT_16	More than 67% of Batch QC's were not meeting acceptance criteria due to sample Mix up suspected (HQC_01, LQC-A_02, LQC-B_02 and MQC-A_02 QCs concentrations were observed in other nearby study samples).
210809\SUBJECT_17	All CCs were not meeting acceptance criteria. Therefore Calibration curve is not with in acceptance (More than 75% of CC's were not meeting acceptance criteria).

Please note that analytical run ID : 220809\SUBJECT_22, (Niacin) was within acceptance criteria, inadvertently it was reported in reassay table for niacin. Concentration reported and used for pharmacokinetic and statistical, evaluation for subject 22 (Niacin) was from initial run (SUBJECT_22_220809). Hence, there is no change in concentration data. Amended report with the following changes has been provided herewith in ***Section 5.3.1.4.***

1) Table 2I : Niacin study subject reassays Sr. No. 4, (Page 35) : Subject 22 text removed from this table
2) Table 3A, Table 4A, Table 5A-5B, Table 6A-6C (Page No. 38, 41, 44-45, 50-52 respectively) : In place of Subject 22_REP data, initial data of Subject 22 (SUBJECT_22_220809) has been added

Study Number: PKD 09 278 Analyte: Niacin

Run ID rejected	Remark
160909\SUBJECT_28	Both CS8 (CS8 and CS8D) were not meeting the acceptance criteria. Therefore whole run is rejected for Nicotinuric acid due to calibration curve rejection.

Study Number : PKD 09 278 Analyte: Nicotinuric acid

Run ID rejected	Remark
110909\SUBJECT_13	CS4 & CS5 were not meeting acceptance criteria. Therefore calibration curve is not within acceptance as two consecutive calibration standards were not meeting acceptance criteria.
160909\SUBJECT_28	CS2, CS3, CS7 and CS8 were not meeting acceptance criteria. Calibration curve is not with in acceptance as two consecutive standards were not meeting acceptance criteria.
180909\SUBJECT_28_REP	MQC-A-02 and Both MQC-B and Both HQC were not meeting acceptance criteria. Therefore More than 67% of Batch QC's and /or 50% QCs at each level were not meeting

	acceptance criteria

Please also note that copies of analytical run rejection form for study number PKD_09_277 and PKD_09_278 have been provided herewith in ***Section 5.3.1.4.***

Complete list of original assay values, repeat assay values and reported values of study no. PKD_09_277 for subjects 8, 16 and 17 (Niacin and Nicotinuric acid samples) and 22 (Nicotinuric acid samples) reassayed and study no. PKD_09_278 for subject 28 (Niacin and Nicotinuric acid samples) and subject 13 (Nicotinuric acid samples) along with justification of accepting original/ reassayed value have been provided herewith in ***Section 5.3.1.4.***

Reviewer's Comments #2

As requested, the firm provided detailed justification for the reanalysis of each repeated batch run for niacin and nicotinuric acid. All reasons for reanalysis were due to either quality control samples or calibration curves not meeting acceptance criteria. The original raw batch data was reviewed by the reviewer to verify the validity of batch rejection. The original data for subject 8 for fasting study PKD_277 was submitted by the firm in a response to a telephone amendment[6]. The firm adequately addressed deficiency #3 and the reviewer agrees with the firm's criteria for rejected runs and with the resultant run reanalysis.

FDA's Deficiency #3

The DBE identified several instances where you did not follow the standard operating procedure (SOP) PKD/S/019, Sample Reanalysis and Reporting of Final concentrations, for reassay performed due to inconsistent profiles (code H). An example of this can be seen in study #PKD_09_277 for nicotinuric acid for subject 23 period 3 at 9 hours. The initial assay (145.6 ng/ml) did not differ by greater than 100% from the previous sample (106.0 ng/ml) or the subsequent sample (95.3 ng/ml). Another example is seen study PKD_09_277 for Nicotinuric acid for subject 23 period 4 at 5 hours. The plasma concentration for Nicotinuric acid for subject 23 at 4 and 5 hours in period 4 was 942.6 ng /ml (reassayed 1174.7 ng/mL) and 126.8 ng/ml, respectively. The plasma concentration at Hour-5 differed from that of Hour-4 by greater than 100% but you did not reassay this sample as you did for other samples. Please submit the following :

a) A summary table (Table 1) detailing all reassays that were performed correctly according to section 7.1.7 of SOP PKD/S/019

b) A summary table (Table 2) detailing all reassay that were performed incorrectly according to section 7.1.7 of SOP PKD/S/019 and

c) SAS-transport formatted files containing the original assay data for all samples identified in Table 2. Tables 1and 2 should contain all pertinent information including the initial value, the reassayed value, and the final reported value for each reassayed samples .

[6] EDR: ANDA #200484 Section 5.3.1.4 Fasting Study PKD _09_277 Submit Date: 10/8/2011

Firm's Response #3

Please note that based on FDA's comment we have reviewed whole raw data to identify any other instances, in addition to those referred in FDA's query. In this review, there were no other such sample time points which are qualifying for repeat analysis as per SOP PKD/S/019, Sample Reanalysis and Reporting of final concentrations, for reassay performed due to "inconsistent profiles (code H)".

Explanation of examples referred in above FDA comment is provided below:

A. Please note that in study # PKD 09 277 for Nicotinuric acid for subject 23 period 3 at 9 hours repeat analysis was conducted based on following section of SOP of PKD/S/019 Revision 03, Sample reanalysis and Reporting of Final concentrations:

7.1.7 Inconsistent profile (Code H):

7.1.7.1 Sample shall be repeated in case of inconsistency at any point of profile (except last three measurable concentrations) where concentration is found more or less than 100% from its preceding and succeeding concentration. In case of higher value preceding and succeeding value shall be consider for 100% comparison and in case of dip in profile the lower value shall be consider for 100% comparison.

7.1.7.2 In the elimination phase, in the last three measurable concentration samples, if any concentration is more than 33 % of preceding and succeeding concentration or in case of last measurable concentration, 33 % more than preceding concentration, the sample shall be repeated under code " H"

For subject 23 period 3 at 9 hours, following was the concentration.

Time point	6.00	7.00	8.00	9.00*	10.00*	12.00*	16.00
Concentration	143.2	103.8	106.0	**145.6**	**95.3**	**50.6**	BLQ
% difference from preceding value					**37.4%**		
% difference from succeeding value					**-52.8%**		

For above case, 9.0, 10.0 and 12.0hr concentrations were considered as last three measurable concentration samples. Hence in accordance with section 7.1.7.2 of above mentioned SOP repeat analysis was conducted.

B. Summary of repeat analysis under code H, for subject 23 period 4 samples in study # PKD_09_277 for Nicotinuric acid is tabulated below :

Sample ID	Original value	Code	First repeat value	Code	Second repeat value	Reported value
SUB 23 P4 2.00HRS***	942.6	B	1174.7			1174.7
SUB 23 P4 5.00 HRS	126.8	H ($)	635.2	H ($)	655.6	126.8
SUB 23 P4 6.00 HRS	567.5	H	172.1#	H	187.6	567.5
SUB 23 P4 7.00 HRS	63.9	H ($)	91.0	H ($)	100.9	63.9

($) Control Samples as per section 7.1.7.3 of Sample Reanalysis and Reporting of Final concentrations' SOP.
(#) As the Repeat sample was qualifying in repeat for IS variation so same sample set was repeated again in H code[7]

5.0, 6.0 and 7.0 hr samples were repeated again because of significant internal standard response variation for sample ID SUB_23_P4_6.00 HRS.

We agree with FDA's comment for repeating sample ID SUB_23_P4_5.00 hours. Please note that, 6 hour sample was identified for repeat under inconsistent profile and 5 hour sample was reanalyzed as control sample for this repeat. In first repeat, variation in internal standard response was observed, hence second repeat was conducted. Thus as this sample was repeated twice as a control sample original value was accepted as reportable value for this sample.

1. In first repeat analysis, 6.00hr time point showed IS variation hence second repeat analysis was conducted.
2. Second repeat analysis also showed a same trend as like first repeat. Based on results of this repeat analysis, sample mix-up for original analysis may be suspected but % difference between repeat value obtained at 6 hour was more than 30% with respect to 5 hour initial value if the values of 5 hour and 6 hour were assumed to be interchanged, hence original assay value were accepted.

Based on evaluation of all possibilities and SOP criteria for reporting value after repeat analysis (as per section 7.1.7.3 of SOP PKD/S/019 Revision 03, for all three samples (5.00hr, 6.00hr and 7.00hr), original analysis value was accepted.

However, to evaluate overall impact of possible interchange during first analysis between 5hr and 6hr sample of period – 4, pharmacokinetic and statistical evaluation have been performed with following option.

1. By assuming interchange and accepting value of SUB_23_P4_5.00 HRS as 567.5 and SUB_23_P4_6.00 HRS as 126.8.
2. By considering NRV for 5.0hr and 6.0hr sample and eliminate those from pharmacokinetic and statistical evaluation

[7] EDR: ANDA #200484 Section 5.3.1.4 Fasting Bioanalytical Report Page 32 Submit Date: 9/29/2009

In both the cases, study outcome remained unaffected, indicating no impact of these values on study results. Summary of statistical evaluation is given below :

TABLE 1

(INTERCHANGED VALUES FOR 5 & 6 HRS IN PERIOD 4 OF SUBJECT NO. 23)									
SUMMARY OF STATISTICAL ANALYSIS NICOTINURIC ACID (N = 30)									
Ln- Transformed Data									
PK Variables	**Least Square Means**		**Geometric Means[3]**		**Ratio of Least-Square Means[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV %**		**P-value[4]**
	Test	**Reference**	**Test**	**Reference**			**Test**	**Reference**	
AUC_{0-t}	7.59	7.59	1982.15	1977.85	100.22	91.98 to 109.20	25.92	25.62	0.9660
AUC_{0-inf}	7.64	7.63	2080.55	2064.32	100.79	92.97 to 109.26	26.91	25.01	0. 8719
Cmax	6.63	6.54	754.79	691.49	109.15	101.69 to 117.16	24.55	20.18	0.0430

TABLE 2

(NRV VALUES FOR 5 & 6 HRS IN PERIOD 4 OF SUBJECT NO. 23)									
SUMMARY OF STATISTICAL ANALYSIS NICOTINURIC ACID (N = 30)									
Ln- Transformed Data									
PK Variables	**Least Square Means**		**Geometric Means[3]**		**Ratio of Least-Square Means[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV %**		**P-value[4]**
	Test	**Reference**	**Test**	**Reference**			**Test**	**Reference**	
AUC_{0-t}	7.59	7.59	1982.15	1977.33	100.24	92.00 to 109.22	25.92	25.68	0.9618
AUC_{0-inf}	7.64	7.63	2080.55	2063.81	100.81	92.99 to 109.29	26.89	25.05	0. 8681
Cmax	6.63	6.54	754.79	691.49	109.15	101.69 to 117.16	24.55	20.18	0.0430

[1] Calculated using least square means according to the formula: $e^{(LSM\ Test - LSM\ Reference)} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data;

[3] Least-square geometric means calculated from the analysis of the ln-transformed data as $e^{(least\text{-}square\ mean)}$

[4] P-value is for product effect

a) Please find below summary table (Table 1) detailing all re assays that were performed correctly according to section 7.1.7 of SOP PKD/S/019 along with all pertinent information including the initial value, the reassayed values and the final reported value for each reassayed samples.

Observed IS variation hence repeated again.
$ Observed IS variation in control samples hence repeated again

Table 1

Sample Identification (Subject, Period, Time)	Concentrations (ng/mL)					
	Original Value	Code	Repeat Value-1	Code	Repeat Value-2	Reported Value (ng/mL)
SUB_02_P1_9.00 HRS	48.4	H	31.9			48.4
SUB_04_P2_10.00 HRS	312.1	H	335.8			312.1
SUB_04_P2_3.00 HRS	532.4	H	578.7			532.4
SUB_05_P3_10.00 HRS	54.3	H	39.8			54.3
SUB_13_P3_7.00 HRS	52.2	H	48.5			52.2
SUB_14_P4_8.00 HRS	77.2	H	84.5			77.2
SUB_15_P1_2.00 HRS	1284.1	H	947.2			1284.1
SUB_15_P4_12.00 HRS	53.6	H	BLQ			53.6
SUB_20_P4_3.00 HRS	490.9	H	575.9			490.9
SUB_20_P4_5.00 HRS	661.4	H	709.9$	H	745.7	661.4
SUB_22_P1_6.00 HRS	335.6	H	185.1			185.1
SUB_22_P4_1.25 HRS	1558.1	H	1532.8			1558.1
SUB_23_P4_6.00 HRS	567.5	H	172.1 #	H	187.6	567.5
SUB_27_P3_5.00 HRS	160.8	H	185			160.8
SUB_28_P2_3.50 HRS	497.2	H	558.2			497.2
SUB_29_P2_3.50 HRS	105.4	H	105.3			105.4
SUB_29_P3_2.50 HRS	340	H	567.1			567.1
SUB_31_P2_3.50 HRS	417.3	H	467.4			417.3
SUB_32_P2_8.00 HRS	39.3	H	39.3			39.3
SUB_32_P2_12.00 HRS	118.7	H	66.8			66.8
SUB_32_P3_9.00 HRS	269	H	BLQ			BLQ
SUB_33_P2_8.00 HRS	287	H	287.9			287
SUB_34_P3_8.00 HRS	68.6	H	61			68.6
SUB_36_P1_9.00 HRS	146.5	H	162.1			146.5
SUB_36_P3_4.00 HRS	400.4	H	350.6			400.4

b) A summary table (Table 2) detailing all reassay that were performed incorrectly according to section 7.1.7 of SOP PKD/S/019 along with all pertinent information including the initial value, the reassayed and the final reported value for each reassayed samples.

Table 2

Sample Identification (Subject, Period, Time)	Concentrations (ng/mL)					
	Original Value	Code-1	Repeat Value-1	Code-2	Repeat Value-2	Reported Value(ng/mL)
SUB_02_P1_9.00 HRS	48.4	N	BLQ			48.4
SUB_02_P4_10.00 HRS (@)	77.1	N	74.4			77.1
SUB_02_P4_12.00 HRS (@)	74.4	N	79.1			74.4
SUB_02_P4_7.00 HRS (@)	44.8	N	40.8			44.8
SUB_02_P4_8.00 HRS (@)	30.7	N	BLQ			30.7
SUB_04_P2_10.00 HRS	312.1	N	342.2			312.1
SUB_13_P3_7.00 HRS	52.2	N	47.9			52.2
SUB_14_P4_8.00 HRS	77.2	N	86.5			77.2
SUB_15_P4_12.00 HRS	53.6	N	94.2			53.6
SUB_24_P2_5.00 HRS	31.8	N	46.4	N	46.7	31.8
SUB_32_P2_12.00 HRS	118.7	N	74.3	H	66.8	66.8*
SUB_32_P3_9.00 HRS	269.0	N	BLQ	H	BLQ	BLQ
SUB_34_P3_8.00 HRS	68.6	N	63.4			68.6
SUB_36_P1_9.00 HRS	146.5	N	183.9			146.5
SUB_36_P3_4.00 HRS	400.4	N	405.8			400.4

* For justification for accepting this value, refer ANDA section 5.3.1.4, Fasting bioanalytical report (subsection 16.5 Bioanalytical report Table 2A to 2M)

SAS-transport formatted files containing the original assay data for all samples identified in Table 2.

Tables 1 and 2 should contain all pertinent information including the initial value, the reassayed and the final reported value for each reassayed samples.

Please note that SAS-transport formatted files containing the original assay data for all samples identified in table two has been provided herewith in ***section 5.3.1.2.***

c) Please find below criteria for reanalysis performed for sample coded "N", with examples of how the decision was made to perform reanalysis and report the final value for reassays coded as "N".

Table-2 provided above, summarizes reassay that were performed incorrectly, all these samples (except identified as @) were repeated under code F (to confirm the value), this samples were inadvertently repeated as per procedure defined under previous version of the SOP. In newly revised version of the SOP (effective at the time of study), code 'F' was not specified, however as per revised SOP these samples were qualifying for repeat under code H (inconsistent value), which has to be repeated along with control samples. In repeat analysis done as per previous version of SOP, control sample were not analyzed.

To have clear explanation of repeat analysis of samples identified as @, please refer below mentioned table.

Time point Hrs	**5.0**	**6.0**	**7.0**	**8.0**	**9.0**	**10.0**	**12.0**	**16.0**
Subject 2	32.1	BLQ	44.8	30.7	BLQ	77.1	74.1	BLQ
Code in final report	-	BLQ-F	N	N	BLQ-F	N	N	-

For Subject 2 Period 4 sample of 6.0 Hrs & 9.0 Hrs were qualifying for repeat analysis as per SOP PKD_S_019 Section "A sample presenting concentration below lower limit of quantification while quantifiable concentrations (more than 120% of LLOQ) were obtained with the two adjacent sampling time points". So they were reanalyzed to confirm the value on 29 August 2010.

After confirming the values of 6.0 hrs & 9.0 hrs no other samples were qualifying for further repeat analysis as per SOP, however 7.0, 8.0 10.0 & 12.0 hrs were also reanalyzed applying SOP criteria "A sample presenting concentration above lower limit of quantification (more than 120% of LOQ) while non quantifiable concentrations were obtained with the two adjacent sampling time points", as one of the adjacent point value was BLQ for this samples. But these time points were not qualifying for repeat analysis as per SOP (SOP requires two adjacent sampling points to be BLQ) as only one adjacent point is BLQ. Hence reanalysis of all above mentioned samples (7.0, 8.0 10.0 & 12.0 hrs) were marked with code N as incorrectly repeated.

Review's Comment #3

- The Division of Bioequivalence observed that the firm was performing reanalysis of study samples in a non-consistent manner (please refer to examples provided in deficiency comment #3 above). The firm was asked to explain these discrepancies and to reanalyze their data to determine all instances whereby reassay were performed incorrectly. The examples presented to the firm were the following:

  1) For nicotinuric acid for subject 23, Period 3 at 9 hours, the initial assay (145.6 ng/ml) did not differ by greater than 100% from the previous sample

(106.0 ng/ml) or the subsequent sample (95.3 ng/ml), yet the firm **did** perform reanalysis of that time point.

2) For Nicotinuric acid for subject 23, Period 4 at 5 hours. The plasma concentration for Nicotinuric acid for subject 23 at 4 and 5 hours in period 4 was 942.6 ng /ml (reassayed 1174.7 ng/mL) and 126.8 ng/ml, respectively. The plasma concentration at Hour-5 differed from that of Hour-4 by greater than 100% but the firm **did not** reassay this sample as they did for other samples.

Reviewer's Comment #3 Regarding Reanalysis of Subject 23 period 3 at 9 hours

- Period 3 at 9 hours falls within the elimination phase of nicotinuric acid. As per section 7.1.7.2 of SOP PKD/S/019 Revision 3, Sample Reanalysis and Reporting of Final Concentrations, *In the elimination phase, in the last three measurable concentration samples, if any concentration is more than 33 % of preceding and succeeding concentration or in case of last measurable concentration, 33 % more than preceding concentration, the sample shall be repeated under code "H"*. The plasma concentration of subject 23 during period 3 at 9 hours differs by more 33% from the preceding and succeeding concentration and therefore is eligible for reanalysis. In this case, the firm's performance of sample reanalysis was performed as per SOP PKD/S/019, and is found acceptable by the reviewer.

For subject 23 period 3 at 9 hours, following was the concentration.

Time point	6.00	7.00	8.00	9.00*	10.00*	12.00*	16.00
Concentration	143.2	103.8	106.0	**145.6**	**95.3**	**50.6**	BLQ
% difference from preceding value					**37.4%**		
% difference from succeeding value					**-52.8%**		

For above case, 9.0, 10.0 and 12.0hr concentrations were considered as last three measurable concentration samples. Hence in accordance with section 7.1.7.2 of above mentioned SOP repeat analysis was conducted.

Reviewer's Comment #3 Regarding Reanalysis of Subject 23 period 4 at 5 hours

- The prior deficiency was issued related to subject 23 during period 4 (study #PKD_09_277) because the reviewer observed that contrary to SOP PKD/S/019, the firm did not conduct reanalysis for the 5 hour time point despite the result (942.6 ng/mL) differing by greater than 100% from the previous time point (2 hour time point of 126.8 ng/mL). In the current response to the deficiency, the firm acknowledged the validity of this observation made by DB[8].

[8] EDR: ANDA #200484 Cover Letter Submit Date: 2/17/2011

- The firm was asked to provide a summary table (Table 2) detailing all reassays that were performed incorrectly according to Section 7.1.7 of SOP PKD/S/019. In response the firm provided table 2 as shown above in the firm's response to deficiency #3. However, the reviewer was able to identify subjects that were not correctly reassayed as per SOP PKD/S/019 and that were not included in table 2. For example, for study PKD_09_277 for subject 15, Period 1, at 2 hours, the plasma concentration of nicotinuric acid was 1284.1 ng / mL, which exceeded the prior (582 ng / mL) and subsequent (492.4 ng / mL) plasma concentrations by greater than 100%. The firm **did not** reassay subject 15, Period 1 at 2 hours contrary to section 7.1.7 of SOP PKD/S/019. Due to these inconsistencies and the inability of the firm to properly highlight all the reassay inconsistencies, the reviewer used the original analytical data to determine bioequivalence. The results of this analysis for nicotinuric acid for both fasting (PKD_09_277) and fed (PKD_09_278) studies are demonstrated below:

Niacin (Nicotinuric Acid – Original Values) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	1991.3835	1990.5726	1	91.554	109.314
AUC∞ (hr*ng/ml)	2117.2652	2092.5795	1.01	92.397	110.797
Cmax (ng/mL)	757.80504	692.93177	1.09	101.532	117.796

Niacin (Nicotinuric Acid – Original Values) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	9398.9533	9904.2544	0.95	87.878	102.479
AUC∞ (hr*ng/ml)	9643.8458	10554.786	0.91	84.348	98.976
Cmax (ng/mL)	2874.9324	2956.788	0.97	88.529	106.789

The fasting and fed bioequivalence studies using the original study values demonstrate PK parameters that are within the acceptable BE limits of 80.00 to 125.00%. Therefore, the study conclusions reached using either original data or reassayed data demonstrate that the test and reference drug products are bioequivalent.

FDA Deficiency #4:

SOP No. PKD/S/019 Revision 03 became effective after the study sample analyses were completed. Therefore, please provide a copy of the SOP that was effective at the time of analysis and please outline the changes made to the SOP between revision 2 and revision 3. Also, please indicate which revision of the SOP was effective at the time of the study. If PKD/S/019 Revision 2 was the only version of this SOP effective at the time of the study, please submit a copy of this SOP version.

Firm's Response #4:

Please note that SOP No.: PKD/S/019, Revision No.:03 "Sample Reanalysis and Reporting of Final Concentrations", was effective from 10-08-2009 (DD-MM- YYYY). Thus effective date of SOP is 10th August 2009 and first subject sample was analyzed on 14-08-2009 (14th August 2009). Therefore, this SOP was effective before study sample analysis was started.

Reviewer's Comment #4

The firm adequately clarified that SOP No.: PKD/S/019 was effective prior to study samples being analyzed. Deficiency #4 was adequately addressed.

FDA Deficiency #5:

SOP No. PKD/S/033, Chromatographic Analysis of study sample was referenced in SOP no. PKD/S/019 revision 3 but was not included in the application. Please submit a full copy of SOP PKD/S/033 which was effective during the study sample analysis periods.

Firm's Response #5:

Please note SOP No. PKD/S/033 revision 00 entitled "Chromatographic Analysis of study sample" effective at the time of study sample analysis has been provided herewith in ***section 5.3.1.4.***

Reviewer's Comment #5:

This deficiency has been adequately addressed by the firm.

FDA Deficiency #6:

Two concentration ranges for calibration curves (cc) i.e. 29.5, 58.9, 149.3, 345.7, 903.7, 1296.3,1517.3 & 1964.1(ng/ml) and 29.6, 59.2,149.9,347.1,907.1,1301.5,1577.6 and 1972.0 (ng/ml) were used for bioanalysis of nicotinuric acid samples in the Fasted study (study No. PKD_09_277). Please provide an explanation as to why you used two different CC concentration ranges. In addition for each CC concentration range used, please specify all subject samples that were analyzed using such range.

Firm's Response #6:

Please note that two concentration ranges for calibration curves (CC) were used for bioanalysis of Nicotinuric acid samples in the Fasted study (study No. PKD_09_277) because of following reason:
Study sample analysis was started using calibration curve range 29.5, 58.9, 149.3, 345.7, 903.7, 1296.3, 1517.3 & 1964.1(ng/ml) from 13/08/2009 (13th August 2009) and completed on 02/09/2009 (2nd September 2009).

During review of raw data it was noticed that sample ID Subject-32-P4-1.75 was qualifying for repeat analysis, hence repeat analysis of this sample was performed (Analytical Run : Repeat_04_100909) on 10 September 2009 using calibration curve solution prepared on 4th September 2009 for fed study (PKD_09_278). The calibration curve range used was 29.6, 59.2, 149.9, 347.1, 907.1, 1301.5, 1577.6 and 1972.0 (ng/ml). Method validation has been performed for calibration curve range 29.3 to 1975.6 ng/mL for nicotinuric acid. Both ranges used for study sample analysis are with in validated CC range.

Only single analytical Run: Repeat_04_100909 was analyzed using calibration curve range 29.6 to 1972.0 ng/mL.

Reviewer's Comment #6:
The firm explained that calibration curve 29.5 to 1964.1 (ng/mL) was used during all study analysis except for in one case where repeat analysis was conducted and a calibration curve ranging from 29.6 to 1972.0 ng/mL was used. The firm highlights that method validation had been performed for a calibration curve range of 29.3 to 1975.6 ng/mL which encompasses both calibration curves used during study analysis. The reviewer finds the use of two calibration curves during study analysis acceptable. The firm has adequately addressed this deficiency comment.

5 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REVIEW – ANALYTICAL SITE

References: ANDA #090362 and ANDA 090178

The analytical portion of ANDA #200484 took place at Sun Pharmaceutical Tandalja Vadodara – 390 020, India. Analysis began for the current studies on August 14th, 2009.

Regarding ANDA #090362 and ANDA 090178, Sun Pharmaceuticals was inspected by OSI between April 14th-16th, 2010 and April 19-23, 2010)[9,3]. Form-483 was issued by OSI in response to the inspection. The firm's response to the form-483 was evaluated by a DB reviewer on 3/14/2011[10] for ANDA #090362 and on 11/12/2010 for ANDA #090178[11]. The OSI report was evaluated in conjunction with the DB review of the OSI report to determine the impact of the inspectional finding on the current ANDA:

DSI Finding No. 1: Failure to conduct Incurred Sample Reproducibility assessments. The firm did not evaluate method reproducibility for plasma samples collected from study subjects.

Reviewer's Comments on the impact on the current ANDA No. 1:
For ANDA #200484, the firm submitted incurred sample reproducibility assessment data[12]. The bioanalytical method for this study was found to be reproducible with at least 2/3 of the samples found to be reproducible according to SOP No PKD/S/035, Revision No. 02, Identification and Analysis of Incurred Sample (effective date: 7-15-2009). Therefore, the OSI finding #1 should not have an impact on ANDA #200484.

DSI Finding No. 2A and 2B: Failure to provide adequate controls for electronic source records: A) Specific requirements and expiration times for credentials used to access electronic source records and to apply electronic signatures were not defined; B) Physical access to electronic source records were not limited to authorized personnel.

Reviewer's Comments on the impact on the current ANDA No. 2:
In the response to the logical and physical access concerns noted above, the firm indicated that they have updated their SOP to better define logical security measures. The DSI inspector found that the proposed corrective measures indicated in the firm's response was adequate. Since these issues were classified as not clinically significant, the reviewer of the OSI Report considers that the concern cited above does not impact the outcome of current BE studies[10]. Therefore, OSI finding #2 should not have a material impact on the acceptability of ANDA #200484.

---

[9] DARRTS: ANDA #090362 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Submit Date: 6/17/2010
[10] DARRTS: ANDA#090362 REV-BIOEQ-01(General Review) Submit Date: 3/14/2011
[11] DARRTS: ANDA #090178 REV-BIOEQ-01(General Review) Submit Date: 11/12/2010
[12] EDR: ANDA #200484 Section 5.3.1.4 Fasting: Bioanalytical Report Submit Date:

DSI Finding No 3:

A. Precision and accuracy (P&A) validation data generated in run PA01 for levocitirizine[13] method was excluded from P&A global summary results without valid justification.

DSI's Evaluation: During the inspection, the firm was requested to recalculate the precision and accuracy after including the data from the rejected run P&A01. The recalculated results showed that the assay was not as precise and accurate as originally reported but remained within the acceptable limits.

Reviewer's Comments on the impact on the current ANDA No. 3A:

The DB reviewer of the OSI report found that since the OSI's finding that *Precision and accuracy (P&A) validation data generated in run PA01* is specific to the ANDA 090362. This reviewer considers that this OSI finding as an isolated issue and should not have potential impact on the related ANDAs. Therefore, the OSI finding #3A should not have a significant impact on the current ANDA.

B. Dilution linearity was not performed using the study sample matrix (K3 EDTA human plasma). It was performed using only the dilution matrix (CPDA plasma).

DSI's Evaluation: As the subject samples contained K3EDTA as the anticoagulant, the firm should have performed dilution linearity in plasma matrix containing K3EDTA. In their response, the firm acknowledged the observation and revised their SOP to include conduct of dilution linearity experiment in all the blank matrices used during a study. However, there is only one study sample (subject 17, period II, 4h of fed' study PKD/07/072) with concentration above the ULOQ (496.55ng/mL) and this sample was reanalyzed after dilution. Moreover, the dilution QCs were included in the run during the reanalysis. As all the dilution QCs met run acceptance criteria, the observation is not likely to have any significant impact on the results.

Reviewer's Comments on the impact on the current ANDA No. 3B:

The current ANDA submission did used human ethylenediaminetetraacetic acid tripotassium salt (EDTA K_3) plasma to demonstrate dilution integrity[14]. EDTA K_3 was the same anti-coagulant used during subject sample collection. Therefore, this OSI finding should not have an impact on ANDA #200484.

C. For levocitirizine, post-extract stability was performed using standards and QCs stored in auto-ampler (10°C) before auto-sampler stability was demonstrated.

DSI's Evaluation: Nevertheless, source records indicated that the study samples were stored in the auto-sampler for approximately 3h during the longest runs. As the firm demonstrated auto-sampler stability for 64h at 10 DC therefore, the

[13] OSI Finding #3 is the same for both ANDAs #090362 and #090178 except in the case of #090362 inspector refers to levocetirizine and in the case of #090178 the inspector refers to galantamine.

[14] EDR: ANDA #200484 Section 5.3.1.4 Fasting Bioanalytical Method Validation Page 25 Submit Date: 9/29/2009.

observation is not likely to affect the study data.

Reviewer's Comments on the impact on the current ANDA No. 3C:
For the current ANDA, the firm demonstrated auto-sampler stability for 73 hours[15]. Therefore, similar to the conclusion reached by the OSI inspector, this OSI observation should not likely to affect the study data of other ANDA's including ANDA #200484.

Other Findings[11]:

This inspection was requested as "FOR CAUSE" due to the DBE reviewer's concerns with reproducibility of reassayed samples. As noted by DBE, many study samples were reassayed. The reassayed samples and the reassay procedure were reviewed during the inspection. Notably, all samples from Study PKD/07/012, Subject 23 were reassayed due to an undocumented, but suspected, sample mix-up. Comparison of the initial and repeated results suggested the initial evaluation was problematic and likely involved samples assayed in the wrong order. However, due to the lack of documentation, the results from Subject 23 should be omitted. All other reassays were carried out according to acceptable established procedure.

Reviewer's Comments on the impact on the current ANDA related to other findings:
Similar to ANDA #090178, for ANDA #200484 there was a concern with the number and justification of sample reassays performed during the bio-studies. After failed attempts by the firm to justify inconsistencies found in performance of sample reassays, DB used the original study data to determine whether the test drug product met the BE acceptance criteria. As discussed above (Deficiency Comment #3), using the original data from the fasting (#PKD_09_277) and fed (#PKD_09_278) bio-studies, the firm's fasting and fed bioequivalence studies met the BE acceptance criteria of between 80% and 125%.

OSI's Conclusion:
Following evaluation of the inspectional findings and form FDA-483 response from the firm, DSI recommends that the clinical and analytical portions of the studies PKD/07/071 and PKD/07/072 be accepted for Agency review[9].

DB Reviewer's Conclusion:
The integrity of the data presented for ANDA #200484 is not affected by the OSI findings made at the analytical site, Sun Pharmaceutical Tandalja Vadodara – 390 020, India.

6 DEFICIENCY COMMENTS

None.

[15] EDR: ADNA #200484 Section 5.3.1.4 Fasting Bioanalytical Method Validation Page 28 Submit Date: 9/29/2009

7 RECOMMENDATIONS

1. The Division of Bioequivalence accepts the fasting BE study (Study # PKD_09_277) conducted by Sun Pharma Global FZE., on its Niacin Tablet, film coated, extended release, 1000 mg (lot # Lot #GK91008) comparing it to the reference listed drug, Niaspan (Niacin Tablet, film coated, extended release), 1000 mg (Lot#642142E21), manufactured by Abbott Labs.

2. The Division of Bioequivalence accepts the fed BE study (Study #PKD_09_278) conducted by Sun Pharma Global FZE., on its Niacin Tablet, film coated, extended release, 1000 mg (lot # Lot #GK91008) comparing it to the reference listed drug, Niaspan (Niacin Tablet, film coated, extended release), 1000 mg (Lot#642142E21), manufactured by Abbott Labs.

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of water using Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

   1 Hr: NMT (b) (4)%
   3 Hrs: (b) (4)%
   6 Hrs: %
   9 Hrs: %
   12 Hrs: (b) (4)%
   20 Hrs: NLT (b) (4)%

4. The dissolution testing conducted by Sun Pharma Global, on its Niacin film coated, extended release, Tablet, 1000 mg (lot # Lot #GK91008), is acceptable. The firm has conducted acceptable in vivo bioequivalence testing comparing the 1000 mg tablet of the test product with the 1000 mg tablet of the reference product, Niaspan (niacin) tablet, film coated, extended release manufactured by Abbott Labs. The formulation for the 500 mg strength is proportionally similar to the 1000 mg strength of the test product which underwent bioequivalence testing. The DB grants a waiver of in vivo bioequivalence study requirements for the 500 mg tablet of the test product under the Section 21 CFR § 320.24 (b) (6).

5. The Division of Bioequivalence deems the test product Niacin Tablet, film coated, extended release, 500 mg and 1000 mg, manufactured by Sun Pharma Global FZE., to be bioequivalent to the reference product, Niaspan (Niacin Tablet, film coated, extended release), 500 mg and 1000 mg manufactured by Abbott Labs, respectively.

The firm should be informed of the above recommendations.

8 COMMENTS FOR OTHER OGD DISCPLINES

Discipline	Comment
None	None

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200484

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Niacin film coated, extended release Tablets, 500 mg and 1000 mg

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

We acknowledge that you will conduct dissolution testing on your test product as per the following FDA-recommended method and specifications for your test product:

Medium:	Water
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	100 rpm

Specifications:

1 hour:	NMT (b) (4)%
3 hours:	(b) (4)%
6 hours:	%
9 hours:	%
12 hours:	%
20 hours:	NLT (b) (4)%

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

Sincerely yours,

{See appended electronic signature page}

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

9 OUTCOME PAGE

Completed Assignment for 200484 ID: 15215

Reviewer: Lerman, Bruce **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Niacin - Adequate

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15215	2/17/2011	Other	Study Amendment	1	1
15215	2/25/2011	Other	DSI Inspection Report -- Clinical Site	0	0
15215	9/30/2009	Other	DSI Inspection Report -- Analytical Site	1	1
15215	9/6/2011	Other	Study Amendment Without Credit (WC)	0	0
15215	9/20/2011	Other	Study Amendment Without Credit (WC)	0	0
15215	10/11/2011	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	2

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

/s/

BRUCE J LERMAN
10/14/2011

APRIL C BRADDY
10/17/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/17/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200484		
Drug Product Name	Niacin Tablet, film coated, extended release		
Strength(s)	500 and 1000 mg		
Applicant Name	Sun Pharma Global FZE		
Address	270 Prospect Plains Road		
Applicant's Point of Contact	Anne Toland		
Contact's Telephone Number	609-495-2823		
Contact's Fax Number	609-495-2711		
Original Submission Date(s)	09/30/2009		
Submission Date(s) of Amendment(s) Under Review	5/26/2010 – Quality/Stability Information and dissolution amendment 9/6/2010 – Amendment (Submission of SAS files)		
Reviewer	Dr. Bruce Lerman		
Study Number (s)	PKD_09_277	PKD_09_278	
Study Type (s)	Fasting	Fed	
Strength (s)	1000 mg	1000 mg	
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Tandalja Vadodara – 390 020, India		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalja Vadodara – 390 020, India.		
OUTCOME DECISION	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
DSI INSPECTION	**INADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1,9	**Fasting Study**	**1000 mg**	**INADEQUATE**
1,9	**Fed Study**	**1000 mg**	**INADEQUATE**
1,7	**Dissolution**	**1000mg and 500 mg**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Niacin, film coated, extended release, Tablet, 1000 mg, to the corresponding reference product, Niaspan (niacin tablet, film coated, extended release), 1000 mg. Each of the BE studies was designed as a single-dose, two treatment, four period, two sequence, replicated crossover study in healthy male subjects. The firm's fasting and fed BE studies are **incomplete due to deficiencies related to bioanalytical method validation and data analysis.** The results of the bioequivalence studies are summarized in the tables below.

The pharmacokinetic (PK) parameters of the parent drug, niacin, for the test and reference products are highly variable and plasma concentrations for niacin were often found below or close to the limit of quantitation. For the approval of Niaspan, the reference listed drug (RLD) product, nicotinuric acid was accepted as the pharmacokinetic parameter to assess for bioequivalence (BE) because plasma niacin pharmacokinetic parameters were not reliable for the BE assessment due to low niacin plasma concentrations by extensive metabolism[1]. Similar data submissions have previously been accepted by the Division of Bioequivalence[2,3].

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite, nicotinuric acid, were within the CI acceptance criteria. Therefore the studies are acceptable based on the data of the metabolite. The results of niacin are presented for information only. (Some of the point estimates of niacin PK parameters exceeded the limits of [0.80 to 1.25] and the CI of these PK parameters exceeded the limits of [80.00 to 125.00]).

This assessment is in accordance with the Agency's current BE recommendations for Niacin, film coated, extended release Tablets[10].

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	1982.1479	1977.8473	1	91.977	109.196
AUC∞ (hr*ng/ml)	2080.5507	2064.3542	1.01	92.972	109.254
Cmax (ng/mL)	754.7901	691.48968	1.09	101.694	117.161

[1] DARRTS: NDA #020381 REV-CLINPHARM-01 (General Review) Final Date: 9/28/2006
[2] Biofile: ANDA #076378 Submit Date: 4/1/2002
(b) (4)
Biofile: ANDA #076250 Submit Date: 5/17/200
(b) (4)

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	456.93653	353.76094	1.29	101.497	164.377
AUC∞ (hr*ng/ml)	603.42166	553.58912	1.09	91.046	130.498
Cmax (ng/mL)	569.76371	418.09805	1.36	101.987	182.091

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	9404.3334	10066.42	0.93	87.046	100.267
AUC∞ (hr*ng/ml)	9664.8362	10616.574	0.91	84.634	97.921
Cmax (ng/mL)	2825.005	2916.1819	0.97	89.181	105.230

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	454.83744	472.21568	0.96	76.536	121.217
AUC∞ (hr*ng/ml)	876.82085	760.17914	1.15	97.920	135.868
Cmax (ng/mL)	439.84306	430.26045	1.02	78.309	133.451

The firm's dissolution testing data with the FDA-recommended method are now acceptable. Initially, the firm's dissolution was not acceptable (DARRTS: ANDA #200484 REV-BIOEQ-02(Dissolution Review) Submit Date: 3/31/2010) because the firm had not acknowledged the FDA-recommended specifications.

On 5/26/2010, the firm acknowledged the FDA-recommended dissolution method and specifications.

Despite the firm meeting the requirements for a bio-waiver of their 500 mg Niacin extended release, Tablet, the Division of Bioequivalence cannot grant the waiver until the bioanalytical method validation deficiencies are addressed.

For the clinical site (Sun Pharmaceutical Industries, Tandalja, Vadodara, 390020, Gujarat, India), there is a routine inspection request entered for this current ANDA application (ANDA #200484). The outcome is still pending.[4]

For the analytical site (Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara - 390020, Gujarat, India) there was a routine inspection completed for ANDA #078271 (6/29/2009 result: voluntary action indicated and ANDA #090362 (6/17/2010 result: voluntary action indicated and ANDA #090178 (6/8/2010 result: voluntary action indicated)[5]. The DSI report for ANDA #078271 has been reviewed by DBE and found to be incomplete [DARRTS: #078271 (REV-BIOEQ-01(General Review) Submit Date: 7/134/2009]. The DSI reports for ANDA #090362 and # ANDA 090178 have not yet been reviewed by DBE.

This application is incomplete with deficiencies.

[4] DARRTS: FRM-CONSULT-09(DSI Bioequivalence Audit Request) submit 5/26/2010
[5] DARRTS: CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Submit 6/8/2010

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Niacin Tablet, film coated, extended release, 500 mg and 1000 mg
Reference Product	Niaspan, niacin tablet, film coated, extended release, 500 mg and 1000 mg
RLD Manufacturer[6]	Abbott Labs
NDA No.	N020381
RLD Approval Date[6]	July 28th, 1997
Indication[7]	• To reduce elevated TC, LDL-C, Apo B and TG, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia • In combination with simvastatin or lovastatin: to treat primary hyperlipidemia and mixed dyslipidemia when treatment with NIASPAN, simvastatin, or lovastatin monotherapy is considered inadequate • To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia • In combination with a bile acid binding resin: ▪ Slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hyperlipidemia. ▪ As an adjunct to diet to reduce elevated TC and LDL-C in adult patients with primary hyperlipidemia • To reduce TG in adult patients with severe hypertriglyceridemia.

3.2 PK/PD Information

Bioavailability[7]	Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Time to reach the maximum niacin plasma concentrations was about 5 hours following NIASPAN. To reduce the risk of gastrointestinal (GI) upset, administration of NIASPAN with a low-fat meal or snack is recommended. Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent.

[6] Electronic Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020381&TABLE1=OB_Rx Search Term: Niacin Last Access: 8-3-2010

[7] DRUGS@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory Search Term: Niaspan Last Access: 8-3-10

Food Effect[7]	Should be taken with a low-fat snack[7]. Administration with food maximizes bioavailability[8]
Tmax	Approximately 5 hours
Metabolism[7]	The pharmacokinetic profile of niacin is complicated due to extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose NIASPAN administration. Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.
Excretion[7]	Following single and multiple doses, approximately 60 to 76% of the niacin dose administered as NIASPAN was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.
Half-life[9]	Niacin: 3.82 ± 3.58 (hours) Nicotinuric Acid: 2.40 ± 0.85 (hours)
Drug Specific Issues (if any)[7]	**WARNINGS AND PRECAUTIONS** • **Severe hepatic toxicity has occurred in patients substituting sustained-release niacin for immediate-release niacin at equivalent doses.** • Myopathy has been reported in patients taking NIASPAN. The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with NIASPAN, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism. • Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. • Use with caution in patients with unstable angina or in the acute phase of an MI. • NIASPAN can increase serum glucose levels. Glucose levels should be closely monitored in diabetic or potentially diabetic patients particularly during the first few months of use or dose adjustment. **USE IN SPECIFIC POPULATIONS** • Renal impairment: NIASPAN should be used with caution in

[8] Clinical Pharmacology: Search Term: Niaspan – Pharmacokinetics Last Access: 9-23-2010 http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=1473&sec=monphar

[9] NDA: 020381 REV-CLINPHARM-01 (General Review) Final Date: 8/13/2009

	patients with renal impairment. • Hepatic impairment: NIASPAN is contraindicated in active liver disease or significant or unexplained hepatic dysfunction or unexplained elevations of serum transaminases Gender Steady-state plasma concentrations of niacin and metabolites after administration of NIASPAN are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. This gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders

3.3 OGD Recommendations for Drug Product[10]

Number of studies recommended:	3, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	1000 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Applicants may consider using a reference-scaled average bioequivalence approach for niacin. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	1000 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Applicants may consider using a reference-scaled average bioequivalence approach for niacin. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

[10] External Product Bioequivalence Recommendations
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188541.pdf Search Term: Niacin Date Recommended:12/2009 Niacin Last Access: 8-3-10

3.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	750 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	Applicants may consider using a reference-scaled average bioequivalence approach for niacin. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

Analytes to measure (in plasma/serum/blood):	Niacin and its metabolite nicotinuric acid in plasma
Bioequivalence based on:	(90% CI): Niacin If niacin cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for nicotinuric acid.
Waiver request of in-vivo testing:	500 mg based on (i) acceptable bioequivalence studies on the 1000 mg strength, (ii) proportionally similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Source of most recent recommendations:	External Product Bioequivalence Recommendations Draft Guidance Effective 12/2009 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188541.pdf
Summary of OGD or DBE History (for details, see Appendix 4.4):	There are no reviewed protocols for Niacin as a monotherapy.[11] There are several reviewed control documents for Niacin Extended-Release Tablets. None of the protocol documents were submitted by Sun Pharma[12]. There are two previously approved ANDAs for Niacin, Extended Release Tablets[13]: ANDA #076378 (500 mg and 750 mg) (Approval Date: 4/26/2005) (Barr) ANDA #076250 (1000 mg) (Approval Date: 4/14/2005) (Barr) ** Approval both ANDA 076378 and ANDA 076250 were based on bioequivalent plasma concentrations of Nicotinuric Acid. There are several ANDAs under review for Niacin, Extended-Release Tablets ANDA #090446[14] ANDA #090860[15] ANDA #090892[16] * The above ANDAs used Nicotinuric Acid to determine bioequivalence of Niacin. ** These above ANDAs have been reviewed by Division of Bioequivalence but are still pending final approval. Two important caveat recommendations have been highlighted in control document #01-342[17] related to bioequivalence testing of Niacin, extended release, Tablets. These recommendations are copied below

Document Excerpt from Control Document #01-342[17]

[11] FDA Protocol Database: Search Term: Niacin Last Access: 9-10-10
[12] FDA Control Database, Search Term: Niacin Last Access: 8-3-10
[13] Electronic Orange Book Search Term Niacin Last Access 8-24-10
[14] DARRTS: ANDA #090446 REV-BIOEQ-01 (General Review) Final Date: 06/15/2010
[15] DARRTS: ANDA #090860 REV-BIOEQ-01 (General Review) Submit Date: 11/4/2008
[14] DARRTS: ANDA #090892 REV-BIOEQ-01 (General Review) Final Date: 07/6/2010
[17] FDA Control Database, (b) (4) Last Access: 8-3-10
Review Completed: 7/30/2001

2. For bioequivalence studies of niacin extended release tablets, please quantify plasma concentrations of the parent drug and the metabolite, nicotinuric acid. If niacin cannot be reliably measured using a selective and sensitive analytical method, nicotinuric acid data should be subjected to a confidence interval approach for bioequivalence assessment. If niacin can be reliably measured, niacin data should be subjected to a confidence interval approach for bioequivalence assessment. Plasma concentration data of niacin and nicotinuric acid should be submitted to the Agency.

3. For data analysis, the DBE recommends the use of the average bioequivalence (ABE) approach for replicate and non-replicate bioequivalence studies. However, you have the option to analyze the data using the individual bioequivalence (IBE) criterion. If you choose to conduct the IBE analysis, the Division recommends that you justify your selection with any information available. You should pre-specify in the protocol the commitment to do this analysis exclusively. You should recruit study subjects from the general population as described in the guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations". Please also refer to the guidance, "Statistical Approaches to Establishing Bioequivalence" for study design and data analysis.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	Total : 2 1- Dissolution 2- Long Term Stability (Section 5.3.1.4)

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1	Analyte 2
Bioanalytical method validation report location	**EDR: ANDA #200484 Report No.: MV_NIA_187; Section 5-3-1-4; Submit Date: 9/29/2009**	**EDR: ANDA #200484 Report No.: MV_NIA_187; Section 5-3-1-4; Submit Date: 9/29/2009**
Study Report Number	PKD_09-277 (Fasting) PKD_09-278 (Fed)	PKD_09-277 (Fasting) PKD_09-278 (Fed)
Analyte	Niacin	Nicotinuric Acid
Internal standard (IS)	(b) (4)	
Method description	Extraction method: Refer Method Validation report (MV_NIA_187); Page No.20 (Solid Phase Extraction); Analytical method: LC-MS/MS	Extraction method: Refer Method Validation report (MV_NIA_187); Page No.20 (Solid Phase Extraction); Analytical method: LC-MS/MS
Limit of quantitation	LLOQ : 19.8 ng/mL, ULOQ : 1982.8 ng/mL	LLOQ : 29.3 ng/mL, ULOQ : 1975.6 ng/mL
% recovery (and %CV) at each concentration tested	QC Low A : 103.5% %CV 2.6% QC Low B : 95.9% %CV 1.9% QC Med A: 98.1% %CV 3.7% QC Med B : 97.9% %CV 3.4% QC High : 96.0% %CV 3.1%	QC Low A : 103.6% %CV 2.7% QC Low B : 96.2% %CV 3.1% QC Med A: 98.1% %CV 4.0% QC Med B : 93.5% %CV 3.3% QC High : 91.4% %CV 3.3%
% recovery of analyte in combination with concomitant drug[18]	QC Low A : 100.8% %CV 2.6% QC Low B : 95.2% %CV 2.5% QC Med A: 97.5% %CV 2.5% QC Med B : 97.6% %CV 3.2% QC High : 95.9% %CV 2.7%	QC Low A : 103.9% %CV 2.6% QC Low B : 93.7% %CV 3.1% QC Med A: 95.9% %CV 2.5% QC Med B : 93.5% %CV 2.3% QC High : 90.1% %CV 3.4%
Average recovery of IS (%)	84.8% %CV 3.1%	84.8% %CV 3.1%
Average recovery of IS with concomitant drug (%)	84.0% %CV 2.9	84.0% %CV 2.9%
Standard curve concentrations (ng/mL)	19.8, 39.7, 146.7, 341.0, 892.2, 1288.8, 1566.4, 1982.8 ng/mL	29.3, 58.7, 148.7, 344.3, 899.8, 1291.0, 1564.9, 1975.6 ng / mL
QC concentrations (ng/mL)	Low A QC : 61.0 ng / mL Low B QC : 183.1 ng / mL Medium QC A : 508.6 ng / mL Medium QC B : 935.8 ng / mL High QC : 1627.5 ng / mL	Low A QC : 92.3 Low B QC : 276.8 Medium QC A : 512.5 Medium QC B : 984.1 High QC : 1681.1
QC Intraday precision range (%)	1.0% to 5.1%	2.1% to 7.0%
QC Intraday accuracy range (%)	93.1% to 109.3%	90.3% to 107.5%
QC Interday precision range (%)	1.0% to 12.2% & 1.8% to 9.1%	2.1% to 11.4% & 1.8% to 7.8%
QC Interday accuracy range (%)	91.3% to 110.0% & 94.7% to 104.9%	90.3% to 114.7% & 89.8% to 99.8%

[18] Aspirin was added with Niacin to determine effect of co-administered drug. EDR #200484 Section 5.3.14 Bioanalytical Method Validation Submit Date: 9/29/2009 Page 32

Bench-top stability (hrs)	14 hours at room temperature (With/Without Aspirin & or with/without Monochromatic light)	14 hours at room temperature (With/Without Aspirin & or with/without Monochromatic light)
Stock stability (days)	41 days @ 2-8°C	41 days @ 2-8°C
Processed stability (hrs)	73 hours @ 10°C ± 2°C	73 hours @ 10°C ± 2°C
Freeze-thaw stability (cycles)	04 cycles	04 cycles
Long-term storage stability (days)	45 Days @ -20°C±5°	45 Days @ -20°C±5°
Dilution integrity	- 4 times of CS8 concentration (6103.1 ng/ml) diluted 5 folds. - % Accuracy : 1/5th : 105.5 - % Precision : 1/5th : 2.4	- 4 times of CS8 concentration (6212.0 ng/ml) diluted 5 folds. - % Accuracy : 1/5th : 108.0 - % Precision : 1/5th : 2.0
Selectivity	No significant interference observed in blank plasma samples	No significant interference observed in blank plasma samples
Bioanalytical method is acceptable	Acceptable	Acceptable

Standard Operating Procedures, SOPs Submitted:

1. Determination of Niacin and Nicotinuric acid (metabolite of Niacin) in human plasma using Liquid Chromatography method with Tandem Mass spectrometry-Micro mass Quattro Premier XE[19] (effective date: 05-09-09). Revision No. 01 Supersedes: 00

2. Evaluation of stability of drug (s) in biological matrix and solutions[20]. SOP No. PKD/S/010 Revision No: 0.02 (effective date: 08-06-2009) Supersedes: 01

3. Bioanalytical Method Validation (effective Date:7-3-2009) [21]. SOP No. PKD/S/013 Revision 02 supersedes: 01

4. Verification of chromatograms, Peak Integration and Chromatographic Acceptance Criteria (effective date: 12-18-2008) [22]. SOP No. PKD/S/015 Revision 01 Supersedes: 00

5. Sample Reanalysis and Reporting of Final Concentrations (effective Date: 10-8-2009)[23]. SOP No: PKD/S/019 Revision 03 Supersedes: 02

6. Preparation, Identification and Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Control Samples (effective Date: 7/3/2009)[24]. SOP. No: PKD/S/034 Revision No. 01 Supersedes Revision:00

[19] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 104 Submit date 9/29/2009
[20] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 1959 Submit date 9/29/2009
[21] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 1984 Submit date 9/29/2009
[22] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 2040 Submit date 9/29/2009
[23] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 2064 Submit date 9/29/2009
[24] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 2085 Submit date 9/29/2009

7. Identification and analysis of incurred sample (effective Date: 7/15/2009)[25]. SOP No.: PKD/S/035 Revision No. 02 Supersedes No. 01.

Comments on the Pre-Study Method Validation:

1. The firm used ethylenediaminetetraacetic acid tripotassium salt (K_3-EDTA) as an anticoagulant for the method validation and collection of samples during the clinical studies[26].

2. The mean recovery values of Niacin from the low to high concentrations were 103.5%, 95.9%, 98.1%, 97.9% and 96%, respectively. The mean recovery value of the internal standard was 84.8%. The % coefficient of variation (%CV) for the quality control (QC) samples and internal standard were within acceptable ranges.

3. The mean recovery values of Niacin co-administered with aspirin from the low to high concentrations were 100.8%, 95.2%, 97.5%, 97.6%, 95.9%, respectively. The mean recovery value of the internal standard when aspirin is co-administered, is 84%. The %CV for the QC samples and internal standard were within acceptable ranges.

4. The mean recovery values of Nicotinuric Acid from the low to high concentrations were 103.6%, 96.2%, 98.1%, 93.5%, and 91.4%, respectively. The % CVs for the QC samples were within acceptable ranges.

5. The mean recovery values of Nicotinuric Acid co-administered with aspirin from the low to high concentrations were 103.9%, 93.7%, 95.9%, 93.5%, and 90.1%, respectively. The %CVs for the QC samples were within acceptable ranges.

6. In an amendment submitted 5/26/2010, the firm provided long term stability data for Niacin and Nicotinuric Acid in biological matrix at -20^{o}C for up to 130 days[27]. This submission adequately addressed a deficiency issued in a previous dissolution review[28].

7. The pre-study method validation is complete. However, this may changed based on the outcome of the DSI inspection.

---

[25] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 2108 Submit date 9/29/2009
[26] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5 Page 7 Submit date 9/29/2009
[27] EDR: ANDA #200484 Cover Letter and Response and Section 5.3.14 Submit Date: 5.3.1.4
[28] DARRTS: ANDA #200484 REV-BIOEQ-02(Dissolution Review) Submit Date: 3/31/2010).

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Summary of Bioavailability Study for Niacin 1000 mg ER Tablet (Fasting study)
Pharmacokinetic data for Niacin (Fasting)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Nicotinuric acid (NUA)) (N=30)						
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	Study Report Location
PKD_09_277	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Niacin 1000mg Extended release Tablets of Sun Pharmaceutical Industries Limited, India and Niaspan® (Niacin) 1000mg Extended release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, in 36 healthy human adult subjects, under fasting conditions.	A Randomized, open label, two treatment, four period, two sequence, single dose, replicated crossover, bioequivalence study with washout periods of 7, 10 and 11 days respectively between drug administration under fasting conditions.	**Test:** Niacin 1000 mg/ ER Tablet /Oral Batch No: GK91008B	30 healthy male subjects (30/0) Mean age (Range) : 30.5 (18 - 47)	818.43 +/- 335.292 (41.0)	1.62 (0.75 – 5.00)	2254.4233 +/- 1308.52468 (58.0)	2351.8072 +/- 1329.75502 (56.5)	1.3315 +/- 1.27579 (95.8)	0.68722 +/- 0.239969 (34.9)	Section 5.3.1.2
			Reference: Niaspan® (Niacin) 1000 mg/ ER Tablet /Oral Lot No.: 642142E21		729.39 +/- 249.442 (34.2)	1.75 (0.75 – 6.00)	2174.4390 +/- 1072.79662 (49.3)	2258.8330 +/- 1081.04098 (47.9)	1.2762 +/- 0.56582 (44.3)	0.63647 +/- 0.236282 (37.1)	

[1]**Arithmetic mean ± standard deviations (% CV) except for Tmax (Range) for which the median are reported.**

Summary of Bioavailability Study for Niacin 1000 mg ER Tablet (Fasting study)
Pharmacokinetic data for Nicotinuric Acid (Fasting)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Niacin) (N=30)						
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	#AUC_{0-inf} (ng*hr/mL)	#$T_{1/2}$ (hr)	#Kel (1/hr)	Study Report Location
PKD_09_277	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Niacin 1000mg Extended release Tablets of Sun Pharmaceutical Industries Limited, India and Niaspan® (Niacin) 1000mg Extended release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, in 36 healthy human adult subjects, under fasting conditions.	A Randomized, open label, two treatment, four period, two sequence, single dose, replicated crossover, bioequivalence study with washout periods of 7, 10 and 11 days respectively between drug administration under fasting conditions.	**Test:** Niacin 1000 mg/ ER Tablet /Oral Batch No: GK91008B	30 healthy male subjects (30/0) Mean age (Range) : 30.5 (18 - 47)	797.67 +/- 546.083 (68.5)	1.50 (0.25 – 5.00)	707.8098 +/- 678.55994 (95.9)	874.8478 +/- 760.19052 (86.9)	1.5668 +/- 1.68844 (107.8)	1.30457 +/- 1.288387 (98.8)	Section 5.3.1.2
			Reference: Niaspan® (Niacin) 1000 mg/ ER Tablet /Oral Lot No.: 642142E21		612.13 +/- 478.691 (78.2)	1.25 (0.50 – 3.50)	585.8365 +/- 553.67515 (94.5)	835.1301 +/- 834.96581 (100.0)	2.8369 +/- 6.95185 (245.0)	1.04659 +/- 0.988081 (94.4)	

[1]**Arithmetic mean ± standard deviations (% CV) except for Tmax (Range) for which the median are reported**

Summary of Bioavailability Study for Niacin 1000 mg ER Tablets (Fed study)
Pharmacokinetic data for Niacin (Fed)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Nicotinuric acid (NUA)) (N=32)						
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	Study Report Location
PKD_09_278	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Niacin 1000mg Extended release Tablets of Sun Pharmaceutical Industries Limited, India and Niaspan® (Niacin) 1000mg Extended release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, in 36 healthy human adult subjects, under fed conditions.	A Randomized, open label, two treatment, four period, two sequence, single dose, replicated crossover, bioequivalence study with washout periods of 7, 16 and 5 days respectively between drug administration under fed conditions.	**Test:** Niacin 1000 mg/ ER Tablet /Oral Batch No: GK91008B	32 healthy male subjects (32/0) Mean age (Range) : 31.8 (18 - 50)	3252.32 +/- 1776.756 (54.6)	5.00 (1.50 – 16.00)	11263.2992 +/- 7516.17101 (66.7)	11606.8050 +/- 7731.98035 (66.6)	2.1065 +/- 0.86046 (40.8)	0.38588 +/- 0.159447 (41.3)	Section 5.3.1.2
			Reference: Niaspan® (Niacin) 1000 mg/ ER Tablet /Oral Lot No.: 642142E21		3272.50 +/- 1593.543 (48.7)	5.00 (2.00 – 6.50)	12016.5004 +/- 7997.35567 (66.6)	12595.9656 +/- 8173.80524 (64.9)	3.3496 +/- 7.83498 (233.9)	0.39188 +/- 0.182809 (46.6)	

Summary of Bioavailability Study for Niacin 1000 mg ER Tablets (Fed study)
Pharmacokinetic data for Nicotinuric Acid (Fed)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, orm, Route) Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Niacin) (N=32)						
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	#AUC_{0-inf} (ng*hr/mL)	#$T_{1/2}$ (hr)	#Kel (1/hr)	Study Report Location
PKD_09_278	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Niacin 1000mg Extended release Tablets of Sun Pharmaceutical Industries Limited, India and Niaspan® (Niacin) 1000mg Extended release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, in 36 healthy human adult subjects, under fed conditions.	A Randomized, open label, two treatment, four period, two sequence, single dose, replicated crossover, bioequivalence study with washout periods of 7, 16 and 5 days respectively between drug administration under fed conditions.	**Test:** Niacin 1000 mg/ ER Tablet /Oral Batch No: GK91008B	32 healthy male subjects (32/0) Mean age (Range) : 31.8 (18 - 50)	1040.71 +/- 1381.161 (132.7)	5.00 (1.50 – 16.00)	1383.2816 +/- 2476.37857 (179.0)	2020.6733 +/- 2772.57085 (137.2)	3.8670 +/- 5.71391 (147.8)	0.91784 +/- 1.025443 (111.7)	Section 5.3.1.2
			Reference: Niaspan® (Niacin) 1000 mg/ ER Tablet /Oral Lot No.: 642142E21		911.68 +/- 1141.473 (125.2)	4.50 (1.50 – 7.00)	1218.9887 +/- 1960.37012 (160.8)	1590.4915 +/- 2095.75423 (131.8)	3.2009 +/- 3.83005 (119.7)	0.61161 +/- 0.735768 (120.3)	

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

A. Nicotinuric Acid (Active Metabolite)

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	1982.1479	1977.8473	1.00	91.977	109.196
AUC∞ (ng*hr/mL)	2080.5507	2064.3542	1.01	92.972	109.254
Cmax (ng/mL)	754.7901	691.4896	1.09	101.694	117.161

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No.PKD_09_278) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	9404.33	10066.42	0.93	87.046	100.267
AUC∞ (ng*hr/mL)	9664.8362	10616.574	0.91	84.634	97.921
Cmax (ng/mL)	2825.005	2916.1819	0.97	89.181	105.230

B. Niacin (parent drug) (for information only)

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	456.93653	353.76094	1.29	101.497	164.377
AUC∞ (ng*hr/mL)	603.42166	553.58912	1.09	91.046	130.498
Cmax (ng/mL)	569.76371	418.09805	1.36	101.987	182.091

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng*hr/mL)	454.83744	472.21568	0.96	76.536	121.217
AUC∞ (ng*hr/mL)	876.82085	760.17914	1.15	97.920	135.868
Cmax (ng/mL)	439.84306	430.26045	1.02	78.309	133.451

Table 3. Reanalysis of Study Samples

Fasted Study, Study No. PKD_09_277 (Niacin) Location in final report: Section 5-3-1-4; 16.5: Page 38								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Unacceptable internal standard response	12	15	0.48	0.60	12	15	0.48	0.60
Incomplete Analysis	1	5	0.04	0.20	1	5	0.04	0.20
Sample concentration above ULOQ	4	1	0.16	0.04	4	1	0.16	0.04
Rejected analytical run	168	168	6.67	6.67	167	165	6.63	6.55
Total	185	189	7.34	7.50	184	186	7.3	7.38

*Note: Total of 2519 samples were analyzed

Fasted Study, Study No. PKD_09_277 (Nicotinuric Acid) Niacin 1000 mg ER Tablets (Fasting) Location in final report: Section 5-3-1-4; 16.5: Page 39								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Unacceptable internal standard response	11	15	0.44	0.60	11	15	0.44	0.60
Incomplete analysis	4	5	0.16	0.20	4	5	0.16	0.20
Sample concentration above ULOQ	1	0	0.04	0.00	1	0	0.04	0.00
Sample reanalyzed to obtain confirming value	10	10	0.40	0.40	5	4	0.20	0.16
Inconsistent Profile	15	13	0.60	0.52	2	2	0.08	0.08
Sample repeated by error	7	9	0.28	0.36	0	0	0.00	0.00
Rejected analytical run	168	168	6.67	6.67	164	165	6.51	6.55
Total	216	220	8.57	8.73	187	191	7.42	7.58

*Note: Total of 2519 samples were analyzed

Fed Study, Study No. PKD_09_278 (Niacin) Niacin 1000 mg ER Tablets (Fed) Location in final report: Section 5-3-1-4; 16.5: Page 73								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Unacceptable internal standard response	9	13	0.33	0.48	9	12	0.33	0.45
Incomplete analysis	1	17	0.04	0.63	1	17	0.04	0.63
Sample concentration above upper limit of quantitation	55	58	2.05	2.16	55	58	2.05	2.16
Sample reanalyzed to obtain confirming value	1	1	0.04	0.04	1	1	0.04	0.04
Sample reanalyzed or reinjected by error	1	1	0.04	0.04	0	0	0.00	0.00
Rejected analytical run	42	42	1.56	1.56	41	40	1.53	1.49
Total	109	132	4.06	4.91	107	128	3.98	4.76

Note: Total 2688 samples were analyzed

Fed Study, Study No. PKD 09 278 (Nicotinuric Acid) Niacin 1000 mg ER Tablets (Fed) Location in final report: Section 5-3-1-4; 16.5: Page 74								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Poor chromatography	1	0	0.04	0.00	1	0	0.04	0.00
Unacceptable internal standard response	8	16	0.30	0.60	5	15	0.19	0.56
Incomplete analysis	2	15	0.07	0.56	2	9	0.07	0.33
Sample concentration above upper limit of quantitation	222	242	8.26	9.00	220	241	8.18	8.97
Sample reanalyzed to obtain confirming value	1	3	0.04	0.11	0	1	0.00	0.04
Inconsistent Profile	41	26	1.53	0.97	4	0	0.15	0.00
Sample reanalyzed or reinjected by error	4	3	0.15	0.11	0	0	0.00	0.00
Rejected analytical run	126	126	4.69	4.69	71	67	2.64	2.49
Total	405	431	15.07	16.03	303	333	11.27	12.39

Note: Total 2688 samples were analyzed

Did use of recalculated plasma concentration data change study outcome?
Uncertain

Comments from the Reviewer:

1. For the Fasted Study, Study No. PKD_09_277, sample reanalysis was conducted for Niacin and Nicotinuric Acid for all samples pertaining to subject 16. The firm indicated that sample reanalysis was conducted due to suspected "sample mix up" (Code J).

   The firm will be asked to provide an adequate and detailed explanation as to why they believed the samples were mixed up. In addition, the firm will be asked to provide a summary table listing the original assayed values, the reassayed values and the reported values for this subject.

2. For **the** Fasted Study, Study No. PKD_09_277, for subjects 8, 16, 17, and 22, all samples were reassayed for Niacin and Nicotinuric Acid due to "rejected analytical run" (code J). In addition, for Fed Study, Study No. PKD_09_278, for subject 28 (niacin and nicotinuric acid samples), and subject 13 (nicotinuric acid samples), entire subject samples were reanalyzed due to "rejected analytical run" (code J).

   There are several criteria outlined in Section 7.1.9 of the Standard Operating Procedure (SOP) PKD/S/019 Revision 03, entitled Sample Reanalysis and Reporting of Final Concentrations, detailing how samples can be classified under the reason of "rejected analytical runs." As stated in section 7.1.9.3 of this SOP, the firm will be asked to submit documentation of the "*investigated and detailed justification of the reanalysis of the batch [form-Attachment-3]"* as required by SOP PKD/S/019 Revision 3.

   In addition, the firm will be asked to submit in tabular format a complete list of original assay values, repeat assay values, and reported values of these subjects, for evaluation. For each subject, the firm should also include a brief explanation as to how the final reported value was chosen.

3. SOP No. PKD/S/019 Revision 03 became effective after the study sample analysis was completed[29]. Therefore, the firm will be asked to provide a copy of the SOP that was effective at the time of analysis and to outline the changes made to the SOP between revision 2 and revision 3. The firm will be asked to indicate which revision of the SOP was effective at the time of the study.

4. SOP No. PKD/S/033, Chromatographic Analysis of Study Sample was referenced in SOP No. PKD/S/019 revision 3 but was not included in the application. The firm will be asked to submit a full copy of SOP PKD/S/033 which was effective during the study sample analysis periods.

[29] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 2064

5. For the Fasted Study (Study No. PKD_09_277) and the Fed Study (Study No. PKD_09_278), subjects were reassayed for Niacin and/or Nicotinuric Acid in order "to obtain confirming value" (designated as code F). The reviewer verified that the initial reason for performing the reassay was acceptable (i.e initial assay was performed due to sample being below limit of quantitation. Reassay was performed twice to confirm reported value).

6. The reviewer identified several instances where the firm did not follow standard operating procedure (SOP) PKD/S/019, Sample Reanalysis and Reporting of Final Concentrations, for reassay performed due to inconsistent profiles (code H). An example of this can be seen for study #PKD_09_277 for nicotinuric acid for subject 23 period 3 at 9 hours. The initial assay (145.6 ng/mL) did not differ by greater than 100% from the previous sample (106.0 ng/mL) or the subsequent sample (95.3 ng/mL). Another example is seen for study PKD_09_277 for nicotinuric acid for subject 23 period 4 at 5 hours. The plasma concentration for nicotinuric acid for subject 23 at 4 and 5 hours in period 4 was 942.6 ng/mL (reassayed 1174.7 ng/mL) and 126.8 ng/mL, respectively. The plasma concentration of period 5 differed from period 4 by greater than 100%, but the firm did not reassay this sample as it did for other samples. The firm will be asked to submit 1) a summary table (table 1) detailing all reassays that were performed correctly according to section 7.1.7 of SOP PKD/S/019; 2) a summary table (table 2) detailing all reassays that were performed incorrectly according to section 7.1.7 of SOP PKD/S/019; and 3) SAS-transport files containing the original data for all samples identified in table 2. Table 1 and 2 should contain all pertinent information including the initial value, the reassayed value, and the final reported value.

   In addition, section 7.1.7.5 is extremely unclear as to how repeat analysis was performed. The firm will be asked to explain how section 7.1.7.5 affects sample reanalysis and for every sample coded as N (incorrectly repeated) to summarize on a case by case basis how this decision was made. The firm will be asked to provide concrete examples of how the decision was made to perform reanalysis and report the final value for reassays coded as N (examples should use data from the study sample reassays tables provided in the Bioanalytical and Analytical method report.

3.7 Formulation

Location in appendix	Section 4.2, Page 76
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: ANDA#200484 REV-BIOEQ-02(Dissolution Review) Submit Date: 03/31/2010
Source of Method (USP, FDA or Firm)	FDA
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	Apparatus I (Basket)
Rotation (rpm)	100 rpm
DBE-recommended specifications	**Not TO BE Released UNDER FOI** 1 hr: NMT (b)(4)% 3 hr: (b)(4)% 6 hr: % 9 hr: % 12 hr: (b)(4)% 20 hr: NLT (b)(4)%
If a modified-release tablet, was testing done on ½ tablets?	No
F2 metric calculated?	N/A- extended release tablet
If no, reason why F2 not calculated	
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

Reviewer's Comments:

The firm's dissolution testing data with the FDA-recommended method are now acceptable. Initially, the firm's dissolution was not acceptable because the firm had not acknowledged the FDA-recommended specifications. In an amendment submitted 5/26/2010, the firm accepted the FDA's proposed specifications of:[30]

1 Hr: NMT (b)(4)%
3 Hrs: (b)(4)%
6 Hrs: %
9 Hrs: %
12 Hrs: (b)(4)%
20 Hrs: NLT (b)(4)%

The firm also conducted acceptable dissolution testing in three different dissolution media (0.1 N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer). Based on dissolution data, the reviewer found no evidence of dose dumping.

[30] EDR: ANDA #200484 Cover Letter and Response Submit Date: 5/26/2010.

3.9 Waiver Request(s)

Strengths for which waivers are requested	500 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	No
If not then why?	Due to deficiencies outlined below the ANDA is incomplete and a waiver cannot be granted.

3.10 Deficiency Comments

1. For the Fasted Study, Study No. PKD_09_277, sample reanalysis was conducted for Niacin and Nicotinuric Acid for all samples pertaining to subject 16. The firm indicated that sample reanalysis was conducted due to suspected "sample mix up" (Code J).

   The firm will be asked to provide an adequate and detailed explanation as to why they believed the samples were mixed up. In addition, the firm will be asked to provide a summary table listing the original assayed values, the reassayed values and the reported values for this subject.

2. For the Fasted Study, Study No. PKD_09_277, for subjects 8, 16, 17, and 22, all samples were reassayed for Niacin and Nicotinuric Acid due to "rejected analytical run". In addition, for Fed Study, Study No. PKD_09_278, for subject 28 (niacin and nicotinuric acid samples), and subject 13 (nicotinuric acid samples), entire subject samples were reanalyzed due to "rejected analytical run" (code J).

   - There are several criteria outlined in Section 7.1.9 of the Standard Operating Procedure (SOP) PKD/S/019 Revision 03, entitled Sample Reanalysis and Reporting of Final Concentrations, detailing how samples can be classified under the reason of "rejected analytical runs." As stated in section 7.1.9.3 of this SOP, the firm will be asked to submit documentation of the "*investigated and detailed justification of the reanalysis of the batch [form-Attachment-3]"* as required by SOP PKD/S/019 Revision 3.

   - In addition, the firm will be asked to submit in tabular format a complete list of original assay values, repeat assay values, and reported values of these subjects, for evaluation. For each subject, the firm should also include a brief explanation as to how the final reported value was chosen.

3. SOP No. PKD/S/019 Revision 03 became effective after the study sample analysis was completed[31]. Therefore, the firm will be asked to provide a copy of the SOP that was effective at the time of analysis and to outline the changes made to the SOP

[31] EDR: ANDA #200484 Section 5.3.1.4 Appendix 16.5.1 and 16.5.4 Page 2064

between revision 2 and revision 3. The firm will be asked to indicate which revision of the SOP was effective at the time of the study.

4. SOP No. PKD/S/033, Chromatographic Analysis of Study Sample was referenced in SOP No. PKD/S/019 revision 3 but was not included in the application. The firm will be asked to submit a full copy of SOP PKD/S/033 which was effective during the study sample analysis periods.

5. Two concentration ranges for calibration curves (CC) (i.e., 29.5, 58.9, 149.3, 345.7, 903.7, 1296.3, 1517.3 & 1964.1 (ng/ml) and 29.6, 59.2, 149.9, 347.1, 907.1, 1301.5, 1577.6 and 1972.0 (ng/ml)) were used for bioanalysis of nicotinuric acid samples in the Fasted Study (Study No. PKD_09_277). The firm will be asked to provide an explanation as to why they used two different CC concentration ranges. In addition, for each CC concentration range used, the firm will be asked to specify all subject samples that were analyzed using such range.

6. The DBE identified several instances where the firm did not follow the standard operating procedure (SOP) PKD/S/019, Sample Reanalysis and Reporting of Final Concentrations, for reassay performed due to "inconsistent profiles (code H)". An example of this can be seen for Study #PKD_09_277 for nicotinuric acid for subject 23 period 3 at 9 hours. The initial assay (145.6 ng/mL) did not differ by greater than 100% from the previous sample (106.0 ng/mL) or the subsequent sample (95.3 ng/mL). Another example is seen for Study PKD_09_277 for nicotinuric acid for subject 23 period 4 at 5 hours. The plasma concentration for nicotinuric acid for subject 23 at 4 and 5 hours in period 4 was 942.6 ng/mL (reassayed 1174.7 ng/mL) and 126.8 ng/mL, respectively. The plasma concentration at Hour-5 differed from that of Hour-4 by greater than 100%, but you did not reassay this sample as you did for other samples. The firm will be asked to submit 1) a summary table (Table 1) detailing all reassays that were performed correctly according to section 7.1.7 of SOP PKD/S/019; 2) a summary table (Table 2) detailing all reassays that were performed incorrectly according to section 7.1.7 of SOP PKD/S/019; and 3) SAS-Transport formatted files containing the original assay data for all samples identified in Table 2. Tables 1 and 2 should contain all pertinent information including the initial value, the reassayed value, and the final reported value for each reassayed sample.

   In addition, section 7.1.7.5 (Result of sample repeated as PK inconsistent profile)is extremely unclear as to how reanalysis was performed for samples coded "N". Please clearly explain how the criteria stated in section 7.1.7.5 affects sample reanalysis and for every sample coded as N ("incorrectly repeated"): The firm will be asked to explain concretely how this decision was made for each of these "N-coded" samples.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study number (PKD_09_277) incomplete due to the deficiencies mentioned above. The firm, Sun Pharma Global FZE, conducted the fasting BE study on its test drug product, Niacin Tablet, film coated extended release, 1000 mg (Lot #GK91008), comparing it to the reference listed drug, Niaspan (Niacin Tablet, film coated, extended release) 1000 mg (Lot#642142E21), manufactured by Abbott Labs.

2. The Division of Bioequivalence finds the fasting BE study number (PKD_09_278) incomplete due to the deficiencies mentioned above. The firm, Sun Pharma Global FZE, conducted the fasting BE study on its test drug product, Niacin Tablet, film coated extended release, 1000 mg (Lot #GK91008), comparing it to the reference listed drug, Niaspan (Niacin Tablet, film coated, extended release) 1000 mg (Lot#642142E21), manufactured by Abbott Labs.

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of water using apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   1 Hr: NMT (b) (4)%
   3 Hrs: (b) (4)%
   6 Hrs: %
   9 Hrs: %
   12 Hrs: (b) (4)%
   20 Hrs: NLT (b) (4)%

The firm should be informed of the above deficiency comments and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
Bio PM	For the clinical site (Sun Pharmaceutical Industries, Tandalja, Vadodara, 390020, Gujarat, India), there was a routine inspection request entered for this current ANDA application (ANDA #200484). The outcome is still pending.[32] For the analytical site (Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara - 390020, Gujarat, India) there was a routine inspection completed for ANDA #078271 (6/29/2009 result: voluntary action indicated and ANDA #090362 (6/17/2010 result: voluntary action indicated and ANDA #090178 (6/8/2010 result: voluntary action indicated). The DSI report for ANDA #078271 has been reviewed by DBE and found to be incomplete DARRTS: #078271 (REV-BIOEQ-01(General Review) Submit Date: 7/134/2009 The DSI reports for ANDA #090362 and # ANDA 090178 have not yet been reviewed by DBE.

[32] DARRTS: FRM-CONSULT-09(DSI Bioequivalence Audit Request) submit 5/26/2010

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[33]

Study Number	PKD_09_277
Study Title	A randomized, open label, two treatment, four period, two sequence, single dose, replicated crossover, bioequivalence study of Niacin 1000mg Extended release Tablets of Sun Pharmaceutical Industries Limited, India and Niaspan® (Niacin) 1000mg Extended release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, in 36 healthy human adult subjects, under fasting conditions.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020.
Principal Investigator	Dr. Aman Khanna
Dosing Dates	Period I: 2nd June 2009, Period II: 9th June 2009, Period III: 19th June 2009 and Period IV: 30th June 2009
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020.
Analysis Dates	From 14th August 2009 to 18th September 2009 (5 days)
Analytical Director	Mr. (b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 2nd June, 2009 to 18th September, 2009 (109 days)

Table 5. Product information[34]

Product	Test	Reference
Treatment ID	A	B
Product Name	Niacin Extended Release Tablets, 1000 mg	Niaspan® (Niacin extended-release tablets), 1000 mg
Manufacturer	Sun Pharmaceutical Industries Limited India.	Abbott Laboratories, North Chicago, IL 60064 USA
Batch/Lot No.	GK91008B	642142E21

[33] EDR: ANDA #200484 Section 5.3.1.2 Fasting Synopsis and Fasting Study Summary Submit Date: 9/29/2009
[34] EDR: ANDA #200484 Section 5.3.1.3 Product Information Submit date 9/29/2009

Manufacture Date	May 2009	
Expiration Date		28th January 2011
Strength	1000 mg	1000 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4) Tablets	
Production Batch Size	Tablets	
Potency (Assay)	98.9 %	99.0 %
Content Uniformity (mean, %CV)[35]	99.5%, %CV=0.6%	
Dose Administered	1000 mg	1000 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study[36]

Number of Subjects	36 Enrolled 6 Discontinued 30 Completed
No. of Sequences	2
No. of Periods	4 Period I: 2nd June 2009, Period II: 9th June 2009, Period III: 19th June 2009 and Period IV: 30th June 2009
No. of Treatments	2
No. of Groups	1
Washout Period	Period I, II, III and IV were separated by washout period of 7, 10 and 11 days respectively.
Randomization Scheme[37]	(Please see randomization scheme below)
Blood Sampling Times	0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00 and 16.00 hours post-dose. (21 Time points)
Blood Volume Collected/Sample	6 mL pre-dose 4 mL post dose samples
Blood Sample Processing/Storage	All blood samples were drawn into blood collection tubes containing K_3 EDTA[38]. Study blood samples were centrifuged at 3000 rpm under refrigeration at 4°C for 10 min within 1.5 hr of blood sample collection. Plasma sample were divided in to two aliquots (original & duplicate) and stored within 2 hours of the blood sampling in suitably labeled polypropylene tubes at –20°± 5° C or colder until transfer of study sample.
IRB Approval	May 30th, 2009
Informed Consent	May 30th, 2009

[35] EDR: ANDA #200484 Section 2.3.P Drug Product Submit Date: 9/29/2009
[36] EDR: ANDA #200484 Section 5.3.1.2 Fasting: Synopsis Submit Date: 9/29/2009
[37] EDR: ANDA #200484 Section 5.3.1.2 Fasting: Study Protocol Submit Date: 9/29/2009
[38] EDR: ANDA #200484 Section 5.3.1.2 Fasting: Study Summary Report Section 9.5.4

Length of Fasting[39]	Supervised fast for at least 10 hours prior to dosing, and 4 hours after dosing was maintained
Length of Confinement[39]	12 hours prior to drug administration until after the 24-hour post-dose
Safety Monitoring[39]	Seated blood pressure, pulse rate will be recorded after check-in, pre-dose and at 1.0, 2.0, 4.0, 8.0, 12.0 hrs and at checkout after drug administration. Oral temperature recording will be done at the time of check-in, are pre-dose, 4.0, 12.0 hours post dose and at checkout. For the safety of subjects, Haematology, urine and biochemistry investigations will be done. Beta, HCG pregnancy test, will be done at check-in of each period for female volunteers.

Randomization Scheme[37]:

SUBJECT ID	seq	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
001	2	B	A	B	A
002	1	A	B	A	B
003	1	A	B	A	B
004	2	B	A	B	A
005	2	B	A	B	A
006	1	A	B	A	B
007	2	B	A	B	A
008	1	A	B	A	B
009	2	B	A	B	A
010	1	A	B	A	B
011	1	A	B	A	B
012	2	B	A	B	A
013	2	B	A	B	A
014	1	A	B	A	B
015	1	A	B	A	B
016	2	B	A	B	A
017	1	A	B	A	B
018	2	B	A	B	A
019	1	A	B	A	B
020	2	B	A	B	A
021	1	A	B	A	B

[39] EDR: ANDA #200484 Section 5.3.1.2 Fasting: Study summary report

SUBJECT ID	seq	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
022	2	B	A	B	A
023	1	A	B	A	B
024	2	B	A	B	A
025	1	A	B	A	B
026	2	B	A	B	A
027	2	B	A	B	A
028	1	A	B	A	B
029	1	A	B	A	B
030	2	B	A	B	A
031	1	A	B	A	B
032	2	B	A	B	A
033	2	B	A	B	A
034	2	B	A	B	A
035	1	A	B	A	B
036	1	A	B	A	B

Comments on Study Design:

The study design is complete.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

		Study No. PKD_09_277 (Fasting)	
		Treatment Groups	
		Test Product N= 30	Reference Product N=30
Age (Years)	Mean ± SD	30.5 +/- 7.58	30.5 +/- 7.58
	Range	18 - 47	18 - 47
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18-40	28 (93.33%)	28 (93.33%)
	41-64	2 (6.67%)	2 (6.67%)
	65-75	0 (0.00%)	0 (0.00%)
	>75	0 (0.00%)	0 (0.00%)
Sex	Female	0 (0.00%)	0 (0.00%)
	Male	30 (100%)	30 (100%)
Race	Asian	30 (100%)	30 (100%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	21.84 +/- 1.587	21.84 +/- 1.587
	Range	19.1 – 24.9	19.1 – 24.9
Other factors		-	-

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No.: PKD_09_277						
Subject No.	**Reason For Dropout/replacement**			**Period**	**Replaced?**	**Replaced With**
	Cause	**Date/Time**	**Treatment**			
01	Adverse event (significant pre-study Lab. report) before dosing in Period III	18/06/09 09:39 pm	A*	III	No	NA
07	Adverse event before dosing in Period IV	29/06/09 10:00 pm	B**	IV	No	NA
09	Adverse event in Period I	02/06/09 08:35 am	B	I	No	NA
11	Urine scan for drug of abuse found positive before dosing in Period IV	29/06/09 NA	A**	IV	No	NA
25	Withdrew himself without any reason, voluntarily from the study in Period II	09/06/09 10:50 am	B	II	No	NA
30	Adverse event in Period I	02/06/09 08:45 am	B	I	No	NA
02#	Adverse event before dosing in Period I	02/06/09 05:45 am	NA	I	Yes	E02

*** Drug treatment of Period II and ** Drug treatment of Period III**

Subject No. 02 was dropped due to adverse event before dosing of period I and this subject was replaced by extra subject.

Breakdown of adverse events by subject[40]:

Period III

Sub No.	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	cause	Action Taken
		Investigators Term	Preferred Term								
01	B (PI) A (PII)	Low Hb value	Haemoglobin decreased	18/06/09	09:39 pm	8:00 am* 02/06/09 09/06/09	01/07/09 10:47 am	1	NA	4	4,5
Treatment: A = Test, B = Reference											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn											
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

***Dosing time and date of period I and II**

Period IV

Sub No.	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	cause	Action Taken
		Investigators Term	Preferred Term								
07	B*	Fever	Pyrexia	29/06/09	Approx. 07:00 pm	8:12 am* 19/06/09	30/06/09 07:30 am	2	3	4	4,5
		Urine RBC	Red blood cells urine positive		09:26 pm		01/07/09 09:18 am	1	1		3
Treatment: A = Test, B = Reference											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn											
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

*** Dosing time, drug treatment and date of period III**

[40] EDR: ANDA #200484 Section 5.3.1.2 Fasting: Adverse Event Listings Submit Date: 9/29/2009

PRE-TREATMENT ADVERSE EVENT

Sub No.	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	cause	Action Taken
		Investigators Term	Preferred Term								
#02	NA	Loose motion	Diarrhoea	02/06/09	Approx. 05:00 am	NA	02/06/09 09:02 am	1	3	4	4,5

Intensity : 1 = Mild, 2 = Moderate, 3 = Severe
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.

 # This subject was replaced by extra subject no. E-02

POST-TREATMENT ADVERSE EVENT

Period I

Sub No.	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	cause	Action Taken
		Investigators Term	Preferred Term								
09	B	Vomiting	Vomiting	02/06/09	08:33 am	8:16 am 02/06/09	02/06/09 09:46 am	1	1	3	4,5
30	B	Vomiting	Vomiting	02/06/09	08:37 am	8:22 am 02/06/09	02/06/09 09:50 am	1	1	3	4,5
		Burning sensation in epigastrium	Gastritis								

Treatment: A = Test, B = Reference
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.

Table 9. Study Adverse Events, Fasting Bioequivalence Study

	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study No.: PKD_09_277	
Med DRA System Organ Class Preferred Terms	Adverse Events	
	Test n (%)	Reference n (%)
A. Single Treatment Emergent Events		
General disorders and administration site conditions		
Pyrexia	0 (0.00)	1 (20.00)
Gastrointestinal disorders		
Vomiting	0 (0.00)	2 (40.00)
Gastritis	0 (0.00)	1 (20.00)
Investigations		
Red blood cells urine positive	0 (0.00)	1 (20.00)
Total	**0 (0.00)**	**5 (100.00)**
B. Adverse Events considered for both formulation*		
Investigations		
Hemoglobin decreased	1 (100.00)	
Total	**1 (100.00)**	

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No: PKD_09_277
There was no protocol deviation observed during conduct of study and reporting of results.

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. No serious adverse events (SAEs) were reported during the fasting BE Study.

2. Two (2) subjects (subjects 9 and 30) experienced emesis while taking the reference drug product. Both subjects were withdrawn from study[41] as recommended by Agency guidance, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (effective Date: March 2003). Note: Median Tmax were 1.62 h for Treatment A and 1.65 h for treatment B.[42]

[41] EDR: ANDA #200484 Section 5.3.1.2 Adverse Event Listing Submit Date: 9/23/2009
[42] EDR: ANDA #200484 Section 5.3.1.2 Study Summary Report Submit Date: 9/23/2009

POST-TREATMENT ADVERSE EVENT

Period I

Sub No.	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	cause	Action Taken
		Investigators Term	Preferred Term								
09	B	Vomiting	Vomiting	02/06/09	08:33 am	8:16 am 02/06/09	02/06/09 09:46 am	1	1	3	4,5
30	B	Vomiting	Vomiting	02/06/09	08:37 am	8:22 am 02/06/09	02/06/09 09:50 am	1	1	3	4,5
		Burning sensation in epigastrium	Gastritis								
Treatment: A = Test, B = Reference											
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe											
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn											
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.											
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.											

3. Six (6) subjects (Subjects 1,7,9,11,25, and 30) withdrew from the study and were not replaced. One (1) subject withdrew from the study before Period 1 dosing and was replaced with a standby subject. All withdrawals and replacements of subjects were conducted according to stated firm's protocol.

4. There were no protocol deviations during the fasting portion of the BE study as indicated in Section 16.2.2[43].

5. No blood sampling deviations were reported by the firm.

[43] EDR: ANDA #200484 Module 5 Section 5.3.1.2 Section 16.2.2 Submit Date: 9/29/2009

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses - Niacin

Bioequivalence Study No. PKD_09_277 (Fasting) **Analyte Name : Niacin**								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	19.8	39.7	146.9	341.4	893.1	1290.1	1567.9	1980.8
Inter Day Precision (% C.V.)	2.1	4.1	4.5	3.3	3.2	3.5	2.3	3.8
Inter Day Accuracy (% Actual)	99.1	102.2	97.1	101.6	100.2	100.6	100.0	99.1
Linearity	0.9969 to 0.9999 (r Value)							
Linearity range (ng/mL)	19.8 to 1980.8							
Limit Of Quantitation (ng/mL)	19.8							

Bioequivalence Study No. PKD_09_277 (Fasting) **Analyte Name : Niacin**					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	60.9	182.7	507.6	934.0	1624.3
Inter Day Precision (% C.V.)	5.8	7.0	5.1	6.8	4.6

Inter Day Accuracy (% Actual)	101.2	99.6	100.3	99.6	99.2

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses – Nicotinuric Acid

Bioequivalence Study No. PKD_09_277 (Fasting) **Analyte Name : Nicotinuric Acid**								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	29.5	58.9	149.3	345.7	903.5	1296.3	1571.3	1964.1
Inter Day Precision (% C.V.)	2.2	4.4	5.3	3.8	4.4	5.6	3.6	4.8
Inter Day Accuracy (% Actual)	99.7	101.3	97.1	102.9	99.9	99.3	98.8	100.9
Linearity	0.9954 to 0.9998 (r Value)							
Linearity range (ng/mL)	29.5 to 1964.1							
Limit Of Quantitation (ng/mL)	29.5							

Bioequivalence Study No. PKD_09_277 (Fasting) **Analyte Name : Nicotinuric Acid**					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	92.5	277.4	513.7	986.3	1697.0
Inter Day Precision (% C.V.)	8.2	6.5	6.8	9.6	7.2

Inter Day Accuracy (% Actual)	99.2	97.8	99.7	97.9	96.5

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses – Nicotinuric Acid (* For repeat-04 calibration curve range changed)

Bioequivalence Study No. PKD_09_277 (Fasting) **Analyte Name : Nicotinuric Acid**								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL) *	29.6	59.2	149.9	347.1	907.1	1301.5	1577.6	1972.0
Inter Day Precision (% C.V.)	NA	NA	NA	NA	NA	NA	NA	NA
Inter Day Accuracy (% Actual)	102.9	96.4	98.5	89.0	93.4	101.0	109.9	108.9
Linearity	0.9998 (r Value)							
Linearity range (ng/mL)	29.6 to 1972.0							
Limit Of Quantitation (ng/mL)	29.6							

Bioequivalence Study No. PKD_09_277 (Fasting) **Analyte Name : Nicotinuric Acid**					
Parameter	**Quality Control Samples**				
Concentration (ng/mL) *	88.7	266.0	492.5	945.6	1615.4
Inter Day Precision (% C.V.)	2.2	9.5	1.7	2.5	3.9
Inter Day Accuracy (% Actual)	102.4	103.4	96.1	101.4	102.6

Comments on Study Assay Validation:

1. The firm demonstrated assay validation using two different standard curves for Nicotinuric Acid. The firm did not explain the reason for performing two sets of assay validation assays. The firm will be asked to explain why two different standard curves were used. In addition, the firm will be asked to specify which standard curve was used for each subject.

2. To evaluate reproducibility of data[44] generated in the fasting BE study 4.8% (120 out of 2519 samples) of incurred study samples were randomly selected and reassayed[45]. The bioanalytical method for this study was found to be reproducible with at least 2/3 of the samples found to be reproducible according to SOP No PKD/S/035, Revision No. 02, Identification and Analysis of Incurred Sample (effective date: 7-15-2009)[45].

The study assay validation was incomplete.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	2, 3, 4, 5, 6, 8, and 10 / 30 subjects (serial) (23% of chromatograms)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

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

SOP No.	Effective Date of SOP	SOP Title
PKD/S/013	7-3-2009	Bioanalytical Method Validation

[44] Currently, the FDA does not have recommendations concerning incurred sample reproducibility (ISR) studies.
[45] EDR: ANDA #200484 Section 5.3.1.4 Fasting: Bioanalytical Report

PKD/S/035	7/15/2009	Identification and analysis of incurred sample
PKD/S/019	10-08-2009	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 03)

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	No
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	As detailed above, the reviewer requested additional information related to repeat assays. In addition, the reviewer requested that SOP PKD/S/109 Revision 2 be submitted, which was the SOP in affect at the time of data analysis.

Summary/Conclusions, Study Assays:

SOP PKD/S/019, Sample reanalysis and Reporting of Final concentrations (Revision No.: 03), was only effective 10-08-2009, which is after data analysis took place. The firm will be asked to submit the SOP PKD/S/019 that was effective when data analysis was being performed and to detail subsequent revisions made to this SOP.

Study assays are incomplete.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Replicate 1 (period 1 and 2)- Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_277 (Fasting Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=30)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	2360.53	62.60	684.29	8473.64	2275.14	58.15	798.61	6320.01	1.04
AUC∞ (hr *ng/ml)	2484.67	60.48	775.20	8603.98	2351.01	56.62	842.10	6429.04	1.06
Cmax (ng/ml)	835.62	42.35	301.00	1758.70	740.55	36.19	388.10	1443.10	1.13
Tmax* (hr)	1.98	54.49	0.75	5.00	1.86	47.49	1.00	4.00	1.07
Kel (hr^{-1})	0.66	39.14	0.08	1.05	0.65	36.45	0.29	1.20	1.02
T1/2 (hr)	1.52	109.58	0.66	9.12	1.23	40.09	0.58	2.37	1.23

* Tmax values are presented as median, range

Replicate 2 (period 3 and 4)- Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_277 (Fasting Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=30)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	2148.32	52.59	516.15	5430.27	2073.73	36.41	788.49	3662.11	1.04
AUC∞ (hr *ng/ml)	2218.95	51.44	596.38	5576.01	2166.65	35.39	825.73	3773.28	1.02
Cmax (ng/ml)	801.24	40.02	326.40	1558.10	718.24	32.50	384.50	1174.70	1.12
Tmax* (hr)	1.82	52.74	0.75	5.00	1.93	51.72	0.75	6.00	0.94
Kel (hr^{-1})	0.72	30.92	0.17	1.00	0.63	38.39	0.21	1.10	1.14
T1/2 (hr)	1.14	59.90	0.69	4.16	1.32	48.14	0.63	3.30	0.87

Replicate 1 (period 1 and 2)- Niacin from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_277 (Fasting Bioequivalence data for (Niacin) from Niacin 1000 mg ER Tablets) (N=30)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	709.87	100.82	29.71	3495.93	582.01	104.73	22.48	2302.94	1.22
AUC∞ (hr *ng/ml)	907.00	85.95	86.48	3683.09	752.76	87.18	115.21	2319.52	1.20
Cmax (ng/ml)	780.68	74.74	30.90	2611.80	580.02	86.16	42.50	1943.70	1.35
Tmax* (hr)	1.63	59.21	0.25	3.50	1.27	56.05	0.50	3.00	1.28
Kel (hr^{-1})	1.57	92.43	0.12	5.64	1.37	87.11	0.17	4.93	1.15
T1/2 (hr)	1.21	127.09	0.12	5.98	0.97	99.07	0.14	4.05	1.24

Replicate 2 (period 3 and 4)- Niacin from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_277 (Fasting Bioequivalence data for (Niacin) from Niacin 1000 mg ER Tablets) (N=30)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	705.75	92.32	81.25	2486.88	589.67	85.15	18.80	1783.19	1.20
AUC∞ (hr *ng/ml)	846.02	89.25	181.49	2786.79	906.37	107.07	123.11	5203.13	0.93
Cmax (ng/ml)	814.66	63.27	41.00	1886.00	644.24	71.86	50.40	1717.30	1.26
Tmax* (hr)	1.40	77.43	0.25	5.00	1.31	51.34	0.50	3.50	1.07
Kel (hr^{-1})	1.06	102.38	0.12	4.39	0.77	87.60	0.02	2.69	1.39
T1/2 (hr)	1.89	94.23	0.16	5.76	4.45	207.27	0.26	42.98	0.42

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

Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PKD 09 277 (Fasting Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets)				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	1982.15	1977.85	100.22	91.98 to 109.20
AUC∞ (hr *ng/ml)	2080.55	2064.36	100.78	92.97 to 109.25
Cmax (ng/ml)	754.79	691.49	109.15	101.69 to 117.16

Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PKD 09 277 (Fasting Bioequivalence data for Niacin from Niacin 1000 mg ER Tablet)				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	456.93653	353.76094	1.29	101.50 to 164.38
AUC∞ (hr *ng/ml)	603.42166	553.58912	1.09	91.05 to 130.50
Cmax (ng/ml)	569.76371	418.09805	1.36	101.99 to 182.09

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

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	1982.1479	1977.8473	1	91.977	109.196
AUC∞ (hr*ng/ml)	2080.5507	2064.3542	1.01	92.972	109.254
Cmax (ng/mL)	754.7901	691.48968	1.09	101.694	117.161

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. PKD_09_277) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	456.93653	353.76094	1.29	101.497	164.377
AUC∞ (hr*ng/ml)	603.42166	553.58912	1.09	91.046	130.498
Cmax (ng/mL)	569.76371	418.09805	1.36	101.987	182.091

Table 17. Additional Study Information, Fasting Study No. PKD_09_277

	Nicotinuric Acid		Niacin	
	Test	Ref	Test	Ref
Within subject variance, AUC0-t	0.05258	0.2736	0.8631	0.7604
Between subject variance, AUC0-t	0.1229	0.01362	0.5234	.16348
Within subject variance, AUC∞	0.00246	0.06386	0.7882	0.330
Between subject variance, AUC∞	0.11772	0.01362	0.3486	0.25126
Within subject variance, Cmax	0.05955	0.03601	0.4593	0.5586
Between subject variance, Cmax	0.11162	0.07408	0.4466	0.4002
	Test		**Reference**	
Kel and AUC∞ determined for how many subjects?	30		30	
Do you agree or disagree with firm's decision?	Agree		Agree	
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0		0	
first measurable drug concentration as Cmax	0		0	
Were the subjects dosed as more than one group?	No		No	

Ratio of AUC0-t/AUC∞ (Nicotinuric Acid)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	30	0.9609	0.8223	0.9914
Reference	30	0.9662	0.8701	0.9939

Ratio of AUC0-t/AUC∞ (Niacin)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	30	0.811026	0.0619	0.9939
Reference	30	0.854108	0.1195	0.9971

Comments on Pharmacokinetic and Statistical Analysis:

1. The reviewer specified the linear range used to calculate Kel and therefore used the SAS code CALKE for statistical analysis. Because this was a 2 sequence, 4 period, replicate study, the reviewer used the SAS program modified-replicate.sas.

2. Because the detection of Niacin in plasma is highly variable, it could not be used to determine bioequivalence. As per FDA recommendation, if niacin cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for Nicotinuric Acid[10]. Nicotinuric Acid as a proxy of Niacin has been used in other ANDA submissions to determine bioequivalence[2,3].

3. The mean AUC_t/AUC_∞ ratio for nicotinuric acid is greater than 0.9 for both test and reference and therefore indicates that the firm's sampling schedule was carried out for a sufficient period of time. The minimum AUC_t/AUC_∞ ratio did not fall below 0.80 for either test or reference.

4. The mean AUC_t/AUC_∞ ratio for niacin is greater than 0.8 for both the test and reference; however, the ranges of the ratios vary greatly. This is expected due to the high variability associated with this particular analyte and is further supported by the results obtained in the study for this particular analyte.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study with 1 x 1000 mg Niacin Extended Release Tablets is incomplete due to deficiencies outlined in Section 3.10. In addition, it is pending the outcome of DSI inspections.

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

Nicotinuric Acid – Replicate 1 (period 1 and 2)

	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	28.60	119.06	0.00	133.40	13.47	232.33	0.00	119.90	2.12
0.5	302.35	63.79	0.00	730.20	208.38	75.26	0.00	711.80	1.45
0.75	455.82	53.03	51.60	968.20	369.69	57.24	61.10	887.90	1.23
1.0	486.59	57.05	115.20	1211.30	485.40	50.19	52.40	1037.90	1.00
1.25	525.86	59.21	81.70	1487.80	545.29	40.24	127.40	954.80	0.96
1.50	569.38	53.34	115.40	1457.60	528.14	41.41	107.90	1141.20	1.08
1.75	497.90	45.46	109.40	1099.90	535.20	44.21	101.90	1376.80	0.93
2.0	524.25	56.24	110.70	1284.10	530.10	44.51	70.50	1286.60	0.99
2.5	522.90	55.60	130.50	1132.60	518.22	55.07	191.40	1443.10	1.01
3.0	403.95	53.73	90.30	963.10	450.15	61.14	108.50	1335.30	0.90
3.5	383.82	85.43	56.80	1500.10	369.55	58.94	105.40	956.60	1.04
4.0	342.24	87.21	41.20	1437.00	323.26	90.42	72.70	1303.70	1.06
5.0	229.45	140.01	0.00	1758.70	221.53	102.21	40.80	878.30	1.04
6.0	119.33	219.82	0.00	1463.40	115.01	138.74	0.00	799.30	1.04
7.0	73.57	226.74	0.00	913.10	77.51	227.28	0.00	934.70	0.95
8.0	45.14	203.39	0.00	339.80	42.55	277.37	0.00	604.40	1.06
9.0	31.18	186.77	0.00	228.20	31.49	307.10	0.00	523.40	0.99
10.0	28.32	233.50	0.00	312.10	9.10	241.55	0.00	82.80	3.11
12.0	12.44	220.95	0.00	105.10	5.85	269.21	0.00	62.30	2.13
16.0	0.00	.	0.00	0.00	1.20	547.72	0.00	36.00	0.00

Nicotinuric Acid – Replicate 2 (period 3 and 4)

	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	30.75	214.94	0.00	320.20	5.48	261.88	0.00	47.40	5.62
0.5	284.91	59.90	0.00	606.00	185.91	86.78	0.00	622.20	1.53
0.75	439.23	60.09	39.50	915.50	346.87	65.09	0.00	870.40	1.27
1.0	462.44	55.64	30.30	926.90	426.68	58.12	0.00	980.70	1.08

1.25	518.00	63.92	0.00	1558.10	469.96	55.82	39.20	1092.50	1.10
1.50	534.16	57.80	33.20	1321.70	496.40	49.00	33.20	1151.10	1.08
1.75	558.23	59.11	45.90	1337.70	537.79	46.25	89.40	1154.90	1.04
2.0	587.08	56.26	115.20	1451.70	575.97	44.14	177.70	1174.70	1.02
2.5	531.25	61.50	149.20	1533.00	512.13	37.78	124.00	951.20	1.04
3.0	493.53	71.97	77.40	1532.10	409.63	43.90	115.40	798.80	1.20
3.5	359.14	70.61	41.70	1173.50	377.94	43.78	99.20	698.30	0.95
4.0	278.52	69.66	48.90	790.90	306.18	54.92	67.30	745.00	0.91
5.0	177.55	88.74	0.00	661.40	173.69	76.38	32.10	623.90	1.02
6.0	80.92	99.27	0.00	292.20	99.54	131.63	0.00	567.50	0.81
7.0	42.11	149.89	0.00	264.50	44.42	125.59	0.00	287.60	0.95
8.0	17.40	201.52	0.00	141.90	24.47	130.91	0.00	127.40	0.71
9.0	9.43	312.09	0.00	145.60	9.71	188.92	0.00	57.90	0.97
10.0	5.54	346.98	0.00	95.30	11.00	199.22	0.00	77.10	0.50
12.0	2.78	389.74	0.00	50.60	11.53	198.69	0.00	74.40	0.24
16.0	1.11	547.72	0.00	33.20	0.00	.	0.00	0.00	.

Niacin – Replicate 1 (period 1 and 2)

	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	196.18	165.59	0.00	1454.90	75.70	238.57	0.00	750.00	2.59
0.5	361.32	148.79	0.00	2246.60	205.04	171.02	0.00	1190.10	1.76
0.75	317.76	180.13	0.00	2611.80	282.10	151.59	0.00	1662.40	1.13
1.0	302.19	172.22	0.00	2078.60	333.19	124.65	0.00	1533.40	0.91
1.25	299.06	155.84	0.00	1775.90	298.58	124.02	0.00	1257.70	1.00
1.50	284.24	129.47	0.00	1253.60	194.97	126.43	0.00	1049.20	1.46
1.75	237.17	173.59	0.00	1610.90	157.61	158.76	0.00	948.60	1.50
2.0	160.57	166.04	0.00	1008.20	101.60	155.81	0.00	695.50	1.58
2.5	126.57	213.16	0.00	1120.10	149.88	240.69	0.00	1943.70	0.84
3.0	37.27	203.63	0.00	338.60	100.65	217.76	0.00	940.10	0.37
3.5	109.44	275.84	0.00	1385.20	32.62	197.53	0.00	275.50	3.35
4.0	16.01	155.79	0.00	112.20	25.15	288.37	0.00	387.00	0.64
5.0	15.48	408.25	0.00	345.60	12.03	369.23	0.00	217.40	1.29
6.0	0.78	547.72	0.00	23.30	2.32	547.72	0.00	69.60	0.33
7.0	4.40	376.08	0.00	86.50	0.99	547.72	0.00	29.70	4.44

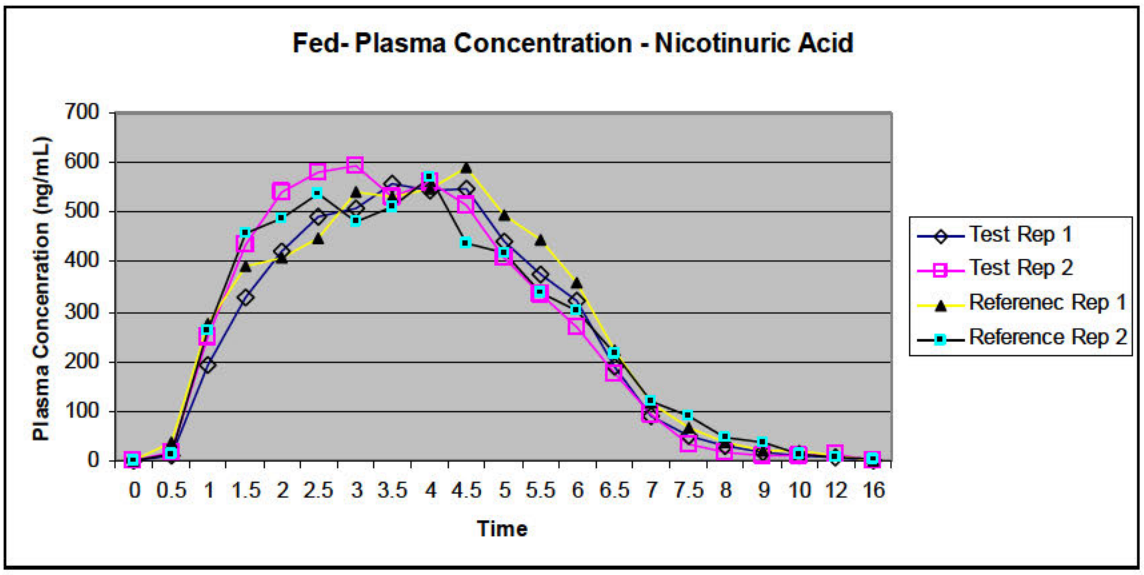
8.0	5.09	384.22	0.00	86.60	0.68	547.72	0.00	20.40	7.49
9.0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
10.0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
12.0	1.58	547.72	0.00	47.40	0.00	.	0.00	0.00	.
16.0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.

Niacin – Replicate 2 (period 3 and 4)

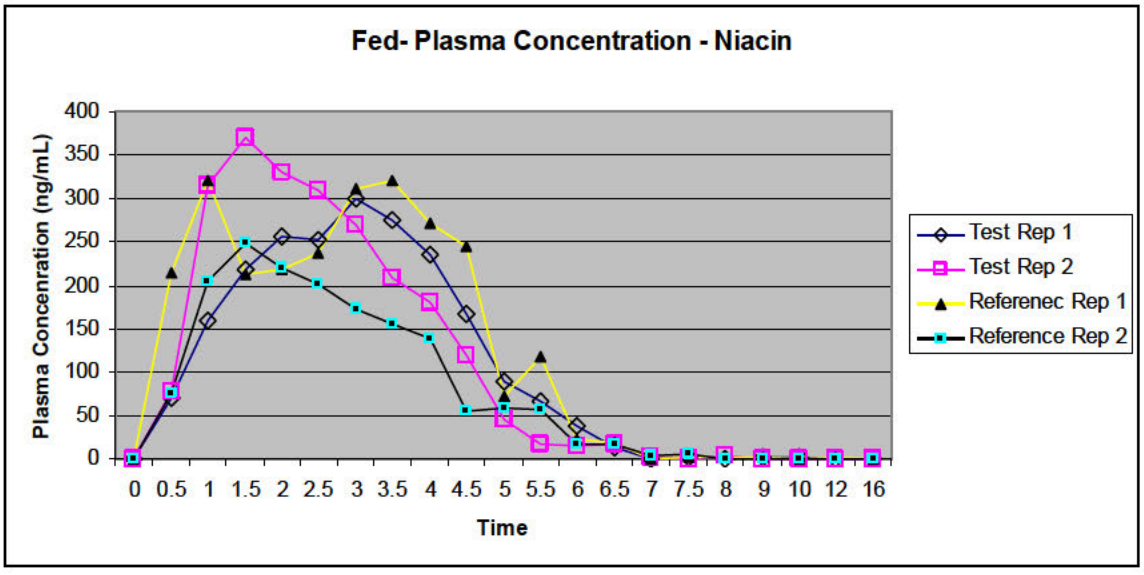
	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	151.06	230.80	0.00	1562.20	23.10	253.90	0.00	255.70	6.54
0.5	282.13	129.20	0.00	1668.80	142.56	164.54	0.00	875.60	1.98
0.75	251.71	147.80	0.00	1583.40	208.28	119.97	0.00	872.50	1.21
1.0	191.15	151.49	0.00	1314.50	193.85	150.15	0.00	1011.70	0.99
1.25	206.65	157.78	0.00	1167.80	215.57	140.15	0.00	972.80	0.96
1.50	297.08	149.38	0.00	1573.80	275.06	150.01	0.00	1717.30	1.08
1.75	277.49	154.10	0.00	1369.10	284.68	129.04	0.00	1450.60	0.97
2.0	274.46	155.63	0.00	1886.00	284.89	147.29	0.00	1530.80	0.96
2.5	206.74	201.57	0.00	1771.50	100.57	134.23	0.00	649.40	2.06
3.0	79.56	201.39	0.00	634.00	45.84	149.67	0.00	298.80	1.74
3.5	55.30	202.07	0.00	425.60	58.59	250.29	0.00	798.20	0.94
4.0	19.02	139.87	0.00	130.30	32.20	115.02	0.00	159.80	0.59
5.0	11.35	149.54	0.00	65.10	29.22	286.56	0.00	451.60	0.39
6.0	2.26	306.70	0.00	25.60	1.69	380.64	0.00	25.90	1.33
7.0	2.12	305.63	0.00	22.70	1.83	547.72	0.00	54.90	1.16
8.0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
9.0	2.09	305.32	0.00	21.80	1.33	380.56	0.00	19.90	1.58
10.0	0.00	.	0.00	0.00	1.40	380.62	0.00	21.40	0.00
12.0	0.00	.	0.00	0.00	0.79	547.72	0.00	23.80	0.00
16.0	0.76	547.72	0.00	22.70	0.00	.	0.00	0.00	.

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

Nicotinuric Acid – Replicate 1 (period 1 and 2) and Replicate 2 (period 3 and 4)



Niacin Replicate 1 (period 1 and 2) and Replicate 2 (period 3 and 4)



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	**PKD_09_278**
Study Title	A randomized, open label, two treatment, four period, two sequence, single dose, replicated crossover, bioequivalence study of Niacin 1000mg Extended release Tablets of Sun Pharmaceutical Industries Limited, India and Niaspan® (Niacin) 1000mg Extended release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, in 36 healthy human adult subjects, under fed conditions.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (INDIA) Phone: 91-265-2350789, 91-265-6615500; Fax: 91-265-2354897
Principal Investigator	Dr. Aman Khanna
Dosing Dates	Period I: 4th June 2009; Period II: 11th June 2009, Period III: 27th June 2009 Period IV: 2nd July 2009
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India. Tel: +91-265-6615500, 2350789 Fax: 91-265-2354897
Analysis Dates	From 6th September, 2009 to 22nd September, 2009
Analytical Director	Mr. (b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 4th June, 2009 to 22nd September, 2009 (111 days)

Table 20. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Niacin Extended Release Tablets, 1000 mg	Niaspan® (Niacin extended-release tablets), 1000 mg
Manufacturer	Sun Pharmaceutical Industries Limited India.	Abbott Laboratories, North Chicago, IL 60064 USA
Batch/Lot No.	GK91008B	642142E21
Manufacture Date	May 2009	N/A
Expiration Date	N/A	28th January 2011
Strength	1000 mg	1000 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4) Tablets	N/A
Production Batch Size	Tablets	N/A
Potency	98.9 %	99.0 %
Content Uniformity (AV)[35]	99.5%, %CV=0.6%	
Dose Administered	1000 mg	1000 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study[46]

No. of Subjects	36 Enrolled 4 Discontinued 32 Completed
No. of Sequences	2
No. of Periods	4 Period I: June 4th, 2009, Period II: June 11th, 2009, Period III June 27th, 2009 and Period IV: July 2nd 2009
No. of Treatments	2
No. of Groups	1
Washout Period	Period I, II, III and IV were separated by washout period of 7, 16 and 5 days respectively
Randomization Scheme[47]	(Please see below)
Blood Sampling Times	0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0 hours post-dosing. (21 time points)
Blood Volume Collected/Sample	6 mL will be collected pre-dose 4 mL will be collected post-dose at each time point

[46] EDR: ANDA #200484 Section 5.3.1.2 Fed: Synopsis Submit Date 9/29/2009
[47] EDR: ANDA #200484 Section 5.3.1.2 Fed: Protocol Submit Date 9/29/2009

Blood Sample Processing/Storage	All blood samples were drawn into blood collection tubes containing K_3 EDTA. Study blood samples were centrifuged at 3000 rpm under refrigeration at 4°C for 10 min within 1.5 hr of blood sample collection. Plasma sample were divided in to two aliquots (original & duplicate) and stored within 2 hours of the blood sampling in suitably labeled polypropylene tubes at –20°± 5° C or colder until transfer of study sample.
IRB Approval	May 30th, 2009
Informed Consent	May 30th, 2009
Length of Fasting Before Meal[47]	Overnight fast for at least 10 hours, subjects will receive single oral dose of the assigned formulation with 240mL of water after administration of high calorie high fat breakfast at least 30 minutes prior to dosing.
Length of Confinement[47]	From at least 12 hours prior to drug administration until after 24 hours post dose.
Safety Monitoring[47]	Seated blood pressure, pulse rate will be recorded after check-in, pre-dose and at 1.0, 2.0, 4.0, 8.0, 12.0 hrs and at checkout after drug administration. Oral temperature recording will be done at the time of check-in, are pre-dose, 4.0, 12.0 hours post dose and at checkout. For the safety of subjects, Haematology, urine and biochemistry investigations will be done. Beta, HCG pregnancy test, will be done at check-in of each period for female volunteers.

Standard FDA Meal Used?	Yes	
If No, then meal components and composition is listed in the tables below		
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study[48]		
Composition	**Percent**	**Kcal**
Fat	57.01	537
Carbohydrate	26.96	254
Protein	16.03	151
Total		942

[48] EDR: ANDA #200484 Section 5.3.1.2 Composition of meal used in FED BE Submit Date: 9/23/2009

Fed Randomization Scheme[49]:

SUBJECT ID	seq	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
001	2	B	A	B	A
002	1	A	B	A	B
003	1	A	B	A	B
004	2	B	A	B	A
005	2	B	A	B	A
006	1	A	B	A	B
007	1	A	B	A	B
008	2	B	A	B	A
009	2	B	A	B	A
010	1	A	B	A	B
011	1	A	B	A	B
012	2	B	A	B	A
013	1	A	B	A	B
014	2	B	A	B	A
015	2	B	A	B	A
016	1	A	B	A	B
017	2	B	A	B	A
018	1	A	B	A	B
019	1	A	B	A	B
020	2	B	A	B	A
021	1	A	B	A	B
022	2	B	A	B	A

[49] EDR: ANDA #200484 Section 5.3.1.2 Fed Randomization Scheme Submit Date 9/29/2009

SUBJECT ID	seq	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
023	1	A	B	A	B
024	2	B	A	B	A
025	1	A	B	A	B
026	2	B	A	B	A
027	1	A	B	A	B
028	2	B	A	B	A
029	1	A	B	A	B
030	2	B	A	B	A
031	1	A	B	A	B
032	2	B	A	B	A
033	1	A	B	A	B
034	1	A	B	A	B
035	2	B	A	B	A
036	2	B	A	B	A

Comments on Study Design:

The study design is complete.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

		Study No. PKD_09_278 (Fed)	
		Treatment Groups	
		Test Product N= 32	Reference Product N=32
Age (Years)	Mean ± SD	31.8 +/- 7.58	31.8 +/- 7.58
	Range	18 - 50	18 - 50
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18-40	29 (90.63%)	29 (90.63%)
	41-64	3 (9.38%)	3 (9.38%)
	65-75	0 (0.00%)	0 (0.00%)
	>75	0 (0.00%)	0 (0.00%)
Sex	Female	0 (0.00%)	0 (0.00%)
	Male	32 (100%)	32 (100%)
Race	Asian	32 (100%)	32 (100%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	21.71 +/- 1.865	21.71 +/- 1.865
	Range	19.0 - 24.9	19.0 - 24.9
Other factors		-	-

Table 23. Dropout Information, Fed Bioequivalence Study

Study No.: PKD_09_278						
Subject No.	**Reason For Dropout/replacement**			**Period**	**Replaced?**	**Replaced With**
	Cause	**Time/Date**	**Treatment**			
17	Did not appear for Period II	10/06/09 NA	B*	II	No	NA
24	Did not appear for Period II	10/06/09 NA	B*	II	No	NA
25	Adverse event (significant pre-study Lab. report) before dosing in Period III	26/06/09 09:30 pm	B**	III	No	NA
33	Did not appear for Period III	26/06/09 NA	B**	III	No	NA

*** Drug treatment of Period I and ** Drug treatment of Period II**

Table 24. Study Adverse Events, Fed Bioequivalence Study

	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No.: PKD_09_278	
Med DRA System Organ Class Preferred Terms	**Adverse Events**	
	Test n (%)	**Reference n (%)**
A. Single Treatment Emergent Events		
Skin and subcutaneous tissue disorders		
Rash	0 (0.00)	1 (33.33)
Vascular disorders		
Flushing	1 (100.00)	0 (0.00)
Gastrointestinal disorders		
Dyspepsia	0 (0.00)	1 (33.33)
Diarrhoea	0 (0.00)	1 (33.33)
Total	**1 (100.00)**	**3 (100.00)**
B. Adverse Events considered for both formulation*		
Investigations		
Hemoglobin decreased	2 (22.22)	
Alanine aminotransferase decreased	1 (11.11)	
Aspartate aminotransferase increased	1 (11.11)	
Haematocrit decreased	1 (11.11)	
Platelet count increased	1 (11.11)	
White blood cells urine positive	2 (22.22)	
Red blood cells urine positive	1 (11.11)	
Total	**9 (100.00)**	

* Significant lab abnormality observed during lab assessment (hematology and biochemistry) for subject no. 25 (period III check-in) 03, 05, 06, and 32 (period IV check-out). Since there were no lab assessment done between period I and III, & period III and IV, these adverse events were considered to have emerged from both the formulation.

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No: PKD_09_278		
Type	**Subject (Test)**	**Subject (Reference)**
For subject No.: 30 in Period II high-calorie high-fast breakfast have been given 29 minutes prior to drug administration.	Subject No. 30 (01 subject)	NA

Comments on Adverse Events/Protocol Deviations:

1. No serious adverse events were reported during the fasting BE study.

2. Four (4) subjects withdrew from the study and were not replaced. None of the subjects withdrew for serious health reasons. All withdrawals of subjects were conducted according to stated firm's protocol.

3. No significant protocol deviations occurred.

4. No blood sampling deviations were reported.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Summary of standard Curve and QC Data for Bioequivalence Sample Analyses - Niacin

Bioequivalence Study No. PKD_09_278 (Fed) **Analyte Name : Niacin**								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	20.1	40.2	67.1	138.1	394.6	552.4	670.8	828.6
Inter Day Precision (% C.V.)	2.0	3.4	3.7	3.1	3.3	3.2	2.8	3.1
Inter Day Accuracy (% Actual)	99.2	100.3	100.6	104.3	98.0	99.7	99.4	98.6
Linearity	0.9945 to 0.9999 (r Value)							
Linearity range (ng/mL)	20.1 to 828.6							
Limit Of Quantitation (ng/mL)	20.1							

Bioequivalence Study No. PKD_09_278 (Fed) Analyte Name : Niacin					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	60.8	182.4	218.5	397.3	675.5
Inter Day Precision (% C.V.)	4.7	5.0	5.3	5.6	5.3
Inter Day Accuracy (% Actual)	98.8	103.4	95.9	97.5	94.9

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses – Nicotinuric Acid

Bioequivalence Study No. PKD_09_278 (Fed) Analyte Name : Nicotinuric Acid								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	29.6	59.2	149.9	347.1	907.1	1301.5	1577.6	1972.0
Inter Day Precision (% C.V.)	2.4	4.6	4.4	4.9	5.1	4.4	2.9	4.4
Inter Day Accuracy (% Actual)	103.7	93.3	99.5	93.9	95.4	99.6	110.9	106.1
Linearity	0.9918 to 0.9992 (r Value)							
Linearity range (ng/mL)	29.6 to 1972.0							
Limit Of Quantitation (ng/mL)	29.6							

Bioequivalence Study No. PKD_09_278 (Fed) Analyte Name : Nicotinuric Acid					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	88.7	266.0	492.5	945.6	1615.4
Inter Day Precision (% C.V.)	7.5	6.0	7.9	8.8	8.6
Inter Day Accuracy (% Actual)	101.8	100.6	102.2	104.1	101.1

Comments on Study Assay Validation:

To evaluate reproducibility[50] of data generated in the fasting BE study 4.8% (128 out of 2688 samples) of incurred study samples were randomly selected and reassayed[51]. The bioanalytical method for this study was found to be reproducible with at least 2/3 of the samples found to be reproducible according to SOP No PKD/S/035, Revision No. 02, Identification and Analysis of Incurred Sample (effective date: 7-15-2009)[45].

Study assay validation is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	1, 2, 3, 4, 5, 6, and 7 (7/32) (21% of chromatograms)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

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

SOP No.	Effective Date of SOP	SOP Title
PKD/S/013	7-3-2009	Bioanalytical Method Validation
PKD/S/035	7/15/2009	Identification and analysis of incurred sample
PKD/S/019	10-08-2009	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 03)

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	No
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	As detailed above, the reviewer requested additional information related to repeat assays. In addition, the reviewer requested that SOP PKD/S/109 Revision 2 be submitted, which was the SOP in affect at the time of data analysis.

Summary/Conclusions, Study Assays:

Study assay analysis is incomplete due to deficiencies outlined above. In addition, there is a DSI inspection pending.

[50] Currently, the FDA does not have recommendations concerning incurred sample reproducibility (ISR) studies.
[51] EDR: ANDA #200484 Section 5.3.1.4 Fed: Bioanalytical Report Submit Date: 9/29/2009

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Replicate 1 (period 1 and 2)- Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_278 (Fed Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=32)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	10893.02	67.08	2912.60	32885.73	11315.35	71.61	3394.55	43225.73	0.96
AUC∞ (hr *ng/ml)	11324.76	67.13	3017.03	34466.66	12097.32	70.27	3903.52	43935.19	0.94
Cmax (ng/ml)	3180.54	56.12	867.60	8939.20	3258.37	50.58	979.00	8418.90	0.98
Tmax* (hr)	4.59	27.01	2.00	7.00	4.58	25.74	2.00	6.00	1.00
Kel (hr^{-1})	0.40	43.14	0.14	0.96	0.38	52.83	0.03	0.78	1.04
T1/2 (hr)	2.07	43.08	0.72	4.95	2.94	122.75	0.89	20.98	0.70

Replicate 2 (period 3 and 4)- Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_278 (Fed Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=32)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	11633.57	67.21	3426.63	34902.45	12717.65	62.56	3789.58	34571.15	0.91
AUC∞ (hr *ng/ml)	11897.92	67.06	3524.11	35671.60	13094.98	60.62	3903.77	35211.13	0.91
Cmax (ng/ml)	3324.09	53.97	911.50	7560.20	3286.64	47.56	1141.10	6863.70	1.01
Tmax* (hr)	5.03	45.64	1.50	16.00	4.47	27.84	2.00	6.50	1.13
Kel (hr^{-1})	0.37	39.58	0.16	0.68	0.40	40.88	0.01	0.78	0.93
T1/2 (hr)	2.15	39.18	1.03	4.44	3.76	280.55	0.89	61.47	0.57

Replicate 1 (Period 1 and 2)- Niacin from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_278 (Fed Bioequivalence data for (Niacin) from Niacin 1000 mg ER Tablets) (N=32)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	1267.01	178.81	5.08	11220.30	1168.93	139.38	12.40	6377.28	1.08
AUC∞ (hr *ng/ml)	1812.20	139.52	156.66	11243.35	1440.21	114.89	140.43	6393.09	1.26
Cmax (ng/ml)	1044.92	143.45	20.30	6094.10	890.85	122.72	0.00	4876.70	1.17
Tmax* (hr)	4.42	30.27	1.50	6.50	4.32	29.50	2.00	7.00	1.02
Kel (hr^{-1})	0.52	121.73	0.03	2.25	0.62	133.07	0.03	3.39	0.82
T1/2 (hr)	4.21	113.63	0.31	21.88	3.90	124.52	0.20	24.42	1.08

Replicate 2 (period 3 and 4)- Niacin from Niacin 1000 mg ER Tablets Niacin 1000 mg ER Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals									
Fasting Bioequivalence Study, Study No. PKD_09_278 (Fed Bioequivalence data for (Niacin) from Niacin 1000 mg ER Tablets) (N=32)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	1499.56	180.21	25.73	11386.53	1305.57	174.38	21.78	10562.60	1.15
AUC∞ (hr *ng/ml)	2229.14	136.36	234.24	11393.61	1765.80	144.00	151.52	10654.43	1.26
Cmax (ng/ml)	1036.49	123.17	21.10	4947.00	932.52	129.21	27.20	4849.00	1.11
Tmax* (hr)	4.81	50.47	1.50	16.00	4.50	26.62	1.50	6.50	1.07
Kel (hr^{-1})	1.32	90.19	0.03	4.03	0.60	104.54	0.10	2.41	2.21
T1/2 (hr)	3.52	187.54	0.17	27.06	2.39	79.70	0.29	6.82	1.47

* Tmax values are presented as median, range

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

Niacin 1000 mg ER Tablet Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD 09 278 (Fed Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=32)				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	9404.33	10066.42	93.42	87.05 to 100.27
AUC∞ (hr *ng/ml)	9664.85	10616.58	91.04	84.63 to 97.92
Cmax (ng/ml)	2825.00	2916.18	96.87	89.18 to 105.23

Niacin 1000 mg ER Tablet Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD_09_278 (Fed Bioequivalence data for Niacin from Niacin 1000 mg ER Tablet) (N=32)				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	454.84	472.22	96.32	76.54 to 121.22
AUC∞ (hr *ng/ml)	876.81	760.20	115.34	97.92 to 135.86
Cmax (ng/ml)	439.84	430.26	102.23	78.31 to 133.45

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

Niacin (Nicotinuric Acid) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Nicotinuric Acid					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	9404.3334	10066.42	0.93	87.046	100.267
AUC∞ (hr*ng/ml)	9664.8362	10616.574	0.91	84.634	97.921
Cmax (ng/mL)	2825.005	2916.1819	0.97	89.181	105.230

Niacin (Niacin) Dose (1 x 1000 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study (Study No. PKD_09_278) Niacin					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr*ng/ml)	454.83744	472.21568	0.96	76.536	121.217
AUC∞ (hr*ng/ml)	876.82085	760.17914	1.15	97.920	135.868
Cmax (ng/mL)	439.84306	430.26045	1.02	78.309	133.451

Table 32. Additional Study Information, Fed BE Study No Study No. PKD_09_278

	Nicotinuric Acid		Niacin	
	Test	Ref	Test	Ref
Within subject variance, AUC0-t	0.1096	0.2658	0.8074	1.2647
Between subject variance, AUC0-t	0.19141	0.13506	0.9242	1.45
Within subject variance, AUC∞	0.1076	0.2662	1.0546	0.5892
Between subject variance, AUC∞	0.18697	0.12313	0.6464	1.826
Within subject variance, Cmax	0.07389	0.07666	0.9253	0.4197
Between subject variance, Cmax	0.2272	0.16704	1.31	1.27
	Test		**Reference**	
Kel and AUC∞ determined for how many subjects?	32		32	
Do you agree or disagree with firm's decision?	Agree		Agree	
Indicate the number of subjects with the following:				
measurable drug concentrations at 0 hr	0		0	
first measurable drug concentration as Cmax	0		0	
Were the subjects dosed as more than one group?	No		No	

Ratio of AUC0-t/AUC∞ (Nicotinuric Acid)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	32	0.9781	0.8124	0.9963
Reference	32	0.9599	0.55686	0.9969

Ratio of AUC0-t/AUC∞ (Niacin)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	32	0.408777	0.009196	0.998277
Reference	32	0.854089	0.073273	0.998591

Comments on Pharmacokinetic and Statistical Analysis:

1. The reviewer specified the linear range used to calculate Kel and therefore used the SAS code CALKE for statistical analysis. Because this was a 2 sequence, 4 period, replicate study, the reviewed used the SAS program modified-replicate.sas.

2. Because the detection of Niacin in plasma is highly variable, it could not be used to determine bioequivalence. As per FDA recommendation, if niacin cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for Nicotinuric Acid[10]. Nicotinuric Acid as a proxy of Niacin has been used in other ANDA submissions to determine bioequivalence[2,3].

3. The mean AUC_t/AUC_∞ ratio for nicotinuric acid is greater than 0.9 for both test and reference and therefore indicates that the firm's sampling schedule was carried out for a sufficient period of time. For nicotinuric acid, the minimum AUC_t/AUC_∞ ratio did not fall below 0.80 for either test or reference.

4. The mean AUC_t/AUC_∞ ratio for niacin is greater than 0.8 for only the reference product. The mean for the test is less than 0.5. The ranges of the ratios vary greatly for both test and reference products. This is expected due to the high variability associated with this particular analyte and is further supported by the results obtained in the study for this particular analyte.

5. Food effect: It is documented that food intake maximizes bioavailability of niacin[8]. The analysis of Nicotinuric Acid plasma concentrations during the fed and fasting studies indicate that there is a food effect when ingesting this drug product. There was an approximate 274% and 131% increase in Nicotinuric Acid Cmax and Tmax, respectively, due to food intake in subjects that took the test drug product. This food effect was also observed with the reference product which demonstrated a 318% and 146% increase in Cmax and Tmax of Nicotinuric Acid, respectively.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The single-dose fed bioequivalence study with 1 x 1000 mg Niacin Extended Release Tablets is incomplete due to deficiencies outlined in Section 3.10. In addition, it is pending the outcome of DSI inspections.

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

Nicotinuric Acid Replicate 1 (period 1 and period 2)

	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	14.65	343.63	0.00	275.10	6.49	421.66	0.00	142.50	2.26
0.5	201.57	189.10	0.00	1449.10	141.64	219.20	0.00	1485.90	1.42
0.75	448.36	130.13	0.00	2240.20	404.94	133.06	0.00	2110.60	1.11
1.0	809.68	88.81	0.00	2745.80	851.60	91.45	0.00	3526.70	0.95
1.25	1167.16	89.79	0.00	4858.40	1257.48	80.15	0.00	3683.40	0.93
1.50	1321.37	88.86	57.80	4430.40	1620.98	85.40	161.50	5248.40	0.82
1.75	1413.66	79.96	159.20	4504.20	1815.18	93.25	193.00	6850.30	0.78
2.0	1670.81	77.03	143.60	6101.80	1937.95	74.33	195.80	5447.60	0.86
2.5	1893.66	71.84	220.10	6138.80	2097.79	81.69	198.60	7866.70	0.90
3.0	1996.98	72.67	172.00	5409.10	2184.93	80.26	157.90	8418.90	0.91
3.5	2501.41	64.47	144.90	6211.10	2391.91	70.44	201.90	8076.30	1.05
4.0	1695.54	90.89	87.60	6760.20	1791.08	94.44	148.70	8346.40	0.95
5.0	1152.23	102.05	74.80	5851.20	1198.31	108.65	89.10	6481.80	0.96
6.0	943.54	175.47	57.80	8939.20	932.34	152.49	74.50	7927.00	1.01
7.0	676.27	192.21	0.00	7061.00	599.41	146.34	59.50	4971.50	1.13
8.0	534.50	181.85	0.00	5300.50	439.96	124.85	31.00	3127.90	1.21
9.0	359.67	206.26	0.00	4189.30	283.28	122.53	0.00	1521.10	1.27
10.0	187.77	151.51	0.00	1313.00	202.44	123.22	0.00	1016.60	0.93
12.0	263.22	138.17	0.00	1396.20	232.55	167.22	0.00	1751.60	1.13
16.0	86.59	197.83	0.00	665.80	65.44	161.84	0.00	530.20	1.32
CMAX	3180.54	56.12	867.60	8939.20	3258.37	50.58	979.00	8418.90	0.98
TMAX	4.59	27.01	2.00	7.00	4.58	25.74	2.00	6.00	1.00
THAL	2.07	43.08	0.72	4.95	2.94	122.75	0.89	20.98	0.70

Nicotinuric Acid Replicate 2 (period 3 and period 4)									
	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	29.84	256.70	0.00	389.80	44.07	411.52	0.00	1020.60	0.68
0.5	306.79	162.79	0.00	1763.80	394.08	181.65	0.00	3326.30	0.78
0.75	695.01	117.22	0.00	2937.30	844.77	132.45	0.00	5349.20	0.82
1.0	1107.64	96.47	31.40	3590.20	1265.94	93.48	0.00	5535.40	0.87
1.25	1288.47	97.38	0.00	5216.20	1680.35	84.75	138.30	5790.20	0.77
1.50	1527.96	96.14	50.40	6341.90	1778.53	82.54	216.30	5428.20	0.86
1.75	1880.39	88.63	126.50	6057.40	2026.81	70.41	199.20	6045.50	0.93
2.0	2185.47	83.71	249.80	6270.10	2234.92	77.11	335.60	6863.70	0.98
2.5	2182.66	74.21	364.50	5555.30	2365.30	60.46	320.90	5125.80	0.92
3.0	2239.15	71.72	382.30	7438.00	2308.29	58.08	238.60	5235.50	0.97
3.5	2272.73	68.94	498.00	7541.30	2450.62	52.93	659.30	5252.50	0.93
4.0	1732.47	81.63	340.00	6445.10	1593.78	73.36	284.20	5468.10	1.09
5.0	1086.63	123.41	195.60	7560.20	1210.37	103.26	149.80	6848.80	0.90
6.0	831.37	156.70	174.20	7449.70	860.74	126.78	98.00	5980.30	0.97
7.0	637.63	165.46	91.60	6033.90	662.71	131.84	68.80	4609.90	0.96
8.0	438.00	157.72	51.50	3900.80	477.83	106.37	111.10	2255.50	0.92
9.0	259.38	146.59	44.40	1961.80	325.23	115.46	50.90	1500.50	0.80
10.0	180.58	129.06	30.70	1099.10	250.90	143.99	39.10	1749.50	0.72
12.0	185.36	125.62	0.00	1048.40	244.21	153.07	0.00	1466.60	0.76
16.0	147.06	403.18	0.00	3379.00	55.64	122.95	0.00	270.10	2.64
CMAX	3322.15	54.90	911.50	7560.20	3286.64	47.56	1141.10	6863.70	1.01
TMAX	5.05	46.20	1.50	16.00	4.47	27.84	2.00	6.50	1.13
THAL	2.15	39.62	1.03	4.44	3.76	280.55	0.89	61.47	0.57

Niacin Replicate 1 (Period 1 and Period 2)

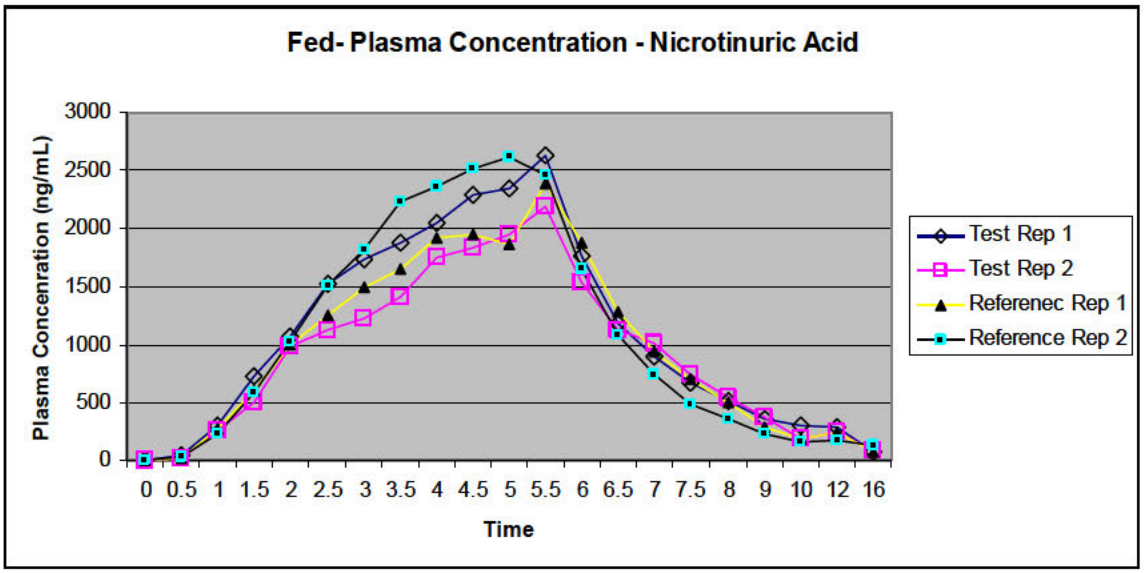
	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.5	8.04	385.38	0.00	171.00	30.42	565.69	0.00	973.50	0.26
0.75	24.39	326.09	0.00	441.80	86.58	412.73	0.00	2011.70	0.28
1.0	94.57	291.49	0.00	1220.40	154.68	399.28	0.00	3494.00	0.61
1.25	195.36	332.01	0.00	3520.20	258.64	269.34	0.00	3299.10	0.76
1.50	201.11	269.33	0.00	2191.90	175.03	242.54	0.00	2276.60	1.15
1.75	237.35	385.61	0.00	5159.00	174.22	195.75	0.00	1497.80	1.36
2.0	225.29	266.61	0.00	3069.50	199.58	232.89	0.00	1785.40	1.13
2.5	137.09	190.60	0.00	1348.20	360.74	162.05	0.00	1796.20	0.38
3.0	330.05	252.91	0.00	4644.00	230.46	186.90	0.00	1648.90	1.43
3.5	446.19	243.11	0.00	6094.10	346.36	258.79	0.00	4876.70	1.29
4.0	274.00	335.85	0.00	4237.50	114.75	258.85	0.00	1525.80	2.39
5.0	195.41	372.79	0.00	3537.10	23.48	133.20	0.00	133.80	8.32
6.0	80.19	426.31	0.00	1930.40	32.29	275.96	0.00	496.30	2.48
7.0	32.80	208.31	0.00	335.40	22.20	257.89	0.00	324.20	1.48
8.0	22.11	208.64	0.00	262.00	12.92	129.05	0.00	66.30	1.71
9.0	9.64	145.58	0.00	40.40	21.64	288.34	0.00	353.70	0.45
10.0	4.08	237.39	0.00	28.70	14.11	322.11	0.00	253.50	0.29
12.0	2.41	318.69	0.00	30.30	6.10	258.17	0.00	58.10	0.40
16.0	0.92	565.69	0.00	29.40	0.00	.	0.00	0.00	.
CMAX	1044.92	143.45	20.30	6094.10	890.85	122.72	0.00	4876.70	1.17
TMAX	4.42	30.27	1.50	6.50	4.32	29.50	2.00	7.00	1.02
THAL	4.21	113.63	0.31	21.88	3.90	124.52	0.20	24.42	1.08

Niacin Replicate 2 (period 3 and period 4)

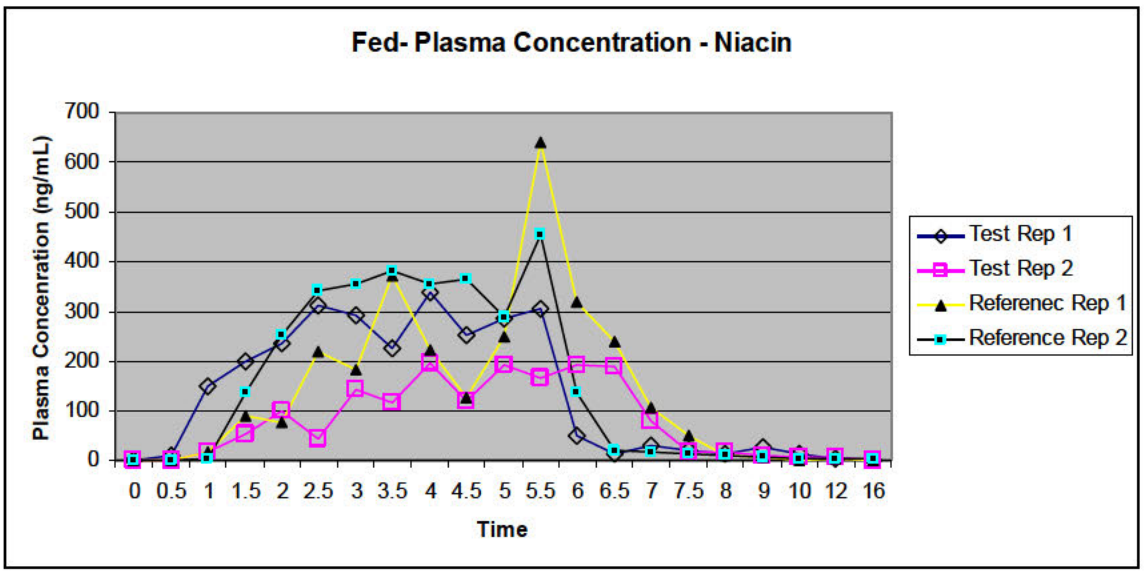
	Treatment A				Treatment B				T/R
Time	Mean	CV%	Min	Max	Mean	CV%	Min	Max	Ratio
0	0.00	.	0.00	0.00	0.00	.	0.00	0.00	.
0.25	0.00	.	0.00	0.00	10.35	565.69	0.00	331.30	0.00
0.5	13.83	326.56	0.00	221.00	132.87	480.64	0.00	3611.40	0.10
0.75	138.21	278.60	0.00	1529.50	223.39	388.07	0.00	4849.00	0.62
1.0	151.41	315.48	0.00	2629.70	259.92	272.34	0.00	3642.70	0.58
1.25	199.78	326.89	0.00	2923.70	262.54	303.48	0.00	4197.60	0.76
1.50	285.95	286.78	0.00	3740.70	307.70	268.51	0.00	3097.70	0.93
1.75	413.99	205.83	0.00	3050.90	264.38	188.55	0.00	2015.30	1.57
2.0	333.89	274.01	0.00	4007.30	349.17	198.21	0.00	3133.50	0.96
2.5	230.52	255.84	0.00	2969.40	129.96	230.90	0.00	1681.60	1.77
3.0	214.36	224.29	0.00	2332.50	233.86	175.27	0.00	2086.30	0.92
3.5	509.14	195.74	0.00	4947.00	260.14	150.87	0.00	1490.60	1.96
4.0	224.92	356.25	0.00	4297.50	76.75	298.12	0.00	1144.30	2.93
5.0	165.20	523.31	0.00	4901.90	70.83	464.78	0.00	1868.50	2.33
6.0	97.31	510.86	0.00	2820.80	17.81	176.35	0.00	168.70	5.47
7.0	33.73	429.31	0.00	823.30	7.58	166.88	0.00	35.60	4.45
8.0	4.65	214.66	0.00	31.30	9.67	159.75	0.00	54.30	0.48
9.0	2.62	316.30	0.00	29.50	14.28	304.12	0.00	243.40	0.18
10.0	1.39	565.69	0.00	44.60	5.75	259.96	0.00	74.80	0.24
12.0	1.97	419.78	0.00	42.90	2.02	397.37	0.00	36.70	0.98
16.0	4.34	565.69	0.00	138.90	0.00	.	0.00	0.00	.
CMAX	1057.01	122.27	21.10	4947.00	932.52	129.21	27.20	4849.00	1.13
TMAX	4.82	51.18	1.50	16.00	4.50	26.62	1.50	6.50	1.07
THAL	3.65	184.49	0.17	27.06	2.39	79.70	0.29	6.82	1.53

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

Nicotinuric Acid Replicate 1 (period 1 and period 2) and Replicate 2 (period 3 and period 4)



Niacin Replicate 1 (period 1 and period 2) and Replicate 2 (period 3 and period 4)



4.2 Formulation Data[52]

(b) (4)

[52] EDR: ANDA #200484 Section 2.7.1 CTD Tables Submit Date 9/29/2009

Following this page, 3 Pages Withheld in Full as (b)(4)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Product formulation acceptable.

[55] DPRF Database: Search Term: (b) (4) Last Access: 9-24-2010
[56] START!REF Database: Search Term: (b) (4) Last Access: 9-24-2010
http://online.statref.com/Document/Document.aspx?docAddress=QmwnBpl7wKQfTVfM1ntUYQ%3d%3d&Scroll=91&Index=0&SessionId=132E9B2KMOUTWRTB

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

Reviewer's Comments:

1. Based on the maximum daily dose of Niacin, all excipients used in the 500 mg and 1000 mg test product are within allowable limits.

2. (b) (4) . According to the SUPAC-MR guidance , the ratios of inactive ingredients (in this case, rate

[58] Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (Effective September 1997).

controlling inactive ingredients) to total weight between the 500 mg and 1000 mg strength test products are proportional based on criteria for a level 1 change in components and composition. Specifically, for a level 1 change, the guidance recommends that the *total additive effect of all release controlling excipient changes should not be more than 5% w/w of the total release controlling excipients in the original approved formulation*.

3. The formulations are acceptable.

4.3 Dissolution Data

Dissolution Review Path	DARRTS: ANDA #200484 REV-BIOEQ-02(Dissolution Review) Submit Date: 3/31/2010

Table 34. Dissolution Data

Dissolution Conditions	Apparatus	USP Type I (Basket)												
	Speed of Rotation	100 rpm												
	Medium	(b) (4) water (b) (4)												
	Volume	900 ml												
	Time Point	1,2,3,4,6,8,9,12,16,20 and 24 hrs												
	Temperature	37° C ± 0.5° C												
Proposed Specification*	Time (Hrs)	% Release												
	1 Hrs	NMT (b) (4) %												
	3 Hrs	(b) (4) %												
	6 Hrs	%												
	9 Hrs	%												
	12 Hrs	%												
	20 Hrs	NLT (b) %												
	24 Hrs	NLT (4) %												
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India													
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
					1 hrs	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	9 hrs	12hrs	16 hrs	20 hrs	24 hrs	
INN/050/09	23/05/09	Batch #: GK91008 Mfg Date: 05/2009	1000 mg Tablets	12												Module 5 Section 5.3.1.3
				Mean (%)	11	17	22	27	36	44	48	58	71	80	88	
				Range (%)											(b) (4)	
				% RSD	5.0	3.9	3.4	2.4	2.0	2.1	2.3	1.5	0.9	1.2	0.8	
	24/05/09	Batch #: 642142E21 Exp. Date: 28/01/2011	1000 mg Tablets	12												
				Mean (%)	8	15	20	25	35	43	47	58	71	82	89	
				Range (%)											(b) (4)	
				% RSD	5.9	2.6	2.2	2.0	2.3	1.3	1.6	1.2	1.1	0.9	1.1	

Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**0.1 N HCl**
	Volume	**900 ml**
	Time Point	**1,3,6,9,12,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**
Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4)%
	3 Hrs	(b) (4)%
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4)%
	24 Hrs	NLT (b) (4)%
Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**	

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) 1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	Study Report Location
INN/053/09	31/05/09	**Batch #: GK91008 Mfg Date: 05/2009**	**1000 mg Tablets**	**12**								**Module 5 Section 5.3.1.3**
				Mean (%)	18	36	55	70	81	98	103	
				Range (%)							(b) (4)	
				% RSD	3.7	2.0	1.9	1.1	1.0	1.0	1.0	
	31/05/09	**Batch #: 642142E21 Exp. Date: 28/01/2011**	**1000 mg Tablets**	**12**								
				Mean (%)	16	33	53	68	80	100	103	
				Range (%)							(b) (4)	
				% RSD	3.1	1.7	1.5	1.8	1.3	1.3	1.2	

Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**pH 4.5 Acetate Buffer**
	Volume	**900 ml**
	Time Point	**1,3,6,9,12,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**

Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT (b) (4) %

Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/055/09	03/06/09	**Batch #: GK91008 Mfg Date: 05/2009**	**1000 mg Tablets**	**12**								**Module 5 Section 5.3.1.3**
				Mean (%)	12	23	37	48	58	80	87	
				Range (%)							(b) (4)	
				% RSD	5.9	3.9	3.4	3.1	3.1	2.2	1.8	
	04/06/09	**Batch #: 642142E21 Exp. Date: 28/01/2011**	**1000 mg Tablets**	**12**								
				Mean (%)	8	20	35	47	60	83	91	
				Range (%)							(b) (4)	
				% RSD	5.5	3.6	2.8	2.1	1.7	0.9	1.1	

Table 5 D: Summary of In vitro Dissolution Studies (1000 MG) – pH 6.8 Phosphate Buffer

Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**pH 6.8 Phosphate Buffer**
	Volume	**900 ml**
	Time Point	**1,3,6,9,12,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**

Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**

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) 1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	Study Report Location
INN/055/09	11/06/09	**Batch #: GK91008 Mfg Date: 05/2009**	**1000 mg Tablets**	**12**								**Module 5 Section 5.3.1.3**
				Mean (%)	11	23	37	47	58	78	84	
				Range (%)							(b) (4)	
				% RSD	5.2	3.1	2.9	3.0	3.5	4.3	4.0	
	11/06/09	**Batch #: 642142E21 Exp. Date: 28/01/2011**	**1000 mg Tablets**	**12**								
				Mean (%)	8	20	34	47	57	81	87	
				Range (%)							(b) (4)	
				% RSD	5.5	3.4	2.9	1.6	2.3	3.5	3.3	

Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**(b) (4) water (b) (4)**
	Volume	**900 ml**
	Time Point	**1,2,3,4,6,8,9,12,16,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**

Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**

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) 1 hrs	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	9 hrs	12hrs	16 hrs	20 hrs	24 hrs	Study Report Location
INN/051/09	25/05/09	**Batch #: GK91007 Mfg Date: 05/2009**	**500 mg Tablets**	**12**												**Module 5 Section 5.3.1.3**
				Mean (%)	12	19	25	30	40	49	53	63	75	84	91	
				Range (%)											(b) (4)	
				% RSD	5.1	5.1	5.4	4.9	5.5	5.4	5.7	5.0	4.8	4.2	3.7	
	26/05/09	**Batch #: 687342E21 Exp. Date: 30/05/2011**	**500 mg Tablets**	**12**												
				Mean (%)	11	18	24	30	41	50	54	67	82	94	101	
				Range (%)											(b) (4)	
				% RSD	3.6	2.9	3.1	3.5	2.5	2.7	2.5	2.4	1.8	1.4	1.1	

Table 5 F: Summary of In vitro Dissolution Studies (500 MG) – 0.1 N HCl

Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**0.1 N HCl**
	Volume	**900 ml**
	Time Point	**1,3,6,9,12,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**
Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4)%
	3 Hrs	(b) (4)%
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4)%
	24 Hrs	NLT (b) (4)%
Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**	

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) 1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	Study Report Location
INN/054/09	02/06/09	**Batch #: GK91007 Mfg Date: 05/2009**	**500 mg Tablets**	**12**								**Module 5 Section 5.3.1.3**
				Mean (%)	21	41	61	75	87	103	103	
				Range (%)							(b) (4)	
				% RSD	1.9	2.3	2.4	2.1	1.9	1.2	1.4	
	22/09/09	**Batch #: 687342E21 Exp. Date: 30/05/2011**	**500 mg Tablets**	**12**								
				Mean (%)	19	41	63	83	95	102	102	
				Range (%)							(b) (4)	
				% RSD	2.1	1.7	1.3	2.0	1.3	1.7	1.3	

Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**pH 4.5 Acetate Buffer**
	Volume	**900 ml**
	Time Point	**1,3,6,9,12,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**

Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4)%
	3 Hrs	(b) (4)%
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4)%
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**

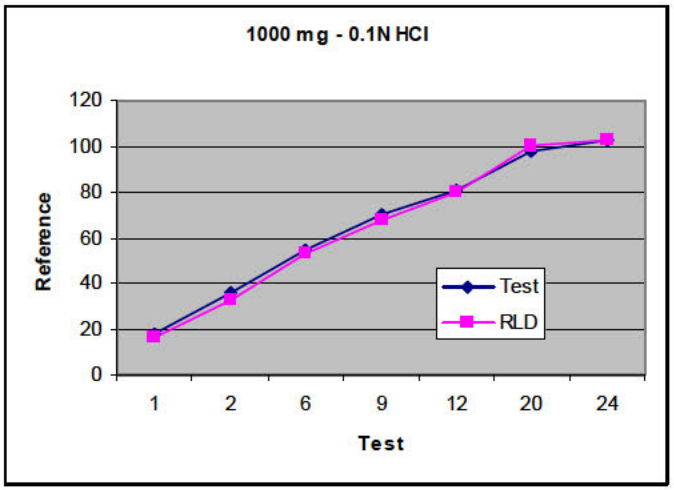
Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes) 1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	Study Report Location
INN/056/09	06/06/09	**Batch #: GK91007 Mfg Date: 05/2009**	**500 mg Tablets**	**12**								**Module 5 Section 5.3.1.3**
				Mean (%)	13	26	41	53	64	86	93	
				Range (%)							(b) (4)	
				% RSD	3.0	3.1	3.1	3.1	3.4	2.4	2.6	
	23/09/09	**Batch #: 687342E21 Exp. Date: 30/05/2011**	**500 mg Tablets**	**12**								
				Mean (%)	11	23	43	54	67	93	100	
				Range (%)							(b) (4)	
				% RSD	2.6	2.1	3.1	2.9	2.6	1.9	1.8	

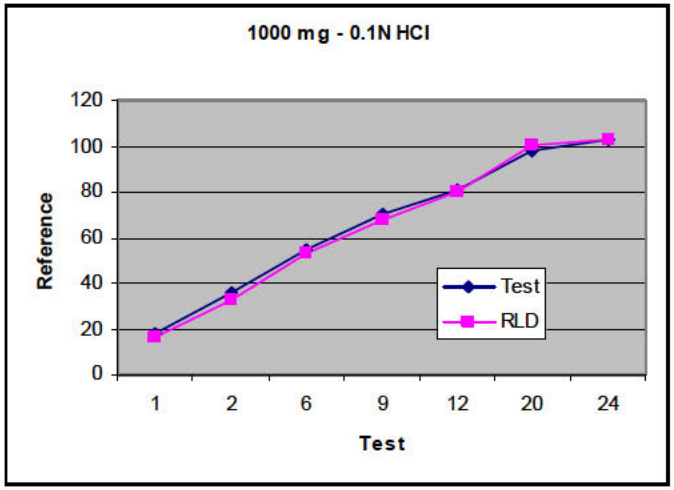
Table 3.11: Summary of In Vitro Dissolution Studies (500 MG) – pH 6.8 Phosphate Buffer

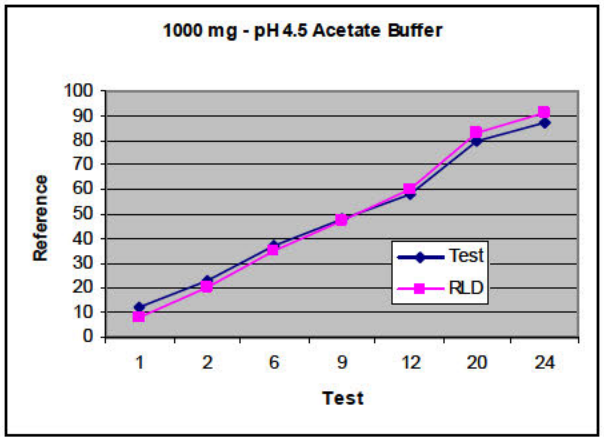
Dissolution Conditions	Apparatus	**USP Type I (Basket)**
	Speed of Rotation	**100 rpm**
	Medium	**pH 6.8 Phosphate Buffer**
	Volume	**900 ml**
	Time Point	**1,3,6,9,12,20 and 24 hrs**
	Temperature	**37° C ± 0.5° C**
Proposed Specification*	**Time (Hrs)**	**% Release**
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) %
	24 Hrs	NLT (4) %
Dissolution Testing Site (Name & Address)	**Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India**	

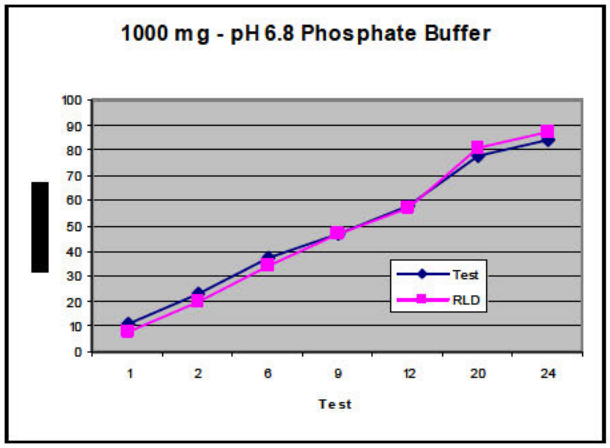
Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes) 1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	Study Report Location
INN/057/09	07/06/09	**Batch #: GK91007 Mfg Date: 05/2009**	**500 mg Tablets**	**12**								**Module 5 Section 5.3.1.3**
				Mean (%)	13	26	41	53	64	86	94	
				Range (%)							(b) (4)	
				% RSD	3.6	2.2	3.1	2.5	2.6	2.0	2.8	
	22/09/09	**Batch #:687342E21 Exp. Date: 30/05/2011**	**500 mg Tablets**	**12**								
				Mean (%)	10	24	39	53	65	92	100	
				Range (%)							(b) (4)	
				% RSD	3.8	2.2	1.7	2.0	1.8	1.1	1.2	

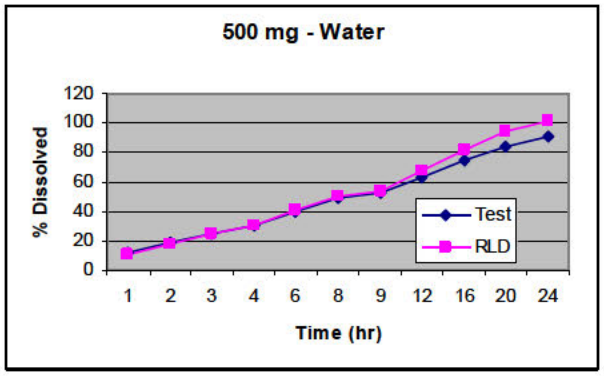
Figure 3. Dissolution Profiles

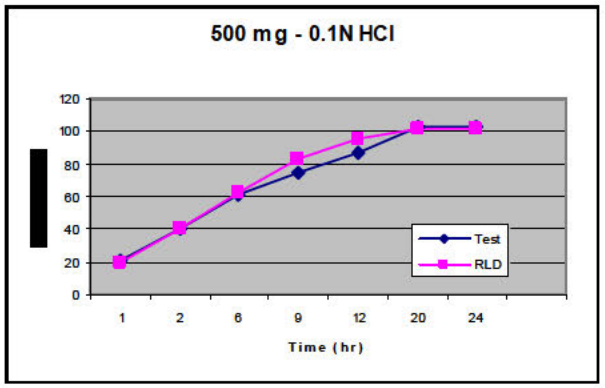


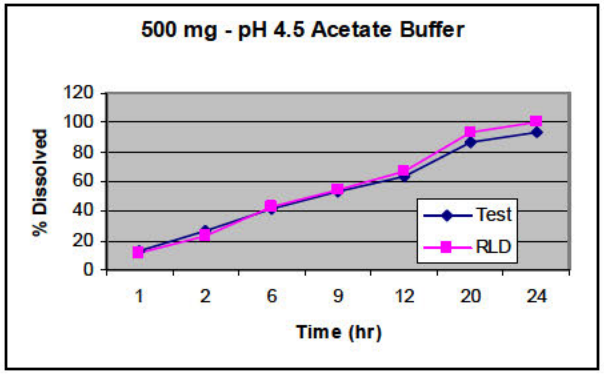


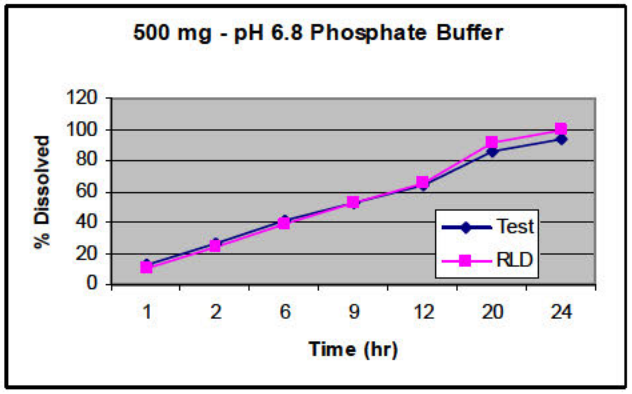





500 mg - Water
% Dissolved
120
100
80
60
40
20
0
1 2 3 4 6 8 9 12 16 20 24
Time (hr)
Test
RLD


500 mg - 0.1N HCl
120
100
80
60
40
20
0
1 2 6 9 12 20 24
Time (hr)
Test
RLD


500 mg - pH 4.5 Acetate Buffer
% Dissolved
120
100
80
60
40
20
0
1 2 6 9 12 20 24
Time (hr)
Test
RLD


500 mg - pH 6.8 Phosphate Buffer
% Dissolved
120
100
80
60
40
20
0
1 2 6 9 12 20 24
Time (hr)
Test
RLD

4.4 Detailed Regulatory History (If Applicable)

None.

4.5 Consult Reviews

None.

APPEARS THIS WAY ON ORIGINAL

4.6 SAS Output

Nicotinuric Acid - Fasted

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	2	1	1	1	A	0	100.2	307.0	510.6	544.2	613.6	707.0	523.8	457.0	274.6	217.4	218.5	177.6	64.9
2	2	1	2	1	B	0	35.6	296.2	399.5	577.8	534.5	416.3	533.0	565.6	335.7	273.5	189.4	104.0	43.5
3	2	1	3	1	A	0	0.0	220.8	285.8	301.6	312.3	371.5	521.8	646.2	737.4	469.0	383.5	248.6	90.7
4	2	1	4	1	B	0	32.9	305.1	555.7	495.6	307.9	325.4	274.1	233.6	303.9	193.1	99.2	67.3	32.1
5	3	1	1	1	A	0	51.4	642.8	720.0	654.8	630.1	515.5	625.6	1184.3	972.6	963.1	691.5	459.1	324.6
6	3	1	2	1	B	0	0.0	186.3	420.7	466.4	570.4	594.8	772.2	661.4	787.6	485.8	722.2	489.0	439.2
7	3	1	3	1	A	0	67.8	574.9	904.0	842.1	799.2	824.1	719.9	677.1	611.7	428.7	232.1	151.8	67.6
8	3	1	4	1	B	0	0.0	367.0	708.2	980.7	972.2	809.5	622.5	846.9	884.4	746.2	441.7	293.3	113.4
9	4	2	1	1	B	0	0.0	378.1	458.6	665.9	610.1	654.0	656.3	873.2	479.6	737.7	500.1	370.2	203.3
10	4	2	2	1	A	0	39.7	248.9	250.8	266.8	417.4	551.0	506.2	456.9	1132.6	532.4	1295.4	1437.0	1758.7
11	4	2	3	1	B	0	47.4	354.9	572.5	759.2	602.5	591.8	662.8	670.8	402.9	228.0	144.5	91.1	46.8
12	4	2	4	1	A	0	151.5	606.0	786.0	796.5	753.5	760.5	727.3	695.4	684.7	580.8	385.4	260.3	128.4
13	5	2	1	1	B	0	0.0	133.1	334.2	531.7	381.2	251.0	351.6	371.6	427.0	419.2	235.2	233.9	120.7
14	5	2	2	1	A	0	0.0	421.9	750.6	711.2	594.2	887.1	386.7	291.0	219.2	134.2	90.8	45.3	0.0
15	5	2	3	1	B	0	0.0	89.5	172.5	233.4	255.2	262.4	345.6	340.0	307.2	349.2	489.5	425.5	204.3
16	5	2	4	1	A	0	0.0	40.3	279.8	512.4	441.4	524.4	492.8	401.7	261.1	178.8	157.4	97.7	46.6
17	6	1	1	1	A	0	42.8	459.4	633.8	770.3	727.6	656.1	641.5	667.7	373.7	187.2	105.2	77.6	39.3
18	6	1	2	1	B	0	0.0	245.5	443.1	553.7	620.3	577.5	593.8	588.6	562.0	354.6	405.7	219.2	91.3
19	6	1	3	1	A	0	0.0	170.4	546.1	609.2	732.3	649.9	596.2	600.4	575.6	531.0	224.3	106.6	71.0
20	6	1	4	1	B	0	0.0	0.0	331.4	501.1	531.6	589.1	566.4	542.0	609.6	487.4	400.0	298.2	133.6
21	8	1	1	1	A	0	0.0	477.7	677.2	591.3	565.2	536.9	462.9	437.9	393.1	337.9	224.0	171.7	199.7
22	8	1	2	1	B	0	0.0	276.4	322.9	425.6	514.6	462.3	406.2	369.6	213.8	150.6	122.3	91.0	97.0
23	8	1	3	1	A	0	97.0	561.6	703.8	576.8	499.2	491.5	520.5	473.2	341.3	255.9	205.4	176.8	107.0
24	8	1	4	1	B	0	0.0	405.1	522.2	569.8	521.1	449.6	416.1	389.3	354.1	329.6	213.6	165.1	287.5
25	10	1	1	1	A	0	0.0	82.0	281.3	363.1	366.5	317.2	231.4	165.3	130.5	141.1	125.9	52.7	0.0
26	10	1	2	1	B	0	0.0	116.3	245.0	388.1	313.5	304.4	277.4	230.3	191.4	177.8	214.1	108.9	40.8
27	10	1	3	1	A	0	0.0	168.7	288.0	371.4	330.9	283.2	273.6	308.5	211.5	237.6	158.5	101.8	39.6
28	10	1	4	1	B	0	0.0	152.8	302.7	384.5	307.1	281.4	332.9	212.1	124.0	115.4	147.7	76.8	34.9
29	12	2	1	1	B	0	0.0	127.9	246.5	328.9	371.4	398.0	612.6	591.5	549.0	643.2	710.7	1009.5	677.1
30	12	2	2	1	A	0	0.0	252.7	468.8	469.7	362.4	440.7	292.2	327.5	867.2	441.0	1500.1	823.9	262.0
31	12	2	3	1	B	0	0.0	123.2	308.3	405.9	538.1	.	591.5	489.0	424.4	443.1	517.0	145.1	142.3
32	12	2	4	1	A	0	0.0	356.9	915.5	926.9	678.4	646.0	654.3	626.3	614.7	482.6	296.1	316.8	187.9
33	13	2	1	1	B	0	0.0	107.4	79.0	115.6	480.8	608.0	708.9	643.8	447.5	320.6	497.9	339.9	429.4
34	13	2	2	1	A	0	51.4	303.6	363.2	289.2	225.5	324.4	397.1	403.8	923.0	655.8	584.5	306.0	254.1
35	13	2	3	1	B	0	0.0	129.2	160.1	217.2	272.3	297.3	603.7	573.9	363.8	468.6	405.3	263.8	116.5
36	13	2	4	1	A	0	0.0	272.7	264.0	226.2	330.1	526.6	421.8	587.2	551.8	580.7	367.2	284.8	234.3

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
37	14	1	1	1	A	0	0.0	340.2	841.6	1064.3	1155.5	1104.0	685.0	448.1	567.3	336.7	168.2	96.1	59.9
38	14	1	2	1	B	0	0.0	342.8	502.4	512.2	424.4	445.5	521.4	595.5	684.6	432.0	401.6	164.9	81.6
39	14	1	3	1	A	0	35.9	187.8	235.6	641.0	762.7	711.2	585.8	517.7	386.5	354.3	223.2	123.3	48.9
40	14	1	4	1	B	0	0.0	622.2	870.4	712.3	689.4	638.1	718.3	807.5	520.6	262.5	498.3	290.7	129.3
41	15	1	1	1	A	0	0.0	41.5	117.9	335.4	713.5	492.0	582.0	1284.1	492.4	554.0	622.8	654.1	206.6
42	15	1	2	1	B	0	0.0	60.8	322.2	549.6	543.8	611.0	422.7	518.4	686.4	495.3	289.7	228.2	88.8
43	15	1	3	1	A	0	0.0	72.0	148.1	308.4	439.5	1063.0	1086.6	791.3	843.4	569.9	533.4	446.8	296.0
44	15	1	4	1	B	0	0.0	37.1	282.3	438.8	449.9	453.8	486.1	543.1	636.9	424.1	355.1	248.0	90.1
45	16	2	1	1	B	0	0.0	132.5	766.4	797.7	860.0	772.6	666.2	577.2	423.0	534.5	760.2	747.1	442.1
46	16	2	2	1	A	0	0.0	97.3	197.1	189.5	449.6	778.2	665.1	744.0	588.8	616.4	479.3	280.2	287.3
47	16	2	3	1	B	0	0.0	90.6	347.7	340.1	1092.5	1151.1	911.3	723.9	579.6	543.4	568.0	614.0	264.8
48	16	2	4	1	A	0	0.0	466.8	756.4	675.6	856.0	735.5	1121.8	1133.3	982.5	894.8	474.2	590.8	561.2
49	17	1	1	1	A	0	29.6	529.2	593.6	480.1	542.3	872.3	453.6	384.5	222.4	144.2	141.4	116.8	54.4
50	17	1	2	1	B	0	0.0	217.0	607.8	693.7	719.4	601.1	508.2	285.6	518.6	415.8	202.5	145.4	154.3
51	17	1	3	1	A	0	0.0	495.8	638.3	556.9	475.1	319.2	256.8	211.1	205.6	208.7	101.1	67.5	33.2
52	17	1	4	1	B	0	0.0	171.8	312.9	465.7	431.0	557.1	417.7	311.9	440.6	250.5	258.5	326.9	130.5
53	18	2	1	1	B	0	0.0	305.7	605.0	742.8	895.9	515.0	891.9	741.8	564.2	427.7	240.2	244.6	131.1
54	18	2	2	1	A	0	43.6	147.1	434.6	398.2	451.2	587.3	918.7	773.1	712.3	392.4	519.4	643.2	218.1
55	18	2	3	1	B	0	0.0	66.0	213.6	389.6	313.6	442.9	654.8	770.3	809.6	492.7	373.5	262.4	185.6
56	18	2	4	1	A	0	43.1	268.7	431.3	470.7	563.1	767.2	712.8	683.7	410.6	591.8	568.3	285.6	132.1
57	19	1	1	1	A	0	0.0	116.4	457.0	644.1	756.2	496.5	461.6	673.5	604.6	323.5	203.7	120.8	99.0
58	19	1	2	1	B	0	0.0	286.3	506.2	759.8	736.2	717.9	595.2	461.2	321.6	193.0	109.3	72.7	44.7
59	19	1	3	1	A	0	0.0	249.7	486.0	480.2	530.3	551.0	347.7	501.3	503.3	399.1	302.4	229.8	75.1
60	19	1	4	1	B	0	44.0	301.8	413.8	519.1	589.7	551.5	433.6	530.0	362.2	200.7	134.0	103.2	49.0
61	20	2	1	1	B	0	0.0	118.6	413.1	538.2	563.0	562.3	574.8	478.1	383.9	353.2	163.1	97.9	51.9
62	20	2	2	1	A	0	0.0	147.9	221.6	136.6	81.7	371.3	322.9	235.8	258.0	425.4	486.3	444.0	434.2
63	20	2	3	1	B	0	0.0	74.6	86.5	61.8	47.3	65.8	133.6	1098.8	871.0	704.6	552.4	385.6	185.8
64	20	2	4	1	A	0	0.0	113.8	118.7	79.4	45.9	33.2	45.9	115.2	213.2	490.9	220.4	132.0	661.4
65	21	1	1	1	A	0	32.9	188.8	188.4	160.1	305.3	342.3	546.7	378.6	219.5	258.4	214.9	385.6	403.1
66	21	1	2	1	B	0	0.0	112.6	172.9	306.5	351.3	413.2	467.8	485.3	434.7	324.5	352.7	206.8	73.5
67	21	1	3	1	A	0	0.0	164.4	133.5	98.1	196.9	332.4	439.3	598.2	818.9	844.5	442.1	330.1	115.9
68	21	1	4	1	B	0	0.0	217.4	353.0	460.0	429.2	609.8	377.4	317.3	393.6	313.0	266.0	287.1	170.7
69	22	2	1	1	B	0	0.0	278.8	485.8	438.3	635.7	593.0	720.1	672.0	463.1	432.2	224.6	130.4	128.4
70	22	2	2	1	A	0	0.0	436.8	456.1	505.4	489.3	740.7	549.1	644.1	866.5	603.8	509.2	555.4	158.6
71	22	2	3	1	B	0	0.0	273.4	458.2	683.4	797.7	671.1	882.2	760.7	653.5	651.6	618.6	745.0	212.7
72	22	2	4	1	A	0	0.0	343.1	638.7	650.7	1558.1	752.6	594.0	610.6	356.2	230.4	122.5	142.4	216.4
73	23	1	1	1	A	0	29.5	561.5	968.2	1211.3	1487.8	1457.6	1069.6	1054.4	1062.8	795.4	351.6	305.8	92.1
74	23	1	2	1	B	0	30.1	325.1	597.8	679.5	925.1	1141.2	1376.8	1286.6	1029.5	1335.3	956.6	864.4	695.3
75	23	1	3	1	A	0	83.8	558.4	797.4	903.2	992.0	1321.7	1337.7	1255.0	1350.5	1532.1	869.2	756.6	325.6
76	23	1	4	1	B	0	0.0	307.8	573.5	612.1	685.3	820.6	895.6	1174.7	677.6	491.0	607.4	569.3	126.8

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
77	24	2	1	1	B	0	0.0	95.2	186.0	314.0	412.5	395.8	355.1	349.5	194.9	108.5	144.6	128.6	45.9
78	24	2	2	1	A	0	46.0	338.3	423.4	462.5	505.7	440.0	363.3	288.0	214.1	130.5	129.2	63.5	31.8
79	24	2	3	1	B	0	0.0	0.0	0.0	51.2	324.7	403.0	313.2	400.4	422.5	172.9	175.4	237.5	71.8
80	24	2	4	1	A	0	0.0	123.2	158.0	234.0	351.0	390.5	294.0	225.5	391.4	199.5	315.7	336.1	164.5
81	26	2	1	1	B	0	0.0	130.6	277.8	599.3	764.5	762.8	565.8	497.6	530.3	462.0	355.6	182.3	80.2
82	26	2	2	1	A	0	133.4	490.0	618.9	610.0	600.2	444.5	364.3	368.6	175.0	90.3	56.8	41.2	0.0
83	26	2	3	1	B	0	0.0	206.8	533.9	589.5	688.4	609.1	744.5	616.9	457.7	265.4	334.4	253.5	72.6
84	26	2	4	1	A	0	35.8	414.4	670.1	733.7	547.3	347.7	310.8	227.0	200.5	115.7	77.3	53.7	0.0
85	27	2	1	1	B	0	0.0	0.0	78.5	157.5	150.0	107.9	177.5	172.7	299.7	385.3	581.1	369.2	208.7
86	27	2	2	1	A	0	0.0	0.0	64.1	115.2	320.5	569.2	509.3	519.9	421.7	295.6	205.6	152.5	60.7
87	27	2	3	1	B	0	0.0	0.0	0.0	0.0	59.1	162.5	216.1	177.7	355.6	333.2	371.1	363.0	160.8
88	27	2	4	1	A	0	0.0	0.0	39.5	30.3	0.0	95.0	97.5	194.8	377.8	278.9	357.1	352.9	250.6
89	28	1	1	1	A	0	37.0	429.5	691.3	1001.8	1182.2	1241.1	1099.9	982.5	794.2	706.5	534.9	509.0	452.6
90	28	1	2	1	B	0	0.0	117.5	121.7	167.2	473.4	548.9	365.9	418.9	1443.1	1181.1	497.2	1303.7	878.3
91	28	1	3	1	A	0	56.3	146.8	105.6	180.2	876.5	1159.1	1331.0	1451.7	1533.0	1509.9	1173.5	790.9	431.2
92	28	1	4	1	B	0	0.0	181.0	422.1	632.6	802.0	841.4	814.3	669.6	673.6	582.5	452.3	354.8	623.9
93	29	1	1	1	A	0	79.8	730.2	837.7	705.0	607.9	454.8	356.1	298.3	257.2	358.7	160.3	109.6	51.3
94	29	1	2	1	B	0	0.0	86.9	113.5	114.4	321.4	283.1	268.5	356.8	1232.5	749.3	105.4	317.6	218.8
95	29	1	3	1	A	0	320.2	480.6	332.0	215.6	220.8	232.9	474.5	1046.0	567.1	969.9	757.9	533.9	275.3
96	29	1	4	1	B	0	0.0	78.1	116.5	127.9	253.3	421.1	547.2	884.2	613.9	393.4	361.0	231.0	126.3
97	31	1	1	1	A	0	0.0	36.4	221.8	225.6	180.5	172.5	245.4	301.0	257.1	171.3	137.9	108.8	61.2
98	31	1	2	1	B	0	0.0	43.7	61.1	52.4	127.4	160.6	101.9	70.5	302.4	159.2	417.3	128.0	84.5
99	31	1	3	1	A	0	0.0	141.7	326.4	298.1	253.3	129.7	124.7	136.8	149.2	77.4	41.7	48.9	0.0
100	31	1	4	1	B	0	0.0	0.0	58.1	57.1	39.2	33.2	89.4	357.1	501.2	255.4	179.4	107.3	67.2
101	32	2	1	1	B	0	0.0	70.9	274.8	367.1	402.3	502.7	528.2	625.8	482.1	421.1	378.0	389.0	547.8
102	32	2	2	1	A	0	0.0	300.1	293.5	270.4	242.3	321.9	300.0	379.8	552.4	449.1	380.1	408.9	335.4
103	32	2	3	1	B	0	0.0	142.3	174.0	232.2	263.9	443.5	648.1	362.2	349.2	323.7	340.0	442.1	515.4
104	32	2	4	1	A	0	0.0	244.9	260.1	305.9	208.4	374.6	.	835.1	252.3	254.7	235.5	234.1	212.5
105	33	2	1	1	B	0	70.6	37.0	104.2	190.9	287.3	406.3	372.4	383.5	330.9	305.1	437.7	313.9	287.7
106	33	2	2	1	A	0	0.0	0.0	51.6	122.2	159.6	115.4	109.4	110.7	334.6	350.5	335.8	396.9	424.1
107	33	2	3	1	B	0	0.0	40.6	114.7	117.0	228.2	449.1	591.6	573.4	411.8	373.7	355.3	394.7	199.8
108	33	2	4	1	A	0	0.0	148.5	287.7	196.4	122.9	131.3	129.3	221.8	571.8	358.0	703.6	306.1	117.8
109	34	2	1	1	B	0	119.9	711.8	887.9	1037.9	954.8	1005.3	634.9	924.8	442.1	679.6	515.5	325.3	107.0
110	34	2	2	1	A	0	62.4	254.7	415.6	450.9	317.9	233.2	349.6	421.0	720.5	425.5	366.6	310.7	112.9
111	34	2	3	1	B	0	40.0	570.5	812.5	810.5	676.2	756.0	1154.9	777.1	461.6	660.0	698.3	250.6	115.4
112	34	2	4	1	A	0	0.0	313.2	829.4	760.4	863.9	487.3	627.0	644.5	377.0	235.1	127.7	86.9	36.7
113	35	1	1	1	A	0	46.0	330.0	406.2	388.2	305.4	443.0	475.4	319.2	644.8	603.4	362.9	394.0	169.2
114	35	1	2	1	B	0	47.7	398.2	557.6	644.7	613.8	518.3	507.8	584.5	442.0	286.4	180.2	189.0	92.4
115	35	1	3	1	A	0	31.2	363.2	443.8	582.5	563.2	420.0	671.2	782.0	579.0	534.4	432.8	361.7	227.1
116	35	1	4	1	B	0	0.0	162.1	318.4	555.5	610.7	426.3	395.6	780.1	951.2	798.8	645.4	626.2	338.9

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
117	36	1	1	1	A	0	32.3	358.7	518.1	460.4	418.6	467.6	442.5	726.8	434.4	476.8	311.7	619.3	267.8
118	36	1	2	1	B	0	100.1	512.1	498.4	844.5	799.6	513.5	520.8	521.2	343.4	260.4	175.8	183.1	60.6
119	36	1	3	1	A	0	0.0	278.1	367.2	308.8	235.8	592.0	625.3	413.7	278.0	410.9	284.6	400.4	172.0
120	36	1	4	1	B	0	0.0	106.4	310.5	396.6	319.6	213.7	292.7	344.7	446.2	435.1	335.3	266.4	261.9

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
1	45.8	0.0	32.7	48.4	33.8	0.0	0.0	12	20
2	36.9	0.0	0.0	0.0	0.0	0.0	0.0	12	20
3	40.7	0.0	0.0	0.0	0.0	0.0	0.0	14	20
4	0.0	44.8	30.7	0.0	77.1	74.4	0.0	13	20
5	98.5	154.3	282.3	228.2	127.1	36.0	0.0	13	20
6	256.3	138.4	75.6	43.2	0.0	0.0	0.0	14	20
7	36.7	40.8	39.2	0.0	30.6	32.8	0.0	14	20
8	82.6	51.6	48.3	38.3	63.2	73.9	0.0	14	20
9	101.8	108.2	81.2	46.3	0.0	0.0	0.0	15	20
10	1463.4	913.1	339.8	168.5	312.1	62.5	0.0	16	20
11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
12	68.1	37.6	0.0	0.0	0.0	0.0	0.0	14	20
13	45.7	38.9	0.0	0.0	0.0	0.0	0.0	14	20
14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
15	62.6	35.3	30.5	35.3	54.3	30.0	0.0	16	20
16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
18	37.1	0.0	0.0	0.0	0.0	0.0	0.0	14	20
19	51.1	0.0	0.0	0.0	0.0	0.0	0.0	14	20
20	54.7	0.0	0.0	0.0	0.0	0.0	0.0	14	20
21	82.7	38.4	0.0	0.0	0.0	0.0	0.0	14	20
22	45.6	0.0	0.0	0.0	0.0	0.0	0.0	14	20
23	59.7	0.0	0.0	0.0	0.0	0.0	0.0	14	20
24	98.8	50.8	35.2	0.0	0.0	0.0	0.0	14	20
25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
26	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
27	0.0	0.0	0.0	0.0	0.0	0.0	0.0	15	20
28	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
29	799.3	934.7	604.4	523.4	82.8	44.4	36.0	17	20
30	117.2	56.5	56.7	30.3	0.0	0.0	0.0	16	20
31	47.7	0.0	0.0	0.0	0.0	0.0	0.0	16	20
32	82.3	42.6	0.0	0.0	0.0	0.0	0.0	14	20
33	234.0	70.3	30.5	0.0	0.0	0.0	0.0	14	20
34	88.7	40.7	0.0	0.0	0.0	0.0	0.0	14	20

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
35	39.1	52.2	0.0	0.0	0.0	0.0	0.0	15	20
36	223.6	83.9	37.7	0.0	0.0	0.0	0.0	15	20
37	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
38	39.1	30.4	0.0	0.0	0.0	0.0	0.0	14	20
39	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
40	60.9	43.1	77.2	0.0	0.0	0.0	0.0	14	20
41	79.5	39.4	0.0	0.0	0.0	0.0	0.0	17	20
42	62.3	42.8	35.9	34.5	41.1	62.3	0.0	14	20
43	111.2	42.7	31.9	0.0	0.0	0.0	0.0	14	20
44	40.7	39.0	36.8	0.0	30.5	53.6	0.0	14	20
45	89.7	61.1	0.0	0.0	0.0	0.0	0.0	16	20
46	92.1	41.9	0.0	0.0	0.0	0.0	0.0	15	20
47	68.3	0.0	0.0	0.0	0.0	0.0	0.0	14	20
48	292.2	197.8	55.6	0.0	0.0	0.0	0.0	14	20
49	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
50	111.7	37.2	0.0	0.0	0.0	0.0	0.0	14	20
51	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
52	66.8	32.2	0.0	0.0	0.0	0.0	0.0	14	20
53	41.8	0.0	0.0	0.0	0.0	0.0	0.0	14	20
54	94.5	52.7	0.0	0.0	0.0	0.0	0.0	17	20
55	106.1	54.1	0.0	0.0	0.0	0.0	0.0	14	20
56	52.7	30.1	0.0	0.0	0.0	0.0	0.0	15	20
57	46.1	0.0	0.0	0.0	0.0	0.0	0.0	14	20
58	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
59	35.1	0.0	0.0	0.0	0.0	0.0	0.0	14	20
60	0.0	0.0	0.0	0.0	0.0	41.9	0.0	14	20
61	33.2	0.0	0.0	0.0	0.0	0.0	0.0	14	20
62	201.4	112.3	56.2	30.8	0.0	0.0	0.0	14	20
63	54.4	35.5	0.0	0.0	0.0	0.0	0.0	14	20
64	201.2	92.2	43.0	42.2	0.0	0.0	0.0	15	20
65	175.3	55.4	0.0	0.0	0.0	0.0	0.0	18	22
66	49.8	0.0	0.0	0.0	0.0	0.0	0.0	14	20
67	47.7	0.0	0.0	0.0	0.0	0.0	0.0	14	20
68	58.5	30.9	0.0	0.0	0.0	0.0	0.0	14	20
69	185.1	78.7	0.0	0.0	0.0	0.0	0.0	14	20
70	80.1	104.8	38.1	0.0	0.0	0.0	0.0	14	20
71	146.5	83.3	58.0	57.9	0.0	0.0	0.0	14	20
72	234.5	264.5	66.6	35.5	0.0	0.0	0.0	14	20
73	103.1	70.8	84.9	90.0	85.0	34.7	0.0	14	20
74	297.2	282.7	242.5	107.9	68.3	35.6	0.0	15	20

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
75	143.2	103.8	106.0	145.6	95.3	50.6	0.0	15	20
76	567.5	63.9	41.6	40.9	33.0	42.7	0.0	16	20
77	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
78	48.8	45.4	0.0	0.0	0.0	0.0	0.0	14	20
79	31.7	0.0	30.0	0.0	0.0	0.0	0.0	14	20
80	60.2	29.9	0.0	0.0	0.0	0.0	0.0	14	20
81	44.2	0.0	0.0	0.0	0.0	0.0	0.0	14	20
82	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
83	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
84	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
85	68.8	30.5	0.0	0.0	0.0	0.0	0.0	16	20
86	31.8	0.0	0.0	0.0	0.0	0.0	0.0	14	20
87	437.0	287.6	127.4	49.2	30.1	0.0	0.0	14	20
88	94.1	35.7	0.0	0.0	40.4	0.0	0.0	14	20
89	160.7	79.4	46.0	41.6	0.0	0.0	0.0	14	20
90	356.1	242.6	128.2	75.2	37.4	0.0	0.0	14	20
91	227.9	134.4	141.9	59.7	0.0	0.0	0.0	14	20
92	374.0	135.7	68.4	34.1	41.9	0.0	0.0	14	20
93	0.0	0.0	0.0	0.0	0.0	0.0	0.0	15	20
94	67.6	37.6	0.0	32.0	0.0	0.0	0.0	14	20
95	99.8	49.0	0.0	0.0	0.0	0.0	0.0	15	20
96	46.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
97	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
98	30.9	0.0	0.0	0.0	0.0	0.0	0.0	14	20
99	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
100	34.7	39.6	0.0	0.0	0.0	0.0	0.0	14	20
101	224.4	100.1	47.2	46.5	0.0	0.0	0.0	14	20
102	122.1	85.0	39.3	83.9	77.8	66.8	0.0	14	20
103	147.1	68.3	36.1	0.0	0.0	0.0	0.0	14	20
104	85.2	42.3	0.0	0.0	0.0	0.0	33.2	14	20
105	106.1	45.7	0.0	0.0	0.0	0.0	0.0	14	20
106	90.9	128.1	287.0	67.3	104.0	105.1	0.0	14	20
107	82.8	30.8	0.0	0.0	0.0	0.0	0.0	14	20
108	41.7	0.0	0.0	0.0	0.0	0.0	0.0	16	20
109	29.5	0.0	0.0	0.0	0.0	0.0	0.0	15	20
110	37.9	0.0	0.0	0.0	0.0	0.0	0.0	14	20
111	54.4	33.4	68.6	0.0	0.0	0.0	0.0	16	20
112	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
113	55.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
114	56.0	45.5	31.0	35.6	43.3	0.0	0.0	14	20

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
115	70.5	36.0	0.0	0.0	0.0	0.0	0.0	14	20
116	129.9	82.2	45.3	35.7	0.0	29.5	0.0	14	20
117	264.4	188.8	91.3	146.5	109.7	68.2	0.0	14	20
118	0.0	0.0	0.0	0.0	0.0	33.3	0.0	14	20
119	68.3	0.0	0.0	0.0	0.0	0.0	0.0	15	20
120	93.5	38.3	0.0	0.0	0.0	0.0	0.0	14	20

Niacin

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	2	1	1	1	A	0	322.9	24.4	546.6	125.0	845.0	135.9	22.0	34.1	0.0	0.0	0.0	21.1	0.0
2	2	1	2	1	B	0	20.5	37.2	421.3	630.0	75.7	311.5	191.0	26.5	0.0	0.0	0.0	0.0	0.0
3	2	1	3	1	A	0	0.0	0.0	24.4	32.6	39.1	412.4	313.7	1886.0	784.2	32.9	42.5	35.3	34.4
4	2	1	4	1	B	0	0.0	211.1	289.2	33.0	27.5	32.2	27.3	34.2	26.8	31.5	22.3	25.7	0.0
5	3	1	1	1	A	0	163.8	24.1	0.0	0.0	0.0	0.0	401.1	113.4	0.0	33.9	24.4	0.0	22.6
6	3	1	2	1	B	0	0.0	0.0	0.0	35.2	21.7	77.6	0.0	0.0	0.0	0.0	26.3	0.0	0.0
7	3	1	3	1	A	0	140.4	309.8	153.1	83.7	52.4	27.3	25.3	22.2	0.0	0.0	0.0	0.0	0.0
8	3	1	4	1	B	0	0.0	647.4	351.5	248.8	123.6	26.2	20.9	29.3	31.2	27.1	0.0	20.0	0.0
9	4	2	1	1	B	0	34.0	0.0	30.9	29.9	0.0	20.0	62.0	0.0	0.0	0.0	0.0	0.0	0.0
10	4	2	2	1	A	0	0.0	0.0	0.0	0.0	0.0	0.0	24.2	0.0	225.9	0.0	1385.2	20.4	345.6
11	4	2	3	1	B	0	60.2	89.3	26.2	46.3	0.0	0.0	27.5	82.6	0.0	0.0	0.0	0.0	0.0
12	4	2	4	1	A	0	557.0	159.9	59.0	21.5	24.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
13	5	2	1	1	B	0	0.0	42.5	0.0	27.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	20.3	0.0
14	5	2	2	1	A	0	0.0	864.6	576.7	171.2	25.6	199.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15	5	2	3	1	B	0	0.0	0.0	0.0	0.0	0.0	35.4	20.8	0.0	0.0	35.3	798.2	83.7	27.8
16	5	2	4	1	A	0	0.0	173.5	594.9	55.3	35.3	26.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
17	6	1	1	1	A	0	622.0	2246.6	2611.8	2078.6	1775.9	1253.6	1610.9	1008.2	49.4	0.0	0.0	0.0	0.0
18	6	1	2	1	B	0	750.0	1190.1	1662.4	1088.5	1170.3	1049.2	948.6	257.6	95.9	167.9	0.0	0.0	0.0
19	6	1	3	1	A	0	1088.4	1668.8	1583.4	1314.5	1126.4	763.9	581.6	371.5	88.6	0.0	0.0	0.0	0.0
20	6	1	4	1	B	0	0.0	32.0	872.5	1011.7	752.5	534.3	419.1	603.6	282.0	58.2	140.7	0.0	0.0
21	8	1	1	1	A	0	281.7	536.3	144.7	64.0	30.8	25.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
22	8	1	2	1	B	0	72.8	130.4	0.0	72.2	73.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
23	8	1	3	1	A	0	1562.2	961.4	289.5	59.2	27.9	24.7	30.6	0.0	0.0	22.6	21.2	23.1	24.6
24	8	1	4	1	B	0	170.0	632.4	117.4	35.9	0.0	22.1	0.0	0.0	20.9	20.0	0.0	0.0	0.0
25	10	1	1	1	A	0	0.0	0.0	360.5	422.0	237.4	0.0	0.0	0.0	20.1	0.0	0.0	0.0	0.0

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
26	10	1	2	1	B	0	0.0	71.9	337.4	475.1	173.4	98.1	35.4	33.0	22.7	42.8	23.3	0.0	0.0
27	10	1	3	1	A	0	0.0	310.5	540.2	116.0	133.7	26.2	115.0	37.8	24.3	24.1	29.3	21.2	23.3
28	10	1	4	1	B	0	0.0	44.0	386.4	76.4	20.4	25.7	36.3	0.0	0.0	29.1	0.0	0.0	0.0
29	12	2	1	1	B	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	257.0	184.8	91.5	116.3
30	12	2	2	1	A	0	0.0	85.9	0.0	0.0	0.0	0.0	0.0	159.2	0.0	0.0	898.0	29.8	0.0
31	12	2	3	1	B	0	0.0	0.0	0.0	0.0	274.9	.	24.7	29.3	24.0	24.4	54.0	26.6	30.4
32	12	2	4	1	A	0	0.0	415.8	526.7	83.3	28.4	78.4	29.9	30.0	55.2	23.8	21.9	22.7	0.0
33	13	2	1	1	B	0	0.0	0.0	0.0	25.8	770.1	253.7	676.1	60.3	0.0	113.8	0.0	0.0	0.0
34	13	2	2	1	A	0	71.1	294.2	23.6	30.9	0.0	23.7	117.8	0.0	1020.7	49.6	303.5	37.7	0.0
35	13	2	3	1	B	0	0.0	0.0	0.0	0.0	0.0	69.5	473.9	61.9	205.2	26.3	27.8	21.9	0.0
36	13	2	4	1	A	0	0.0	0.0	0.0	0.0	0.0	366.7	226.7	152.5	54.6	26.3	0.0	0.0	0.0
37	14	1	1	1	A	0	23.9	401.5	872.8	602.6	334.2	48.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
38	14	1	2	1	B	0	0.0	258.2	66.1	0.0	34.0	26.1	56.9	228.0	31.1	0.0	0.0	0.0	0.0
39	14	1	3	1	A	0	0.0	0.0	72.3	763.5	291.5	54.5	24.1	40.0	34.8	30.0	0.0	0.0	0.0
40	14	1	4	1	B	0	112.7	875.6	522.4	83.4	0.0	111.3	248.7	19.9	0.0	0.0	19.8	23.8	0.0
41	15	1	1	1	A	0	0.0	0.0	37.6	439.5	631.4	654.4	567.1	539.6	54.6	34.3	47.2	40.4	0.0
42	15	1	2	1	B	0	0.0	145.3	508.3	240.5	68.4	184.7	81.9	156.9	37.8	0.0	0.0	0.0	0.0
43	15	1	3	1	A	0	0.0	0.0	50.2	452.6	427.7	1573.8	1197.7	354.7	110.5	40.2	39.6	27.5	0.0
44	15	1	4	1	B	0	0.0	132.1	582.9	213.6	72.4	188.5	116.7	206.8	43.2	20.5	0.0	0.0	0.0
45	16	2	1	1	B	0	0.0	309.1	953.4	844.3	565.7	420.8	109.0	65.1	0.0	86.3	52.9	23.9	0.0
46	16	2	2	1	A	0	0.0	41.4	0.0	227.0	866.6	804.4	1063.8	949.0	224.1	105.0	53.5	20.2	0.0
47	16	2	3	1	B	0	0.0	89.3	0.0	789.2	698.3	1717.3	1450.6	687.9	285.5	277.8	65.6	98.4	0.0
48	16	2	4	1	A	0	149.6	75.9	1197.6	310.7	217.7	385.5	1369.1	816.6	408.3	70.1	35.8	46.6	26.1
49	17	1	1	1	A	0	292.9	149.0	0.0	28.7	47.0	993.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
50	17	1	2	1	B	0	0.0	34.2	107.2	56.3	0.0	0.0	0.0	0.0	60.7	0.0	0.0	0.0	0.0
51	17	1	3	1	A	0	306.3	329.9	41.0	0.0	0.0	21.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
52	17	1	4	1	B	0	0.0	0.0	50.0	0.0	0.0	50.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
53	18	2	1	1	B	0	231.7	887.3	1271.9	1533.4	1257.7	0.0	549.0	174.9	221.6	21.9	0.0	53.2	0.0
54	18	2	2	1	A	0	34.4	357.5	88.7	220.0	119.6	780.6	1280.0	357.9	86.7	0.0	411.3	29.5	0.0
55	18	2	3	1	B	0	28.5	0.0	545.0	25.7	272.4	528.7	466.5	1085.2	211.7	85.5	33.0	34.8	25.5
56	18	2	4	1	A	0	36.6	445.3	279.3	175.0	558.4	501.1	339.1	96.0	147.0	634.0	32.4	0.0	0.0
57	19	1	1	1	A	0	0.0	0.0	0.0	54.0	0.0	0.0	40.4	71.7	21.9	22.5	0.0	0.0	0.0
58	19	1	2	1	B	0	0.0	46.9	185.3	234.7	106.0	21.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
59	19	1	3	1	A	0	0.0	492.4	33.2	66.9	71.1	36.4	26.9	27.2	23.1	26.4	27.4	30.4	24.9
60	19	1	4	1	B	0	65.9	100.5	29.7	61.1	34.9	35.2	37.2	25.9	23.6	24.1	0.0	0.0	0.0
61	20	2	1	1	B	0	0.0	133.7	52.4	83.8	97.3	58.7	51.1	29.1	26.7	35.4	34.8	24.2	0.0
62	20	2	2	1	A	0	0.0	0.0	0.0	0.0	20.2	58.9	0.0	0.0	71.2	0.0	83.8	0.0	0.0
63	20	2	3	1	B	0	0.0	0.0	0.0	0.0	0.0	0.0	917.2	1494.2	69.6	42.8	58.3	33.0	38.7
64	20	2	4	1	A	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	38.5	25.7	0.0	23.8	41.0
65	21	1	1	1	A	0	42.0	0.0	0.0	0.0	95.0	32.0	32.5	0.0	20.2	0.0	0.0	0.0	28.7

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
66	21	1	2	1	B	0	0.0	0.0	0.0	62.7	0.0	111.3	58.7	38.6	185.3	0.0	74.3	0.0	0.0
67	21	1	3	1	A	0	0.0	0.0	0.0	0.0	30.2	24.9	59.8	96.7	1771.5	110.7	44.1	36.2	33.0
68	21	1	4	1	B	0	0.0	0.0	29.7	33.4	247.0	40.8	32.9	43.3	42.2	34.7	25.7	66.8	20.4
69	22	2	1	1	B	0	0.0	110.5	0.0	0.0	0.0	240.0	23.2	0.0	25.8	0.0	0.0	0.0	0.0
70	22	2	2	1	A	0	47.8	59.8	0.0	0.0	67.5	0.0	0.0	103.6	56.4	27.3	0.0	43.6	0.0
71	22	2	3	1	B	0	0.0	0.0	36.3	0.0	20.1	214.5	75.6	60.2	97.7	61.7	29.9	49.7	21.7
72	22	2	4	1	A	0	0.0	127.9	25.3	89.4	38.8	20.9	0.0	22.3	0.0	0.0	0.0	0.0	0.0
73	23	1	1	1	A	0	167.1	1546.7	1435.6	1354.0	1239.2	884.2	601.7	384.8	204.4	0.0	0.0	0.0	0.0
74	23	1	2	1	B	0	0.0	151.9	98.1	300.7	699.8	868.5	741.2	412.8	309.6	786.0	165.5	0.0	0.0
75	23	1	3	1	A	0	299.7	523.1	554.3	508.1	915.1	1191.7	1107.4	682.2	1208.3	544.4	61.3	24.6	20.7
76	23	1	4	1	B	0	0.0	355.5	467.3	292.6	556.5	943.3	655.9	420.8	68.3	22.1	32.2	30.3	0.0
77	24	2	1	1	B	0	0.0	0.0	233.1	1143.4	823.6	429.1	284.6	133.3	0.0	0.0	0.0	0.0	0.0
78	24	2	2	1	A	0	872.2	1278.7	1200.7	1156.2	863.6	462.2	114.6	0.0	0.0	0.0	0.0	0.0	0.0
79	24	2	3	1	B	0	0.0	0.0	0.0	264.2	926.5	357.0	288.1	572.7	244.3	0.0	21.7	22.6	20.6
80	24	2	4	1	A	0	0.0	0.0	35.9	163.0	352.9	116.1	0.0	75.0	31.2	21.7	350.1	21.5	0.0
81	26	2	1	1	B	0	0.0	0.0	145.4	559.5	567.4	176.5	32.6	0.0	275.0	21.6	0.0	0.0	0.0
82	26	2	2	1	A	0	1454.9	1004.5	557.7	355.7	34.5	27.5	24.0	0.0	0.0	0.0	0.0	0.0	0.0
83	26	2	3	1	B	0	0.0	104.2	462.8	675.2	713.3	821.8	626.6	254.3	53.0	27.6	30.4	24.8	24.1
84	26	2	4	1	A	0	25.1	733.5	309.9	268.2	19.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
85	27	2	1	1	B	0	0.0	0.0	0.0	0.0	0.0	238.4	0.0	0.0	32.3	190.4	28.7	24.9	0.0
86	27	2	2	1	A	0	0.0	0.0	0.0	168.4	409.1	570.0	337.6	188.0	41.1	23.7	0.0	0.0	0.0
87	27	2	3	1	B	0	0.0	0.0	0.0	0.0	95.3	0.0	0.0	0.0	64.3	22.3	26.9	58.9	25.1
88	27	2	4	1	A	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	91.4	24.8	0.0	425.6	21.6	27.3
89	28	1	1	1	A	0	82.9	596.3	517.5	1432.5	1137.2	522.2	358.3	132.1	63.6	24.9	0.0	20.6	0.0
90	28	1	2	1	B	0	0.0	0.0	0.0	359.6	703.4	122.7	0.0	695.5	1943.7	940.1	0.0	387.0	27.1
91	28	1	3	1	A	0	0.0	0.0	0.0	561.2	1167.8	709.5	1003.1	1146.7	918.8	417.8	73.8	0.0	0.0
92	28	1	4	1	B	0	0.0	141.3	185.5	845.9	972.8	540.1	135.3	264.0	190.6	22.1	0.0	30.6	451.6
93	29	1	1	1	A	0	536.7	435.1	128.7	26.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
94	29	1	2	1	B	0	0.0	0.0	0.0	37.6	0.0	0.0	0.0	73.4	459.1	23.0	0.0	0.0	0.0
95	29	1	3	1	A	0	0.0	0.0	0.0	0.0	50.4	0.0	921.5	521.6	29.6	61.0	28.4	20.9	20.1
96	29	1	4	1	B	0	0.0	0.0	0.0	0.0	0.0	56.6	52.9	65.4	20.8	21.2	0.0	20.7	0.0
97	31	1	1	1	A	0	0.0	0.0	27.3	0.0	0.0	0.0	24.5	30.9	20.7	0.0	0.0	0.0	0.0
98	31	1	2	1	B	0	0.0	0.0	0.0	0.0	32.8	0.0	0.0	0.0	369.3	0.0	275.5	0.0	0.0
99	31	1	3	1	A	0	0.0	253.1	28.1	0.0	23.8	0.0	0.0	0.0	20.0	0.0	0.0	0.0	0.0
100	31	1	4	1	B	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	328.5	44.3	22.3	0.0	0.0	0.0
101	32	2	1	1	B	0	0.0	23.1	164.5	213.4	481.3	227.8	333.7	369.8	134.5	140.8	28.9	64.6	217.4
102	32	2	2	1	A	0	104.5	265.4	81.8	20.2	134.1	156.8	326.3	171.4	326.9	235.6	0.0	61.6	35.4
103	32	2	3	1	B	0	0.0	52.4	0.0	112.5	83.3	1192.0	815.5	132.2	102.4	60.7	191.3	159.8	129.3
104	32	2	4	1	A	0	32.9	297.7	396.7	56.2	253.6	1195.9	0.0	607.3	103.7	92.3	20.1	29.2	65.1
105	33	2	1	1	B	0	0.0	0.0	0.0	96.1	111.0	320.2	117.8	0.0	157.1	67.8	21.3	0.0	0.0

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
106	33	2	2	1	A	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	338.6	0.0	0.0	32.2
107	33	2	3	1	B	0	0.0	0.0	0.0	0.0	180.0	340.4	619.9	179.4	74.2	21.8	0.0	47.3	0.0
108	33	2	4	1	A	0	0.0	222.5	0.0	0.0	0.0	0.0	0.0	524.6	103.6	152.8	356.6	0.0	0.0
109	34	2	1	1	B	0	236.2	795.5	605.7	174.9	246.7	76.7	77.1	114.7	73.8	124.7	38.0	0.0	0.0
110	34	2	2	1	A	0	175.1	220.6	94.8	0.0	0.0	133.3	25.3	441.4	119.5	68.1	0.0	22.4	0.0
111	34	2	3	1	B	0	255.7	589.0	485.1	503.5	237.8	192.1	48.0	289.3	21.5	34.2	43.6	0.0	27.4
112	34	2	4	1	A	0	67.3	700.6	356.7	344.0	114.6	118.6	38.4	33.1	85.5	0.0	0.0	0.0	0.0
113	35	1	1	1	A	0	524.3	306.6	198.4	89.3	0.0	621.3	44.1	0.0	1120.1	120.6	49.2	112.2	0.0
114	35	1	2	1	B	0	391.0	632.3	753.1	801.3	292.3	214.4	261.7	151.5	34.3	0.0	0.0	65.0	0.0
115	35	1	3	1	A	0	185.3	115.9	399.6	209.5	32.0	151.4	756.4	549.0	94.9	29.9	0.0	55.6	0.0
116	35	1	4	1	B	0	0.0	141.5	537.6	463.1	157.6	0.0	843.6	1530.8	649.4	298.8	111.5	86.5	0.0
117	36	1	1	1	A	0	65.2	100.5	27.3	0.0	58.0	139.6	98.8	131.9	49.7	34.1	27.2	20.7	0.0
118	36	1	2	1	B	0	534.9	1151.1	866.5	869.7	584.9	301.3	36.6	27.0	0.0	0.0	24.4	0.0	0.0
119	36	1	3	1	A	0	81.0	146.5	0.0	0.0	166.9	1084.2	158.5	49.3	41.1	0.0	48.9	130.3	0.0
120	36	1	4	1	B	0	0.0	39.1	270.9	0.0	0.0	26.6	58.8	45.1	120.5	23.1	24.7	0.0	34.0

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	14
2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	14
3	20.6	19.9	0.0	20.8	0.0	0.0	0.0	14	21
4	0.0	0.0	0.0	0.0	0.0	23.8	0.0	8	14
5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	18
6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	11
7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	14
8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	14
9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	11
10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16	19
11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	10
12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	10
13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	10
14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	12
15	0.0	0.0	0.0	19.9	20.7	0.0	0.0	16	19
16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	12
17	0.0	0.0	86.6	0.0	0.0	0.0	0.0	12	16
18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	14
19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	13
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	12
21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	12
22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	12
23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	12

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	10
25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	12
26	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	13
27	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
28	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	13
29	69.6	29.7	20.4	0.0	0.0	0.0	0.0	18	22
30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16	19
31	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16	19
32	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	19
33	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	14
34	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	18
35	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	18
36	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	16
37	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	12
38	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	16
39	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	12
40	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	10
41	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	15
42	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	12
43	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	15
44	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	17
45	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	13
46	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	18
47	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	16
48	25.6	21.0	0.0	0.0	0.0	0.0	0.0	12	16
49	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	9
50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	10
51	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8	10
52	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	13
53	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	18
54	0.0	24.2	0.0	0.0	0.0	0.0	0.0	12	15
55	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	17
56	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	13
57	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	16
58	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	17
59	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	19
60	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	16
61	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10	18
62	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16	19
63	0.0	0.0	0.0	0.0	21.4	0.0	0.0	13	19

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
64	21.5	0.0	0.0	21.8	0.0	0.0	0.0	14	20
65	23.3	0.0	0.0	0.0	0.0	0.0	0.0	10	15
66	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	18
67	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	20
68	0.0	0.0	0.0	0.0	0.0	0.0	0.0	17	21
69	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	14
70	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	16
71	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	16
72	0.0	22.7	0.0	0.0	0.0	0.0	0.0	9	12
73	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	15
74	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	14
75	0.0	0.0	0.0	20.1	0.0	0.0	0.0	14	19
76	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	18
77	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	14
78	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	13
79	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	19
80	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	16
81	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	13
82	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	13
83	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	19
84	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	11
85	0.0	0.0	0.0	0.0	0.0	0.0	0.0	15	19
86	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	16
87	25.9	54.9	0.0	19.9	0.0	0.0	0.0	17	22
88	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16	20
89	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	16
90	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	16
91	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	18
92	24.9	0.0	0.0	0.0	0.0	0.0	0.0	9	12
93	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	10
94	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	17
95	0.0	0.0	0.0	0.0	0.0	0.0	22.7	12	19
96	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	19
97	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	16
98	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16	18
99	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	12
100	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	17
101	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	17
102	0.0	0.0	0.0	0.0	0.0	47.4	0.0	14	19
103	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	15

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
104	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	19
105	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	18
106	0.0	21.3	66.1	0.0	0.0	0.0	0.0	15	22
107	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	16
108	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	15
109	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	9
110	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	12
111	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	12
112	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7	13
113	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6	10
114	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	15
115	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	16
116	0.0	0.0	0.0	0.0	0.0	0.0	0.0	13	18
117	0.0	86.5	0.0	0.0	0.0	0.0	0.0	11	18
118	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9	14
119	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11	15
120	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14	19

4.6.1 Fasting Study Data and Study Output

Nicotinuric Acid

```
                                        LAUCT                          08:19 Friday,
September 10, 2010  30

                                The Mixed Procedure

                                Model Information

Data Set                        WORK.REPL
Dependent Variable              lauct
Covariance Structures           Factor Analytic, Variance
                                Components
Subject Effects                 subj, subj
Group Effect                    trt
Estimation Method               REML
Residual Variance Method        None
Fixed Effects SE Method         Model-Based
Degrees of Freedom Method       Satterthwaite

                            Class Level Information

  Class     Levels    Values

  SEQ            2    1 2
  subj          30    2 3 4 5 6 8 10 12 13 14 15 16
                      17 18 19 20 21 22 23 24 26 27
                      28 29 31 32 33 34 35 36
  PER            4    1 2 3 4
  trt            2    A B
```

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	30
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	119
Number of Observations Used	119
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	175.33361780	
1	3	150.65240554	0.01052572
2	3	150.32859047	0.00207373
3	1	150.27281020	0.00001596
4	1	150.27234984	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	2	0.1229	0.04092
2	trt	B	2	0.04092	0.01362

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.3506
FA(2,1)	subj		0.1167
FA(2,2)	subj		0
Residual	subj	trt A	0.05258
Residual	subj	trt B	0.2736

Fit Statistics

-2 Res Log Likelihood	150.3
AIC (smaller is better)	158.3
AICC (smaller is better)	158.6
BIC (smaller is better)	163.9

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	25.06	<.0001

Type 3 Tests of Fixed Effects

Num	Den

Effect	DF	DF	F Value	Pr > F
SEQ	1	29.9	0.12	0.7308
PER	3	52.8	0.13	0.9429
trt	1	38.4	0.09	0.7679

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.02550	0.08580	38.4	-0.30	0.7679	0.1	-0.1701	0.1191

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	7.5787	0.07068	28	107.22	<.0001
trt	B	7.6042	0.07146	47.8	106.42	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauct
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	30	2 3 4 5 6 8 10 12 13 14 15 16 17 18 19 20 21 22 23 24 26 27 28 29 31 32 33 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	30
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	119
Number of Observations Used	119
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	175.33361780	
1	3	150.65240554	0.01052572
2	3	150.32859047	0.00207373
3	1	150.27281020	0.00001596
4	1	150.27234984	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	2	0.1229	0.04092
2	trt	B	2	0.04092	0.01362

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.3506
FA(2,1)	subj		0.1167
FA(2,2)	subj		0
Residual	subj	trt A	0.05258
Residual	subj	trt B	0.2736

Fit Statistics

-2 Res Log Likelihood	150.3
AIC (smaller is better)	158.3
AICC (smaller is better)	158.6
BIC (smaller is better)	163.9

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	25.06	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	29.9	0.12	0.7308
PER	3	52.8	0.13	0.9429
trt	1	38.4	0.09	0.7679

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.02550	0.08580	38.4	-0.30	0.7679	0.1	-0.1701	0.1191

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	7.5787	0.07068	28	107.22	<.0001
trt	B	7.6042	0.07146	47.8	106.42	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lcmax
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	30	2 3 4 5 6 8 10 12 13 14 15 16 17 18 19 20 21 22 23 24 26 27 28 29 31 32 33 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	30
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	119
Number of Observations Used	119
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	118.75120858	
1	2	56.18139077	0.00000984
2	1	56.18063884	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	2	0.1116	0.08978
2	trt	B	2	0.08978	0.07407

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.3341
FA(2,1)	subj		0.2687
FA(2,2)	subj		0.04331
Residual	subj	trt A	0.05955
Residual	subj	trt B	0.03601

Fit Statistics

-2 Res Log Likelihood	56.2
AIC (smaller is better)	66.2
AICC (smaller is better)	66.7
BIC (smaller is better)	73.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	62.57	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	28	0.03	0.8748
PER	3	64.2	0.21	0.8879
trt	1	27.8	3.60	0.0681

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.08094	0.04264	27.8	1.90	0.0681	0.1	0.008387	0.1535

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	6.6264	0.06881	28	96.30	<.0001
trt	B	6.5455	0.05563	28.2	117.65	<.0001

200484 FAST FIRM TO REVIEWER RATIO

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	2	1	1	1	1	1449.58	1553.49	707.0	A	1695.13	1790.32	707.0	1.16939	1.15245	1
2	2	1	3	1	1	1308.00	1389.79	737.4	A	1838.23	1882.97	737.4	1.40537	1.35486	1
3	2	1	2	1	2	1838.23	1895.78	577.8	B	1449.58	1501.75	577.8	0.78857	0.79216	1
4	2	1	4	1	2	4376.64	4547.74	555.7	B	1308.00	1661.69	555.7	0.29886	0.36539	1
5	3	1	1	1	1	3296.38	3366.31	1184.3	A	4376.64	4434.92	1184.3	1.32771	1.31744	1
6	3	1	3	1	1	3191.64	3386.73	904.0	A	2450.01	2536.60	904.0	0.76763	0.74898	1
7	3	1	2	1	2	2450.01	2505.99	787.6	B	3296.38	3370.11	787.6	1.34545	1.34482	1
8	3	1	4	1	2	2837.20	2975.70	980.7	B	3191.64	3412.69	980.7	1.12492	1.14685	1
9	4	2	2	1	1	1628.75	1726.35	1758.7	A	8473.64	8603.97	1758.7	5.20254	4.98390	1
10	4	2	4	1	1	1537.03	1600.37	796.5	A	2642.08	2703.31	796.5	1.71895	1.68918	1
11	4	2	1	1	2	8473.64	8625.04	873.2	B	2837.20	2949.37	873.2	0.33483	0.34195	1
12	4	2	3	1	2	2642.08	2689.75	759.2	B	1628.75	1688.10	759.2	0.61647	0.62760	1
13	5	2	2	1	1	1838.68	1871.76	887.1	A	1280.48	1330.44	887.1	0.69641	0.71079	1
14	5	2	4	1	1	1644.16	1700.66	524.4	A	1118.64	1185.63	524.4	0.68037	0.69716	1
15	5	2	1	1	2	1280.48	1357.33	531.7	B	1537.03	1603.03	531.7	1.20036	1.18101	1
16	5	2	3	1	2	1118.64	1258.33	489.5	B	1838.68	1928.60	489.5	1.64367	1.53267	1
17	6	1	1	1	1	1914.60	1970.83	770.3	A	1644.16	1703.72	770.3	0.85875	0.86447	1
18	6	1	3	1	1	1966.25	2115.05	732.3	A	1893.13	2032.12	732.3	0.96281	0.96079	1
19	6	1	2	1	2	1893.13	1950.66	620.3	B	1914.60	1956.37	620.3	1.01134	1.00293	1
20	6	1	4	1	2	1899.89	1945.17	609.6	B	1966.25	2030.76	609.6	1.03493	1.04400	1
21	8	1	1	1	1	1172.00	1227.31	677.2	A	1899.89	1946.47	677.2	1.62106	1.58596	1
22	8	1	3	1	1	1894.14	1958.99	703.8	A	1710.80	1820.78	703.8	0.90321	0.92945	1
23	8	1	2	1	2	1710.80	1828.57	514.6	B	1172.00	1261.95	514.6	0.68506	0.69013	1
24	8	1	4	1	2	684.29	786.42	569.8	B	1894.14	1962.35	569.8	2.76804	2.49530	1
25	10	1	1	1	1	891.26	961.64	366.5	A	684.29	775.20	366.5	0.76777	0.80612	1
26	10	1	3	1	1	788.49	826.12	371.4	A	944.59	987.29	371.4	1.19797	1.19509	1
27	10	1	2	1	2	944.59	981.00	388.1	B	891.26	928.78	388.1	0.94355	0.94677	1
28	10	1	4	1	2	6320.01	6358.43	384.5	B	788.49	825.73	384.5	0.12476	0.12986	1
29	12	2	2	1	1	1783.55	1852.29	1500.1	A	3224.06	3267.73	1500.1	1.80767	1.76415	1
30	12	2	4	1	1	2403.23	2444.33	926.9	A	2505.16	2562.57	926.9	1.04242	1.04837	1
31	12	2	1	1	2	3224.06	3315.83	1009.5	B	6320.01	6429.02	1009.5	1.96026	1.93889	1
32	12	2	3	1	2	2505.16	2561.67	591.5	B	1783.55	1846.82	591.5	0.71195	0.72094	1
33	13	2	2	1	1	1633.56	1690.57	923.0	A	2314.33	2358.77	923.0	1.41673	1.39525	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
34	13	2	4	1	1	2103.81	2171.11	587.2	A	2254.65	2297.01	587.2	1.07170	1.05799	1
35	13	2	1	1	2	2314.33	2358.87	708.9	B	2403.23	2436.61	708.9	1.03841	1.03296	1
36	13	2	3	1	2	2254.65	2323.82	603.7	B	1633.56	1729.35	603.7	0.72453	0.74418	1
37	14	1	1	1	1	1929.16	1966.39	1155.5	A	2103.81	2177.17	1155.5	1.09053	1.10719	1
38	14	1	3	1	1	2496.11	2573.34	762.7	A	1583.06	1631.98	762.7	0.63421	0.63419	1
39	14	1	2	1	2	1583.06	1649.36	684.6	B	1929.16	1970.38	684.6	1.21863	1.19463	1
40	14	1	4	1	2	2683.09	2775.42	870.4	B	2496.11	2677.05	870.4	0.93031	0.96456	1
41	15	1	1	1	1	2117.03	2192.22	1284.1	A	2683.09	2730.64	1284.1	1.26739	1.24561	1
42	15	1	3	1	1	1940.66	2018.94	1086.6	A	2850.44	2897.03	1086.6	1.46880	1.43492	1
43	15	1	2	1	2	2850.44	2959.42	686.4	B	2117.03	2329.84	686.4	0.74270	0.78726	1
44	15	1	4	1	2	3196.83	3397.68	636.9	B	1940.66	2116.84	636.9	0.60706	0.62303	1
45	16	2	2	1	1	2859.74	2930.69	778.2	A	2325.95	2369.48	778.2	0.81334	0.80850	1
46	16	2	4	1	1	1388.16	1462.42	1133.3	A	4275.86	4351.76	1133.3	3.08023	2.97573	1
47	16	2	1	1	2	2325.95	2371.96	860.0	B	3196.83	3263.92	860.0	1.37442	1.37604	1
48	16	2	3	1	2	4275.86	4326.50	1151.1	B	2859.74	2921.94	1151.1	0.66881	0.67536	1
49	17	1	1	1	1	1906.00	1962.79	872.3	A	1388.16	1471.22	872.3	0.72831	0.74955	1
50	17	1	3	1	1	1639.39	1683.04	638.3	A	1089.61	1134.62	638.3	0.66465	0.67415	1
51	17	1	2	1	2	1089.61	1164.35	719.4	B	1906.00	1989.75	719.4	1.74925	1.70888	1
52	17	1	4	1	2	2218.75	2278.49	557.1	B	1639.39	1685.41	557.1	0.73888	0.73970	1
53	18	2	2	1	1	2162.44	2238.61	918.7	A	2668.49	2742.70	918.7	1.23402	1.22518	1
54	18	2	4	1	1	1764.06	1824.17	767.2	A	2270.01	2309.26	767.2	1.28681	1.26592	1
55	18	2	1	1	2	2668.49	2746.40	895.9	B	2218.75	2280.55	895.9	0.83146	0.83038	1
56	18	2	3	1	2	2270.01	2318.84	809.6	B	2162.44	2250.21	809.6	0.95261	0.97040	1
57	19	1	1	1	1	1462.18	1527.40	756.2	A	1764.06	1831.33	756.2	1.20646	1.19899	1
58	19	1	3	1	1	1428.88	1475.53	551.0	A	1716.61	1755.69	551.0	1.20137	1.18987	1
59	19	1	2	1	2	1716.61	1759.26	759.8	B	1462.18	1516.49	759.8	0.85178	0.86200	1
60	19	1	4	1	2	1463.81	1590.29	589.7	B	1428.88	1588.52	589.7	0.97613	0.99889	1
61	20	2	2	1	1	2140.60	2196.72	486.3	A	2146.28	2194.97	486.3	1.00265	0.99920	1
62	20	2	4	1	1	1824.80	1903.42	661.4	A	1732.58	1792.46	661.4	0.94946	0.94171	1
63	20	2	1	1	2	2146.28	2203.24	574.8	B	1463.81	1525.22	574.8	0.68202	0.69226	1
64	20	2	3	1	2	1732.58	1785.32	1098.8	B	2140.60	2184.97	1098.8	1.23550	1.22385	1
65	21	1	1	1	1	1447.51	1497.70	546.7	A	1824.80	1880.63	546.7	1.26065	1.25568	1
66	21	1	3	1	1	1676.96	1708.91	844.5	A	2005.55	2054.87	844.5	1.19594	1.20244	1
67	21	1	2	1	2	2005.55	2065.25	485.3	B	1447.51	1509.84	485.3	0.72175	0.73107	1
68	21	1	4	1	2	2050.53	2151.97	609.8	B	1676.96	1716.79	609.8	0.81782	0.79778	1
69	22	2	2	1	1	3276.81	3380.09	866.5	A	2804.74	2872.70	866.5	0.85593	0.84989	1
70	22	2	4	1	1	4029.12	4063.68	1558.1	A	2624.38	2659.73	1558.1	0.65135	0.65451	1
71	22	2	1	1	2	2804.74	2900.80	720.1	B	2050.53	2248.97	720.1	0.73109	0.77529	1
72	22	2	3	1	2	2624.38	2706.91	882.2	B	3276.81	3411.45	882.2	1.24861	1.26027	1
73	23	1	1	1	1	5824.03	5929.88	1487.8	A	4029.13	4132.31	1487.8	0.69181	0.69686	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
74	23	1	3	1	1	3662.11	3785.10	1532.1	A	5430.28	5576.02	1532.1	1.48283	1.47315	1
75	23	1	2	1	2	5430.27	5569.52	1376.8	B	5824.03	5922.00	1376.8	1.07251	1.06329	1
76	23	1	4	1	2	914.11	1033.61	1174.7	B	3662.11	3773.29	1174.7	4.00620	3.65059	1
77	24	2	2	1	1	1105.20	1167.75	505.7	A	1140.63	1235.29	505.7	1.03205	1.05783	1
78	24	2	4	1	1	1874.78	1928.26	391.4	A	1417.26	1453.44	391.4	0.75596	0.75376	1
79	24	2	1	1	2	1140.63	1220.64	412.5	B	914.11	995.01	412.5	0.80141	0.81516	1
80	24	2	3	1	2	1417.26	1478.46	422.5	B	1105.20	1166.61	422.5	0.77981	0.78907	1
81	26	2	2	1	1	1829.56	1900.59	618.9	A	1124.90	1165.21	618.9	0.61485	0.61308	1
82	26	2	4	1	1	1435.31	1475.05	733.7	A	1060.25	1130.21	733.7	0.73869	0.76622	1
83	26	2	1	1	2	1124.90	1183.05	764.5	B	1874.78	1937.16	764.5	1.66661	1.63743	1
84	26	2	3	1	2	1060.25	1111.32	744.5	B	1829.56	1898.61	744.5	1.72559	1.70842	1
85	27	2	2	1	1	2055.31	2095.33	569.2	A	1241.96	1284.24	569.2	0.60427	0.61291	1
86	27	2	4	1	1	3948.19	4063.33	377.8	A	1310.80	1422.60	377.8	0.33200	0.35011	1
87	27	2	1	1	2	1241.96	1279.65	581.1	B	1435.31	1471.46	581.1	1.15568	1.14989	1
88	27	2	3	1	2	1310.80	1367.57	437.0	B	2055.31	2097.61	437.0	1.56798	1.53382	1
89	28	1	1	1	1	4843.31	4921.31	1241.1	A	3948.19	4034.95	1241.1	0.81518	0.81989	1
90	28	1	3	1	1	3551.80	3633.70	1533.0	A	5174.89	5291.57	1533.0	1.45698	1.45625	1
91	28	1	2	1	2	5174.89	5272.07	1443.1	B	4843.31	4904.20	1443.1	0.93593	0.93022	1
92	28	1	4	1	2	1550.69	1634.69	841.4	B	3551.80	3620.41	841.4	2.29047	2.21474	1
93	29	1	1	1	1	2052.55	2094.68	837.7	A	1550.69	1618.23	837.7	0.75549	0.77254	1
94	29	1	3	1	1	1724.30	1781.96	1046.0	A	2908.88	2970.30	1046.0	1.68699	1.66687	1
95	29	1	2	1	2	2908.88	3007.19	1232.5	B	2052.55	2116.75	1232.5	0.70562	0.70390	1
96	29	1	4	1	2	778.78	865.39	884.2	B	1724.30	1789.40	884.2	2.21412	2.06775	1
97	31	1	1	1	1	798.61	855.16	301.0	A	778.78	890.78	301.0	0.97516	1.04165	1
98	31	1	3	1	1	873.34	938.31	326.4	A	516.15	596.38	326.4	0.59101	0.63559	1
99	31	1	2	1	2	516.15	584.97	417.3	B	798.61	842.10	417.3	1.54725	1.43956	1
100	31	1	4	1	2	2646.28	2727.40	501.2	B	873.34	942.43	501.2	0.33003	0.34554	1
101	32	2	2	1	1	2198.70	2673.70	552.4	A	2421.15	3299.99	552.4	1.10117	1.23424	1
102	32	2	4	1	1	1699.91	1973.89	835.1	A	1766.08	1965.07	835.1	1.03892	0.99553	1
103	32	2	1	1	2	2421.15	2524.05	625.8	B	2646.28	2717.90	625.8	1.09298	1.07680	1
104	32	2	3	1	2	1766.08	1813.34	648.1	B	2198.70	2250.09	648.1	1.24496	1.24086	1
105	33	2	2	1	1	1764.75	1986.33	424.1	A	2247.69	3003.87	424.1	1.27366	1.51227	1
106	33	2	4	1	1	2869.25	2898.85	703.6	A	1522.13	1563.96	703.6	0.53050	0.53951	1
107	33	2	1	1	2	2247.69	2361.94	437.7	B	1699.91	1749.59	437.7	0.75629	0.74074	1
108	33	2	3	1	2	1522.13	1566.73	591.6	B	1764.75	1797.70	591.6	1.15940	1.14742	1
109	34	2	2	1	1	2831.96	2897.18	720.5	A	1800.13	1836.15	720.5	0.63565	0.63377	1
110	34	2	4	1	1	2016.00	2081.81	863.9	A	1665.41	1709.33	863.9	0.82610	0.82108	1
111	34	2	1	1	2	1800.13	1831.70	1037.9	B	2869.25	2893.83	1037.9	1.59392	1.57986	1
112	34	2	3	1	2	1665.41	1731.95	1154.9	B	2831.96	2956.33	1154.9	1.70046	1.70694	1
113	35	1	1	1	1	1919.41	1963.39	644.8	A	2016.00	2071.87	644.8	1.05032	1.05525	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
114	35	1	3	1	1	3238.54	3274.99	782.0	A	2422.00	2466.49	782.0	0.74787	0.75313	1
115	35	1	2	1	2	2422.00	2517.54	644.7	B	1919.41	2034.33	644.7	0.79249	0.80806	1
116	35	1	4	1	2	3214.58	3371.46	951.2	B	3238.54	3306.40	951.2	1.00745	0.98070	1
117	36	1	1	1	1	1763.73	1895.66	726.8	A	3214.58	3484.78	726.8	1.82261	1.83829	1
118	36	1	3	1	1	1721.79	1765.10	625.3	A	1750.14	1827.38	625.3	1.01647	1.03528	1
119	36	1	2	1	2	1750.14	1976.22	844.5	B	1763.73	1873.95	844.5	1.00776	0.94825	1
120	36	1	4	1	.	.	.	.	B	1721.79	1761.63	446.2	.	.	.

Niacin (Fasting Study)

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	2	1	1	1	1	523.51	547.10	845.0	A	523.51	547.10	845.0	1.00000	1.00000	1
2	2	1	3	1	1	1454.38	1600.65	1886.0	A	1454.38	1600.65	1886.0	1.00000	1.00000	1
3	2	1	2	1	2	425.11	430.49	630.0	B	425.11	430.49	630.0	1.00000	1.00000	1
4	2	1	4	1	2	251.28	1207.10	289.2	B	251.28	1208.85	289.2	1.00000	1.00145	1
5	3	1	1	1	1	230.23	258.59	401.1	A	230.23	258.59	401.1	1.00000	0.99999	1
6	3	1	3	1	1	200.78	254.45	309.8	A	200.78	254.45	309.8	1.00000	1.00000	1
7	3	1	2	1	2	40.20	.	77.6	B	40.20	.	77.6	1.00000	.	1
8	3	1	4	1	2	399.74	466.96	647.4	B	399.74	466.96	647.4	1.00000	1.00000	1
9	4	2	2	1	1	999.70	1887.90	1385.2	A	999.70	1887.96	1385.2	1.00000	1.00003	1
10	4	2	4	1	1	202.35	209.58	557.0	A	202.35	209.58	557.0	1.00000	1.00000	1
11	4	2	1	1	2	36.45	.	62.0	B	36.45	.	62.0	1.00000	.	1
12	4	2	3	1	2	72.70	5203.13	89.3	B	72.70	5194.85	89.3	1.00000	0.99841	1
13	5	2	2	1	1	434.41	516.66	864.6	A	434.41	516.66	864.6	1.00000	1.00000	1
14	5	2	4	1	1	218.09	236.42	594.9	A	218.09	236.42	594.9	1.00000	1.00000	1
15	5	2	1	1	2	22.48	141.12	42.5	B	22.48	141.15	42.5	1.00000	1.00019	1
16	5	2	3	1	2	551.63	865.26	798.2	B	551.63	865.22	798.2	1.00000	0.99995	1
17	6	1	1	1	1	3495.93	3683.09	2611.8	A	3495.93	3683.09	2611.8	1.00000	1.00000	1
18	6	1	3	1	1	2193.21	2227.82	1668.8	A	2193.21	2227.82	1668.8	1.00000	1.00000	1
19	6	1	2	1	2	2151.30	2283.79	1662.4	B	2151.30	2283.79	1662.4	1.00000	1.00000	1
20	6	1	4	1	2	1337.15	1482.73	1011.7	B	1337.15	1482.73	1011.7	1.00000	1.00000	1
21	8	1	1	1	1	267.55	275.85	536.3	A	267.55	275.85	536.3	1.00000	1.00000	1
22	8	1	3	1	1	790.40	824.89	1562.2	A	790.40	824.89	1562.2	1.00000	1.00000	1
23	8	1	2	1	2	78.09	168.44	130.4	B	78.09	168.44	130.4	1.00001	0.99998	1
24	8	1	4	1	2	259.90	567.59	632.4	B	259.90	567.45	632.4	1.00000	0.99975	1
25	10	1	1	1	1	260.00	269.99	422.0	A	260.00	269.99	422.0	1.00000	1.00000	1
26	10	1	3	1	1	390.98	431.45	540.2	A	390.98	431.45	540.2	1.00000	1.00000	1
27	10	1	2	1	2	348.78	372.55	475.1	B	348.78	372.55	475.1	1.00000	1.00000	1
28	10	1	4	1	2	154.58	192.85	386.4	B	154.58	192.85	386.4	1.00000	0.99999	1
29	12	2	2	1	1	537.63	.	898.0	A	537.63	.	898.0	1.00000	.	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
30	12	2	4	1	1	358.00	399.29	526.7	A	358.00	399.29	526.7	1.00000	1.00000	1
31	12	2	1	1	2	515.33	548.91	257.0	B	515.33	548.91	257.0	1.00000	1.00000	1
32	12	2	3	1	2	209.69	319.59	274.9	B	209.69	319.60	274.9	1.00000	1.00003	1
33	13	2	2	1	1	836.65	859.97	1020.7	A	836.65	859.97	1020.7	1.00000	1.00000	1
34	13	2	4	1	1	239.41	254.18	366.7	A	239.41	254.18	366.7	1.00000	1.00000	1
35	13	2	1	1	2	482.49	592.12	770.1	B	482.49	592.12	770.1	1.00000	1.00000	1
36	13	2	3	1	2	294.19	312.81	473.9	B	294.19	312.81	473.9	1.00000	1.00000	1
37	14	1	1	1	1	564.83	574.48	872.8	A	564.83	574.48	872.8	1.00000	1.00000	1
38	14	1	3	1	1	341.37	445.65	763.5	A	341.38	445.66	763.5	1.00000	1.00002	1
39	14	1	2	1	2	203.60	270.32	258.2	B	203.60	270.32	258.2	1.00000	1.00000	1
40	14	1	4	1	2	511.84	536.81	875.6	B	511.84	536.81	875.6	1.00000	1.00000	1
41	15	1	1	1	1	863.00	893.73	654.4	A	863.00	893.73	654.4	1.00000	1.00000	1
42	15	1	3	1	1	1160.54	1176.63	1573.8	A	1160.54	1176.63	1573.8	1.00000	1.00000	1
43	15	1	2	1	2	375.56	409.41	508.3	B	375.56	409.41	508.3	1.00000	1.00000	1
44	15	1	4	1	2	430.83	439.69	582.9	B	430.83	439.69	582.9	1.00000	1.00000	1
45	16	2	2	1	1	1303.03	1315.82	1063.8	A	1303.03	1315.82	1063.8	1.00000	1.00000	1
46	16	2	4	1	1	1587.00	1668.18	1369.1	A	1587.00	1668.17	1369.1	1.00000	1.00000	1
47	16	2	1	1	2	900.56	919.18	953.4	B	900.56	919.18	953.4	1.00000	1.00000	1
48	16	2	3	1	2	1783.19	1859.79	1717.3	B	1783.19	1859.79	1717.3	1.00000	1.00000	1
49	17	1	1	1	1	253.60	.	993.6	A	253.60	.	993.6	1.00000	.	1
50	17	1	3	1	1	172.01	181.49	329.9	A	172.01	181.49	329.9	1.00000	1.00000	1
51	17	1	2	1	2	64.60	377.33	107.2	B	64.60	377.28	107.2	1.00000	0.99988	1
52	17	1	4	1	2	18.80	.	50.4	B	18.80	.	50.4	1.00000	.	1
53	18	2	2	1	1	1137.64	1176.51	1280.0	A	1137.64	1176.51	1280.0	1.00000	1.00000	1
54	18	2	4	1	1	1018.30	.	634.0	A	1018.30	.	634.0	1.00000	.	1
55	18	2	1	1	2	1633.39	1673.19	1533.4	B	1633.39	1673.19	1533.4	1.00000	1.00000	1
56	18	2	3	1	2	1077.60	1099.10	1085.2	B	1077.60	1099.10	1085.2	1.00000	1.00000	1
57	19	1	1	1	1	67.06	86.48	71.7	A	67.06	86.48	71.7	0.99999	1.00000	1
58	19	1	3	1	1	265.62	393.25	492.4	A	265.63	393.26	492.4	1.00000	1.00002	1
59	19	1	2	1	2	145.95	150.54	234.7	B	145.95	150.54	234.7	1.00000	1.00000	1
60	19	1	4	1	2	118.66	178.20	100.5	B	118.66	178.20	100.5	1.00000	0.99999	1
61	20	2	2	1	1	76.33	.	83.8	A	76.33	.	83.8	1.00000	.	1
62	20	2	4	1	1	123.35	304.41	41.0	A	123.35	304.40	41.0	1.00000	0.99996	1
63	20	2	1	1	2	184.66	244.92	133.7	B	184.66	244.92	133.7	1.00000	0.99999	1
64	20	2	3	1	2	949.13	1111.99	1494.2	B	949.13	1111.99	1494.2	1.00000	1.00001	1
65	21	1	1	1	1	100.83	264.56	95.0	A	100.83	264.60	95.0	1.00000	1.00014	1
66	21	1	3	1	1	1071.79	1256.25	1771.5	A	1071.79	1256.24	1771.5	1.00000	0.99999	1
67	21	1	2	1	2	183.88	.	185.3	B	183.88	.	185.3	1.00000	.	1
68	21	1	4	1	2	223.79	291.05	247.0	B	223.79	291.06	247.0	1.00000	1.00003	1
69	22	2	2	1	1	135.38	239.91	103.6	A	135.38	239.91	103.6	1.00000	1.00003	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
70	22	2	4	1	1	95.29	251.19	127.9	A	95.29	251.15	127.9	0.99999	0.99981	1
71	22	2	1	1	2	99.88	115.21	240.0	B	99.88	115.21	240.0	1.00000	1.00000	1
72	22	2	3	1	2	251.98	292.48	214.5	B	251.98	292.47	214.5	1.00000	0.99999	1
73	23	1	1	1	1	2002.53	2141.75	1546.7	A	2002.53	2141.75	1546.7	1.00000	1.00000	1
74	23	1	3	1	1	2486.88	2526.12	1208.3	A	2486.88	2526.12	1208.3	1.00000	1.00000	1
75	23	1	2	1	2	1459.03	1751.79	868.5	B	1459.03	1751.77	868.5	1.00000	0.99999	1
76	23	1	4	1	2	1044.45	1063.79	943.3	B	1044.45	1063.79	943.3	1.00000	1.00000	1
77	24	2	2	1	1	1472.73	1501.10	1278.7	A	1472.73	1501.10	1278.7	1.00000	1.00000	1
78	24	2	4	1	1	401.98	442.65	352.9	A	401.98	442.65	352.9	1.00000	1.00000	1
79	24	2	1	1	2	745.11	801.85	1143.4	B	745.11	801.85	1143.4	1.00000	1.00000	1
80	24	2	3	1	2	833.96	852.60	926.5	B	833.96	852.60	926.5	1.00000	1.00000	1
81	26	2	2	1	1	861.70	894.77	1454.9	A	861.70	894.77	1454.9	1.00000	1.00000	1
82	26	2	4	1	1	336.66	341.20	733.5	A	336.66	341.20	733.5	1.00000	1.00000	1
83	26	2	1	1	2	513.25	532.93	567.4	B	513.25	532.93	567.4	1.00000	1.00000	1
84	26	2	3	1	2	1032.49	1054.92	821.8	B	1032.49	1054.92	821.8	1.00000	1.00000	1
85	27	2	2	1	1	468.25	478.83	570.0	A	468.25	478.83	570.0	1.00000	1.00000	1
86	27	2	4	1	1	289.33	307.10	425.6	A	289.33	307.10	425.6	1.00000	1.00000	1
87	27	2	1	1	2	191.53	203.77	238.4	B	191.53	203.77	238.4	1.00000	1.00000	1
88	27	2	3	1	2	240.60	399.67	95.3	B	240.60	399.62	95.3	1.00000	0.99986	1
89	28	1	1	1	1	1260.66	1273.75	1432.5	A	1260.66	1273.75	1432.5	1.00000	1.00000	1
90	28	1	3	1	1	1977.16	2006.43	1167.8	A	1977.16	2006.43	1167.8	1.00000	1.00000	1
91	28	1	2	1	2	2302.94	2319.52	1943.7	B	2302.94	2319.52	1943.7	1.00000	1.00000	1
92	28	1	4	1	2	1397.58	1449.93	972.8	B	1397.58	1449.93	972.8	1.00000	1.00000	1
93	29	1	1	1	1	278.38	282.99	536.7	A	278.38	282.99	536.7	1.00000	1.00000	1
94	29	1	3	1	1	579.25	737.22	921.5	A	579.25	737.18	921.5	1.00000	0.99995	1
95	29	1	2	1	2	272.23	.	459.1	B	272.23	.	459.1	1.00000	.	1
96	29	1	4	1	2	78.08	123.11	65.4	B	78.08	123.11	65.4	1.00000	0.99998	1
97	31	1	1	1	1	29.71	.	30.9	A	29.71	.	30.9	0.99998	.	1
98	31	1	3	1	1	81.25	190.12	253.1	A	81.25	190.12	253.1	1.00000	0.99999	1
99	31	1	2	1	2	261.73	.	369.3	B	261.73	.	369.3	1.00000	.	1
100	31	1	4	1	2	150.91	159.20	328.5	B	150.91	159.20	328.5	1.00000	1.00000	1
101	32	2	2	1	1	746.80	1050.06	326.9	A	746.80	1050.02	326.9	1.00000	0.99996	1
102	32	2	4	1	1	948.49	1015.18	1195.9	A	948.49	1015.18	1195.9	1.00000	1.00000	1
103	32	2	1	1	2	808.88	1343.03	481.3	B	808.88	1342.98	481.3	1.00000	0.99996	1
104	32	2	3	1	2	975.20	1484.05	1192.0	B	975.20	1484.08	1192.0	1.00000	1.00002	1
105	33	2	2	1	1	255.85	437.44	338.6	A	255.85	437.45	338.6	1.00000	1.00002	1
106	33	2	4	1	1	469.70	2786.79	524.6	A	469.70	2786.88	524.6	1.00000	1.00003	1
107	33	2	1	1	2	279.05	289.71	320.2	B	279.05	289.71	320.2	1.00000	1.00000	1
108	33	2	3	1	2	412.18	455.16	619.9	B	412.18	455.16	619.9	1.00000	1.00000	1
109	34	2	2	1	1	427.20	447.28	441.4	A	427.20	447.28	441.4	1.00000	1.00000	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
110	34	2	4	1	1	468.84	531.36	700.6	A	468.84	531.36	700.6	1.00000	1.00000	1
111	34	2	1	1	2	704.96	752.73	795.5	B	704.96	752.73	795.5	1.00000	1.00000	1
112	34	2	3	1	2	749.64	784.74	589.0	B	749.64	784.74	589.0	1.00000	1.00000	1
113	35	1	1	1	1	1119.00	1190.93	1120.1	A	1119.00	1190.93	1120.1	1.00000	1.00000	1
114	35	1	3	1	1	744.70	787.73	756.4	A	744.70	787.73	756.4	1.00000	1.00000	1
115	35	1	2	1	2	926.74	1007.93	801.3	B	926.74	1007.92	801.3	1.00000	1.00000	1
116	35	1	4	1	2	1661.38	1718.97	1530.8	B	1661.38	1718.97	1530.8	1.00000	1.00000	1
117	36	1	1	1	1	286.09	1032.42	139.6	A	286.09	1032.62	139.6	1.00000	1.00019	1
118	36	1	3	1	1	505.34	746.77	1084.2	A	505.34	746.75	1084.2	1.00000	0.99997	1
119	36	1	2	1	2	1102.48	1118.35	1151.1	B	1102.48	1118.35	1151.1	1.00000	1.00000	1
120	36	1	4	1	2	216.91	311.44	270.9	B	216.91	311.43	270.9	1.00000	0.99999	1

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauct
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	30	2 3 4 5 6 8 10 12 13 14 15 16 17 18 19 20 21 22 23 24 26 27 28 29 31 32 33 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	30
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	119
Number of Observations Used	119

Number of Observations Not Used 0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	356.99879780	
1	2	346.51098859	0.00000002
2	1	346.51098738	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	2	0.5235	0.2273
2	trt	B	2	0.2273	0.1635

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.7235
FA(2,1)	subj		0.3141
FA(2,2)	subj		0.2546
Residual	subj	trt A	0.8631
Residual	subj	trt B	0.7604

Fit Statistics

-2 Res Log Likelihood	346.5
AIC (smaller is better)	356.5
AICC (smaller is better)	357.1
BIC (smaller is better)	363.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	10.49	0.0330

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	28.1	0.51	0.4810
PER	3	67.4	2.28	0.0873
trt	1	28.2	0.52	0.4785

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.1347	0.1876	28.2	-0.72	0.4785	0.1	-0.4537	0.1843

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	5.9300	0.1788	28	33.16	<.0001
trt	B	6.0647	0.1357	28.3	44.68	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauci
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	30	2 3 4 5 6 8 10 12 13 14 15 16 17 18 19 20 21 22 23 24 26 27 28 29 31 32 33 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	30
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	119
Number of Observations Used	108
Number of Observations Not Used	11

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	293.00253851	
1	2	278.60479922	0.00159601

2	1	278.52593160	0.00003553
3	1	278.52428400	0.00000003
4	1	278.52428266	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	2	0.3487	0.1869
2	trt	B	2	0.1869	0.2513

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.5905
FA(2,1)	subj		0.3165
FA(2,2)	subj		0.3887
Residual	subj	trt A	0.7882
Residual	subj	trt B	0.3300

Fit Statistics

-2 Res Log Likelihood	278.5
AIC (smaller is better)	288.5
AICC (smaller is better)	289.1
BIC (smaller is better)	295.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	14.48	0.0059

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	26.7	1.39	0.2485
PER	3	51.1	1.81	0.1573
trt	1	25.5	0.17	0.6828

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.07002	0.1694	25.5	-0.41	0.6828	0.1	-0.3592	0.2191

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	6.2898	0.1626	27	38.69	<.0001
trt	B	6.3598	0.1220	24.7	52.15	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lcmax
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	30	2 3 4 5 6 8 10 12 13 14 15 16 17 18 19 20 21 22 23 24 26 27 28 29 31 32 33 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	30
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	119
Number of Observations Used	119
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	334.88239011	
1	2	316.70026152	0.00000001

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	2	0.4466	0.2525
2	trt	B	2	0.2525	0.4429

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.6683
FA(2,1)	subj		0.3779
FA(2,2)	subj		0.5478
Residual	subj	trt A	0.4593
Residual	subj	trt B	0.5586

Fit Statistics

-2 Res Log Likelihood	316.7
AIC (smaller is better)	326.7
AICC (smaller is better)	327.3
BIC (smaller is better)	333.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	18.18	0.0011

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	28.1	0.06	0.8016
PER	3	66.5	3.26	0.0269
trt	1	27.6	3.00	0.0946

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.3003	0.1735	27.6	1.73	0.0946	0.1	0.005013	0.5957

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	6.3452	0.1505	28	42.17	<.0001
trt	B	6.0449	0.1561	28	38.72	<.0001

4.6.2 Fed Study Data and Study Output

Nicotinuric Acid

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	1	2	1	1	B	0	0.0	45.5	288.2	431 0	451 8	389.4	193.0	195.8	198 6	157 9	442.4	979.0	376.1
2	1	2	2	1	A	0	0.0	0.0	184.7	427 3	612 8	265.4	321.7	321.7	285 0	229 6	1324.7	454.1	236.1
3	1	2	3	1	B	0	0.0	93.3	954.7	836.1	429.4	216.3	656.6	335.6	493 0	1036 0	1940.6	1122.2	696.5
4	1	2	4	1	A	0	0.0	35.6	89.5	667 0	563 5	963.2	1763.9	998.7	794 3	1389.1	2213.0	1295.7	717.2
5	2	1	1	1	A	0	0.0	139.9	116.9	1388 5	1244.7	655.5	1146.7	3442.9	2487 0	3479.4	2905.6	1623.5	1089.2
6	2	1	2	1	B	0	0.0	112.3	187.9	126.7	862 6	3360.2	1584.8	1170.7	1466.7	1368.4	1785.4	860.8	534.8
7	2	1	3	1	A	0	0.0	160.8	908.8	1034 5	1255 0	1257.9	1255.3	1335.1	1265 6	1828.1	2018.0	1096.7	645.6
8	2	1	4	1	B	0	0.0	764.2	1210.1	2431 8	1854 2	2532.9	2696.8	1308.6	1930 6	1149 0	2512.0	1014.3	485.1
9	3	1	1	1	A	0	0.0	52.8	408.7	522 6	759.7	478.1	687.0	1938.8	1448.1	2263 9	2617.7	1078.7	753.2
10	3	1	2	1	B	0	0.0	0.0	307.9	1095 3	973 6	579.8	383.2	540.3	1658.7	1826 0	3763.8	2744.3	1324.2
11	3	1	3	1	A	0	0.0	0.0	429.1	1454 0	1606 2	1016.0	591.8	515.6	755.1	1711 0	1905.1	2389.4	1035.3
12	3	1	4	1	B	0	125.5	563.7	868.7	604.7	1368 5	1165.5	1154.6	1851.9	1853 9	2316 3	2844.7	1687.2	910.7
13	4	2	1	1	B	0	0.0	0.0	1945.6	3526.7	3673.7	2847.7	1536.1	1411.8	1403 6	1830 5	3126.0	1859.8	1817.3
14	4	2	2	1	A	0	33.5	352.9	549.7	1518.4	1452 5	1611.0	3798.7	2877.4	1955 8	1329 9	927.3	710.3	472.6
15	4	2	3	1	B	0	0.0	0.0	353.4	1851 8	3154 9	3926.7	3198.6	3712.5	3651 2	2783 2	2620.0	1560.9	1424.5
16	4	2	4	1	A	0	0.0	187.2	571.0	1278.4	2862.1	3757.4	4234.6	4478.9	4100 3	2367 6	1411.3	898.5	726.2
17	5	2	1	1	B	0	0.0	42.4	863.7	727 5	466.7	552.0	413.0	442.6	548.7	1828 6	1941.2	1549.5	991.5
18	5	2	2	1	A	0	56.2	713.3	912.2	949 0	1164 2	1571.9	1497.6	1879.5	2080 8	1960 6	1431.6	1127.9	848.0
19	5	2	3	1	B	0	0.0	109.4	465.1	826.7	1200 5	1170.4	1508.1	1688.4	2462 6	1705 2	1410.3	1161.9	884.7
20	5	2	4	1	A	0	0.0	0.0	90.5	79 5	58 5	77.3	126.5	932.4	709 2	1285 9	1173.0	738.2	418.4
21	6	1	1	1	A	0	0.0	0.0	390.2	1253 0	1777 6	912.0	503.4	391.7	1344.7	1495 6	1080.2	485.8	242.4
22	6	1	2	1	B	0	0.0	29.6	36.4	777 9	1222 2	761.3	2069.8	1814.6	1228.7	1583 2	3351.6	1963.7	876.8
23	6	1	3	1	A	0	0.0	39.8	108.0	79.4	49.4	453.4	1141.8	1369.1	878 5	2173 8	2870.1	1760.5	734.5
24	6	1	4	1	B	0	0.0	0.0	916.4	997.1	1059 6	1315.3	1323.9	1262.8	1349 3	1592 0	1787.1	893.6	424.5
25	7	1	1	1	A	0	0.0	104.1	112.9	107 6	135 9	695.8	511.0	544.0	606 9	960.1	1725.3	677.5	525.1
26	7	1	2	1	B	0	0.0	0.0	239.0	694 8	495 8	238.3	374.4	1788.6	1676 2	2311 3	1304.1	1003.0	494.4
27	7	1	3	1	A	0	0.0	0.0	232.9	942.4	629.1	443.7	595.8	730.7	627 5	749 0	1177.8	1645.7	890.9
28	7	1	4	1	B	0	0.0	550.9	550.1	951 0	803 9	614.6	426.2	417.7	646.1	878 9	1141.1	978.8	537.1
29	8	2	1	1	B	0	0.0	335.8	540.8	1915.7	1761 0	1245.7	736.4	494.1	296 5	213 8	201.9	148.7	89.1
30	8	2	2	1	A	0	0.0	52.0	281.4	1706 6	599 0	1253.5	702.8	501.6	220.1	172 0	144.9	87.6	74.8
31	8	2	3	1	B	0	59.9	280.6	563.8	690 3	548 3	502.9	299.9	506.6	956.1	522 5	1378.8	977.3	656.5
32	8	2	4	1	A	0	0.0	0.0	296.4	789 2	318.1	583.0	521.9	911.5	872.7	541.1	498.0	367.5	195.6
33	9	2	1	1	B	0	0.0	0.0	0.0	745 3	832.4	3347.5	2515.5	2883.0	2493.1	1947.4	1233.2	680.0	367.5
34	9	2	2	1	A	0	0.0	0.0	0.0	347 8	1398 6	2800.5	1752.8	2396.7	1960 5	924 2	3113.2	1795.3	882.7
35	9	2	3	1	B	0	0.0	0.0	128.4	1442 3	2706 3	2361.3	1871.6	923.9	4403 6	2450 6	2503.4	1519.0	1115.7
36	9	2	4	1	A	0	0.0	0.0	227.9	457 5	1591 2	1930.6	3656.6	4835.7	3490.4	2246 5	1744.2	933.6	522.2
37	10	1	1	1	A	0	0.0	0.0	0.0	0 0	0 0	57.8	1414.0	1571.0	1858.4	1581 5	2693.2	1432.9	710.4

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
38	10	1	2	1	B	0	0.0	0.0	0.0	37 0	245.4	472.2	579.3	690.8	464 8	720 3	2789.8	1099.5	567.1
39	10	1	3	1	A	0	0.0	0.0	0.0	31.4	381.4	429.3	492.9	511.0	949 3	1504 5	2538.0	2660.2	1253.7
40	10	1	4	1	B	0	0.0	0.0	0.0	0 0	170.4	1475.1	1308.7	1454.6	2909 0	2521 2	3705.7	1786.2	963.3
41	11	1	1	1	A	0	47.8	1449.1	1629.2	1225.7	1883.4	2885.3	4504.2	2261.5	1233.1	749 8	481.6	273.2	234.8
42	11	1	2	1	B	0	142.5	805.9	1153.4	1958 2	2544 5	3351.2	1994.4	1156.5	712 0	384 6	336.9	229.0	154.0
43	11	1	3	1	A	0	46.7	1030.5	1978.9	3590 2	3163 8	2832.6	548.6	2802.3	1275 3	695.7	527.6	340.0	239.1
44	11	1	4	1	B	0	103.9	1005.4	1690.8	2680.7	2997 2	2012.4	2979.0	1949.9	1547 8	1183.4	817.1	579.4	379.9
45	12	2	1	1	B	0	0.0	0.0	0.0	294 5	1708.1	2386.8	2799.3	2481.3	4110 3	4862 8	2653.9	1919.5	1640.4
46	12	2	2	1	A	0	0.0	0.0	33.8	341 5	479 8	667.2	1725.1	2394.4	2919.4	2237 6	4419.4	2363.9	2185.7
47	12	2	3	1	B	0	0.0	0.0	379.0	910 3	1812 0	1773.6	1691.9	2096.5	2638 5	3079 2	2601.3	1206.7	965.1
48	12	2	4	1	A	0	0.0	31.0	269.9	694 8	1231 0	1519.4	2186.4	2670.0	3716 9	2711.4	1853.1	1677.3	1094.7
49	13	1	1	1	A	0	275.1	1171.5	1674.6	1488 9	1380 9	1414.4	1276.5	1416.3	1877 8	1762.4	4596.8	2413.6	1208.9
50	13	1	2	1	B	0	0.0	601.1	652.6	848 3	1095 3	1454.9	1646.5	3965.0	3177.4	3944 3	3157.4	2121.6	1591.4
51	13	1	3	1	A	0	37.9	1411.2	2937.3	2994 3	3746 9	2959.2	3254.2	4213.0	4185.7	3132 0	3399.5	1484.2	1091.5
52	13	1	4	1	B	0	0.0	1264.1	1858.9	2443 2	2012 8	1748.9	1764.5	1617.9	1754 6	2943.4	2897.4	2725.3	2551.1
53	14	2	1	1	B	0	0.0	0.0	0.0	0 0	0 0	1360.0	646.6	558.7	732.4	818.1	713.2	356.8	221.8
54	14	2	2	1	A	0	0.0	0.0	0.0	105 9	87 3	326.7	739.8	1064.7	518 2	1019 9	689.5	344.7	194.4
55	14	2	3	1	B	0	0.0	0.0	0.0	57 5	358 8	756.9	3745.6	938.4	731 2	548 9	659.3	284.2	149.8
56	14	2	4	1	A	0	0.0	0.0	66.4	37 3	0 0	50.4	461.2	670.5	1488 3	2450 9	1570.2	811.0	388.6
57	15	2	1	1	B	0	0.0	0.0	301.9	1866 2	977 9	591.7	1279.2	1264.1	2268.4	1425 5	1771.3	718.9	362.6
58	15	2	2	1	A	0	0.0	0.0	0.0	0 0	0 0	255.2	384.8	386.7	832 6	949 2	3051.8	2246.1	973.3
59	15	2	3	1	B	0	0.0	0.0	0.0	0 0	138 3	508.9	1275.0	1893.0	1543 0	3249 5	3243.6	1053.3	549.5
60	15	2	4	1	A	0	0.0	0.0	49.7	78.1	39 6	191.3	628.8	1272.3	1081 8	3484.7	2892.5	898.2	421.0
61	16	1	1	1	A	0	0.0	0.0	71.2	93 2	184 6	491.5	791.8	867.6	850 0	862.4	826.9	569.1	372.9
62	16	1	2	1	B	0	0.0	0.0	33.4	184 5	611 6	917.5	771.0	906.6	790 3	1234.4	1106.8	646.0	437.2
63	16	1	3	1	A	0	0.0	0.0	150.0	519.4	338.1	198.1	962.7	249.8	364 5	555.7	918.9	420.3	259.7
64	16	1	4	1	B	0	0.0	0.0	217.7	126 8	350.7	232.6	647.9	640.8	1246 6	1123.7	1074.4	538.6	279.7
65	18	1	1	1	A	0	0.0	64.7	383.5	292 0	1088 9	786.6	1001.1	410.2	391 9	217 5	1872.0	1923.8	1318.0
66	18	1	2	1	B	0	0.0	78.2	321.0	773.4	1023.1	465.2	421.5	1052.1	1547 6	1293.7	2358.4	2890.1	1942.2
67	18	1	3	1	A	0	70.2	90.5	63.0	132 2	484 8	1126.0	3348.4	685.9	834 6	382 3	2245.1	1570.8	1063.2
68	18	1	4	1	B	0	0.0	68.5	187.7	82 0	245.1	429.1	638.8	835.8	320 9	238 6	711.0	1490.7	1851.7
69	19	1	1	1	A	0	0.0	0.0	323.9	379.7	1087 2	1302.9	2161.9	1691.8	2547 0	3549 6	2694.8	1039.2	1367.6
70	19	1	2	1	B	0	0.0	0.0	0.0	0 0	146 8	394.0	607.8	674.9	885.7	1222 0	2363.3	2310.1	1073.8
71	19	1	3	1	A	0	0.0	0.0	0.0	44.4	70 0	236.1	615.1	1413.1	1844 5	2159 5	2494.3	2645.9	1399.8
72	19	1	4	1	B	0	0.0	0.0	74.1	1090 0	1630.4	1869.4	1999.6	2401.6	2753 3	2670 5	2467.9	1678.8	1784.9
73	20	2	1	1	B	0	0.0	167.3	127.6	813 2	3683.4	4641.6	5778.7	4805.7	3619.1	3000 6	4542.4	3537.2	1912.5
74	20	2	2	1	A	0	0.0	0.0	1196.3	800.7	2492 2	3767.1	4081.7	6101.8	6138 8	5409.1	5343.1	4345.6	2345.2
75	20	2	3	1	B	0	0.0	628.1	3416.7	3442 3	5790 2	5058.7	2697.8	4354.4	4094.4	4657 3	5252.5	4998.2	3034.0
76	20	2	4	1	A	0	0.0	301.1	1455.9	3457 0	5216 2	6341.9	6057.4	6032.3	5131 8	7292 3	7541.3	3534.8	1813.5
77	21	1	1	1	A	0	0.0	0.0	0.0	987 9	1893.1	684.5	1012.5	1380.6	720.1	434 6	1371.5	861.2	484.5
78	21	1	2	1	B	0	0.0	0.0	108.3	1009 9	1388.1	725.3	1521.9	1861.7	3035 5	2735 3	3064.9	1422.1	1041.0
79	21	1	3	1	A	0	0.0	422.6	821.5	421.1	3092.1	3963.1	4930.4	5159.4	4872 8	2850 9	1770.5	1529.0	973.2
80	21	1	4	1	B	0	0.0	0.0	103.1	1230.4	2596 8	4706.4	6045.5	6863.7	5125 8	3645 5	3271.5	1857.7	1326.1
81	22	2	1	1	B	0	0.0	0.0	1287.0	1409.4	2470 3	1614.3	3299.6	3624.7	3238.1	1718 0	1271.5	623.9	310.0
82	22	2	2	1	A	0	0.0	0.0	152.7	891 9	3174 6	3459.0	2869.6	2218.8	2772.1	1787.1	2377.8	1074.8	703.4
83	22	2	3	1	B	0	0.0	0.0	1182.8	1829 2	4069 0	3975.3	2890.1	2834.2	2774 2	2036.7	1271.1	860.9	485.2
84	22	2	4	1	A	0	129.1	111.6	1463.6	2493 2	2314 3	1155.1	1240.8	1804.4	2404 6	2763 0	2377.8	1900.9	1248.4

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
85	23	1	1	1	A	0	0.0	0.0	531.5	1312 0	1531 6	1305.5	849.5	1141.1	897 5	1433.4	1399.7	722.3	1016.0
86	23	1	2	1	B	0	0.0	0.0	89.7	803 0	535.7	311.3	365.3	659.4	1092 5	1313.7	1957.8	1295.0	548.9
87	23	1	3	1	A	0	0.0	0.0	554.0	1329 3	714.1	416.2	574.6	736.6	864 6	1075.4	1237.3	1488.2	886.7
88	23	1	4	1	B	0	0.0	0.0	0.0	294.1	610.4	681.0	605.6	898.5	1241.1	1139 3	1487.7	1260.5	613.9
89	26	2	1	1	B	0	0.0	0.0	0.0	474 0	1396.7	2881.8	2885.7	3397.4	5332 6	3939.4	4392.3	1871.6	1171.9
90	26	2	2	1	A	0	0.0	51.6	303.7	2745 8	4858.4	4430.4	2220.0	2327.9	5038 8	3309 9	5526.8	3604.6	2066.1
91	26	2	3	1	B	0	0.0	0.0	302.0	427.7	2677 0	1797.0	3396.2	4604.9	3993 9	4488 2	4150.3	1537.9	1618.3
92	26	2	4	1	A	0	30.5	878.8	1937.6	2193.1	2065.4	3436.4	4268.0	4551.5	5254 9	3590 6	3605.0	2237.3	1103.6
93	27	1	1	1	A	0	0.0	0.0	0.0	0 0	0 0	151.8	243.2	143.6	3084 9	4171.1	5568.4	6760.2	4051.3
94	27	1	2	1	B	0	0.0	0.0	448.4	490 0	1185.7	5248.4	6850.3	5447.6	7866.7	8418 9	8076.3	8346.4	6481.8
95	27	1	3	1	A	0	146.6	279.7	428.4	2092 2	1448.4	3104.2	4710.1	4384.4	2061.4	1698.7	4768.6	6445.1	7560.2
96	27	1	4	1	B	0	0.0	35.1	0.0	1345 0	1395 0	2179.7	3713.7	5380.3	4325 6	3618 0	4521.6	5468.1	6848.8
97	28	2	1	1	B	0	65.1	276.4	392.8	561 2	883.1	655.5	430.4	631.5	1188 0	1599 9	1925.5	943.3	373.4
98	28	2	2	1	A	0	56.1	496.0	277.7	521 2	400 0	489.8	627.4	1544.2	1585 3	1301.7	1919.5	1753.3	1607.8
99	28	2	3	1	B	0	0.0	0.0	160.2	540.1	727 2	605.0	1778.3	2217.2	1951 2	3523 6	2841.0	1461.3	801.5
100	28	2	4	1	A	0	0.0	0.0	42.3	238.7	264.7	567.0	371.3	655.8	1106 6	2850.1	1932.7	874.5	311.2
101	29	1	1	1	A	0	0.0	0.0	87.1	221 8	295.4	652.1	702.9	802.1	1218 8	2539 3	2430.7	1075.7	639.8
102	29	1	2	1	B	0	0.0	0.0	164.7	71 0	35.7	161.5	256.2	875.5	605 9	747 8	1257.0	1128.3	793.8
103	29	1	3	1	A	0	0.0	201.0	563.8	306 2	265 0	578.7	1032.6	825.8	1253 2	2233 9	1575.5	947.4	516.4
104	29	1	4	1	B	0	0.0	0.0	416.7	569.1	1074.1	831.1	757.9	2715.4	1896 3	1287 0	1063.3	665.7	355.7
105	30	2	1	1	B	0	0.0	179.5	470.3	1401 5	1969 5	1817.5	4007.0	4071.2	3456 5	5373 3	1420.9	1824.3	1872.9
106	30	2	2	1	A	0	0.0	1119.9	2240.2	1830.1	911 8	565.0	614.4	801.5	2766.7	5135 6	3868.5	2558.5	1593.7
107	30	2	3	1	B	0	0.0	376.1	1292.9	1851 5	1345 9	1250.1	2991.5	1522.1	3213 3	2729 9	4011.6	2422.1	1757.3
108	30	2	4	1	A	0	389.8	1763.8	2087.3	2902.4	2071 5	2458.9	1815.2	3309.5	4172 3	2940.7	2570.9	1750.6	876.7
109	31	1	1	1	A	0	0.0	232.4	1352.8	2273 6	2613 2	3389.4	2098.2	2890.5	2387 6	2403.7	2404.2	1353.7	671.9
110	31	1	2	1	B	0	0.0	1485.9	2110.6	2123 8	2777 6	2702.0	2550.3	3103.2	1894.1	1253 2	1145.8	626.8	402.0
111	31	1	3	1	A	0	0.0	1702.8	2596.8	2040.4	1651 8	2191.6	2095.2	2486.3	1525 9	1261 2	1348.4	1311.8	570.5
112	31	1	4	1	B	0	100.4	1916.6	1784.2	2637 8	2436 3	1206.8	1194.5	2520.1	2192 5	2076 2	1769.9	1090.7	506.4
113	32	2	1	1	B	0	0.0	372.6	654.2	1315 0	2966 3	2141.4	1867.3	2394.8	1480.4	1685 3	2282.5	1749.5	969.4
114	32	2	2	1	A	0	0.0	299.5	942.9	1363 2	1415 5	2022.0	2735.3	1576.0	2494 9	1274 0	1232.4	1877.9	1115.9
115	32	2	3	1	B	0	0.0	1252.0	1158.7	1127 6	754.1	837.2	905.3	642.9	795 0	709 8	1346.1	804.5	884.6
116	32	2	4	1	A	0	104.2	555.5	971.3	1242 8	1360.7	1429.1	1466.8	1058.6	1210 2	923 6	923.0	999.7	728.0
117	34	1	1	1	A	0	0.0	82.5	42.0	204.7	566 6	233.0	159.2	375.8	634.4	1707 2	1438.8	822.8	516.9
118	34	1	2	1	B	0	0.0	0.0	90.9	293 8	719.7	684.6	669.3	1139.0	1343.1	1456.7	2230.9	1626.0	1073.2
119	34	1	3	1	A	0	0.0	206.8	163.8	504 5	369 2	221.3	564.8	1679.6	1812.7	1519 9	1751.7	1126.2	308.3
120	34	1	4	1	B	0	0.0	77.7	46.5	164 9	194.1	251.9	199.2	534.8	1006 0	2143 8	2023.1	1242.0	515.1
121	35	2	1	1	B	0	0.0	0.0	110.1	421 6	965 9	3218.9	5270.7	3819.0	5145.7	4707 5	6410.2	6509.8	4611.4
122	35	2	2	1	A	0	0.0	0.0	0.0	61 5	542 2	940.0	979.5	4320.8	4099 9	5249.7	6211.1	5866.4	5851.2
123	35	2	3	1	B	0	1020. 6	3326.3	5349.2	5535.4	5196 0	5428.2	5126.2	5152.2	5028 5	4582 3	5220.9	3774.8	2498.8
124	35	2	4	1	A	0	0.0	193.7	441.7	1057.4	968.4	2451.6	4125.0	6270.1	5555 3	7438 0	6708.0	6351.6	3658.2
125	36	2	1	1	B	0	0.0	0.0	31.7	60.7	169 0	351.9	1781.2	2692.1	2171 3	2995 2	2162.6	1730.1	1921.6
126	36	2	2	1	A	0	0.0	67.9	147.8	547 6	1317 3	1762.9	1122.9	1482.6	1340 0	2001 9	2356.2	933.2	517.6
127	36	2	3	1	B	0	0.0	298.7	1400.8	1492 6	2063 8	3491.8	3368.8	5440.2	4860 6	5235 5	3873.5	1298.1	875.9
128	36	2	4	1	A	0	0.0	213.3	242.9	262 3	1040 6	554.6	533.7	385.2	3384 2	1845 8	1167.0	1308.1	1120.1

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
1	230.5	410.3	422.0	127.4	55.4	87.6	105.0	21	25
2	131.3	80.3	70.8	326.5	76.2	113.8	42.7	16	21
3	415.8	311.4	199.4	123.7	65.5	33.4	0.0	16	20
4	369.1	238.3	171.5	101.7	61.9	0.0	0.0	16	21
5	796.0	463.8	511.8	648.7	278.1	80.8	0.0	15	21
6	300.3	253.3	217.5	104.2	180.3	146.9	104.5	16	21
7	421.7	255.9	175.2	201.7	122.9	133.9	39.6	18	25
8	293.9	199.8	134.3	96.0	55.2	29.6	0.0	16	21
9	478.0	304.2	246.9	142.6	85.6	66.2	0.0	16	21
10	859.5	468.9	408.6	306.7	357.5	884.3	64.5	16	21
11	736.9	418.1	311.1	194.0	117.5	663.8	65.1	16	21
12	629.6	454.9	289.6	359.7	296.4	95.7	0.0	16	21
13	941.1	651.1	425.8	413.1	136.5	99.6	34.6	16	21
14	369.3	278.1	251.8	132.3	86.1	48.5	0.0	16	21
15	916.2	601.2	443.1	243.9	152.7	88.2	35.0	16	21
16	500.8	460.8	343.5	236.9	151.8	76.3	0.0	16	21
17	740.9	543.0	429.9	217.5	106.6	38.5	52.4	16	21
18	607.4	385.8	209.6	126.2	69.1	41.0	0.0	16	21
19	587.2	365.0	262.5	192.8	62.1	37.7	39.9	16	21
20	232.0	127.1	102.7	61.6	30.7	36.3	54.4	16	21
21	169.4	94.9	60.2	43.7	0.0	0.0	0.0	16	21
22	656.8	328.9	226.8	119.3	62.5	31.0	0.0	16	21
23	366.5	214.2	138.1	82.4	126.0	1048.4	42.8	16	21
24	259.5	197.1	111.8	58.2	39.5	0.0	0.0	16	21
25	393.0	420.7	194.5	70.5	41.7	269.7	0.0	16	21
26	333.7	200.2	134.4	98.4	45.4	0.0	0.0	16	21
27	524.0	266.3	153.5	125.3	92.1	69.8	153.7	17	22
28	236.2	206.9	143.9	133.9	65.5	261.0	0.0	16	21
29	74.5	59.5	31.0	0.0	0.0	0.0	0.0	16	21
30	57.8	0.0	0.0	0.0	0.0	0.0	0.0	16	21
31	428.5	350.3	196.3	95.9	40.9	0.0	0.0	16	21
32	195.0	91.6	129.5	72.8	79.8	370.8	0.0	16	21
33	254.2	168.5	129.7	84.6	54.5	57.1	36.4	16	21
34	557.0	447.0	224.7	128.1	87.7	30.6	0.0	16	21
35	967.6	643.6	419.9	164.4	99.2	38.6	0.0	16	21
36	383.6	233.3	172.7	89.3	68.9	42.6	34.4	16	21
37	509.6	330.8	250.3	164.0	111.1	248.8	51.1	16	21
38	259.7	314.5	176.9	118.4	320.0	1238.6	530.2	16	21
39	613.5	412.1	321.1	175.3	169.4	355.0	211.3	16	21
40	568.8	392.6	287.5	172.4	153.5	448.0	40.8	16	21

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
41	181.6	125.8	93.4	48.3	47.7	35.9	65.1	16	21
42	94.3	74.3	52.1	53.9	38.7	0.0	0.0	16	21
43	174.2	124.2	458.0	81.6	56.2	35.8	0.0	16	21
44	411.3	325.9	201.4	84.4	48.9	0.0	0.0	16	21
45	1502.3	841.1	706.9	309.6	177.8	90.0	0.0	16	21
46	1441.2	1206.4	901.8	395.4	172.7	98.5	31.3	16	21
47	1223.5	661.6	545.1	1500.5	963.7	227.1	43.7	16	21
48	984.8	685.2	317.9	164.5	96.0	49.1	37.2	16	21
49	603.9	389.7	575.6	442.6	649.5	426.1	53.8	16	21
50	1704.4	874.8	556.4	337.3	150.2	78.6	30.1	16	21
51	722.9	544.7	51.5	235.7	141.0	203.8	61.3	16	21
52	2521.9	1905.7	1243.0	903.4	326.9	150.1	49.5	16	21
53	110.4	78.8	54.7	43.0	114.2	198.5	66.4	16	21
54	118.6	80.4	45.5	36.7	54.1	185.3	0.0	16	21
55	98.0	68.8	213.2	795.1	1749.5	1466.6	81.3	16	21
56	249.8	164.9	115.8	57.2	106.7	361.1	3379.0	16	21
57	235.6	171.2	111.7	88.7	47.1	87.4	229.0	16	21
58	468.7	276.3	172.6	108.7	56.9	323.7	84.1	16	21
59	415.7	285.2	887.3	139.2	60.4	147.2	108.5	16	21
60	338.7	251.6	223.9	96.0	51.6	56.2	51.1	16	21
61	209.5	212.0	256.3	161.5	68.9	375.5	230.8	16	21
62	245.7	150.0	111.3	80.4	48.1	0.0	0.0	16	21
63	175.6	408.5	134.1	349.3	133.6	45.1	0.0	16	21
64	202.0	134.1	111.1	50.9	39.1	36.1	40.3	16	21
65	957.9	357.2	505.1	192.8	100.3	32.3	0.0	16	21
66	1668.1	1382.6	591.3	248.3	187.2	62.1	0.0	17	22
67	836.4	399.2	220.5	116.0	67.4	38.4	0.0	17	22
68	785.8	342.0	245.8	139.8	98.1	262.7	210.0	17	22
69	804.3	440.8	297.7	188.6	122.6	55.8	0.0	16	21
70	1062.5	636.8	720.3	460.9	147.6	84.5	0.0	16	21
71	1480.6	839.8	1165.9	590.2	237.5	83.8	0.0	16	21
72	1357.7	489.5	428.4	180.4	112.7	77.2	0.0	16	21
73	1023.6	583.4	529.0	404.7	682.0	1751.6	75.2	16	21
74	1699.5	919.6	867.4	696.9	638.8	416.2	96.8	16	21
75	2154.1	1999.2	1525.4	456.4	262.6	96.3	67.3	16	21
76	1823.1	1672.6	685.5	406.3	243.5	117.8	43.9	16	21
77	351.8	194.0	139.1	119.6	61.2	1243.3	83.1	16	21
78	680.7	510.3	413.8	1242.1	876.8	525.1	126.7	16	21
79	757.9	765.6	532.4	423.3	200.5	78.6	33.0	16	21
80	1186.0	976.6	723.2	364.4	206.6	321.2	270.1	16	21

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
81	239.5	147.4	121.0	79.8	40.2	48.0	0.0	16	21
82	355.4	232.7	162.5	115.4	60.9	34.1	0.0	16	21
83	282.7	196.1	131.7	99.1	48.3	0.0	0.0	16	21
84	551.9	342.9	206.3	91.0	58.6	32.4	0.0	16	21
85	375.2	266.6	251.3	306.3	91.9	34.8	0.0	16	21
86	287.3	190.2	211.3	87.5	90.4	145.2	165.0	16	21
87	419.4	211.3	143.3	75.3	44.9	57.2	31.4	16	21
88	336.9	251.1	207.9	110.4	52.2	36.4	117.3	16	21
89	615.1	406.1	420.3	209.1	149.1	136.6	65.8	16	21
90	1062.8	797.6	434.1	245.4	177.9	100.3	36.8	16	21
91	1484.3	917.2	617.0	352.0	288.1	1396.2	130.0	16	21
92	653.6	451.1	320.4	182.5	115.0	66.7	43.0	16	21
93	8939.2	7061.0	5300.5	4189.3	1313.0	525.4	544.0	16	21
94	7927.0	4971.5	3127.9	1521.1	1016.6	522.5	193.4	16	21
95	7449.7	6033.9	3900.8	1961.8	1099.1	547.6	208.9	17	22
96	5980.3	4609.9	2255.5	1235.9	773.3	983.7	162.7	18	23
97	683.4	206.9	522.7	165.7	95.2	63.7	0.0	16	21
98	878.3	451.3	232.4	114.4	72.8	0.0	0.0	16	21
99	575.2	384.5	239.4	98.8	73.9	48.2	0.0	15	20
100	236.4	142.8	229.1	71.7	77.9	177.1	0.0	15	20
101	370.5	408.4	703.1	238.0	115.2	1045.7	139.7	16	21
102	468.1	691.7	525.0	270.7	135.5	408.1	127.5	16	21
103	495.7	370.1	247.8	107.4	81.2	49.3	0.0	16	21
104	251.8	159.2	119.6	82.0	48.0	46.1	44.7	16	21
105	1403.4	880.8	584.3	285.3	143.8	61.6	0.0	16	21
106	1059.2	701.5	475.8	282.1	146.2	64.6	0.0	16	21
107	1083.7	1181.4	886.0	667.3	553.0	358.8	37.7	16	21
108	732.9	400.1	332.3	155.6	196.9	43.0	0.0	16	21
109	484.3	302.5	240.5	146.3	98.2	48.9	0.0	16	21
110	272.4	209.1	154.4	98.2	70.7	45.7	0.0	16	21
111	364.4	264.2	703.7	118.4	79.6	42.2	0.0	16	21
112	356.2	262.7	169.5	121.7	51.1	51.5	31.7	16	21
113	625.9	399.3	259.7	123.1	73.2	43.9	0.0	16	21
114	533.8	430.3	564.3	206.9	115.3	40.2	665.8	16	21
115	331.6	254.8	226.5	126.1	264.1	77.2	0.0	16	21
116	537.3	474.3	287.4	156.6	84.8	35.1	0.0	16	21
117	464.3	470.7	294.2	99.6	64.0	324.1	58.6	16	21
118	134.5	76.5	79.4	73.9	72.4	48.6	0.0	16	21
119	176.9	824.7	80.3	44.4	497.2	480.3	30.5	16	21
120	315.5	160.5	111.8	68.0	49.7	51.1	50.4	16	21

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
121	2949.2	1571.0	1116.8	1027.0	646.6	371.6	87.5	16	21
122	4452.0	3317.0	2416.4	1284.6	878.5	1396.2	543.0	16	21
123	406.9	1574.3	1493.4	1051.7	742.0	450.5	162.3	16	21
124	2437.6	1708.9	1246.3	1198.6	898.2	354.4	185.4	16	21
125	1250.3	729.0	505.9	264.9	156.1	84.7	0.0	16	21
126	312.5	193.1	153.7	107.5	66.4	716.7	44.1	16	21
127	479.3	343.6	220.2	139.0	186.2	498.2	57.3	16	21
128	661.0	605.8	393.8	275.9	190.2	179.7	0.0	16	21

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauct
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	32	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22 23 26 27 28 29 30 31 32 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	32
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	127
Number of Observations Used	127
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion

0	1	236.85906438	
1	3	201.90300531	0.01916067
2	2	201.68160714	0.00251211
3	3	201.64645198	0.00046761
4	1	201.64168617	0.00000030
5	1	201.64168309	0.00000000

The Mixed Procedure

Convergence criteria met.

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	1	0.1912	0.1607
2	trt	B	1	0.1607	0.1350

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.4373
FA(2,1)	subj		0.3675
FA(2,2)	subj		0
Residual	subj	trt A	0.1096
Residual	subj	trt B	0.2658

Fit Statistics

-2 Res Log Likelihood	201.6
AIC (smaller is better)	209.6
AICC (smaller is better)	210.0
BIC (smaller is better)	215.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	35.22	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	30.1	0.29	0.5963
PER	3	75.3	1.49	0.2254
trt	1	71.2	0.08	0.7752

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.02231	0.07784	71.2	0.29	0.7752	0.1	-0.1074	0.1520

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	9.2038	0.08792	30.2	104.69	<.0001
trt	B	9.1815	0.09150	33	100.34	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauci
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	32	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22 23 26 27 28 29 30 31 32 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	32
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	127
Number of Observations Used	126
Number of Observations Not Used	1

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	232.53377424	
1	3	199.36859671	0.02625285
2	2	199.05347727	0.00455642
3	3	198.99162693	0.00028009
4	1	198.98864507	0.00000009
5	1	198.98864405	0.00000000

The Mixed Procedure

Convergence criteria met.

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	1	0.1870	0.1518
2	trt	B	1	0.1518	0.1231

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.4324
FA(2,1)	subj		0.3509
FA(2,2)	subj		2.18E-18
Residual	subj	trt A	0.1076
Residual	subj	trt B	0.2662

Fit Statistics

-2 Res Log Likelihood	199.0
AIC (smaller is better)	207.0
AICC (smaller is better)	207.3
BIC (smaller is better)	212.9

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	33.55	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	30.3	0.28	0.6017
PER	3	74	1.27	0.2907
trt	1	69.1	0.01	0.9105

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.008837	0.07832	69.1	0.11	0.9105	0.1	-0.1217	0.1394

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	9.2385	0.08724	30.4	105.89	<.0001
trt	B	9.2296	0.08948	33.5	103.14	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lcmax
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	32	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22 23 26 27 28 29 30 31 32 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	32
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	127
Number of Observations Used	127
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	205.94680355	
1	4	124.33100064	0.00383947
2	1	124.13447600	0.00002780
3	1	124.13310192	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	1	0.2272	0.1948

2 trt B 1 0.1948 0.1670

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.4767
FA(2,1)	subj		0.4087
FA(2,2)	subj		1.52E-18
Residual	subj	trt A	0.07389
Residual	subj	trt B	0.07666

Fit Statistics

-2 Res Log Likelihood	124.1
AIC (smaller is better)	132.1
AICC (smaller is better)	132.5
BIC (smaller is better)	138.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	81.81	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	30.1	1.11	0.3008
PER	3	88.7	0.30	0.8288
trt	1	73.9	0.42	0.5184

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.03259	0.05022	73.9	-0.65	0.5184	0.1	-0.1162	0.05106

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	7.9454	0.09100	30.3	87.32	<.0001
trt	B	7.9780	0.08011	30.4	99.59	<.0001

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	2	1	1	5173.65	5324.58	1324.7	A	3358 05	3550 99	1324.7	0.64907	0.66691	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
2	1	2	4	1	1	12020.30	12178.89	2213 0	A	6310 33	6431 81	2213.0	0.52497	0.52811	1
3	1	2	1	1	2	3358.05	3565.03	979 0	B	3394 55	3903.48	979.0	1.01087	1.09493	1
4	1	2	3	1	2	6310.33	6431.44	1940 6	B	5173 65	5239 00	1940.6	0.81987	0.81459	1
5	2	1	1	1	1	8174.93	8327.84	3479.4	A	12020 30	12138 53	3479.4	1.47039	1.45758	1
6	2	1	3	1	1	10500.78	10651.11	2018 0	A	8367 85	8568 98	2018.0	0.79688	0.80452	1
7	2	1	2	1	2	8367.85	8807.36	3360 2	B	8174 93	9334 98	3360.2	0.97694	1.05991	1
8	2	1	4	1	2	7418.13	7589.85	2696 8	B	10500.78	10577 56	2696.8	1.41556	1.39365	1
9	3	1	1	1	1	12194.05	12328.29	2617.7	A	7418.13	7555 90	2617.7	0.60834	0.61289	1
10	3	1	3	1	1	10317.40	10685.19	2389.4	A	10006 98	10257.16	2389.4	0.96991	0.95994	1
11	3	1	2	1	2	10006.98	10225.95	3763 8	B	12194 05	12411 00	3763.8	1.21856	1.21368	1
12	3	1	4	1	2	14590.70	14666.08	2844.7	B	10317.40	10525 87	2844.7	0.70712	0.71770	1
13	4	2	2	1	1	16017.43	16099.55	3798.7	A	9617 50	9731 29	3798.7	0.60044	0.60444	1
14	4	2	4	1	1	6745.78	6884.25	4478 9	A	14716 08	14917.74	4478.9	2.18152	2.16694	1
15	4	2	1	1	2	9617.50	9824.94	3673.7	B	14590.70	14738 67	3673.7	1.51710	1.50013	1
16	4	2	3	1	2	14716.08	15029.42	3926.7	B	16017.43	16161.19	3926.7	1.08843	1.07530	1
17	5	2	2	1	1	8448.48	8515.76	2080 8	A	9021 05	9090 20	2080.8	1.06777	1.06746	1
18	5	2	4	1	1	5137.45	5268.72	1285 9	A	3426 63	3590 03	1285.9	0.66699	0.68139	1
19	5	2	1	1	2	9021.05	9125.48	1941 2	B	6745.78	6879 23	1941.2	0.74778	0.75385	1
20	5	2	3	1	2	3426.63	3557.68	2462 6	B	8448.48	8544 59	2462.6	2.46554	2.40173	1
21	6	1	1	1	1	8764.90	8797.28	1777 6	A	5137.45	5183 09	1777.6	0.58614	0.58917	1
22	6	1	3	1	1	6850.90	6997.90	2870.1	A	9725 28	9884 54	2870.1	1.41956	1.41250	1
23	6	1	2	1	2	9725.28	9806.41	3351 6	B	8764 90	8823 67	3351.6	0.90125	0.89979	1
24	6	1	4	1	2	4308.58	4699.73	1787.1	B	6850 90	6908.19	1787.1	1.59006	1.46991	1
25	7	1	1	1	1	5798.80	5919.00	1725 3	A	4308 58	5022 62	1725.3	0.74301	0.84856	1
26	7	1	3	1	1	5070.82	6241.23	1645.7	A	5623 28	6312.47	1645.7	1.10895	1.01142	1
27	7	1	2	1	2	5623.27	5819.62	2311 3	B	5798 80	5856 80	2311.3	1.03121	1.00639	1
28	7	1	4	1	2	4064.50	4166.04	1141.1	B	5070 83	5925.74	1141.1	1.24759	1.42239	1
29	8	2	2	1	1	4624.73	4698.62	1706 6	A	2912 60	3017 02	1706.6	0.62979	0.64211	1
30	8	2	4	1	1	9241.53	9392.25	911 5	A	3751 23	5286 93	911.5	0.40591	0.56290	1
31	8	2	1	1	2	2912.60	2997.34	1915.7	B	4064 50	4109 95	1915.7	1.39549	1.37120	1
32	8	2	3	1	2	3751.23	4226.24	1378 8	B	4624.73	4677.12	1378.8	1.23286	1.10669	1
33	9	2	2	1	1	12185.38	12263.93	3113 2	A	9646 93	9709 20	3113.2	0.79168	0.79169	1
34	9	2	4	1	1	7446.78	7558.49	4835.7	A	11645.43	11720 63	4835.7	1.56382	1.55066	1
35	9	2	1	1	2	9646.93	9718.71	3347 5	B	9241 53	9326 91	3347.5	0.95798	0.95969	1
36	9	2	3	1	2	11645.43	11716.88	4403 6	B	12185 38	12265 55	4403.6	1.04637	1.04683	1
37	10	1	1	1	1	9627.48	11612.50	2693 2	A	7446.78	7638 08	2693.2	0.77349	0.65775	1
38	10	1	3	1	1	10671.68	10893.05	2660 2	A	8046.48	9193.16	2660.2	0.75400	0.84395	1
39	10	1	2	1	2	8046.48	14449.51	2789 8	B	9627.48	25674 30	2789.8	1.19648	1.77683	1
40	10	1	4	1	2	10010.85	10204.77	3705.7	B	10671 68	10793 21	3705.7	1.06601	1.05766	1
41	11	1	1	1	1	7658.18	7764.70	4504 2	A	10010 85	10190 05	4504.2	1.30721	1.31236	1
42	11	1	3	1	1	10591.95	10774.69	3590 2	A	10230 05	10363 83	3590.2	0.96583	0.96187	1
43	11	1	2	1	2	10230.05	10284.13	3351 2	B	7658.18	7716 64	3351.2	0.74860	0.75034	1
44	11	1	4	1	2	14796.63	14943.18	2997 2	B	10591 95	10671 58	2997.2	0.71584	0.71414	1
45	12	2	2	1	1	14643.18	14796.56	4419.4	A	12896 60	13006.45	4419.4	0.88072	0.87902	1
46	12	2	4	1	1	14710.10	14828.97	3716 9	A	11431 58	11513.77	3716.9	0.77712	0.77644	1
47	12	2	1	1	2	12896.60	12951.13	4862 8	B	14796 63	14953.41	4862.8	1.14733	1.15460	1
48	12	2	3	1	2	11431.58	11504.20	3079 2	B	14643.18	14728.49	3079.2	1.28094	1.28027	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
49	13	1	1	1	1	14693.40	14763.43	4596 8	A	14710.10	14835 29	4596.8	1.00114	1.00487	1
50	13	1	3	1	1	17880.15	18006.59	4213 0	A	19277 08	19433 63	4213.0	1.07813	1.07925	1
51	13	1	2	1	2	19277.07	19509.36	3965 0	B	14693.40	14807.45	3965.0	0.76222	0.75899	1
52	13	1	4	1	2	3782.03	3996.70	2943.4	B	17880.15	18040 20	2943.4	4.72767	4.51377	1
53	14	2	2	1	1	12340.35	12562.36	1064.7	A	2982 33	3488 33	1064.7	0.24167	0.27768	1
54	14	2	4	1	1	7580.58	.	3379 0	A	12350.15	.	3379.0	1.62918	.	1
55	14	2	1	1	2	2982.33	3766.17	1360 0	B	3782 03	4062 85	1360.0	1.26815	1.07878	1
56	14	2	3	1	2	12350.15	18587.92	3745 6	B	12340 35	12490.43	3745.6	0.99921	0.67196	1
57	15	2	2	1	1	8631.38	9001.56	3051 8	A	6375.15	6662.12	3051.8	0.73860	0.74011	1
58	15	2	4	1	1	5246.53	6084.58	3484.7	A	6426 28	6611 83	3484.7	1.22486	1.08665	1
59	15	2	1	1	2	6375.15	6714.40	2268.4	B	7580 58	8504.40	2268.4	1.18908	1.26659	1
60	15	2	3	1	2	6426.28	6588.50	3249 5	B	8631 38	8975.77	3249.5	1.34314	1.36234	1
61	16	1	1	1	1	4205.43	4548.75	867 6	A	5246 53	6893 58	867.6	1.24756	1.51549	1
62	16	1	3	1	1	3789.58	3850.41	962.7	A	3456 03	3524.11	962.7	0.91198	0.91525	1
63	16	1	2	1	2	3456.03	3559.25	1234.4	B	4205.43	4315 51	1234.4	1.21684	1.21248	1
64	16	1	4	1	2	6287.03	6378.55	1246 6	B	3789 58	3903.78	1246.6	0.60276	0.61202	1
65	18	1	1	1	1	9643.28	9748.28	1923 8	A	6287 03	6341 64	1923.8	0.65196	0.65054	1
66	18	1	3	1	1	5793.25	6103.67	3348.4	A	7087.18	7143 94	3348.4	1.22335	1.17043	1
67	18	1	2	1	2	7087.18	7144.68	2890.1	B	9643 28	9736 26	2890.1	1.36067	1.36273	1
68	18	1	4	1	2	10346.93	10715.97	1851.7	B	5793 25	7182 33	1851.7	0.55990	0.67025	1
69	19	1	1	1	1	6995.88	7204.93	3549 6	A	10346 93	10484 98	3549.6	1.47900	1.45525	1
70	19	1	3	1	1	11881.80	11998.05	2645 9	A	9526 23	9652.41	2645.9	0.80175	0.80450	1
71	19	1	2	1	2	9526.23	9683.68	2363 3	B	6995 88	7154 64	2363.3	0.73438	0.73883	1
72	19	1	4	1	2	26347.80	26480.12	2753 3	B	11881 80	12017 64	2753.3	0.45096	0.45384	1
73	20	2	2	1	1	28206.80	28416.00	6138 8	A	26068 20	26369.15	6138.8	0.92418	0.92797	1
74	20	2	4	1	1	9399.98	9696.76	7541 3	A	30562.48	30719 26	7541.3	3.25134	3.16799	1
75	20	2	1	1	2	26068.20	26384.13	5778.7	B	26347 80	26593 27	5778.7	1.01073	1.00793	1
76	20	2	3	1	2	30562.48	30656.54	5790 2	B	28206 80	28351 00	5790.2	0.92292	0.92479	1
77	21	1	1	1	1	14248.85	14883.30	1893.1	A	9399 98	9816 20	1893.1	0.65970	0.65954	1
78	21	1	3	1	1	22188.05	22869.78	5159.4	A	17590 20	17673 50	5159.4	0.79278	0.77279	1
79	21	1	2	1	2	17590.20	17692.15	3064 9	B	14248 85	14640 22	3064.9	0.81004	0.82750	1
80	21	1	4	1	2	10905.70	11064.64	6863.7	B	22188 05	23082 32	6863.7	2.03454	2.08613	1
81	22	2	2	1	1	12565.78	12679.29	3459 0	A	11397 68	11477 82	3459.0	0.90704	0.90524	1
82	22	2	4	1	1	7058.38	7161.52	2763 0	A	11516 83	11612 86	2763.0	1.63165	1.62156	1
83	22	2	1	1	2	11397.68	11451.70	3624.7	B	10905.70	10981.74	3624.7	0.95684	0.95896	1
84	22	2	3	1	2	11516.83	11560.36	4069 0	B	12565.78	12630 67	4069.0	1.09108	1.09258	1
85	23	1	1	1	1	5872.08	6182.23	1531 6	A	7058 38	7123.79	1531.6	1.20202	1.15230	1
86	23	1	3	1	1	5398.48	5727.60	1488 2	A	5738 38	5826.49	1488.2	1.06296	1.01727	1
87	23	1	2	1	2	5738.38	5891.70	1957 8	B	5872 08	6677 85	1957.8	1.02330	1.13343	1
88	23	1	4	1	2	15671.68	15902.31	1487.7	B	5398.48	5809 65	1487.7	0.34447	0.36533	1
89	26	2	2	1	1	21392.95	21891.23	5526 8	A	20384 53	20525 57	5526.8	0.95286	0.93762	1
90	26	2	4	1	1	32885.73	36368.44	5254 9	A	19010.10	19285 37	5254.9	0.57807	0.53028	1
91	26	2	1	1	2	20384.53	20623.49	5332 6	B	15671 68	16098 86	5332.6	0.76880	0.78061	1
92	26	2	3	1	2	19010.10	19159.77	4604 9	B	21392 95	21845.41	4604.9	1.12535	1.14017	1
93	27	1	1	1	1	43225.73	43787.77	8939 2	A	32885.73	34466.76	8939.2	0.76079	0.78713	1
94	27	1	3	1	1	32074.53	32673.57	7560 2	A	34902.45	35671 55	7560.2	1.08817	1.09176	1
95	27	1	2	1	2	34902.45	35668.77	8418 9	B	43225.73	43935 29	8418.9	1.23847	1.23176	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
96	27	1	4	1	2	6172.42	6341.26	6848 8	B	32074 53	32505.77	6848.8	5.19642	5.12608	1
97	28	2	2	1	1	9220.55	9303.60	1919 5	A	7279 90	7405 34	1919.5	0.78953	0.79597	1
98	28	2	4	1	1	10076.93	10389.59	2850.1	A	5334 53	5730 89	2850.1	0.52938	0.55160	1
99	28	2	1	1	2	7279.90	7521.12	1925 5	B	6172.43	6383.46	1925.5	0.84787	0.84874	1
100	28	2	3	1	2	5334.53	6086.22	3523 6	B	9220 55	9425.14	3523.6	1.72847	1.54860	1
101	29	1	1	1	1	5975.60	6595.13	2539 3	A	10076 93	10755 83	2539.3	1.68635	1.63087	1
102	29	1	3	1	1	6493.05	6666.24	2233 9	A	6047 00	6238 00	2233.9	0.93130	0.93576	1
103	29	1	2	1	2	6047.00	6289.26	1257 0	B	5975 60	6602 05	1257.0	0.98819	1.04973	1
104	29	1	4	1	2	16075.12	21526.45	2715.4	B	6493 05	10456 95	2715.4	0.40392	0.48577	1
105	30	2	2	1	1	16827.80	16899.19	5135 6	A	13806.15	13928.48	5135.6	0.82044	0.82421	1
106	30	2	4	1	1	12951.88	13031.44	4172 3	A	15864.48	15934.44	4172.3	1.22488	1.22277	1
107	30	2	1	1	2	13806.15	13906.84	5373 3	B	16075.13	16171.13	5373.3	1.16435	1.16282	1
108	30	2	3	1	2	15864.48	15979.02	4011 6	B	16827 80	16928 23	4011.6	1.06072	1.05940	1
109	31	1	1	1	1	11694.15	11820.08	3389.4	A	12951 88	13086 62	3389.4	1.10755	1.10715	1
110	31	1	3	1	1	11569.03	11662.23	2596 8	A	11513.43	11637 51	2596.8	0.99519	0.99788	1
111	31	1	2	1	2	11513.43	11682.43	3103 2	B	11694.15	11877.16	3103.2	1.01570	1.01667	1
112	31	1	4	1	2	10923.53	11036.47	2637 8	B	11569 03	11650 58	2637.8	1.05909	1.05564	1
113	32	2	2	1	1	6671.43	6995.11	2735 3	A	11912 08	14704 07	2735.3	1.78554	2.10205	1
114	32	2	4	1	1	5365.20	5467.33	1466 8	A	7527 00	7588.17	1466.8	1.40293	1.38791	1
115	32	2	1	1	2	11912.08	12974.80	2966 3	B	10923 53	10993 59	2966.3	0.91701	0.84730	1
116	32	2	3	1	2	7527.00	7614.88	1346.1	B	6671.43	6864.70	1346.1	0.88633	0.90149	1
117	34	1	1	1	1	6059.75	6230.16	1707 2	A	5365 20	5570 69	1707.2	0.88538	0.89415	1
118	34	1	3	1	1	4918.05	5019.42	1812.7	A	7967 53	8028 87	1812.7	1.62006	1.59956	1
119	34	1	2	1	2	7967.53	8216.10	2230 9	B	6059.75	6455 81	2230.9	0.76056	0.78575	1
120	34	1	4	1	2	26979.80	27214.76	2143 8	B	4918 05	5053 38	2143.8	0.18229	0.18569	1
121	35	2	2	1	1	34571.15	35228.50	6211.1	A	30634 90	32834 26	6211.1	0.88614	0.93204	1
122	35	2	4	1	1	9986.53	10304.83	7438 0	A	29597 38	30294 20	7438.0	2.96373	2.93981	1
123	35	2	1	1	2	30634.90	32210.18	6509 8	B	26979 80	27233 62	6509.8	0.88069	0.84550	1
124	35	2	3	1	2	29597.38	30328.45	5535.4	B	34571.15	35211.16	5535.4	1.16805	1.16099	1
125	36	2	2	1	1	19454.25	19683.45	2356 2	A	9612.43	9788 85	2356.2	0.49410	0.49731	1
126	36	2	4	1	.	.	.	.	A	7698 55	8187 87	3384.2	.	.	.
127	36	2	1	1	2	9612.43	9692.39	2995 2	B	9986 53	10140.10	2995.2	1.03892	1.04619	1
128	36	2	3	1	2	7698.55	8169.22	5440 2	B	19454 25	19604 33	5440.2	2.52700	2.39978	1

Niacin (Fed Study)

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	1	2	1	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	0.0	0.0	49 6	0 0
2	1	2	2	1	A	0	0.0	0.0	0 0	20.3	0.0	0.0	0 0	0.0	0.0	0.0	0.0	0 0	0 0
3	1	2	3	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	422.1	391.0	0 0	0 0
4	1	2	4	1	A	0	0.0	0.0	0 0	0.0	23.3	0.0	83 9	0.0	101.3	121.6	369.8	0 0	0 0
5	2	1	1	1	A	0	0.0	0.0	0 0	23.5	0.0	0.0	26 2	1185.4	34.6	30.8	63.3	25 6	25 0
6	2	1	2	1	B	0	0.0	0.0	0 0	0.0	25.6	109.2	0 0	43.4	24.2	23.9	21.0	0 0	0 0
7	2	1	3	1	A	0	0.0	0.0	0 0	0.0	0.0	49.5	0 0	47.3	0.0	51.6	27.3	0 0	0 0
8	2	1	4	1	B	0	0.0	0.0	0 0	50.6	21.8	107.7	0 0	28.9	40.4	0.0	21.3	0 0	0 0
9	3	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	29 0	26.5	21.9	27.5	26.3	0 0	0 0
10	3	1	2	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	65.1	29.5	1105.8	0 0	0 0
11	3	1	3	1	A	0	0.0	0.0	0 0	158.4	0.0	0.0	0 0	0.0	23.2	30.8	783.3	0 0	0 0
12	3	1	4	1	B	0	0.0	0.0	0 0	0.0	24.2	0.0	0 0	39.8	36.4	38.0	393.8	0 0	0 0
13	4	2	1	1	B	0	0.0	0.0	2011.7	3494.0	3299.1	196.6	35 2	46.8	31.8	868.7	1525.6	105 0	55 5
14	4	2	2	1	A	0	0.0	20.8	67 2	47.7	31.2	1782. 0	5159 0	1235.0	48.4	31.7	29.2	30.1	27 2
15	4	2	3	1	B	0	0.0	0.0	0 0	1563.6	1590.5	3097. 7	968 2	3133.5	1681.6	619.3	875.4	36.7	40 9
16	4	2	4	1	A	0	0.0	22.8	0 0	2629.7	2923.7	2878. 5	3030 5	3391.3	366.3	355.4	33.8	25.7	26 5
17	5	2	1	1	B	0	0.0	0.0	55.7	0.0	0.0	0.0	0 0	20.2	22.7	313.5	54.3	39 3	33.4
18	5	2	2	1	A	0	0.0	0.0	0 0	0.0	0.0	90.4	0 0	88.6	176.8	36.3	27.0	40 6	23 6
19	5	2	3	1	B	0	0.0	0.0	0 0	0.0	23.9	0.0	188 0	117.5	262.7	58.9	32.1	21.1	24.7
20	5	2	4	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	56.3	0.0	193.9	26.2	0 0	0 0
21	6	1	1	1	A	0	0.0	0.0	47 8	0.0	0.0	0.0	0 0	0.0	21.9	22.3	22.0	0 0	0 0
22	6	1	2	1	B	0	0.0	0.0	0 0	0.0	0.0	23.7	21.7	40.5	0.0	0.0	36.7	20 5	0 0
23	6	1	3	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	25.3	357.1	0 0	0 0
24	6	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	33.2	20.7	0 0	0 0
25	7	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	58.8	0 0	0.0	0.0	198.8	601.7	30 5	0 0
26	7	1	2	1	B	0	0.0	0.0	0 0	41.0	0.0	0.0	304.1	464.1	1796.2	608.0	146.1	20 5	0 0
27	7	1	3	1	A	0	0.0	0.0	44 0	0.0	50.3	0.0	0 0	69.0	28.4	0.0	1738.4	365.4	66.1
28	7	1	4	1	B	0	0.0	21.5	0 0	0.0	94.2	0.0	0 0	0.0	20.3	0.0	597.6	0 0	0 0
29	8	2	1	1	B	0	0.0	0.0	0 0	161.6	25.8	60.5	0 0	0.0	0.0	0.0	0.0	0 0	0 0
30	8	2	2	1	A	0	0.0	0.0	0 0	0.0	0.0	20.4	0 0	36.4	0.0	0.0	20.1	0 0	0 0
31	8	2	3	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	21.2	20.7	41.0	24 9	20 6
32	8	2	4	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	20.1	20.8	0.0	0.0	0.0	0 0	0 0
33	9	2	1	1	B	0	0.0	0.0	0 0	0.0	30.1	214.3	0 0	37.0	21.1	23.0	0.0	0 0	0 0
34	9	2	2	1	A	0	0.0	0.0	0 0	0.0	76.9	0.0	0 0	86.1	0.0	0.0	1070.2	0 0	0 0
35	9	2	3	1	B	0	0.0	0.0	0 0	23.6	0.0	0.0	0 0	26.1	220.7	79.1	28.9	22 5	0 0
36	9	2	4	1	A	0	0.0	0.0	0 0	0.0	23.8	0.0	1464.7	260.7	0.0	0.0	0.0	0 0	0 0
37	10	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	30.6	27.4	61.7	94.0	0 0	0 0
38	10	1	2	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	31.4	0.0	0.0	184.2	30.9	0 0	0 0
39	10	1	3	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	131.1	21.0	647.0	0 0	0 0
40	10	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	33.9	0 0	33.5	23.6	329.9	160.6	0 0	0 0
41	11	1	1	1	A	0	0.0	0.0	0 0	0.0	1048.6	0.0	128 9	25.7	25.2	20.3	21.7	0 0	0 0

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
42	11	1	2	1	B	0	0.0	0.0	28 6	0.0	84.3	135.6	30 6	27.9	25.9	0.0	27.0	22.1	0 0
43	11	1	3	1	A	0	0.0	0.0	284 9	312.4	85.1	73.1	29.4	24.6	22.0	21.2	23.4	0 0	0 0
44	11	1	4	1	B	0	0.0	0.0	34.7	76.3	0.0	0.0	303 6	278.3	31.1	20.8	22.9	21 6	0 0
45	12	2	1	1	B	0	0.0	0.0	0 0	113.4	54.1	23.3	156 5	102.7	1696.0	785.7	33.1	27 0	35 8
46	12	2	2	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	105 0	100.5	195.5	257.4	803.4	49 9	28.4
47	12	2	3	1	B	0	0.0	0.0	132 0	0.0	31.5	26.3	56 3	371.8	99.8	553.7	25.9	0 0	31.4
48	12	2	4	1	A	0	0.0	0.0	0 0	0.0	26.1	30.5	234 3	124.2	96.5	67.6	23.0	23.4	28 9
49	13	1	1	1	A	0	0.0	28.7	69 9	0.0	27.3	21.4	24 3	39.1	25.7	661.9	631.8	94 9	25 0
50	13	1	2	1	B	0	0.0	0.0	0 0	0.0	20.2	23.0	534 3	0.0	173.1	168.0	107.9	39.1	29 6
51	13	1	3	1	A	0	0.0	221.0	741 3	390.7	75.8	103.9	0 0	27.3	33.4	136.8	37.9	24 6	0 0
52	13	1	4	1	B	0	0.0	27.1	68.4	40.0	0.0	0.0	25 9	0.0	43.4	24.0	46.8	249 3	143 6
53	14	2	1	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	0.0	0.0	0 0	0 0
54	14	2	2	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	29.7	0.0	0.0	0.0	0.0	0 0	0 0
55	14	2	3	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	361 0	0.0	0.0	0.0	0.0	0 0	0 0
56	14	2	4	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	50.0	0.0	0.0	0 0	0 0
57	15	2	1	1	B	0	0.0	0.0	73.4	32.8	0.0	0.0	53.1	0.0	434.9	23.2	25.9	0 0	0 0
58	15	2	2	1	A	0	0.0	0.0	0 0	0.0	0.0	21.4	0 0	0.0	0.0	0.0	1054.4	21.1	0 0
59	15	2	3	1	B	0	0.0	0.0	0 0	0.0	0.0	91.8	427 9	98.2	117.2	134.1	31.6	0 0	0 0
60	15	2	4	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	284.1	49.0	307.5	262.0	36.6	0 0	0 0
61	16	1	1	1	A	0	0.0	0.0	0 0	0.0	37.7	0.0	41.1	0.0	34.5	27.6	38.6	0 0	0 0
62	16	1	2	1	B	0	0.0	0.0	0 0	0.0	213.7	41.1	57.4	0.0	188.5	63.3	68.8	0 0	0 0
63	16	1	3	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	30.9	83.0	47.2	0 0	0 0
64	16	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	36 3	0.0	39.1	93.9	0.0	0 0	0 0
65	18	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	0.0	50.2	0 0	0 0
66	18	1	2	1	B	0	0.0	0.0	24.7	0.0	0.0	0.0	0 0	0.0	34.8	29.4	492.6	106 5	0 0
67	18	1	3	1	A	0	0.0	0.0	0 0	21.6	42.1	0.0	497.7	0.0	0.0	0.0	145.2	75 8	0 0
68	18	1	4	1	B	0	0.0	0.0	0 0	0.0	28.3	0.0	0 0	0.0	0.0	0.0	32.9	1144 3	0 0
69	19	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	20 6	31.4	201.1	234.2	317.8	32.1	22.1
70	19	1	2	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	33.1	70.4	77 2	28 6
71	19	1	3	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	55.4	31.4	854.4	26 0	0 0
72	19	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	40 9	66.5	82.9	70.1	34.9	36 0	33 2
73	20	2	1	1	B	0	0.0	0.0	0 0	30.6	53.8	704.1	56 9	39.9	60.6	41.9	101.2	45.4	41 6
74	20	2	2	1	A	0	0.0	0.0	0 0	0.0	0.0	184.6	381 0	109.1	402.0	68.5	589.3	35 2	29 5
75	20	2	3	1	B	0	0.0	0.0	28 3	577.1	821.1	36.1	45 0	42.2	29.5	35.5	1490.6	31 0	33 2
76	20	2	4	1	A	0	0.0	0.0	0 0	584.2	60.0	299.2	300 6	184.7	148.7	1353.4	33.5	35 8	20 9
77	21	1	1	1	A	0	0.0	0.0	0 0	1220.4	0.0	0.0	31.1	0.0	0.0	0.0	49.7	0 0	0 0
78	21	1	2	1	B	0	0.0	0.0	0 0	258.6	0.0	0.0	107.7	0.0	931.7	38.5	0.0	0 0	0 0
79	21	1	3	1	A	0	0.0	0.0	0 0	0.0	2398.9	556.6	2289.7	1257.4	239.8	0.0	596.0	0 0	0 0
80	21	1	4	1	B	0	0.0	0.0	0 0	339.9	0.0	1617. 7	2015 3	938.8	129.1	0.0	114.1	0 0	0 0
81	22	2	1	1	B	0	0.0	0.0	174 3	328.3	354.8	410.2	1497 8	1758.5	243.1	36.2	28.4	22 2	0 0
82	22	2	2	1	A	0	0.0	0.0	0 0	924.6	3520.2	1482. 5	635.4	271.9	462.3	509.0	167.3	24.4	22 6
83	22	2	3	1	B	0	0.0	0.0	782 6	616.2	4197.6	3041. 3	719.1	691.2	270.1	30.4	25.7	20 2	0 0
84	22	2	4	1	A	0	0.0	0.0	1472.7	499.2	377.6	66.2	24 9	197.7	1738.1	481.5	439.2	497 5	23 0
85	23	1	1	1	A	0	0.0	0.0	51 2	0.0	62.7	26.0	21 3	66.5	57.2	100.8	166.4	31 3	27 2

Obs	SUB	SEQ	PER	GROUP	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
86	23	1	2	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	33.5	92.0	231.7	26 3	21 8
87	23	1	3	1	A	0	0.0	0.0	50 6	0.0	0.0	0.0	25 8	20.1	25.7	41.8	1528.5	21 9	27 3
88	23	1	4	1	B	0	0.0	0.0	0 0	0.0	73.5	0.0	0 0	0.0	61.0	24.7	104.2	0 0	0 0
89	26	2	1	1	B	0	0.0	0.0	0 0	0.0	0.0	75.8	23 5	33.7	855.5	27.7	41.6	21 3	20 2
90	26	2	2	1	A	0	0.0	0.0	0 0	33.4	70.4	21.9	0 0	25.0	38.5	186.1	51.1	28 5	32.7
91	26	2	3	1	B	0	0.0	0.0	0 0	0.0	23.0	27.2	275 2	38.1	149.2	264.3	87.1	26.7	0 0
92	26	2	4	1	A	0	0.0	0.0	0 0	0.0	39.7	78.9	22 9	284.1	24.5	27.3	26.7	0 0	0 0
93	27	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	115.4	798.1	702.4	3206 5	3537.1
94	27	1	2	1	B	0	0.0	0.0	0 0	0.0	102.2	426.8	301 3	121.4	971.7	1603.5	744.5	810 3	133 8
95	27	1	3	1	A	0	0.0	0.0	0 0	33.4	22.5	792.5	817.1	28.0	0.0	21.3	2524.0	4297 5	4901 9
96	27	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	66.9	453 5	918.9	44.4	306.6	468.9	653 0	1868 5
97	28	2	1	1	B	0	0.0	0.0	29 5	27.8	0.0	21.3	0 0	73.1	121.0	50.9	157.7	118.4	28 3
98	28	2	2	1	A	0	0.0	0.0	0 0	24.1	0.0	31.7	27 2	31.2	52.3	144.9	809.0	154 6	90 6
99	28	2	3	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	31.7	118.5	33.6	2086.3	162.7	33.4	32 5
100	28	2	4	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	69.6	0.0	899.4	133.7	22 3	21.1
101	29	1	1	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	24 0	21.5	24.2	36.1	41.6	50 0	0 0
102	29	1	2	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	21.5	0.0	0.0	22.8	21.7	29 6
103	29	1	3	1	A	0	0.0	0.0	0 0	0.0	40.3	0.0	0 0	0.0	205.9	38.4	25.3	26 6	24 3
104	29	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	27.2	0.0	20.7	21.9	0 0	0 0
105	30	2	1	1	B	0	0.0	0.0	0 0	0.0	262.7	0.0	465 6	52.1	34.8	75.4	0.0	35 5	34 5
106	30	2	2	1	A	0	0.0	0.0	36 8	0.0	0.0	0.0	0 0	77.7	148.1	374.0	34.5	28 8	22 3
107	30	2	3	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	70 0	95.4	31.0	27.2	371.7	0 0	0 0
108	30	2	4	1	A	0	0.0	0.0	24 8	28.2	0.0	0.0	20.4	38.8	288.1	22.5	32.3	0 0	0 0
109	31	1	1	1	A	0	0.0	36.9	441 8	255.1	796.4	2191. 9	44 0	567.3	543.8	532.1	597.1	41.4	42.7
110	31	1	2	1	B	0	0.0	973.5	43 8	402.1	1431.1	616.7	221 6	1785.4	127.0	47.6	36.5	33 9	28 9
111	31	1	3	1	A	0	0.0	110.4	1529 5	38.8	152.6	162.7	979.4	283.9	34.5	37.1	321.9	30 3	29.4
112	31	1	4	1	B	0	0.0	370.1	755 9	1006.6	28.2	23.8	38.7	654.9	46.2	120.9	50.1	35.7	38 0
113	32	2	1	1	B	0	0.0	0.0	328 8	29.6	1969.7	127.5	45 5	191.4	157.0	60.4	167.7	58 2	38 0
114	32	2	2	1	A	0	0.0	171.0	65 9	477.2	289.8	386.1	748 5	57.0	60.4	34.8	82.8	605.1	29 3
115	32	2	3	1	B	0	0.0	149.5	89 0	22.2	0.0	0.0	45 6	0.0	36.6	232.6	1005.9	22 9	0 0
116	32	2	4	1	A	0	0.0	88.4	250.4	148.6	0.0	318.2	36 5	24.6	32.9	22.6	157.2	70.1	29 9
117	34	1	1	1	A	0	0.0	0.0	0 0	0.0	115.3	0.0	0 0	0.0	80.8	337.6	0.0	0 0	0 0
118	34	1	2	1	B	0	0.0	0.0	0 0	0.0	23.3	0.0	29 6	119.9	112.9	27.2	386.6	144 6	20.1
119	34	1	3	1	A	0	0.0	0.0	0 0	0.0	0.0	0.0	34.7	186.7	22.6	0.0	20.7	25 3	0 0
120	34	1	4	1	B	0	0.0	0.0	0 0	0.0	0.0	0.0	0 0	0.0	0.0	227.1	48.8	20.4	0 0
121	35	2	1	1	B	0	0.0	0.0	0 0	29.8	326.1	2276. 6	1164 0	261.4	1692.3	471.0	4876.7	1525 8	85 6
122	35	2	2	1	A	0	0.0	0.0	0 0	0.0	27.0	0.0	93 6	3069.5	1348.2	4644.0	6094.1	4237 5	2267 9
123	35	2	3	1	B	0	331.3	3611. 4	4849 0	3642.7	706.0	1642. 8	1851.1	1897.5	442.5	809.3	1313.5	56 2	0 0
124	35	2	4	1	A	0	0.0	0.0	24 5	0.0	0.0	3740. 7	3050 9	4007.3	2969.4	2332.5	4947.0	1629 2	58.1
125	36	2	1	1	B	0	0.0	0.0	0 0	0.0	0.0	114.7	437 3	1145.6	1688.2	1648.9	542.0	301 6	85 9
126	36	2	2	1	A	0	0.0	0.0	0 0	0.0	148.1	116.5	25 3	27.2	240.6	1185.2	21.1	0 0	0 0
127	36	2	3	1	B	0	0.0	72.2	408.7	358.6	737.5	33.1	507 0	1556.7	165.2	800.0	301.8	0 0	0 0
128	36	2	4	1	A	0	0.0	0.0	0 0	0.0	51.0	0.0	0 0	31.2	400.4	180.0	355.8	0 0	29.1

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
5	24.6	24.0	27.7	30.1	28.6	0.0	0.0	12	17
6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
13	45.6	48.5	36.8	53.2	25.4	26.0	0.0	12	17
14	26.5	27.0	30.2	22.4	0.0	0.0	0.0	12	17
15	38.4	35.6	32.0	27.8	0.0	0.0	0.0	12	17
16	23.7	26.0	22.4	0.0	0.0	0.0	0.0	12	17
17	33.4	30.3	28.3	32.4	25.2	0.0	0.0	12	17
18	21.3	20.6	0.0	0.0	0.0	0.0	0.0	12	17
19	25.0	0.0	25.5	29.5	0.0	0.0	0.0	12	17
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
26	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
27	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
28	0.0	0.0	0.0	0.0	74.8	0.0	0.0	12	17
29	0.0	20.8	0.0	0.0	0.0	0.0	0.0	12	17
30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
31	25.6	22.2	21.4	0.0	0.0	0.0	0.0	12	17
32	21.1	0.0	0.0	0.0	0.0	0.0	0.0	12	17
33	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
34	0.0	22.7	0.0	0.0	0.0	0.0	0.0	12	17
35	22.3	0.0	0.0	0.0	0.0	0.0	0.0	12	17
36	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
37	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
38	0.0	0.0	0.0	0.0	48.2	58.1	0.0	12	17

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
39	0.0	0.0	0.0	0.0	0.0	20.2	0.0	12	17
40	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
41	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
42	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
43	0.0	0.0	20.9	0.0	0.0	0.0	0.0	12	17
44	22.7	0.0	0.0	0.0	0.0	0.0	0.0	12	17
45	28.2	25.4	0.0	20.3	0.0	0.0	0.0	12	17
46	26.1	28.3	25.1	0.0	0.0	0.0	0.0	12	17
47	23.0	0.0	25.0	29.5	0.0	0.0	0.0	12	17
48	23.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
49	21.0	23.8	27.7	40.4	28.7	24.1	0.0	12	17
50	20.9	25.8	22.3	0.0	253.5	0.0	0.0	12	17
51	22.7	21.6	0.0	0.0	0.0	0.0	0.0	12	17
52	45.7	24.6	0.0	25.1	23.9	0.0	0.0	12	17
53	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
54	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
55	0.0	0.0	0.0	243.4	22.5	0.0	0.0	12	17
56	0.0	0.0	0.0	0.0	0.0	0.0	138.9	12	17
57	0.0	0.0	0.0	0.0	0.0	20.1	0.0	12	17
58	0.0	0.0	0.0	0.0	0.0	22.8	0.0	12	17
59	22.4	0.0	54.3	0.0	0.0	0.0	0.0	12	17
60	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
61	0.0	0.0	25.1	0.0	0.0	0.0	0.0	12	17
62	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
63	0.0	62.1	0.0	0.0	0.0	0.0	0.0	12	17
64	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
65	0.0	0.0	24.3	0.0	0.0	0.0	0.0	12	17
66	41.7	0.0	0.0	0.0	0.0	0.0	0.0	12	17
67	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
68	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
69	27.0	25.2	20.9	24.1	0.0	0.0	0.0	12	17
70	25.8	22.7	28.5	30.0	20.6	0.0	0.0	12	17
71	32.0	0.0	28.1	29.5	0.0	0.0	0.0	12	17
72	33.7	0.0	33.5	0.0	0.0	0.0	0.0	12	17
73	34.3	32.0	27.9	35.2	27.4	33.6	0.0	12	17
74	24.5	22.2	32.6	25.5	0.0	0.0	0.0	12	17
75	32.7	33.1	35.8	0.0	21.9	0.0	0.0	12	17
76	26.6	22.3	0.0	0.0	0.0	0.0	0.0	12	17
77	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
78	0.0	0.0	0.0	353.7	0.0	0.0	0.0	12	17

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
79	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
80	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
81	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
82	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
83	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
84	21.9	0.0	0.0	0.0	0.0	0.0	0.0	12	17
85	60.2	27.4	24.2	34.3	22.1	0.0	0.0	12	17
86	0.0	0.0	21.3	0.0	0.0	0.0	0.0	12	17
87	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
88	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
89	0.0	0.0	66.3	0.0	0.0	0.0	0.0	12	17
90	0.0	23.2	22.8	0.0	0.0	0.0	0.0	12	17
91	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
92	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
93	1930.4	212.7	262.0	35.0	26.6	0.0	0.0	12	17
94	496.3	324.2	27.3	29.6	22.3	0.0	0.0	12	17
95	2820.8	823.3	31.3	28.2	0.0	0.0	0.0	12	17
96	168.7	21.2	0.0	0.0	0.0	27.9	0.0	12	17
97	139.3	42.5	34.9	30.1	28.8	0.0	0.0	12	17
98	32.7	33.8	28.3	22.7	0.0	0.0	0.0	12	17
99	32.0	25.0	24.9	26.5	0.0	0.0	0.0	12	17
100	21.4	0.0	0.0	0.0	0.0	0.0	0.0	12	17
101	28.8	40.5	25.5	22.1	0.0	30.3	0.0	12	17
102	39.0	27.4	27.2	20.7	0.0	0.0	0.0	12	17
103	23.2	22.8	20.8	0.0	0.0	0.0	0.0	12	17
104	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
105	35.3	25.6	22.3	22.2	0.0	0.0	0.0	12	17
106	0.0	20.9	20.1	0.0	0.0	0.0	0.0	12	17
107	22.0	27.4	24.4	25.0	20.1	0.0	0.0	12	17
108	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
109	42.0	37.2	36.3	31.3	24.6	0.0	0.0	12	17
110	24.6	28.1	26.3	20.8	0.0	0.0	0.0	12	17
111	29.2	28.5	25.3	26.2	0.0	0.0	0.0	12	17
112	35.2	33.1	32.7	26.9	0.0	0.0	0.0	12	17
113	34.4	35.4	23.8	22.1	0.0	0.0	0.0	12	17
114	0.0	101.3	29.8	20.6	0.0	0.0	29.4	12	17
115	20.4	20.2	0.0	23.2	20.9	0.0	0.0	12	17
116	21.5	20.8	0.0	0.0	0.0	0.0	0.0	12	17
117	0.0	23.5	0.0	0.0	0.0	0.0	0.0	12	17
118	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17

Obs	c15	c16	c17	c18	c19	c20	c21	ke_first	ke_last
119	0.0	21.0	0.0	0.0	44.6	42.9	0.0	12	17
120	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
121	34.4	21.7	0.0	0.0	0.0	0.0	0.0	12	17
122	300.9	335.4	45.0	0.0	0.0	0.0	0.0	12	17
123	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
124	26.9	0.0	0.0	0.0	0.0	0.0	0.0	12	17
125	0.0	0.0	20.3	22.1	0.0	57.4	0.0	12	17
126	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12	17
127	0.0	0.0	0.0	0.0	0.0	36.7	0.0	12	17
128	0.0	31.0	0.0	0.0	0.0	0.0	0.0	12	17

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauct
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	32	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22 23 26 27 28 29 30 31 32 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	32
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	127
Number of Observations Used	126
Number of Observations Not Used	1

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	456.56687511	
1	2	418.54148968	0.00000101
2	1	418.54138983	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	1	0.9243	1.0404
2	trt	B	1	1.0404	1.4493

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.9614
FA(2,1)	subj		1.0822
FA(2,2)	subj		0.5274
Residual	subj	trt A	0.8074
Residual	subj	trt B	1.2647

Fit Statistics

-2 Res Log Likelihood	418.5
AIC (smaller is better)	428.5
AICC (smaller is better)	429.1
BIC (smaller is better)	435.9

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	38.03	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	30.2	0.52	0.4752
PER	3	69.2	2.16	0.1004
trt	1	30.5	0.89	0.3521

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.1942	0.2055	30.5	-0.94	0.3521	0.1	-0.5427	0.1544

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	6.0869	0.2044	30	29.78	<.0001
trt	B	6.2810	0.2559	30.2	24.55	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lauci
Covariance Structures	Factor Analytic, Variance Components
Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	32	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22 23 26 27 28 29 30 31 32 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	32
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	127
Number of Observations Used	96
Number of Observations Not Used	31

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	312.42697506	
1	2	295.98702388	0.00375012
2	1	295.70962869	0.00023119
3	1	295.69386568	0.00000127
4	1	295.69378259	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	1	0.6465	0.5889
2	trt	B	1	0.5889	0.8263

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		0.8040
FA(2,1)	subj		0.7325
FA(2,2)	subj		0.5384
Residual	subj	trt A	1.0546
Residual	subj	trt B	0.5892

Fit Statistics

-2 Res Log Likelihood	295.7
AIC (smaller is better)	305.7
AICC (smaller is better)	306.4
BIC (smaller is better)	313.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	16.73	0.0022

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	24	0.08	0.7822
PER	3	45	0.26	0.8542
trt	1	19.8	0.04	0.8350

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	-0.04661	0.2208	19.8	-0.21	0.8350	0.1	-0.4276	0.3344

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	6.7686	0.2180	21.4	31.04	<.0001
trt	B	6.8153	0.2007	28	33.95	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.REPL
Dependent Variable	lcmax
Covariance Structures	Factor Analytic, Variance

Components

Subject Effects	subj, subj
Group Effect	trt
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Satterthwaite

Class Level Information

Class	Levels	Values
SEQ	2	1 2
subj	32	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 18 19 20 21 22 23 26 27 28 29 30 31 32 34 35 36
PER	4	1 2 3 4
trt	2	A B

Dimensions

Covariance Parameters	5
Columns in X	9
Columns in Z Per Subject	2
Subjects	32
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	127
Number of Observations Used	126
Number of Observations Not Used	1

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	441.18717058	
1	3	376.80335865	0.00002064
2	1	376.80169338	0.00000006
3	1	376.80168876	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	trt	subj	Col1	Col2
1	trt	A	1	1.3150	1.2382
2	trt	B	1	1.2382	1.2700

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
FA(1,1)	subj		1.1467
FA(2,1)	subj		1.0797
FA(2,2)	subj		0.3228
Residual	subj	trt A	0.9253
Residual	subj	trt B	0.4197

Fit Statistics

-2 Res Log Likelihood	376.8
AIC (smaller is better)	386.8
AICC (smaller is better)	387.3
BIC (smaller is better)	394.1

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	64.39	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SEQ	1	30	1.52	0.2272

PER	3	66.5	2.22	0.0945
trt	1	29.9	0.05	0.8164

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
T VS. R	0.03694	0.1577	29.9	0.23	0.8164	0.1	-0.2307	0.3046

The Mixed Procedure

Least Squares Means

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
trt	A	6.1011	0.2363	30.1	25.82	<.0001
trt	B	6.0642	0.2154	30	28.15	<.0001

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	2	1	1	308 80		20 3	A	5 08		20 3	0 0164		1
2	1	2	4	1	1	796 68		369 8	A	257 50		369 8	0 3232		1
3	1	2	1	1	2	5 08		49 6	B	12 40		49 6	2 4433		1
4	1	2	3	1	2	257 50		422 1	B	308 80		422 1	1 1992		1
5	2	1	1	1	1	118 40	184 52	1185 4	A	796 68	886 72	1185 4	6 7287	4 8055	1
6	2	1	3	1	1	130 03		51 6	A	81 03		51 6	0 6231		1
7	2	1	2	1	2	81 03	121 32	109 2	B	118 40	149 40	109 2	1 4613	1 2314	1
8	2	1	4	1	2	59 03	103 03	107 7	B	130 03	165 67	107 7	2 2029	1 6079	1
9	3	1	1	1	1	323 75	35207 03	29 0	A	59 03	889 14	29 0	0 1823	0 0253	1
10	3	1	3	1	1	167 65		783 3	A	302 03		783 3	1 8015		1
11	3	1	2	1	2	302 03		1105 8	B	323 75		1105 8	1 0719		1
12	3	1	4	1	2	6026 95		393 8	B	167 65		393 8	0 0278		1
13	4	2	2	1	1	6878 60	7131 10	5159 0	A	4315 35	4518 83	5159 0	0 6274	0 6337	1
14	4	2	4	1	1	367 63	390 07	3391 3	A	7872 55	7892 51	3391 3	21 4146	20 2333	1
15	4	2	1	1	2	4315 35	4435 33	3494 0	B	6026 95	6166 19	3494 0	1 3966	1 3902	1
16	4	2	3	1	2	7872 55	8013 79	3133 5	B	6878 60	7053 84	3133 5	0 8737	0 8802	1
17	5	2	2	1	1	410 83	627 74	176 8	A	257 45	408 97	176 8	0 6267	0 6515	1
18	5	2	4	1	1	51 50		193 9	A	131 65		193 9	2 5563		1
19	5	2	1	1	2	257 45	420 94	313 5	B	367 63	567 58	313 5	1 4279	1 3483	1
20	5	2	3	1	2	131 65	208 98	262 7	B	410 83	497 90	262 7	3 1206	2 3825	1
21	6	1	1	1	1	66 43	164 42	47 8	A	51 50	156 65	47 8	0 7753	0 9528	1
22	6	1	3	1	1	21 78		357 1	A	101 93		357 1	4 6808		1
23	6	1	2	1	2	101 93	1391 09	40 5	B	66 43	140 42	40 5	0 6517	0 1009	1
24	6	1	4	1	2	437 28		33 2	B	21 78		33 2	0 0498		1
25	7	1	1	1	1	1684 88		601 7	A	437 28		601 7	0 2595		1
26	7	1	3	1	1	404 20	427 08	1738 4	A	1164 28	1184 49	1738 4	2 8804	2 7735	1
27	7	1	2	1	2	1164 28	1183 78	1796 2	B	1684 88	1690 92	1796 2	1 4471	1 4284	1
28	7	1	4	1	2	129 15		597 6	B	404 20		597 6	3 1297		1
29	8	2	2	1	1	93 45		36 4	A	33 43		36 4	0 3577		1
30	8	2	4	1	1	157 00		21 1	A	25 73		21 1	0 1639		1
31	8	2	1	1	2	33 43	116 48	161 6	B	129 15	215 11	161 6	3 8639	1 8467	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
32	8	2	3	1	2	25 73	143 47	41 0	B	93 45	212 87	41 0	3 6327	1 4837	1
33	9	2	2	1	1	206 03		1070 2	A	622 28		1070 2	3 0204		1
34	9	2	4	1	1	83 35		1464 7	A	809 43		1464 7	9 7112		1
35	9	2	1	1	2	622 28	641 35	214 3	B	157 00	176 33	214 3	0 2523	0 2749	1
36	9	2	3	1	2	809 43	1101 43	220 7	B	206 03	231 00	220 7	0 2545	0 2097	1
37	10	1	1	1	1	253 65		94 0	A	83 35		94 0	0 3286		1
38	10	1	3	1	1	250 60		647 0	A	419 75		647 0	1 6750		1
39	10	1	2	1	2	419 75	729 09	184 2	B	253 65	1143 05	184 2	0 6043	1 5678	1
40	10	1	4	1	2	629 78		329 9	B	250 60		329 9	0 3979		1
41	11	1	1	1	1	185 48	202 25	1048 6	A	629 78	646 25	1048 6	3 3955	3 1953	1
42	11	1	3	1	1	400 33	460 17	312 4	A	443 28	498 38	312 4	1 1073	1 0830	1
43	11	1	2	1	2	443 28	654 60	135 6	B	185 48	408 99	135 6	0 4184	0 6248	1
44	11	1	4	1	2	1550 75	1576 11	303 6	B	400 33	428 68	303 6	0 2581	0 2720	1
45	12	2	2	1	1	709 35	816 39	803 4	A	803 53	894 61	803 4	1 1328	1 0958	1
46	12	2	4	1	1	975 73	1010 79	234 3	A	333 00	366 46	234 3	0 3413	0 3626	1
47	12	2	1	1	2	803 53	959 52	1696 0	B	1550 75	1676 91	1696 0	1 9299	1 7477	1
48	12	2	3	1	2	333 00	380 76	553 7	B	709 35	770 61	553 7	2 1302	2 0239	1
49	13	1	1	1	1	714 42	2297 81	661 9	A	975 73	1126 27	661 9	1 3657	0 4902	1
50	13	1	3	1	1	406 45	685 00	741 3	A	913 10	1164 85	741 3	2 2465	1 7005	1
51	13	1	2	1	2	913 10	998 85	534 3	B	714 43	1720 87	534 3	0 7824	1 7229	1
52	13	1	4	1	2			249 3	B	406 45	450 84	249 3			1
53	14	2	2	1	1	435 15		29 7	A	7 43		29 7	0 0171		1
54	14	2	4	1	1	341 75		138 9	A	302 80		138 9	0 8860		1
55	14	2	1	1	2	7 43		0 0	B	0 00		0 0	0 0000		
56	14	2	3	1	2	302 80	754 80	361 0	B	435 15	508 36	361 0	1 4371	0 6735	1
57	15	2	2	1	1	475 18	636 54	1054 4	A	571 25	639 02	1054 4	1 2022	1 0039	1
58	15	2	4	1	1	96 03	107 82	307 5	A	460 45	477 65	307 5	4 7951	4 4301	1
59	15	2	1	1	2	571 25	1374 07	434 9	B	341 75	1049 97	434 9	0 5982	0 7641	1
60	15	2	3	1	2	460 45	541 60	427 9	B	475 18	595 56	427 9	1 0320	1 0996	1
61	16	1	1	1	1	299 20	1015 87	41 1	A	96 03	357 55	41 1	0 3209	0 3520	1
62	16	1	3	1	1	61 18	2209 92	83 0	A	96 08	1517 42	83 0	1 5705	0 6866	1
63	16	1	2	1	2	96 08	157 69	213 7	B	299 20	367 46	213 7	3 1142	2 3303	1
64	16	1	4	1	2	31 18		93 9	B	61 18		93 9	1 9623		1
65	18	1	1	1	1	354 43		50 2	A	31 18		50 2	0 0880		1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
66	18	1	3	1	1	316 68	1920 01	497 7	A	372 25	478 46	497 7	1 1755	0 2492	1
67	18	1	2	1	2	372 25	421 31	492 6	B	354 43	381 42	492 6	0 9521	0 9053	1
68	18	1	4	1	2	483 48		1144 3	B	316 68		1144 3	0 6550		1
69	19	1	1	1	1	190 58	231 08	317 8	A	483 48	530 86	317 8	2 5369	2 2973	1
70	19	1	3	1	1	207 48	259 32	854 4	A	535 43	581 08	854 4	2 5807	2 2408	1
71	19	1	2	1	2	535 43	717 19	77 2	B	190 58	317 50	77 2	0 3559	0 4427	1
72	19	1	4	1	2	751 98	882 56	82 9	B	207 48	337 69	82 9	0 2759	0 3826	1
73	20	2	2	1	1	1655 50	1692 26	589 3	A	960 15	1002 95	589 3	0 5800	0 5927	1
74	20	2	4	1	1	638 18	678 15	1353 4	A	1529 38	1547 31	1353 4	2 3965	2 2817	1
75	20	2	1	1	2	960 15	1201 17	704 1	B	751 98	1069 50	704 1	0 7832	0 8904	1
76	20	2	3	1	2	1529 38	1647 87	1490 6	B	1655 50	1771 85	1490 6	1 0825	1 0752	1
77	21	1	1	1	1	845 10	1260 05	1220 4	A	638 18	696 48	1220 4	0 7551	0 5527	1
78	21	1	3	1	1	2548 93	2792 62	2398 9	A	3520 20	4793 29	2398 9	1 3811	1 7164	1
79	21	1	2	1	2	3520 20		931 7	B	845 10		931 7	0 2401		1
80	21	1	4	1	2	2421 35	2436 12	2015 3	B	2548 93	2624 85	2015 3	1 0527	1 0775	1
81	22	2	2	1	1	5192 15	5201 11	3520 2	A	4004 45	4014 48	3520 2	0 7713	0 7718	1
82	22	2	4	1	1	412 60	425 13	1738 1	A	2914 28	2926 69	1738 1	7 0632	6 8843	1
83	22	2	1	1	2	4004 45	4050 67	1758 5	B	2421 35	2466 75	1758 5	0 6047	0 6090	1
84	22	2	3	1	2	2914 28	2967 85	4197 6	B	5192 15	5241 57	4197 6	1 7816	1 7661	1
85	23	1	1	1	1	207 98	288 44	166 4	A	412 60	496 08	166 4	1 9839	1 7199	1
86	23	1	3	1	1	105 65	131 54	1528 5	A	864 03	870 81	1528 5	8 1782	6 6202	1
87	23	1	2	1	2	864 03	1186 34	231 7	B	207 98	459 54	231 7	0 2407	0 3874	1
88	23	1	4	1	2	566 23		104 2	B	105 65		104 2	0 1866		1
89	26	2	2	1	1	438 73	543 39	186 1	A	261 10	350 48	186 1	0 5951	0 6450	1
90	26	2	4	1	1	5496 10	5515 14	284 1	A	245 38	264 49	284 1	0 0446	0 0480	1
91	26	2	1	1	2	261 10	312 53	855 5	B	566 23	715 80	855 5	2 1686	2 2903	1
92	26	2	3	1	2	245 38	257 02	275 2	B	438 73	450 37	275 2	1 7880	1 7523	1
93	27	1	1	1	1	3079 23	3094 53	3537 1	A	5496 10	5514 36	3537 1	1 7849	1 7820	1
94	27	1	3	1	1	2513 20	2525 02	4901 9	A	8578 73	8590 67	4901 9	3 4135	3 4022	1
95	27	1	2	1	2	8578 73	8609 92	1603 5	B	3079 23	3103 90	1603 5	0 3589	0 3605	1
96	27	1	4	1	2	475 58	534 54	1868 5	B	2513 20	2570 33	1868 5	5 2846	4 8085	1
97	28	2	2	1	1	1309 78	1412 09	809 0	A	748 63	836 28	809 0	0 5716	0 5922	1
98	28	2	4	1	1	204 88	221 13	899 4	A	578 40	589 88	899 4	2 8232	2 6676	1
99	28	2	1	1	2	748 63	984 84	157 7	B	475 58	775 40	157 7	0 6353	0 7873	1

Obs	SUBJ	SEQ	PER	GROUP	treat	FDAAREA	FDAAUCI	FDACMAX	trt	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
100	28	2	3	1	2	578 40	789 03	2086 3	B	1309 78	1570 58	2086 3	2 2645	1 9905	1
101	29	1	1	1	1	111 75	418 87	50 0	A	204 88	654 34	50 0	1 8333	1 5621	1
102	29	1	3	1	1	29 43	226 54	205 9	A	208 60	395 77	205 9	7 0892	1 7470	1
103	29	1	2	1	2	208 60	281 38	39 0	B	111 75	184 17	39 0	0 5357	0 6545	1
104	29	1	4	1	2	538 58	674 85	27 2	B	29 43	163 90	27 2	0 0546	0 2429	1
105	30	2	2	1	1	375 70	668 70	374 0	A	376 58	669 51	374 0	1 0023	1 0012	1
106	30	2	4	1	1	3155 68	3166 92	288 1	A	219 48	234 24	288 1	0 0695	0 0740	1
107	30	2	1	1	2	376 58	445 55	465 6	B	538 58	614 76	465 6	1 4302	1 3798	1
108	30	2	3	1	2	219 48	526 51	371 7	B	375 70	566 77	371 7	1 7118	1 0765	1
109	31	1	1	1	1	2930 53	3054 33	2191 9	A	3155 68	3302 11	2191 9	1 0768	1 0811	1
110	31	1	3	1	1	1656 68	2124 50	1529 5	A	1916 18	2371 99	1529 5	1 1566	1 1165	1
111	31	1	2	1	2	1916 18	2043 73	1785 4	B	2930 53	3031 79	1785 4	1 5294	1 4835	1
112	31	1	4	1	2	1650 70	1819 66	1006 6	B	1656 68	1862 32	1006 6	1 0036	1 0234	1
113	32	2	2	1	1	856 10	990 76	748 5	A	1656 35	1845 84	748 5	1 9348	1 8630	1
114	32	2	4	1	1	272 73	295 20	318 2	A	605 65	625 55	318 2	2 2207	2 1190	1
115	32	2	1	1	2	1656 35	1753 67	1969 7	B	1650 70	1723 85	1969 7	0 9966	0 9830	1
116	32	2	3	1	2	605 65	646 09	1005 9	B	856 10	896 73	1005 9	1 4135	1 3879	1
117	34	1	1	1	1	427 08		337 6	A	272 73		337 6	0 6386		1
118	34	1	3	1	1	143 05	939 93	186 7	A	265 30	1940 14	186 7	1 8546	2 0641	1
119	34	1	2	1	2	265 30	279 81	386 6	B	427 08	433 87	386 6	1 6098	1 5506	1
120	34	1	4	1	2	6377 28	6386 28	227 1	B	143 05	151 52	227 1	0 0224	0 0237	1
121	35	2	2	1	1	10562 60	10591 38	6094 1	A	11220 30	11243 35	6094 1	1 0623	1 0616	1
122	35	2	4	1	1	3076 83	3091 95	4947 0	A	11386 53	11393 61	4947 0	3 7007	3 6849	1
123	35	2	1	1	2	11220 30	11253 09	4876 7	B	6377 28	6393 09	4876 7	0 5684	0 5681	1
124	35	2	3	1	2	11386 53	11430 48	4849 0	B	10562 60	10654 44	4849 0	0 9276	0 9321	1
125	36	2	2	1	1	2507 10		1185 2	A	876 73		1185 2	0 3497		1
126	36	2	4	1					A	531 50	564 13	400 4			
127	36	2	1	1	2	876 73	915 31	1688 2	B	3076 83	3181 77	1688 2	3 5095	3 4762	1
128	36	2	3	1	2	531 50	610 82	1556 7	B	2507 10	2601 02	1556 7	4 7170	4 2582	1

BIOEQUIVALENCE DEFICIENCIES

ANDA: 200484

APPLICANT: Sun Pharma Global

DRUG PRODUCT: Niacin Tablets, film coated, extended release, 500 mg and 1000 mg

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

1. For the Fasted Study, No. PKD_09_277, sample reanalysis was conducted for Niacin and Nicotinuric Acid for all samples pertaining to subject 16. You indicated that sample reanalysis was conducted due to suspected "sample mix up" (Code J). Please provide an adequate and detailed explanation as to why you believed the samples were mixed up. In addition, please provide a summary table listing the original assayed values, the reassayed values and the reported values for this subject.

2. For the Fasted Study, Study No. PKD_09_277, for subjects 8, 16, 17, and 22, all samples were reassayed for Niacin and Nicotinuric Acid due to "rejected analytical run" (code J). In addition, for Fed Study, Study No. PKD_09_278, for subject 28 (niacin and nicotinuric acid samples), and subject 13 (nicotinuric acid samples), entire subject samples were reanalyzed due to "rejected analytical run" (code J).

   There are several criteria outlined in Section 7.1.9 of the Standard Operating Procedure (SOP) PKD/S/019 Revision 03, entitled Sample Reanalysis and Reporting of Final Concentrations, detailing how samples can be classified as "rejected analytical runs." As required in section 7.1.9.3 of this SOP, for each subject reanalysis, please submit documentation of the "*investigated and detailed justification of the reanalysis of the batch [form-Attachment-3]".*

   In addition, please submit in tabular format a complete list of original assay values, repeat assay values, and reported values of these subjects, for evaluation. For

each subject, please clearly justify why the original or reassayed value was reported.

3. The DBE identified several instances where you did not follow the standard operating procedure (SOP) PKD/S/019, Sample Reanalysis and Reporting of Final Concentrations, for reassay performed due to "inconsistent profiles (code H)". An example of this can be seen for Study #PKD_09_277 for nicotinuric acid for subject 23 period 3 at 9 hours. The initial assay (145.6 ng/mL) did not differ by greater than 100% from the previous sample (106.0 ng/mL) or the subsequent sample (95.3 ng/mL). Another example is seen for Study PKD_09_277 for nicotinuric acid for subject 23 period 4 at 5 hours. The plasma concentration for nicotinuric acid for subject 23 at 4 and 5 hours in period 4 was 942.6 ng/mL (reassayed 1174.7 ng/mL) and 126.8 ng/mL, respectively. The plasma concentration at Hour-5 differed from that of Hour-4 by greater than 100%, but you did not reassay this sample as you did for other samples. Please submit 1) a summary table (Table 1) detailing all reassays that were performed correctly according to section 7.1.7 of SOP PKD/S/019; 2) a summary table (Table 2) detailing all reassays that were performed incorrectly according to section 7.1.7 of SOP PKD/S/019; and 3) SAS-Transport formatted files containing the original assay data for all samples identified in Table 2. Tables 1 and 2 should contain all pertinent information including the initial value, the reassayed value, and the final reported value for each reassayed sample.

   In addition, section 7.1.7.5 (Result of sample repeated as PK inconsistent profile)is extremely unclear as to how reanalysis was performed for samples coded "N". Please provide concrete examples of how the decision was made to perform reanalysis and report the final value for reassays coded as N.

4. SOP No. PKD/S/019 Revision 03 became effective after the study sample analyses were completed. Therefore, please provide a copy of the SOP that was effective at the time of analysis and please outline the changes made to the SOP between revision 2 and revision 3. Please also indicate which revision of the SOP was effective at the time of the study. If PKD/S/019 Revision 2 was the only version of this SOP effective at the time of the study, please submit a copy of this version of SOP.

5. SOP No. PKD/S/033, Chromatographic Analysis of Study Sample was referenced in SOP No. PKD/S/019 revision 3 but was not included in the application. Please submit a full copy of SOP PKD/S/033 which was effective during the study sample analysis periods.

6. Two concentration ranges for calibration curves (CC) [i.e., 29.5, 58.9, 149.3, 345.7, 903.7, 1296.3, 1517.3 & 1964.1 (ng/ml) and 29.6, 59.2, 149.9, 347.1, 907.1, 1301.5, 1577.6 and 1972.0 (ng/ml)] were used for bioanalysis of nicotinuric acid samples in the Fasted Study (Study No. PKD_09_277). Please provide an explanation as to why you used two different CC concentration ranges. In addition, for each CC concentration range used, please specify all subject samples that were analyzed using such range.

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

4.7 Outcome Page

Completed Assignment for 200484 ID: 12189

Reviewer: Lerman, Bruce **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
12189	9/29/2009	Bioequivalence Study	Fasting Study	1	1
12189	9/29/2009	Bioequivalence Study	Fed Study	1	1
12189	9/29/2009	Other	Dissolution Waiver	1	1
12189	5/26/2010	Other	Study Amendment Without Credit (WC)	0	0
12189	9/6/2010	Other	Study Amendment Without Credit (WC)	0	0
				Bean 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/

BRUCE J LERMAN
11/08/2010

APRIL C BRADDY
11/12/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
11/13/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	200484		
Drug Product Name	Niacin Extended-Release Tablets		
Strength (s)	500 mg and 1000 mg		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P.O.Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Ms. Anne Toland Sun Pharmaceutical Industries, Inc. 270 Prospect Plains Road Cranbury, NJ 08512		
Contact's Phone Number	609-495-2823		
Contact's Fax Number	609-495-2711		
Submission Date(s)	29-September-2009		
First Generic	No		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	PKD_09_277	PKD_09_278	
Study Type (s)	Fasting	Fed	
Strength(s)	1000 mg	1000 mg	
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (INDIA)		
Analytical Site	Sun Pharmaceutical Industries Ltd.,		
Analytical Address	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India.		

OVERALL DISSOLUTION REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**PENDING**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**500 mg**	**INADEQUATE**
1	**DISSOLUTION**	**1000 mg**	**INADEQUATE**
1	**FASTING STUDY**	**1000 mg**	**PENDING REVIEW**
1	**FASTING STUDY**	**1000 mg**	**PENDING REVIEW**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

This application references the (RLD), Niaspan® Extended Release Tablets, manufactured by Abbott (NDA 020381, approved date: July 28, 1997).

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. However, the firm proposed specifications are not acceptable. Based on the submitted data, the Division of Bioequivalence (DBE) recommends the following specifications:

1 Hr: NMT (b) (4)%
3 Hrs: (b) (4)%
6 Hrs: %
9 Hrs: %
12 Hrs: (b) (4)%
20 Hrs: NLT (b) (4)%

The firm will be requested to acknowledge the dissolution method and the above specifications.

The firm also conducted acceptable dissolution testing in three different dissolution media (0.1 N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer).

The firm did not provide the long term stability (LTS) data of niacin in frozen plasma samples. The firm is requested to submit LTS data for at least 111 days to cover the entire length of the maximum storage duration of the BE study samples (i.e., from the time when the first blood sample was drawn until the time when the last plasma sample was analyzed).

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

Table 1: SUBMISSION CONTENT CHECKLIST

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

DBE External Dissolution Database for Niacin

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Niacin	Tablet (Extended Release)	I (Basket)	100	Water	900	1, 3, 6, 9, 12, 15, 20 and 24 hours	06/10/2009

DBE Internal Dissolution Database for Niacin (Not TO BE Released UNDER FOI)

Dosage Form: Tablet (ER)
Medium: Water
Apparatus: I (Basket)
Speed/RPMs: 100
Modify Date:
Sampling Times: 1, 3, 6, 9, 12, 20, 24 hrs
Volume: 900
Notes: Added 7/23/09 by NT (Ref: N020381 SCS 010 1/28/00 &SCS 027 6/29/06)
Specification: 1 hr: NMT (b)(4)%, 3 hr: (b)(4)%, 6 hr: (b)(4)%, 9 hr: (b)(4)%, 12 hr: (b)(4) (b)(4)%, 20 hr: NLT (b)(4)%

RLD Information

Active Ingredient:	NIACIN
Dosage Form;Route:	TABLET, EXTENDED RELEASE; ORAL
Proprietary Name:	NIASPAN
Applicant:	ABBOTT
Strength:	1GM
Application Number:	N020381
Product Number:	004
Approval Date:	Jul 28, 1997
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX

Contains Nonbinding Recommendations

Draft Guidance on Niacin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Niacin

Form/Route: Extended Release Tablets/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: Applicants may consider using a reference-scaled average bioequivalence approach for niacin. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability $\geq$30%). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008).

---

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: See above

---

3. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 750 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: See above.

Analytes to measure (in appropriate biological fluid): Niacin and its metabolite nicotinuric acid in plasma.

Bioequivalence based on (90% CI): Niacin.

If niacin cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for nicotinuric acid.

Waiver request of in-vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 1000 mg strength, (ii) proportionally similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. Specifications will be determined upon review of the data submitted in the application.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

(Summary of In vitro Dissolution Studies (1000 MG) - QC Release Media)

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	(b) (4) water (b) (4)
	Volume	900 ml
	Time Point	1,2,3,4,6,8,9,12,16,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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) 1 hrs	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	9 hrs	12hrs	16 hrs	20 hrs	24 hrs	Study Report Location
INN/050 /09	23/05/09	Batch #: GK91008 Mfg Date: 05/2009	1000 mg Tablets	12												Module 5 Section 5.3.1.3
				Mean (%)	11	17	22	27	36	44	48	58	71	80	88	
				Range (%)	(b) (4)											
				% RSD	5.0	3.9	3.4	2.4	2.0	2.1	2.3	1.5	0.9	1.2	0.8	
	24/05/09	Batch #: 642142E21 Exp. Date: 28/01/2011	1000 mg Tablets	12												
				Mean (%)	8	15	20	25	35	43	47	58	71	82	89	
				Range (%)	(b) (4)											
				% RSD	5.9	2.6	2.2	2.0	2.3	1.3	1.6	1.2	1.1	0.9	1.1	

Summary of In vitro Dissolution Studies (1000 MG) – 0.1 N HCl

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	0.1 N HCl
	Volume	900 ml
	Time Point	1,3,6,9,12,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b)(4) %
	3 Hrs	(b)(4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b)(4) %
	24 Hrs	NLT (b)(4) %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/053/09	31/05/09	Batch #: GK91008 Mfg Date: 05/2009	1000 mg Tablets	12								Module 5 Section 5.3.1.3
				Mean (%)	18	36	55	70	81	98	103	
				Range (%)	(b)(4)							
				% RSD	3.7	2.0	1.9	1.1	1.0	1.0	1.0	
	31/05/09	Batch #: 642142E21 Exp. Date: 28/01/2011	1000 mg Tablets	12								
				Mean (%)	16	33	53	68	80	100	103	
				Range (%)	(b)(4)							
				% RSD	3.1	1.7	1.5	1.8	1.3	1.3	1.2	

Summary of In vitro Dissolution Studies (1000 MG) – pH 4.5 Acetate Buffer

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	pH 4.5 Acetate Buffer
	Volume	900 ml
	Time Point	1,3,6,9,12,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b)(4) %
	3 Hrs	(b)(4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b)(4) %
	24 Hrs	NLT (b)(4) %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/055/09	03/06/09	Batch #: GK91008 Mfg Date: 05/2009	1000 mg Tablets	12								Module 5 Section 5.3.1.3
				Mean (%)	12	23	37	48	58	80	87	
				Range (%)	(b)(4)							
				% RSD	5.9	3.9	3.4	3.1	3.1	2.2	1.8	
	04/06/09	Batch #: 642142E21 Exp. Date: 28/01/2011	1000 mg Tablets	12								
				Mean (%)	8	20	35	47	60	83	91	
				Range (%)	(b)(4)							
				% RSD	5.5	3.6	2.8	2.1	1.7	0.9	1.1	

Summary of In vitro Dissolution Studies (1000 MG) – pH 6.8 Phosphate Buffer

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	pH 6.8 Phosphate Buffer
	Volume	900 ml
	Time Point	1,3,6,9,12,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b)(4) %
	3 Hrs	(b)(4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b)(4) %
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/055/09	11/06/09	Batch #: GK91008 Mfg Date: 05/2009	1000 mg Tablets	12								Module 5 Section 5.3.1.3
				Mean (%)	11	23	37	47	58	78	84	
				Range (%)	(b)(4)							
				% RSD	5.2	3.1	2.9	3.0	3.5	4.3	4.0	
	11/06/09	Batch #: 642142E21 Exp. Date: 28/01/2011	1000 mg Tablets	12								
				Mean (%)	8	20	34	47	57	81	87	
				Range (%)	(b)(4)							
				% RSD	5.5	3.4	2.9	1.6	2.3	3.5	3.3	

Summary of In vitro Dissolution Studies (500 MG) - QC Release Media

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	(b) (4) water (b) (4)
	Volume	900 ml
	Time Point	1,2,3,4,6,8,9,12,16,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	2 hrs	3 hrs	4 hrs	6 hrs	8 hrs	9 hrs	12hrs	16 hrs	20 hrs	24 hrs	
INN/051/09	25/05/09	Batch #: GK91007 Mfg Date: 05/2009	500 mg Tablets	12												Module 5 Section 5.3.1.3
				Mean (%)	12	19	25	30	40	49	53	63	75	84	91	
				Range (%)	(b) (4)											
				% RSD	5.1	5.1	5.4	4.9	5.5	5.4	5.7	5.0	4.8	4.2	3.7	
	26/05/09	Batch #: 687342E21 Exp. Date: 30/05/2011	500 mg Tablets	12												
				Mean (%)	11	18	24	30	41	50	54	67	82	94	101	
				Range (%)	(b) (4)											
				% RSD	3.6	2.9	3.1	3.5	2.5	2.7	2.5	2.4	1.8	1.4	1.1	

Summary of In vitro Dissolution Studies (500 MG) – 0.1 N HCl

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	0.1 N HCl
	Volume	900 ml
	Time Point	1,3,6,9,12,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT (b) (4) %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/054/09	02/06/09	Batch #: GK91007 Mfg Date: 05/2009	500 mg Tablets	12								Module 5 Section 5.3.1.3
				Mean (%)	21	41	61	75	87	103	103	
				Range (%)							(b) (4)	
				% RSD	1.9	2.3	2.4	2.1	1.9	1.2	1.4	
	22/09/09	Batch #: 687342E21 Exp. Date: 30/05/2011	500 mg Tablets	12								
				Mean (%)	19	41	63	83	95	102	102	
				Range (%)							(b) (4)	
				% RSD	2.1	1.7	1.3	2.0	1.3	1.7	1.3	

Summary of In vitro Dissolution Studies (500 MG) pH 4.5 Acetate Buffer

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	pH 4.5 Acetate Buffer
	Volume	900 ml
	Time Point	1,3,6,9,12,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b) (4) %
	3 Hrs	(b) (4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b) (4) %
	24 Hrs	NLT %

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/056/09	06/06/09	Batch #: GK91007 Mfg Date: 05/2009	500 mg Tablets	12								Module 5 Section 5.3.1.3
				Mean (%)	13	26	41	53	64	86	93	
				Range (%)							(b) (4)	
				% RSD	3.0	3.1	3.1	3.1	3.4	2.4	2.6	
	23/09/09	Batch #: 687342E21 Exp. Date: 30/05/2011	500 mg Tablets	12								
				Mean (%)	11	23	43	54	67	93	100	
				Range (%)							(b) (4)	
				% RSD	2.6	2.1	3.1	2.9	2.6	1.9	1.8	

Summary of In vitro Dissolution Studies (500 MG) – pH 6.8 Phosphate Buffer

Dissolution Conditions	Apparatus	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	pH 6.8 Phosphate Buffer
	Volume	900 ml
	Time Point	1,3,6,9,12,20 and 24 hrs
	Temperature	37° C ± 0.5° C

Proposed Specification	Time (Hrs)	% Release
	1 Hrs	NMT (b)(4) %
	3 Hrs	(b)(4) %
	6 Hrs	%
	9 Hrs	%
	12 Hrs	%
	20 Hrs	NLT (b)(4)%
	24 Hrs	NLT (b)(4)%

Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries, Survey No 259/15, Dadra – 396191, UT of Dadra and Nagar Haveli , India

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
					1 hrs	3 hrs	6 hrs	9 hrs	12 hrs	20 hrs	24 hrs	
INN/057/09	07/06/09	Batch #: GK91007 Mfg Date: 05/2009	500 mg Tablets	12								Module 5 Section 5.3.1.3
				Mean (%)	13	26	41	53	64	86	94	
				Range (%)	(b)(4)							
				% RSD	3.6	2.2	3.1	2.5	2.6	2.0	2.8	
	22/09/09	Batch #:687342E21 Exp. Date: 30/05/2011	500 mg Tablets	12								
				Mean (%)	10	24	39	53	65	92	100	
				Range (%)	(b)(4)							
				% RSD	3.8	2.2	1.7	2.0	1.8	1.1	1.2	

II. COMMENTS:

1. There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. However, the firm's proposed specifications are not acceptable. Based on the submitted data, the DBE recommends the following specifications:

1 Hr: NMT (b)(4)%
3 Hrs: (b)(4)%
6 Hrs: %
9 Hrs: %
12 Hrs: (b)(4)%
20 Hrs: NLT (b)(4)%

The firm will be requested to acknowledge the above specifications.

2. The firm also conducted dissolution testing in three different dissolution media (0.1 N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer). Results of f_2 values are provided below.

% RELEASE								
Time (Hrs)	0.1N HCl		4.5 pH buffer		Water		6.8 pH buffer	
	GK91007 (500mg)	GK91008 (1000 mg)	GK91007 (500mg)	GK91008 (1000 mg)	GK91007 (500mg)	GK91008 (1000 mg)	GK91007 (500mg)	GK91008 (1000 mg)
0	0	0	0	0	0	0	0	0
1	21	18	13	12	12	11	13	11
3	41	36	26	23	25	22	26	23
6	61	55	41	37	40	36	41	37
9	75	70	53	48	53	48	53	47
12	87	81	64	58	63	58	64	58
20	103	98	86	80	84	80	86	78
24	103	103	93	87	91	88	94	84
f2	**65.82**		**65.62**		**70.29**		**60.26**	

Note: The dissolution test using water is the regulatory method.

Reviewer comments on f_2: All f_2 values are acceptable (above 50).

III. DEFICIENCY COMMENTS:

1. Based on the submitted data, the firm should acknowledge the following specifications:

1 Hr: NMT [redacted]%
3 Hrs: [redacted]%
6 Hrs: [redacted]%
9 Hrs: [redacted]%
12 Hrs: [redacted]%
20 Hrs: NLT [redacted]%

2. The firm did not provide the long term stability (LTS) data of niacin in frozen plasma samples. The firm is requested to submit LTS data for at least 111 days to cover the entire length of the maximum storage duration of the BE study samples (i.e., from the time when the first blood sample was drawn until the time when the last plasma sample was analyzed).

IV. RECOMMENDATIONS:

The in vitro dissolution testing conducted by Sun Pharma Global FZE on its test product, Niacin Extended-Release Tablets, 500 mg and 1000 mg comparing it to Niaspan® Tablets, 500 mg, and 1000 mg, manufactured by Abbott is incomplete for the reason given in deficiency comment #1.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	200484
APPLICANT:	Sun Pharma Global FZE
DRUG PRODUCT:	Niacin Extended-Release Tablets, 500 mg and 1000 mg

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

1. Your dissolution testing data are acceptable. However, your proposed dissolution specifications are not acceptable. Based on the submitted data, please acknowledge your acceptance of the following FDA-recommended method and specifications:

Medium:	Water
Volume:	900 mL
Apparatus:	I (basket)
Speed:	100 rpm
Sampling Times:	1, 3, 6, 9, 20 and 20 hours
Specifications:	1 Hr: NMT (b) (4)%
	3 Hrs: (b) (4)%
	6 Hrs: %
	9 Hrs: %
	12 Hrs: %
	20 Hrs: NLT (b) (4)%

2. You have not provided the long term stability (LTS) data of niacin in frozen plasma samples. Please provide LTS data for at least 111 days to cover the entire length of the maximum storage duration of the Bioequivalence study samples (i.e., from the time when the first blood sample was drawn until the time when the last plasma sample was analyzed).

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

ANDA: 200484

Completed Assignment for 200484 ID: 10716

Reviewer: Wahba, Zakaria **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10716	9/29/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

ANDA 200484

Dissolution Review	
Dissolution Review	1
Dissolution Review Total	*1*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

ZAKARIA Z WAHBA
03/29/2010

MOHEB H MAKARY
03/29/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/31/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

OTHER REVIEWS

M E M O R A N D U M

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

DATE: February 24, 2011

TO: Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs (HFD-650)

FROM: Sripal R. Mada, Ph.D.
GLP and Bioequivalence Branch
Division of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of EIR Covering ANDA 200-484, Niacin Extended-Release Tablets, 500 mg and 1000 mg from Sun Pharma Global FZE, United Arab Emirates

At the request of the Division of Bioequivalence (DBE), the Division of Scientific Investigations (DSI) audited clinical portions of the following bioequivalence (BE) studies:

PKD_09_277: "A Randomized, Open Label, Two Treatment, Four Period, Two Sequence, Single Dose, Replicated Crossover, Bioequivalence Study of Niacin 1000 mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India and NIASPAN® (Niacin) 1000 mg Extended Release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, In 36 Healthy Human Adult Subjects, Under Fasting Conditions"

PKD_09_278: "A Randomized, Open Label, Two Treatment, Four Period, Two Sequence, Single Dose, Replicated Crossover, Bioequivalence Study of Niacin 1000 mg Extended Release Tablets of Sun Pharmaceutical Industries Limited, India and NIASPAN® (Niacin) 1000 mg Extended Release Tablets of Abbott Laboratories, North Chicago, IL 60064 USA, In 36 Healthy Human Adult Subjects, Under Fed Conditions"

Inspection of clinical portions was conducted at **Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara 390 020, India**. Following the inspection (October 25-29, 2010), No Form FDA-483 was issued and no significant findings were uncovered during the inspection.

Conclusion:

Following the inspection, DSI recommends that the clinical portions of studies PKD_09_277 and PKD_09_278 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Sripal R. Mada, Ph.D., Bioequivalence
GLP and Bioequivalence Branch, DSI

Final Classification:

NAI – Sun Pharmaceutical Industries Ltd., Vadodara, India
FEI: 3004520013

cc:
DSI/Ball
DSI/GLPBB/Mada/Dejernett/Yau/Haidar/CF
HFD-650/Solana-Sodeinde/Conner
HFR-SE1522/Chester
Draft: SRM 02/23/2011
Edit: MKY 02/24/2011
DSI: 6078; O:\Bioequiv\EIRCover\200484sum.nia.doc
FACTS: 1182770

Email: CDER DSI PM TRACK

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

/s/

SRIPAL R MADA
02/24/2011

MARTIN K YAU
02/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200484

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: IV	**Team: 43**	**PM: Anh Bui**

Electronic ANDA: Yes ☒ No ☐

ANDA #:200484
Firm Name:Sun Pharma Global FZE
ANDA Name:Niacin Extended-release Tablets USP, 500 mg and 1000 mg
RLD Name:Niaspan by AbbVie Inc.; NDA 20381

Electronic AP Routing Summary Located:
V:\Chemistry Division IV\Team 43\Electronic AP Summary

AP/TA Letter Located:
V:\Chemistry Division IV\Team 43\Final Version for DARRTS Folder\Approval Letters for Bob

Project Manager Evaluation: **Date: 03/27/14 Initials:** ab

☒ Previously reviewed and tentatively approved --- Date 06/10/13
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 09/30/09	Date of Application 09/29/09	Date Acceptable for Filing 12/16/09
Patent Certification (type) PIV	Date Patent/Excl. expires 03/15/18	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☒ Acceptable ☐ OAI *EES Date Acceptable: 11/13/2013* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 06/06/13 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 10/17/11 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 04/11/2014 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 04/14/14 REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☐ Bob West / Peter Rickman

☐ Kathleen Uhl

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 3/31/2014**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Niaspan ER NDA# 20-381 Date Checked 4/17/14 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled:3/1/2013 Is applicant eligible for 180 day NO Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐	

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA previously TA'd on 6/10/2013. At the time the TA was issued the reason cited for TA was an unexpired 30 month stay of approval. This stay of approval was a second 30 month stay that resulted from the sponsor's change in certifications from PIII to PIV on the '930, '715, '967, '691, '229 and '848 patents. There had been an earlier 30 month stay related to suit on the '428 and '035 patents but this stay expired on 7/5/2012. The CA related to the '930, '715, '967, '691, '229 and '848 patents will expire on 4/20/2014. However, since each of these 6 patents has expired there can be no 30 month stay once the patent expires. The remaining unexpired patents which protect Niacin are the '428(exp. 5/27/2017) and the '035(exp. 3/15/2018).

Sponsor submitted a request for Final Approval on 3/21/2014 in which they assert they are eligible for Full Approval once 180 day exclusivity expires on 3/20/2014. In March of 2013, Sun submitted a copy of an Order-Stipulated Dismissal without Prejudice in the D of DE for CA 10 CV 0112. This is the CA that was originally filed against Sun for infringement of the '428 and '035 patents.

This ANDA is eligible for Full Approval as the CA pertaining to the only two remaining unexpired patents-the '428 and '035-was dismissed, all other patents have expired and the 180 day exclusivity granted to Barr's ANDA 76378 expired on 3/19/2014.

ANDA is eligible for Full Approval.

2. ***Labeling Endorsement***

Reviewer, BT: Labeling Team Leader, RW:

Date04/14/14 Date04/14/14

REMS required? REMS acceptable?

☐Yes ☐No ☐Yes ☐No ☐n/a

Comments:

From: Turner, Betty
Sent: Monday, April 14, 2014 8:14 AM
To: Bui, Yen Anh; Payne, Angela
Cc: Wu, Ruby (Chi-Ann)
Subject: FW: Please endorse ANDAs 200484 and 201273 for final approval--Div 4/ Team 43

Good morning Bui,

There are no changes for the labeling of ANDA 200484 AND 201273.

Letter:
ANDA 200484:

- In the address line add the following as the second line “U.S. Agent for Sun Pharma Global FZE”.
- Revise the established name by using lower case “r” in “release”.

ANDA 201273:

- In the address line revise “US Agent…” to read “U. S. Agent…”
- Revise the established name by using lower case “r” in “release”.

Thanks,

Betty
From: Bui, Yen Anh
Sent: Friday, April 11, 2014 6:01 PM
To: Turner, Betty; Wu, Ruby (Chi-Ann)
Subject: Please endorse ANDAs 200484 and 201273 for final approval--Div 4/ Team 43

Hi Betty and Ruby,

These ANDAs are ready for final approval.
Would you please provide labeling endorsement.

Thank you so much!
Have a great weekend!
Anh

Anh Bui, Pharm.D.
LT, United States Public Health Service
Regulatory Project Manager
Office of Generic Drugs, FDA
MPN 2, HFD-617, Rm N147
Rockville, MD 20855
Phone: (240)-276-9613

3. ***Paragraph IV Evaluation*** **PIV's Only**
   David Read **Date 4Apr2014**
   OGD Regulatory Counsel **InitialsDTR**
   Pre-MMA Language included ☐
   Post-MMA Language Included ☐
   Comments:Minor changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 15 April 2014**
   Chemistry Div. **IV (Iser)** **InitialsUA for NY**
   Comments:CMC OK for Approval. Upinder Atwal, Ph.D., Acting Deputy Director, Division of Chemistry IV.

OGD Office Management Evaluation

5. Peter Rickman **Date 4/17/14**
Director, DLPS **Initials rlw/for**

Para.IV Patent Cert: Yes☐ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: This ANDA was granted tentative approval on June 10, 2013. Final approval was blocked at that time by the 30-month stay of approval associated with ongoing patent litigation. Refer to the administrative summary prepared at the time of the tentative approval. Since the tentative approval, all patents except for the '428 and '035 patents have expired. Litigation with regard to the '428 and '035 patents was dismissed. This dismissal removed the legal barrier to approval of this ANDA.

Final-printed labeling (FPL) found acceptable for approval /11/14, as endorsed 4/14/14. No REMS is required.

CMC remains acceptable for approval - as endorsed 4/15/14 (above).

OR

6. Robert L. West **Date 4/17/14**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☒
Petition: Yes☐ No☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 12/11/13 (Verified 4/17/14). No "OAI" Alerts noted.

Of the patents currently listed in the "Orange Book", only two patents - the '428 and the '035 - remain unexpired. Sun Pharma Global provided a paragraph IV certification to each of those patents and was sued within the 45-day period. All litigation with respect to these patents was subsequently dismissed. There is no exclusivity currently listed in the "Orange Book" for this drug product.

No applicant is currently entitled to 180-day generic drug exclusivity for this drug product.

This ANDA is the "sister" ANDA to Sun Pharma Global's ANDA 201273 for the 750 mg strength of this drug product.

This ANDA is recommended for approval.

7. ***OGD Director Evaluation***
Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 4/17/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐

Press Release Acceptable ☐

Comments:

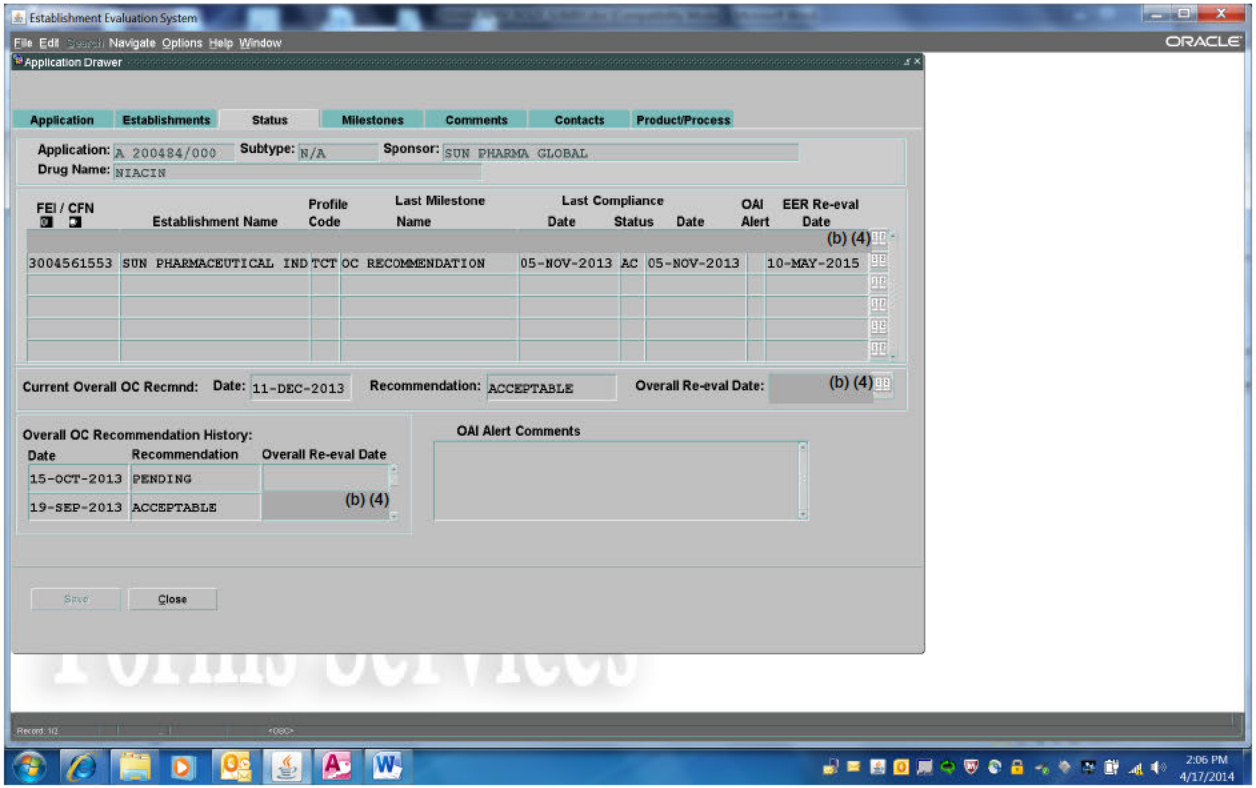
8. Project Manager **Date 04/23/14**
Initials ab

Comments:

Check Communication and Routing Summary into DARRTS

APPEARS THIS WAY ON ORIGINAL

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
Application: A 200484/000
Subtype: N/A
Sponsor: SUN PHARMA GLOBAL
Drug Name: NIACIN
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Last Compliance Status
OAI Date
OAI Alert
EER Re-eval Date
(b) (4)
3004561553 SUN PHARMACEUTICAL IND TCT OC RECOMMENDATION 05-NOV-2013 AC 05-NOV-2013 10-MAY-2015
Current Overall OC Recmnd: Date: 11-DEC-2013
Recommendation: ACCEPTABLE
Overall Re-eval Date: (b) (4)
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
15-OCT-2013 PENDING
19-SEP-2013 ACCEPTABLE (b) (4)
OAI Alert Comments
Save
Close
2:06 PM
4/17/2014

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020381 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020381	004	6080428	May 27, 2017			U - 331	
N020381	004	6080428	May 27, 2017			U - 1138	
N020381	004	6080428	May 27, 2017			U - 1139	
N020381	004	6080428	May 27, 2017			U - 1141	

Revised, Jun 2013

Reference ID: 3494004

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020381	004	6080428	May 27, 2017			U - 1140	
N020381	004	6129930	Sep 20, 2013		Y	U - 354	
N020381	004	6129930	Sep 20, 2013		Y	U - 1139	
N020381	004	6129930	Sep 20, 2013		Y	U - 1140	
N020381	004	6129930	Sep 20, 2013		Y	U - 1138	
N020381	004	6129930	Sep 20, 2013		Y	U - 1141	
N020381	004	6406715	Sep 20, 2013		Y	U - 450	
N020381	004	6469035	Mar 15,			U - 768	

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
			2018				
N020381	004	6469035	Mar 15, 2018			U - 1142	
N020381	004	6469035	Mar 15, 2018			U - 1145	
N020381	004	6469035	Mar 15, 2018			U - 1144	
N020381	004	6469035	Mar 15, 2018			U - 1143	
N020381	004	6676967	Sep 20, 2013			U - 548	
N020381	004	6676967	Sep 20, 2013			U - 1140	
N020381	004	6676967	Sep 20, 2013			U - 1139	

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020381	004	6676967	Sep 20, 2013			U - 1138	
N020381	004	6676967	Sep 20, 2013			U - 1141	
N020381	004	6676967	Sep 20, 2013			U - 1146	
N020381	004	6746691	Sep 20, 2013		Y	U - 586	
N020381	004	6818229	Sep 20, 2013		Y		
N020381	004	7011848	Sep 20, 2013			U - 712	
N020381	004	7011848	Sep 20, 2013			U - 1148	
N020381	004	7011848	Sep 20,			U -	

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
			2013			1147	
N020381	004	7011848	Sep 20, 2013			U - 1141	
N020381	004	7011848	Sep 20, 2013			U - 1140	
N020381	004	7998506	Sep 20, 2013			U - 1141	
N020381	004	7998506	Sep 20, 2013			U - 1139	
N020381	004	7998506	Sep 20, 2013			U - 1140	
N020381	004	7998506	Sep 20, 2013			U - 1138	

Exclusivity Data

There is no unexpired exclusivity for this product.

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

/s/

YEN ANH BUI
04/23/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 200484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sun Pharma Global FZE

TEL: (609) 495-2808

US AGENT: Caraco Pharmaceutical Laboratories, Ltd.
ATTN: Kalpana R. Vanam

FAX: (609) 495-2711

FDA CONTACT PHONE: (240) 276-9613

FROM: Yen Anh Bui

Dear Sir or Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated February 8, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-release Tablets USP, 500 mg and 1000 mg.

Reference also made to your amendment dated March 21, 2014.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Yen Anh Bui at (240) 276-9613.

We have completed our review, as amended, and have the following comments:

LABELING:

Labeling Deficiencies determined on March 26, 2014, based on your submission dated March 21, 2014.

1. GENERAL COMMENT:

   Does your product meet the USP dissolution test? If your product does not meet the USP dissolution test, please add the disclaimer "USP Dissolution Test Pending" to the end of the DESCRIPTION section in your insert labeling.

2. CONTAINER:

   a. We note that the labels submitted in the amendment dated March 21, 2014, contains a logo for the distributor and a logo for the manufacturer. The labels submitted November 21, 2011, contained only the manufacturer's logo. Please comment.

   b. We encourage you to revise the established name to read "Niacin Extended-release Tablets, USP" [use lower case "r" in "release"]. Please note that this deficiency is annual reportable.

3. INSERT:

   a. WARNINGS AND PRECAUTIONS, Mortality and Coronary Heart Disease Morbidity: Replace "niacin" with "niacin extended-release" except in the section of the sentence as follows. "…or matching placebo (IR Niacin, 100 to 150 mg, n = 1696)."

   b. ADVERSE REACTIONS, Clinical Studies Experience: In the last paragraph that begins with "In AIM-HIGH involving 3, 414 patients…" replace "niacin" with "niacin extended-release" except in the section of the sentence as follows. "…or matching placebo (IR Niacin, 100 mg to 150 mg, n = 1696)."

   c. Please refer to container comment 2(a).

4. PATIENT INFORMATION LEAFLET:

   Please refer to container comment 2(a).

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Sincerely yours,

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

KYLE T SNYDER
03/28/2014

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: IV	Team: 43	PM: Dat Doan

Electronic ANDA: Yes ☒ No ☐

ANDA #:200484
Firm Name:Sun Pharma Global FZE
ANDA Name:Niacin Extended-Release Tablets USP, 500 mg and 1000 mg
RLD Name:Abbott Laboratories; NDA 20381; Niaspan

Electronic AP Routing Summary Located:
Z:\Chemistry Division IV\Team 43\Electronic AP Summary

AP/TA Letter Located:
Z:\Chemistry Division IV\Team 43\Final Version for DARRTS Folder\Approval Letters for Bob

Project Manager Evaluation: **Date:** **Initials:**

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 9/30/09	Date of Application 9/29/09	Date Acceptable for Filing 12/16/09
Patent Certification (type) IV	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 2/10/12* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 6/6/13 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 10/17/11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 12/29/12 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____
GDUFA User Fee Obligation Status Met☐ Unmet☐**: Date:** _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☐ Office of Management, Fee Verification, Date emailed: _____; Date OM Response: _____

☐ Labeling Endorsement, Date emailed: _____ REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Gregory Geba

☐Filed AP Routing Summary in DARRTs Reference ID: 3322009	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Office of Management***
CDER Collections (cdercollections@fda.hhs.gov)

Date Emailed:
Date Verification response received from OM:

GDUFA User Fee Obligation Status Met☐ Unmet☐: **Date:** _____*

☐ Misbranding statement in letter for no Facility Fee payment
☐ Misbranding statement in letter for Failure to Self-ID
☐ Backlog fee not paid for ANDA in question statement in letter

Comments:DARRTS shows GDUFA fees met

*NOTE: If OM verification was completed prior to the close of the fiscal year, obtain a new OM verification response for the current fiscal year.

2. ***Regulatory Support Branch Evaluation***
Martin Shimer **Date: 1/23/2013**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Niaspan NDA# 20-381 Date Checked 6/7/13 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☐ No ☒ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☐ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☐ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 9/30/2009, BOS=Niaspan NDA 20-381, PIV to '428, '930, '715, '035, '967, '691, '229, '848. ANDA ack for filing for the 500 mg and 1 g strengths with a PIV on 9/30/2009 (LO dated 12/16/2009). Patent Amendment rec'd on 1/5/2010-PIV to '428, '035 PIII to '930, '715, '967, '691, '229, '848. Patent Amendment rec'd on 1/14/2010-notice sent via (b) (4) to Abbott Labs in Abbott Park, IL with notice delivered on 1/5/2010. Patent Amendment rec'd on 4/28/2010- CA 10 CV 0112 filed in the D of DE on 2/12/2010 for infringement of the '428 and '035 patents, since suit was filed within 45 days there was an automatic 30 month stay of approval which expired on 7/5/2012. Patent Amendment rec'd on 1/11/2011-restatement of certs to address change in patent exp. of the '229 patent which now expires on 9/20/13, certifications are the same as the 1/5/2010 amendment. Patent Amendment rec'd on 9/27/2011-split PIV/section viii for the '035 and PIII cert to newly listed '506 patent. Patent Amendment rec'd on 10/21/2011-change from PIII to PIV on the '930, '715, '967, '691, '229, '848, and '506. Patent Amendment rec'd on 10/24/2011-notice sent via (b) (4) (b) (4) to Abbott Labs in Abbott Park IL with notice delivered on 10/20/2011. Patent Amendment rec'd on 12/20/2011-changed back to PIV cert on the '035 patent (previously split PIV/section viii). '428-PIV orig, sued, 30 month exp. 7/5/12 '930-PIV 10/21/11 amend-sued within 45 days, 30 month exp. 4/20/2014 '715-PIV 10/21/11 amend-sued within 45 days, 30 month exp. 4/20/2014 '035-PIV orig, sued, 30 month exp. 7/5/12 '967-PIV 10/21/11 amend-sued within 45 days, 30 month exp. 4/20/2014 '691-PIV 10/21/11 amend-sued within 45 days, 30 month exp. 4/20/2014	

'229-PIV 10/21/2011 amend-sued within 45 days, 30 month exp. 4/20/2014
'848-PIV 10/21/2011 amend-sued within 45 days, 30 month exp. 4/20/2014
'506-PIV 10/21/2011 amend-not sued
Sun's US Agent contacted via e-mail on 1/16/13 for additional patent information.
Patent Amendment rec'd on 1/22/2013-suit filed in the D of DE, CA # 11 CV 1190 on 12/2/2011 for infringement of the '930, '715, '967, '691, '229, and '848 patents, cover letter of the amendment indicates that litigation remains ongoing.
A 30 month stay applies to the suit filed against Sun on 12/2/2011 as each of the 6 patents for which Sun was sued were listed in the OB at the time Sun submitted their ANDA. It is noted that Sun's original application contained PIV certs to these patents but Sun amended their ANDA to provide for PIII certs prior to submitting notice-amendment for PIII certs rec'd on 1/5/2010, notice for PIV sent on 1/14/2010. 30 month stay related to the '428 patent has expired.

Language in TA letter should indicated that 1st 30 month stay associated with the '428 expired on 7/5/2012 but there is a second 30 month stay associated with the 6 patents noted above which has not yet expired.

3. ***Labeling Endorsement***

Reviewer, :
Date_____
Initials_____

Labeling Team Leader, :
Date 6/7/13
Initials rlw/for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:
Labeling found acceptable for approval (FPL) 12/29/12. No REMS is required.

4. ***Paragraph IV Evaluation*** **PIV's Only**

David Read
OGD Regulatory Counsel
Date 10Apr2013
InitialsDTR
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:TA letter okay.

5. ***Quality Division Director /Deputy Director Evaluation***

Chemistry Div. **IV (Iser)**
Date 6/6/13
Initialsdd
Comments:Final CMC review edorsed by R. Iser, Director, Division of Chemistry IV 6/6/13.

OGD Office Management Evaluation

6. Peter Rickman
Director, DLPS
Date 6/7/13
Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Bioequivalence studies (fasting and non-fasting) on the 1,000 mg strength found acceptable. In-vitro dissolution testing for both strengths also found acceptable. Waiver granted for the 500 mg strength under 21 CFR 320.22(d)(2). Bio study sites have acceptable OSI inspection histories. Office-level bio endorsed 10/17/11.

Labeling found acceptable for tentative approval 12/29/12. No REMS is required.

CMC found acceptable for approval (Chemistry Review #3 - Addendum #1) 6/6/13.

OR

7. Robert L. West **Date 6/7/13**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☒ No☐
Petition: Yes☐ No☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Refer to the comments above by M. Shimer pertaining to the regulatory and legal history of this ANDA. Sun Pharma Global provided paragraph IV certifications to each of the listed patents and was sued on each patent (except not sued on the '506 patent). The 30-month statutory hold with respect to the '428 and '035 patents expired on July 5, 2012. The 30-month statutory hold with respect to the '930, '715, '967, '691, '229 and '848 patents will expire on April 20, 2014. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

Note: Barr's ANDA 76-250 (1,000 mg) and ANDA 76-378 (500 mg and 750 mg) for this drug product were approved On April 14, 2005 and April 26, 2005, respectively. Both are currently listed in the discontinued section of the "Orange Book".

This ANDA is recommended for tentative approval.

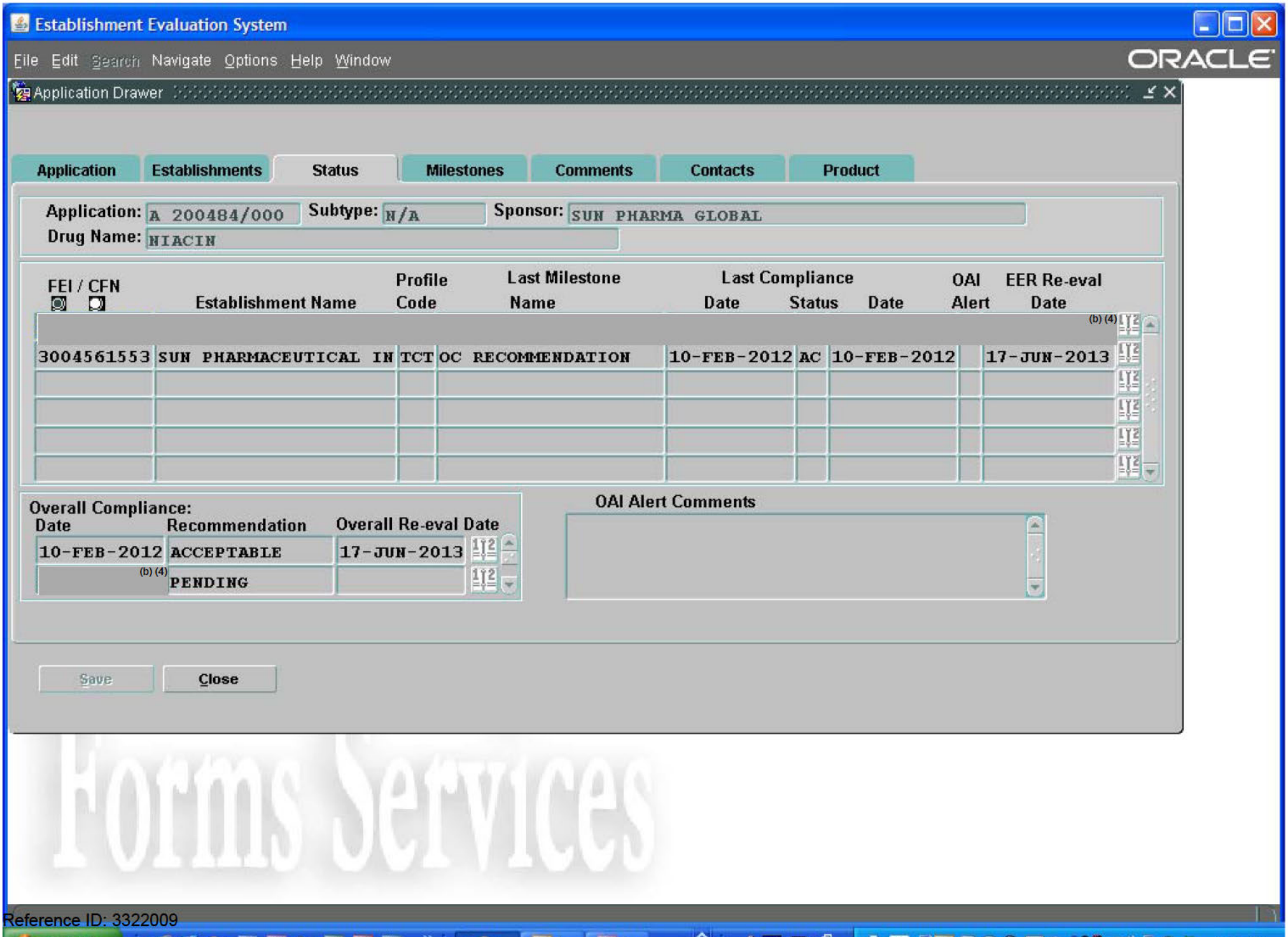
8. ***OGD Director Evaluation***
Gregory Geba
Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 6/7/13.

First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 6/10/2013
Initials mg
GDUFA User Fee Obligation Status Met☐ Unmet☐

Check Communication and Routing Summary into DARRTS



Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

-

Patent and Exclusivity Search Results from query on Appl No 020381 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020381	004	6080428	May 27, 2017			U - 1138	
N020381	004	6080428	May 27, 2017			U - 1139	
N020381	004	6080428	May 27, 2017			U - 1140	
N020381	004	6080428	May 27, 2017			U - 1141	
N020381	004	6080428	May 27, 2017			U - 331	
N020381	004	6129930	Sep 20, 2013		Y	U - 1138	
N020381	004	6129930	Sep 20, 2013		Y	U - 1139	

N020381	004	6129930	Sep 20, 2013	Y	U - 1140	
N020381	004	6129930	Sep 20, 2013	Y	U - 1141	
N020381	004	6129930	Sep 20, 2013	Y	U - 354	
N020381	004	6406715	Sep 20, 2013	Y	U - 450	
N020381	004	6469035	Mar 15, 2018		U - 1142	
N020381	004	6469035	Mar 15, 2018		U - 1143	
N020381	004	6469035	Mar 15, 2018		U - 1144	
N020381	004	6469035	Mar 15, 2018		U - 1145	
N020381	004	6469035	Mar 15, 2018		U - 768	
N020381	004	6676967	Sep 20, 2013		U - 1138	
N020381	004	6676967	Sep 20, 2013		U - 1139	
N020381	004	6676967	Sep 20, 2013		U - 1140	
N020381	004	6676967	Sep 20, 2013		U - 1141	
N020381	004	6676967	Sep 20, 2013		U - 1146	
N020381	004	6676967	Sep 20, 2013		U - 548	
N020381	004	6746691	Sep 20, 2013	Y	U - 586	
N020381	004	6818229	Sep 20, 2013	Y		
N020381	004	7011848	Sep 20, 2013		U - 1140	
N020381	004	7011848	Sep 20, 2013		U - 1141	
N020381	004	7011848	Sep 20, 2013		U - 1147	
N020381	004	7011848	Sep 20, 2013		U - 1148	
N020381	004	7011848	Sep 20, 2013		U - 712	
N020381	004	7998506	Sep 20, 2013		U - 1138	
N020381	004	7998506	Sep 20, 2013		U - 1139	

N020381	004	7998506	Sep 20, 2013		U - 1140	
N020381	004	7998506	Sep 20, 2013		U - 1141	

Exclusivity Data

There is no unexpired exclusivity for this product.

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

/s/

MARK A GONITZKE
06/10/2013

Turner, Betty

From: Turner, Betty
Sent: Wednesday, January 02, 2013 3:08 PM
To: 'Robert.Kurkiewicz@sunpharmausa.com'
Subject: ANDA 200484 Niacin Extended-Release Tablets

Dear Mr. Kurkiewicz,

The following are requested revisions from the review of your amendment dated May 8, 2012, for Niacin Extended-Release Tablets USP, 500 mg and 1000 mg. The revisions are "POST-APPROVAL" revisions and may be submitted as a Supplement-Changes Being Effected.

1. GENERAL COMMENT
   Please note this product is the subject of a USP monograph. We encourage you to add "USP" to your established name in the container and insert labeling.

2. CONTAINER
   Please note that the RLD uses the following colors for their product; 500 mg (blue); 750 mg (orange) and 1000 mg (green). We notice that you proposed the following colors for your product; (b) (4)

3. INSERT
   a. We encourage you to add "USP" in the Title, Dosage and Administration, Description and How Supplied sections.
   b. HIGHLIGHTS, ADVERSE EVENTS – Please revise the statement "To report SUSPECTED ADVERSE REACTIONS…" to include the manufacturer's name and phone number to be in accord with 21 CFR 201.57(a)(11)(ii).

   c. 12.3 Pharmacokinetics, Absorption

      Upon further review, please revise the second paragraph to read as follows.

      "Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent."

Please contact me if you have questions.

Regards,
Betty

Betty Turner, Pharm.D.
Labeling Reviewer
Office of Generic Drugs
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855
Tel: 240-276-8728
betty.turner@fda.hhs.gov

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

/s/

BETTY B TURNER
01/02/2013

QUALITY DEFICIENCY - MINOR

ANDA 200484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Sun Pharmaceutical Industries, Inc.

TEL: 313-556-4105

ATTN: Robert Kurkiewicz

FAX: 248-926-0231

FROM: Mark Gonitzke

FDA CONTACT PHONE: (240) 276-8422

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated September 29, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-release Tablets, 500 mg and 1000 mg.

Reference is also made to your amendment dated September 30, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

ANDA: 200848 **APPLICANT: Sun Pharmaceutical Industries, Inc.**

DRUG PRODUCT: Niacin Extended-release Tablets, 500 mg and 1000 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The Drug Master File# (b) (4) is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies. Please also make any applicable changes to the drug substance specifications based on consultation with DMF holder and provide the revised specifications and certificate of analysis.

2. Please provide updated long-term stability data if available.

Sincerely yours,

{See appended electronic signature page}

Robert Iser
Acting Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

SUSAN ZUK
02/10/2012

Telephone Fax

ANDA 200-484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Sun Pharmaceutical Industries,Inc.
U.S. Agent for Sun Pharma Global FZE

TEL: 609-495-2823

FAX: 609-495-2711

ATTN: Anne Toland

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-Release Tablets 500 mg and 1000 mg.

Pages (including cover): _3_

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200484 Date of Submission: November 21, 2011

Applicant's Name: Sun Pharma Global FZE

Established Name: Niacin Extended-Release Tablets 500 mg and 1000 mg

---

Labeling Deficiencies:

1. **CONTAINER** (30s, 90s, 100s and 1000s)

   We encourage you to add “Pharmacist: dispense with patient package insert” to the principal display panel.

2. **PACKAGE INSERT**

   You may not “carve out” the indication “In combination with simvastatin and lovastatin...”. According to the electronic Orange Book, the ‘035 patent does not have the use code associated with this indication. You may only file a “viii” to the use codes listed in the Orange Book. Please contact the Regulatory Support Staff for further information about patent certifications.

   Please revise your labeling accordingly.

Submit labels and labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last labeling submission with all differences annotated and explained.

Sincerely Yours,

{See appended electronic signature page}

_____
Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

JOHN F GRACE
11/30/2011

TELEPHONE REQUEST

Date: 10-4-2011

ANDA#: 200484

Firm: Sun Pharma Global FZE

Drug Product: Niacin Tablet, film coated, extended release, 500 and 1000 mg

Contact: Robert Kurkiewicz, Sr. VP-Regulatory Affairs

Reviewer: Bruce Lerman, Ph.D.

Re: Request for Information

- For the fasting study (study # PKD_09_277) please submit the original analytical run data for subject 8 for run ID PKD_09_277.PRO\sample08\180809\subject_08

END OF TELEPHONE REQUEST

From: Solana-Sodeinde, Diana A
Sent: Thursday, October 06, 2011 10:36 AM
To: Braddy, April
Cc: Lerman, Bruce; Lu, Dongmei
Subject: RE: TELEPHONE REQUEST (for raw data) 200484 Sun Pharma 10-4-2011.doc

Done!

Called and left a vm for firm to submit your request. I will let you know when I hear from them.

Thank you,

Diana (Lola) Solana-Sodeinde, Pharm. D.

LCDR, USPHS, Regulatory Health Project Manager,
Division of BioEquivalence I, Branch X,
Office of Generic Drugs,
Center for Drugs, Evaluation and Research
Food & Drug Administration.

7520 Standish Place,
Rockville, MD 20855
work: (240) 276-8782
fax: (240) 276-8766

From: Braddy, April
Sent: Wednesday, October 05, 2011 9:01 AM
To: Solana-Sodeinde, Diana A
Cc: Lerman, Bruce; Lu, Dongmei; Braddy, April
Subject: FW: TELEPHONE REQUEST (for raw data) 200484 Sun Pharma 10-4-2011.doc

Good morning, Diana:

The telephone request is okay. Please contact the firm to request the information as outlined in the document.

Thanks,

April

From: Lerman, Bruce
Sent: Tuesday, October 04, 2011 9:51 AM
To: Lu, Dongmei
Cc: Braddy, April
Subject: TELEPHONE REQUEST (for raw data) 200484 Sun Pharma 10-4-2011.doc

<< File: TELEPHONE REQUEST (for raw data) 200484 Sun Pharma 10-4-2011.doc >>

Hi Dongmei,

Can you review the attached telephone request and submit to the project manager assigned to us in Diana's absence?

Thanks,
Bruce

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

/s/

DIANA A SOLANA-SODEINDE
10/06/2011

TELEPHONE REQUEST

Date: 8-24-2011

ANDA#: 200484

Firm: Sun Pharma Global FZE

Drug Product: Niacin Tablet, film coated, extended release, 500 and 1000 mg

Contact: Robert Kurkiewicz at 313-556-4105

Re: Request for Information

- For the fasting study (study # PKD_09_277) and fed study (study #PKD_09_278), please submit in separate SAS transport files, the original plasma concentration data and pharmacokinetic data for both Niacin and Nicotinuric Acid for all subjects.

Comments:
On 9/8/2011, the reviewer contacted me that the firm had submitted an incomplete response. They only submitted analytical run data for the Niacin product.

On 9/8/2011, they were requested to re-submit a complete response to also include the analytical run data for the Nicotinuric Acid product within 7-10 business days via eCTD gateway submission.

END OF TELEPHONE REQUEST

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

/s/

DIANA A SOLANA-SODEINDE
09/08/2011

TELEPHONE REQUEST

Date: 8-24-2011

ANDA#: 200484

Firm: Sun Pharma Global FZE

Drug Product: Niacin Tablet, film coated, extended release, 500 and 1000 mg

Contact: Robert Kurkiewicz at 313-556-4105

Reviewer: Bruce Lerman, Ph.D.

Re: Request for Information

- For the fasting study (study # PKD_09_277) and fed study (study #PKD_09_278), please submit in separate SAS transport files, the original plasma concentration data and pharmacokinetic data for both Niacin and Nicotinuric Acid for all subjects.

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

/s/

NAM J CHUN
08/24/2011

Vu, Thuyanh (Ann)

From: Vu, Thuyanh (Ann)
Sent: Wednesday, July 20, 2011 1:42 PM
To: 'Anne.Toland@sunpharmausa.com'
Subject: 201273 and 200484 (niacin extended-release tablets)

Ms. Toland,

Because your firm did not perform bioavailability studies on the dosage form equivalence of the 500 mg and 1000 mg tablet strengths, please revise:

"Single-dose bioavailability studies have demonstrated that the 500 mg and 1000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablet strengths are not dosage form equivalent" to

(b) (4)

This text is located in subsection 12.3 Pharmacokinetics, Absorption. Please submit this revision in your next labeling amendment.

Thanks
Ann

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

/s/

THUYANH VU
07/20/2011

QUALITY DEFICIENCY - MINOR

ANDA 200484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sun Pharmaceutical Industries, Inc. TEL: (609) 495-2823

ATTN: Anne Toland FAX: (609) 495-2711

FROM: Mark Gonitzke FDA CONTACT PHONE: (240) 276-8422

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 29, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-release Tablets, 500 mg and 1000 mg.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

ANDA: **200484**

APPLICANT: **Sun Pharmaceutical Industries Ltd.**

DRUG PRODUCT: Niacin Extended-release Tablets, 500 mg and 1000 mg

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. (b) (4)

10.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The Drug Master File (b) (4) is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has responded to the deficiencies. Please also make any applicable changes to the drug substance specifications based on consultation with DMF holder and provide the revised specifications and certificate of analysis.

2. Please provide all available long-term stability data.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

SUSAN ZUK
01/20/2011

From:	Shimer, Martin
To:	"John.Dauer@sunpharmausa.com";
cc:	Shimer, Martin;
Subject:	RE: Request for Approval to Rely on (b) (4) As Proof of Delivery (ANDA No. 20-484 for Niacin ER tablets)
Date:	Monday, January 04, 2010 6:25:06 AM

Mr. Dauer,

It is permissible to use (b) (4) in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 200484.

Regards,

Martin H. Shimer

-----Original Message-----
From: John.Dauer@sunpharmausa.com [mailto:John.Dauer@sunpharmausa.com]
Sent: Thursday, December 31, 2009 12:14 AM
To: Shimer, Martin
Subject: Request for Approval to Rely on (b) (4) As Proof of Delivery (ANDA No. 20-484 for Niacin ER tablets)

Dear Mr. Shimer,

I am Chief Patent Counsel for Sun Pharmaceutical Industries, Inc.. I am writing on behalf of Sun in connection with its ANDA No. 20 0484 for a drug product named Niacin Extended-release Tablets, 500 mg and 1000 mg.

I am writing to request permission to use and rely on overnight courier services in lieu of the U.S. Postal Service certified mail, return receipt delivery service for purposes of providing notice to the NDA holder and any patent assignees associated with Paragraph IV certifications contained within the aforementioned ANDA. More specifically, we request permission to use and rely on (b) (4) as proof of delivery of a notice letter directed to Abbott Laboratories in Abbott Park, IL, U.S.A. (NDA holder and patent owner). Please let me know whether Sun can rely on (b) (4) for purposes of demonstrating delivery of the notice letter.

If you have any questions, then please let me know.

Best regards,
John

==========
John L. Dauer, Jr.
Chief Patent Counsel
Sun Pharmaceutical Industries Inc.
270 Prospect Plains Rd.
Cranbury, NJ 08512
Office (609) 495-2865
Mobile (b) (6)
Fax (609) 495-2715
==========

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

/s/

MARTIN H Shimer
01/18/2011

BIOEQUIVALENCE AMENDMENT

ANDA 200484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(240-276-9327)

APPLICANT: Sun Pharma Global FZE

TEL: 609-495-2823

ATTN: Anne Toland

FAX: 609-495-2711

FROM: Diana Solana-Sodeinde

FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on September 30, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-Release tablets, 500 and 1000 mg.

Reference is also made to your amendments dated May 26, 2010 and September 6, 2010.

The Division of Bioequivalence has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 200484

APPLICANT: Sun Pharma Global

DRUG PRODUCT: Niacin Extended-Release Tablets, 500 mg and 1000 mg

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

1. For the Fasted Study, No. PKD_09_277, sample reanalysis was conducted for Niacin and Nicotinuric Acid for all samples pertaining to subject 16. You indicated that the sample reanalysis was conducted due to suspected "sample mix up" (Code J). Please provide an adequate and detailed explanation as to why you believed the samples were mixed up. In addition, please provide a summary table listing the original assayed values, the reassayed values and the reported values for this subject.

2. For the Fasted Study, Study No. PKD_09_277, all samples for subjects 8, 16, 17, and 22 were reassayed for Niacin and Nicotinuric Acid due to "rejected analytical run" (code J). In addition, for Fed Study, Study No. PKD_09_278, the entire subject samples for subject 28 (niacin and nicotinuric acid samples) and subject 13 (nicotinuric acid samples) were reanalyzed due to "rejected analytical run" (code J).

   There are several criteria outlined in Section 7.1.9 of the Standard Operating Procedure (SOP) PKD/S/019 Revision 03, entitled Sample Reanalysis and Reporting of Final Concentrations, detailing how samples can be classified as "rejected analytical runs." As required in section 7.1.9.3 of this SOP, for each subject reanalysis, please submit documentation of the "*investigated and detailed justification of the reanalysis of the batch [form-Attachment-3]".*

   In addition, please submit in tabular format, a complete list of original assay values, repeat assay values and reported values of these subjects for evaluation. For each subject, please clearly justify why the original or reassayed value was reported.

3. The DBE identified several instances where you did not follow the standard operating procedure (SOP) PKD/S/019, Sample Reanalysis and Reporting of Final Concentrations, for reassay performed due to "inconsistent profiles (code H)". An example of this can be seen in Study #PKD_09_277 for nicotinuric acid for subject 23 period 3 at 9 hours. The initial assay (145.6 ng/mL) did not differ by greater than 100% from the previous sample (106.0 ng/mL) or the subsequent sample (95.3 ng/mL). Another example is seen Study PKD_09_277 for nicotinuric acid for subject 23 period 4 at 5 hours. The plasma concentration for nicotinuric acid for subject 23 at 4 and 5 hours in period 4 was 942.6 ng/mL (reassayed 1174.7 ng/mL) and 126.8 ng/mL, respectively. The plasma concentration at Hour-5 differed from that of Hour-4 by greater than 100% but you did not reassay this sample as you did for other samples. Please submit the following:

   a) A summary table (Table 1) detailing all reassays that were performed correctly according to section 7.1.7 of SOP PKD/S/019;

b) A summary table (Table 2) detailing all reassays that were performed incorrectly according to section 7.1.7 of SOP PKD/S/019; and
c) SAS-Transport formatted files containing the original assay data for all samples identified in Table 2. Tables 1 and 2 should contain all pertinent information including the initial value, the reassayed value, and the final reported value for each reassayed sample.

In addition, section 7.1.7.5 (Result of sample repeated as PK inconsistent profile) is extremely unclear as to how reanalysis was performed for samples coded "N". Please provide concrete examples of how the decision was made to perform reanalysis and report the final value for reassays coded as "N".

4. SOP No. PKD/S/019 Revision 03 became effective after the study sample analyses were completed. Therefore, please provide a copy of the SOP that was effective at the time of analysis and please outline the changes made to the SOP between revision 2 and revision 3. Also, please indicate which revision of the SOP was effective at the time of the study. If PKD/S/019 Revision 2 was the only version of this SOP effective at the time of the study, please submit a copy of this SOP version.

5. SOP No. PKD/S/033, Chromatographic Analysis of Study Sample was referenced in SOP No. PKD/S/019 revision 3 but was not included in the application. Please submit a full copy of SOP PKD/S/033 which was effective during the study sample analysis periods.

6. Two concentration ranges for calibration curves (CC) [i.e., 29.5, 58.9, 149.3, 345.7, 903.7, 1296.3, 1517.3 & 1964.1 (ng/ml) and 29.6, 59.2, 149.9, 347.1, 907.1, 1301.5, 1577.6 and 1972.0 (ng/ml)] were used for bioanalysis of nicotinuric acid samples in the Fasted Study (Study No. PKD_09_277). Please provide an explanation as to why you used two different CC concentration ranges. In addition, for each CC concentration range used, please specify all subject samples that were analyzed using such range.

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

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

/s/

DALE P CONNER
11/22/2010

MEMORANDUM

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

Date Requested: 5/20/2010

TO: Joseph Salewski
Deputy Director
Division of Scientific Investigations
WO, Bldg 51, Rm 5348

FROM: Dale P. Conner, Pharm D
Director, Division of Bioequivalence I, HFD-650

SUBJECT: Biopharmaceutics Compliance Program 7348.001

REQUEST FOR INSPECTION

Electronic Submission: Yes
Bio Study Status: Only Dissolution review is complete. The Bio review of the pK Studies will be reviewed at a later date.
Priority: B
Due Date: 11/16/2010

ANDA No.	200484
Drug Product Name	Niacin Extended-Release Tablets
Strength (s)	500 mg and 1000 mg
Applicant Name	Sun Pharma Global FZE
Address	Office # 43, Block Y, SAIF Zone, P.O.Box # 122304, Sharjah, U.A.E
Applicant's Point of Contact	Ms. Anne Toland Sun Pharmaceutical Industries, Inc. 270 Prospect Plains Road Cranbury, NJ 08512
Contact's Phone Number	609-495-2823
Contact's Fax Number	609-495-2711
Submission Date(s)	29-September-2009
First Generic	No

Study Number (s)	PKD_09_277	PKD_09_278	
Study Type (s)	Fasting	Fed	
Strength(s)	1000 mg	1000 mg	
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (INDIA)		

Reason for Inspection: Routine

Comments:

Please note that there is a pending For-Cause DSI request that was entered for the Analytical site (also located at the Clinical Site Address) on 1/4/2010 for ANDA 090362. The outcome for this DSI inspection is still pending.

In this specific memo, the Division of Bioequivalence is hereby requesting for a Routine DSI inspection of only the clinical site for this ANDA (ANDA 200484).

Project Manager: Solana-Sodeinde, Diana

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

DIANA A SOLANA-SODEINDE
05/20/2010

DALE P CONNER
05/21/2010

BIOEQUIVALENCE AMENDMENT

ANDA 200484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(240-276-9327)

APPLICANT: Sun Pharma Global FZE TEL: (609) 495-2823

ATTN: Anne Toland FAX: (609) 495-2711

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on September 29, 2009 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-Release Tablets, 500 mg and 1000 mg.

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **1** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request **Bioequivalence Long Term Stability Data**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA:	200484
APPLICANT:	Sun Pharma Global FZE
DRUG PRODUCT:	Niacin Extended-Release Tablets, 500 mg and 1000 mg

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

1. Your dissolution testing data are acceptable. However, your proposed dissolution specifications are not acceptable. Based on the submitted data, please acknowledge your acceptance of the following FDA-recommended method and specifications:

Medium:	Water
Volume:	900 mL
Apparatus:	I (basket)
Speed:	100 rpm
Sampling Times:	1, 3, 6, 9, 12 and 20 hours
Specifications:	1 Hr: NMT (b) (4) %
	3 Hrs: (b) (4) %
	6 Hrs: %
	9 Hrs: %
	12 Hrs: %
	20 Hrs: NLT (b) (4) %

2. You have not provided the long term stability (LTS) data of niacin in frozen plasma samples. Please provide LTS data for at least 111 days to cover the entire length of the maximum storage duration of the Bioequivalence study samples (i.e. from the time when the first blood sample was drawn until the time when the last plasma sample was analyzed).

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

DALE P CONNER
04/19/2010

Telephone Fax

ANDA 200-484

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Sun Pharmaceutical Industries,Inc.
U.S. Agent for Sun Pharma Global FZE

TEL: 609-495-2823

FAX: 609-495-2711

ATTN: Anne Toland

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Niacin Extended-Release Tablets 500 mg and 1000 mg.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200-484 Date of Submission: September 29, 2009

Applicant's Name: Sun Pharma Global FZE

Established Name: Niacin Extended-Release Tablets 500 mg and 1000 mg

---

Labeling Deficiencies:

1. **CONTAINER** (30s, 100s and 1000s)

(b) (4)

2. **PACKAGE INSERT**

   a. GENERAL COMMENT

      Please note that the established name is "niacin extended release". There are many instances in the insert that you replaced "Niaspan" with "niacin" instead of "niacin extended release". This is especially glaring in the section 14.4 where the insert specified a combination tablet of niacin extended release and simvastatin. Please revise accordingly.

   b. HIGHLIGHTS, ADVERSE REACTIONS:

      We note that you did not state your contact number for patients to report adverse reactions. Please provide your contact number.

   c. 6.1 Clinical Studies Experience

      Second paragraph, second sentence, add "burning sensation/skin burning sensation" between "sweating" and "chills".

   d. 6.2 Postmarketing Experience

      Third paragraph, add "burning sensation/skin burning sensation" between "sweating" and "skin discoloration"

Submit labels and labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last labeling submission with all differences annotated and explained.

Sincerely Yours,

{See appended electronic signature page}

_____

Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

JOHN F GRACE
03/25/2010
for Wm Peter Rickman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 200484

Sun Pharmaceutical Industries, Inc.
US Agent for Sun Pharma Global FZE
Attention: Anne Toland
270 Prospect Plains Road
Cranbury, NJ 08512

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated December 3, 2009 and your correspondence dated December 8, 2009.

NAME OF DRUG: Niacin Extended-release Tablets, 500 mg and 1000 mg

DATE OF APPLICATION: September 28, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 30, 2009

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the

patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing

agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Leigh Ann Bradford
Project Manager
240-276-8453

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

MARTIN H Shimer
12/16/2009
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
** **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 200484 **FIRM NAME**: SUN PHARMA GLOBAL

PIV: YES **Electronic or Paper Submission:** ECTD FORMAT (ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: NIACIN
DOSAGE FORM: EXTENDED-RELEASE TABLETS, 500 MG AND 1000 MG

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC3 Team 12 ☒***Activity***	***Bio Team 8: Bing Li*** ☒***Activity***
ANDA/Quality RPM: Leign Ann Bradford ☒ ***FYI***	Bio PM: Nam J. Chun (Esther) ☒ ***FYI***
Quality Team Leader: Iser, Robert No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☐***Activity***
Labeling Reviewer: Thuyanh (Ann) Vu ☒***Activity***	***Micro Review (No)*** ☐***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: SEPTEMBER 29, 2009 **Received Date**: SEPTEMBER 30, 2009

Comments: EC- 2 YES **On Cards:** YES
Therapeutic Code: 30201600 LIPID ALTERING AGENTS

Archival copy: ECTD FORMAT (ELECTRONIC DATA) **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

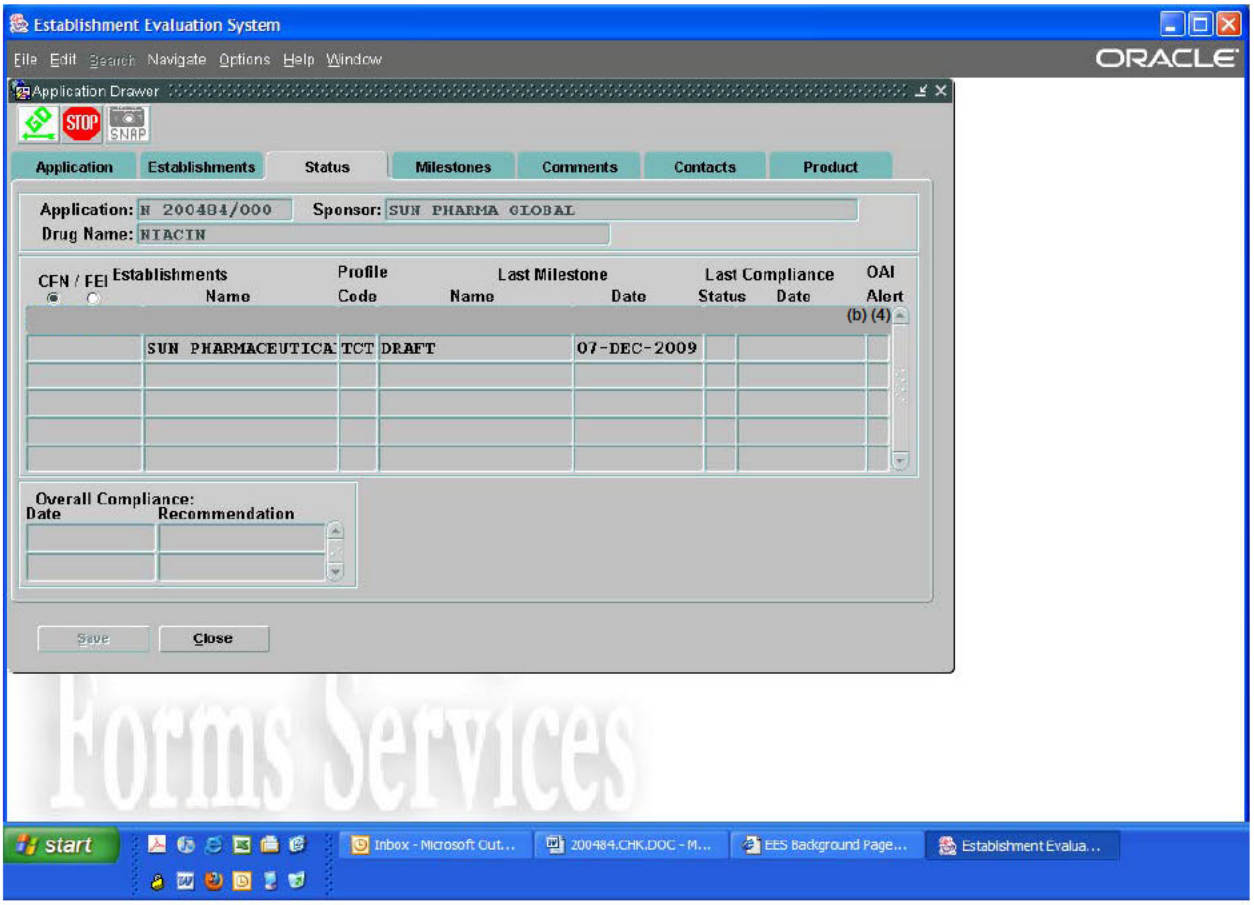
PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Ted Palat **Date 12/07/2009**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☒ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA: 609-495-2823 Anne Toland
1. submit qualitative breakdown of opadry II Pink. *ok*

Note: The BE studies measure niacin and its metabolite, nicotinuric acid. The studies pass based on the metabolite but do not pass based on the parent compound. We consider this a review issue. Niacin cannot always be reliably measured per the draft guidance on Niacin.



Contains Nonbinding Recommendations

Draft Guidance on Niacin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Niacin

Form/Route: Extended Release Tablets/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population.

---

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Healthy males and nonpregnant females, general population.

---

3. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 750 mg
   Subjects: Healthy males and nonpregnant females, general population.

Analytes to measure (in appropriate biological fluid): Niacin and its metabolite nicotinuric acid in plasma.

Bioequivalence based on (90% CI): If niacin cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for nicotinuric acid.

Waiver request of in-vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 1000 mg strength, (ii) proportionally similar 500 mg formulations to the 1000 mg strength, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: SEPTEMBER 29, 2009	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒

1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES , form 3454 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) YES	☒

1.3.5

1.3.5.1 Patent Information ☒

Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations

1.3.5.2 Patent Certification

1. Patent number(s) PIV – '428, '930, '715, '035, '967, '691, '229, '848

Patent and Exclusivity Search Results from query on Appl No 020381 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020381	002	6080428	May 27, 2017			U-331	
020381	002	6129930	Sep 20, 2013			U-354	
020381	002	6406715	Sep 20, 2013			U-450	
020381	002	6469035	Mar 15, 2018			U-768	
020381	002	6676967	Sep 20, 2013			U-548	
020381	002	6746691	Sep 20, 2013			U-586	
020381	002	6818229	Feb 15, 2014		Y		
020381	002	7011848	Sep 20, 2013			U-712	

Exclusivity Data

There is no unexpired exclusivity for this product.

U-331	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-354	METHOD OF TREATING HYPERLIPIDEMIA WITH NICOTINIC ACID WITHOUT CAUSING TREATMENT-LIMITING ELEVATIONS IN URIC ACID OR GLUCOSE LEVELS OR CAUSING LIVER DAMAGE, BY DOSING ONCE PER DAY IN THE EVENING OR AT NIGHT
U-450	INTERMEDIATE REL NICOTINIC ACID FORMULATIONS HAVING UNIQUE URINARY METAB PROFILES RESULTING FROM ABSORPTION PROFILES OF NICOTINIC ACID FROM THE INTERMEDIATE NICOTINIC ACID FORMULATIONS,SUITABLE FOR TX HYPERLIPIDEMIA FOLLOWING QD DOSING
U-768	A METHOD OF REDUCING THE CAPACITY OF EXTENDED RELEASE NICOTINIC ACID TO PROVOKE A FLUSHING REACTION BY PRETREATING AN INDIVIDUAL WITH A FLUSH INHIBITING AGENT PRIOR TO THE ADMINISTRATION OF THE EXTENDED RELEASE NICOTINIC ACID
U-548	A METHOD OF REDUCING FLUSH IN AN INDIVIDUAL BEING TREATED FOR A LIPIDEMIC DISORDER AND EFFECTIVELY TREATING THE LIPIDEMIC DISORDER
U-586	AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH
U-712	A METHOD OF USING A NICOTINIC ACID FORMULATION TO REDUCE ELEVATED TC, LDL-C AND TG LEVELS, AND RAISE HDL-C LEVELS IN PATIENTS WITH HYPERLIPIDEMIA

2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☐
   PIV ☒ (Statement of Notification) ☒
3. Expiration of Patent(s): 3/15/2018
   a. Pediatric exclusivity submitted? NO
   b. Expiration of Pediatric Exclusivity? NA
4. Exclusivity Statement: YES no exclusivity

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES, DMF (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒

(b) (4)

[redacted]

1.12.11	**Basis for Submission OK** NDA# : 20-381 Ref Listed Drug: NIASPAN Firm: ABBOTT LABORATORIES ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): 500 MG (YES)	☒

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** YES **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) **Manufacture** **Who manufactures the drug substance?** Name & Address of the manufacturer of Niacin is as follows, (b) (4) [redacted] 2. Function or Responsibility YES 3. Type II DMF number for API YES 4. CFN or FEI numbers YES	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) ROV-0031208, ROV-0041208 **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

Following this page, 3 Pages Withheld in Full as (b)(4)

3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **Who manufactures the drug product?** Sun Pharmaceutical Industries- Dadra Survey No. 259/15, Dadra- 396 191, UT of Dadra & Nagar Haveli, India. 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers YES **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 500 mg = (b) (4) tablets 1000 mg = (b) (4) tablets 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes **16 HOW SUPPLIED/STORAGE AND HANDLING** Niacin extended-release tablets are supplied as unscored, pink, film-coated, capsule-shaped tablets containing 500 or 1000 mg of niacin USP in an extended-release formulation. Tablets are debossed 'S' on one side and the tablet strength (500 or 1000) on the other side. Tablets are supplied as follows: 500 mg tablets: Bottles of 30's with Child Resistant Cap.....NDC 47335-539-83 Bottles of 100's with Child Resistant Cap.....NDC 47335-539-88 Bottles of 100's with Non Child Resistant Cap.....NDC 47335-539-08 Bottles of 1000's with Non Child Resistant Cap.....NDC 47335-539-18 1000 mg tablets Bottles of 30's with Child Resistant Cap.....NDC 47335-531-83 Bottles of 100's with Child Resistant Cap.....NDC 47335-531-88 Bottles of 100's with Non Child Resistant Cap.....NDC 47335-531-08 Bottles of 1000's with Non Child Resistant Cap.....NDC 47335-531-18 Storage: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container with child-resistant closure. 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES	☒

Reconciliation Summary : packaging

Counts	Niacin Extended Release Tablets, 500 mg Batch # GK91007	Niacin Extended Release Tablets, 1000 mg, Batch # GK91008
	(b) (4)	
30 (CRC)		
100 (CRC)		
100 (NCRC)		
1000 (NCRC)		
Total quantity packed		
(b) (4)		
(b) (4)		

3.2.R.1.P.2 Information on Components NO

3.2.R.2.P Comparability Protocols NO

3.2.R.3.P Methods Validation Package YES

Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions)

(Required for Non-USP drugs)

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) **Table 6: Formulation Data** (b) (4) [redacted] b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) NA **2. Lot Numbers of Products used in BE Study(ies):** ANDA: GK91008B, RLD: 642142E21 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

5.3.1.2 Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) NO ☒

Table 3A (1): Statistical Summary of the Comparative Bioavailability Data (Fasting study)

Niacin 1000 mg ER Tablet Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD_09_277 (Fasting Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=30)				
Parameter	**Test**	**Reference**	**Ratio %**	**90% C.I**
AUC_{0-t} (ng*hr/mL)	1982.15	1977.85	100.22	91.98 to 109.20
AUC_{0-inf} (ng*hr/mL)	2080.55	2064.36	100.78	92.97 to 109.25
C_{max} (ng/mL)	754.79	691.49	109.15	101.69 to 117.16

Table 3A (2): Statistical Summary of the Comparative Bioavailability Data (Fasting study)

Niacin 1000 mg ER Tablet Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD_09_277 (Fasting Bioequivalence data for Niacin from Niacin 1000 mg ER Tablet) (N=30)				
Parameter	**Test**	**Reference**	**Ratio %**	**90% C.I**
AUC_{0-t} (ng*hr/mL)	456.94	353.76	129.17	101.50 to 164.38
AUC_{0-inf} (ng*hr/mL)	603.42	553.58	109.00	91.05 to 130.50
C_{max} (ng/mL)	569.76	418.10	136.28	101.99 to 182.09

Niacin 1000 mg ER Tablet Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD_09_278 (Fed Bioequivalence data for (Nicotinuric acid (NUA) from Niacin 1000 mg ER Tablets) (N=32)				
Parameter	**Test**	**Reference**	**Ratio %**	**90% C.I**
AUC_{0-t} (ng*hr/mL)	9404.33	10066.42	93.42	87.05 to 100.27
AUC_{0-inf} (ng*hr/mL)	9664.85	10616.58	91.04	84.63 to 97.92
C_{max} (ng/mL)	2825.00	2916.18	96.87	89.18 to 105.23

Table 3B (2): Statistical Summary of the Comparative Bioavailability Data (Fed study)

Niacin 1000 mg ER Tablet Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals				
Study No. PKD_09_278 (Fed Bioequivalence data for Niacin from Niacin 1000 mg ER Tablet) (N=32)				
Parameter	**Test**	**Reference**	**Ratio %**	**90% C.I**
AUC_{0-t} (ng*hr/mL)	454.84	472.22	96.32	76.54 to 121.22
#AUC_{0-inf} (ng*hr/mL)	876.81	760.20	115.34	97.92 to 135.86
C_{max} (ng/mL)	439.84	430.26	102.23	78.31 to 133.45

#N= 27 for Test and 30 for Reference

2. Summary Bioequivalence tables:
   Table 10. Study Information YES
   Table 12. Dropout Information YES
   Table 13. Protocol Deviations YES

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   Table 11. Product Information YES
   Table 16. Composition of Meal Used in Fed Bioequivalence Study YES

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   Table 9. Reanalysis of Study Samples YES
   Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES
   Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7

Case Report Forms and Individual Patient Listing YES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Sun Pharmaceutical Industries, Ltd.
Attention: E. Venu Madhav
Tandalja, Vadodara-390020
India

APR 06 2007

Reference Number: OGD #07-0039

Dear Mr. Madhav:

This letter is in response to your correspondence dated January 4, 2007. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Niacin Extended Release Tablets, 500 mg, 750 mg and 1000 mg. OGD provides the following comments:

1. The following studies are recommended to establish bioequivalence of niacin extended-release tablets:

   a. Single-dose, fasting in-vivo bioequivalence studies comparing Niacin Extended-Release Tablets, 750 mg and 1000 mg to the respective strength of the reference listed drug (RLD) Niaspan® (Niacin) Extended-Release Tablets, 750 mg and 1000 mg. The RLD labeling states that single-dose bioavailability studies have demonstrated that the 500 mg and the 1000 mg *tablet strengths are dosage form equivalent, but the 500 mg and 750 mg* tablet strengths are not dosage form equivalent.

   b. A single-dose, fed *in-vivo* bioequivalence study comparing Niacin Extended-Release Tablets, 1000 mg, to the reference listed drug (RLD) Niaspan® (Niacin) Extended-Release Tablets.

2. Please measure both the parent compound, niacin, and its metabolite, nicotinuric acid, in plasma.

3. Niacin Extended-release Tablets, 500 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) an acceptable bioequivalence study on the 1000 mg strength, (2) acceptable dissolution testing of the 500 mg and 1000 mg strengths, and (3) proportional similarity in the formulations of the 500 mg and 1000 mg strengths

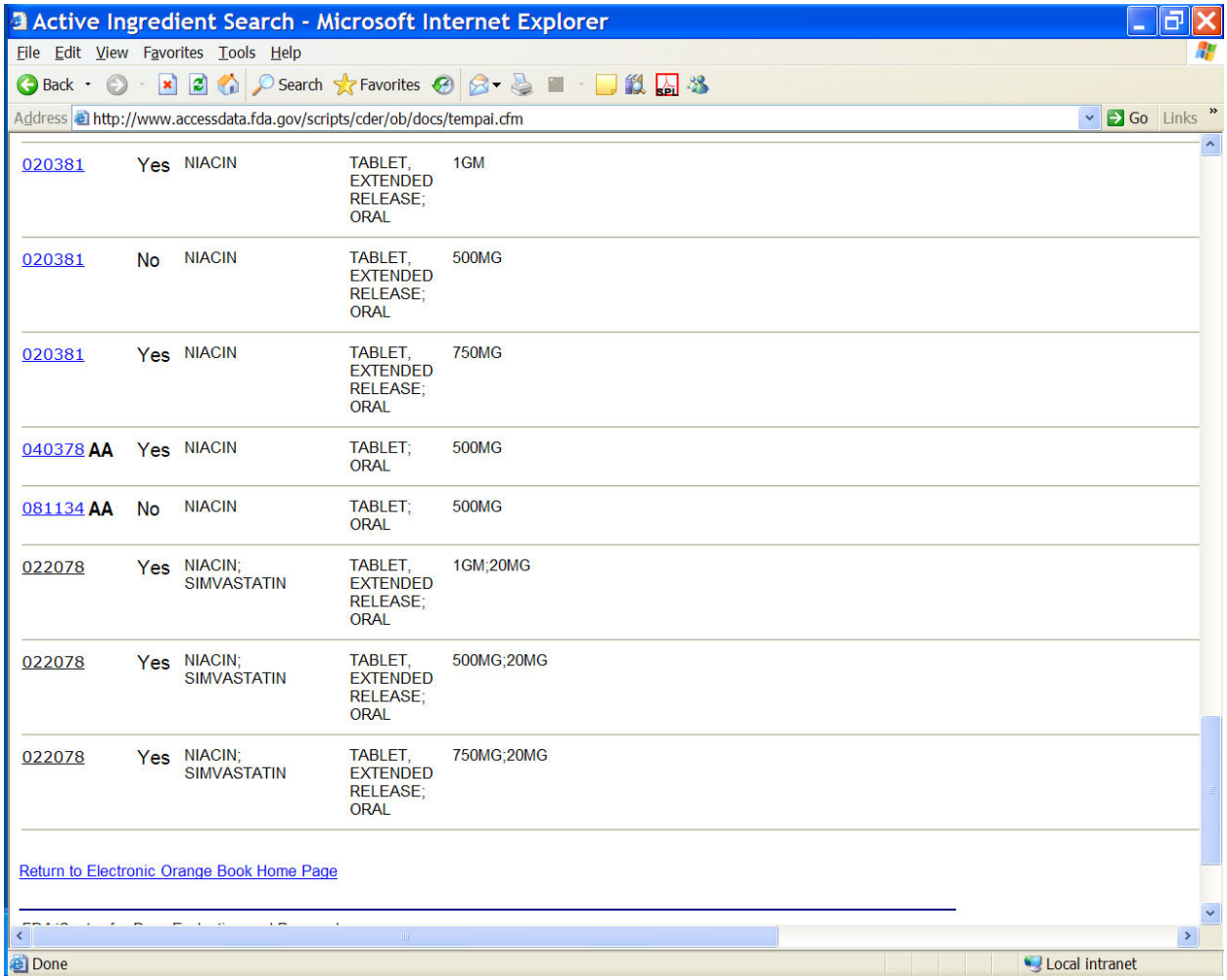
5.2 Tabular Listing of All Clinical Studies 3

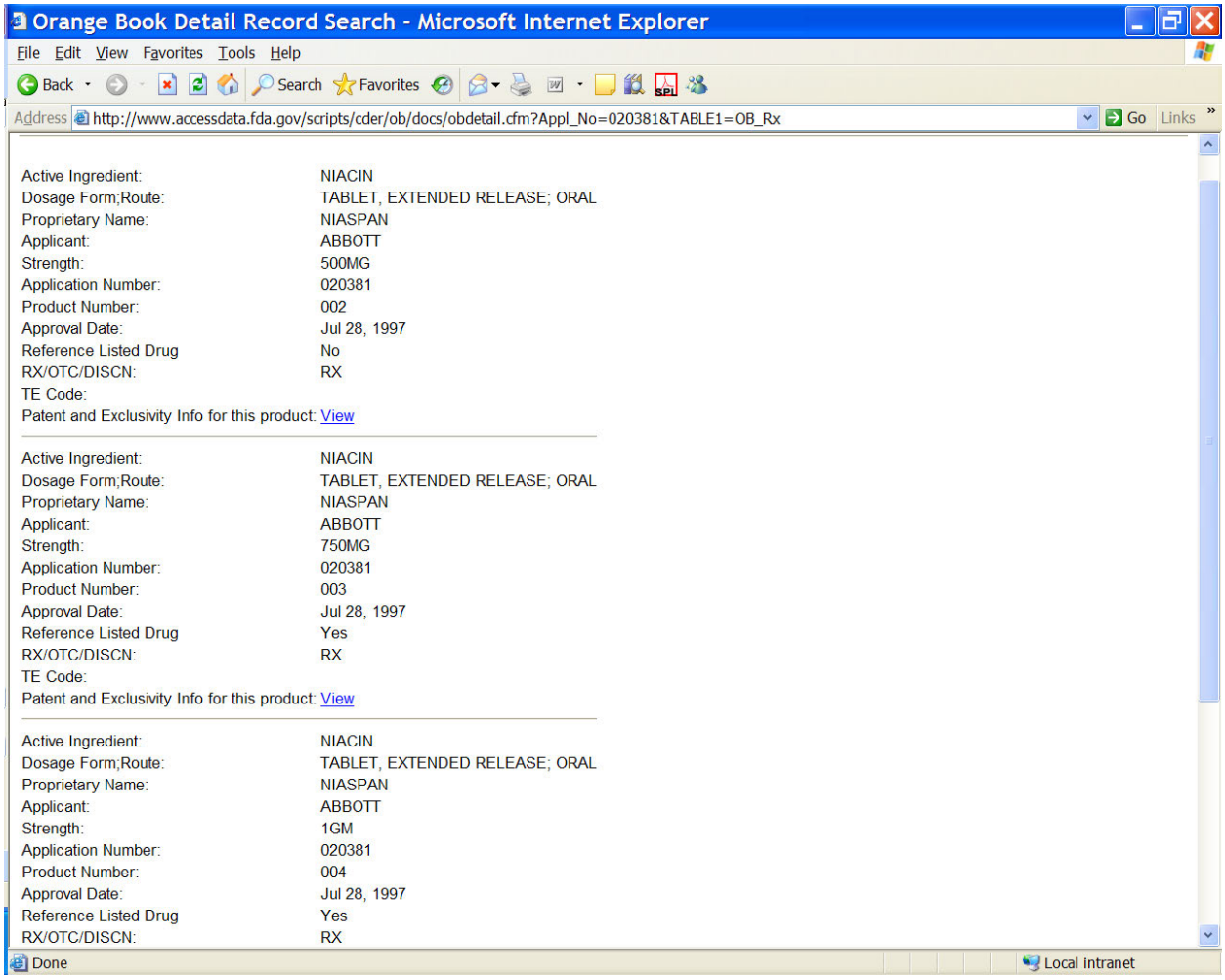
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 1000 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) NO 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☐

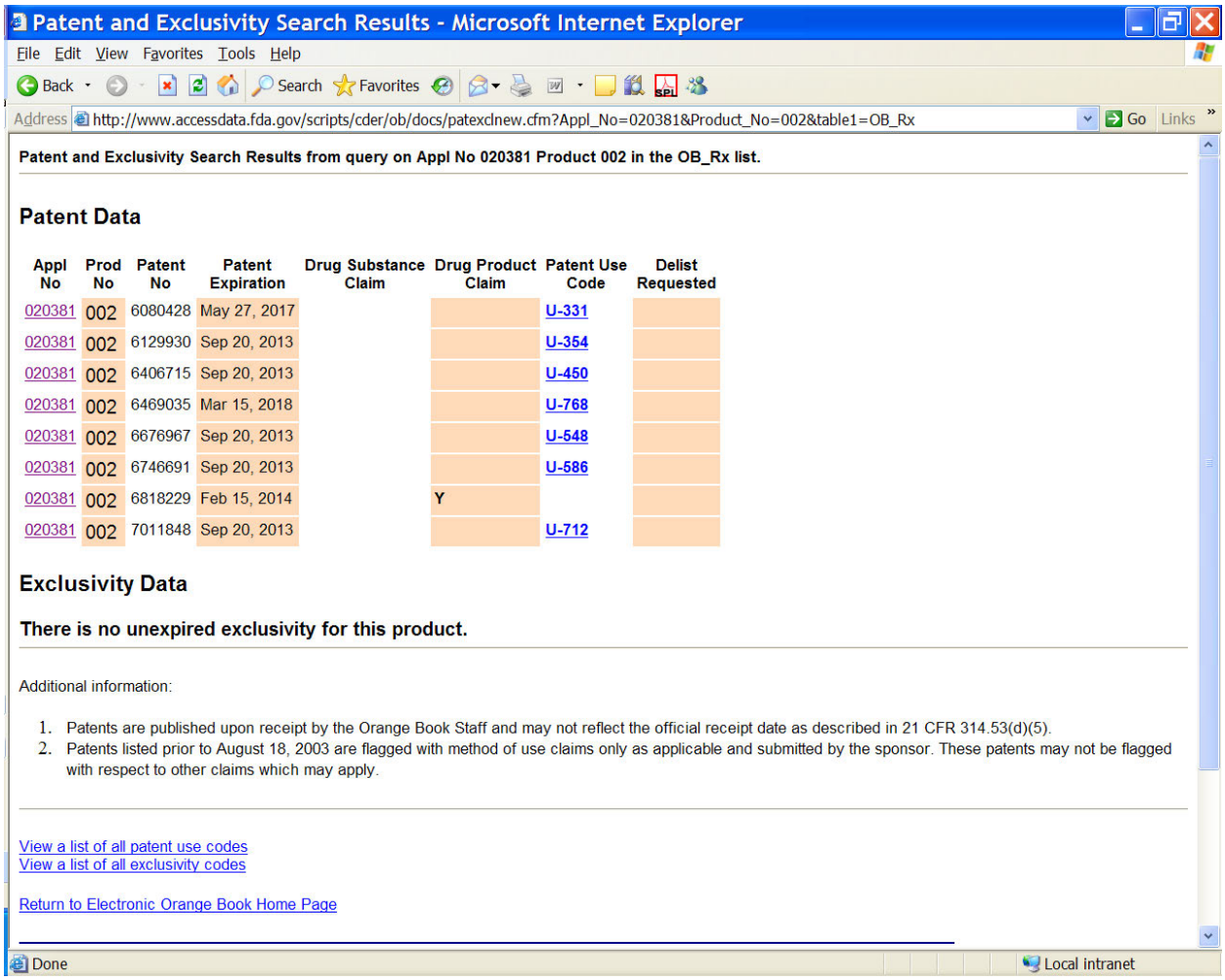
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐

Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
020381 Yes NIACIN TABLET, EXTENDED RELEASE; ORAL 1GM
020381 No NIACIN TABLET, EXTENDED RELEASE; ORAL 500MG
020381 Yes NIACIN TABLET, EXTENDED RELEASE; ORAL 750MG
040378 AA Yes NIACIN TABLET; ORAL 500MG
081134 AA No NIACIN TABLET; ORAL 500MG
022078 Yes NIACIN; SIMVASTATIN TABLET, EXTENDED RELEASE; ORAL 1GM;20MG
022078 Yes NIACIN; SIMVASTATIN TABLET, EXTENDED RELEASE; ORAL 500MG;20MG
022078 Yes NIACIN; SIMVASTATIN TABLET, EXTENDED RELEASE; ORAL 750MG;20MG
Return to Electronic Orange Book Home Page
Done
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020381&TABLE1=OB_Rx
Go Links
Active Ingredient: NIACIN
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: NIASPAN
Applicant: ABBOTT
Strength: 500MG
Application Number: 020381
Product Number: 002
Approval Date: Jul 28, 1997
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: NIACIN
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: NIASPAN
Applicant: ABBOTT
Strength: 750MG
Application Number: 020381
Product Number: 003
Approval Date: Jul 28, 1997
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: NIACIN
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: NIASPAN
Applicant: ABBOTT
Strength: 1GM
Application Number: 020381
Product Number: 004
Approval Date: Jul 28, 1997
Reference Listed Drug Yes
RX/OTC/DISCN: RX
Done
Local intranet



Patent and Exclusivity Search Results from query on Appl No 020381 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020381	002	6080428	May 27, 2017			U-331	
020381	002	6129930	Sep 20, 2013			U-354	
020381	002	6406715	Sep 20, 2013			U-450	
020381	002	6469035	Mar 15, 2018			U-768	
020381	002	6676967	Sep 20, 2013			U-548	
020381	002	6746691	Sep 20, 2013			U-586	
020381	002	6818229	Feb 15, 2014		Y		
020381	002	7011848	Sep 20, 2013			U-712	

Exclusivity Data

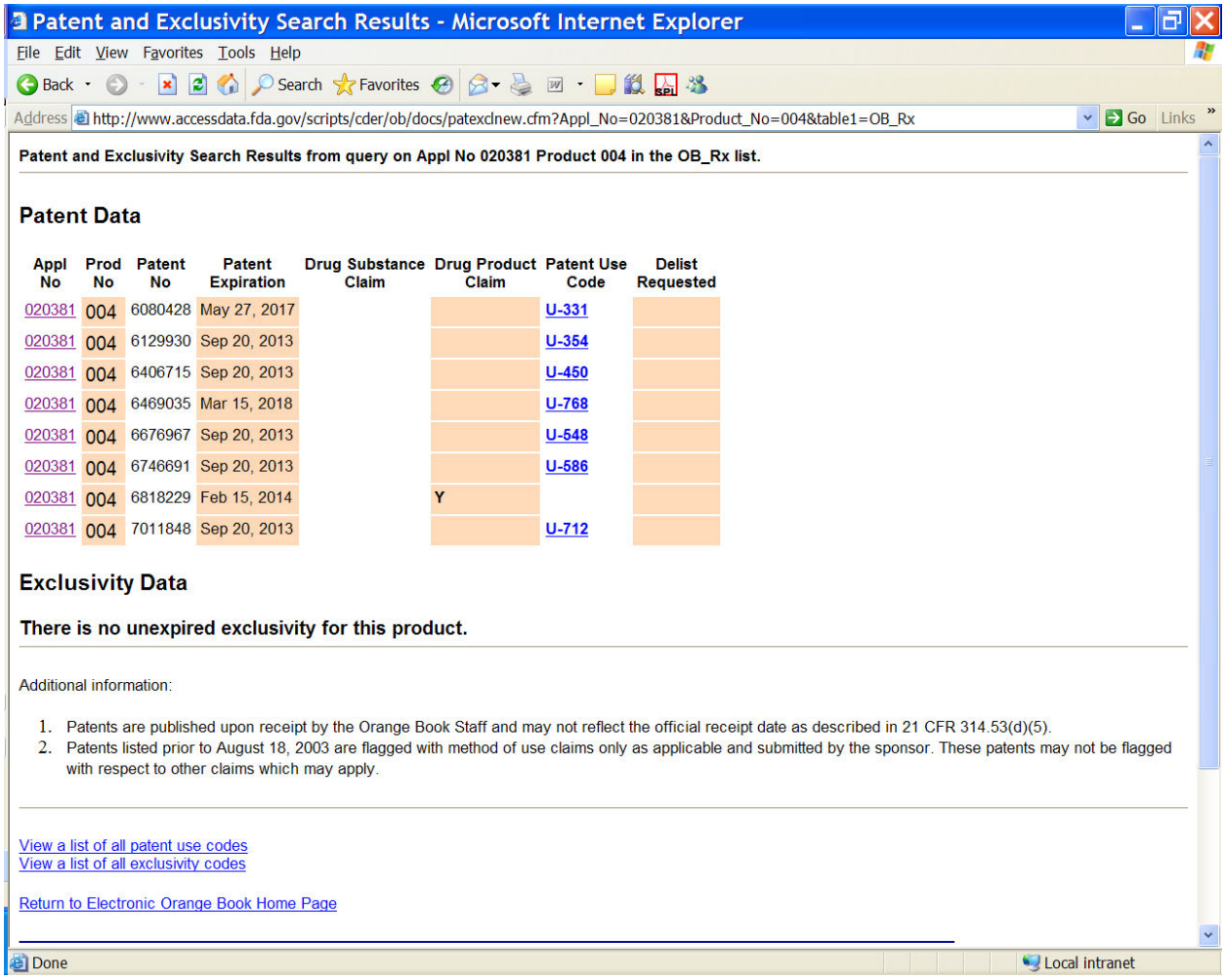
There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page


Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020381&Product_No=004&table1=OB_Rx
Go Links
Patent and Exclusivity Search Results from query on Appl No 020381 Product 004 in the OB_Rx list.
Patent Data
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
020381 | 004 | 6080428 | May 27, 2017 | | | U-331 |
020381 | 004 | 6129930 | Sep 20, 2013 | | | U-354 |
020381 | 004 | 6406715 | Sep 20, 2013 | | | U-450 |
020381 | 004 | 6469035 | Mar 15, 2018 | | | U-768 |
020381 | 004 | 6676967 | Sep 20, 2013 | | | U-548 |
020381 | 004 | 6746691 | Sep 20, 2013 | | | U-586 |
020381 | 004 | 6818229 | Feb 15, 2014 | | Y | |
020381 | 004 | 7011848 | Sep 20, 2013 | | | U-712 |
Exclusivity Data
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
Done
Local intranet

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200484	ORIG-1	SUN PHARMA GLOBAL FZE	NIACIN

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

/s/

TED C PALAT
12/15/2009

MARTIN H Shimer
12/16/2009