CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 090922

Name: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets USP, 5 mg/120mg (OTC)

Sponsor: Sun Pharmaceutical Industries Limited

Approval Date: September 28, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090922

Sun Pharmaceutical Industries Limited (C/O Caraco)
Attention: Robert Kurkiewicz
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 16, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets USP, 5 mg/120 mg (OTC).

Reference is also made to your amendments dated June 6, 2009; February 9, and December 17, 2010; February 1, February 14, April 18, and December 31, 2011; and February 13, 2012.

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 Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets USP, 5 mg/120 mg (OTC) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Zyrtec-D 12 Hour, of McNeil Consumer Healthcare (McNeil).

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:

Apparatus: USP Apparatus I (Basket) at 100 rpm
Medium: 500 mL of 0.1 N HCl at 37±0.5°C
Specifications:

Cetirizine:
NLT 80% (Q) in 30 min

Pseudoephedrine:
1 hour: 30-50%
2 hour: 50-70 %
6 hour: NLT 80%

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when 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, McNeil's Zyrtec-D 12 Hour, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations(the "Orange Book"):

U.S. Patent Number	Expiration Date
6,469,009 (the '009 patent)	July 13, 2019
6,489,329 (the '329 patent)	April 8, 2016
7,014,867 (the '867 patent)	June 10, 2022
7,226,614 (the '614 patent)	June 10, 2022

With respect to each of these patents, your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets USP, 5 mg/120 mg (OTC), under this ANDA. You have notified the agency that Sun Pharmaceutical Industries Ltd. (Sun) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Sun within the statutory 45-day period.

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. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

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}

Gregory P. Geba, M.D., M.P.H.
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

09/28/2012

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

LABELING

Black

(b) (4)

Size: 115x32mm

[CRC]

Unvarnish area: 28x8mm

Layer 2

Drug Facts

Active ingredients (in each extended-release tablet)	Purpose
Cetirizine HCl, USP 5 mg	Antihistamine
Pseudoephedrine HCl, USP 120 mg	Nasal Decongestant

Drug Facts (continued)

Uses

- temporarily relieves these symptoms due to hay fever or other upper respiratory allergies
  - runny nose
  - sneezing
  - itchy, watery eyes
  - itching of nose or throat
  - nasal congestion
- reduces swelling of nasal passages
- temporarily relieves sinus congestion and pressure
- temporarily restores freer breathing through the nose

Layer 3

Drug Facts (continued)

Warnings

Do not use

- if you have ever had an allergic reaction to this product or any of its ingredients or to an antihistamine containing hydroxyzine
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product

Drug Facts (continued)

Ask a doctor before use if you have

- heart disease
- thyroid disease
- diabetes
- glaucoma
- high blood pressure
- trouble urinating due to an enlarged prostate gland
- liver or kidney disease. Your doctor should determine if you need a different dose

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

Layer 4

Drug Facts (continued)

When using this product

- **do not use more than directed**
- drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives, and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery

Stop use and ask a doctor if

- an allergic reaction to this product occurs. Seek medical help right away
- you get nervous, dizzy, or sleepless
- symptoms do not improve within 7 days or are accompanied by fever

Drug Facts (continued)

If pregnant or breast feeding:

- if breast feeding, not recommended
- if pregnant, ask a health professional before use

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away

Directions

- do not break or chew tablet; swallow tablet whole

Layer 5

Drug Facts (continued)

adults and children 12 years and over	take 1 tablet every 12 hours; do not take more than 2 tablets in 24 hours
adults 65 years and over	ask a doctor
children under 12 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor

Drug Facts (continued)

Other information

- store between 20° to 25°C (68° to 77°F)
- do not use if inner safety seal is open or torn
- see top layer for lot number and expiration date

Inactive ingredients

hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, stearic acid, titanium dioxide

Layer 6

Drug Facts (continued)

Imprinting Ink Contents: ammonium hydroxide, iron oxide black, isopropyl alcohol, N-butyl alcohol, propylene glycol, shellac glaze

Questions?

Call toll free 1-800-818-4555 weekdays

Layer 7

Blank Layer

115 mm

Labeling Format Information:

Fonts: Helvetica narrow, Bold, Bold Italic, Helvetica Condensed

Drug Facts:	9 pt	Leading:	7.5 pt
Header:	8 pt	Bullets:	6 pt
Subheader:	6 pt	Barlines:	1 pt
Body Text:	6 pt	Hairlines:	0.5 pt
Drug Facts (continued)	8 pt		

Horizontal Scale: 85 100% Average Kerning: 0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

LABELING REVIEWS

Supersedes review signed off May 17, 2011

APPROVAL SUMMARY

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

ANDA Number:	090922
Dates of Submission:	February 13, 2012 (amendment)
Applicant's Name:	Sun Pharmaceutical Industries Limited
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets USP, 5 mg/120 mg (OTC)

APPROVAL SUMMARY

CONTAINER LABELS (bottles of 30s)
Satisfactory in FPL as of the February 13, 2012 e-submission.

Post-approval request: The following label revision will be emailed to the firm ['robert.kurkiewicz@caraco.com'] after this review has been signed off. The firm can submit revised label in the annual report:

Uses: “itching of the nose or throat” [add “the”]

NOTE TO THE CHEMIST:

From: Robert.Kurkiewicz@caraco.com [mailto:Robert.Kurkiewicz@caraco.com] **On Behalf Of** RobertKurkiewicz/Caraco%CARACO@CARACO.COM
Sent: Tuesday, February 28, 2012 12:00 PM
To: Wu, Ruby (Chi-Ann)
Subject: Fw: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

Per your request.

Bob
----- Forwarded by Robert Kurkiewicz/CARACO on 02/28/2012 11:59 AM -----

Subject: Re: Fw: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

---

Please forward this details to FDA.

Diameter: 9 mm

Thickness: 5 mm

From: Zhang, Quan
Sent: Thursday, February 23, 2012 10:18 AM
To: Wu, Ruby (Chi-Ann)
Cc: Park, Linda
Subject: RE: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

Hi Ruby,

I could not locate the tablets size information from my review and the original submission. Please let me know if you can find it somewhere.

Thanks,

Quan

From: Zhang, Quan
Sent: Thursday, February 23, 2012 10:03 AM
To: Wu, Ruby (Chi-Ann)
Cc: Park, Linda
Subject: RE: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

Hi Ann,

I went back to my review, USP monograph, and bio review. The firm's drug product do meet the dissolution test specified in the USP and the dissolution is **adequate**.

The dissolution testing is acceptable and complete Adequate.

Apparatus:	USP Apparatus I (Basket) at 100 rpm
Medium:	500 mL of 0.1 N HCl at 37±0.5°C
Specifications:	For Cetirizine: NLT 80% (Q) in 30 min; For Pseudoephedrine: 1 hour 30-50% 2 hour 50-70 % 6 hour NLT 80%

I will find out the size of the tablets soon.

Thanks,

Quan

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, February 23, 2012 10:00 AM
To: Wu, Ruby (Chi-Ann); Zhang, Quan
Cc: Park, Linda
Subject: RE: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

Hi Quan,

Another question…what is the size of the tablets?

Thanks,

Ruby

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, February 23, 2012 9:43 AM
To: Zhang, Quan
Cc: Park, Linda
Subject: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

Good morning Quan,

The drug product is not subject of a USP monograph. Does the drug product meet the dissolution test specified in the USP?

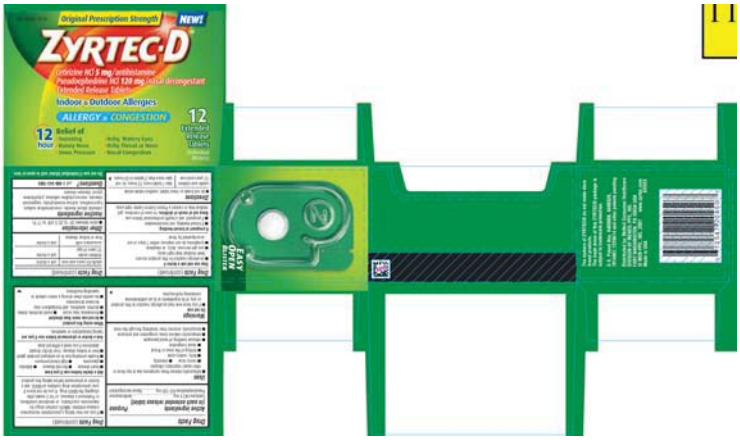
Thanks,

Ruby
Labeling reviewer

FOR THE RECORD:

Burhan Nour performed the previous reviews

1. The following review is based on the on the labeling of Zyrtec-D 12 Hour Extended Release Tablets (NDA 021150/S-007) approved November 9, 2007, held by McNeil Consumer Healthcare.



USP Monograph: (checked 2/23/12)

Add the following:
Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets
ADDITIONAL REQUIREMENTS
- Packaging and Storage: Preserve in well-closed containers. Store at controlled room temperature.

PF: information already reflected in the current monograph. (checked 2/23/12)

2. PATENTS/EXCLUSIVITIES

Patent Data NDA 021150

No	Expiration	Use Code	Use	File	Labeling Impact
6469009	JUL 13, 2019	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None
6489329	APR 8, 2016			IV	None
7014867	Jun 10, 2012			IV	None
7226614	Jun 10, 2012	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None

Exclusivity Data NDA 021150

There is no unexpired exclusivity for this product.

3. MANUFACTURING FACILITY
Sun Pharmaceutical Industries Ltd.,
Acme Plaza, Andheri-Kurla Road,
Andheri (East), Mumbai-400 059, India

4. SCORING:
NDA - unscored
ANDA - unscored

5. STORAGE CONDITIONS:
NDA - Store between 20° to 25°C (68° to 77°F)
ANDA - Store between 20° to 25°C (68° to 77°F)

6. PRODUCT DESCRIPTION
RLD: film-coated, bi-layer
Product Characteristics

Color	WHITE (White to off white)	Score	no score
Shape	ROUND (Biconvex)	Size	10mm
Flavor		Imprint Code	Zyrtec;D

ANDA: Diameter: 9 mm
White, film coated circular tablets with '915' imprinted with black ink on one side and plain on other side.

From chemistry review: The drug product contains 5 mg of Cetirizine HCl in the immediate release layer and 120 mg pseudoephedrine in the extended release layer (mimics RLD).

From: Wu, Ruby (Chi-Ann)
Sent: Thursday, February 23, 2012 10:23 AM
To: 'robert.kurkiewicz@caraco.com'
Subject: ANDA 90922 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets

Good morning Robert,

I'm currently reviewing the labeling portion of your ANDA. Can you tell me the size of the tablets? I usually looked in the SPL data elements section of your ANDA for this information but you didn't provide SPL.

Thanks,

Ruby

7. INACTIVE INGREDIENTS:

Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg

Excipients	Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg (Sun Pharmaceutical Industries Ltd.)	Zyrtec-D 12 Hour® (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets, 5 mg/120 mg (McNeil Consumer Healthcare)
Hydroxyethyl cellulose	✓	×
Magnesium stearate	✓	✓
Microcrystalline cellulose	✓	✓
Stearic acid	✓	×
Hydroxypropyl cellulose	✓#1, #2	×
Hypromellose	✓#1, #2	✓
Titanium dioxide	✓#2	✓
Colloidal silicon dioxide	×	✓
Croscarmellose sodium	×	✓
Lactose monohydrate	×	✓
Polyethylene glycol	×	✓
(b) (4)		

Composition of black printing ink for Sun's Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg is: (b) (4) iron oxide black, isopropyl alcohol, N-butyl alcohol, propylene glycol, shellac glaze.

Key : ✓ = Present; × = Absent

8. PACKAGING CONFIGURATIONS:
NDA- packages of 12 blisters and 24 blisters

ANDA- bottles of 30s

9. CONTAINER/CLOSURE SYSTEM:
Update 4/18/2011:
The firm is no longer planning to market (b) (4) and (b) (4) tablet count bottles. (See response to 1/25/2011 deficiency comment, submitted on 4/18/2011)

a. As per 21 CFR 1314.20, to set the daily sales limit of pseudoephedrine base to 3.6 gram per purchaser, we hereby exclude the package sizes of (b) (4) (b) (4)

Type	Description Count 30's	(b) (4)
White round HDPE Bottles	40 cc	
Polypropylene closures	33 mm CRC	

CRC : Child resistant closure (b) (4)

The proposed container/closure systems comply with USP <661> and USP <671> requirements.

10. TAMPER EVIDENCE STATEMENT

"Do not use if inner safety seal imprinted with 'Sealed for Your Protection' is torn or missing."

A picture of the safety seal is provided for your reference as follows:

11. PSEUDOEPHEDRINE LIMITS

Update 4/18/2011:

The firm is no longer planning to market (b) (4) and (b) (4) tablet count bottles. (See response to 1/25/2011 deficiency comment, submitted on 4/18/2011)

a. As per 21 CFR 1314.20, to set the daily sales limit of pseudoephedrine base to 3.6 gram per purchaser, we hereby exclude the package sizes of (b) (4) (b) (4)

Firm submitted labeling for the (b) (4) and (b) (4) tablet count bottles, however this exceed the daily 3.6 gram sales limit of pseudoephedrine.

Equivalency Charts

The following is not found within DEA law or regulations; DEA provides this for informational purposes only:

A. Effective April 8, 2006, the daily sales limit of ephedrine base, pseudoephedrine base, or phenylpropanolamine base is 3.6 grams per purchaser, regardless of number of transactions.

Ingredient	Number of Tablets [as base]
25 mg Ephedrine HCl	175
25 mg Ephedrine Sulfate	186
30 mg Pseudoephedrine HCl	146
60 mg Pseudoephedrine HCl	73
120 mg Pseudoephedrine HCl	36
30 mg Pseudoephedrine Sulfate	155
60 mg Pseudoephedrine Sulfate	77
120 mg Pseudoephedrine Sulfate	38
Phenylpropanolamine	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

12. OTC FORMAT

21 CFR 201.66

- The letter height or type size for the title "Drug Facts" shall appear in a type size larger than the largest type size used in the Drug Facts labeling.
- The letter height or type size for the title "Drug Facts (continued)" shall be no smaller than 8-point type.
- The letter height or type size for the headings in paragraphs (c)(2) through (c)(9) of this section shall be the larger of either 8-point or greater type, or 2-point sizes greater than the point size of the text.
- The letter height or type size for the subheadings and all other information described in paragraphs (c)(2) through (c)(9) of this section shall be no smaller than 6-point type.
- The title, heading, subheadings, and information in paragraphs (c)(1) through (c)(9) of this section shall be legible and clearly presented, shall have at least 0.5-point leading (i.e., space between two lines of text), and shall not have letters that touch.
- When there is more than one statement, each individual statement listed under the headings and subheadings in paragraphs (c)(4) through (c)(7) of this section shall be preceded by a solid square or solid circle bullet of 5-point type size.

Labeling Format Information:

Fonts: Helvetica narrow, Bold, Bold Italic, Helvett Condensed

Drug Facts:	9 pt	Leading:	7.5 pt
Header:	8 pt	Bullets:	6 pt
Subheader:	6 pt	Barlines:	1 pt
Body Text:	6 pt	Hairlines:	0.5 pt
Drug Facts (continued)	8 pt		

Horizontal Scale: 85 - 100% Average Kerning: 0

Date of Review:	February 28, 2012
Primary Reviewer:	Ruby Wu
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/

CHI-ANN Y WU
02/28/2012

ANGELA M PAYNE
02/29/2012

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

ANDA Number:	090922
Dates of Submission:	April 18, 2011
Applicant's Name:	Sun Pharmaceutical Industries Limited
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg (OTC)

REMS required?
☐ **Yes** ☒ **No**

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

BASIS OF APPROVAL:

APPROVAL SUMMARY

CONTAINER LABELS (bottles of 30s)
Satisfactory in FPL as of the April 18, 2011 e-submission.

REFERENCE LISTED DRUG:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Zyrtec-D 12 Hour Extended Release Tablets
NDA Number: 021150
NDA Drug Name: Zyrtec-D 12 Hour Extended Release® Tablets
NDA Firm: Pfizer Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA 021150/S-007, approved November 9, 2007
This supplement provided for the OTC switch
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-side comparison
Basis of Approval for the Package Insert: Side-by-side comparison

FOR THE RECORD:

1. The following review is based on the on the labeling of Zyrtec-D 12 Hour Extended Release Tablets (NDA 021150/S-007) approved November 9, 2007, held by McNeil Consumer Healthcare.

   USP Monograph: None (checked 1/17/2010)

   MedWatch: No reports since labeling approved 11/9/2007 (checked 1/17/2010)

2. PATENTS/EXCLUSIVITIES

   Patent Data NDA 021150

No	Expiration	Use Code	Use	File	Labeling Impact
6469009	JUL 13, 2019	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None
6489329	APR 8, 2016			IV	None
7014867	Jun 10, 2012			IV	None
7226614	Jun 10, 2012	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None

   Exclusivity Data NDA 021150

   There is no unexpired exclusivity for this product.

3. MANUFACTURING FACILITY
   Sun Pharmaceutical Industries Ltd.,
   Acme Plaza, Andheri-Kurla Road,
   Andheri (East), Mumbai-400 059, India

4. SCORING:
   NDA - unscored
   ANDA - unscored

5. STORAGE CONDITIONS:
   NDA - Store between 20° to 25°C (68° to 77°F)
   ANDA - Store between 20° to 25°C (68° to 77°F)

6. PRODUCT DESCRIPTION
   White, film coated circular tablets with '915' imprinted with black ink on one side and plain on other side.

7. INACTIVE INGREDIENTS:

Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg

Excipients	Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg (Sun Pharmaceutical Industries Ltd.)	Zyrtec-D 12 Hour® (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets, 5 mg/120 mg (McNeil Consumer Healthcare)
Hydroxyethyl cellulose	✓	×
Magnesium stearate	✓	✓
Microcrystalline cellulose	✓	✓
Stearic acid	✓	×
Hydroxypropyl cellulose	✓#1, #2	×
Hypromellose	✓#1, #2	✓
Titanium dioxide	✓#2	✓
Colloidal silicon dioxide	×	✓
Croscarmellose sodium	×	✓
Lactose monohydrate	×	✓
Polyethylene glycol	×	✓
(b) (4)		

Composition of black printing ink for Sun's Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg/120 mg is: (b) (4) iron oxide black, isopropyl alcohol, N-butyl alcohol, propylene glycol, shellac glaze.

Key : ✓ = Present; × = Absent

8. PACKAGING CONFIGURATIONS:
   NDA- packages of 12 blisters and 24 blisters

   ANDA- bottles of 30s

9. CONTAINER/CLOSURE SYSTEM:

Update 4/18/2011:

The firm is no longer planning to market (b) (4) and (b) (4) tablet count bottles. (See response to 1/25/2011 deficiency comment, submitted on 4/18/2011)

a. As per 21 CFR 1314.20, to set the daily sales limit of pseudoephedrine base to 3.6 gram per purchaser, we hereby exclude the package sizes of (b) (4) (b) (4)

Type	Description	
	Count	
	30's	(b) (4)
White round HDPE Bottles	40 cc	
Polypropylene closures	33 mm CRC	
CRC : Child resistant closure (b) (4)		

10. TAMPER EVIDENCE STATEMENT

"Do not use if inner safety seal imprinted with 'Sealed for Your Protection' is torn or missing."

A picture of the safety seal is provided for your reference as follows:

11. PSEUDOEPHEDRINE LIMITS

Update 4/18/2011:

The firm is no longer planning to market (b) (4) and (b) (4) tablet count bottles. (See response to 1/25/2011 deficiency comment, submitted on 4/18/2011)

a. As per 21 CFR 1314.20, to set the daily sales limit of pseudoephedrine base to 3.6 gram per purchaser, we hereby exclude the package sizes of (b) (4) (b) (4)

Firm submitted labeling for the (b) (4) and (b) (4) tablet count bottles, however this exceed the daily 3.6 gram sales limit of pseudoephedrine.

Equivalency Charts

The following is not found within DEA law or regulations; DEA provides this for informational purposes only:

A. Effective April 8, 2006, the daily sales limit of ephedrine base, pseudoephedrine base, or phenylpropanolamine base is 3.6 grams per purchaser, regardless of number of transactions.

Ingredient	Number of Tablets [as base]
25 mg Ephedrine HCl	175
25 mg Ephedrine Sulfate	186
30 mg Pseudoephedrine HCl	146
60 mg Pseudoephedrine HCl	73
120 mg Pseudoephedrine HCl	36
30 mg Pseudoephedrine Sulfate	155
60 mg Pseudoephedrine Sulfate	77
120 mg Pseudoephedrine Sulfate	38
Phenylpropanolamine	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

Date of Review: May 15, 2011

Dates of Submission: April 18, 2011

Primary Reviewer: Burhan Nour

Team Leader: John Grace

Following this page, 2 pages withheld in full (b)(4)

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

/s/

BURHAN A NOUR
05/16/2011

JOHN F GRACE
05/17/2011

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

ANDA Number:	090922
Dates of Submission:	October 16, 2008
Applicant's Name:	Sun Pharmaceutical Industries Limited
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg (OTC)

Labeling Deficiencies:

1. CONTAINER LABELS (bottles of 30s (b) (4), and (b) (4)):

a. We note your containers of (b) (4) and (b) (4) tablets exceed the daily sales limit of Pseudoephedrine HCL. We note 21 CFR 1314.20 sets the daily sales limit of pseudoephedrine base to 3.6 gram per purchaser. Please delete the package sizes that exceed the daily sales limit.

Equivalency Charts

The following is not found within DEA law or regulations; DEA provides this for informational purposes only:

A. Effective April 8, 2006, the daily sales limit of ephedrine base, pseudoephedrine base, or phenylpropanolamine base is 3.6 grams per purchaser, regardless of number of transactions.

Ingredient	Number of Tablets [as base]
25 mg Ephedrine HCl	175
25 mg Ephedrine Sulfate	186
30 mg Pseudoephedrine HCl	146
60 mg Pseudoephedrine HCl	73
120 mg Pseudoephedrine HCl	36
30 mg Pseudoephedrine Sulfate	155
60 mg Pseudoephedrine Sulfate	77
120 mg Pseudoephedrine Sulfate	38
Phenylpropanolamine	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

b. Your labels state the following: "Do not use if inner safety seal is torn or missing." However, your application does not include any documentation regarding this safety seal. In addition, 21 CFR 211.132(b)(1) requires that the safety seal must include an "identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture)", and that the identifying characteristic must be referenced in the safety seal statement on the label. Please submit information about the seal and revise your safety seal statement to include the identifying characteristic.

2. OTC DRUG FACTS (bottles of 30s (b) (4) and (b) (4):

a. In order for us to verify your compliance with the labeling format requirements of 21 CFR 201.66, please submit a format legend for each size of your container labels.

b. We note that “hydroxypropyl cellulose” is included in the list of **Inactive Ingredients**. Meanwhile, it is not listed in your Component and Composition Statement. Please explain.

c. See comments under container above.

Revise your labeling, as instructed above, and submit final printed 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://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

REMS required?
☐ **Yes** ☒ **No**

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

BASIS OF APPROVAL:

APPROVAL SUMMARY

CONTAINER LABELS (bottles of 30)

See comments above

REFERENCE LISTED DRUG:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Zyrtec-D 12 Hour Extended Release Tablets
NDA Number: 021150
NDA Drug Name: Zyrtec-D 12 Hour Extended Release® Tablets
NDA Firm: Pfizer Pharmaceuticals
Date of Approval of NDA Insert and supplement: NDA 021150/S-007, approved November 9, 2007
This supplement provided for the OTC switch
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-side comparison
Basis of Approval for the Package Insert: Side-by-side comparison

FOR THE RECORD:

1. The following review is based on the on the labeling of Zyrtec-D 12 Hour Extended Release Tablets (NDA 021150/S-007) approved November 9, 2007, held by McNeil Consumer Healthcare.

   USP Monograph: None (checked 1/17/2010)

   MedWatch: No reports since labeling approved 11/9/2007 (checked 1/17/2010)

2. PATENTS/EXCLUSIVITIES

   Patent Data NDA 021150

No	Expiration	Use Code	Use	File	Labeling Impact
6469009	JUL 13, 2019	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None
6489329	APR 8, 2016			IV	None
7014867	Jun 10, 2012			IV	None
7226614	Jun 10, 2012	U-295	Treatment of seasonal and perennial allergic rhinitis symptoms	IV	None

   Exclusivity Data NDA 021150

   There is no unexpired exclusivity for this product.

3. MANUFACTURING FACILITY
   Sun Pharmaceutical Industries Ltd.,
   Acme Plaza, Andheri-Kurla Road,
   Andheri (East), Mumbai-400 059, India

4. SCORING:
   NDA - unscored
   ANDA - unscored

5. STORAGE CONDITIONS:
   NDA - Store between 20° to 25°C (68° to 77°F)
   ANDA - Store between 20° to 25°C (68° to 77°F)

6. DISPENSING RECOMMENDATIONS:
   NDA -
   ANDA -

7. INACTIVE INGREDIENTS:

   Functionality of excipients in the formulation

Sr. #	Ingredients	Function
1.	Hydroxyethyl Celluose, NF (b) (4)	(b) (4)
2.	Microcrystalline Cellulose, NF	
3.	Stearic Acid, NF	
4.	Magnesium Stearate, NF	
5.	(b) (4)	
6.		
7.		
8.	Isopropyl Alcohol, USP	
9.	(b) (4)	

8. PACKAGING CONFIGURATIONS:
   NDA- packages of 12 blisters and 24 blisters

   ANDA- bottles of 30 (b) (4) and (b) (4)

9. TAMPER EVIDENCE STATEMENT
   "Do not use if inner safety seal is torn or missing."

10. CONTAINER/CLOSURE SYSTEM:

Type	Description	
	Count	
	30's	(b) (4)
White round HDPE Bottles	40 cc	
Polypropylene closures	33 mm CRC	
CRC : Child resistant closure (b) (4)		

11. PRODUCT DESCRIPTION
White, film coated circular tablets with '915' imprinted with black ink on one side and plain on other side.

12. PSEUDOEPHEDRINE LIMITS
Firm submitted labeling for the (b) (4) and (b) (4) tablet count bottles, however this exceed the daily 3.6 gram sales limit of pseudoephedrine.

Equivalency Charts

The following is not found within DEA law or regulations; DEA provides this for informational purposes only:

A. Effective April 8, 2006, the daily sales limit of ephedrine base, pseudoephedrine base, or phenylpropanolamine base is 3.6 grams per purchaser, regardless of number of transactions.

Ingredient	Number of Tablets [as base]
25 mg Ephedrine HCl	175
25 mg Ephedrine Sulfate	186
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120 mg Pseudoephedrine HCl	36
30 mg Pseudoephedrine Sulfate	155
60 mg Pseudoephedrine Sulfate	77
120 mg Pseudoephedrine Sulfate	38
Phenylpropanolamine	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

Date of Review: January 18, 2011

Dates of Submission: October 16, 2008

Primary Reviewer: Burhan Nour

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/

BURHAN A NOUR
01/20/2011

JOHN F GRACE
01/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

CHEMISTRY REVIEWS

CMC Approvable per FDA Rev # 3 on 9/13/12

ANDA 90-922

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride

Extended-Release Tablets, 5 mg / 120 mg

Sun Pharmaceutical Industries Ltd.

Quan Zhang, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **90-922**

2. REVIEW #: **3**

3. REVIEW DATE: **11-Sep-2012**

4. REVIEWER: **Quan Zhang, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original	16-Oct-2008
Accept for filing	22-Oct-2008
Bioequivalence amendment (AB)	06-Jun-2009
CMC Amendment (type AC: Bio dissolution, Uniformity of Dosage Units, & stability data)	06-Jun-2009
FDA: CMC Rev# 1- Minor Deficient	22-Jul-2009
FDA: Bio Adequate	12-Apr-2011
FDA: Labeling Deficient	25-Jan-2011
Firm: CMC Minor Amendment	9-Feb-2010
Firm: Quality/facility information	14-Feb-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Firm: Administrative change	25-Jul-2011
Firm: **Quality/Response**	**31-Dec-2011**
Firm: Labeling amendment	13-Feb-2012
FDA: Labeling review (AC & Tablet size info)	29-Feb-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharmaceutical Industries Ltd.

Address: Acme Plaza, Andheri-Kurla Road,
Andheri East
Mumbai 400059, India

Representative: (new)	Robert Kurkiewicz; Sr.VP-Regulatory Affairs **Sun Pharmaceutical Industries Ltd. (C/O Caraco)** (different from Rev # 2) 1150 Elijah McCoy Drive Detroit, MI 48202
Telephone:	(313)-556-4105
Fax:	(248)-926-0231

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA

Non-Proprietary Name (USAN): Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

Code Name/# (ONDC only):

Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

	LISTED DRUG	**PROPOSED ANDA**
RLD	**Zyrtec –D 12 Hour®** Extended Release Tablets	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets
NDA/Holder	**NDA 21-150**/ McNeil Consumer Healthcare (Pfizer)	**ANDA** 90-922/Sun
Dosage form	Tablets	Tablets
Route of Administration	Oral	Oral
Strengths	5 mg / 120 mg	5 mg / 120 mg
Patent Certification:		Paragraph IV
Exclusivity:	No unexpired exclusivity for this product; statement included	

U.S. Patent Number	Expiration Date
6,469,009 (the '009 patent)	July 13, 2019
6,489,329 (the '329 patent)	April 8, 2016
7,014,867 (the '867 patent)	June 10, 2022
7,226,614 (the '614 patent)	June 10, 2022

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets

(MDD $_{\text{cetirizine HCl}}$ = 10 mg/day)

(MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _x__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

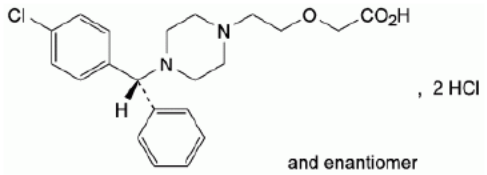
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

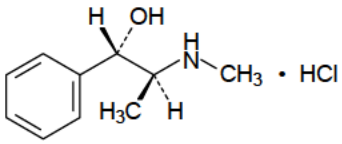
A. Cetirizine Hydrochloride:

- (±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
- $C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



B. Pseudoephedrine Hydrochloride:

- (+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
- $C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]
17889	II	Sun	Cetirizine HCl	1	**Adequate in Rev# 7 on 19-Sep-2012 per Q. Zhang**

(b) (4)	II	(b) (4)	3	Adequate in Rev# 12 on Apr.5.2012 per M. Shaikh
	III		4	N/A
	III		4	N/A
	III		4	N/A
	III		4	N/A
			4	N/A
	III		4	N/A
	III		4	N/A
	III		4	N/A
	III		4	N/A

[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: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	REVIEWER
Chemistry	**AC on 11-Sep-2012**	Q. Zhang
Labeling	AC as 17-May-2011	B. Nour
Bioequivalence	AC on 12-Apr-2011	D. Suman
EES	Overall AC as 25-May-2010	
Microbiology	N/A	
Methods Validation	Not requested per current OGD policy (USP)	
EA	Exclusion from requirement for environmental assessment	Q. Zhang
Radiopharmaceutical	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:

Following this page, 72 pages withheld in full (b)(4)

cc: ANDA # 90-922 Oiginal
ANDA DUP
DIV FILE
Field Copy

Endorsements Block:

HFD-647/Quan Zhang, Ph.D./ 13-Sep-2012

HFD-647/ Team Leader / Bing Wu, Ph.D./

HFD-617/ Project Manager/ Frank Nice/9/20/12

F/T by FN

V:\\Chemistry Division II\Team 24\Final Version for DFS\90922N03_RQZ.doc

TYPE OF LETTER: **CMC recommend for Approval**

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

/s/

QUAN ZHANG
09/21/2012
ANDA_90922N03_AP

BINGYUAN WU
09/21/2012

FRANK J NICE
09/21/2012

ANDA 90-922

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride

Extended-Release Tablets, 5 mg / 120 mg

Sun Pharmaceutical Industries Ltd.

Quan Zhang, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **90-922**

2. REVIEW #: **2**

3. REVIEW DATE: **25-May-2011**

4. REVIEWER: **Quan Zhang, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original	16-Oct-2008
Accept for filing	22-Oct-2008
Bioequivalence amendment (AB)	06-Jun-2009
CMC Amendment (type AC: Bio dissolution, Uniformity of Dosage Units, & stability data)	06-Jun-2009
FDA: CMC Rev# 1- Minor Deficient	22-Jul-2009
FDA: Bio Adequate	12-Apr-2011
FDA: Labeling Deficient	25-Jan-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Firm: CMC Minor Amendment	9-Feb-2010
Firm: Quality/facility information *	14-Feb-2011

* see review on p.41 of this review. The firm will not be use the alternate packaging and testing facility which is located in Cranbury, NJ 08512, USA.

7. NAME & ADDRESS OF APPLICANT:

Name:	Sun Pharmaceutical Industries Ltd.
Address:	Acme Plaza, Andheri-Kurla Road, Andheri East Mumbai 400059, India
Representative:	Mr. Anthony. C. Celeste **Kendle Regulatory Affairs**, USA (Formerly A.A.C. Consulting Group Inc.) 7361 Calhoun Place, Suite 5000 Rockville, MD 20855-2765, USA
Telephone:	(301)-838-3120 (301)-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA
Non-Proprietary Name (USAN): Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets
Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

	LISTED DRUG	PROPOSED ANDA
RLD	**Zyrtec –D** 12 hour Extended Release Tablets	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets
NDA/Holder	**NDA 21-150**/ McNeil Consumer Healthcare (Pfizer)	**ANDA** 90-922/Sun
Dosage form	Tablets	Tablets
Route of Administration	Oral	Oral
Strengths	5 mg / 120 mg	5 mg / 120 mg
	Patent Certification:	Paragraph IV
	Exclusivity:	No unexpired exclusivity for this product; statement included

U.S. Patent Number	Expiration Date
6,469,009 (the '009 patent)	July 13, 2019
6,489,329 (the '329 patent)	April 8, 2016
7,014,867 (the '867 patent)	June 10, 2022
7,226,614 (the '614 patent)	June 10, 2022

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets (MDD $_{\text{cetirizine HCl}}$ = 10 mg/day) (MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _x__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

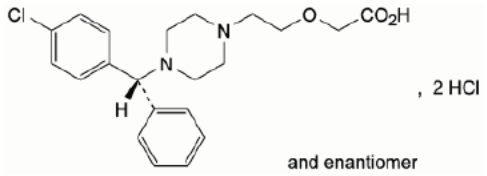
_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

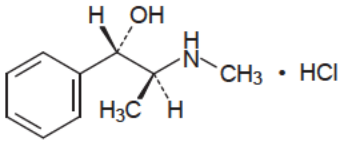
A. Cetirizine Hydrochloride:

- (±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
- $C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



B. Pseudoephedrine Hydrochloride:

- (+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
- $C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]
17889	II	Sun	Cetirizine HCl	1	**Adequate in Rev# 6 on 23-May-2011 per Q. Zhang**
(b) (4)	II		(b) (4)	3	Adequate in Rev# 11 on May.2011 per S. Read
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
				4	N/A
	III			4	N/A

(b) (4)		(b) (4)		
	III		4	N/A
	III		4	N/A
	III		4	N/A

[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: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	REVIEWER
Chemistry	Minor deficiency on 25-May-2011	Q. Zhang
Labeling	AC as 17-May-2011	B. Nour
Bioequivalence	AC on 12-Apr-2011	D. Suman
EES	Overall AC as 25-May-2010	
Microbiology	N/A	
Methods Validation	Not requested per current OGD policy (USP)	
EA	Exclusion from requirement for environmental assessment	Q. Zhang
Radiopharmaceutical	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:

Following this page, 83 pages withheld in full (b)(4)

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-922 APPLICANT: Sun Pharmaceuticals Industries, Ltd.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets USP, 5 mg/120 mg

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.

6. (b) (4)

Sincerely yours,

Glen J. Smith
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 90-922 Oiginal
ANDA DUP
DIV FILE
Field Copy

Endorsements Block:

HFD-647/Quan Zhang, Ph.D./ 25-May-2011

HFD-647/ Team Leader / S. M. Rosencrance Ph.D./

HFD-617/ Project Manager/ L. Park

F/T by LP

V:\\Chemistry Division II\Team 24\Final Version for DFS\90922N02_RQZ.doc

TYPE OF LETTER: **Minor Deficiency**

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

/s/

QUAN ZHANG
06/01/2011
ANDA 90922 N02_Minor

LINDA M PARK
06/02/2011

SUSAN M ROSENCRANCE
06/02/2011

ANDA 90-922

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride

Extended-Release Tablets, 5 mg / 120 mg

Sun Pharmaceutical Industries Ltd.

Quan Zhang, Ph.D.

OGD, DC II

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **90-922**

2. REVIEW #: **1**

3. REVIEW DATE: **9-Jul-2009; 16-Jul-2009**

4. REVIEWER: **Quan Zhang, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Oct-2008
Accept for filing	22-Oct-2008
Bioequivalence amendment (AB)	06-Jun-2009
CMC Amendment (type AC: Bio dissolution, Uniformity of Dosage Units, & stability data)	06-Jun-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Sun Pharmaceutical Industries Ltd.
Address:	Acme Plaza, Andheri-Kurla Road, Andheri East Mumbai 400059, India
Representative:	Mr. Anthony. C. Celeste **Kendle Regulatory Affairs**, USA (Formerly A.A.C. Consulting Group Inc.) 7361 Calhoun Place, Suite 5000 Rockville, MD 20855-2765, USA
Telephone:	(301)-838-3120 (301)-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA

Non-Proprietary Name (USAN): Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

	LISTED DRUG	PROPOSED ANDA
RLD	Zyrtec –D 12 hour Extended Release Tablets	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets
NDA/Holder	**NDA 21-150**/ McNeil Consumer Healthcare (Pfizer)	**ANDA** 90-922/Sun
Dosage form	Tablets	Tablets
Route of Administration	Oral	Oral
Strengths	5 mg / 120 mg	5 mg / 120 mg
	Patent Certification:	Paragraph IV
	Exclusivity:	No unexpired exclusivity for this product; statement included

U.S. Patent Number	Expiration Date
6,469,009 (the '009 patent)	July 13, 2019
6,489,329 (the '329 patent)	April 8, 2016
7,014,867 (the '867 patent)	June 10, 2022
7,226,614 (the '614 patent)	June 10, 2022

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets (MDD $_{\text{cetirizine HCl}}$ = 10 mg/day) (MDD $_{\text{pseudoephedrine HCl}}$ = 240 mg/day)

12. STRENGTH/POTENCY: 5 mg / 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _x__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

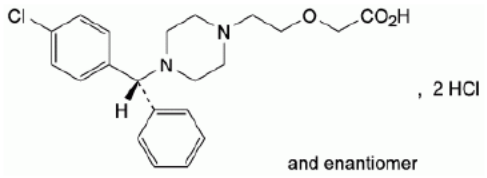
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

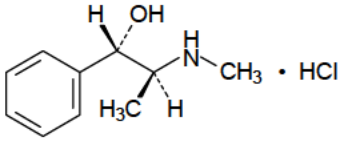
A. Cetirizine Hydrochloride:

- (±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride
- $C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



B. Pseudoephedrine Hydrochloride:

- (+) (1S-2S)-2-Methylamino-1-Phenyl-1-Propanol-Hydrochloride
- $C_{10}H_{16}ClNO$ MW = 201.7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]
17889	II	Sun	Cetirizine HCl	3	**Adequate** in Rev# 4 on 30-Jan-2008 by V. Prabhu
(b) (4)	II		(b) (4)	3	**Adequate** in Rev# 9 on 30-Apr-2009 by S. Patankar
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
				4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A

		(b) (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: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	REVIEWER
Chemistry	Minor on 16-Jul-2009	Q. Zhang
Labeling	Pending as 16-Jul-2009	Postelle Birch
Bioequivalence	Deficient on 17-Mar-2009	X.Jiang
EES	Overall PN As 9-Jul-2009 (DP manufacturer PN, others AC)	
Microbiology	N/A	
Methods Validation	Not requested per current OGD policy (USP)	
EA	Exclusion from requirement for environmental assessment	Q. Zhang
Radiopharmaceutical	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:

Following this page, 63 pages withheld in full (b)(4)

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-922 APPLICANT: Sun Pharmaceuticals Industries, Ltd.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.

Following this page, 1 page withheld in full (b)(4)

(b) (4)

21. [redacted]

22.

23.

24.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Review of the Labeling is pending and BA/BE portions of this ANDA is deficient. We may request additional information at the completion of these reviews.

2. Evaluation of all the finished drug product site establishments is pending.

3. Please provide all available room temperature stability data.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 90-922 Oiginal
ANDA DUP
DIV FILE
Field Copy

Endorsements Block:

HFD-647/Quan Zhang, Ph.D., Reviewer/ 09-Jul-2009; 16-Jul-2009

HFD-630/Shing Hou Liu, Ph.D., Team Leader/15-Jul-2009: 20-Jul-2009

HFD-617/L. Bradford, Project Manager/20-Jul-2009

F/T by/ LB 20-Jul-2009

V:\FIRMSAM\SUN\LTRS&REV\90922.R01.doc

TYPE OF LETTER: NOT APPROVABLE - Minor

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

/s/

Quan Zhang
7/20/2009 03:44:34 PM
CHEMIST

Leigh Ann Bradford
7/20/2009 04:18:59 PM
CSO

Shing Hou Liu
7/22/2009 02:53:53 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	090922		
Drug Product Name	Cetirizine Dihydrochloride(IR) and Pseudoephedrine Hydrochloride (ER) Extended Release Tablets		
Strength(s)	5 mg/120 mg		
Applicant Name	Sun Pharmaceutical Industries Ltd.		
Address	Kendle International 7361 Calhoun Place, Suite 500 Rockville MD 20855-2765		
Applicant's Point of Contact	Anthony Celeste		
Contact's Telephone Number	301-838-3120		
Contact's Fax Number	301-838-3182		
Original Submission Date(s)	October 16, 2008 June 6, 2009 (Dissolution acknowledgement)		
Submission Date(s) of Amendment(s) Under Review	December 17, 2010 February 1, 2011 (Telephone Amendment)		
Reviewer	Suman Dandamudi		
Study Number (s)	PKD/08/021	PKD/08/022	
Study Type (s)	Fasting	Fed	
Strength (s)	5 mg/120 mg	5 mg/120 mg	
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Near R. C. Patel Estate, Akota Road, Akota Vadodara-390020, Gujarat, India		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalija, Vadodara-390020 Gujarat, India		
OVERALL REVIEW RESULT	**ADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**5 MG/120 MG**	**ADEQUATE**
1	**FASTING STUDY**	**5 MG/120 MG**	**ADEQUATE**
1	**FED STUDY**	**5 MG/120 MG**	**ADEQUATE**

1 EXECUTIVE SUMMARY

The submission references NDA 021150, ZYRTEC-D 12 hr® (Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride) Extended Release Tablets, 5 mg/120 mg from McNeil. There are 3 earlier bioequivalence documents on this ANDA (090922). Those are i) a " dissolution only" review , ii) a "full ANDA" review and iii) a telephone request for additional data dated 01/28/2011.

DISSOLUTION TESTING:
As per the "dissolution only" review the DBE requested the firm to accept and acknowledge the following dissolution method and specifications. The firm did so in the 06/06/2009 amendment. **Thus, the dissolution testing is acceptable and complete Adequate)**.

Apparatus:	USP Apparatus I (Basket) at 100 rpm
Medium:	500 mL of 0.1 N HCl at 37±0.5°C
Specifications:	For Cetirizine: NLT 80% (Q) in 30 min; For Pseudoephedrine: 1 hour 30-50% 2 hour 50-70 % 6 hour NLT 80%

BIOEQUIVALENCE (BE) STUDIES:
As per the "full ANDA" review there were **5 deficiencies**. The **5 deficiencies** were i) a request for resubmission of entire analytical report for the fasting BE study (PKD/08/021), ii) a request for complete raw numerical data for the fed BE study (PKD/08/022), iii) a request for explanation of the low mean recovery of 32% for pseudoephedrine seen in the report MV/CEPS/021, iv) a request for submission of at least 20% chromatograms for the fed BE study (PKD/08/022), v) a request for the Certificate of Analysis (COA) for the reference drug product (lot # 03607L).

The firm responded to the **5 deficiencies** in the amendment dated 12/17/2010 (1st amendment). There were inadequate data in this amendment (1st amendment). The firm therefore submitted the missing information in the subsequent amendment dated 02/01/2011(telephone amendment). The current review evaluates the amendments dated 12/17/2010 and 02/01/2011(telephone amendment). The firm's response to the **5 deficiencies is acceptable**. **Thus, the fasting and fed BE studies are now acceptable and complete (Adequate)**.

DSI INSPECTIONS:
The clinical site was inspected for ANDA 090745 (routine) on 6/16/2010 and the outcome was **NAI**. The analytical site was inspected for ANDA 090745 (Routine) on 6/16/2010 and the outcome was VAI [**DARRTS: BISWAS, GOPA 06/17/2010 N/A 06/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 Archive]**. The reviewer has reviewed the DSI report and determined that the DSI report does not have any item that would affect the integrity of the analytical study submitted in this ANDA[1].

No Division of Scientific Investigations (DSI) inspection is pending or necessary for clinical and analytical sites.

The application is **acceptable (adequate).**

2 TABLE OF CONTENTS

3 BACKGROUND INFORMATION

1. Sun Pharmaceuticals has submitted ANDA 090922 for its product, Cetirizine Dihydrochloride and pseudoephedrine Hydrochloride Tablets, 5 mg/120 mg. The submission references NDA 021150, ZYRTEC-D 12 hr® (Cetirizine Dihydrochloride and pseudoephedrine Hydrochloride) Tablets, 5 mg/120 mg from McNeil.

[1] The routine DSI inspection of the analytical site was completed on 6/16/2010 and the outcome is VAI (voluntary action indicated) (for parent ANDA 090745). The DSI findings included: 1) Failure to conduct Incurred Sample Reproducibility assessments; 2) Failure to provide adequate controls for electronic source records. The DSI findings for studies conducted for ANDA 090745 are not expected to change the outcome of the current BE study. For ANDA 090745, after reviewing the DSI report, the studies were found still acceptable (DARRTS, DARRTS: BISWAS, GOPA 06/17/2010 N/A 06/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 Archive). The current reviewer did not considered the two DSI findings to have any impact on the current studies.

2. DBE had done a **"dissolution only"** review on this ANDA [**DARRTS for ANDA 090922: JIANG, XIAOJIAN 03/17/2009 N/A 03/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive].** The firm conducted its dissolution testing using the FDA-recommended dissolution method Cetirizine Dihydrochloride and pseudoephedrine Hydrochloride Tablets, 5 mg/120 mg:

Medium:	0.1 N HCl
Apparatus:	USP apparatus I (Basket)
Speed:	100 RPM

The firm's initially proposed specifications were not acceptable and DBE recommended the firm to acknowledge the following FDA-recommended specifications.

Cetirizine-NLT 80% (Q) in 30 minutes
Pseudoephedrine- 1 hr: 30%-50%,
2hrs: 50%-70%
6hrs: NLT 80%

In its amendment dated on 06/06/2009, the firm acknowledged the FDA-recommended dissolution specification. The dissolution testing is acceptable. In addition to conducting dissolution testing in 0.1 N HCl, the firm also conducted dissolution testing in pH 4.5 acetate buffer, pH 6.8 phosphate buffer and water. The firm also conducted in vitro alcohol dose dumping testing of pseudoephedrine ER component for the test product using the following dissolution method: 900 ml, 0.1 N HCl, USP apparatus I (Basket) at 100 rpm, with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media. The test product did not show any risk of dose-dumping in the presence of alcohol.

3. The firm, in its original application, also submitted the fasting and fed bioequivalence studies comparing its Cetirizine and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg, to the McNeil's, ZYRTEC-D 12 hour® (Cetirizine and Pseudoephedrine) Tablets, 5 mg/120 mg. The BE studies were found incomplete **[DARRTS: DANDAMUDI, SUMAN 09/20/2010 N/A 09/20/2010 REV-BIOEQ-01(General Review) Original-1 Archive]** due **to 5 deficiencies**. The **5 deficiencies** were i) a request for resubmission of entire analytical report for the fasting BE study (PKD/08/021), ii) a request for complete raw numerical data for the fed BE study (PKD/08/022), iii) a request for explanation of the low mean recovery of 32% for pseudoephedrine seen in the report MV/CEPS/021, iv) a request for submission of at least 20% chromatograms for the fed BE study (PKD/08/022), v) a request for the Certificate of Analysis (COA) for the reference drug product (lot # 03607L).

4. In the current amendment, the firm re-submitted the analytical report of the fasting study and the raw numerical data for fed BE study of Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Tablets. The firm also provided the explanation for the low recovery of pseudoephedrine in their method validation.

4 SUBMISSION SUMMARY

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

See the review of the original submission in **DARRTS for ANDA 090922-DANDAMUDI, SUMAN 09/20/2010 N/A 09/20/2010 REV-BIOEQ-01(General Review) Original-1 Archive.**

B. Contents of Submission

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

C. Review of Submission

Deficiency 1: *The DBE could not open the electronic file for the analytical report of the fasting study probably because it was corrupt. Please resubmit the entire analytical report of the fasting (Study No: PKD/08/021) bioequivalence (BE) study.*

Firm's Response to Deficiency 1: As requested by the DBE please note that the bioanalytical study report for fasting study (PKD/08/021) has been provided in section 5.3.1.4 of this version of eCTD.

Reviewer's Comments on Firm's Response: In the original application, the firm submitted the analytical report of the fasting study, however the reviewer could not open the electronic file since it was corrupt. So the firm was asked to resubmit the entire analytical report of the fasting study.

In the current amendment the firm submitted the analytical report for the sample analysis of the Fasting Study No. PKD/08/021.

Bioanalytical Results

Bioequivalence Study No. PKD/08/021 Cetirizine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	5.00	10.00	20.00	50.00	139.99	199.98	239.98	299.97
Inter day Precision (%CV)	5.0	2.9	4.0	3.7	2.5	2.9	2.7	2.9
Inter day Accuracy (% Bias)	104.3	97.4	95.7	103.4	98.5	100.9	98.9	100.7
Linearity	0.9973 to 0.9999 (r value)							
Linearity Range (ng/mL)	5.00 to 299.97							
Sensitivity/LOQ (ng/mL)	5.00							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	15.00	69.99	149.99	249.98
Inter day Precision (%CV)	5.7	7.3	7.4	8.4
Inter day Accuracy (% Bias)	102.3	99.7	100.7	103.0

Bioequivalence Study No. PKD/08/021 Pseudoephedrine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	10.0	20.0	100.0	200.0	560.0	860.1	1020.1	1252.1
Inter day Precision (%CV)	8.6	3.9	3.5	4.3	2.9	3.2	1.8	3.6
Inter day Accuracy (% Bias)	108.4	100.3	95.5	97.4	98.1	99.7	98.4	103.0
Linearity	0.9949 to 1.0000 (r Value)							
Linearity Range (ng/mL)	10.0 to 1252.1							
Sensitivity/LOQ (ng/mL)	10.0							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	30.0	260.0	580.1	1060.1
Inter day Precision (%CV)	8.8	6.9	19.3	8.8
Inter day Accuracy (% Bias)	100.7	97.4	100.5	99.0

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

In the current amendment (Document 10 in DARRTS) the firm also submitted the analytical raw data for all the assay runs of the study subject samples. However the firm submitted the raw numerical data from the assay runs of **only 1-30 subjects.** In the telephone request the firm was asked to submit the complete raw numerical data of ALL assay and reassay runs of subjects 31-44 of Fasting study, including the data of peak

height/area for the drug, peak height/area for the internal standard, ratio of the peak height/area for the drug to the peak height/area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples. In the telephone amendment dated February 1, 2011 the firm submitted the analytical raw data (document 11 in DARRTS) for all the assay runs of complete study subject samples. The reviewer's comments regarding the sample re analysis are provided below

Repeat Analysis

Cetirizine

Fasted Study, Study No. PKD/08/021 Additional Information in 5.3.1.4 of the Bioanalytical Report								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Unacceptable internal standard response	27	2	1.28%	0.10%	27	2	1.28%	0.10%
Incomplete analysis	2	0	0.10%	0.00%	2	0	0.10%	0.00%
Inconsistent profile	1	0	0.05%	0.00%	0	0	0.00%	0.00%
Rejected analytical run	108	106	5.13%	5.04%	54	53	2.57%	2.52%
Total	138	108	6.56%	5.13%	83	55	3.94%	2.61%

Pseudoephedrine

Fasted Study, Study No. PKD/08/021 Additional Information in 5.3.1.4 of the Bioanalytical Report								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Unacceptable internal standard response	27	1	1.28%	0.05%	27	1	1.28%	0.05%
Incomplete analysis	2	0	0.10%	0.00%	2	0	0.10%	0.00%
Rejected analytical run	108	108	5.13%	5.13%	81	81	3.85%	3.85%
Total	137	109	6.51%	5.18%	110	82	5.23%	3.90%

SOP's dealing with Bioanalytical Repeats of Study Samples

SOP No.	**Effective Date of SOP**	**SOP Title**
PKD/S/019	13/02/2008	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 01)
Were all SOPs followed?		Yes

Did recalculation of PK parameters change the study outcome?	There is no PK repeat
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	

Cetirizine
The firm reassayed the study samples because of the analytical reasons, "Unacceptable internal standard response", "Incomplete Analysis", "Inconsistent profile" and "Rejected Analytical Run". The samples reassayed because of the above reasons were acceptable except "Inconsistent profile". After checking the raw data, the firm reanalyzing the study samples due to "Inconsistent profile" was found to be unacceptable. Samples reassayed without an objective criterion defined in a reanalysis standard operating procedure (SOP) are considered essentially questionable "PK repeats" and only the original assay values should be used in the final data analysis.

The firm reassayed subject 25, period I, 36 hr time point for the reason of "Inconsistent profile". However the firm used original value for the pharmacokinetic analysis. The SOP's of sample re-analysis were provided and are acceptable.

Pseudoephedrine
The firm reassayed the study samples because of the analytical reasons. The SOP's of sample re-analysis were provided and are acceptable.

The firm's response to the 1st deficiency is acceptable.

Deficiency 2: *For Fed (Study No: PKD/08/022) BE study, you have submitted the raw numerical data from the assay runs of **only 20%** of the subjects. Please submit complete raw numerical data of **ALL** assay and reassay runs of both Fasting and Fed studies, including the data of peak height/area for the drug, peak height/area for the internal standard, ratio of the peak height/area for the drug to the peak height/area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples.*

Firm's Response to Deficiency 2: Please note that data for all the assay and reassay runs of Fed study (PKD/08/022), including the data of peak height/area for the drug, peak height/area for the internal standard, ratio of the peak height/area for the drug to the peak height/area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples has been provided in ***section 5.3.1.4***. The data for all the assay and reassay runs for Fasting study (PKD/08/021) has been included in the Fasting study bioanalytical report provided in ***section 5.3.1.4***.

Reviewer's Comments on Firm's Response: The firm in its original application did not submit the analytical raw data for all the assay runs of the fed study subject samples. So the

reviewers comments regarding the sample reanalysis were not provided in the review of original application.

Cetirizine:
The firm reassayed the study samples because of the analytical reasons, "Unacceptable internal standard response", "Sample reanalyzed to obtain conforming value" and "Inconsistent profile". The samples reassayed because of the above reasons were acceptable except "Sample reanalyzed to obtain conforming value", "Inconsistent profile". After checking the raw data, the firm reanalyzing the study samples due to "Sample reanalyzed to obtain conforming value", "Inconsistent profile" was found to be unacceptable. Samples reassayed without an objective criterion defined in a reanalysis standard operating procedure (SOP) are considered essentially questionable "PK repeats" and only the original assay values should be used in the final data analysis.

The firm reassayed subject 2, period I, 36 hr time point and subject 30, period I, 30 hr time point samples for the reason of "Sample reanalyzed to obtain conforming value". The firm also reassayed subject 2, period I, 48 hr time point, subject 10, period I, 2 hr time point, subject 33, period I, 36 hr time point and subject 34, period I, 48 hr time point samples for the reason of "Inconsistent profile". The reviewer used the original values and re-calculated the confidence intervals for these study samples. The 90% confidence intervals of LAUC0-t, LAUC∞ and LCmax, are still within the acceptable limits of 80-125% (see table below). Therefore, the reassay did not compromise the study outcome.

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	1255.47	1270.02	0.99	95.94	101.85
AUC∞ (hr *ng/mL)	1332.34	1359.58	0.98	95.20	100.88
Cmax (ng/mL)	121.22	116.12	1.04	99.95	109.03

Pseudoephedrine:
The firm reassayed the study samples because of the analytical reasons, "Unacceptable internal standard response", "Sample reanalyzed to obtain conforming value", "Inconsistent profile" and "Rejected analytical run". The samples reassayed because of the above reasons were acceptable except "Sample reanalyzed to obtain conforming value", "Inconsistent profile". After checking the raw data, the firm reanalyzing the study samples due to "Sample reanalyzed to obtain conforming value", "Inconsistent profile" was found to be unacceptable. Samples reassayed without an objective criterion defined in a reanalysis standard operating procedure (SOP) are considered essentially questionable "PK repeats" and only the original assay values should be used in the final data analysis.

The firm reassayed subject 3, period I, 0 hr with IS time point and subject 29, period II, 0 hr with IS time point and subject 40, period I, 0 hr with IS time point samples for the reason of "Sample reanalyzed to obtain conforming value". The firm also reassayed subject 33, period I, 36 hr time point sample for the reason of "Inconsistent profile". The reviewer used the original values and re-calculated the confidence intervals for these study samples. The 90% confidence intervals of LAUC0-t, LAUC∞ and LCmax, are still within the acceptable limits of 80-125% (see table below). Therefore, the reassay did not compromise the study outcome.

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	4141.44	4088.38	1.01	98.01	104.70
AUC∞ (hr *ng/mL)	4256.12	4195.94	1.01	98.16	104.81
Cmax (ng/mL)	378.16	350.47	1.08	104.55	111.37

The firm's response to the 2nd deficiency is acceptable.

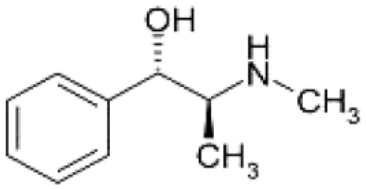
Deficiency 3: *The mean percent recovery value of pseudoephedrine is 32%. Please explain the reason for such low value of the recovery of the analyte pseudoephedrine reported in method validation report No MV/CEPS/021.*

Firm's Response to Deficiency 3: Please find below explanation for the low recovery of pseudoephedrine in biological matrix:

1. During sample processing (b) (4) was not used which could (b) (4) Following are the reasons selecting method without (b) (4).

   - Pseudoephedrine is basic Compound (pKa 9.9). Basic compound extraction is better in basic condition and ionized better at acidic pH in LC/MS/MS. Please refer following structural information of Pseudoephedrine.

     Molecular weight: 165.23
     Solubility: 7mg/L in water
     Pka: 9.9
     Molecular structure:



- Pseudoephedrine has amino functional group which has greater ability for protonation therefore mode of ionization selected is electrospray with positive polarity along with acidic pH mobile phase to achieve better ionization & signal reproducibility.

2. Additionally, the possible phospholipid and other matrix component in organic layer during protein precipitation method could induce matrix effect. But as per method validation data, there is no matrix effect which is evident from results (Recovery experiment, Precision & Accuracy data and Matrix effect) provided in Table 1, Table 2 and Table 3.

3. Method validation and recovery results have been evaluated further and followings are observations for Pseudoephedrine. The results express that recovery is highly precise and reproducible across the range where low recovery (around 30%) would not have any impact on concentration obtained after sample analysis.

   - Mean recovery observed is 29.3, 31.6, 32.4 and 33.8 for LOW QC, MED QC A, MED QC B and HQC respectively.
   - % CV observed 4.0%, 1.8%, 3.0% and 2.1% for LOW QC, MED QC A, MED QC B and HQC respectively.
   - Mean recovery and % CV observed 31.78 and 5.9 respectively across the range and also Global P & A data further confirm to well precise and accurate method.

Reviewer's Comments on Firm's Response: The ionization state of the analyte molecule depends on the pH of the mobile phase. The ionization efficiency in LC/MS with electrospray (ESI) in positive ion mode will be drastically lowered in high pH mobile phases. It is common practice to employ volatile weak acids for enhancing the ionization of basic compounds in electrospray. So the firm stated that since pseudoephedrine has amino functional group which has greater ability for protonation therefore mode of ionization selected is electrospray with positive polarity along with acidic pH mobile phase to achieve better ionization & signal reproducibility. At the acidic conditions, the extraction of pseudoephedrine is lowered, since the basic compounds have better extraction at the basic pH. The firm stated that even though the recovery of pseudoephedrine is low, the results are consistent and reproducible at all the quality control concentrations. The firm's response to **the 3rd deficiency is acceptable.**

Deficiency 4: *For the Fed (Study No PKD/08/022) BE study, you have submitted the chromatograms of cetirizine for 7 subjects i.e. 18% of the subjects.* ***For future submissions****, please submit chromatograms of at least 20% of the subjects.*

Firm's Response to Deficiency 4: As recommended by the DBE for future submission we will provide chromatograms for at least 20% of the subjects. Chromatograms of cetirizine for subject No. 9 and 10 of the fed study (PKD/08/022) have been provided in ***section 5.3.1.4*** of this version of eCTD.

Reviewer's Comments on Firm's Response: In the original application, the firm submitted chromatograms of cetirizine for 7 subjects i.e. 18% of the subjects. In the current amendment the firm submitted chromatograms for two additional subjects. The firm's response to **the 4th deficiency is acceptable.**

Deficiency 5: *Please provide the certificate of analysis for the reference product (lot# 03607L).*

Firm's Response to Deficiency 5: Please note that the certificate of analysis for the reference product had already been provided in submitted ANDA section 5.3.1.2. Please find the copy of reference product certificate of analysis herewith in ***section 5.3.1.2*** for your ready reference.

Reviewer's Comments on Firm's Response: The reviewer could not find the certificate of analysis for the reference product in the original application. Thus the potency and content uniformity of the reference product could not be verified. The firm in the current amendment submitted the certificate of analysis of reference product. The firm's response to **the 5th deficiency is acceptable.**

D. Deficiency Comments

None

E. Recommendations

1. The Division of Bioequivalence accepts the **fasting** BE study No. PKD/08/021 conducted by the Sun Pharmaceutical Industries, Ltd. on its Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg/120 mg, lot # GK71416C, comparing it to McNeil's ZYRTEC-D 12 hour® (Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride) Tablets, 5 mg/120 mg, lot 03607L.

2. The Division of Bioequivalence accepts the **fed** BE study No. PKD/08/022 conducted by the Sun Pharmaceutical Industries, Ltd. on its Cetirizine

Dihydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg/120 mg, lot # GK71416C, comparing it to McNeil's ZYRTEC-D 12 hour® (Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride) Tablets, 5 mg/120 mg, lot 03607L.

3. The firm's *in vitro* dissolution testing is **acceptable**. The dissolution testing should be conducted in 500 mL of 0.1 N HCl, at 37ºC ± 0.5ºC using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification:

Cetirizine-NLT 80% (Q) in 30 minutes
Pseudoephedrine- 1 hr: 30%-50%,
2hrs: 50%-70%
6hrs: NLT 80%

F. Comments for Other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090922

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg/120 mg

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page and has no further question at this time.

We acknowledge that you will conduct dissolution testing for the test product using the following FDA-recommended dissolution method and specification:

The dissolution testing should be conducted in 500 mL of 0.1 N HCl, at 37°C + 0.5° C using USP apparatus I (Basket) at 100 rpm.

The test product should meet the following specification:

Cetirizine-NLT 80% (Q) in 30 minutes
Pseudoephedrine- 1 hr: 30%-50%,
2hrs: 50%-70%
6hrs: NLT 80%

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

Sincerely yours,

{See appended electronic signature page}

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

5 OUTCOME PAGE

ANDA: 090922

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13230	12/17/2010	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	0

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

/s/

SUMAN DANDAMUDI
04/11/2011

SHRINIWAS G NERURKAR
04/12/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
04/12/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090922		
Drug Product Name	Cetirizine Dihydrochloride(IR) and Pseudoephedrine Hydrochloride (ER) Extended Release Tablets		
Strength(s)	5 mg/120 mg		
Applicant Name	Sun Pharmaceutical Industries Ltd.		
Address	Kendle International 7361 Calhoun Place, Suite 500 Rockville MD 20855-2765		
Applicant's Point of Contact	Anthony Celeste		
Contact's Telephone Number	301-838-3120		
Contact's Fax Number	301-838-3182		
Original Submission Date(s)	DATE OF APPLICATION: October 16, 2008 DATE (RECEIVED) ACCEPTABLE FOR FILING: October 22, 2008		
Submission Date(s) of Amendment(s) Under Review	06/06/2009 (Dissolution acknowledgement)		
Reviewer	Suman Dandamudi		
Study Number (s)	PKD/08/021	PKD/08/022	
Study Type (s)	Fasting	Fed	
Strength (s)	5 mg/120 mg	5 mg/120 mg	
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Near R. C. Patel Estate, Akota Road, Akota Vadodara-390020, Gujarat, India		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalija, Vadodara-390020 Gujarat, India		
OVERALL REVIEW RESULT	**INADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**5 MG/120 MG**	**ADEQUATE**
1	**FASTING STUDY**	**5 MG/120 MG**	**INADEQUATE**
1	**FED STUDY**	**5 MG/120 MG**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Cetirizine and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg, to the corresponding reference listed product, ZYRTEC-D 12 hour® (Cetirizine and Pseudoephedrine) Tablets, 5 mg/120 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The BE study results are summarized in the tables below:

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/08/021, N=39					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1535.02	1524.19	1.01	97.59	103.93
AUC∞ (hr *ng/ml)	1619.52	1618.47	1.00	96.84	103.39
Cmax (ng/ml)	180.03	171.85	1.05	101.24	108.41

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/08/021, N=39					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	4601.27	4599.39	1.00	96.53	103.68
AUC∞ (hr *ng/ml)	4729.56	4733.14	1.00	96.41	103.56
Cmax (ng/ml)	382.72	364.38	1.05	101.72	108.46

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	1254.25	1271.26	0.99	95.77	101.64
AUC∞ (hr *ng/mL)	1350.61	1361.18	0.99	96.03	102.53
Cmax (ng/mL)	121.22	116.12	1.04	99.95	109.03

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	4141.44	4088.25	1.01	98.01	104.70
AUC∞ (hr *ng/mL)	4256.12	4195.81	1.01	98.17	104.82
Cmax (ng/mL)	378.16	350.47	1.08	104.55	111.37

However, the fasting and fed studies are **incomplete** due to deficiency related to analytical parts of the study. The reviewer could not open the analytical report of the fasting study (Study No PKD/08/021) since it was corrupt. Therefore it is not possible to know whether the firm has submitted entire analytical raw data. In addition the firm did not submit the analytical raw data from the study runs of all the subjects in the fed BE study.

The firm has conducted acceptable comparative dissolution testing on Cetirizine and Pseudoephedrine Extended Release Tablets, using the FDA-recommended dissolution method ([**DARRTS: file JIANG, XIAOJIAN 03/17/2009 N/A 03/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive**]. On 6/6/2009, the firm acknowledged the FDA-recommended dissolution specification.

The clinical site was inspected for ANDA 090745 (routine) on 6/16/2010 and the outcome was NAI. The analytical site was inspected for ANDA 090745 (routine) on 6/16/2010 and the outcome was VAI. The Bioequivalence review of the DSI inspection report [**DARRTS: REV-BIOEQ-01 (General Review) NWAKAMA, PATRICK ANDA-090745 07/12/2010 FINAL 07/19/2010 N/A Archive**] does not have items that would apply to the integrity of the analytical data submitted in this ANDA. No Division of Scientific Investigations (DSI) inspection is pending or necessary for clinical and analytical sites.

The application is **Incomplete.**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1, 2]

Test Product	Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg/ 120 mg
Reference Product	ZYRTEC-D 12 hour® (Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride) Extended Release Tablets, 5 mg/120 mg
RLD Manufacturer	McNeil
NDA No.	021150
RLD Approval Date	November 9, 2007
Indication	Zyrtec-D 12 hour extended release tablets are indicated for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older.

3.2 PK/PD Information[2, 3]

Bioavailability	The bioavailability of cetirizine and pseudoephedrine from the combination Extended-Release drug product is not significantly different from that achieved with separate administration of a cetirizine 5 mg tablet and a pseudoephedrine 120 mg extended release caplet. Co-administration of cetirizine and pseudoephedrine does not significantly affect the bioavailability of either component.
Food Effect	Food had no significant effect on the AUC of cetirizine, but T_{max} was delayed by 1.8 hours and C_{max} was decreased by 30%. Food had no significant effect on the pharmacokinetics of pseudoephedrine. Zyrtec-D 12 HOUR® Tablets may be given with or without food.
Tmax	Cetirizine-2.2 hrs, Pseudoephedrine-4.4 hrs
Metabolism	Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting low first pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified. 1-7% of the pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after a single dose.
Excretion	A human mass balance study of cetirizine indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine

[1] Online-Orange Book (2010). http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
[2] Labeling for the RLD Product.
[3] Online-Clinical Pharmacology (2010). http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=585

	as unchanged drug.
Half-life	Cetirizine: 7.9 hours; pseudoephedrine: 6.0 hours
Drug Specific Issues (if any)	Pregnancy category C. Because there are no adequate and well-controlled trials in pregnant women, ZYRTEC-D 12 hour Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because Cetirizine and Pseudoephedrine are excreted in milk, use of ZYRTEC-D 12 hour Extended Release Tablets in nursing mothers is not recommended.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	5 mg/120 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	5 mg/120 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Cetirizine and Pseudoephedrine
Bioequivalence based on:	90% CI for both analytes
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Based on Guidance for Industry: Individual product Bioequivalence Recommendations; February 2008. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081292
Summary of OGD or DBE History (for details, see Appendix 4.4)	Currently there are two approved generic products of Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablets, listed in the Orange Book: • ANDA # 077170 (Ivax approved on February 25, 2008) • ANDA # 077991 (Sandoz approved on March 5, 2008)

3.4 Contents of Submission

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

3.5 Pre-Study Bioanalytical Method Validation

Cetirizine

Information Requested	Data
Bioanalytical method validation Report location	Validation No.: MV/CEPS/021; Section 5.3.1.4
Analyte	Cetirizine
Internal standard (IS)	(b) (4)
Method description	Extraction method: Refer Method Validation report (MV/CEPS/021); Page No.16 (Protein Precipitation Extraction); Analytical method: LC-MS/MS
Limit of quantitation	LLOQ : 5.00 ng/mL, ULOQ : 299.97 ng/mL
% recovery (and %CV) at each concentration tested	QC Low : 89.8%, %CV- 4.5% QC Med A: 87.4%, %CV- 3.7% QC Med B : 87.1%, %CV- 4.6% QC High : 92.9%, %CV- 4.0%
Average recovery of IS (%)	79.4%, %CV- 5.8%
Standard curve concentrations (units/mL)	5.00, 10.00, 20.00, 50.00, 139.98, 199.98, 239.98, 299.97
QC concentrations (units/mL)	Low QC : 15.00 ng/mL Medium QC A : 69.99 ng/mL Medium QC B : 149.99 ng/mL High QC : 249.98 ng/mL
QC Intraday precision range (%)	2.1% to 10.7%
QC Intraday accuracy range (%)	99.0% to 110.4%
QC Interday precision range (%)	1.4% to 10.7%
QC Interday accuracy range (%)	95.0% to 113.6%
Bench-top stability (hrs)	Appx. 22 hours at room temperature
Stock stability (days)	24 days @ 2-8°C
Processed stability (hrs)	Appx.57 hours @ 10°C ± 2°C
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	88 Days @ -20°C ± 5°C
Dilution integrity	3 times of CS8 concentration (899.92 ng/ml) diluted 5 folds.
Selectivity	No interfering peaks noted in blank plasma samples

Pseudoephedrine

Information Requested	Data
Bioanalytical method validation Report location	Validation No.: MV/CEPS/021; Section 5.3.1.4
Analyte	Pseudoephedrine
Internal standard (IS)	(b) (4)
Method description	Extraction method: Refer Method Validation report (MV/CEPS/021); Page No.16 (Protein Precipitation Extraction); Analytical method: LC-MS/MS
Limit of quantitation	LLOQ : 10.0 ng/mL, ULOQ : 1252.1 ng/mL
% recovery (and %CV) at each concentration tested	QC Low : 29.3% QC Med A: 31.6% QC Med B: 32.4% QC High : 33.8%
Average recovery of IS (%)	79.4%
Standard curve concentrations (units/mL)	10.0, 20.0, 100.0, 200.0, 560.0, 860.1, 1020.1, 1252.1
QC concentrations (units/mL)	Low QC : 30.0 ng/mL Medium QC A : 260.0 ng/mL Medium QC B : 580.1 ng/mL High QC : 1060.1 ng/mL
QC Intraday precision range (%)	2.1% to 11.0%
QC Intraday accuracy range (%)	95.0% to 106.1
QC Interday precision range (%)	2.0% to 8.3%
QC Interday accuracy range (%)	98.0% to 110.4%
Bench-top stability (hrs)	Appx. 22 hours at room temperature
Stock stability (days)	24 days @ 2-8°C
Processed stability (hrs)	Appx.57 hours @ 10°C ± 2°C
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	88 Days @ -20°C ± 5°C
Dilution integrity	3 times of CS8 concentration (3760.3 ng/ml) diluted 5 folds.
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Incomplete

Comments on the Pre-Study Method Validation:

- The long term storage data of 88 days for both cetirizine and pseudoephedrine exceed the storage period for the samples of both the fasted (38 days) and fed (53 days) BE studies.

- The firm used K3 EDTA as anticoagulant in their fasting and fed BE studies. It used the same anticoagulant in pre-study and with-in study validations. The calibration standards and quality control samples were prepared with human plasma containing K3 EDTA.

- The mean percent recovery value of pseudoephedrine is 32%. The firm should explain the reason for such low value of the recovery of the analyte pseudoephedrine reported in method validation report No MV/CEPS/021.

- In order to judge the impact of the low pseudoephedrine recovery, the reviewer compared the pharmacokinetic data of pseudoephedrine from the other ANDAs to that in the current ANDA. It is noticed that in spite of low recovery, the pharmacokinetic data of pseudoephedrine in the current submission is similar to that in the other ANDAs' (see table below).

Least Square Geometric Means of pseudoephedrine in fasting study

Pharmacokinetic Parameter	ANDA 090922 (Current Submission)		ANDA 077991		ANDA 077170	
	Test	Reference	Test	Reference	Test	Reference
AUC0-t (ng *hr/mL)	4601.27	4599.39	4590.84	4429.14	4164.28	4158.57
AUC∞ (ng *hr/mL)	4729.56	4733.14	4624.93	4455.37	4265.06	4285.98
Cmax (ng/mL)	382.72	364.38	351.13	343.85	319.73	332.47

Least Square Geometric Means of pseudoephedrine in fed study

Pharmacokinetic Parameter	ANDA 090922 (Current Submission)		ANDA 077991		ANDA 077170	
	Test	Reference	Test	Reference	Test	Reference
AUC0-t (ng *hr/mL)	4141.44	4088.25	4040.37	4088.37	4012.63	3985.73
AUC∞ (ng *hr/mL)	4256.12	4195.81	4058.58	4004.96	4117.00	4063.08
Cmax (ng/mL)	378.16	350.47	375.78	361.64	362.64	363.86

- The pre-study validation data are incomplete.

3.6 In Vivo Studies

Table 1. Summary of all *in vivo* Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Cetirizine- Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hour/mL)	AUC_{∞} (ng*hour/mL)	$T½$ (hr)	K_{el} (hr-1)	
PKD/08/021	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride 5 mg/120 mg Extended Release tablets of Sun Pharmaceutical Industries Limited, India and Zyrtec-D12 hour® Extended Release Tablets of Pfizer Inc, NY, NY 10017, in 44 healthy human adult subjects, under fasting conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study with 7 days washout period between each drug administration under fasting conditions.	**Test product** Oral Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablet, 5 mg/120 mg, Sun Lot No. GK71416C Mfg. Date; September 2007	39 Healthy Male subjects Mean age: 29.5 Years (Range= 19-44)	Mean= 181.926 % CV= 15.7	Mean= 0.75 Range= 0.5-1.75	Mean= 1565.8550 % CV= 20.7	Mean= 1650.6251 % CV= 20.6	Mean= 8.1974 % CV= 20.4	Mean= 0.08779 % CV= 19.1	**Module 5**
			Ref. Product Oral Zyrtec-D 12 hour® (Cetirizine HCl and Pseudoephedrine HCl) Extended Release Tablet, 5 mg/120 mg , MCNeil Lot No. 03607L Exp. Date March 2010		Mean= 173.989 % CV= 16.1	Mean= 0.75 Range= 0.5-2.00	Mean= 1565.5878 % CV= 24.1	Mean= 1659.2439 % CV= 23.3	Mean= 8.4216 % CV= 20.4	Mean= 0.08573 % CV= 20.9	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Pseudoephedrine- Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hour/ mL)	AUC_{∞} (ng*hour/ mL)	$T½$ (hr)	K_{el} (hr-1)	
PKD/08/ 021	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride 5 mg/120 mg Extended Release tablets of Sun Pharmaceutical Industries Limited, India and Zyrtec-D12 hour® Extended Release Tablets of Pfizer Inc, NY, NY 10017, in 44 healthy human adult subjects, under fasting conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study with 7 days washout period between each drug administration under fasting conditions.	**Test product** Oral Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablet, 5 mg/120 mg, Sun Lot No. GK71416C Mfg. Date September 2007	39 Healthy Male subjects Mean age: 29.5 Years (Range= 19-44)	Mean= 386.17 % CV= 14.3	Mean= 5.00 Range= 3.0-8.0	Mean= 4705.6538 % CV= 21.2	Mean= 4829.4280 % CV= 21.1	Mean= 5.6295 % CV= 20.0	Mean= 0.12733 % CV= 17.8	**Module 5**
			Ref. Product Oral Zyrtec-D 12 hour® (Cetirizine HCl and Pseudoephedrine HCl) Extended Release Tablet, 5 mg/120 mg , MCNeil Lot No. 03607L Exp. Date March 2010		Mean= 367.70 % CV= 14.3	Mean= 4.50 Range= 2.5-7.5	Mean= 4688.4638 % CV= 19.7	Mean= 4820.4486 % CV= 19.7	Mean= 5.8994 % CV= 21.9	Mean= 0.12236 % CV= 19.7	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Cetirizine- Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hour/mL)	AUC_{∞} (ng*hour/mL)	T½ (hr)	K_{el} (hr-1)	
PKD/08/022	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride 5 mg/120 mg Extended Release tablets of Sun Pharmaceutical Industries Limited, India and Zyrtec-D12 hour® Extended Release Tablets of Pfizer Inc, NY, NY 10017, in 44 healthy human adult subjects, under fed conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study with 7 days washout period between each drug administration under fed conditions.	**Test product** Oral Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablet, 5 mg/120 mg, Sun Lot No. GK71416C Mfg. Date September 2007	41 Healthy Male subjects Mean age: 27.2 Years (Range= 18-42)	Mean= 123.593 % CV= 20.1	Mean= 2.33 Range= 1.0-5.5	Mean= 1315.4682 % CV= 28.1	Mean= 1419.4665 % CV= 30.6	Mean= 8.6489 % CV= 25.8	Mean= 0.08372 % CV= 18.0	**Module 5**
			Ref. Product Oral Zyrtec-D 12 hour® (Cetirizine HCl and Pseudoephedrine HCl) Extended Release Tablet, 5 mg/120 mg , MCNeil Lot No. 03607L Exp. Date March 2010		Mean= 117.951 % CV= 17.4	Mean= 2.67 Range= 0.5-6.5	Mean= 1331.1386 % CV= 27.2	Mean= 1426.8289 % CV= 27.8	Mean= 8.5603 % CV= 23	Mean= 0.08411 % CV= 17.2	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Pseudoephedrine- Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hour/ mL)	AUC_{∞} (ng*hour/ mL)	$T½$ (hr)	K_{el} (hr-1)	
PKD/08/ 022	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride 5 mg/120 mg Extended Release tablets of Sun Pharmaceutical Industries Limited, India and Zyrtec-D12 hour® Extended Release Tablets of Pfizer Inc, NY, NY 10017, in 44 healthy human adult subjects, under fed conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study with 7 days washout period between each drug administration under fed conditions.	**Test product** Oral Cetirizine HCl and Pseudoephedrine HCl Extended Release Tablet, 5 mg/120 mg, Sun Lot No. GK71416C Mfg. Date September 2007	41 Healthy Male subjects Mean age: 27.2 Years (Range= 18-42)	Mean= 384.45 % CV= 19.9	Mean= 5.5 Range= 2.67-7.5	Mean= 4247.1377 % CV= 22.4	Mean= 4362.2101 % CV= 22.1	Mean= 5.3559 % CV= 19.6	Mean= 0.13413 % CV= 18.9	**Module 5**
			Ref. Product Oral Zyrtec-D 12 hour® (Cetirizine HCl and Pseudoephedrine HCl) Extended Release Tablet, 5 mg/120 mg , MCNeil Lot No. 03607L Exp. Date March 2010		Mean= 354.91 % CV= 16.7	Mean= 5.5 Range= 2.67-10.0	Mean= 4176.1238 % CV= 20.1	Mean= 4284.1235 % CV= 20.0	Mean= 5.2443 % CV= 19.5	Mean= 0.13626 % CV= 16.6	

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

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/08/021, N=39					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1535.02	1524.19	1.01	97.59	103.93
AUC∞ (hr *ng/ml)	1619.52	1618.47	1.00	96.84	103.39
Cmax (ng/ml)	180.03	171.85	1.05	101.24	108.41

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/08/021, N=39					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	4601.27	4599.39	1.00	96.53	103.68
AUC∞ (hr *ng/ml)	4729.56	4733.14	1.00	96.41	103.56
Cmax (ng/ml)	382.72	364.38	1.05	101.72	108.46

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	1254.25	1271.26	0.99	95.77	101.64
AUC∞ (hr *ng/mL)	1350.61	1361.18	0.99	96.03	102.53
Cmax (ng/mL)	121.22	116.12	1.04	99.95	109.03

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	4141.44	4088.25	1.01	98.01	104.70
AUC∞ (hr *ng/mL)	4256.12	4195.81	1.01	98.17	104.82
Cmax (ng/mL)	378.16	350.47	1.08	104.55	111.37

Table 3. Reanalysis of Study Samples

Cetirizine

Fasted Study, Study No. PKD/08/021 Additional Information in 5.3.1.4 of the Bioanalytical Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Unacceptable internal standard response	27	2	1.28%	0.10%	27	2	1.28%	0.10%
Incomplete analysis	2	0	0.10%	0.00%	2	0	0.10%	0.00%
Inconsistent profile	1	0	0.05%	0.00%	0	0	0.00%	0.00%
Rejected analytical run	108	106	5.13%	5.04%	54	53	2.57%	2.52%
Total	138	108	6.56%	5.13%	83	55	3.94%	2.61%

Pseudoephedrine

Fasted Study, Study No. PKD/08/021 Additional Information in 5.3.1.4 of the Bioanalytical Report								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Unacceptable internal standard response	27	1	1.28%	0.05%	27	1	1.28%	0.05%
Incomplete analysis	2	0	0.10%	0.00%	2	0	0.10%	0.00%
Rejected analytical run	108	108	5.13%	5.13%	81	81	3.85%	3.85%
Total	137	109	6.51%	5.18%	110	82	5.23%	3.90%

Cetirizine

Fed Study, Study No. PKD/08/022 Additional Information in 5.3.1.4 of the Bioanalytical Report								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Unacceptable internal standard response	5	6	0.23%	0.28%	5	6	0.23%	0.28%
Sample reanalyzed to obtain confirming value	1	1	0.05%	0.05%	0	1	0.00%	0.05%
Inconsistent profile	2	2	0.09%	0.09%	2	1	0.09%	0.05%
Total	8	9	0.38%	0.42%	7	8	0.33%	0.38%

Pseudoephedrine

Fed Study, Study No. PKD/08/022 Additional Information in 5.3.1.4 of the Bioanalytical Report								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Unacceptable internal standard response	5	6	0.23%	0.28%	4	6	0.19%	0.28%
Sample reanalyzed to obtain confirming value	1	2	0.05%	0.09%	1	2	0.05%	0.09%
Inconsistent profile	1	0	0.05%	0.00%	0	0	0.00%	0.00%
Rejected analytical run	26	26	1.22%	1.22%	26	26	1.22%	1.22%
Total	34	34	6.56%	5.13%	31	34	1.46%	1.60%

Comments from the Reviewer:

Fasting Study: This submission is an electronic application. There is an error in opening the analytical report of the fasting study. The file got corrupt.

Fed Study
The firm submitted the analytical raw data from the study runs of only 20% of the subjects. The firm should submit complete raw data of all sample analysis including the peak area for the drug, peak area for the internal standard, the ratio of the peak area for the drug to the peak area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples.

The reviewer comment(s) regarding the reassayed samples will be provided after the firm responds the above deficiency comments.

3.7 Formulation

Location in appendix	Section 4.2, Formulation Data
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**Acceptable**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: Dissolution Review of ANDA090922
Source of Method (USP, FDA or Firm)	FDA
Medium	0.1N HCl
Volume (mL)	500 mL
USP Apparatus type	I (Basket)
Rotation (rpm)	100 rpm
DBE-recommended specifications	Cetirizine-NLT 80% (Q) in 30 minutes Pseudoephedrine- 1 hr: 30%-50%, 2hrs: 50%-70% 6hrs: NLT 80%
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Cetirizine- No Pseudoephedrine- 72.39
If no, reason why F2 not calculated	Cetirizine- Rapidly dissolving
Is method acceptable?	**ACCEPTABLE**
If not then why?	

Reviewer's notes:

DBE had done earlier "Dissolution Only Review" for the test product, and found the following:

There is no USP method for this product, but there is an FDA-recommended method. The firm conducted its dissolution testing using the FDA- recommended dissolution method. The firm's initially proposed specifications were not acceptable and DBE recommended the firm to acknowledge the following FDA-recommended specifications:

Cetirizine-NLT 80% (Q) in 30 minutes
Pseudoephedrine- 1 hr: 30%-50%,
2hrs: 50%-70%
6hrs: NLT 80%

In addition to conducting dissolution testing in 0.1 N HCl, the firm also conducted dissolution testing in pH 4.5 acetate buffer, pH 6.8 phosphate buffer and water.
In its amendment dated on 06/06/2009, the firm acknowledged the FDA-recommended dissolution specification.

The firm also conducted in vitro alcohol dose dumping testing of pseudoephedrine ER component for the test product using the following dissolution method: 900 ml, 0.1 N HCl, USP apparatus I (Basket) at 100 rpm, with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media. The test product did not show any risk of dose-dumping in the presence of alcohol. The dose dumping testing is not requested for this product and was reviewed for information only.

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested *in vivo*?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	

3.10 Deficiency Comments

1. The DBE could not open the electronic file for the analytical report of the fasting study probably it was corrupt. The firm should re submit the entire analytical report of the fasting (Study No: PKD/08/021) BE study.

2. For the Fed (Study No PKD/08/022) BE study, the firm submitted the analytical raw data from the study runs of only 20% of the subjects. The firm should

submit complete raw data of all sample analysis including the peak area for the drug, peak area for the internal standard, the ratio of the peak area for the drug to the peak area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples

3. The mean percent recovery value of pseudoephedrine is 32%. The firm should explain the reason for such low value of the recovery of the analyte pseudoephedrine reported in method validation report No MV/CEPS/021.

4. For the Fed (Study No PKD/08/022) BE study, the firm submitted the chromatograms of cetirizine for 7 subjects i.e. 18% of the subjects. For future submissions, the firm should submit chromatograms of at least 20% of the subjects.

5. The firm should provide the certificate of analysis for the reference product (lot# 03607L).

3.11 Recommendations

1. The Division of Bioequivalence finds the **fasting** BE study No. PKD/08/021 conducted by the Sun Pharmaceutical Industries, Ltd. on its Cetirizine and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg, lot # GK71416C, comparing it to McNeil's ZYRTEC-D 12 hour® (Cetirizine and Pseudoephedrine) Tablets, 5 mg/120 mg, lot 03607L, incomplete due to deficiencies mentioned above.

2. The Division of Bioequivalence finds the **fed** BE study No. PKD/08/022 conducted by the Sun Pharmaceutical Industries, Ltd. on its Cetirizine and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg, lot # GK71416C, comparing it to McNeil's ZYRTEC-D 12 hour® (Cetirizine and Pseudoephedrine) Tablets, 5 mg/120 mg, lot 03607L, incomplete due to deficiencies mentioned above.

3. The firm's *in vitro* dissolution testing is **acceptable**. The dissolution testing should be conducted in 500 mL of 0.1 N HCl, at 37ºC ± 0.5ºC using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification:

Cetirizine-NLT 80% (Q) in 30 minutes
Pseudoephedrine- 1 hr: 30%-50%,
2hrs: 50%-70%
6hrs: NLT 80%

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	PKD/08/021
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride 5/120 mg extended release tablets of Sun Pharmaceutical Industries Limited, India and Zyrtec-D 12 hour® (Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride) 5/120 mg extended release tablets of Pfizer Inc, NY, NY 10017, in 44 healthy human adult subjects, under fasting conditions.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Near R.C. Patel Estate, Akota Road, Akota Vadodara – 390 020 Phone No.: 91-265-2339103, 91-265-2330815
Principal Investigator	Dr. Aman Khanna
Dosing Dates	Period I: 13th May 2008; Period II: 20th May 2008
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, Gujarat, India. Tel: 91-265-2350789, 91-265-6615500
Analysis Dates	From 05th June 2008 to 19th June 2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From : 13th May 2008 to 19th June 2008 (38 days)

Table 5. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets	Zyrtec-D 12 hour®
Manufacturer	Sun Pharmaceuticals	McNeil Consumer Health Care
Batch/Lot No.	GK71416C	03607L
Manufacture Date	September 2007	
Expiration Date		03/2010
Strength	5 mg/ 120 mg	5 mg/ 120 mg
Dosage Form	Extended Release Tablets	Extended Release Tablets
Bio-Batch Size	(b) (4) Tablets	
Production Batch Size	Tablets	
Potency (Assay)	Cetirizine- 97.2% Pseudoephedrine-100.8%	Cetirizine- 97.1% Pseudoephedrine-99.3%
Content Uniformity (mean, %CV)	Cetirizine- Mean- 96.5%, AV 10.83, %CV- 3.8% Pseudoephedrine- Mean- 99.6%, AV 3.33, %CV- 1.4%	Cetirizine- AV 3.46, %CV- 1.5% Pseudoephedrine- AV 1.73, %CV- 0.7%
Dose Administered	1 x 5/120 mg	1 x 5/120 mg
Route of Administration	Oral	Oral

Comments: The firm did not provide the certificate of Analysis for the reference product.

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

Number of Subjects	44 Enrolled and dosed 39 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	Group 1: AB: 1, 2, 7, 8, 9, 11, 14, 16, 17, 20, 22, 23, 25, 27, 29, 31, 33, 34, 39, 40, 43, 44 BA: 3, 4, 5, 6, 10, 12, 13, 15, 18, 19, 21, 24, 26, 28, 30, 32, 35, 36, 37, 38, 41, 42
Blood Sampling Times	Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 12, 16, 24, 30, 36, and 48 hours post dose
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Blood samples were collected by direct venipuncture using pre-labeled vacutainers containing K3 EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C to separate plasma. The plasma from each vacutainer was divided into duplicate propylene tubes. Plasma samples were immediately frozen at -20° C ± 5° C for storage and later analysis. The time between sample collection and placement in freezer did not exceed 1.5 hours.
IRB Approval	Approved on 05/10/2008
Informed Consent	Yes
Length of Fasting	Ten hours prior to dosing and additional 4 hours after dosing
Length of Confinement	At least 12 hours prior to dosing until after the 48 hour blood collection
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured throughout the study.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. PKD/08/021			
		Treatment Groups	
		Test Product N =39	Reference Product N =39
Age (years)	Mean ± SD	29.5 ± 6.50	29.5 ± 6.50
	Range	19 – 44	19 – 44
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	36 (92.31%)	36 (92.31%)
	41 – 64	3 (7.69%)	3 (7.69%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Female	0 (0.0%)	0 (0.0%)
	Male	39 (100%)	39 (100%)
Race	Asian	39 (100%)	39 (100%)
	Black	0 (0.0%)	0 (0.0%)
	Caucasian	0 (0.0%)	0 (0.0%)
	Hispanic	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
BMI (Kg/m^2)	Mean + SD	21.27 ± 1.808	21.27 ± 1.808
	Range	18.7 – 24.7	18.7 – 24.7
Other Factors			

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
04	Not reported in period II	II	NO
31	Due to AE/ Required concomitant medication (Boil over right arm)	I	NO
33	Due to AE/ Required concomitant medication (Inflammation over vein puncture site)	I	NO
37	Voluntarily withdrawn	I	NO
41	Due to urine scan drug of abuse found positive	II	NO

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. PKD/08/021	
	Test (N=)	Reference(N=)
A. Single Treatment Emergent Events		
Body as a whole		
Mild fever	1 (33.33%)	0 (0.00%)
Boil over right arm	1 (33.33%)	0 (0.00%)
Inflammation over vein puncture site of right hand and pain	1 (33.33%)	0 (0.00%)
Total	**3 (100.0%)**	**0 (0.00%)**
B. Adverse Events considered for both formulation*		
Significant WBC in Urine	1	
Significant RBC in Urine	1	
Decreased WBC Value	1	
Increased AST Value	1	
Increased ALT Value	3	
Total	7	

*Since no hematology and biochemistry assessments were done after period I, the adverse events are considered for both the formulation. So it has not been taken in to calculation. However, it has been considered while calculating the total no. of subject experienced adverse event.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Fasting Study Number – PKD/08/021		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
24 hours Vitals were not recorded in both the periods.	All	All

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There was no sampling time deviations occurred during the study.
- All adverse events were mild in intensity. There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. PKD/08/021 Cetirizine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	5.00	10.00	20.00	50.00	139.99	199.98	239.98	299.97
Inter day Precision (%CV)	5.0	2.9	4.0	3.7	2.5	2.9	2.7	2.9
Inter day Accuracy (%Actual)	104.3	97.4	95.7	103.4	98.5	100.9	98.9	100.7
Linearity	0.9973 to 0.9999 (r value)							
Linearity Range (ng/mL)	5.00 to 299.97							
Sensitivity/LOQ (ng/mL)	5.00							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	15.00	69.99	149.99	249.98
Inter day Precision (%CV)	5.7	7.3	7.4	8.4
Inter day Accuracy (%Actual)	102.3	99.7	100.7	103.0

Bioequivalence Study No. PKD/08/021 Pseudoephedrine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	10.0	20.0	100.0	200.0	560.0	860.1	1020.1	1252.1
Inter day Precision (%CV)	8.6	3.9	3.5	4.3	2.9	3.2	1.8	3.6
Inter day Accuracy (%Actual)	108.4	100.3	95.5	97.4	98.1	99.7	98.4	103.0
Linearity	0.9949 to 1.0000 (r Value)							
Linearity Range (ng/mL)	10.0 to 1252.1							
Sensitivity/LOQ (ng/mL)	10.0							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	30.0	260.0	580.1	1060.1
Inter day Precision (%CV)	8.8	6.9	19.3	8.8
Inter day Accuracy (%Actual)	100.7	97.4	100.5	99.0

Comments on Study Assay Validation:

Incomplete. There is an error in opening the analytical report of the fasting study. The file got corrupt.

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

Comments on Chromatograms:

Incomplete. There is an error in opening the analytical report of the fasting study. The file got corrupt.

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

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	13/02/2008	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 01)

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	The analytical report file got corrupt. The reviewer comment(s) regarding the reassay samples will be provided after the firm responds the deficiency comments
Did recalculation of PK parameters change the study outcome?	Please see the above comments
Does the reviewer agree with the outcome of the repeat assays?	Please see the above comments
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Incomplete. There is an error in opening the analytical report of the fasting study. The file got corrupt.

4.1.1.4 Pharmacokinetic Results

Please note that the information below is obtained based on the assumption that the firm's analytical data is acceptable. The PK parameter calculation results may change upon the DBE's receipt of additional information and re-evaluation of the firm's analytical report.

Table 14. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Mean plasma concentrations are presented in Table 18 and Figure 1

Cetirizine

Fasting Bioequivalence Study, Study No. PKD/08/021, N=39									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	1565.855	20.70	990.15	2279.05	1563.976	24.04	974.27	2778.08	1.00
AUC∞ (hr *ng/ml)	1651.662	20.49	1030.52	2379.54	1657.586	23.05	1028.87	2896.90	1.00
Cmax (ng/ml)	181.926	15.74	132.34	262.29	173.989	16.08	126.36	241.55	1.05
Tmax* (hr)	0.750	.	0.50	1.75	0.750	.	0.50	2.00	1.00
Kel (hr^{-1})	0.086	17.77	0.06	0.13	0.085	16.09	0.06	0.12	1.02
T1/2 (hr)	8.286	17.29	5.19	12.35	8.380	16.49	5.89	11.90	0.99

Tmax values are presented as median, range.

Pseudoephedrine

Fasting Bioequivalence Study, Study No. PKD/08/021, N=39									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	4705.654	21.23	2509.31	6843.81	4684.665	19.62	2928.30	6712.45	1.00
AUC∞ (hr *ng/ml)	4832.980	20.85	2567.91	6979.92	4818.956	19.42	3037.75	6849.72	1.00
Cmax (ng/ml)	386.167	14.33	280.90	541.70	367.703	14.26	279.30	503.50	1.05
Tmax* (hr)	5.000	.	3.00	8.00	4.500	.	2.50	7.50	1.11
Kel (hr^{-1})	0.125	16.86	0.05	0.17	0.120	17.04	0.05	0.17	1.03
T1/2 (hr)	5.779	24.61	3.98	13.04	5.965	23.20	4.06	12.78	0.97

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

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PKD/08/021				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng *hr/mL)	1535.02	1525.51	100.62	97.52 - 103.83
AUC∞ (ng *hr/mL)	1618.11	1619.39	99.92	96.76 - 103.19
Cmax (ng/mL)	180.03	171.85	104.76	101.24 - 108.41

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PKD/08/021				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng *hr/mL)	4601.27	4602.82	99.97	96.45-103.61
AUC∞ (ng *hr/mL)	4723.35	4732.67	99.80	96.28 - 103.45
Cmax (ng/mL)	382.72	364.38	105.03	101.72 - 108.46

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

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/08/021, N=39					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1535.02	1524.19	1.01	97.59	103.93
AUC∞ (hr *ng/ml)	1619.52	1618.47	1.00	96.84	103.39
Cmax (ng/ml)	180.03	171.85	1.05	101.24	108.41

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/08/021, N=39					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	4601.27	4599.39	1.00	96.53	103.68
AUC∞ (hr *ng/ml)	4729.56	4733.14	1.00	96.41	103.56
Cmax (ng/ml)	382.72	364.38	1.05	101.72	108.46

Table 17. Additional Study Information, Fasting Study No. PKD/08/021

Cetirizine

Root mean square error, AUC0-t	0.0823	
Root mean square error, AUC∞	0.0857	
Root mean square error, Cmax	0.0895	
	Test	Reference
Kel and AUC∞ determined for how many subjects?	39	39
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	39	0.95	0.91	0.97
Reference	39	0.94	0.81	0.97

Pseudoephedrine

Root mean square error, AUC0-t	0.0936	
Root mean square error, AUC∞	0.0936	
Root mean square error, Cmax	0.0839	
	Test	Reference
Kel and AUC∞ determined for how many subjects?	39	39
Do you agree or disagree with firm's decision?	Yes	Yes

Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	39	0.97	0.92	0.99
Reference	39	0.97	0.92	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Incomplete due to the deficiency stated in the Deficiency Section.

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

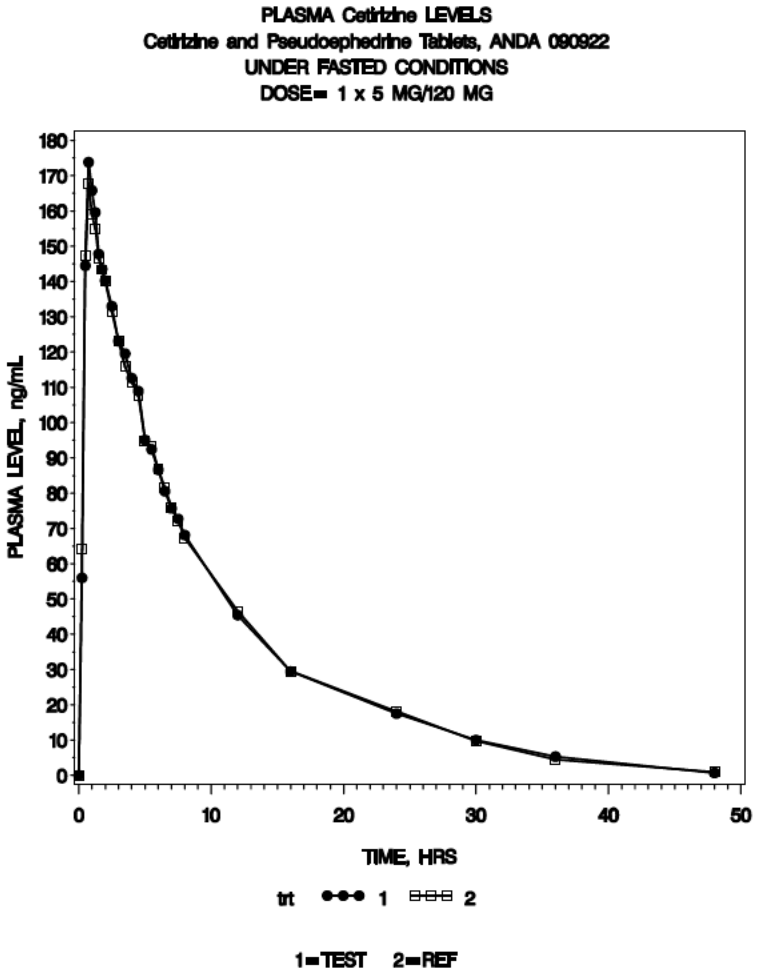
Cetirizine

	Test (n=39)		Reference (n=39)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.25	55.97	78.33	64.02	70.48	0.87
0.50	144.48	28.06	147.43	26.65	0.98
0.75	173.81	20.90	167.70	17.15	1.04
1.00	165.80	13.86	159.06	16.27	1.04
1.25	159.57	14.30	154.86	15.64	1.03
1.50	147.80	13.18	146.36	15.74	1.01
1.75	143.53	12.90	143.38	15.67	1.00
2.00	140.28	14.52	140.21	16.55	1.00
2.50	132.99	13.55	131.41	16.37	1.01
3.00	123.08	14.36	123.19	18.02	1.00
3.50	119.55	14.28	115.84	23.37	1.03
4.00	112.59	15.89	111.49	16.34	1.01
4.50	108.92	14.52	107.62	18.36	1.01
5.00	95.09	15.33	94.96	18.75	1.00
5.50	92.40	15.20	93.19	20.55	0.99
6.00	86.61	15.72	86.93	18.50	1.00
6.50	80.56	16.77	81.48	18.53	0.99
7.00	75.70	17.78	75.90	20.51	1.00
7.50	72.72	16.97	72.24	19.89	1.01
8.00	68.13	18.58	67.24	21.57	1.01
12.00	45.41	23.79	46.59	24.93	0.97
16.00	29.45	28.98	29.61	30.67	0.99
24.00	17.52	36.56	18.10	38.27	0.97
30.00	9.99	50.92	9.75	54.77	1.02
36.00	5.33	87.42	4.46	109.98	1.19
48.00	0.69	303.37	0.93	240.85	0.74

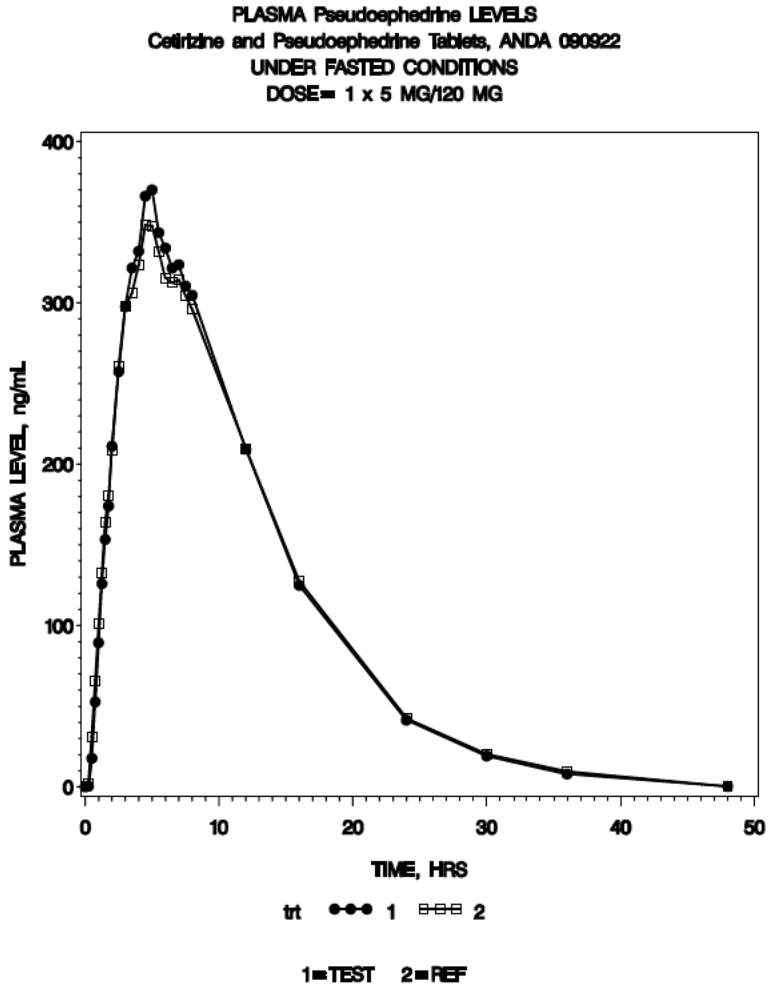
Pseudoephedrine

	Test (n=39)		Reference (n=39)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.25	0.38	624.50	2.38	219.93	0.16
0.50	17.67	64.66	31.29	49.61	0.56
0.75	52.70	36.33	65.65	34.88	0.80
1.00	89.40	29.90	101.10	27.75	0.88
1.25	126.01	28.58	132.32	23.45	0.95
1.50	153.37	29.28	163.80	21.90	0.94
1.75	174.05	25.19	180.58	17.83	0.96
2.00	211.24	22.37	208.71	21.74	1.01
2.50	257.37	16.98	260.45	15.53	0.99
3.00	297.76	16.02	297.59	14.73	1.00
3.50	321.63	14.94	306.18	21.37	1.05
4.00	332.09	16.36	323.42	14.47	1.03
4.50	366.21	15.43	348.24	14.86	1.05
5.00	370.13	13.86	347.85	16.80	1.06
5.50	343.58	16.10	331.75	16.51	1.04
6.00	334.02	16.01	315.63	17.05	1.06
6.50	321.56	17.14	312.56	19.43	1.03
7.00	323.71	18.52	314.15	19.57	1.03
7.50	310.52	18.38	304.60	18.98	1.02
8.00	304.75	20.36	295.92	19.04	1.03
12.00	209.31	26.41	209.89	25.51	1.00
16.00	124.86	33.17	127.56	29.45	0.98
24.00	41.43	40.77	42.63	37.23	0.97
30.00	19.15	51.48	20.25	51.29	0.95
36.00	7.94	107.16	9.51	88.48	0.84
48.00	0.32	624.50	0.28	624.50	1.13

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



Pseudoephedrine



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	PKD/08/022
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride 5 mg/120mg extended release tablets of Sun pharmaceutical Industries Limited, India and Zyrtec-D 12 hour® (Cetirizine Hydrochloride + Pseudoephedrine Hydrochloride) 5/120 mg extended release tablets of Pfizer Inc, NY, NY 10017, in 44 healthy human adult subjects, under fed conditions.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Near R.C. Patel Estate, Akota Road, Akota Vadodara – 390 020 Phone No.: 91-265-2339103, 91-265-2330815
Principal Investigator	Dr. Aman Khanna.
Dosing Dates	Period I: 14th May 2008; Period II: 21st May 2008
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, Gujarat, India. Tel: +91-265-6615500, 91-265-2350789
Analysis Dates	From 23rd June 2008 to 5th July 2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 14th May 2008 to 5th July 2008 (53 days)

Table 20. Product Information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets	Zyrtec-D 12 hour®
Manufacturer	Sun Pharmaceuticals	McNeil Consumer Health Care
Batch/Lot No.	GK71416C	03607L
Manufacture Date	September 2007	
Expiration Date		03/2010
Strength	5 mg/ 120 mg	5 mg/ 120 mg
Dosage Form	Tablets	Tablets
Bio-Batch Size	(b) (4) Tablets	
Production Batch Size	Tablets	
Potency (Assay)	Cetirizine- 97.2% Pseudoephedrine-100.8%	Cetirizine- 97.1% Pseudoephedrine-99.3%
Content Uniformity (mean, %CV)	Cetirizine- Mean- 96.5%, AV 10.83, %CV- 3.8% Pseudoephedrine- Mean- 99.6%, AV 3.33, %CV- 1.4%	Cetirizine- AV 3.46, %CV- 1.5% Pseudoephedrine- AV 1.73, %CV- 0.7%
Dose Administered	1 x 5/120 mg	1 x 5/120 mg
Route of Administration	Oral	Oral

Comments: The firm did not provide the certificate of Analysis for the reference product.

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

No. of Subjects	44 Enrolled 42 Dosed 41 Completed and Analyzed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	Group 1: AB: 1, 2, 6, 8, 9, 12, 13, 15, 17, 19, 21, 24, 26, 28, 31, 32, 33, 35, 37, 39, 41, 43 BA: 3, 4, 5, 7, 10, 11, 14, 16, 18, 20, 22, 23, 25, 27, 29, 30, 34, 36, 38, 40, 42, 44
Blood Sampling Times	Predose, 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 24, 30, 36 and 48 hours post dose
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Blood samples were collected by direct venipuncture using pre-labeled vacutainers containing K3 EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C to separate plasma. The plasma from each vacutainer was divided into duplicate propylene tubes. Plasma samples were immediately frozen at -20° C ± 5° C for storage and later analysis. The time between sample collection and placement in freezer did not exceed 1.5 hours.
IRB Approval	Yes (approved on 05/10/2008)
Informed Consent	Yes
Length of Fasting Before Meal	The subjects were fasted 10 hours overnight. A standard high fat breakfast was given 30 minutes prior to dosing
Length of Confinement	At least 12 hours prior to dosing until after the 48 hour blood collection
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured through out the study.

Standard FDA Meal Used?	No

Composition of meal used in fed Bioequivalence study

Study No. PKD/08/022 (Fed)		
Composition of Meal used in fed Bioequivalence study		
Composition	Percent of total Kcal	Kcal
Fat	57.01	537
Carbohydrate	26.96	254

Protein	16.03	151
Total	100.00	942

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

		Fasting Bioequivalence Study No. PKD/08/022	
		Treatment Groups	
		Test Product N =41	Reference Product N =41
Age (years)	Mean ± SD	27.2 ± 6.01	27.2 ± 6.01
	Range	18 – 42	18 – 42
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 39	40 (97.56%)	40 (97.56%)
	40 – 64	1 (2.44%)	1 (2.44%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Female	0 (0.0%)	0 (0.0%)
	Male	41 (100%)	41 (100%)
Race	Asian	41 (100%)	41 (100%)
	Black	0 (0.0%)	0 (0.0%)
	Caucasian	0 (0.0%)	0 (0.0%)
	Hispanic	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
BMI (Kg/m^2)	Mean + SD	21.29 ± 1.940	21.29 ± 1.940
	Range	18.7 – 24.7	18.7 – 24.7
Other Factors			

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
5	Adverse events /Required concomitant medication (Maculo-Papular rash on both thighs and hands)	I	NO
21	Incomplete meal consumption for -0.5 hrs	I	NO
32	Incomplete meal consumption for -0.5 hrs	I	NO

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. PKD/08/022	
	Test (N=41)	Reference(N=41)
A. Single Treatment Emergent Events		
Body as a whole		
Pain in right hand	0 (0.00%)	1 (20.00%)
Fever/Body ache	0 (0.00%)	1 (20.00%)
Gastrointestinal System		
Vomiting	1(100.0%)	0 (0.00%)
Loose Motion	0 (0.00%)	1 (20.00%)
Skin and Appendices		
Maculo-papular rash on both Thighs & Hands	0 (0.00%)	1 (20.00%)
Maculo-papular rash on both Abdomen & Thighs	0 (0.00%)	1 (20.00%)
Total	**1 (100.0%)**	**5 (100.0%)**
B. Adverse Events considered for both formulation*		
High ALT	2	
High ALT & AST	1	
High WBC	1	
TOTAL	**4**	

*Since no hematology and biochemistry assessments were done after period I, the adverse event considered for both the formulation. So it has not been taken in to calculation. However, it has been considered while calculating the total no. of subject experienced adverse event.

Table 25. Protocol Deviations, Fed Bioequivalence Study

Fed Study Number – **PKD/08/022**		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
24 hours Vitals were not recorded in both the periods.	All	All

Comments on Adverse Events/Protocol Deviations:

- Subject 28 (Period I) who received test product experienced vomiting. The effect was observed at 4.16 hours, which is before 2X median of Tmax. Subject 28 was excluded from the statistical analysis.

- All adverse events were mild in intensity. There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

- There was no sampling time deviations occurred during the study.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. PKD/08/022 Cetirizine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	5.00	10.00	20.00	50.00	139.99	199.98	239.98	299.97
Inter day Precision (%CV)	4.6	2.7	2.8	3.1	2.3	2.3	2.3	2.0
Inter day Accuracy (%Actual)	102.9	99.1	99.6	99.3	98.6	99.4	100.0	101.2
Linearity	0.9981 to 1.0000 (r value)							
Linearity Range (ng/mL)	5.00 to 299.97							
Sensitivity/LOQ (ng/mL)	5.00							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	15.00	69.99	149.99	249.98
Inter day Precision (%CV)	7.2	8.1	6.9	6.4
Inter day Accuracy (%Actual)	101.1	103.3	103.3	101.1

Bioequivalence Study No. PKD/08/022 Pseudoephedrine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	10.0	20.0	100.0	200.0	560.0	860.1	1020.1	1252.1
Inter day Precision (%CV)	7.5	4.7	4.0	3.9	2.9	2.4	2.4	2.6
Inter day Accuracy (%Actual)	103.0	99.9	98.1	99.2	99.2	99.0	101.2	100.4
Linearity	0.9981 to 1.0000 (r Value)							
Linearity Range (ng/mL)	10.0 to 1252.1							
Sensitivity/LOQ (ng/mL)	10.0							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	30.0	260.0	580.1	1060.1
Inter day Precision (%CV)	8.9	8.0	13.6	9.8
Inter day Accuracy (%Actual)	96.9	99.0	103.0	102.1

Comments on Study Assay Validation:

Acceptable.

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

Comments on Chromatograms:

Acceptable. The firm submitted the chromatograms of cetirizine for 7 subjects i.e. 18% of the subjects. For future submissions, the firm should submit chromatograms of 20% of the subjects

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

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	13/02/2008	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 01)

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	The Analytical Raw Data were not submitted for all the subjects. The reviewer comment(s) regarding the reassay samples will be provided after the firm responds the deficiency comments
Did recalculation of PK parameters change the study outcome?	Please see the above comments
Does the reviewer agree with the outcome of the repeat assays?	Please see the above comments
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Incomplete. The firm did not submit the analytical raw data from study runs of all the subjects.

4.1.2.4 Pharmacokinetic Results

Please note that the information below is obtained based on the assumption that the firm's repeated assays are acceptable, and the reviewer used the firm's repeated assay values for the calculation. The PK parameter calculation results may change upon the DBE's receipt of additional information and re-evaluation of the firm's repeated assays.

Table 29. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Mean plasma concentrations are presented in Table 33 and Figure 2

Cetirizine

Fed Bioequivalence Study, Study No. PKD/08/022, N=40									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	1297.730	27.55	799.61	2513.34	1314.371	26.85	834.13	2465.62	0.99
AUC∞ (hr *ng/ml)	1404.365	30.73	879.03	2985.28	1406.904	27.04	917.00	2756.35	1.00
Cmax (ng/ml)	123.491	20.37	77.28	192.67	118.012	17.65	79.48	160.69	1.05
Tmax* (hr)	2.330	.	1.00	5.50	2.500	.	0.50	6.50	0.93
Kel (hr^{-1})	0.083	17.13	0.04	0.11	0.083	13.20	0.05	0.10	1.00
T1/2 (hr)	8.669	25.33	6.21	17.56	8.474	15.01	6.66	12.80	1.02

* Tmax values are presented as median, range.

Pseudoephedrine

Fed Bioequivalence Study, Study No. PKD/08/022, N=40									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	4250.594	22.66	2623.97	6443.01	4174.826	20.35	2738.85	5969.46	1.02
AUC∞ (hr *ng/ml)	4364.534	22.28	2698.51	6541.38	4282.758	20.19	2835.16	6278.78	1.02
Cmax (ng/ml)	385.418	20.02	274.90	625.10	355.475	16.89	245.20	465.50	1.08
Tmax* (hr)	5.500	.	2.67	7.50	5.500	.	2.67	10.00	1.00
Kel (hr^{-1})	0.135	14.56	0.10	0.18	0.134	12.94	0.09	0.18	1.00
T1/2 (hr)	5.243	14.31	3.85	6.84	5.246	13.41	3.93	7.75	1.00

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

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. PKD/08/022				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng *hr/mL)	1255.07	1272.43	98.64	95.72 - 101.64
AUC∞ (ng *hr/mL)	1347.54	1361.31	98.99	95.92 - 102.16
Cmax (ng/mL)	121.22	116.12	104.39	99.95 - 109.03

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. PKD/08/022				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng *hr/mL)	4143.24	4089.37	101.32	98.04 - 104.71
AUC∞ (ng *hr/mL)	4259.06	4196.13	101.50	98.22 - 104.89
Cmax (ng/mL)	378.16	350.47	107.90	104.55 - 111.37

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

Cetirizine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	1254.25	1271.26	0.99	95.77	101.64
AUC∞ (hr *ng/mL)	1350.61	1361.18	0.99	96.03	102.53
Cmax (ng/mL)	121.22	116.12	1.04	99.95	109.03

Pseudoephedrine

Cetirizine and Pseudoephedrine Extended Release Tablets 5 mg/ 120 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD/08/022, N=40					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	4141.44	4088.25	1.01	98.01	104.70
AUC∞ (hr *ng/mL)	4256.12	4195.81	1.01	98.17	104.82
Cmax (ng/mL)	378.16	350.47	1.08	104.55	111.37

Table 32. Additional Study Information

Cetirizine

Root mean square error, AUC0-t	0.0788	
Root mean square error, AUC∞	0.0868	
Root mean square error, Cmax	0.1151	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	40	40
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	40	0.93	0.67	0.97
Reference	40	0.93	0.88	0.96

Pseudoephedrine

Root mean square error, AUC0-t	0.0875	
Root mean square error, AUC∞	0.0868	
Root mean square error, Cmax	0.0837	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	40	40
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		

measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	40	0.97	0.95	0.99
Reference	40	0.97	0.95	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- Subject 28 (Period I) who received test product experienced vomiting. The effect was observed at 4.16 hours, which is before 2X median of Tmax. So Subject 28 was excluded from the statistical analysis.

- The 90% CI's for the least squares geometric means of Ln AUCt and LnCmax calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

Incomplete due to the deficiency stated in the Deficiency Section.

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

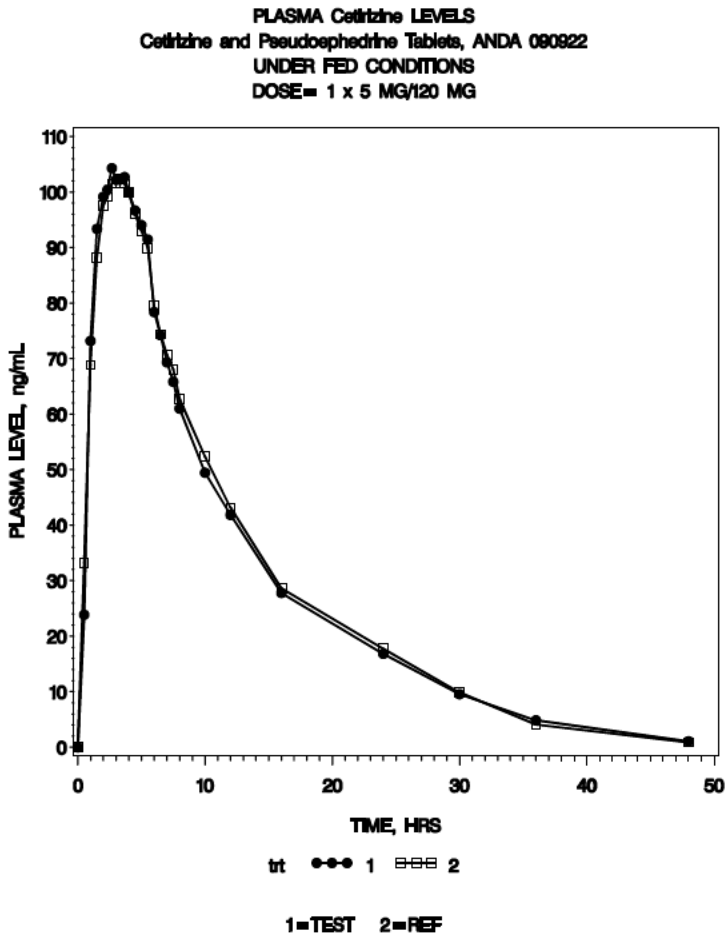
Cetirizine

	Test (n=40)		Reference (n=40)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	23.87	119.72	33.22	111.32	0.72
1.00	73.20	63.54	68.88	65.44	1.06
1.50	93.37	41.23	88.13	42.62	1.06
2.00	99.15	29.05	97.57	29.34	1.02
2.33	100.41	27.16	99.15	23.87	1.01
2.67	104.28	19.88	101.53	21.55	1.03
3.00	102.17	14.82	101.72	21.06	1.00
3.33	102.23	14.48	102.32	22.24	1.00
3.67	102.70	16.97	101.50	21.65	1.01
4.00	99.94	19.20	99.98	21.62	1.00
4.50	96.67	19.95	96.03	19.93	1.01
5.00	94.04	21.29	93.04	22.26	1.01
5.50	91.44	26.32	89.87	22.39	1.02
6.00	78.37	23.07	79.46	23.03	0.99
6.50	74.19	23.46	74.41	23.82	1.00
7.00	69.32	24.09	70.69	25.14	0.98
7.50	65.83	24.60	68.02	24.57	0.97
8.00	61.00	26.47	62.70	25.11	0.97
10.00	49.45	25.57	52.33	27.33	0.94
12.00	41.84	27.35	43.16	28.69	0.97
16.00	27.78	34.46	28.60	34.16	0.97
24.00	16.83	45.07	17.74	45.23	0.95
30.00	9.56	63.06	9.87	63.63	0.97
36.00	4.86	148.45	4.08	105.83	1.19
48.00	1.08	315.96	0.91	333.84	1.18

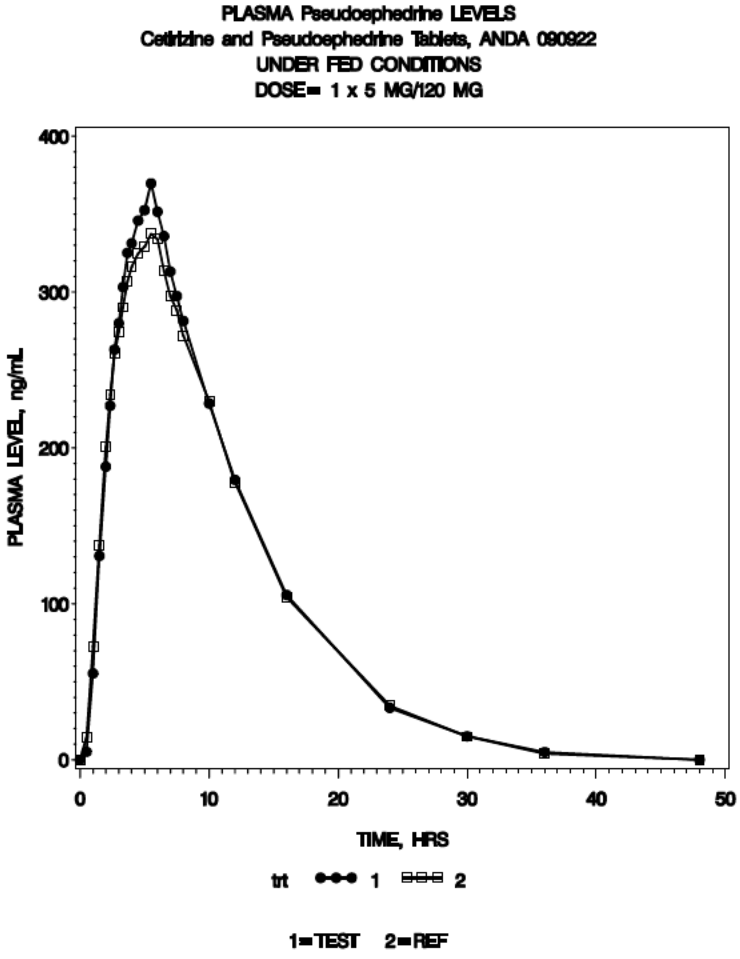
Pseudoephedrine

	Test (n=40)		Reference (n=40)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	5.10	201.40	13.99	133.69	0.36
1.00	55.40	74.10	72.68	72.46	0.76
1.50	130.77	50.82	137.79	46.43	0.95
2.00	188.02	42.41	200.94	32.83	0.94
2.33	227.13	40.43	234.08	25.58	0.97
2.67	263.08	32.80	260.35	23.39	1.01
3.00	279.98	26.95	274.54	21.65	1.02
3.33	303.21	25.80	290.24	20.85	1.04
3.67	325.17	23.08	306.75	20.72	1.06
4.00	331.29	20.91	316.10	18.54	1.05
4.50	345.84	19.26	324.71	17.92	1.07
5.00	352.50	19.77	329.01	17.19	1.07
5.50	369.75	20.64	337.28	16.65	1.10
6.00	351.53	19.06	333.99	17.20	1.05
6.50	335.86	19.98	313.59	19.30	1.07
7.00	313.13	19.88	297.27	17.71	1.05
7.50	297.40	21.98	288.42	18.96	1.03
8.00	281.43	23.28	271.98	18.10	1.03
10.00	228.57	26.38	229.91	27.14	0.99
12.00	179.51	28.70	177.84	24.92	1.01
16.00	105.72	36.36	104.28	31.32	1.01
24.00	33.29	41.11	34.61	41.41	0.96
30.00	15.02	63.84	14.94	65.90	1.01
36.00	4.87	154.91	3.92	169.76	1.24
48.00	0.00	.	0.00	.	.

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



Pseudoephedrine



4.2 Formulation Data

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet	Functional category
(b) (4)			

Ingredient	Maximum amount/day based on MDD of Cetirizine and Pseudoephedrine Amount (mg)	Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit	Amount exceed or below the IIG limit of approved drug product/unit
Hydroxyethyl Cellulose, NF (b) (4))	(b) (4)	150 mg	Below
Microcrystalline Cellulose, NF (b) (4)		1385.3 mg	Below
Stearic Acid, NF		187.5 mg	Below
Magnesium Stearate, NF		400.748 mg	Below
(b) (4)		(b) (4)	

* MDD of Cetirizine is 10 mg/day and Pseudoephedrine is 240 mg/day orally

PRODUCT IDENTIFIER: (b) (4)

PRODUCT DESCRIPTION:

(b) (4)

(b) (4)

Ingredient	Amount (mg) /Tablet	Maximum amount/day based on MDD of Cetirizine and Pseudoephedrine Amount (mg)	Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit	Amount exceed or below the IIG limit of approved drug product/unit
(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

Reviewer's Comments on Formulation:

- The amounts of all inactive ingredients in the tablet are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products, based on MDD.

- The formulation is acceptable.

4.3 Dissolution Data

Dissolution Review Path	DARRTS: Dissolution Review of ANDA 090922

Table 34. Dissolution Data

Cetirizine- 0.1 N HCl

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	0.1 N Hydrochloric acid
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0.5° C
Proposed Specification	Not less than (b) (4) *(Q)* of label amount of Cetirizine Dihydrochloride is dissolved in 30 minutes	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & 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
					15	30	45	60	
INN/01/08	09/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12					Module 5 Section 5.3.1.2
				Mean	86 %	95 %	96 %	96 %	
				Range				(b) (4)	
				% C.V	4.6	4.4	4.2	4.3	
	09/01/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12					
				Mean	88 %	94 %	95 %	96 %	
				Range				(b) (4)	
				% C.V	8.5	5.7	5.0	5.1	

Cetirizine- pH 4.5 Acetate Buffer

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Acetate Buffer pH 4.5
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0.5° C
Proposed Specification*	Not less than (b) (4) *(Q)* of label amount of Cetirizine Dihydrochloride is dissolved in 30 minutes	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & 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
					15	30	45	60	
INN/03/08	09/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12					Module 5 Section 5.3.1.2
				Mean	57 %	82 %	87 %	89 %	
				Range	(b) (4)				
				% C.V	19.5	8.9	4.7	4.3	
	20/07/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12					
				Mean	84 %	90 %	92 %	93 %	
				Range	(b) (4)				
				% C.V	8.2	5.7	4.4	3.9	

Cetirizine- pH 6.8 Phosphate Buffer

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Phosphate Buffer pH 6.8
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0.5° C
Proposed Specification*	Not less than [redacted] (b) (4) *(Q)* of label amount of Cetirizine Dihydrochloride is dissolved in 30 minutes	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & 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
					15	30	45	60	
INN/04/08	10/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12	[redacted]				Module 5 Section 5.3.1.2
				Mean	52 %	76 %	82 %	82 %	
				Range	[redacted] (b) (4)				
				% C.V	3.7	2.9	2.9	4.2	
	16/07/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12	[redacted]				
				Mean	87 %	91 %	93 %	94 %	
				Range	[redacted] (b) (4)				
				% C.V	9.5	7.5	6.9	6.5	

Cetirizine- Water

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Water
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0.5° C
Proposed Specification*	Not less than [(b) (4)] *(Q)* of label amount of Cetirizine Dihydrochloride is dissolved in 30 minutes	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & 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
					15	30	45	60	
INN/02/08	08/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12					Module 5 Section 5.3.1.2
				Mean	68 %	90 %	93 %	94 %	
				Range	[(b) (4)]				
				% C.V	12.9	7.2	5.5	5.4	
	19/07/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12					
				Mean	85 %	89 %	91 %	92 %	
				Range	[(b) (4)]				
				% C.V	7.7	6.4	5.4	5.7	

Pseudoephedrine- 0.1 N HCl

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	0.1 N Hydrochloric acid
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0.5° C
Proposed Specification	1 Hour Between (b) (4)	2 Hours Between (b) (4) 6 Hours Not less than 80%
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/01/08	09/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12									Module 5 Section 5.3.1.2
				Mean	10 %	24 %	33 %	40 %	61 %	85 %	97 %	102 %	
				Range	(b) (4)								
				% C.V	8.6	3.8	2.2	2.3	1.5	1.2	1.3	1.6	
	09/01/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12									
				Mean	17 %	27 %	36 %	43 %	62 %	84 %	95 %	100 %	
				Range	(b) (4)								
				% C.V	5.0	4.2	3.5	3.3	2.6	2.2	2.0	1.7	

Pseudoephedrine- pH 4.5 Acetate Buffer

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Acetate Buffer pH 4.5
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0.5° C
Proposed Specification*	1 Hour Between (b) (4)	2 Hours Between (b) (4) / 6 Hours Not less than (b) (4)
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/03/08	09/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12									Module 5 Section 5.3.1.2
				Mean	8 %	22 %	31 %	39 %	60 %	85 %	95 %	100 %	
				Range	(b) (4)								
				% C.V	18.6	10.4	7.6	6.5	3.5	1.3	0.8	1.0	
	20/07/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12									
				Mean	18 %	28 %	36 %	42 %	61 %	84 %	95 %	100 %	
				Range	(b) (4)								
				% C.V	7.8	7.7	7.6	6.5	6.7	3.9	2.7	2.2	

Pseudoephedrine- pH 6.8 Phosphate Buffer

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Phosphate Buffer pH 6.8
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0.5° C
Proposed Specification*	1 Hour Between (b) (4)	2 Hours Between (b) (4)	6 Hours Not less than (b) (4)
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & Nagar Haveli, India		

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/04/08	10/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12									Module 5 Section 5.3.1.2
				Mean	8 %	21 %	29 %	36 %	55 %	78 %	90 %	96 %	
				Range	(b) (4)								
				% C.V	6.5	3.0	2.0	2.3	1.4	1.7	1.3	1.2	
	16/07/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12									
				Mean	17 %	27 %	35 %	42 %	61 %	83 %	93 %	99 %	
				Range	(b) (4)								
				% C.V	4.9	5.7	4.0	3.2	3.3	2.1	1.8	1.8	

Pseudoephedrine- Water

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Water
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0.5° C
Proposed Specification*	1 Hour Between (b) (4)	2 Hours Between (b) (4) / 6 Hours Not less than (b) (4)
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No. 259/15, Dadra-396 191, U.T. of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/02/08	08/01/08	Batch #: GK71416 Mfg Date: Sep. 2007	5mg/120mg Tablets	12									Module 5 Section 5.3.1.2
				Mean	10 %	23 %	33 %	40 %	62 %	86 %	98 %	102 %	
				Range	(b) (4)								
				% C.V	13.7	8.2	5.9	5.6	3.6	1.6	0.8	0.8	
	19/07/08	Batch #: 03607L Exp. Date: Mar. 2010	5mg/120mg Tablets	12									
				Mean	18 %	28 %	36 %	43 %	62 %	86 %	96 %	99 %	
				Range	(b) (4)								
				% C.V	7.3	8.2	7.3	6.7	5.9	4.8	3.5	2.5	

Reviewer's Comments on Dissolution:

- There is no USP method for this product, but there is an FDA-recommended method. The firm conducted its dissolution testing using FDA- recommended dissolution method.

- The firm's initially proposed specifications were not acceptable and DBE recommended the firm to acknowledge the following FDA-recommended specifications (**DARRTS for ANDA 090922: JIANG, XIAOJIAN 03/17/2009 N/A 03/17/2009 REV-BIOEQ-02(Dissolution Review) Original-1 Archive)**:

  Cetirizine-NLT 80% (Q) in 30 minutes
  Pseudoephedrine- 1 hr: 30%-50%,
  2hrs: 50%-70%
  6hrs: NLT 80%

  In its amendment dated on 06/06/2009, the firm acknowledged the FDA-recommended dissolution specification

- In addition to conducting dissolution testing in 0.1 N HCl, the firm also conducted dissolution testing in pH 4.5 acetate buffer, pH 6.8 phosphate buffer and water.

- The firm also conducted in vitro alcohol dose dumping testing of pseudoephedrine ER component for the test product using the following dissolution method: 900 ml, 0.1 N HCl, USP apparatus I (Basket) at 100 rpm, with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media. The data show that the % dissolved from the test product in media with various ethanol concentrations is comparable to % dissolution of the test product in media without alcohol. Therefore, no further comparison with the RLD is necessary. The test product does not show any risk of dose-dumping in the presence of alcohol. The dose dumping testing is not requested for this product and was reviewed for information only.

4.4 SAS Output

4.4.1 Fasting Study Data

Cetirizine

Following this page, 58 pages withheld in full (b)(4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090922

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Cetirizine and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg

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

1. The DBE could not open the electronic file for the analytical report of the fasting study probably because it was corrupt. Please resubmit the entire analytical report of the fasting (Study No: PKD/08/021) bioequivalence (BE) study.

2. For Fed (Study No: PKD/08/022) BE study, you have submitted the raw numerical data from the assay runs of **only 20%** of the subjects. Please submit complete raw numerical data of **ALL** assay and reassay runs of both Fasting and Fed studies, including the data of peak height/area for the drug, peak height/area for the internal standard, ratio of the peak height/area for the drug to the peak height/area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples.

3. The mean percent recovery value of pseudoephedrine is 32%. Please explain the reason for such low value of the recovery of the analyte pseudoephedrine reported in method validation report No MV/CEPS/021.

4. For the Fed (Study No PKD/08/022) BE study, you have submitted the chromatograms of cetirizine for 7 subjects i.e. 18% of the subjects. **For future submissions**, please submit chromatograms of at least 20% of the subjects.

5. Please provide the certificate of analysis for the reference product (lot# 03607L).

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

4.5 Outcome Page

ANDA: 090922

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
12010	10/16/2008	Bioequivalence Study	Fasting Study	1	1
12010	10/16/2008	Bioequivalence Study	Fed Study	1	1
				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/

SUMAN DANDAMUDI
09/16/2010

SHRINIWAS G NERURKAR
09/20/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/20/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90-922	
Drug Product Name	Cetirizine HCl (IR component) and Pseudoephedrine HCl (ER component) Extended-Release Tablets	
Strength (s)	5 mg/120 mg	
Applicant Name	Sun Pharmaceutical Industries Ltd.	
Address	Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400059, India	
Applicant's Point of Contact	Anthony Celeste Kendle International, 7361, Calhoun Place, Suite 500, Rockville, MD 20855-2765	
Contact's Phone Number	301-838-3120	
Contact's Fax Number	301-838-3182	
Submission Date(s)	Oct 16, 2008	
First Generic	No	
Reviewer	Xiaojian Jiang, Ph.D.	
Study Number (s)	PKD/08/021	PKD/08/022
Study Type (s)	Fasting study	Fed study
Strength(s)	5 mg/100 mg	5 mg/100 mg
Clinical Site and Address	Sun Pharmaceutical Industries Ltd. Near R.C. Patel Estate, Akota Road, Akota Vadodara – 390 020	
Analytical Site and Address	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, Gujarat, India.	
OUTCOME DECISION	**INCOMPLETE**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The product references Zyrtec-D 12 hour® (Cetirizine HCl and Pseudoephedrine HCl) ER Tablets, 5 mg/120 mg (McNeil, NDA 21150).

There is no USP method for this product but there is an FDA-recommended method (500 mL of 0.1 N HCl, basket at 100 rpm). The firm conducted its dissolution testing using FDA-recommended method as well as in three other media (500 ml of pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer and Water, with basket at 100 rpm). Based on the submitted data, the DBE recommends the following FDA-recommended dissolution method and data-driven specifications:

Method: 500 mL of 0.1 N HCl using apparatus I (Basket) at 100 rpm

Specifications:

For Cetirizine: NLT 80% (Q) in 30 min;

For Pseudoephedrine:

1 hour	30-50%
2 hour	50-70 %
6 hour	NLT 80%

Please note that the "on-the –file" specifications are NLT 80% (Q) in 30 min for Cetirizine and 1 hr: 30-50%, 2 hr: 50-70% and 6 hr: NLT 80% for Pseudoephedrine.

The firm conducted in vitro alcohol dose-dumping testing of the pseudoephedrine ER component for the test product only using the following dissolution method: 900 ml, 0.1 N HCl, USP apparatus I (Basket) at 100 rpm, with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media[1]. The data show that the % dissolved from the test product in media with various ethanol concentrations is comparable to % dissolution of the test product in media without alcohol. Therefore, no further comparison with the RLD is necessary. The test product does not show any risk of dose-dumping in the presence of alcohol. The dose dumping testing is not requested for this product and reviewed for information only.

The Long Term Storage Stability (LTSS) of 88 days for both Cetirizine and Pseudoephedrine at -20°C ± 5°C is sufficient to cover the maximum storage time of the study samples (53 days at -20°C ± 5°C).

NO DSI inspection is necessary or pending.

The DBE will review the fasted and fed BE study at a later date.

[1] Per the current Guidance for Industry: Individual Product Bioequivalence Recommendations (for Cetirizine HCl and Pseudoephedrine HCl ER tablet, posted on 2/2008, the DBE does not request alcohol dose dumping testing for this product.)

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.					

External database:

Cetirizine HCl/Pseudoephedrine HCl	Tablet (Extended Release)	I (Basket)	100	0.1 N HCl	500	0.17, 0.25, 0.5, 1, 2, 6, and 8 hours	06/18/2007

Internal database:

Cetirizine HCl/Pseudoephedrine HCl (ER)

Dosage Form: Tablet (ER)

Medium: 0.1 N HCl

Apparatus: I (Basket)

Speed/RPMs: 100

Modify Date: 6/27/2007

Sampling Times:

Volume: 500

Notes:

Specification: Cet:NLT80% (Q)in 30 min, Pseudo:1hr:30-50, 2hr:50-70, 6hr:NLT80%(Q)

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

For Cetirizine

FDA-recommended method:

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	0 1 N Hydrochloric acid
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0 5° C
Proposed Specification	Not less than (b) (4) *Q)* of label amount of Cetirizine Dihydrochloride is dissolved in 30 minutes	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & 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
					15	30	45	60	
INN/01/08	09/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12					Module 5 Section 5 3 1 2
				Mean	86 %	95 %	96 %	96 %	
				Range	(b) (4)				
				% C.V	4 6	4 4	4 2	4 3	
	09/01/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12					
				Mean	88 %	94 %	95 %	96 %	
				Range	(b) (4)				
				% C.V	8 5	5 7	5 0	5 1	

Multimedia dissolution testing:

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Acetate Buffer pH 4 5
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0 5° C
Proposed Specification*	NA	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & 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
					15	30	45	60	
INN/03/08	09/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12					Module 5 Section 5 3 1 2
				Mean	57 %	82 %	87 %	89 %	
				Range	(b) (4)				
				% C.V	19 5	8 9	4 7	4 3	
	20/07/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12					
				Mean	84 %	90 %	92 %	93 %	
				Range	(b) (4)				
				% C.V	8 2	5 7	4 4	3 9	

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Phosphate Buffer pH 6 8
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0 5° C
Proposed Specification*	NA	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & 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
					15	30	45	60	
INN/04/08	10/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12					Module 5 Section 5 3 1 2
				Mean	52 %	76 %	82 %	82 %	
				Range	(b) (4)				
				% C.V	3 7	2 9	2 9	4 2	
	16/07/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12					
				Mean	87 %	91 %	93 %	94 %	
				Range	(b) (4)				
				% C.V	9 5	7 5	6 9	6 5	

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Water
	Volume	500 ml
	Time Point	15, 30, 45 and 60 minutes
	Temperature	37° C ± 0 5° C
Proposed Specification*	NA	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & 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
					15	30	45	60	
INN/02/08	08/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12					Module 5 Section 5 3 1 2
				Mean	68 %	90 %	93 %	94 %	
				Range	(b) (4)				
				% C.V	12 9	7 2	5 5	5 4	
	19/07/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12					
				Mean	85 %	89 %	91 %	92 %	
				Range	(b) (4)				
				% C.V	7 7	6 4	5 4	5 7	

For Pseudoephedrine HCl:

FDA-recommended method:

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	0 1 N Hydrochloric acid
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0 5° C
Proposed Specification	1 Hour Between (b) (4)	2 Hours Between (b) (4)
		6 Hours Not less than 80%
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/01/08	09/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12									Module 5 Section 5 3 1 2
				Mean	10 %	24 %	33 %	40 %	61 %	85 %	97 %	102 %	
				Range	(b) (4)								
				% C.V	8 6	3 8	2 2	2 3	1 5	1 2	1 3	1 6	
	09/01/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12									
				Mean	17 %	27 %	36 %	43 %	62 %	84 %	95 %	100 %	
				Range	(b) (4)								
				% C.V	5 0	4 2	3 5	3 3	2 6	2 2	2 0	1 7	

Multimedia dissolution testing:

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Acetate Buffer pH 4 5
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0 5° C
Proposed Specification*	NA	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/03/08	09/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12									Module 5 Section 5 3 1 2
				Mean	8 %	22 %	31 %	39 %	60 %	85 %	95 %	100 %	
				Range	(b) (4)								
				% C.V	18 6	10 4	7 6	6 5	3 5	1 3	0 8	1 0	
	20/07/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12									
				Mean	18 %	28 %	36 %	42 %	61 %	84 %	95 %	100 %	
				Range	(b) (4)								
				% C.V	7 8	7 7	7 6	6 5	6 7	3 9	2 7	2 2	

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Phosphate Buffer pH 6 8
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0 5° C
Proposed Specification*	NA	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/04/08	10/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12									Module 5 Section 5 3 1 2
				Mean	8 %	21 %	29 %	36 %	55 %	78 %	90 %	96 %	
				Range	(b) (4)								
				% C.V	6 5	3 0	2 0	2 3	1 4	1 7	1 3	1 2	
	16/07/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12									
				Mean	17 %	27 %	35 %	42 %	61 %	83 %	93 %	99 %	
				Range	(b) (4)								
				% C.V	4 9	5 7	4 0	3 2	3 3	2 1	1 8	1 8	

Dissolution Conditions	**Apparatus**	USP Type I (Basket)
	Speed of Rotation	100 rpm
	Medium	Water
	Volume	500 ml
	Time Point	15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours
	Temperature	37° C ± 0 5° C
Proposed Specification*	NA	
Dissolution Testing Site (Name & Address)	Sun Pharmaceutical Industries Ltd Survey No 259/15, Dadra-396 191, U T of Dadra & Nagar Haveli, India	

Study Ref No.	Testing Date	Product ID/Batch No. (Test-Manufacture Date) (Reference-Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times								Study Report Location
					15 min.	30 min.	45 min.	1 Hr.	2 Hrs.	4 Hrs.	6 Hrs.	8 Hrs.	
INN/02/08	08/01/08	Batch #: GK71416 Mfg Date: Sep 2007	5mg/120mg Tablets	12									Module 5 Section 5 3 1 2
				Mean	10 %	23 %	33 %	40 %	62 %	86 %	98 %	102 %	
				Range	(b) (4)								
				% C.V	13 7	8 2	5 9	5 6	3 6	1 6	0 8	0 8	
	19/07/08	Batch #: 03607L Exp Date: Mar 2010	5mg/120mg Tablets	12									
				Mean	18 %	28 %	36 %	43 %	62 %	86 %	96 %	99 %	
				Range	(b) (4)								
				% C.V	7 3	8 2	7 3	6 7	5 9	4 8	3 5	2 5	

II. COMMENTS:

1. The firm conducted its dissolution testing using FDA-recommended method (500 ml of 0.1 N HCl with basket at 100 rpm) as well as in three other media (500 ml of pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer and Water, with basket at 100 rpm). The dissolution data show that the dissolution of the test product is comparable to corresponding reference product in all medium and there is no evidence of dose dumping in the test product. Based on the submitted data, the DBE recommends the following FDA-recommended dissolution method and data-driven specifications:

   Method: 500 mL of 0.1 N HCl using apparatus I (Basket) at 100 rpm

   Specifications:

   For Cetirizine: NLT 80% (Q) in 30 min;

   For Pseudoephedrine:

1 hour	30-50%
2 hour	50-70 %
6 hour	NLT 80%

2. The firm has conducted alcohol dose-dumping testing on the test product only using the following dissolution method and media:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus I (basket) @ 100 rpm, with and without alcohol (see below):
Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.
Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.
Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.
Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

The results are summarized as follows:

Mean % of labeled amount of pseudoephedrine dissolved at various sampling times (n=12)

Product	Medium	0 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Test	0.1 N HCl	0	14	24	33	43	46	52	58	60
	5% EtOH/95% 0.1N HCl	0	9	21	31	38	44	49	54	58
	20% EtOH/80% 0.1N HCl	0	7	17	26	33	39	44	48	52
	40% EtOH/60% 0.1N HCl	0	4	14	23	29	34	39	43	46
Reference	0.1 N HCl 5% EtOH/95% 0.1N HCl 20% EtOH/80% 0.1N HCl 40% EtOH/60% 0.1N HCl	Not conducted								

	Mean % Drug Release at 2 hours			
	0.1N HCl	5% EtOH in 0.1N HCl	20% EtOH in 0.1N HCl	40% EtOH in 0.1N HCl
5 mg/120 mg				
Test, mean (range)	60 (b) (4)	58 (b) (4)	52 (b) (4)	46 (b) (4)
Reference, mean (range)	Not conducted			

Per DBE memorandum to the ANDA 77176, the DBE compares the % dissolved at 2 hours in 0.1 N HCl with no ethanol to the % dissolved at 2 hours in 40% ethanol/60% 0.1 N HCl (v/v) for the test product. If the % dissolved is comparable for no ethanol versus 40% ethanol, the test product is considered robust and no further comparisons are needed. If, however, the % dissolved from the test product increases as the amount of ethanol in the media increases, then the DBE compares % dissolved data at 2 hours in 40% ethanol for the test product and reference product. If for both products, the % dissolved at 2 hours in 40% ethanol is comparable, then the DBE concludes that the risk of dose-dumping from the generic product is the same as for the reference product.

For Sun's cetirizine HCl and pseudoephedrine ER Tablets, 5 mg/120 mg, the % dissolved from the test product in media with various ethanol concentrations is comparable to % dissolution of the test product in media without alcohol. Therefore, no further comparison with the RLD is necessary. The dose dumping testing is acceptable. The test product does not show any risk of dose-dumping in the presence of alcohol.

III. DEFICIENCY COMMENTS:

1. The firm should acknowledge the acceptance of FDA recommended method and data driven specifications.

IV. RECOMMENDATION:

The *in vitro* dissolution testing conducted by the firm on the test and reference products is acceptable. However, the firm should acknowledge the following FDA recommended dissolution method and data driven specifications:

Method: 500 mL of 0.1 N HCl using apparatus I (Basket) at 100 rpm

Specifications:

For Cetirizine: NLT 80% (Q) in 30 min;

For Pseudoephedrine:

1 hour	30-50%
2 hour	50-70 %
6 hour	NLT 80%

BIOEQUIVALENCE DEFICIENCY

ANDA: 90-922

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiency has been identified:

1. Your dissolution testing is acceptable. However your proposed specifications are not acceptable. Please acknowledge your acceptance of the following FDA-recommended method and data-driven specifications:

   Apparatus: USP Apparatus I (Basket)
   Media: 500 mL of 0.1 N HCl
   Agitation Speed: 100 rpm
   Temperature: 37±0.5°C
   Specifications:

   For Cetirizine: NLT 80% (Q) in 30 min;

   For Pseudoephedrine:

1 hour	30-50%
2 hour	50-70 %
6 hour	NLT 80%

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

Completed Assignment for 90922 ID: 7640

Reviewer: Jiang, Xiaojian **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7640	10/16/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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

/s/

Xiaojian Jiang
3/15/2009 07:42:48 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
3/17/2009 07:45:01 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
3/17/2009 09:10:36 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090922

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: II	**Team: 24**	**PM: Linda Park**

Electronic ANDA: Yes ☒ No ☐

ANDA #:90922
Firm Name:Sun Pharmaceutical Industries Limited
ANDA Name:Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets USP, 5 mg/120 mg (OTC)
RLD Name:Zyrtec-D 12 Hour Extended Release Tablets, McNeil Consumer Healthcare.

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 24\AP Summary

AP/TA Letter Located:
V:\Chemistry Division II\Team 24\AP LTR

Project Manager Evaluation: **Date: 9-23-12 Initials:** LP

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 10-16-08	Date of Application 10-22-08	Date Acceptable for Filing 1-12-09
Patent Certification (type) PIV	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:*_____ ☐ 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) 9-21-12 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 4-12-11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 2-29-12 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) na

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: _____ 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	☐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: 9/25/2012**

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 =_____ NDA#_____
Patent/Exclusivity Certification: Yes ☒ No ☐	Date Checked _____
If Para. IV Certification- did applicant:	Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐	Written request issued ☐
Was applicant sued w/in 45 days:Yes ☐ No ☒	Study Submitted ☐
Has case been settled: Yes ☐ No ☐	
Date settled:	
Is applicant eligible for 180 day	
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 10/22/2008, BOS=Zyrtec D 12 hour NDA 21150, PIV to '009, PIV to '329, PIV to '867, PIV to '614. ANDA ack for filing with a PIV on 10/22/2008(LO dated 1/12/2009). Patent Amendment rec'd on 1/21/2009-restatement of patent certs. Patent Amendment rec'd on 2/6/2009-notice sent via (b) (4) to UCB Pharma in Brussels Belgium with notice delivered on 1/21/2009, notice sent via (b) (4) to McNeil Consumer in Morris Plains NJ with notice delivered on 1/21/2009, notice sent via (b) (4) to Pfizer in NY, NY with notice delivered on 1/21/2009.
Patent Amendment rec'd on 3/18/2009-statement from Sun that they were not sued within 45 days.
In the approval letter for ANDA 77170 the OGD stated that eligibility for 180 day exclusivity was forfeited for this drug product.
There are no patents or exclusivities which block the approval of this ANDA as the applicant was not sued with respect to the 4 listed patents. Application is eligible for immediate Full Approval.

2. ***Labeling Endorsement***

Reviewer, :
Date_____
Initials_____

Labeling Team Leader, :
Date_____
Initials_____

REMS required?
☐Yes ☐No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

From: Wu, Ruby (Chi-Ann)
Sent: Monday, September 24, 2012 9:41 PM
To: Park, Linda; Payne, Angela
Subject: RE: ANDA 90922

Hi Angela,

The labeling ap summary signed off 2/29/12 remains acceptable.

Hi Linda,

Since this is an OTC product and OPDP does not regulate OTC products, (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm) it may not be appropriate to include the "promotional materials" paragraphs in the approval letter.

Thanks,

Ruby

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 27Sep2012**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Ok.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date SMR for**
Chemistry Div. **II (Smith)** **Initials9/26/2012**
Comments:CMC acceptable and complete.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date_____**
Assoc. Dir. For Chemistry **Initials_____**
Comments: (First generic drug review)

OGD Office Management Evaluation

6. Peter Rickman **Date 9/28/2012**
Director, DLPS **Initials wpr**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes ☐ No ☒
Petition: Yes☐ No☒
Comments: BOS=Zyrtec D 12 hour NDA 21150, Applicant provided PIV certs to all listed patents, '009, '329, '867, and '614 patents. Sun provided a statement that they were not sued within the 45 day period. There are no exclusivity issues. 180 day exclusivity was forfeited for this drug product. Chemistry acceptable 9/21/2012. Bio acceptable 4/12/2011 (fasting and fed studies 5/120 mg). Labeling acceptable 2/29/2012 per AP Summary, TL sign-off 9/24/2012. EER acceptable 9/24/2012. Application is okay for immediate Full Approval.

AND/OR

7. Robert L. West **Date _____**
Deputy Director, OGD **Initials _____**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes☐ No☐
Petition: Yes☐ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments:

8. ***OGD Director Evaluation***
Gregory Geba
Deputy Director, OPS
Comments:
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
   Date _____
   Initials _____

   Check Communication and Routing Summary into DARRTS

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/s/

LINDA M PARK
09/28/2012

QUALITY DEFICIENCY - MINOR

ANDA 090922

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sun Pharmaceutical Industries Ltd. TEL: 609-495-2808

ATTN: Vincent P. Andolina FAX: 609-495-2711

FROM: Linda Park FDA CONTACT PHONE: (240) 276-8536

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 16, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg (OTC).

Reference is also made to your amendments dated February 9, 2010; and February 14, 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/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090922 APPLICANT: Sun Pharmaceuticals Industries, Ltd.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets USP, 5 mg/120 mg

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.

6. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

SUSAN M ROSENCRANCE
06/02/2011

Electronic Log Book

Electronic Log Book ID	367
Contact:	Sun Pharmaceutical Industries Ltd.
Contact Person:	Anne Toland
Reason:	Outgoing, FDA Request for Information
Contact Type:	Email
Category:	ANDA
ANDA/Control/Protocol #:	090922
FDA Contact:	Teresa Ramson
Contact Time and Date	1/28/2011 at 4:25:10 PM

Subject: Bioequivalence

Query

In the amendment dated December 17, 2010, for Fasting (Study No: PKD/08/021) BE study, you have submitted the raw numerical data from the assay runs of only 1-30 subjects. Please submit complete raw numerical data of assay and reassay runs for subjects 31-44 of cetirizine and pseudoephedrine of Fasting BE study, including the data of peak height/area for the drug, peak height/area for the internal standard, ratio of the peak height/area for the drug to the peak height/area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples and quality control samples. Please also submit the raw numerical data of all rejected runs.

Response

Dear Teresa,

Thank you. I have received the below e-mail and forwarded the same to the Sun group in India. I expect they will respond within the requested timeframe.

Regards,

Anne Toland
Director, Regulatory Affairs
Sun Pharmaceutical Industries, Inc.
270 Prospect Plains Rd.
Cranbury, NJ 08512
Phone: 609-495-2823
Fax: 609-495-2711

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/s/

TERESA V RAMSON
01/28/2011

Please send an email to the labeling reviewer (burhan.nour@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 090922
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8990)

TO: Sun Pharmaceuticals Industries, Inc., US Agent for Sun Pharmaceuticals Industries Limited

TEL: 609-495-2823

FAX: 609-495-2711

ATTN: Anne Toland

FROM: Burhan Nour

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 Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets.

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

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/

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

ANDA Number:	090922
Dates of Submission:	October 16, 2008
Applicant's Name:	Sun Pharmaceutical Industries Limited
Established Name:	Cetirizine Hydrochloride and Pseudoephedrine HCl Extended Release Tablets, 5 mg/120 mg (OTC)

Labeling Deficiencies:

1. CONTAINER LABELS (bottles of 30s, (b) (4), and (b) (4)):

a. We note your containers of (b) (4) and (b) (4) tablets exceed the daily sales limit of Pseudoephedrine HCL. We note 21 CFR 1314.20 sets the daily sales limit of pseudoephedrine base to 3.6 gram per purchaser. Please delete the package sizes that exceed the daily sales limit.

Equivalency Charts

The following is not found within DEA law or regulations; DEA provides this for informational purposes only:

A. Effective April 8, 2006, the daily sales limit of ephedrine base, pseudoephedrine base, or phenylpropanolamine base is 3.6 grams per purchaser, regardless of number of transactions.

Ingredient	Number of Tablets [as base]
25 mg Ephedrine HCl	175
25 mg Ephedrine Sulfate	186
30 mg Pseudoephedrine HCl	146
60 mg Pseudoephedrine HCl	73
120 mg Pseudoephedrine HCl	36
30 mg Pseudoephedrine Sulfate	155
60 mg Pseudoephedrine Sulfate	77
120 mg Pseudoephedrine Sulfate	38
Phenylpropanolamine	The Food and Drug Administration issued a voluntary recall of this ingredient as being unsafe for human consumption. Veterinary use is by prescription only.

b. Your labels state the following: "Do not use if inner safety seal is torn or missing." However, your application does not include any documentation regarding this safety seal. In addition, 21 CFR 211.132(b)(1) requires that the safety seal must include an "identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture)", and that the identifying characteristic must be referenced in the safety seal statement on the label. Please submit information about the seal and revise your safety seal statement to include the identifying characteristic.

2. OTC DRUG FACTS (bottles of 30s, (b) (4), and (b) (4):

a. In order for us to verify your compliance with the labeling format requirements of 21 CFR 201.66, please submit a format legend for each size of your container labels.

b. We note that “hydroxypropyl cellulose” is included in the list of **Inactive Ingredients**. Meanwhile, it is not listed in your Component and Composition Statement. Please explain.

c. See comments under container above.

Revise your labeling, as instructed above, and submit final printed 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://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

{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

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/s/

JOHN F GRACE
01/25/2011
for Wm Peter Rickman

BIOEQUIVALENCE AMENDMENT

ANDA 090922

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 Pharmaceutical Industries Ltd. TEL: (609) 495 - 2823

ATTN: Anne Toland FAX: (609) 495 - 2711

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on October 16, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended Release Tablets, 5 mg/120 mg.

Reference is also made to your amendment dated June 6, 2009.

The Division of Bioequivalence has completed its review of the submission(s) 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
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 will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** 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: 090922

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Cetirizine and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg

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

1. The DBE could not open the electronic file for the analytical report of the fasting study probably because it was corrupt. Please resubmit the entire analytical report of the fasting (Study No: PKD/08/021) bioequivalence (BE) study.

2. For Fed (Study No: PKD/08/022) BE study, you have submitted the raw numerical data from the assay runs of **only 20%** of the subjects. Please submit complete raw numerical data of **ALL** assay and reassay runs of both Fasting and Fed studies, including the data of peak height/area for the drug, peak height/area for the internal standard, ratio of the peak height/area for the drug to the peak height/area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subject samples, calibration standard concentration samples, and quality control samples.

3. The mean percent recovery value of pseudoephedrine is 32%. Please explain the reason for such low value of the recovery of the analyte pseudoephedrine reported in method validation report No MV/CEPS/021.

4. For the Fed (Study No PKD/08/022) BE study, you have submitted the chromatograms of cetirizine for 7 subjects i.e. 18% of the subjects. **For future submissions**, please submit chromatograms of at least 20% of the subjects.

5. Please provide the certificate of analysis for the reference product (lot# 03607L).

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

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/s/

DALE P CONNER
09/28/2010

COMPLETE RESPONSE -- MINOR

ANDA 90-922

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 Pharmaceutical Industries Ltd.
U.S. Agent: Kendle Regulatory

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony C. Celeste

FDA CONTACT PHONE: (240) 276-8453

FROM: Leigh Ann Bradford

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 16, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Extended-release Tablets, 5 mg/120 mg.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (**3** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. 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. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-922 APPLICANT: Sun Pharmaceuticals Industries, Ltd.

DRUG PRODUCT: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets, 5 mg / 120 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
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7.
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10.

Following this page, 1 page withheld in full (b)(4)

23. (b) (4)

24.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Review of the Labeling is pending and BA/BE portions of this ANDA is deficient. We may request additional information at the completion of these reviews.

2. Evaluation of all the finished drug product site establishments is pending.

3. Please provide all available room temperature stability data.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Shing Hou Liu
7/22/2009 02:48:47 PM
For Vilayat A. Sayeed, Ph.D.

BIOEQUIVALENCE AMENDMENT

ANDA 90-922

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 Pharmaceutical Industries Ltd.
U.S. Agent: Kendle Regulatory

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony C, Celeste

FDA CONTACT PHONE: (240) 276-8782

FROM: Steven Mazzella

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on October 16, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cetirizine Hydrochloride and Pseudoephedrine Extended Release Tablets, 5 mg/120 mg.

The Division of Bioequivalence has completed its review of the submission(s) 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and 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 both an archival (blue) and 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: 90-922

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Cetirizine HCl and Pseudoephedrine HCl Extended-Release Tablets, 5 mg/120 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted at a later date. The following deficiency has been identified:

1. Your dissolution testing is acceptable. However your proposed specifications are not acceptable. Please acknowledge your acceptance of the following FDA-recommended method and data-driven specifications:

   Apparatus: USP Apparatus I (Basket)
   Media: 500 mL of 0.1 N HCl
   Agitation Speed: 100 rpm
   Temperature: 37±0.5°C
   Specifications:

   For Cetirizine: NLT 80% (Q) in 30 min;

   For Pseudoephedrine:

1 hour	30-50%
2 hour	50-70 %
6 hour	NLT 80%

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

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/s/

Dale Conner

4/1/2009 10:11:12 AM

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 #: 90-922 **FIRM NAME**: SUN PHARMACEUTICAL INDUSTRIES LTD.

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

(PER IAIN MARGAND 12/1/08)

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	☐
☐ **BST**	☒ **BDI**	

DRUG NAME: CETIRIZINE DIHYDROCHLORIDE AND PSEUDOEPHEDRINE HYDROCHLORIDE EXTENDED-RELEASE

DOSAGE FORM: TABLETS, 5 MG/120 MG

Random Queue: 4

Chem Team Leader: Liu, Shing Hou Chem PM: Leign Ann Matheny Labeling Reviewer: Postelle Birch
Bio PM: Steven Mazzella

Letter Date: OCTOBER 16, 2008 **Received Date**: OCTOBER 22, 2008

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 6010515 ANTIHISTAMINE

Archival copy: ELECTRONIC (ECTD FORMAT) **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 **Kwadwo Awuah**	**Recommendation:**
Date **12/10/08**	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Contact Person: Mr. Anthony Celeste Phone No. (301) 838-3120

Called Mr. Anthony Celeste on Dec 11, 2008, and asked him to provide a revised 356h with the established name of the subject of the ANDA written out as Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release tablets instead of Cetirizine Dihydrochloride and Pseudoephedrine Hydrochloride Extended-release tablets. This request was made to ensure that the name and labeling being used by the generic drug product is consistent with that of the of the innovator drug product as identified in the Orange Book. (See further explanation below) Revised 356h received the FDA via fax on 12/11/08. An official submission to the ANDA will be hand delivered to 7500 Standish place on 12/12/08.

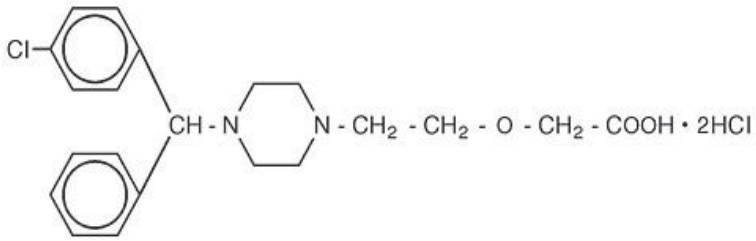
During my review, I noticed that there was a difference in the chemical name being used by the ANDA sponsor and the name of the reference listed name (RLD) listed in the Orange Book. The ANDA submission was for Cetirizine Dihydrochloride/Pseudoephedrine HCL instead of Cetirizine Hydrochloride/Pseudoephedrine. I spoke to Dr. Robert Iser about this on 12/10/08 and he indicated that they are one and the same. He also stated that the correct name is Cetirizine Dihydrochloride since the drug complex usually consists of one Cetirizine molecule combined with 2 Hydrochloride molecules as shown below.

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

Cetirizine Hydrochloride

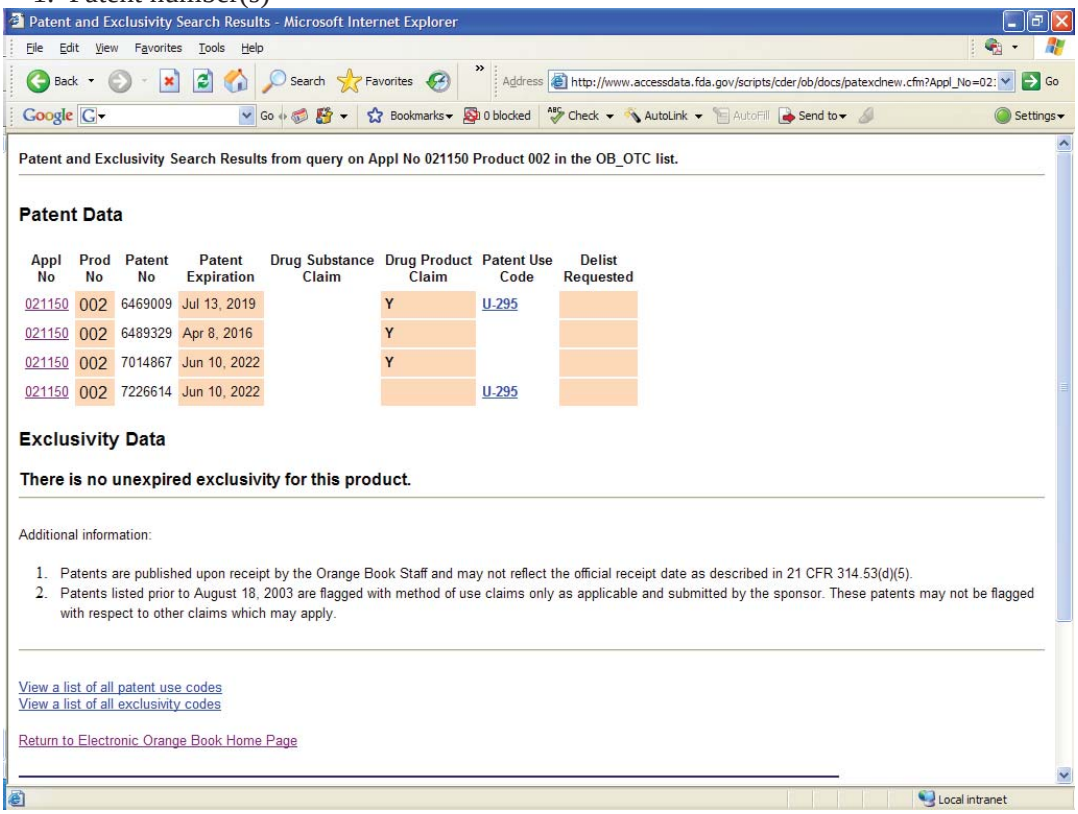
(±)- [2-[4-[4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride

$C_{21}H_{27}Cl_3N_2O_3$ MW = 461.8



MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) OTC YES **Contact Person: Mr. Anthony Celeste Phone No. (301) 838-3120** **(Letter of Non-Repudiation submitted)**	☒
1.2	**Cover Letter** Dated: OCTOBER 16, 2008	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** N/A (e-CTD submission)	☒
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 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
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)  2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☒ **(PIV TO ALL FOUR PATENTS)** 3. Expiration of Patent(s): 6/10/2022 a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: YES	☒
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 (Cetirizine Dihydrochloride DMF # 17889) (Pseudoephedrine Hydrochloride DMF # (b) (4) b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Y	☒

1.12.11	**Basis for Submission** NDA# : 21-150 Ref Listed Drug: ZYRTEC - D Firm: MCNEIL CONSUMER HEALTHCARE 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 as the RLD 2. Active ingredients Cetirizine Dihydrochloride and Pseudoephedrine HCL 3. Inactive ingredients (See attached IIG checklist) 4. Route of administration Oral 5. Dosage Form Extended-release Tablet 6. Strength 5 mg/120 mg	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically N/A ***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 N/A **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** Y **Word Processed e.g., MS Word** Y 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)** Y **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** Y **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** Y **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) –** **REANALYSIS DONE ON SOME SAMPLES – Review Issue as per Dr. Seo** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** Y **Word Processed e.g., MS Word** Y **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Y Table 4. Bioanalytical Method Validation Y Table 6. Formulation Data Y **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution Y **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Y Table 3. Statistical Summary of the Comparative BA Data Y **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Y **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies Y	☒

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) Y 2. Function or Responsibility 3. Type II DMF number for API (Cetirizine Dihydrochloride DMF # 17889) (Pseudoephedrine Hydrochloride DMF # (b) (4) 4. CFN or FEI numbers (Cetirizine FEI – 3003952717)/(Pseudophed CFN – (b) (4)	☒
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) Y **3.2.S.4.2 Analytical Procedures** Y **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) (Cetirizine Lot # PN61692/ Pseudophed Lot # 202806B) **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5 Justification of Specification Y**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition Y 2. Inactive ingredients and amounts are appropriate per IIG - YES (See attached IIG table)	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report Y	☒
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) Y 2. CGMP Certification: YES 3. Function or Responsibility Y 4. CFN or FEI numbers (FEI – 3004561553) **3.2.P.3.2 Batch Formula** Y (ANDA Batch – (b) (4) tabs / Comm. Batch – (b) (4) tabs) **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Y 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y **3.2.P.3.4 Controls of Critical Steps and Intermediates Y** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y (located in Section 3.2.R.1.P.2) **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **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 Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Y **3.2.P.5.2 Analytical Procedures** Y **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form Y **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) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (24 months) **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch **Y**	☒

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) DMFs** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package Y** 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 Y (See attached Recons Page) Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2 Information on Components** Y **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** Y 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) N/A b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers of Products used in BE Study(ies):** (SEE ATTACHED BE REPORT) **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) Y 2. Summary Bioequivalence tables: Table 10. Study Information Y Table 12. Dropout Information Y Table 13. Protocol Deviations Y **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Y Table 16. Composition of Meal Used in Fed Bioequivalence Study Y **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Y Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Y Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☒
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 5 MG/120 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y 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 8/11/2008

Fasting Bioequivalence data for Cetirizine from Cetirizine HCl+ Pseudoephedrine HCl 5/120 mg ER Tablets (N=39) *Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals*				
Parameter	*Test*	*Reference*	*Ratio %*	*90% C.I*
*AUC_{0-t} (ng*hr/mL)*	***7.34***	***7.33***	***100.62***	***97.52 to 103.83***
*AUC_{0-inf} (ng *hr/mL)*	***7.39***	***7.39***	***99.92***	***96.76 to 103.19***
C_{max} (ng /mL)	***5.19***	***5.15***	***104.76***	***101.24 to 108.41***

Fasting Bioequivalence data for Pseudoephedrine from Cetirizine HCl+ Pseudoephedrine HCl 5/120 mg ER Tablets (N=39) *Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals*				
Parameter	*Test*	*Reference*	*Ratio %*	*90% C.I*
*AUC_{0-t} (ng*hr/mL)*	***8.43***	***8.43***	***99.97***	***96.45 to 103.61***
*AUC_{0-inf} (ng *hr/mL)*	***8.46***	***8.46***	***99.80***	***96.28 to 103.45***
C_{max} (ng /mL)	***5.95***	***5.90***	***105.03***	***101.72 to 108.46***

Fed Bioequivalence data for Cetirizine from Cetirizine HCl+ Pseudoephedrine HCl 5/120 mg ER Tablets (N=40) *Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals*				
Parameter	*Test*	*Reference*	*Ratio %*	*90% C.I*
*AUC_{0-t} (ng*hr/mL)*	***7.13***	***7.15***	***98.64***	***95.72 to 101.64***
*AUC_{0-inf} (ng *hr/mL)*	***7.21***	***7.22***	***98.99***	***95.92 to 102.16***
C_{max} (ng /mL)	***4.80***	***4.75***	***104.39***	***99.95 to 109.03***

Fed Bioequivalence data for Pseudoephedrine from Cetirizine HCl+ Pseudoephedrine HCl 5/120 mg ER Tablets (N=40) *Least square Geometric Means, Ratio of the Means and 90% Confidence Intervals*				
Parameter	*Test*	*Reference*	*Ratio %*	*90% C.I*
*AUC_{0-t} (ng*hr/mL)*	***8.33***	***8.32***	***101.32***	***98.04 to 104.71***
*AUC_{0-inf} (ng *hr/mL)*	***8.36***	***8.34***	***101.50***	***98.22 to 104.89***
C_{max} (ng /mL)	***5.94***	***5.86***	***107.90***	***104.55 to 111.37***

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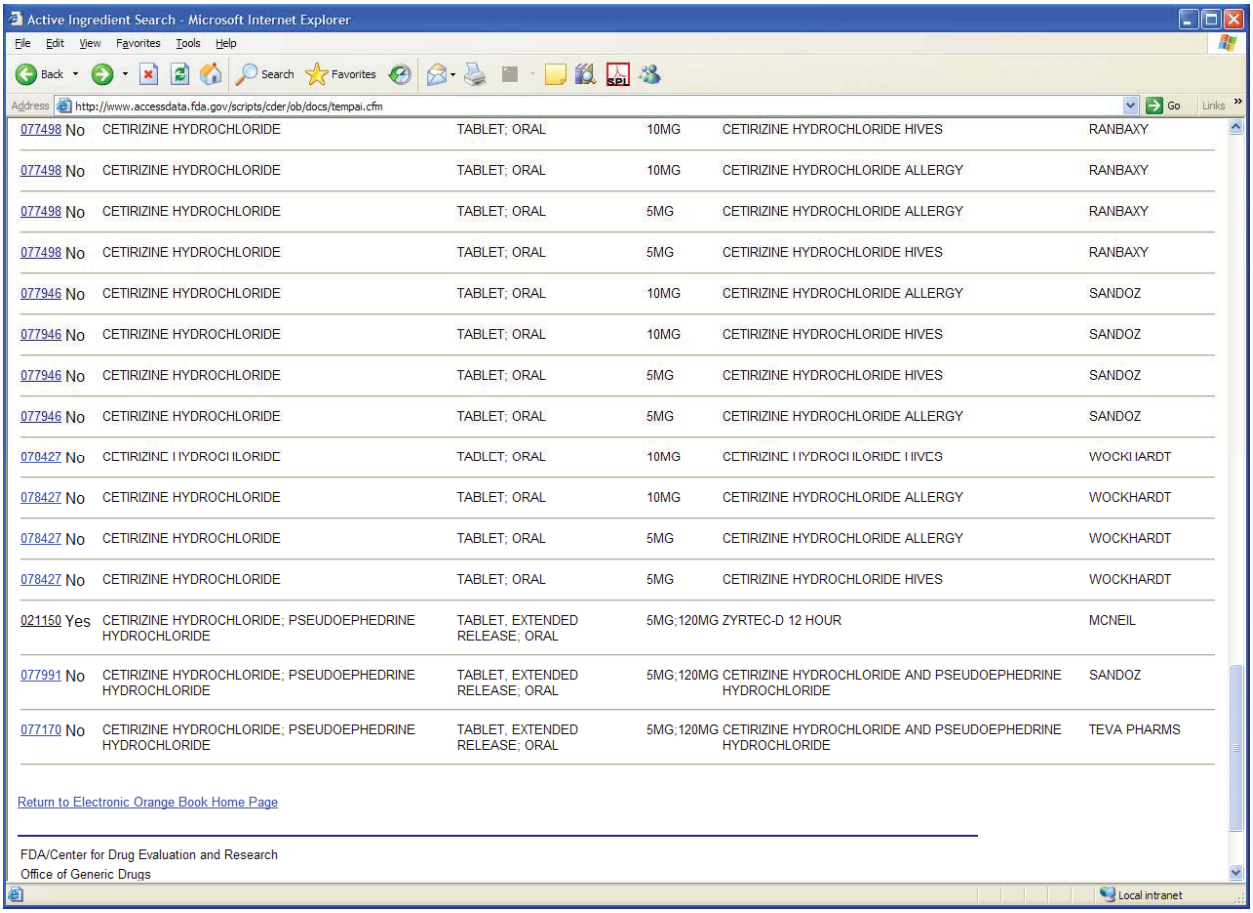

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077498	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	5MG	CETIRIZINE HYDROCHLORIDE HIVES	RANBAXY
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077946	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	10MG	CETIRIZINE HYDROCHLORIDE HIVES	SANDOZ
077946	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	5MG	CETIRIZINE HYDROCHLORIDE HIVES	SANDOZ
077946	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	5MG	CETIRIZINE HYDROCHLORIDE ALLERGY	SANDOZ
078427	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	10MG	CETIRIZINE HYDROCHLORIDE HIVES	WOCKHARDT
078427	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	10MG	CETIRIZINE HYDROCHLORIDE ALLERGY	WOCKHARDT
078427	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	5MG	CETIRIZINE HYDROCHLORIDE ALLERGY	WOCKHARDT
078427	No	CETIRIZINE HYDROCHLORIDE	TABLET; ORAL	5MG	CETIRIZINE HYDROCHLORIDE HIVES	WOCKHARDT
021150	Yes	CETIRIZINE HYDROCHLORIDE; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	5MG;120MG	ZYRTEC-D 12 HOUR	MCNEIL
077991	No	CETIRIZINE HYDROCHLORIDE; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	5MG;120MG	CETIRIZINE HYDROCHLORIDE AND PSEUDOEPHEDRINE HYDROCHLORIDE	SANDOZ
077170	No	CETIRIZINE HYDROCHLORIDE; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	5MG;120MG	CETIRIZINE HYDROCHLORIDE AND PSEUDOEPHEDRINE HYDROCHLORIDE	TEVA PHARMS

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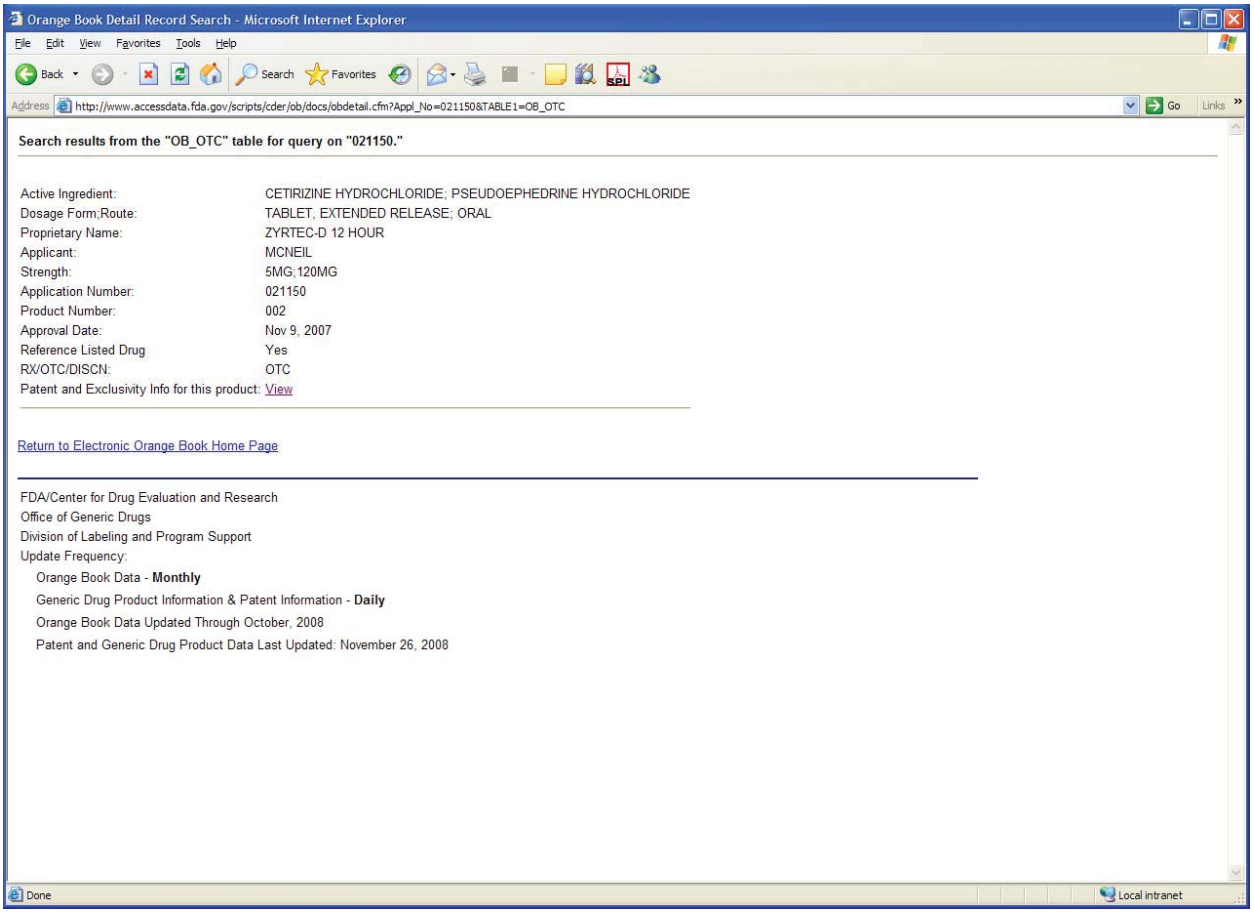
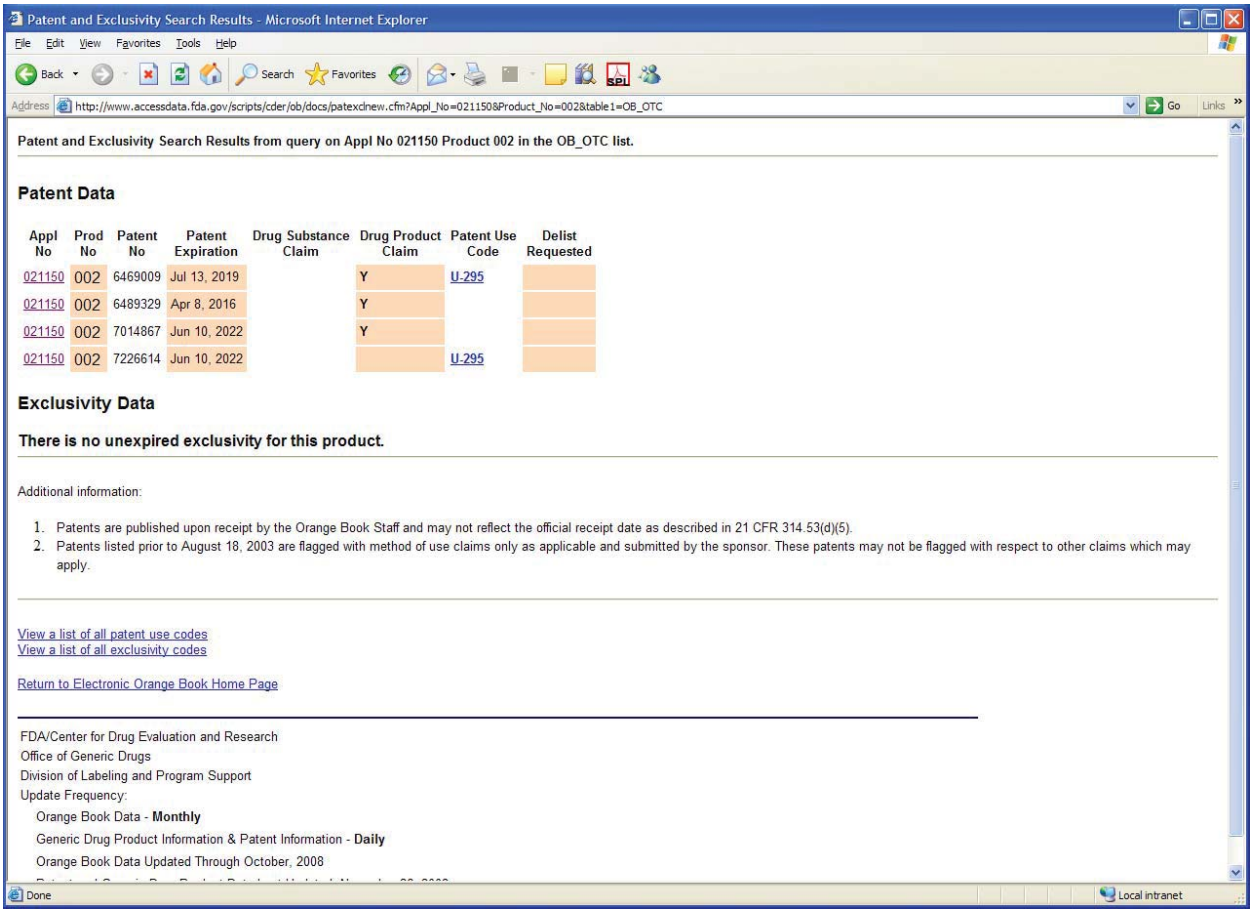

Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021150&TABLE1=OB_OTC
Go Links
Search results from the "OB_OTC" table for query on "021150."
Active Ingredient: CETIRIZINE HYDROCHLORIDE; PSEUDOEPHEDRINE HYDROCHLORIDE
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: ZYRTEC-D 12 HOUR
Applicant: MCNEIL
Strength: 5MG;120MG
Application Number: 021150
Product Number: 002
Approval Date: Nov 9, 2007
Reference Listed Drug Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2008
Patent and Generic Drug Product Data Last Updated: November 26, 2008
Done
Local intranet


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=021150&Product_No=002&table1=OB_OTC
Go Links
Patent and Exclusivity Search Results from query on Appl No 021150 Product 002 in the OB_OTC list.
Patent Data
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
021150 | 002 | 6469009 | Jul 13, 2019 | | Y | U-295 |
021150 | 002 | 6489329 | Apr 8, 2016 | | Y | |
021150 | 002 | 7014867 | Jun 10, 2022 | | Y | |
021150 | 002 | 7226614 | Jun 10, 2022 | | | U-295 |
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
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Office of Generic Drugs
Division of Labeling and Program Support
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Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2008
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/s/

Martin Shimer

1/12/2009 09:53:59 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-922

Kendle International
U.S. Agent for Sun Pharmaceutical Industries Ltd.
Attention: Mr. Anthony Celeste
7361 Calhoun Place
Suite 500
Rockville, MD 20855-2765

Dear Sir:

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 made to the telephone conversation dated December 11, 2008 and your correspondence dated December 11, 2008.

NAME OF DRUG: Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Tablets, 5 mg/120 mg

DATE OF APPLICATION: October 16, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 22, 2008

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
240-276-8478

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/

Martin Shimer
1/12/2009 09:53:38 AM
Signing for Wm Peter Rickman