CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076050

Name: Loratadine and Pseudoephedrine Sulfate
Extended-release Tablets
5 mg/120 mg (12-Hour formulation)

Sponsor: IMPAX Laboratories, Inc.

Approval Date: January 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	X
Labeling	X
Labeling Review(s)	X
Medical Review(s)	
Chemistry Review(s)	X
Bioequivalence Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

APPROVAL LETTER

ANDA 76-050

JAN 30 2003

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 12, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg (12-Hour Formulation) (OTC).

Reference is also made to our Tentative Approval letter dated May 29, 2002, and to your amendments dated April 26, 2001; and October 11, December 4, December 23, and December 27, 2002.

The listed drug product (RLD) referenced in your application, Claritin-D® 12-Hour Extended-release Tablets of Schering Corporation (Schering), is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, (the "Orange Book"), U.S. Patent 4,659,716 (the '716 patent) is scheduled to expire on October 21, 2004, and U.S. Patent 4,863,931 (the '931 patent) is scheduled to expire on March 15, 2009. Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg (12-Hour Formulation), will not infringe on the claims of the '716 or '931 patents, or that the claims of both patents are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against IMPAX Laboratories, Inc. (IMPAX) for infringement of either the '716 or '931 patents that were the subject of the paragraph IV certifications. This action must be brought against IMPAX prior to the expiration of forty-five (45) days from the date the notice provided by IMPAX under Section 505(j)(2)(B)(i) is received by the patent and NDA holders.

You have notified the Agency that IMPAX complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, in February 2001, Schering initiated a patent infringement suit involving Claims 1 and 3 of Schering's '716 patent against you in the United States District Court for the District of New Jersey (Schering Corporation v. IMPAX Laboratories, Inc., Civil Action No. 01CV-0520-JWB). In an order dated August 8, 2002, and entered August 12, 2002, the Chief Judge of the United States District Court for the District of New Jersey granted the defendant's motion for summary judgement, ruling that the contested claims of the '716 patent were invalid. These were the only claims in this case. Reference is made to FDA regulations at 21 C.F.F. 314.107, and in the FDA Guidance published in March 2000 entitled "Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act". With respect to ANDAs such as this one submitted after the March 2000 guidance was issued, an application may be approved and 180-day exclusivity triggered under Section 505(j)(5)(B)(iv)(II) of the Act as of the date the district court enters its decision that the patent is invalid or not infringed. We also note that on August 8, 2002, Schering Corporation appealed the district court's decision to the United States Court of Appeals for the Federal Circuit where it is currently pending.

We note that no action was brought against IMPAX by either the patent holder or the NDA holder with regard to the '931 patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for Over-the-Counter (OTC) use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg (12-Hour Formulation), to be bioequivalent to the listed drug, Claritin-D® 12-Hour Extended-release Tablets, 5 mg/120 mg (12-Hour Formulation) of Schering Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution tests and tolerances are:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl for one hour, then the medium should be replaced with 900 mL of 0.05M phosphate buffer at pH 8.2 containing 0.01% sodium lauryl sulfate (SLS) at 37°C using USP 24 apparatus II (paddle) at 50 rpm. Loratadine and Pseudoephedrine test products should meet the following "interim" specifications:

For Loratadine:

NLT (b)(4)% (Q) dissolved in 60 minutes

For Pseudoephedrine:

1 Hour	NMT (b)(4)%
4 Hours	(b)(4)
12 Hours	NLT (b)(4)%

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data from the first three production size batches in a supplemental application. A "Special Supplememt - Changes Being Effected" (CBE-0) should be submitted when there are no revisions to be proposed to the "interim" specifications or the proposed final specifications are tighter than the "interim" specifications. In all other instances, a Prior Approval Supplement should be submitted.

With respect to 180-day generic drug exclusivity, we note that IMPAX was the first applicant to submit a substantially complete ANDA containing paragraph IV certifications to the '716 and '931 patents for this drug product. Therefore, with this approval, IMPAX is eligible for 180-days of market exclusivity for this drug product with respect to the '716 and '931 patents, as provided for under Section 505(j)(5)(B)(iv) of the Act. With respect to the '716 patent, this exclusivity began to run on the date of entry of the District Court decision referenced above, August 12, 2002. With respect to the '931 patent, such exclusivity will begin to run on the earlier of either (1) the date IMPAX begins commercial marketing of its Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg (12-Hour Formulation), or (2) the date of the decision or order by a court holding that the '931 patent is invalid, unenforceable, or not infringed.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107c)(4). The agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to this ANDA stating the date you commenced commercial marketing of the drug product.

If you have any questions concerning the effective date of approval of an ANDA and the elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, at p. 59710).

Under 21 CFR 314-70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application 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.

Sincerely yours,

Gary Buehler 1/30/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
ANDA 76-050
Division File
Field Copy
HFD-610/RWest
HFD-330/
HFD-205/
HFD-600/C.Parise
HFD-600/H.Hare

Endorsements:
HFD-623/U.Atwal/ 1/13/03
HFD-623/D.Gill/
HFD-617/S.Kim/ 1/13/03
HFD-613/D.Catterson/ Debra M. Catterson 1/13/03
HFD-613/J.Grace/ 1/13/2003

V:\FIRMSAM\IMPAX\LTRS&REV\76050.ap.doc
F/T by:ard/1/7/03

Robert Rupest 1/17/2003
Letter revised per
L.Dickinson
1/30/03

APPROVAL

PS 1/10/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076134

TENTATIVE APPROVAL LETTER

ANDA 76-050

MAY 29 2002

Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 12, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg (12-hour formulation).

Reference is also made to your amendments dated February 9, and November 15, 2001; and February 27, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. However, because of the presence of the patents listed for the reference drug product as explained below, this application is **tentatively approved.** This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, Claritin-D 12 Hour Extended-release Tablets of Schering Corp., is subject to periods of patent protection. These patents, which are listed in the agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book", and their expiration dates are December 19, 2002 (U.S. Patent No. 4,282,233, the '233 patent), October 21, 2004 (U.S. Patent No. 4,659,716, the `716 patent), and March 15, 2009 (U.S. Patent No. 4,863,931, the '931 patent). Your application

contains a patent certification under Section 505(j)(2)(A)(vii)(III) of the Act for the '233 patent stating that you will not market this drug product prior to the expiration of this patent. Your application also contains "Paragraph IV Certifications" under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe upon the '716, or '931 patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Impax Laboratories, Inc. (Impax) for infringement of one or more of the patents that are the subject of the "paragraph IV certifications". This action must be brought against Impax prior to the expiration of forty-five (45) days from the date the notice provided by Impax under paragraph (2)(B)(I) is received. You have notified FDA that Impax has complied with the requirements of Section 505(j)(2)(B) of the Act and that litigation is currently underway in the United States District Court for the District of New Jersey involving a challenge to the '716 patent (Schering Corporation v. Impax Laboratories, Inc., Civil Action No. 01CV-0520 (JAG)). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii)(I), (II), or (III)], or,

   c. the '233, and '716 have expired, and

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

You must amend your application prior to final approval. Your MINOR AMENDMENT - FINAL APPROVAL REQUESTED should notify the agency of the legal issues that may affect the effective date of final approval. This amendment and should also include:

1. a copy of a final order or judgement, a settlement agreement between the parties, a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any significant changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made. Should you wish to make such changes prior to final approval, they should be categorized as representing either "major" or "minor" changes in your cover letter. This amendment will be reviewed according to OGD policies in effect at the time of receipt.

In addition to, or instead of, the pre-approval amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the "Orange Book".

The amendment requesting final approval should be designated as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED in your cover letter. Before you submit the amendment, or if you have questions concerning the status of this application, please contact Ruby Wu, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler 5/29/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-050
Division File
FIELD COPY
HFD-610/RWest
HFD-330/
HFD-205/

Endorsements:
HFD-623/U.Atwal/ U Atwal 4/22/02
HFD-623/D.Gill/ D Gill 4-23-02
HFD-617/R.Wu/4/22/02 RWu 4/23/02
HFD-613/D.Catterson/ Debra M. Catterson 4/23/02
HFD-613/J.Grace/ 4/23/2002

V:\FIRMSAM\IMPAX\LTRS&REV\76050.ta.doc
F/T by: DJ 4/22/02

Robert Lee Test 5/29/2002

TENTATIVE APPROVAL

4/24/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

LABELING

IMPAX

NDC 64896-291-03

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets (12-Hour Formulation)

Loratadine 5 mg/Antihistamine
Pseudoephedrine Sulfate 120 mg/Nasal Decongestant

Allergy & Congestion Non-Drowsy*

Relief of:
Nasal and Sinus Congestion
Sneezing; Runny Nose
Itchy, Watery Eyes
Itchy Throat or Nose

1000 EXTENDED RELEASE TABLETS

Actual Size

*When taken as directed. See Drug Facts Panel.

Drug Facts

Active ingredients (in each tablet)	Purpose
Loratadine 5 mg	Antihistamine
Pseudoephedrine sulfate 120 mg	Nasal decongestant

Uses

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

Warnings

Do not use

- if you have ever had an allergic reaction to this product or any of its ingredients
- 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.

Ask a doctor before use if you have

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

When using this product do not take more than directed.
Taking more than directed may cause drowsiness.

Drug Facts (continued)

Stop use and ask a doctor if

- an allergic reaction to this product occurs. Seek medical help right away.
- symptoms do not improve within 7 days or are accompanied by a fever
- nervousness, dizziness or sleeplessness occurs

If pregnant or breast-feeding, 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 divide, crush, chew or dissolve the tablet

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

Other information

- safety sealed: do not use if the bottle seal imprinted with "sealed for your protection" is open or torn
- store between 15° and 25° C (59° and 77° F)
- keep in a dry place

Inactive ingredients

croscarmellose sodium, dibasic calcium phosphate, hypromellose, lactose monohydrate, magnesium stearate, pharmaceutical ink, povidone, titanium dioxide

Lot No:
Exp. Date:

Manufactured by IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

LABELING REVIEWS

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

ANDA Number:	76-050
Date of Submission:	December 12, 2000 (Original draft labeling)
Applicant's Name:	Impax Laboratories, Inc.
Established Name:	Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 5 mg/120 mg (12 Hour Formulation)

Labeling Deficiencies:

1. **CONTAINER** (Bottles of (b) (4) 1000) and
2. **INSERT:**

Please refer to the attached mocked-up copy of your draft container labels and insert labeling for all of the requested labeling revisions.

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Copy of firm's mocked-up container labels and insert labeling.

9 pages of draft labeling have been withheld immediately following this page as b4 (CCI/TS)

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	X		
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING
   This review was based on the labeling of CLARITIN-D® 12 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation (NDA 19-670/S-010), revised February 1997; approved April 29, 1998. This is the **FIRST GENERIC** application for this drug product.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 19-670

No	Expiration	Use Code	Use	File
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis	P-III
4282233 (Ped)	December 19, 2002	U-77		P-III
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite	P-IV
4659716(Ped)	October 21, 2004	U-142		P-IV
4863931	September 15, 2008			P-IV
4863931(Ped)	March 15, 2009			P-IV

Exclusivity Data For NDA 19-670

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Impax Laboratories, Inc.
   30831 Huntwood Avenue
   Hayward, CA 94544 (Vol. B1.1, Section IX, Page 003953)

4. CONTAINER/CLOSURE (Vol. B 1.2, Section XIII.3, Page 004211)

   (b) (4)

   1000 count: 750 cc wide mouth round white HDPE bottle with fine ribbed white plastic cap, with (b) (4) printed liner

5. INACTIVE INGREDIENTS (Vol. B1.1, Section VII, Page 003823)

   Although IMPAX did list the components in the black ink used to imprint its tablets, the firm did not include this information in the DESCRIPTION section of the insert labeling. This omission is OK and is in keeping with OGD's policy which only "encourages" the inclusion of dyes that may be contained therein, but not necessarily each ingredient.

6. PRODUCT DESCRIPTION

   The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). They are described as follows: white to off white oval, biconvex, coated tablets printed "G 2911" in black on one side.

7. PACKAGING CONFIGURATIONS (Vol. B 1.2, Section XIII.3, Page 004211)

RLD: Bottles of 100, and blister packages of 10 x 10 tablet Unit Dose-Hospital Pack.
ANDA: Bottles of (b) (4) 1000

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None
RLD: Store between 2° and 25° C (36° and 77°F).
ANDA: Store (b) (4) (See USP).

9. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Dispense in a tight container as defined in USP/NF.
ANDA: (b) (4)

10. BIOAVAILABILITY/BIOEQUIVALENCE:
The Division of Bioequivalence concluded on January 4, 2001 that it had completed its review of bioequivalence and had no further questions at the time. (Vol. 1.1, NC 1-11-01)

Date of Review:
August 6, 2001

Date of Submission:
December 12, 2000 (Original draft)

Primary Reviewer:

Date:
8/6/01

Team Leader:

Date:
8/8/2001

---

cc: ANDA: 76-050
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSAM\IMPAX\LTRS&REV\76050na1.l
Review

TENTATIVE APPROVAL SUMMARY

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

ANDA Number: 76-050

Date of Submission: November 15, 2001 (Amendment)

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 5 mg/120 mg (12 Hour Formulation)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **No**. – The firm submitted 4 draft copies of their labels and labeling, which is acceptable for a Tentative Approval. Final Printed Labeling will be submitted by the firm 60 days prior to full approval of this application.

CONTAINER Labels – [Bottles of (b) (4) 1000]:
Satisfactory in **draft** as of the November 15, 2001 submission.

Professional Package INSERT:
Satisfactory in **draft** as of the November 15, 2001 submission.

Revisions needed post-tentative approval: **Yes**. The following are labeling revisions that are mostly editorial in nature, and therefore can be "post-tentative approval" revisions:

1. CONTAINER ((b) (4) 1000's):

   Side panel:

   a. Revise "*Each tablet..." to read "*Each extended-release tablet...".

   b. Insert "USP" after "pseudoephedrine sulfate".

2. INSERT:

   a. General Comment:

      Delete the text appearing on page "000022", because it is an exact copy of the text that appears on page "000021".

   b. CLINICAL PHARMACOLOGY:

      Last paragraph, first sentence, second word: Correct the spelling of "pseudoephedrine".

   c. ADVERSE REACTIONS:

i. Gastrointestinal System: Insert a comma after "eructation".

ii. Liver and Biliary System: Revise "normal" to read "abnormal".

I communicated these revisions to Mark C. Shaw, of IMPAX Laboratories, Inc., by telephone and by facsimile on January 9, 2002.

Patent Data – NDA 19-670

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-670

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: CLARITIN-D® 12 HOUR

NDA Number: 19-670

NDA Drug Name: Loratadine and Pseudoephedrine Extended Release Tablets 5 mg/120 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: April 29, 1998; NDA 19-670/SLR-010

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 with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	

Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?	x		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling of CLARITIN-D® 12 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation (NDA 19-670/S-010), revised February 1997; approved April 29, 1998.

This is the **FIRST GENERIC** application for this drug product.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 19-670

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-670

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The following comments are from the previous reviewer:

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544 (Vol. B1.1, Section IX, Page 003953)

4. CONTAINER/CLOSURE (Vol. B 1.2, Section XIII.3, Page 004211)

(b) (4)

1000 count: 750 cc wide mouth round white HDPE bottle with fine ribbed white plastic cap, with (b) (4) printed liner

5. INACTIVE INGREDIENTS (Vol. B1.1, Section VII, Page 003823)

Although IMPAX did list the components in the black ink used to imprint its tablets, the firm did not include this information in the DESCRIPTION section of the insert labeling. This omission is OK and is in keeping with OGD's policy which only "encourages" the inclusion of dyes that may be contained therein, but not necessarily each ingredient.

6. PRODUCT DESCRIPTION

The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). They are described as follows: white to off white oval, biconvex, coated tablets printed "G 2911" in black on one side.

7. PACKAGING CONFIGURATIONS (Vol. B 1.2, Section XIII.3, Page 004211)

RLD: Bottles of 100, and blister packages of 10 x 10 tablet Unit Dose-Hospital Pack.
ANDA: Bottles of (b) (4) 1000

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None
RLD: Store between 2° and 25° C (36° and 77°F).
ANDA:Store (b) (4) (See USP).

9. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Dispense in a tight container as defined in USP/NF.
ANDA (b) (4)

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on January 4, 2001 that it had completed its review of bioequivalence and had no further questions at the time. (Vol. 1.1, NC 1-11-01)

Date of Review: 1/07/02 Date of Submission: 11/15/01

Primary Reviewer: Debra Catterson Date:
Debra M. Catterson 1/9/02

Team Leader: John Grace Date:
John Grace 1/10/2002

---

cc: ANDA: 76-050
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\impax\ltrs&rev\76050TAP.L.doc
Review

APPROVAL SUMMARY

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

ANDA Number: 76-050

Dates of Submission: December 27, 2002; December 4, 2002; and October 11, 2002 (Amendments)

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 5 mg/120 mg (12 Hour Formulation) (OTC)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER Labels – Bottles of 1000's:
Satisfactory as of the December 27, 2002 submission. [Vol. 4.1]

Revisions needed post-approval: None.

Patent Data – NDA 19-670

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-670

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: CLARITIN-D® 12 HOUR

NDA Number: 19-670

NDA Drug Name: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets 5 mg/120 mg

NDA Firm: Schering Corporation

Date of Approval of NDA Insert and supplement: Nov. 27, 2002; NDA 19-670/SE6-018 (Rx to 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 with innovator labels in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured.		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for CLARITIN-D® 12 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets by Schering Corporation; NDA 19-670/SE6-018 (Rx to OTC switch); approved November 27, 2002.

This is the **FIRST GENERIC** application for this drug product.

2. PATENT/EXCLUSIVITIES

Patent Data – NDA 19-670

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4282233	June 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4282233*PED	December 19, 2002	U-77	Treatment of symptoms of seasonal allergic rhinitis.	III	None
4659716	April 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4659716*PED	October 21, 2004	U-142	Method of treating allergic reactions in a mammal by using this active metabolite.	IV	None
4863931	September 15, 2008	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None
4863931*PED	March 15, 2009	n/a	Antihistaminic fluoro substituted benzocycloheptapyridines (http://www.uspto.gov/patft/index.html)	IV	None

Exclusivity Data– NDA 19-670

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Store between 2° and 30°C (36° and 86°F). Protect from excessive moisture. (Moisture statement is only on the unit dose carton.)
ANDA - Store between 15° and 25°C (59° and 77°F). Keep in a dry place.

4. INACTIVE INGREDIENTS

The listing of inactive ingredients in the Drug Facts labeling appears to be consistent with the listing of inactive ingredients found in the Components and Composition statement. (Vol. B1.1, Section VII, Page 003823.), with one discrepancy: The Drug Facts labeling lists "pharmaceutical ink" under the inactive ingredients, and I could not find this in the original C&C statement. I spoke to Michele Anderson of Impax Labs. on Dec. 18, 2002, and she explained that "pharmaceutical ink" is listed as (b) (4) Black Ink" in the original components and composition statement.

5. CONTAINER/CLOSURE SYSTEM

1000 count: 750 cc wide mouth round white HDPE bottle with fine ribbed white plastic cap, with (b) (4) printed liner
(Vol. B 1.2, Section XIII.3, Page 004211)

6. INPUT FROM THE DIVISION OF OVER-THE-COUNTER DRUG PRODUCTS

Dr. Charles Ganley (supervisory medical officer) and Marina Chang (lead pharmacist) from the OTC Division reviewed the firm's labeling and font size legend, and did not have any objections. Attached is the email correspondence between Dr. Ganley and Ms. Chang and OGD.

Date of Review: 1/03/03 Dates of Submission: 12/27/02; 12/04/02; and 10/11/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 1/3/03

Team Leader: John Grace Date:

John L. Grace 1/6/2003

---

cc:

ANDA: 76-050
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\impax\ltrs&rev\76050APL.doc
Review

Catterson, Debra M

From: Chang, Marina Y
nt: Monday, December 23, 2002 7:22 AM
: Catterson, Debra M
Cc: Ganley, Charles J; Grace, John F
Subject: RE: Revised Loratadine / PSE OTC Label (12-Hour Formulation)

For a quick look, it is fine. I did not read word by word for the Drug Facts content, please verify the content.

Marina

-----Original Message-----
From: Catterson, Debra M
Sent: Friday, December 20, 2002 3:13 PM
To: Chang, Marina Y
Cc: Ganley, Charles J; Grace, John F
Subject: FW: Revised Loratadine / PSE OTC Label (12-Hour Formulation)

Hi Marina,

Attached is Impax Labs' revised OTC Loratadine label. I think it looks OK now, although I will ask Impax to go back to their original font size settings (3.5 pt. Zaph Dingbats, 1 pt. barline, and 1 pt border), since this is what Claritin used on their label.

Could you take a look at this label and let me know if you think we can approve it?

Many thanks!
Debbie

-----Original Message-----
From: Mark Shaw [mailto:mshaw@impaxlabs.com]
Sent: Friday, December 20, 2002 11:24 AM
To: 'CattersonD@cder.fda.gov '
Subject: Revised Loratadine / PSE OTC Label (12-Hour Formulation)

RE: ANDA 76-050

Dear Deborah,

Please find attached a PDF file for the proposed Loratadine and Pseudoephedrine Sulfate Extended Release Tablets (12-Hour Formulation) label. We have incorporated the changes you requested. Please review and

let me know if this label is acceptable. We will then prepare and submit
FPL.

ere are two additional comments I should make:

1. The parenthetical (12-Hour Formulation) is not consistent with the innovator label. Can you please confirm that this text is only relevant to
this immediate-container label.

2. We revised the storage statement based on what we are beginning to see as
a trend within FDA. Stability studies were conducted at the ICH conditions
of 25 deg C +/- 2 deg C // 60% RH +/- 5%. In the past this has always supported a labeled storage condition of (b) (4) C, which is consistent
with USP and ICH. The proposed storage statement on this label is more conservative in that it states a more limited range. For this reason we did
not feel this would be an issue.

Please advise whether the attached label is acceptable. We will then submit
the FPL.

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance
T: (510) 476-2018
F: (510) 476-2091

8

1/8

1 1/4

IMPAX

NDC 64896-291-03

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets (12-Hour Formulation)

Loratadine 5 mg/Antihistamine
Pseudoephedrine Sulfate 120 mg/Nasal Decongestant

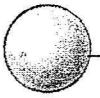
Allergy & Congestion Non-Drowsy*

Relief of:
Nasal and Sinus Congestion
Sneezing; Runny Nose
Itchy, Watery Eyes
Itchy Throat or Nose

1000 EXTENDED RELEASE TABLETS

PS

*When taken as directed. See Drug Facts Panel.



Actual Size

(b) black

Drug Facts

Active ingredients (in each tablet) — **Purpose**
Loratadine 5 mg ..... Antihistamine
Pseudoephedrine sulfate 120 mg ..... Nasal decongestant

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

Warnings
Do not use
- if you have ever had an allergic reaction to this product or any of its ingredients
- 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.

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

When using this product do not take more than directed.
Taking more than directed may cause drowsiness.

Drug Facts (continued)

Stop use and ask a doctor if
- an allergic reaction to this product occurs. Seek medical help right away.
- symptoms do not improve within 7 days or are accompanied by a fever
- nervousness, dizziness or sleeplessness occurs

If pregnant or breast-feeding, 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 divide, crush, chew or dissolve the tablet

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

Other information
- safety sealed: do not use if the bottle seal imprinted with "sealed for your protection" is open or torn
- store between 15° and 25° C (59° and 77° F)
- keep in a dry place

Inactive ingredients
croscarmellose sodium, dibasic calcium phosphate, hypromellose, lactose monohydrate, magnesium stearate, pharmaceutical ink, povidone, titanium dioxide

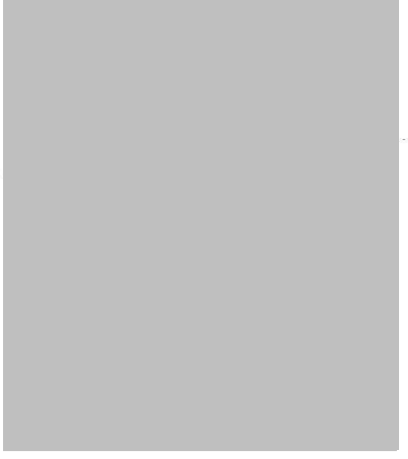
Manufactured by IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Lot No.:
Exp. Date:
Code Area
No Varnish

1

ATTACH LEGEND ON ALL DIGITAL MECHANICALS

(b) (4)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO.: **1** ANDA: **76-050**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® [redacted] of Schering Corporation

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and pseudoephederine sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date December 12, 2000
Acceptable for Filing Date December 13, 2000
New Correspondence Date January 11, 2001
New Correspondence Date January 18, 2001
New Correspondence Date February 9, 2001 (Patent Amendment)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

12. RELATED IND/NDA/DMF(s): **See DMF checklist.**

13. DOSAGE FORM: Extended release tablet

14. POTENCY: **5 mg/120 mg**

15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.

AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2 \cdot H2SO4$. 428.54.
Vasoconstrictor.

16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Minor

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
May 18, 2001

DATE REVISED:
May 30, 2001

1. CHEMISTRY REVIEW NO.: 2 ANDA: **76-050**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® 24 Hour of Schering Corporation
NDA # 20-470

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and pseudoephederine sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date December 12, 2000
Acceptable for Filing Date December 13, 2000
New Correspondence Date January 11, 2001
New Correspondence Date January 18, 2001
New Correspondence Date February 9, 2001 (Patent Amendment)
New Correspondence Date February 21, 2001
Fax Amendment Date July 13, 2001 (this review)
Amendment Date July 17, 2001 (this review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

12. RELATED IND/NDA/DMF(s): See DMF checklist.

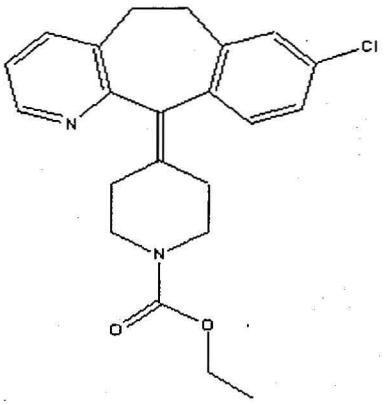
13. DOSAGE FORM: Extended release tablet

14. POTENCY: 5 mg/120 mg

15. CHEMICAL NAME AND STRUCTURE:

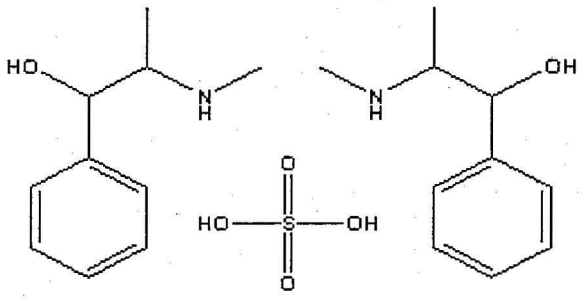
Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-

,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2\bullet H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Facsimile

19. REVIEWER: U.S. Atwal, Ph.D.
DATE COMPLETED: July 26, 2001
DATE REVISED: August 15,2001

1. CHEMISTRY REVIEW NO.: 3 ANDA: **76-050**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D 12 Hour of Schering Corporation
NDA # 20-470

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date December 12, 2000
Acceptable for Filing Date December 13, 2000
New Correspondence Date January 11, 2001
New Correspondence Date January 18, 2001
New Correspondence Date February 9, 2001 (Patent Amendment)
New Correspondence Date February 21, 2001
Fax Amendment Date July 13, 2001
Amendment Date July 17, 2001
Amendment Date August 13, 2001 (This Review)
Minor Amendment Date October 8, 2001 (This Review)
Labeling Amendment Date November 15, 2001

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

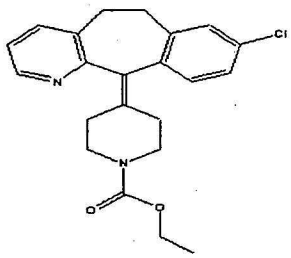
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended release tablet

14. POTENCY: 5 mg/120 mg

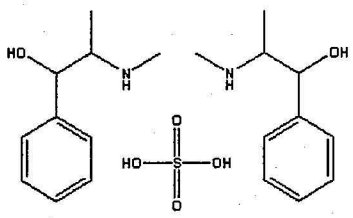
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2•H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Fax.

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
October 29, 2001

DATE REVISED:
November 19, 2001

1. CHEMISTRY REVIEW NO.: 4 ANDA: **76-050**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5mg/120mg) of Schering Corporation; NDA #: 19-670

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date December 12, 2000
Acceptable for Filing Date December 13, 2000
New Correspondence Date January 11, 2001
New Correspondence Date January 18, 2001
New Correspondence Date February 9, 2001 (Patent Amendment)
New Correspondence Date February 21, 2001
Fax Amendment Date July 13, 2001
Amendment Date July 17, 2001
Amendment Date August 13, 2001
Minor Amendment Date October 8, 2001
Labeling Amendment Date November 15, 2001
Amendment Date November 28, 2001 (This Review)
Tcon. Date December 17, 2001 (This Review)
Fax. Amendment Date December 27, 2001 (This Review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

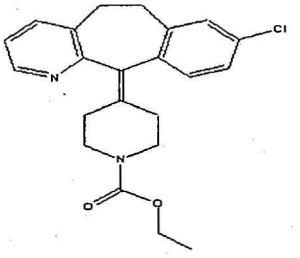
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended release tablet

14. POTENCY: 5 mg/120 mg

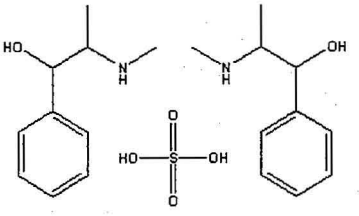
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2•H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not Approvable, Minor

19. REVIEWER:
U.S. Atwal, Ph.D.

DATE COMPLETED:
January 22, 2001

DATE REVISED:
January 29, 2002

1. CHEMISTRY REVIEW NO.: 5 ANDA: **76-050**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5mg/120mg) of Schering Corporation; NDA #: 19-670

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and Pseudoephederine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date December 12, 2000
Acceptable for Filing Date December 13, 2000
New Correspondence Date January 11, 2001
New Correspondence Date January 18, 2001
New Correspondence Date February 9, 2001 (Patent Amendment)
New Correspondence Date February 21, 2001
Fax Amendment Date July 13, 2001
Amendment Date July 17, 2001
Amendment Date August 13, 2001
Minor Amendment Date October 8, 2001
Labeling Amendment Date November 15, 2001
Amendment Date November 28, 2001
Tcon. Date December 17, 2001
Fax. Amendment Date December 27, 2001
Minor Amendment Date February 27, 2002 (This Review)

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: **R_x**

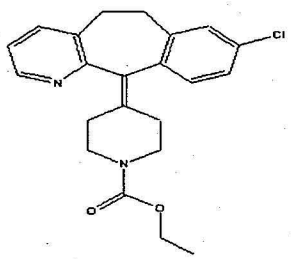
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended release tablet

14. POTENCY: 5 mg/120 mg

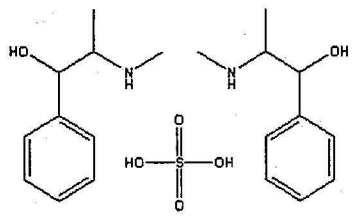
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate. $(C_{10}H_{15}NO)2•H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS: See review.

18. CONCLUSIONS AND RECOMMENDATIONS:
Approvable (Tentative Approval)

19. REVIEWER: U.S. Atwal, Ph.D.

DATE COMPLETED: April 18, 2002

ANDA 76-050 TENTATIVE APPROVAL SUMMARY

PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets

FIRM: IMPAX Laboratories, Inc.

DOSAGE FORM: Extended-Release Tablet

STRENGTH: 5 mg/120 mg

cGMP STATEMENT/EIR UPDATE STATUS: Acceptable on 21-FEB-2001

BIO STUDY: Approve (Per Bio Review Dated 05/24/01)

VALIDATION: Satisfactory (Per NRL's report dated 03/18/02).

STABILITY: Thirteen weeks accelerated (40°C/75% RH) stability data and 52 weeks Controlled Room Temperature, CRT, (25°C±2°C/60%±5% RH) stability data for (b) (4) largest (1000's) package sizes are provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. The reported data are with in established specifications. Thus, 24 month expiration date is justified.

Tests and specifications for the drug product on stability include: (b) (4) (Satisfactory).

LABELING: Tentatively Approved (per review dated 01/07/02).

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: (b) (4) Tablets (Lot #R00017)

SIZE OF STABILITY BATCHES: Stability batch size is the same as the test/bio-batch, i.e. (b) (4) Tablets. The (b) (4) package size on stability is designated as R00017-(b) (4); the 1000's package size on stability is designated as R00017-1000.

PROPOSED PRODUCTION BATCHES: The proposed maximum batch size for production runs is (b) (4) Tablets. The manufacturing process for production batches remains the same as that for the ANDA batch.

CHEMIST: ***U.S. ATWAL, Ph.D.*** ***DATE:*** 4/24/02

SUPERVISOR: ***D. Gill, Ph.D.*** ***DATE:*** 4-23-02

1. CHEMISTRY REVIEW NO.: 6 ANDA: **76-050**

3. NAME AND ADDRESS OF APPLICANT:
Impax Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

4. LEGAL BASIS FOR SUBMISSION:
Claritin-D® (Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5mg/120mg) of Schering Corporation; NDA #: 19-670

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: Loratadine and Pseudoephedrine Sulfate, USP

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:
Original Submission Date December 12, 2000
Acceptable for Filing Date December 13, 2000
New Correspondence Date January 11, 2001
New Correspondence Date January 18, 2001
New Correspondence Date February 9, 2001 (Patent Amendment)
New Correspondence Date February 21, 2001
Fax Amendment Date July 13, 2001
Amendment Date July 17, 2001
Amendment Date August 13, 2001
Minor Amendment Date October 8, 2001
Labeling Amendment Date November 15, 2001
Amendment Date November 28, 2001
Tcon. Date December 17, 2001
Fax. Amendment Date December 27, 2001
Minor Amendment Date February 27, 2002
New Correspondence Date April 17, 2002
New Correspondence Date September 16, 2002 (Patent Amendment).

Minor Amendment Date October 11, 2002, Final Approval Requested.
Labeling Amendment Date December 4, 2002
Correspondence Date December 17, 2002 (this review)
(Re: Tamper Evident Packaging)
Labeling Amendment Date December 23, 2002
Labeling Amendment Date December 27, 2002

10. PHARMACOLOGICAL CATEGORY:
Relief of symptoms of seasonal allergic rhinitis.

11. R_x/OTC: OTC

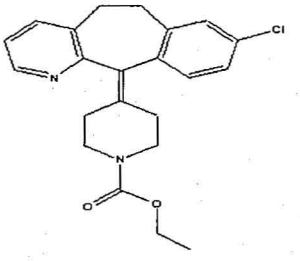
12. RELATED IND/NDA/DMF(s): See DMF checklist.

13. DOSAGE FORM: Extended release tablet

14. POTENCY: 5 mg/120 mg

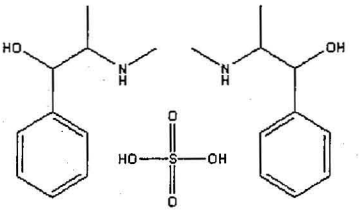
15. CHEMICAL NAME AND STRUCTURE:

Loratadine. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-,ethyl ester. $C_{22}H_{23}ClN_2O_2$. 382.89. 79794-75-5.
Antihistaminic.



AND

Pseudoephedrine Sulfate. Benzenemethanol, α-[1-(methylamino)ethyl]-, [*S*-(*R**,*R**)]-, sulfate.
$(C_{10}H_{15}NO)2 \cdot H2SO4$. 428.54.
Vasoconstrictor.



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS:
See Review

18. CONCLUSIONS AND RECOMMENDATIONS:
Approvable

19. REVIEWER: U.S. Atwal, Ph.D.

DATE COMPLETED: December 19, 2002

12 pages have been withheld as b4 (CCI/TS) immediately following this page

ANDA 76-050 APPROVAL SUMMARY

PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets

FIRM: IMPAX Laboratories, Inc.

DOSAGE FORM: Extended-Release Tablet

STRENGTH: 5 mg/120 mg

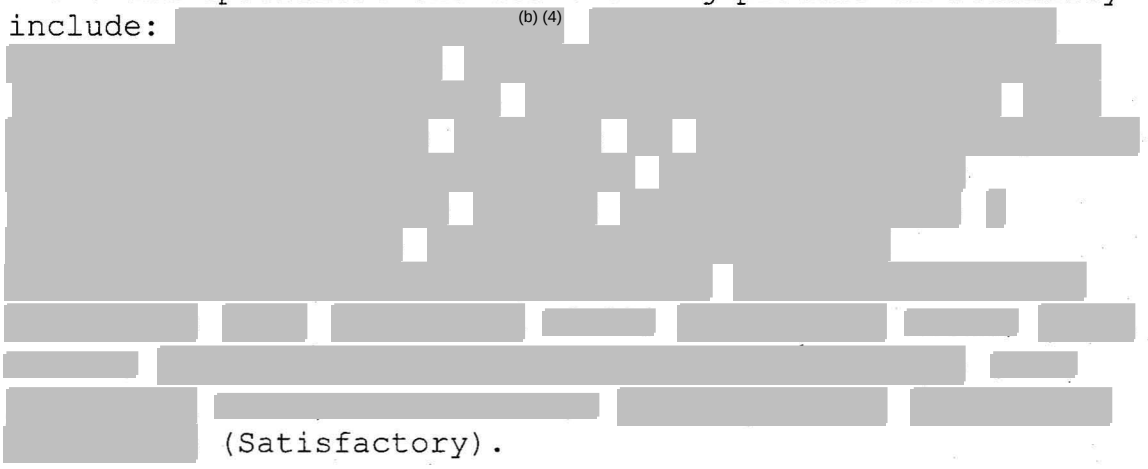
cGMP STATEMENT/EIR UPDATE STATUS: Acceptable on 21-FEB-2001

BIO STUDY: Approve (Per Bio Review Dated 05/24/01)

VALIDATION: Satisfactory (Per NRL's report dated 03/18/02).

STABILITY: Thirteen weeks accelerated (40°C/75% RH) stability data and 52 weeks Controlled Room Temperature, CRT, (25°C±2°C/60%±5% RH) stability data (b) (4) largest (1000's) package sizes are provided. The container/closure system used for the stability study is equivalent to the system proposed for commercial use. The reported data are with in established specifications. Thus, 24 month expiration date is justified.

Tests and specifications for the drug product on stability include: (b) (4)



(Satisfactory).

LABELING: Acceptable 1/6/03

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: [redacted] Tablets (Lot #R00017)

SIZE OF STABILITY BATCHES: Stability batch size is the same as the test/bio-batch, i.e. [redacted] Tablets. The [redacted] package size on stability is designated as R00017-[redacted]; the 1000's package size on stability is designated as R00017-1000.

PROPOSED PRODUCTION BATCHES: The proposed maximum batch size for production runs is [redacted] Tablets. The manufacturing process for production batches remains the same as that for the ANDA batch.

1/13/03

CHEMIST: ***U.S. ATWAL, Ph.D.*** ***DATE: 12/19/02***

SUPERVISOR: ***D. Gill, Ph.D.*** DSGill 1-13-03 ***DATE: 12/20/02***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

BIOEQUIVALENCE REVIEWS

Fasting study

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-050 DRUG NAME Loratadine and Pseudoephedrine Sulfate ER tablets FIRM Impax

DOSAGE FORM(s) ER Tablets, 5 mg/120 mg

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				
Procedure SOP					
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent forms	✓				Subjects signed the consent forms. Consent form sample is enclosed.
Composition					
Summary of study	✓				
Individual Data & Graphs, Linear & Ln	✓				
PK/PD data disk	✓				Blue jacket
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				Gateway
Analytical site	✓				(b) (4)
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				(b) (4) tablets
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	N/A				

Additional comments: Two-way cross-over design study.

Recommendation: COMPLETE / INCOMPLETE

Reviewed by

Kuldeep Dharewal

Concur: Gurupal Singh - Dr. Nevernecan 12-28-00

Date 12/22/00

Revised 6/7/2000

Food- Study

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-050 DRUG NAME Loratadine and Pseudoephedrine Sulfate FIRM Impax

DOSAGE FORM(s) ER tablets, 5 mg/120 mg

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				
Procedure SOP					
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent forms	✓				Subjects signed the consent forms.
Composition	✓				
Summary of study	✓				
Individual Data & Graphs, Linear & Ln	✓				
PK/PD data disk	✓				Blue jacket
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	✓				
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				(b) (4) Tablets
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	N/A				

Additional comments:

Recommendation: (COMPLETE) / INCOMPLETE

Reviewed by
Kuldeep Dhariwal

Concur: Gurgaopal Singh for V. Nerurkar 12/22/00

_____

Date 12/22/00

Revised 6/7/2000

Loratadine/Pseudoephedrine Sulfate
Extended Release Tablets, 5 mg/120 mg
ANDA #**76-050**
Reviewer: Z. Wahba
V:\firmsamnz\IMPAX\ltrs&rev\76050sd.d00

IMPAX Laboratories, Inc.
Hayward, CA
Submission date:
December 12, 2000
April 26, 2001

REVIEW OF TWO BIOEQUIVALENCE STUDIES, AND DISSOLUTION DATA

INTRODUCTION

Type of Submission: Original ANDA
Contents of Submission: Fasting and non-fasting studies, and dissolution data.
Indication: For the relief of symptoms of seasonal allergic rhinitis.
RLD: Schering's Claritin-D® 12 Hour Extended Release Tablet, 5 mg/120 mg.

Recommended dose: Adults and children 12 years of age and over: one tablet twice a day (every 12 hours).

Pharmacokinetics: Loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxy loratadine). The mean elimination half-lives, found in studies in normal adult subjects, were 8.4 hours for loratadine and 28 hours for descarboethoxy loratadine. The bioavailability of loratadine and pseudoephedrine sulfate from Claritin-D® ER tablets is similar to that achieved with separate administration of the components. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. Coadministration of loratadine and pseudoephedrine does not significantly affect the bioavailability of either component.

SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING CONDITIONS (Study Protocol #00157)

A. Study Information:

Sponsor: IMPAX Laboratories
Clinical Facility: Gateway Medical Research, Inc.
Analytical Facility: (b) (4)
Principal Investigator: Irwin Plisco, M.D.
Scientific Director: (b) (4)

B. Treatment Plan:

Study design	Single dose, randomized, two-way crossover study under fasting conditions.
Treatment	A=Test prod. (IMPAX' Loratadine/Pseudoephedrine Sulfate Extended Release Tablet, 5 mg/120 mg) B=Ref. Prod. (Schering's Claritin D® 12-Hour Extended Release Tablet, 5 mg/120 mg)
Dose administered	Each dosing treatment 1X 5 mg/120 mg tablet

Lot\Batch #	Test= Lot #R00017 (b) (4)
	Reference= Lot #9-JRP-2021

Lot size	Test= (b) (4) units Reference= N/A
Content Uniformity	Loratadine Test= 99.6%, Ref.= 105.3% Pseudoephedrine Test= 96.3%, Ref.= 101.9%
Assay	Loratadine Test= 102.6%, Ref.= 105.4% Pseudoephedrine Test= 97.7%, Ref.= 101.3%
Test manufacturing date (or expiration for Ref.)	Test= 07/31/00 Ref.= 04/02
No. of subjects	Recruited=44 (males), Completed=44 Total subjects for statistical analysis =44 (subjects #1-44).
Drop-outs	None
Food & Fluid Intake	Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. The drug products were administered with 240 mL of water at room temperature. Standard meals were provided at appropriate times thereafter.
Clinical study dates	Period-1: 08/26/00, Period-2: 09/09/00
Analytical Study dates	09/18/00 to 11/08/00
Wash out period	14 days

Blood sampling	Pre-dose (0 hour) and at 0.5, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120 and 144 hours.

C. **Averse Events**:
(page 170, Clinical Summary Section, volume C1.2)

Two (2) subjects experienced two adverse events during this study. No serious medical events were reported during the study.

D. **Assay Methodology: (NOT TO BE RELEASED UNDER FOI)**
(See the Validation and Analytical Sections, volume C1.1 and vol.C1.5)

Analyte	Loratadine	Pseudoephedrine
Analytical method	LC/MS/MS	LC/MS/MS
Sensitivity (LOQ)	0.01 ng/mL	2.50 ng/mL
Quality control (QC) samples	0.01, 0.02, 0.40, 3.00 ng/mL	2.50, 5.00, 100, 650 ng/mL
QC samples - validation (Intra-day)	Accuracy = 3.12-16.2% Precision = 88-112%	Accuracy = 2.05-18.6% Precision = 87.6-107%
QC samples - validation (Inter-day)	Accuracy = 7.41-12.1% Precision = 93.5-108%	Accuracy = 7.56-13.9% Precision = 97.3-107%
Linearty	0.01-4.00 ng/mL	2.50-800 ng/mL
Calibration curve validation	Accuracy = 2.10-14.9% Precision = 88.3-109%	Accuracy = 2.65-18% Precision = 95.8-103%
Recovery	Average = 96.7%	Average = 97%
Stability	• Long Term: stable for 5.75 months • Short Term Stability: up to 4 hours • Freeze/thaw Stability: for 3 cycles	• Long Term: stable for 5.75 months • Short Term Stability: up to 4 hours • Freeze/thaw Stability: for 3 cycles
During Study Validation		
Sensitivity (LOQ)	0.01 ng/mL	2.50 ng/mL

Quality control (QC) samples	0.02, 0.40, 3.00 ng/mL	5.00, 100, 650 ng/mL
QC samples validation	Precision = 11.5-17.2% Accuracy = 94.3-104%	Precision = 8.09-10.1% Accuracy = 101-103%
Linearty	0.01-4.00 ng/mL	2.50-800 ng/mL
Calibration curve validation	Precision = 2.25-13.2% Accuracy = 96-107%	Precision = 1.90-9.22% Accuracy = 96.8-106%
Repeat assays during the BE study	Less than 3% of the total number of samples were repeated. There were no repeats for pharmacokinetic reasons.	--

E. IN VIVO BE STUDY & STATISTICAL ANALYSIS:

The plasma concentrations and pharmacokinetic parameters of loratadine and Pseudoephedrine were analyzed using SAS-GLM procedure for analysis of variance. The following plasma concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are presented below:

For Loratadine

Table #1
Mean Loratadine Concentrations in plasma (ng/mL)
Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.02	0.24
0.5	0.34	0.54	0.28	0.57	1.21
1	1.19	2.10	1.04	1.88	1.14
1.25	1.19	1.82	1.17	2.02	1.02
1.5	1.24	2.00	1.06	1.62	1.18
1.75	1.10	1.57	1.03	1.59	1.07
2	1.08	1.62	0.95	1.52	1.13
3	0.73	1.09	0.67	0.91	1.10
4	0.50	0.90	0.47	0.79	1.06
6	0.19	0.32	0.18	0.31	1.04
8	0.11	0.17	0.10	0.16	1.08
12	0.05	0.08	0.05	0.09	1.02
16	0.03	0.05	0.03	0.06	1.01
24	0.02	0.04	0.02	0.04	0.95
36	0.01	0.02	0.02	0.04	0.75
48	0.01	0.02	0.01	0.03	0.84
60	0.01	0.02	0.01	0.02	0.81
72	0.01	0.01	0.01	0.02	0.97

96	0.00	0.01	0.00	0.01	0.73
120	0.00	0.01	0.00	0.01	0.77
144	0.00	0.00	0.00	0.01	0.50

MEAN1=Test-Product MEAN2=Ref.-Product

Table #2
Mean Pharmacokinetic Parameters (Arithmetic) for Loratadine, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	5.95	9.55	5.87	9.66	1.01
AUCT	5.54	8.81	5.35	8.81	1.04
CMAX	1.51	2.24	1.38	2.06	1.09
KE	0.24	0.19	0.22	0.19	1.10
*LAUCI	2.56	1.25	2.62	1.23	0.98
*LAUCT	2.53	1.22	2.48	1.19	1.02
*LCMAX	0.82	1.05	0.76	1.04	1.08
THALF	15.29	23.65	14.34	18.08	1.07
TMAX	1.36	0.61	1.53	0.69	0.89

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
* The values represent the geometric mean (antilog of the means of the logs).

Table #3
LSMeans And The 90% Confidence Intervals (Loratadine), Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	2.51	2.52	1.00	85.01	116.76
LAUCT	2.53	2.48	1.02	87.37	118.63
LCMAX	0.82	0.76	1.08	96.94	120.88

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
LOWCI 12=Lower C.I. for T/R UPPCI12=Upper C.I. for T/R

Comment on the fasting study (Loratadine):
The mean plasma loratadine levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the geometric mean ratios of AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3).

For Descarboethoxyloratadine

The firm submitted the plasma concentrations and pharmacokinetic parameters for the metabolite descarboethoxyloratadine. Based on the recently published CDER Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations", issued 10/2000, posted 10/27/2000, acceptable bioequivalence of this metabolite is not required for approval of this submission. However, descarboethoxyloratadine pharmacokinetic parameters, AUCt, AUCi, Cmax are presented below

Parameter	Test	Reference	T/R	90% CI
AUCt (ng.hr/mL)	19.23	18.66	103.05	91.78, 115.71
AUCi (ng.hr/mL)	21.34	20.89	102.18	91.37, 114.28
Cmax (ng/mL)	1.75	1.67	105.03	97.99, 112.57

Comment on Descarboethoxyloratadine Data: The 90% confidence intervals for the geometric mean ratios of AUCt, AUCi and Cmax were within the acceptable range of 80-125%.

For Pseudoephedrine

Table #4
Mean Pseudoephedrine Concentrations in plasma (ng/mL)
Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.16	1.05	0.00
0.5	79.90	55.58	86.76	72.85	0.92
1	161.63	52.64	160.25	62.48	1.01
1.25	170.15	43.64	176.98	56.73	0.96
1.5	177.34	41.23	175.64	46.71	1.01
1.75	180.41	41.78	180.77	47.53	1.00
2	181.83	40.13	187.16	45.13	0.97
3	189.78	53.06	177.86	41.14	1.07
4	240.63	82.92	172.95	62.44	1.39
6	273.58	78.80	193.24	80.85	1.42
8	230.14	71.70	204.75	82.06	1.12
12	152.15	69.21	171.59	71.93	0.89
16	98.97	56.66	114.19	57.44	0.87
24	39.81	40.61	47.91	43.05	0.83
36	13.92	23.43	16.94	27.48	0.82
48	4.24	12.09	5.43	16.50	0.78
60	2.28	9.55	2.23	9.35	1.02
72	1.17	5.42	1.04	4.85	1.12

MEAN1=Test-Product MEAN2=Ref.-Product

Table #5
Mean Pharmacokinetic Parameters (Arithmetic) for Pseudoephedrine, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4027.13	1964.45	3972.96	2031.95	1.01
AUCT	3954.25	1865.06	3894.59	1960.25	1.02
CMAX	288.34	73.71	259.36	69.13	1.11
KE	0.12	0.03	0.12	0.02	1.00
*LAUCI	3709.92	0.39	3639.21	0.40	1.02
*LAUCT	3651.35	0.38	3569.05	0.40	1.02
*LCMAX	278.25	0.28	250.64	0.27	1.11
THALF	6.38	2.50	6.19	1.87	1.03
TMAX	5.35	1.46	5.73	3.68	0.93

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
* The values represent the geometric mean (antilog of the means of the logs).

Table #6
LSMeans And The 90% Confidence Intervals (Psseudoephedrine), Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	3709.92	3639.21	1.02	96.49	107.70
LAUCT	3651.35	3569.05	1.02	96.73	108.20
LCMAX	278.25	250.64	1.11	102.84	119.83

MEAN1=Test-product MEAN2=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
LOWCI 12=Lower C.I. for T/R UPPCI12=Upper C.I. for T/R

Comment on the fasting study (Pseudoephedrine):
The mean plasma pseudoephedrine levels for the test and reference products were comparable to each other as shown in Table #4 and Figure #2. The 90% confidence intervals for the geometric mean ratios of AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #6).

BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS
(Study protocol #00158)

A. Study Information:

Sponsor: IMPAX Laboratories
Clinical Facility: Gateway Medical Research, Inc.
Analytical Facility: (b) (4)
Principal Investigator: David E. Erasmus, M.D.
Scientific Director: (b) (4)

B. Treatment Plan:

Study design	Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.
Treatment	A=Test prod. (IMPAX' Loratadine/ Pseudoephedrine Sulfate Extended Release Tablet, 5 mg/120 mg), under fasting conditions. B=Test prod. (IMPAX' Loratadine/ Pseudoephedrine Sulfate Extended Release Tablet, 5 mg/120 mg), under non-fasting conditions. C=Ref. Prod. (Schering's Claritin D® 12 Hour Extended Release Tablet, 5 mg/120 mg), under non-fasting conditions.
Dose administered	Each dosing treatment 1X 5 mg/120 mg tablet

Batch\Lot #	Test= Lot #R00017 (b) (4)
	Reference= Lot #9-JRP-2021

Test manufacturing date (or expiration for Ref.)	Test= 07/31/00 Ref.= 04/02
No. of subjects	Enrolled=36 (males), Completed = 34. Total subjects for statistical analysis =34 (subjects #1-3, 5-6, 8-30, and 32-37).
Drop-outs	Subject #4, was unable to participate in Period-2, because of a conflict with his employment. Subject #7, was involved in a car accident during Period-1. Due to concomitant medical therapy, he could not continue to participate in the study. Note: Subject #37, was initially enrolled as #31, but his number was changed to #37 to reflect the time of his actual dosing.

Food & Fluid Intake	Subjects receiving treatments B and C only fasted overnight (for 10 hours). Treatments B and C, subjects were fed a standard high fat breakfast, which was consumed in its entirety 15 minutes before drug administration. Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Each dose was followed by 240 mL of room temperature tap water. Standard meals were provided at appropriate times thereafter.
Clinical study dates	Period-1= 09/24/00; Period-2= 10/08/00; Period-3= 10/22/00
Analytical Study dates	10/31/00 to 12/04/00
Wash out period	14 days
Blood sampling	Pre-dose (0 hour) and at 0.5, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120 and 144 hours.

C. Assay Methodology:

Same as in study #00157 (under fasting conditions).

During Study Validation		
Analyte	Loratadine	Pseudoephedrine
Sensitivity (LOQ)	0.01 ng/mL	2.50 ng/mL
Quality control (QC) samples	0.02, 0.40, 3.00 ng/mL	5.00, 100, 650 ng/mL
QC samples validation	Precision = 9.62-19.1% Accuracy = 99-108%	Precision = 9.32-17.0% Accuracy = 98.2-106%
Linearty	0.01-4.00 ng/mL	2.50-800 ng/mL
Calibration curve validation	Precision = 3.05-13.2% Accuracy = 94.5-105%	Precision = 1.75-14.7% Accuracy = 94-111%
Repeat assays during the BE study	Less than 3% of the total number of samples were repeated. There were no repeats for pharmacokinetic reasons.	Less than 3% of the total number of samples were repeated. There were no repeats for pharmacokinetic reasons.

D. Averse Events:
(page 1887-1888, The Clinical Summary Section, volume C1.7)

Four (14) subjects experienced a total of seventeen (17) adverse events during this study. The adverse events were reported as mild to moderate. The adverse events were judged as 3 possible drug-related, 10 remotely drug-related, and 4 unrelated drug-related.

E. IN VIVO BE STUDY & STATISTICAL ANALYSIS:

The plasma concentrations and pharmacokinetic parameters of loratadine and pseudoephedrine were analyzed using SAS-GLM procedure for analysis of variance. The following plasma concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are presented below:

For Loratadine

Table #7
Mean Loratadine Concentrations in plasma (ng/mL)
Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.48	0.67	0.35	0.47	0.16	0.39	1.35
1	1.29	1.79	1.04	1.18	0.89	1.60	1.24
1.25	1.30	1.72	1.28	1.40	1.07	1.61	1.02
1.5	1.30	1.88	1.39	1.51	1.08	1.28	0.94
1.75	1.15	1.58	1.38	1.40	1.13	1.29	0.83
2	0.96	1.27	1.27	1.20	1.08	1.00	0.76
3	0.63	0.88	1.02	0.99	1.10	1.22	0.62
4	0.39	0.53	0.69	0.81	0.93	1.27	0.56
6	0.16	0.24	0.36	0.49	0.39	0.53	0.46
8	0.08	0.12	0.17	0.23	0.17	0.20	0.47
12	0.04	0.06	0.08	0.11	0.08	0.11	0.51
16	0.03	0.06	0.05	0.09	0.06	0.14	0.56
24	0.03	0.11	0.04	0.08	0.04	0.14	0.79
36	0.03	0.11	0.03	0.08	0.05	0.19	0.93
48	0.03	0.15	0.02	0.07	0.02	0.09	1.46
60	0.04	0.19	0.02	0.07	0.01	0.05	1.96
72	0.04	0.21	0.01	0.05	0.00	0.01	2.86
96	0.01	0.07	0.00	0.01	0.00	0.00	3.38
120	0.00	0.00	0.00	0.00	0.00	0.00	0.41
144	0.00	0.00	0.00	0.00	0.00	0.00	.

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	0.00	1.81
0.5	2.99	2.22
1	1.44	1.17

1.25	1.22	1.20
1.5	1.20	1.28
1.75	1.02	1.22
2	0.90	1.18
3	0.57	0.92
4	0.41	0.74
6	0.42	0.91
8	0.47	1.00
12	0.50	0.98
16	0.49	0.87
24	0.67	0.84
36	0.58	0.62
48	1.33	0.91
60	2.66	1.35
72	8.41	2.94
96	8.45	2.50
120	0.52	1.27
144	.	.

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed

Table #8

Mean Pharmacokinetic Parameters (Arithmetic) for Loratadine, Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	4.90	6.83	8.15	8.55	8.15	9.49	0.60
AUCT	6.61	12.69	7.74	8.25	7.89	9.24	0.85
CMAX	1.51	1.89	1.73	1.56	1.78	1.85	0.87
KE	0.30	0.21	0.18	0.18	0.19	0.17	1.70
*LAUCI	2.60	1.12	4.98	1.03	4.83	1.02	0.52
*LAUCT	2.75	1.25	4.74	1.02	4.65	1.03	0.58
*LCMAX	0.90	1.01	1.24	0.84	1.15	0.93	0.73
THALF	7.40	11.95	14.16	17.19	12.13	16.31	0.52
TMAX	3.24	12.15	2.14	2.54	3.17	5.92	1.52

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.60	1.00
AUCT	0.84	0.98
CMAX	0.85	0.97
KE	1.58	0.93
*LAUCI	0.54	1.03
*LAUCT	0.59	1.02
*LCMAX	0.78	1.08
THALF	0.61	1.17
TMAX	1.02	0.68

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study (loratadine):
The mean plasma loratadine levels for the test and reference products were comparable to each other as shown in Table #7 and Figure #3. The T/R geometric mean ratios (RLSM23) for AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #8).

For Descarboethoxyloratadine

The firm submitted the plasma concentrations and pharmacokinetic parameters for the metabolite descarboethoxyloratadine. Based on the recently published CDER Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations", issued 10/2000, posted 10/27/2000, bioequivalence evaluation of this metabolite is not required for approval of this submission. However, descarboethoxyloratadine pharmacokinetic parameters, AUCt, AUCi, Cmax are presented below:

Parameter	Test (geometric mean)	Reference (geometric mean)	T/R
AUCt (ng.hr/mL)	19.75	20.49	96.36
AUCi (ng.hr/mL)	21.73	22.78	95.40
Cmax (ng/mL)	1.48	1.50	98.20

Comment on Descarboethoxyloratadine Data: The 90% confidence intervals for the geometric mean ratios of AUCt, AUCi and Cmax were within the acceptable range of 0.8 to 1.25.

For Pseudoephedrine

Table #9
Mean Pseudoephedrine Concentrations in plasma (ng/mL)
Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.08	0.48	0.00	0.00	0.00	0.00	.
0.5	86.68	56.10	57.07	50.17	49.43	48.87	1.52
1	144.79	58.78	108.82	54.46	114.45	69.45	1.33
1.25	147.75	53.57	130.08	47.87	135.40	65.89	1.14
1.5	155.41	50.62	139.96	47.09	146.40	59.38	1.11
1.75	154.08	48.12	150.26	55.54	149.53	53.81	1.03
2	152.79	42.47	157.04	52.96	153.04	50.42	0.97
3	172.84	51.49	173.86	64.42	153.06	41.27	0.99
4	233.00	83.43	215.41	71.84	148.54	35.65	1.08

6	265.97	68.36	251.66	62.00	226.67	103.24	1.06
8	215.97	44.37	196.88	44.52	216.18	95.38	1.10
12	129.96	39.32	118.28	36.91	150.53	40.58	1.10
16	75.34	26.83	65.40	25.09	86.48	26.55	1.15
24	28.59	19.65	24.26	17.88	31.60	20.19	1.18
36	9.65	18.07	7.63	16.46	11.31	21.92	1.27
48	4.71	22.92	3.11	13.84	4.60	16.54	1.52
60	3.21	17.85	2.99	13.53	3.01	14.47	1.07
72	3.41	19.27	2.07	10.76	1.50	6.42	1.64

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.5	1.75	1.15
1	1.27	0.95
1.25	1.09	0.96
1.5	1.06	0.96
1.75	1.03	1.00
2	1.00	1.03
3	1.13	1.14
4	1.57	1.45
6	1.17	1.11
8	1.00	0.91
12	0.86	0.79
16	0.87	0.76
24	0.90	0.77
36	0.85	0.67
48	1.03	0.68
60	1.07	0.99
72	2.27	1.38

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed

Table #10
Mean Pharmacokinetic Parameters (Arithmetic) for Pseudoephedrine, Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	3357.16	856.04	3336.72	1810.52	3406.40	1189.93	1.01
AUCT	3462.42	1234.14	3110.46	988.44	3379.43	1065.63	1.11
CMAX	284.84	78.17	281.44	53.38	268.41	79.61	1.01
KE	0.13	0.02	0.13	0.04	0.13	0.03	1.01
*LAUCI	3254.99	0.25	3090.56	0.35	3249.14	0.30	1.05
*LAUCT	3299.15	0.30	2980.08	0.29	3237.13	0.29	1.11
*LCMAX	275.86	0.25	276.39	0.20	257.56	0.29	1.00
THALF	5.26	0.79	7.25	10.89	6.02	3.22	0.73
TMAX	5.31	1.47	5.13	1.21	5.95	2.63	1.04

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.99	0.98
AUCT	1.02	0.92
CMAX	1.06	1.05
KE	1.05	1.04
*LAUCI	1.00	0.95
*LAUCT	1.02	0.92
*LCMAX	1.07	1.07
THALF	0.87	1.21
TMAX	0.89	0.86

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Comment on the non-fasting study (Pseudoephedrine):
The mean plasma pseudoephedrine levels for the test and reference products were comparable to each other as shown in Table #9 and Figure #4. The T/R geometric mean ratios (RLSM23) for AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 (Table #10).

Note: The firm excluded subjects #13 and 32 from its calculation, due to pre-dose plasma concentration greater than 5% of their Cmax values (per the BA/Be guidance, issued on 10/2000). However, the reviewer did additional statistical analysis for pseudoephedrine including subjects #13 and #31, and the results of AUCt, AUCi, and Cmax, were all within the acceptable range of 0.8 to 1.25 that has been set by the Division of Bioequivalence.

FORMULATION (Not to be released under FOI)
(p. #3825, vol. C1.11)

IMPAX's formulation statement for its test products, Loratadine/Pseudoephedrine Sulfate Extended Release Tablet, 5 mg/ 120 mg, is presented below:

Ingredient	Per tablet
Loratadine, (b) (4)	(b) (4)
Pseudoephedrine Sulfate, USP	
Hydroxypropyl methylcellulose, (b) (4)	
(b) (4)	
Povidone, USP (b) (4)	
Croscarmellose sodium, NF (b) (4)	
Dibasic calcium phosphate, (b) (4)	
Lactose monohydrate, NF	(b) (4)
Titanium dioxide, USP	
Magnesium stearate, NF	
(b) (4)	
Total	

(b) (4)

Comment: The Division of Chemistry I will be informed of the (b) (4) in the active ingredients in this product. Sponsors should formulate a generic drug product to the labeled amount of active ingredients in the corresponding RLD.

DISSOLUTION:

The firm's dissolution data are presented below:

(b) (4)

[redacted]

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP 24 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.1 N hydrochloric acid for 1 hour, then phosphate buffer (pH 8.2) w/0.01% SLS
Test Drug: IMPAX' Loratadine/Pseudoephedrine Sulfate Extended Release Tablet, 5 mg/120 mg
Reference Drug: Schering's Claritin-D® Extended Release Tablet, 5 mg/120 mg

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #R00017 Strength(mg) 5 mg Loratadine (p 15, 17, vol. A2.1)			Reference Product Lot #9-JRP-2021 Strength(mg) 5 mg Loratadine (p 23, 25, vol. A2.1)		
	Mean %	Range	%CV	Mean %	Range	%CV
5	36.1	29-42.7	12.4	7.9	0-12.7	63.7
10	73.0	69.9-77.7	3.2	33.1	16.2-43.1	23.1
15	79.8	75.4-85.1	3.7	53.5	41.3-62.3	11.7
30	85.6	79-90.9	4.3	69.8	61.4-77.5	7.4
60	88.9	81.9-95.3	4.3	82.0	75.4-89.2	5.6
Sampling Times (hours)	Test Product Lot #R00017 Strength(mg) 120 mg Pseudoephedrine sulfate (p 14, 16, vol. A2.1)			Reference Product Lot #9-JRP-2021 Strength(mg) 120 mg Pseudoephedrine sulfate (p 22, 24, vol. A2.1)		
	Mean %	Range	%CV	Mean %	Range	%CV
1	45.2	42.2-48	3.9	47.0	44.9-51.1	4.4
2	48.0	45-52.3	4.6	54.3	51.4-58.2	3.8
3	52.8	49.8-56.6	4.0	64.7	46.5-92.8	17.6
4	60.6	57.4-64.4	3.8	74.3	64.1-100.6	16.9
6	83.0	77.2-92.7	5.2	85.0	75.1-106.9	13.5
8	99.0	96.1-102.6	2.2	91.1	81.8-106.6	8.7
10	99.9	96.3-103.2	2.1	96.0	87.3-107.4	5.6
12	100.0	96.3-103.2	2.2	99.3	92.2-107.2	3.7

Comments on the dissolution data:
The sponsor provided the dissolution data applying the following conditions:

Condition	Apparatus	Speed	Media
Condition 1	(b) (4)		
Condition 2	USP Apparatus II (Paddle)	50 (b) (4)	900 mL of 0.1N HCl for one hour, then replace medium with 900 mL 0.05M phosphate buffer at pH 8.2 containing 0.01% sodium lauryl sulfate (SLS)

The sponsor is proposing dissolution condition #1 with the following specifications:

For Loratadine

NLT (b)(4)% (Q) dissolved in one hour

For Pseudoephedrine

1 hour NMT (b)(4)%
4 hours NLT (b)(4)% and NMT (b)(4)%
12 hours NLT (b)(4)%

However, based on the submitted data and comparing the profile of test and reference products using F2 factor (see Tables #1&2, below), the DBE suggests the dissolution condition and specifications should be as follows:

The dissolution testing should be conducted in 900 mL of 0.1N HCl for one hour, then replace medium with 900 mL 0.05M phosphate buffer at pH 8.2 containing 0.01% sodium lauryl sulfate (SLS) at 37°C using USP 24 apparatus II (paddle) at 50 rpm.

For Loratadine

NLT (b)(4)% (Q) dissolved in 60 minutes

For Pseudoephedrine

1 hour NMT (b)(4)%
4 hours NLT % and NMT (b)(4)%
12 hours NLT %

RECOMMENDATION

1. The two bioequivalence studies conducted under fasting and non-fasting conditions by IMPAX Laboratpries, Inc. on its

loratadine/pseudoephedrine sulfate ER tablet, 5/120 mg, lot #R00017, comparing it to Schering's Claritin-D® ER tablet, 5/120 mg, lot #9-JRP-2021, has been found to be acceptable by the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, IMPAX's loratadine/pseudoephedrine sulfate ER tablet, 5/120 mg are bioequivalent to Schering's Claritin-D® ER tablet, 5/120 mg.

2. The dissolution testing conducted by IMPAX Pharmaceuticals, Inc., on its loratadine/pseudoephedrine sulfate ER tablet, 5/120 mg, lot #R00017, is acceptable. The dissolution testing should be conducted in 900 mL of 0.1N HCl for one hour, then replace medium with 900 mL 0.05M phosphate buffer at pH 8.2 containing 0.01% sodium lauryl sulfate (SLS) at 37°C using USP 24 apparatus II (paddle) at 50 rpm. Based on the submitted data the following tentative specifications are suggested for loratadine and pseudoephedrine:

For Loratadine
NLT (b)(4)% (Q) dissolved in 60 minutes

For Pseudoephedrine
1 hour NMT (b) (4)
4 hours NLT (b) (4)
12 hours NLT (b)(4)%

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

BWD 5/17/01
5/18/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara M Davit 5/24/01

Concur: _____ Date: 5/24/2001
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-050 APPLICANT: IMPAX Phamaceuticals, Inc.

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 5 mg/120 mg.

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

We acknowledge that the following dissolution testing method will be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl for one hour, then replace medium with 900 mL 0.05M phosphate buffer at pH 8.2 containing 0.01% sodium lauryl sulfate (SLS) at 37°C using USP 24 apparatus II (paddle) at 50 rpm. Based on the submitted data, the following tentative specifications are suggested for loratadine and pseudoephedrine:

For Loratadine
NLT (b) (4) (Q) dissolved in 60 minutes

For Pseudoephedrine
1 hour NMT (b) (4)
4 hours (b) (4)
12 hours NLT (b) (4) %

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

CC: ANDA #76-050
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Z. Wahba
HFD-655/ Bio Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 5/17/01
HFD-658/ B. Davit BD 5/17/01,
HFD-650/ D. Conner for Dave 5/24/2001

V:\firmsamnz\IMPAX\ltrs&rev\76050sd.d00

BIOEQUIVALENCY - ACCEPTABLE Submission date 12/12/00

Ok 1. FASTING STUDY (STF) Strengths: 5 mg/120 mg
Clinical: Gateway Medical Research, Inc. Outcome: AC
Analytical: (b) (4)

Ok 2. NON-FASTING STUDY (STP) Strengths: 5 mg/120 mg
Clinical: Gateway Medical Research, Inc. Outcome: AC
Analytical: (b) (4)

Ok 3. STUDY AMENDMENT (STA), 4/26/01 Strengths: 5 mg/120 mg
Outcome: AC

OUTCOME DECISIONS: AC - Acceptable

WINBIO COMMENTS: Acceptable

FIG P—1. PLASMA LORATADINE LEVELS

LORATADINE & PSEUDOEPHEDRINE SULFATE EXTENDED RELEASED TABLETS, 5 MG/120 MG, ANDA #76-050
UNDER FASTING CONDITIONS
DOSE=1 X 5 MG/120 MG

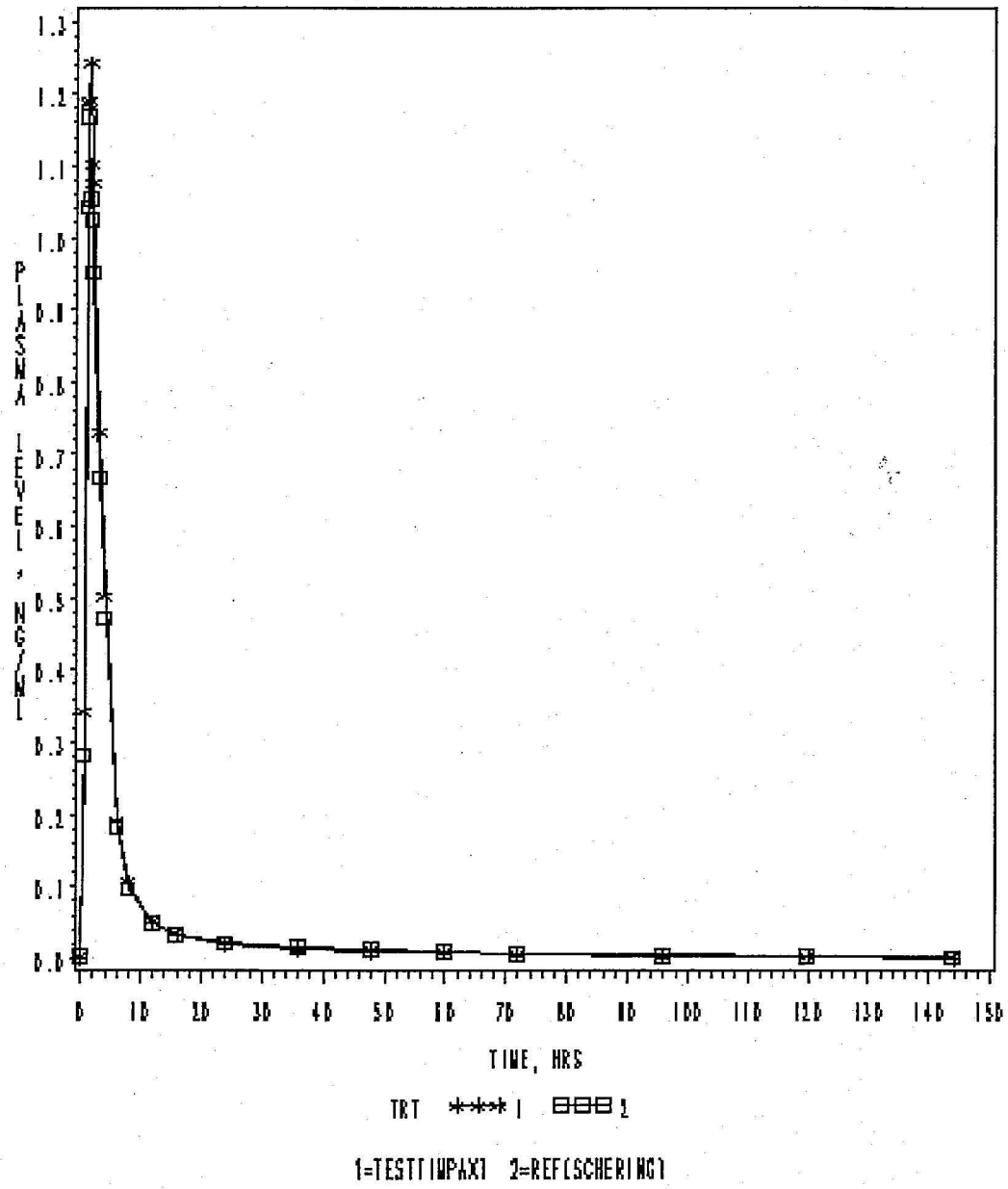


FIG P—2 . PLASMA PSEUDOEPHEDRINE LEVELS

LORATADINE & PSEUDOEPHEDRINE SULFATE EXTENDED RELEASED TABLETS, 5 MG/120 MG, ANDA #76-050
UNDER FASTING CONDITIONS
DOSE=1 X 5 MG/120 MG

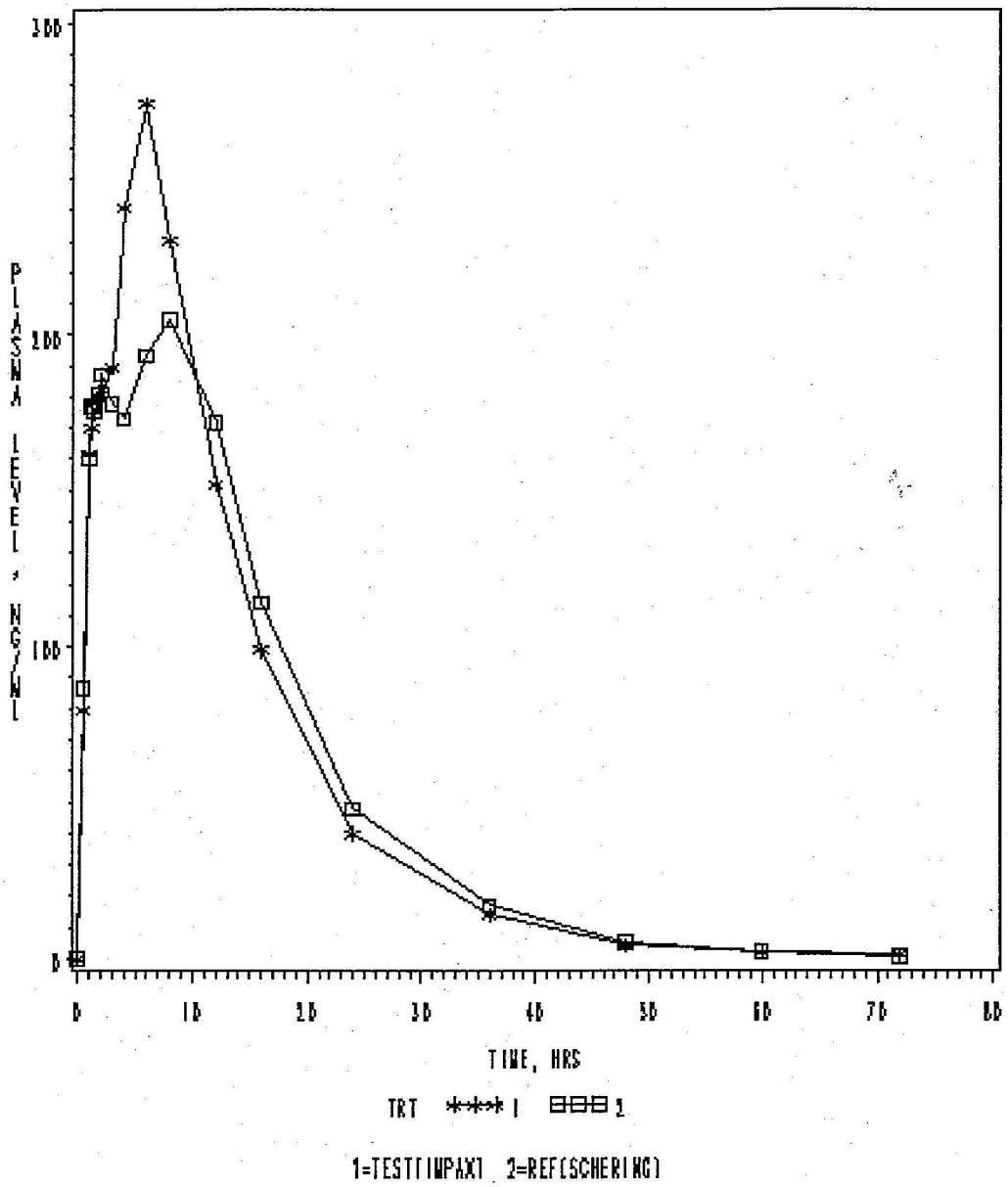


FIG P—3 . PLASMA LORATADINE LEVELS

LORATADINE & PSEUDOEPHEDRINE SULFATE EXTENDED RELEASE TABLETS, 5 MG/120 MG, ANDA #76-050
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 5 MG/120 MG

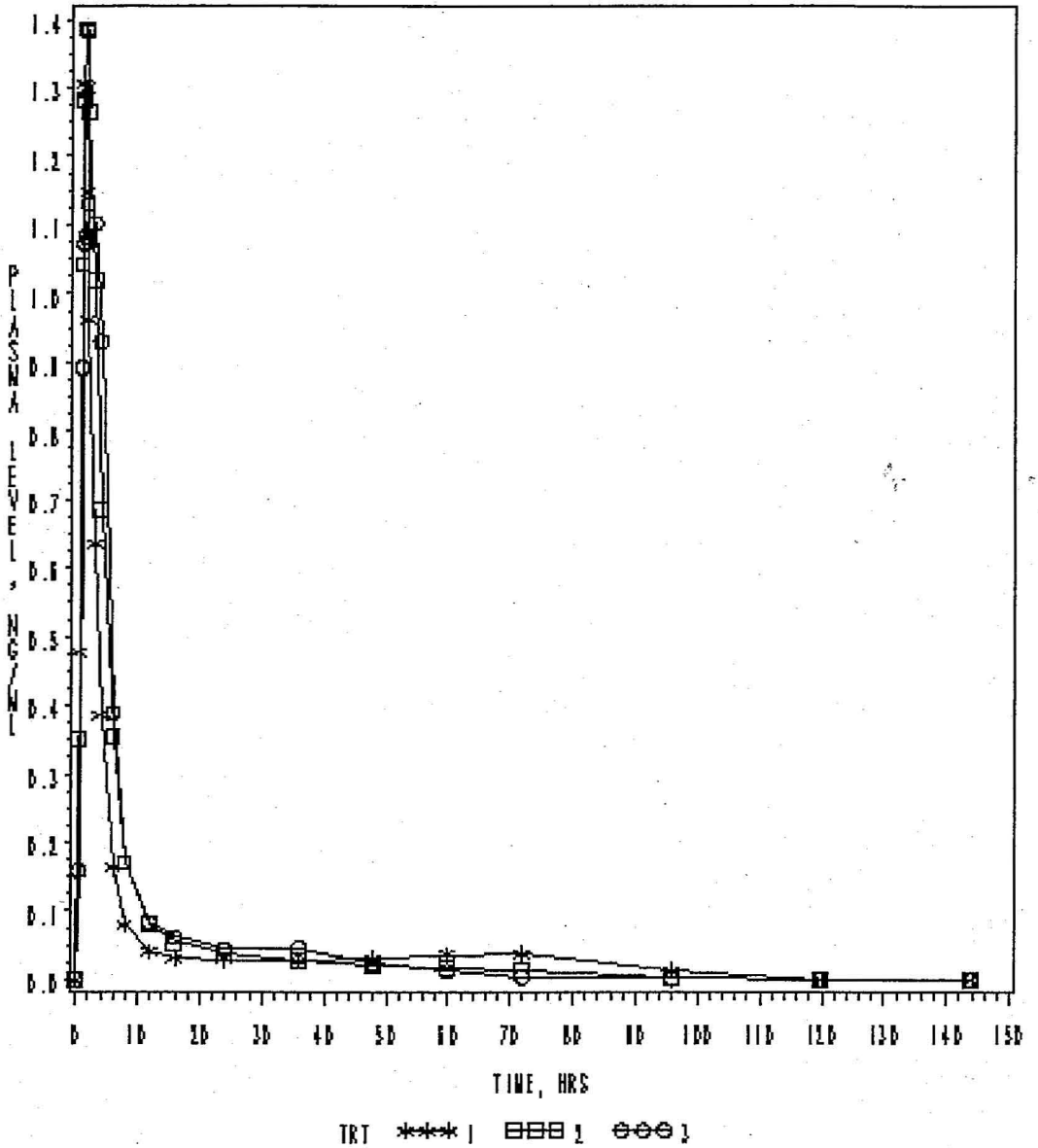


FIG P—4 . PLASMA PSEUDOEPHEDRINE LEVELS

LORATADINE & PSEUDOEPHEDRINE SULFATE EXTENDED RELEASE TABLETS, 5 MG/120 MG, ANDA #75-050
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 5 MG/120 MG

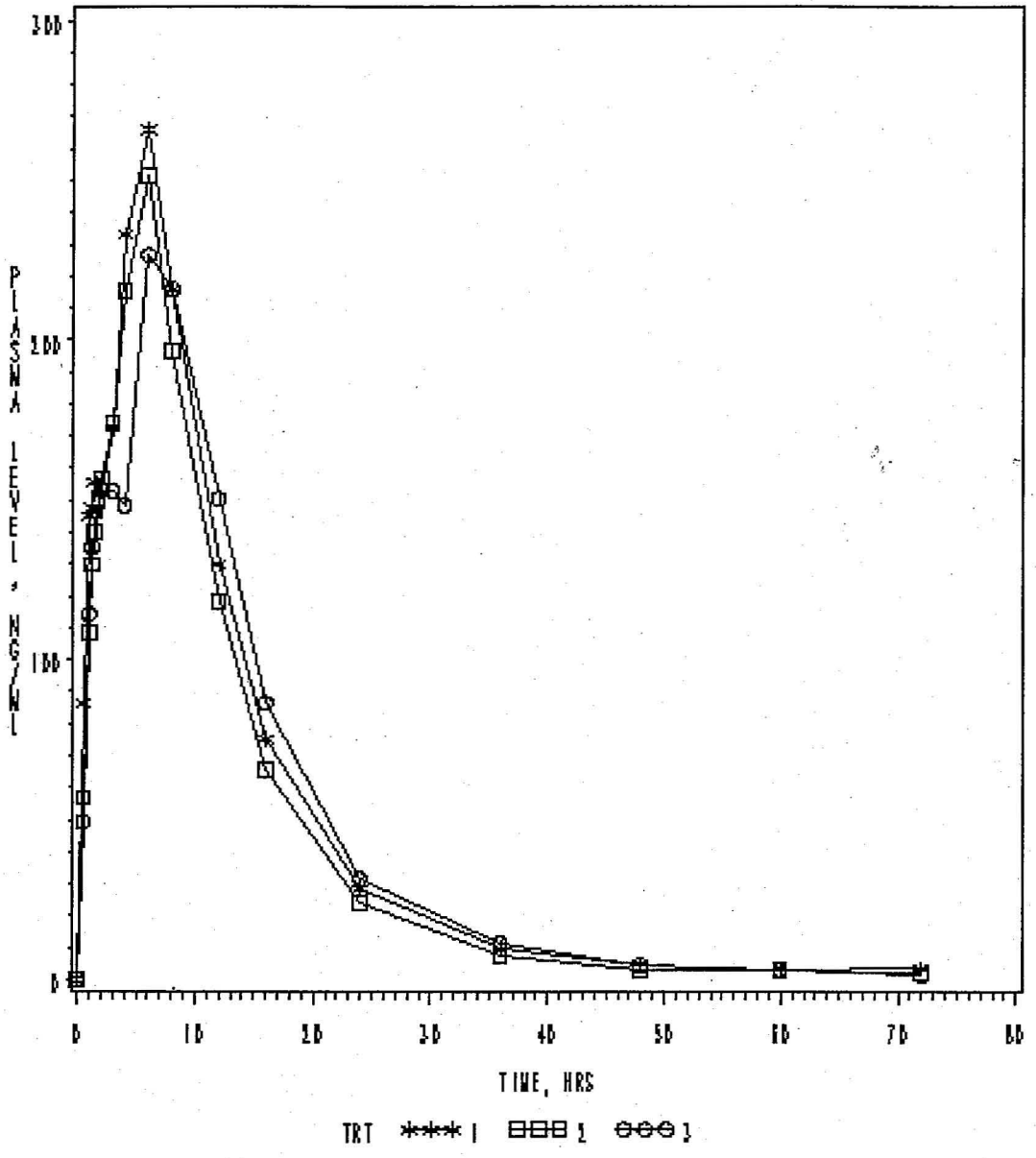


Table #1

ANDA 76-050, Loratadine & Pseudoephedrine Sulfate E R Tablets 5 mg/120 mg

Dissolution Comparison - Profile using the similarity factor F2

(b) (4)

file: 76050tr1.xls

Table #2

ANDA 76-050, Loratadine & Pseudoephedrine Sulfate E R Tablets 5 mg/20 mg

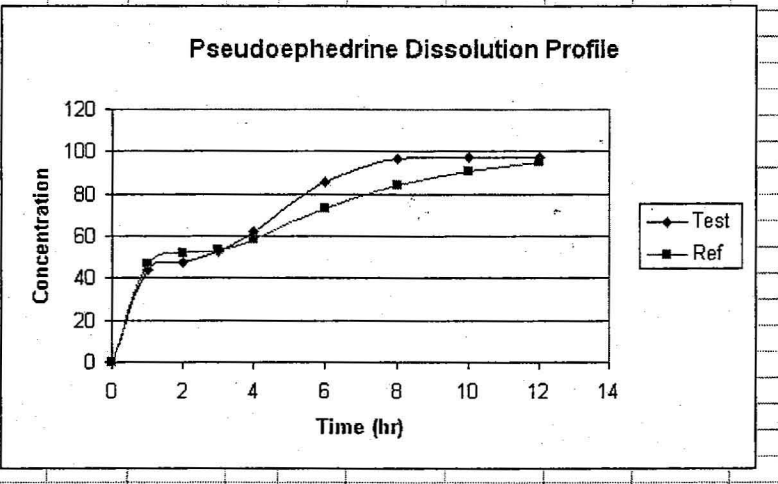
Dissolution Comparison - Profile using the similarity factor F2

Data on Pseudoephedrine

Test -1 - Lot IMPAX R00017 (using Appratus 2 (Paddle), 50 rpm)

Ref - Lot 9-JRP-2021

time (hr)	Test	Ref	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
1	44.2	46.6	-2.4	5.76	32.25	6.45	7.45	0.366372	36.63717	1.56392	78.19609
2	47.8	51.6	-3.8	14.44							
3	53	53.7	-0.7	0.49	**F2=78.2**						
4	62.2	58.8	3.4	11.56							
6	85.6	73									
8	96.6	84.5									
10	97.3	90.8									
12	97.4	95.1									



dissolution comparison

time (hr)	Test	Ref
0	0	0
1	44.2	46.6
2	47.8	51.6
3	53	53.7
4	62.2	58.8
6	85.6	73
8	96.6	84.5
10	97.3	90.8
12	97.4	95.1

file:76050tr2.xls

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-050 SPONSOR : IMPAX Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Tablets Loratadine & Pseudoephedrine Sulfate Extended Release Tabs 5/mg/120mg
STRENGTH(S) : 5 mg/120 mg
TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.
CLINICAL STUDY SITE(S) : Gateway Medical Center
ANALYTICAL SITE(S) : (b) (4)

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, IMPAX's Loratadine and Pseudoephedrine Sulfate ER tablets, 5 mg/120 mg, are bioequivalent to Schering's Claritin-D® ER tablets, 5 mg/120 mg.

DISSOLUTION : The dissolution data are acceptable.

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic ___ New facility _ No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 5/17/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 5/18/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : [signature] DATE : 5/24/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076050

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 12, 2000

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Loratadine and Pseudoephedrine Sulfate
Extended Release Tablets, 5 mg/120mg

Dear Mr. Buehler:

In accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act, IMPAX Laboratories, Inc hereby submits an Abbreviated New Drug Application (ANDA) for loratadine and pseudoephedrine sulfate extended release tablets, 5 mg/120 mg. The reference listed drug, Claritin-D® (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets, is the subject of Schering Corporation's approved NDA 19670. The drug product, which is the subject of this ANDA, differs from the listed product in that the formulation contains different excipients.

This application meets the criteria for an ANDA in that 1) the conditions of use, active ingredient, route of administration, dosage form, and strength are identical to those of the listed drug, 2) bioequivalence has been demonstrated, and 3) patent certification is provided. The labeling complies with all labeling requirements. This application lists IMPAX Laboratories, Inc. as the manufacturing site for the drug product. The submission contains 13 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Also included with this ANDA is an electronic submission of the package insert word processor file, prepared in Microsoft Word. Two (2) write-protected diskettes are included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labels and labeling are included in both the archival and review copies of the application.

Two (2) write-protected diskettes containing the pharmacokinetic data resulting from the bioequivalence studies are also included in the archival copy of this submission, in a plastic insert.

Please note that this ANDA contains two (2) bioequivalence studies in support of the proposed drug product described herein. IMPAX conducted a single-dose fasting study and a single-dose limited food-effect study in healthy, male subjects. Both studies were initiated prior to the publication of FDA's October, 2000 guideline, presenting general considerations for the conduct of such studies.[1] The single-dose fasting study used a two-way, non-replicate crossover design. The limited food-effect study used a three-way, crossover design.

IMPAX discussed the bioequivalence study design criteria with Dr. Lizzie Sanchez on November 28, and with Dr. Shriniwas Nerurkar on November 29, to confirm that the former study designs would be acceptable for this ANDA since these studies were initiated prior to finalization of the October 2000 guideline. We also discussed omission of the formerly recommended multiple-dose study. Based on these discussions, it is IMPAX's understanding that the two bioequivalence studies submitted in support of this ANDA will be acceptable and that the multiple-dose study is no longer generally recommended and thus will not be necessary in support of this ANDA.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

[1] Guidance for Industry: Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations (October 2000, Posted 10/27/00)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : December 21, 2000

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

21-DEC-2000

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg, to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Impax Pharmaceuticals Inc. has submitted ANDA 76-050 for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg. The ANDA contains a certification pursuant to 21 USC 355 (j) (2) (A) (vii) (iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Impax on December 21, 2000 for its Loratadine and Pseudoephedrine Sulfate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

ANDA 76-050

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements JMB 12/22/00 GDPS 12/28/00

_____ Study does **NOT** meet statutory requirements

Reason/Comments:

(1) Fasting study is a two-way cross-over design and not a replicate design as recommended in BA/BE guidance.
(2) Food-study is a three-period, three treatment, six-sequence study.
(3) No Multiple-dose study ~~is~~ as recommended in BA/BE guidance.

Director, Division of Bioequivalence

1/4/01
Date

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

NEW CORRESP MC

January 11, 2001

GENERAL CORRESPONDENCE

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Saundra Middleton (Regulatory Support Branch)

Re: ANDA 76-050
(Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets)

Dear Mr. Buehler:

This correspondence follows a January 11, 2001 telephone conversation with Ms. Saundra Middleton of your office concerning the above-referenced ANDA.

Ms. Middleton requested that IMPAX Laboratories, Inc. (IMPAX) submit a DMF Authorization Letter for DMF (b) (4) (pseudoephedrine sulfate, (b) (4). The letter provided on page 3867 of the original submission was not an authorization letter.

Accompanying this letter is an authorization from (b) (4) permitting FDA to reference DMF (b) (4) on behalf of this submission. This letter replaces the letter appearing on page 3867.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

NDA S. Middleton 1/24/01

NEW CORRESP

pc

January 18, 2001

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Saundra Middleton (Regulatory Support Branch)

Re: ANDA 76-050
(Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets)

Dear Mr. Buehler:

Please find attached General Correspondence from Mark Shaw that is dated and was sent UPS 2nd-Day Air delivery on January 11, 2001. We apologize for the condition of this communication; it was returned by UPS today with a notice that it had been damaged enroute. Mark Shaw is out of town until January 26 and was unable to provide a clean copy.

Sincerely,
IMPAX Laboratories, Inc.

Kaye Donnelly
Sr. Regulatory Affairs Associate

Enclosure

ANDA 76-050

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

JAN 16 2001

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 also made to the telephone conversation dated January 11, 2001 and your correspondence dated January 11, 2001.

NAME OF DRUG: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg

DATE OF APPLICATION: December 12, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 13, 2000

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 court order or judgement 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 Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

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:

Ruby Yu
Project Manager
(301) 827-5849

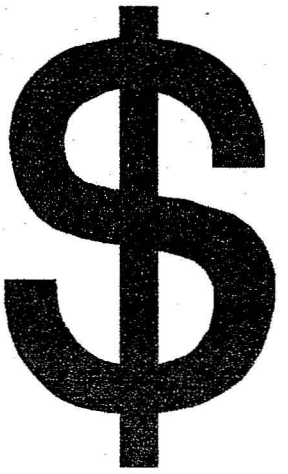
Sincerely yours,

Gregory S. Davis for

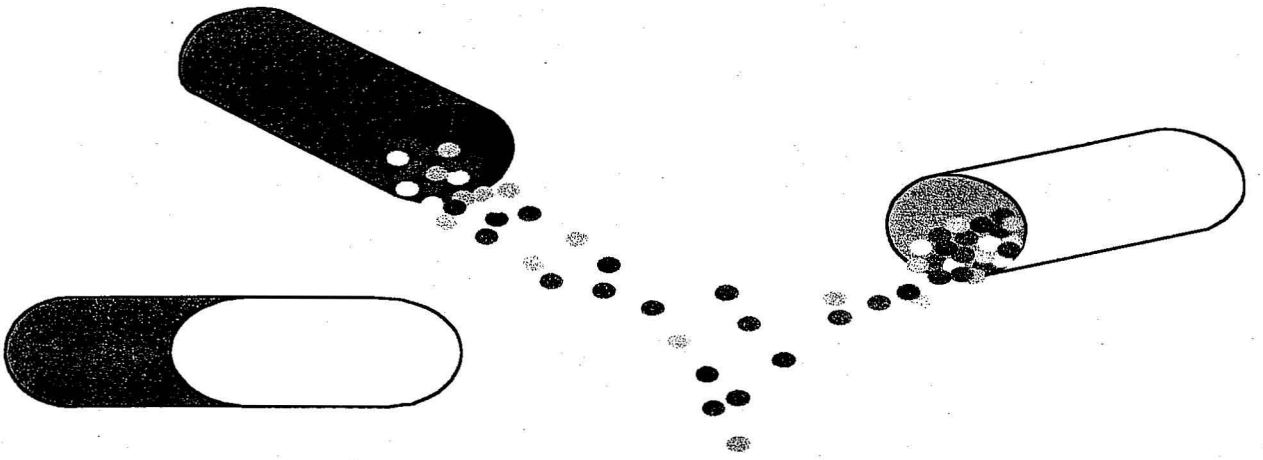
Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-050
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB 18-JAN-2001 date
HFD-615/SMiddleton, CSO date 1/17/01
Word File
V:\FIRMSAM\IMPAX\LTRS&REV\76050.ACK
FT/ EEH 01/17/2001
ANDA Acknowledgment Letter!



FIRST GENERIC



IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

February 9, 2001

PATENT AMENDMENT
NEW CORRESP
NC

2/23/01
NTS

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)
Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

Reference is made to the Office of Generic Drug's January 18, 2001 letter documenting the acceptance for filing of the above-referenced ANDA. The letter requested that IMPAX notify your office in the event that litigation occurred within the 45-day period following notification of the NDA Holder and Patent Owner.

IMPAX hereby confirms that Schering Corporation initiated a lawsuit within the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act. Accordingly, IMPAX is enclosing with this correspondence a copy of the complaint, filed February 1, 2001 in the United States District Court for the District of New Jersey.

If you have any questions regarding this amendment please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON, DC
NEW YORK
LONDON
BRUSSELS
SAN FRANCISCO

MICHAEL S. LABSON
TEL 202.662.5220
FAX 202.778.5220
MLABSON@COV.COM

February 21, 2001

BY HAND DELIVERY

Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP

Re: ANDA No. 76-050
Notice of Filing of Legal Action for Patent Infringement

Ladies and Gentlemen:

Pursuant to 21 C.F.R. § 314.107(f)(2), Schering Corporation ("Schering") hereby notifies FDA that it has filed a legal action for patent infringement within 45 days of receiving notice of a Paragraph IV Certification in connection with the above-referenced abbreviated new drug application ("ANDA"). Schering states as follows:

(i) The ANDA number is 76-050;

(ii) The name of the ANDA applicant is Impax Laboratories, Inc.;

(iii) The established name of the drug is loratadine and pseudoephedrine sulfate extended-release tablets, the strength is 5 mg of loratadine and 120 mg of pseudoephedrine sulfate, and the dosage form is extended-release tablets; and

(iv) Schering hereby certifies that an action for patent infringement, Civil Action No. 01-0520 (JAG), was filed in an appropriate court (the United States District Court for the District of New Jersey) on February 1, 2001. Copies of the Summons and Complaint in that action are enclosed.

Schering received notice of a Paragraph IV Certification alleging the noninfringement, invalidity and/or unenforceability of United States Patent Nos. 4,659,716 and 4,863,931 on January 25, 2001. Schering is the owner of these patents. Schering brought the

above-described action for patent infringement within 45 days of the receipt of notice of the Paragraph IV Certification.

Accordingly, pursuant to Section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, ANDA No. 76-050 cannot be approved until the expiration of the thirty-month period beginning on January 25, 2001 and ending on July 25, 2003, or until such time as ordered by the Court.

Thank you for your attention to this matter.

Sincerely yours,

Michael S. Labson

Counsel for Schering Corporation

Enclosures

United States District Court

DISTRICT OF NEW JERSEY

SCHERING CORPORATION,

Plaintiff,

V.

IMPAX LABORATORIES, INC.,

Defendant.

SUMMONS IN A CIVIL CASE

CASE NUMBER: 01 CV 520 (JAG)

TO: (Name and address of defendant)

IMPAX LABORATORIES, INC.
c/o Registered Agent
CSC CORPORATION SERVICE COMPANY
2711 Centerville Road, Suite 400
Wilmington, Delaware 19808

YOU ARE HEREBY SUMMONED and required to serve upon PLAINTIFF'S ATTORNEY (name and address)

Thomas R. Curtin, Esq.
GRAHAM, CURTIN & SHERIDAN
Four Headquarters Plaza
P.O. Box 1991
Morristown, New Jersey 07962
(973) 292-1700

an answer to the complaint which is herewith served upon you, within twenty (20) days after service of this summons upon you, exclusive of the day of service. If you fail to do so, judgment by default will be taken against you for the relief demanded in the complaint. You must also file your answer with the Clerk of this Court within a reasonable period of time after service.

WILLIAM T. WALSH
CLERK

FEB 0 2 2001
DATE

(BY) DEPUTY CLERK

RETURN OF SERVICE

Service of the Summons and Complaint was made by me DATE: February 07, 2001 at 1:00 p.m.

NAME OF SERVER (PRINT) TITLE:

KEVIN DUNN Private Process Server

Check one box below to indicate appropriate method of service

Served personally upon the defendant. Place where served:

Left copies thereof at the defendant's dwelling house or usual place of abode with a person of suitable age and discretion then residing therein.
Name of the person with whom the summons and complaint were left:

Returned unexecuted:

✓ Other (specify): served IMPAX LABORATORIES, INC., by serving its registered agent, CSC Corporation Service Company, at 2711 Centerville Road, #400, Wilmington, DE 19808: copies were received by Mary Flowers, Process Agent, who was authorized to receive service thereof

STATEMENT OF SERVICE FEES

TRAVEL	SERVICES	TOTAL
-0-	$ 35.00	$ 35.00

DECLARATION OF SERVER

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Return of Service and Statement of Service Fees is true and correct.

Executed on 02/07/01
Date:

Signature of Server
BRANDYWINE PROCESS SERVERS, LTD.
PO BOX 1360 – WILMINGTON, DE 19899-1360
302 – 475 - 2600

Address of Server

Thomas R. Curtin (TC-9745)
George C. Jones (GJ-8973)
Janyce M. Wilson (JW-2995)
GRAHAM, CURTIN & SHERIDAN
A Professional Association
Four Headquarters Plaza
Morristown, New Jersey 07962
(973) 292-1700

ATTORNEYS FOR PLAINTIFF
SCHERING CORPORATION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SCHERING CORPORATION,	:	
Plaintiff,	:	Civil Action
v.	:	No. _____
IMPAX LABORATORIES, INC.,	:	
Defendant.	:	

COMPLAINT

Plaintiff Schering Corporation, for its Complaint against Defendant Impax Laboratories, Inc., hereby alleges as follows:

The Parties

1. Plaintiff Schering Corporation ("Schering") is a New Jersey corporation having a principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033. Upon

information and belief, Defendant Impax Laboratories, Inc. ("Impax") is a Delaware corporation having a place of business at 30831 Huntwood Avenue, Hayward, California 94544.

Nature of the Action

2. This is a civil action for the willful infringement of United States Patent No. 4,659,716 ("the '716 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100 et seq.

Jurisdiction and Venue

3. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

4. This Court has personal jurisdiction over Impax by virtue of, inter alia: (1) its systematic and continuous contacts with New Jersey; and (2) its performance of a tortious act that has caused foreseeable harm within New Jersey.

5. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1400(b).

The Patents

6. On April 21, 1987, the '716 patent, entitled "Antihistaminic 8-(Halo)-Substituted 6,11-Dihydro-11-(4-Piperidylidene)-5H-Benzo[5,6]Cyclohepta[1,2-b]Pyridines," was

duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '716 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '716 patent is attached hereto as Exhibit A.

7. On September 5, 1989, United States Patent No. 4,863,931 ("the '931 patent"), entitled "Antihistaminic Fluoro Substituted Benzocycloheptapyridines" was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '931 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '931 patent is attached hereto as Exhibit B. Impax has represented that it will not infringe the '931 patent. If this representation proves to be incorrect, it may be necessary to expand the above-captioned civil action to include a claim for willful infringement of the '931 patent.

Acts Giving Rise to this Action

8. Upon information and belief, on or before January 23, 2001, Impax submitted Abbreviated New Drug Application ("ANDA") 76-050 to the United States Food and Drug Administration ("the FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). Impax's ANDA seeks the FDA approval necessary for Impax to engage in the commercial manufacture, use,

offer for sale and sale of generic tablets containing 5 milligrams of loratadine and 120 milligrams of pseudoephedrine sulfate per tablet in a 12-hour extended-release formulation ("the Generic Product"). Impax's ANDA specifically seeks FDA approval to market the Generic Product prior to the expiration of the '716 patent.

9. Within its ANDA, Impax alleged under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '716 patent are either invalid, unenforceable or not infringed by the manufacture, use or sale of the Generic Product. Schering received written notification of Impax's ANDA and § 505(j)(2)(A)(vii)(IV) allegation on January 25, 2001.

10. Impax's submission of said ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '716 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Impax commercially uses, offers for sale or sells the Generic Product, or induces or contributes to such conduct, it would further willfully infringe the '716 patent under 35 U.S.C. § 271(a), (b) and/or (c).

11. Impax had actual and constructive notice of the '716 patent prior to filing ANDA 76-050. Accordingly, Impax's infringement of the '716 patent has been, and continues to be, willful.

12. Schering will be irreparably harmed by these infringing activities unless they are enjoined by this Court. Schering does not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Schering prays for judgment as follows:

A. That Impax has willfully infringed the '716 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA 76-050 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration date of the '716 patent, including any extensions;

C. That Impax, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially using, offering for sale or selling the Generic Product, and any other product that infringes or induces or contributes to the infringement of the '716 patent, prior to the expiration of the '716 patent, including any extensions;

D. That Schering be awarded monetary relief if Impax commercially uses, offers for sale or sells the Generic Product, or any other product that infringes or induces or contributes to the infringement of the '716 patent, within the United States

prior to the expiration of the '716 patent, including any extensions, and that any such monetary relief be trebled and awarded to Schering with prejudgment interest;

E. That Schering be awarded the attorney fees, costs and expenses that it incurs prosecuting this action; and

F. That Schering be awarded such other and further relief as this Court deems just and proper.

Dated: February 1, 2001

Respectfully submitted,

Thomas R. Curtin (TC-9745)
George C. Jones (GJ-8973)
Janyce M. Wilson (JW-2995)
GRAHAM, CURTIN & SHERIDAN
A Professional Association
Four Headquarters Plaza
P.O. Box 1991
Morristown, New Jersey 07962
(973) 292-1700

Robert G. Krupka, P.C.
KIRKLAND & ELLIS
777 South Figueroa Street
Los Angeles, California 90017
(213) 680-8400

John M. Desmarais
Sandra A. Bresnick
Peter J. Armenio
Maxine Y. Graham
Monica V. Bhattacharyya
KIRKLAND & ELLIS
Citigroup Center
153 East 53rd Street
New York, New York 10022
(212) 446-4800

ATTORNEYS FOR PLAINTIFF
SCHERING CORPORATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76050/000**
Stamp: **13-DEC-2000** Regulatory Due:
Applicant: **IMPAX LABS**
30831 HUNTWOOD AVE
HAYWARD, CA 94544

Priority:
Action Goal:
Brand Name:
Established Name: **LORATADINE; PSEUDOEPHEDRINE SULFATE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **5 MG/120 MG**

Org Code: **600**
District Goal: **13-NOV-2001**

FDA Contacts: **R. YU** **, Project Manager**
D. GILL **(HFD-623)** **301-827-5848** **, Team Leader**

Overall Recommendation:

ACCEPTABLE on 21-FEB-2001 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: (b) (4) DMF No: (b) (4)
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **9690049**
GLOBAL PHARM INC
865 YORK MILLS ROAD
TORONTO, ONTARIO, CA

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment: **2954383**
IMPAX PHARMACEUTICALS INC
30831 HUNTWOOD AVENUE
HAYWARD, CA 94544

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-FEB-2001**
Decision: **ACCEPTABLE**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

Establishment: (b) (4) DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment: (b) (4) DMF No: (b) (4)
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

April 26, 2001

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT:
DIVISION OF BIOEQUIVALENCE

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This correspondence follows an April 10, 2001 telephone conversation with Steven Mazzella and Zakaria Wahba of the Division of Bioequivalence. Mr. Wahba requested additional documentation and clarification regarding the above-referenced ANDA.

Accompanying this letter, and provided in attachments as necessary, are the additional data and information requested by Mr. Wahba. This correspondence has been designated as a Telephone Amendment to the Division of Bioequivalence, as recommended by Mr. Mazzella.

If you have questions or require additional information, please contact me be telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Angela Orlando for

Mark C. Shaw
Director, Regulatory Affairs and Compliance

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 30 2001
OGD

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 13, 2001

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX AMENDMENT

ORIG AMENDMENT
NIFA

Attn: Ruby Yu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This letter responds to your June 13, 2001, Fax Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry and Bioequivalence comments, IMPAX also acknowledges the following:

1. IMPAX notes that the labeling portion of the application is under review, and that any deficiencies will be conveyed under separate cover.

2. IMPAX acknowledges that method validation will be performed on the drug product by the FDA field laboratory.

3. We note that the DMFs referenced in ANDA 76-050 must be satisfactory at the time of approval of our ANDA, and that some of the DMF holders may require an inspection by the Division of Manufacturing and Product Quality.

4. IMPAX commits to updating specifications for all inactive compendial ingredients to meet current requirements established in the USP/NF.

5. This submission also includes updated long-term stability data for biobatch lot R00017, provided in **Attachment 8**.

6. IMPAX notes that a satisfactory compliance evaluation of the firms referenced in the ANDA is required for approval.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 9**.

Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

July 17, 2001

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX AMENDMENT - ADDENDUM

ORIG AMENDMENT
N/FA

Attn: Ruby Yu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

Reference is made to IMPAX's July 13, 2001 FAX Amendment to the above-referenced ANDA.

The July 13, 2001 amendment included revised test method TLORRS.03, included as Attachment 6, beginning on page 42. During preparation of a related submission that included this same test method as an attachment, IMPAX noticed that the method contained a typographical error on page 5 of 6 (page 46 of the July 13 amendment). Figure 1 is incorrect in that the figure labels for "Placebo+Pseudoephedrine sulfate" and "Sample" were inadvertently reversed. IMPAX has corrected this error and revised the method to version TLORRS.04. A copy is provided in **Attachment 1**.

IMPAX apologizes for any confusion this may cause. Because this submissions includes a revised test method, IMPAX is also submitting a Field Copy of this correspondence to the San Francisco District Office. A Field Copy certification is included herein as **Attachment 2**. Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 20 2001
OGD

cc: Marshalette Edwards, SFDO

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

August 13, 2001

AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

Attn: Ruby Yu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

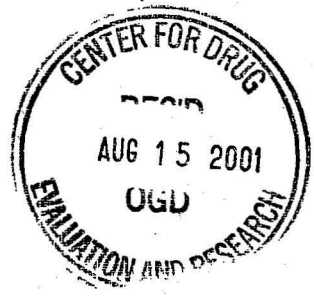
Dear Mr. Buehler:

Reference is made to IMPAX's July 13, 2001 FAX Amendment to the above-referenced ANDA.

The July 13, 2001 amendment included a revised loratadine drug substance specification, included as Attachment 3, beginning on page 18. During preparation of a related submission that included this same specification as an attachment, IMPAX subsequently decided to tighten the total impurities specification, from ≤ (b) (4)% to ≤ (b) (4)%. A copy of the revised specification is provided in **Attachment 1**.

In addition to the specification listed above, IMPAX is also submitting a current version of the loratadine drug substance test method, 067-4. The chemical names of the known impurities have been added to Section 3 of analytical method 067. In addition, the method has been revised to use the relative retention time and relative response factor of each named impurity to calculate the impurity amounts, rather than using external standards. By using authentic standards of impurities (b) (4), IMPAX was able to determine the relative response factor and relative retention time of each impurity in comparison to the parent compound, loratadine. This method revision simplifies the analytical testing in that the revised method no longer requires the preparation of individual impurity standards. The impurity standards are often difficult to acquire and are supplied in very small quantities. The revised method and associated validation report are provided in **Attachment 2**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 3**.

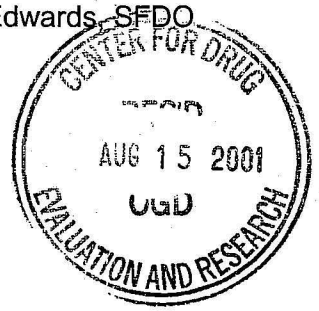


Should you have any additional questions regarding this amendment, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO



IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

October 8, 2001

MINOR AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AM
ORIG AMENDMENT

Attn: Ruby Yu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This letter responds to your August 27, 2001, Fax Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter. Please note that this amendment has been redesignated a "Minor Amendment", as required by current OGD policies.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry comments, IMPAX also acknowledges the following:

1. IMPAX notes that the labeling portion of the application has been reviewed, and the FDA received our Labeling Amendment on August 23, 2001.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 6**.

Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 10 2001
OGD

cc: Marshalette Edwards, SFDO

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

N/AF
ORIG AMENDMENT

November 15, 2001

LABELING AMENDMENT
(Replacement Copy)

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 76-050: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 5 mg/120 mg

Attn: Ruby Wu

Dear Mr. Buehler:

Accompanying this letter is a replacement copy of IMPAX's August 17, 2001 Labeling Amendment to the above-referenced ANDA. This replacement copy is being provided following a November 15, 2001 telephone conversation and request from Ms. Ruby Wu of your office.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 19 2001
OGD

Wiseman, Rosemarie*

From: Wu, Ruby
Sent: Tuesday, December 04, 2001 1:21 PM
To: Wiseman, Rosemarie*
Cc: Green, Wayne*; Washington, Edward*; Beers Block, Patricia M; Atwal, Upinder S; Gill, Devinder S
Subject: 76-050

Hi Rose,

The firm submitted an amendment on November 28, 2001 that includes updated drug substance specification, updated method, and updated MV report. Please make this a gratuitous amendment. The amendment will be reviewed when the firm respond to our November 29, 2001 Deficiency Letter.

Thank you!

Ruby

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

November 28, 2001

AMENDMENT

ORIG AMENDMENT
N/A

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Ruby Wu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This amendment includes an updated loratadine drug substance specification, updated loratadine drug substance method, and updated method validation report. During preparation of a related submission that included this same specification as an attachment, IMPAX tightened the limits for known impurities [redacted] (b) (4) from [redacted] (b) (4) % to ≤ [redacted] (b) (4) %. The limit for total impurities remains set at ≤ [redacted] (b) (4) %. The revised specification is provided in **Attachment 1.** Included in **Attachment 2** is an updated analytical method and validation report, revised to include linearity and recovery data generated to incorporate the new lower specifications.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 3**.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 30 2001
DGD

cc: Marshalette Edwards, SFDO

RECORD OF TELEPHONE CONVERSATION

Reference is made to the fax dated December 11, 2001. The firm requested a t-con to discuss their Loratadine applications.

OGD Response:

The use of the validated titration method for Assay of loratadine is acceptable. The firm will submit the validation report to all ANDAs, if they have not done so already.

Please tighten the limit of the loratadine assay specification to (b) (4) to (b) (4)%.

For all 3 ANDAs, a limit of ≤ (b) (4) for total impurities for the drug substance and drug product release and stability is acceptable.

The proposed specs for the individual impurities mentioned on the fax are also acceptable.

The firm will provide revised specifications.

The firm will also determine the status of the labeling amendment for ANDA 76-011.

DATE
December 17, 2001

ANDA NUMBER
75-989
76-050
76-011

IND NUMBER

TELECON

INITIATED BY: Firm

PRODUCT NAME
Loratadine Applications

FIRM NAME
Impax

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mark Shaw & Michelle Anderson

TELEPHONE NUMBER
510-429-5883

SIGNATURE
John Franolic, Acting TL JF 12/18/01
Upinder Atwal UA 12/18/01
Neeru Takiar NT 12/18
Ruby Wu

V:\FIRMSAM\IMPAX\TELECONS\75989.76050.76011.tc.121701.doc

CC: T-Con Binder Log
ANDA 75-989
76-050
76-011

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 27, 2001

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX AMENDMENT

ORIG AMENDMENT
N/FA

Attn: Ruby Wu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This letter responds to your November 29, 2001, Fax Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

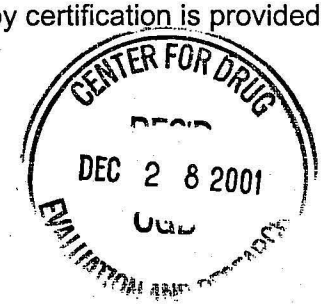
Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry comments, IMPAX also acknowledges the following:

1. Reference is made to a teleconference held on December 17, 2001, between Mark Shaw and Michele Anderson of IMPAX, and Ruby Wu, John Franolic, Upinder Atwal and Neeru Takiar of OGD. The commitments contained in this response reflect the agreements reached during the December 17 telecon.

2. IMPAX notes that analytical methods validation is required, since this drug product is not covered by an official monograph in the USP. Samples for the methods validation were shipped to FDA's Northeast Regional Laboratory on December 3, 2001, following a November 16, 2001 FDA request.

3. IMPAX notes that labeling comments, if any, will follow under separate cover.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 8**.



Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

February 27, 2002

MINOR AMENDMENT
ORIG AMENDMENT
N/AM

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Ruby Wu, Project Manager

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This letter responds to your February 4, 2002, Minor Amendment, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

In addition to responding to the Chemistry comments, IMPAX also acknowledges the following:

1. IMPAX notes that analytical methods validation is required, since this drug product is not covered by an official monograph in the USP. Samples for the methods validation were shipped to FDA's Northeast Regional Laboratory on December 3, 2001, following a November 16, 2001 FDA request.

2. Updated controlled room temperature stability data through 52 weeks are provided in **Attachment 1**.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 2**.

Should you have any questions regarding this response, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Sr. Director, Regulatory Affairs and Compliance

cc: Marshalette Edwards, SFDO

CENTER FOR DRUG EVALUATION AND RESEARCH
MAR 0 1 2002

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Memorandum

DATE: March 18, 2002

FROM: Supervisory Chemist, Drug Chemistry Branch
Northeast Regional Laboratory, HFR-NE560

SUBJECT: ANDA 76-050: Loratadine and Pseudoephedrine SulfateTablets
Impax Labs; Hayward, CA 94544
Sample No. 149054

TO: Upinder S. Atwal, Review Chemist
Office of Generic Drugs, CDER, HFD-623

Through: Diane O'Brien, MV Coordinator
Division of Field Science, HFC-140

The analyses of Loratadine and Pseudoephedrine SulfateTablets and drug substance were performed by the Northeast Regional Laboratory using the firm's method and the samples provided. The following is a summary of the analysis.

Tablets	Results	Specifications
Assay: Loratadine Pseudoephedrine Sulfate	(b) (4)	
Drug Release: Loratadine		
Drug Release: Pseudoephedrine Sulfate		
Identification:		
Chromatographic purity: Psedoephedrine sulfate		
Chromatographic purity: Impurity (b) (4) Unknown (individual) Total impurities		

No major problems were encountered with the firm's method for this product. The method appears to be suitable for regulatory analysis of this product.

Note: Particle size analysis is being done by PHI-DO. The results from this analysis will be sent to the review chemist upon completion.

Ella S. Walker
Supervisory Chemist
Northeast Regional Lab
(718) 340-7008

Sample received: 12/20/01
Sample analysis completed: 03/18/02
Lab Classification: 1

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE **PHILADELPHIA DISTRICT**
FOOD AND DRUG ADMINISTRATION **SCIENCE BRANCH**

MEMORANDUM

DATE: 19 March 2002

FROM: Director, Science Branch
Philadelphia District, HFR-CE160

SUBJECT: ANDA 76-050: Loratadine drug substance
Impax Laboratories, Hayward, CA 94587
RE Sample #: 149054

TO: Upinder Atwal, Review Chemist
CDER, Division of Pulmonary and Allergy Drug Products, HFD-570

The Philadelphia District Laboratory performed the analysis of Loratadine raw material, using the firm's method and samples provided. Attached are the summary of results, worksheets, and comments for the subject ANDA.

The following comments should be considered before approval of the method:

Pertinent sample information is not included in the method, including: the refractive index used for analysis, the RPMs of the small volume dispersion unit used by the firm and the analysis model used in the software.

The method states that the obscuration value desired is between (b)(4)% and (b)(4)% while the instrument manufacturer suggests that the obscuration not be above (b)(4)%.

Based on the analytical results, the ANDA method appears to be suitable for regulatory control of this product. However, the above comments should be considered before final approval.

for Richard E. Nead
W. Charles Becoat

cc: HFR-CE100
HFC-140
HFR-PA150 (San Francisco District Investigations Branch)
Lab B: Harmon, Jr.
File

REN:WCB
ATTACHMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Laboratory Branch
Rm 900 US Customhouse
2nd and Chestnut Sts.
Phila., PA 19106

DATE: March 1, 2002

FROM: Lawrence Harmon, Chemist
Philadelphia District Laboratory

TO: Yvonne Wood, Acting Supervisory Chemist
Philadelphia District Laboratory

SUBJECT: ANDA 76-050
Sample 149054

Applicant: Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, California 94544

Analysis: Particle size analysis was performed on this sample and found to be within the specifications.

REMARKS: Particle size analysis requires the use of refractive index of the material being analyzed. That information was not provided. From the data submitted, I was able to derive that the (b)(4) values for the refractive index were used, and not the real refractive index values. Not enough information was given in the method to perform the analysis. For example I did not know which analysis model to use or RPM's of the small volume dispersion unit. Changes in one or both of those values could change the particle size result. The method states that the obscuration should be between (b)(4)% and (b)(4)%, but the instrument manufacturer suggest that the obscuration should never be above (b)(4)%.

Lawrence Harmon Jr

Lawrence Harmon, Jr. Chemist

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

April 17, 2002

GENERAL CORRESPONDENCE

NEW CORRESP
NC

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Donald B. Hare, Special Assistant

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This letter follows my April 15, 2002 telephone conversation with Mr. Donald Hare of your office regarding a potential Rx to OTC switch in the marketing status of the above-referenced drug product.

By way of background, IMPAX Laboratories, Inc. (IMPAX) submitted ANDA 76-050 in correspondence dated December 12, 2000. The Office of Generic Drugs deemed the ANDA acceptable for filing on December 13, 2000. Based upon publicly available information, IMPAX believes that it was the first applicant to file a substantially complete ANDA containing a Paragraph IV Patent Certification and seeking approval of a generic equivalent to the Reference Listed Drug, Claritin-D® 12-Hour. As such, IMPAX would be entitled to six months of marketing exclusivity following approval of its ANDA.

As you know, the FDA has received several marketing applications seeking approval of various loratadine-containing drug products, including the 12-hour extended-release drug product containing loratadine and pseudoephedrine sulfate (i.e., Claritin-D® 12-Hour). In light of the potential switch in marketing status from Rx to OTC, IMPAX requests confirmation that it will retain six-month marketing exclusivity, awarded for what it believes to be its first-to-file status, should the marketing status of the Claritin®-D 12-Hour product change from Rx to OTC. While we understand this decision may require a filing from the Office of the Chief Counsel, we would appreciate a response on this issue as soon as possible, along with an explanation as to why exclusivity would not be granted, if that is the decision.

IMPAX further requests any guidance your office can provide at this time as to steps it must take should such a switch in marketing status occur. Mr. Hare indicated that, at a minimum, IMPAX must amend its application to change the requested marketing status from Rx to OTC. Please confirm that this should be done, and, if so, when such an amendment should be filed and what information it should contain.

RECEIVED

APR 19 2002

OGD / CDER

Should you have any questions regarding this correspondence, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

cc: Ruby Wu, Project Manager (via FAX)

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-050 Applicant Impax Laboratories Inc

Drug Loratadine and Pseudoephedrine sulfate ER Tablets Strength 5mg / 120mg

APPROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: DRAFT RECEIPT FINAL ACTION

1. Project Manager Ruby Wu Team 4 — Date 4/22/02 — Date 4/23/02
   Review Support Br — Initials RWu — Initials RWu

   Application Summary:

   Original Rec'd date 12/13/00 — EER Status Pending ☐ Acceptable ☒ OAI ☐

   Date Acceptable for Filing 12/13/00 — Date of EER Status 2/21/01

   Patent Certification (type) III + IV — Date of Office Bio Review 5/24/01

   III 233 12/19/02 Date Patent/Exclus.expires — Date of Labeling Approv. Sum 1/16/02

   Citizens Petition/Legal Case Yes ☐ No ☒ — Date of Sterility Assur. App. N/A

   IV '716 10/21/04 (If YES, attach email from PM to CP coord) — Methods Val. Samples Pending Yes ☐ No ☒

   First Generic Yes ☒ No ☐ — 30 Day Clock Start This is TA End

   '931 3/15/09 (If YES, check PETS) — Commitment Rcd. from Firm Yes ☐ No ☐

   Pediatric Exclusivity Tracking PETS) — Modified-release dosage form: Yes ☒ No ☐

   Date checked 4/22/02 NDA# 20641 — Interim Dissol. Specs in AP Ltr: Yes ☐ This is TA

   Nothing Submitted ☐ DSU

   Written request issued ☐ Loratadine

   Study Submitted ☒

   Previously reviewed and tentatively approved ☐ Date

   Previously reviewed and CGMP def./N/A Minor issued ☐ Date

   Comments:

2. Div. Dir./Deputy Dir. — Date 4/23 — Date 4/24
   Chemistry Div. I or II — Initials QS — Initials QS
   Comments: OK for TA from CMC

3. Frank Holcombe — Date — Date 5/22/02
   Assoc. Dir. For Chemistry — Initials — Initials MA
   Comments: (First generic drug review) SATISFACTORY

4. Pat Beers Block — Date — Date
   Supv., Review Support Branch — Initials — Initials
   EER Status: Refer to DLPS review below (Sister ANDA is 75-989 for 10mg/ (b) (4) mg strength)

   Bioequivalence sites:

   Clinical site: — Analytical site:

   Inspection needed: ☐ yes ☐ no — Inspection needed: ☐ yes ☐ no

   Status: ☐acceptable ☐unacceptable ☐ pending — Status: ☐acceptable ☐unacceptable ☐pending

   Date of status: — Date of status:

   Reason: — Reason:

   Bioequivalence office level sign off: Rec'd 5/29/2002

   Labeling Status:

   Microbiology status:

   Patent Certification:

   Controlled Correspondence/Cit.Pet:

   Comments: RLD =

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

September 16, 2002

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Attn.: Ruby Wu

Dear Mr. Buehler:

As requested in the January 18, 2001 Acceptance for Filing letter, please find attached a copy of the court order granting IMPAX's Motion for Summary Judgment, filed August 8, 2002. The court ruled in favor of IMPAX in declaring that Claims 1 and 3 of Schering's patent number 4,659,716 are invalid.

Should you have any questions regarding this information, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
SEP 1 8 2002
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

October 11, 2002

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT –
FINAL APPROVAL REQUESTED

ORIG AMENDMENT
NDA
FPL

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

Pursuant to Tentative Approval letter dated May 29, 2002, IMPAX is hereby requesting final approval of the above application.

Enclosed is the following information:

Attachment 1 – Copy of August 8, 2002 Court Decision. The court ruled in favor of IMPAX in declaring that Claims 1 and 3 of Schering's patent number 4,659,716 are invalid. This was the only patent upon which IMPAX was sued.

Attachment 2 – Final printed labeling.

Other than the minor "post-tentative approval changes" made to the labeling and fully described in this amendment, no changes have been made to the application since the date of tentative approval.

It is IMPAX's opinion that the only barrier to full approval is the expiration of pediatric exclusivity for the 4,282,233 patent, which occurs on December 19, 2002.

Should you have any questions regarding this correspondence, please contact me by telephone (510-429-5883) or by telefax (510-429-5886).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
OCT 15 2002
OGD / CDER

ANDA 76-050

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 12, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 5 mg/120 mg (12-hour formulation).

On November 27, 2002, the FDA approved Schering's supplemental new drug application providing for the over-the-counter (OTC) use of Claritin® (loratadine/pseudoephedrine sulfate) D-12 and D-24 Extended Release Tablets. With this approval, the approved indications for these products are "for the temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy, watery eyes, itching of the nose or throat; temporary reduction of swelling of nasal passages; temporary relief of sinus pressure; and temporary restoration of freer breathing through the nose." The agency has been informed that with the introduction of products labeled for OTC use, these products will no longer be marketed with prescription (Rx) labeling. Thus, since your ANDA currently references the former product with prescription only labeling, your application cannot be approved.

You may submit a revised Form FDA 356h along with appropriate information to this ANDA to indicate the correct reference listed drug (RLD). In addition, we request that you withdraw your former labeling and submit for our review revised final-printed labeling which is consistent in content and format with that which provides for the OTC use of the RLD.

Furthermore, the agency is unaware of any new patent or patent information submitted by Schering to the NDA supplements providing for the switch from prescription to OTC marketing status for loratadine/pseudoephedrine sulfate drug products. As a result, ANDA applicants who submit an amendment to their pending ANDA providing only to amend their proposed labeling to conform with the labeling for the approved reference listed drug will not be required to submit new patent certifications. Please be advised,

however, that submission of additional patents by Schering for the RLD may require you to submit additional ANDA patent certifications.

If you have any questions, please contact: Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 301-827-5845.

Sincerely yours,

Gary J. Buehler 12/3/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
claritin labeling

q:\issues\loratadine\otcanda.doc

Drafted by: C. Parise 11/15/02
Comments by: L. Dickinson 11/22/02

Endorsement(s):

HFD-617/S. Kim/ S. K 11/29/02

V:\FIRMSAM\IMPAX\LTRS&REV\~~76050.OTCANDA.doc~~ 76050.Loratadine OTC.doc
F/T by: sk/11/29/02

M E M O R A N D U M

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

DATE: November 27, 2002

FROM: Gary J. Buehler
Director
Office of Generic Drugs

SUBJECT: Loratadine Over-the-Counter and Patent Certifications

TO: The Records for all active Loratadine ANDA's (list attached)

Loratadine Background

Issue:

Now that the Schering NDA supplements converting the status of loratadine to OTC are approved, will an applicant that has already submitted an ANDA for approval of the Rx version of the drug be required to submit new patent certifications as part of the amendment to seek approval for a generic drug with the new OTC labeling?

Background:

The Schering NDA supplements for OTC use of loratadine products were approved on November 27, 2002. The approved product will be the OTC version of loratadine labeled for treatment of rhinitis only. Schering has indicated that it will not continue to market an Rx loratadine product to treat urticaria.

There are various products that contain loratadine that will migrate to over-the-counter status (i.e., oral tablets, orally disintegrating tablets, oral liquid, loratadine and pseudoephedrine sulfate extended release tablets with 12 hour and 24 hour dosing intervals.

The primary patent, U.S.Patent No. 4,282,223, (the '223 patent) barring ANDA/505(b)(2) approvals expires (with its pediatric exclusivity extension) on December 19, 2002. In the case of the other listed patents, the NDA holder did not sue in response to notice of certification for U.S. Patent No. 4,863,931 (the '931 patent). In addition the 30-month stay either remains in place or

in some instances has expired with respect to U.S. Patent No. 4,659,716 (the '716 patent). In the United States District Court,District of New Jersey, Schering Corporation v. Impax Laboratories, Inc. Civil Action No. 01-0520(JWB), claims 1 and 3 of the '716 patent were found invalid. Claims 1 and 3 were the only claims that Schering asserted as being infringed. This was with respect to Impax's ANDA 76-050 for Loratadine/Pseudoephedrine Sulfate Extended-release Tablets, 5mg/120mg (a generic version of Claritin D-12).

Three 505(b)(2) applications have been submitted for loratadine. These were 505(b)(2) applications because the sponsors (Wyeth, McNeil, Perrigo) were seeking approval for an OTC version of loratadine products (i.e. tablets and orally disintegrating tablets) prior to Schering's submission of an application for an over-the-counter version of Claritin. These three applications would be approvable independent of Claritin going OTC, based upon the agency's stated view that the product may be used safely and effectively OTC. Because these applicants have only been seeking approval for the OTC use, their patent certifications to Schering asserted that their proposed OTC product did not infringe the patent. Only one 505(b)(2), Wyeth's NDA 21-375 for loratadine orally disintegrating tablets, is currently ready for final approval on December 19, 2002.

There are multiple ANDAs for the five different Schering loratadine drug products (syrup, immediate release tablets, rapidly disintegrating tablets, in combination with pseudoephedrine with 12 and 24 hour dosing intervals). These ANDAS are currently for the prescription form of the drug, because that was the approved reference listed drug prior to the switch to OTC. Now that the Schering OTC supplements are approved, and they have withdrawn their prescription product for urticaria, there will no longer be a prescription product to reference. Pending ANDAs, therefore must either be withdrawn or amended to reference the approved OTC form of the drug.

The issue for OGD is what new patent certifications, if any, will be required in ANDA amendments to revise the proposed generic prescription labeling to the new OTC Claritin labeling.

The regulations require that an NDA applicant submit to FDA as part of a supplement (1) any new patents that claim the drug or use of a drug for which approval of the supplement is sought and (2) information on any already submitted patent that claims the changed product. 21 CFR 314.53(d)(2).

According to the review division, Schering is making no changes to its product except to the labeling, and it has submitted no new patents or information on already submitted patents that

protect the new labeling.

FDA has consistently interpreted the FFDCA to require new patent certifications in ANDAs when new patents are submitted for an unchanged RLD before the ANDA is approved. In addition, the agency has required new patent certifications when the RLD is changed in some way (e.g., a new formulation) and a new patent is submitted to claim the change. In addition, the FDA has also required a new patent certification when the ANDA product is changed in some way (e.g., a new formulation) and there are existing patents listed with the FDA. There does not appear to be much experience with changes to the innovator drug product that are not accompanied by new patent information.

Recommendation:

Our view is that, if the ANDA applicant has already submitted adequate patent certifications for those aspects of the drug product that will not be changed by either the NDA supplement or the corresponding ANDA amendment, the inquiry is whether the innovator product has obtained or asserted new protections for the new aspect of the drug that will be duplicated by the generic company or whether existing patents also cover the new aspect of the drug. If the innovator does not assert any new protections for the changed product, the ANDA applicant will have no obligation to submit new patent certifications. If, however, the ANDA applicant changes the proposed generic drug in a way that could change its relation to the patent, then it will be required to certify to the relevant patents. This approach is in accordance with the requirements in 21 CFR 314.94(b)(12)(viii)(C) that "an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate."

In the loratidine case, this would mean that if Schering submits no new patents or patent claims for the OTC loratidine products and the ANDA applicants amend their applications only to conform with the labeling changes Schering made in the listed drug, the ANDA applicants would have no new patent certification obligations. If, however, an ANDA applicant decided to change its product to add the new OTC labeling AND to change the formulation, then that applicant would be required to provide new patent certifications.

Once the new labeling is submitted to an ANDA file, the application may proceed to approval after December 19, 2002, if it is otherwise ready for approval and all scientific and legal issues have been resolved.

q:\issues\loratadine\otcpatentmemo.doc

Drafted by: L. Dickinson, 11/7/02
Revised by: C. Parise 11/15/02
Concur: L. Dickinson 11/22/02
Edited by: R. West 11/27/02
Edited by: G. Buehler 11/27/02

SCHERING CORPORATION

2000 GALLOPING HILL ROAD KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

December 4, 2002

Gary J. Buehler, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

Noted
NTF
2/6/03

RE: ANDA NO. 76-050
Notice of Waiver of Pediatric Exclusivity

Dear Mr. Buehler:

Schering Corporation ("Schering") submits this letter to provide a waiver of pediatric exclusivity for the above-referenced ANDA of Impax Laboratories, Inc. ("Impax"). Schering holds NDA No. 19670 for Claritin-D (5 mg of loratadine and 120 mg of pseudoephedrine sulfate extended release tablets), and received an award of pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act ("FDCA") that applies to this NDA. This waiver is intended to allow approval of the Impax ANDA with an immediate effective date on or after the date of this letter. The waiver is being given only for this specific ANDA, and does not apply to any other ANDA or section 505(b)(2) application.

Additional information regarding the NDA, ANDA, and waiver follows.

NDA

NDA No. 19670 was approved on November 14, 1994. Schering is the sole and exclusive owner of the NDA. The NDA is listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). Three patents are listed in the Orange Book for the NDA, U.S. Patent Nos. 4,282,233, 4,659,716, and 4,863,931. Schering is the owner of these patents.

On August 16, 2000, FDA granted Schering pediatric exclusivity under FDCA section 505A based on studies Schering conducted involving the active moiety loratadine. The pediatric exclusivity applies to the Claritin-D NDA (No. 19670), including in particular to each of the three patents listed for the NDA. The applicable pediatric exclusivity periods are noted in the Orange Book.

On November 27, 2002, a supplemental new drug application providing for over-the-counter use of Claritin-D for relief of symptoms associated with allergic rhinitis was approved.

ANDA

The ANDA number is 76-050. Impax is the ANDA applicant. The established name of the drug is loratadine and pseudoephedrine sulfate extended-release tablets, the strength is 5 mg of loratadine and 120 mg of pseudoephedrine sulfate, and the dosage form is extended-release tablets.

Patent Litigation and Pediatric Exclusivity

On January 25, 2001, Schering received notice of a paragraph IV certification from Impax relating to U.S. Patent Nos. 4,659,716 and 4,863,931. On February 1, 2001, Schering commenced an action against Impax for infringement of U.S. Patent

No. 4,659,716. On February 21, 2001, Schering notified the Office of Generic Drugs that it had commenced patent infringement litigation against Impax within 45 days of the receipt of that notice and that, consequently, the ANDA could not be approved until the expiration of the 30-month period on July 25, 2003, or until such time as ordered by the court. The United States District Court for the District of New Jersey issued an order on August 29, 2002 declaring claims 1 and 3 of U.S. Patent No. 4,659,716 invalid. Claims 1 and 3 were the only claims of that patent asserted to have been infringed by Impax. That order has been appealed, and is pending before the Court of Appeals for the Federal Circuit.

Impax also included in its ANDA a paragraph III certification relating to U.S. Patent No. 4,282,233. This patent expired on June 19, 2002. However, as noted above, Schering received pediatric exclusivity, which as relates to this patent will not expire until December 19, 2002.

Notice of Waiver of Pediatric Exclusivity

Schering hereby waives the remaining pediatric exclusivity for its NDA No. 19670 with respect to Impax's ANDA No. 76-050 for 5 mg of loratadine and 120 mg of pseudoephedrine sulfate extended-release tablets, and does not object to FDA's approval of this Impax ANDA with an immediate effective date on or after the date of this letter. The waiver does not apply to any other ANDA or section 505(b)(2) application.

Thank you for your attention to this matter.

Sincerely yours,

Joseph F. Lamendola, Ph.D.
Vice President
Worldwide Regulatory Affairs

cc Elizabeth H. Dickinson, Esq., Office of Chief Counsel

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 4, 2002

LABELING AMENDMENT

ORIG AMENDMENT

N/AF

FPL

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Sarah Kim, Project Manager

Re: ANDA 76-050: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 5 mg/120 mg

Dear Mr. Buehler:

Accompanying this letter are 12 copies of the final printed container label in the OTC Drug Facts format. IMPAX is submitting OTC labeling for Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 5 mg/120 mg, 1000 count bulk container label to comply with the change in marketing status of the Reference Listed Drug from prescription (Rx) to over-the-counter OTC. A side-by-side comparison between the Schering-Plough OTC label for D-12 and IMPAX OTC label is provided.

The OTC marketing status for this application has been indicated on FDA Form 356h. The Statement of Rx/OTC Marketing Status (Section V.5) has also been revised following the November 27, 2002 switch of the Reference Listed Drug, Claritin® D-12, from Rx to OTC marketing status.

Schering-Plough has waived pediatric exclusivity with regard to this product. Schering informed the Office of Generic Drugs of this decision. A copy of Schering-Plough's correspondence accompanies this submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (~~510-429-5883~~) or by telefax (510-~~429-5886~~).

476-2091

Sincerely,
IMPAX Laboratories, Inc.

510-476-2018
new #

Michele Adler for

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
DEC 0 6 2002
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 17, 2002

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GENERAL CORRESPONDENCE
TAMPER-EVIDENT PACKAGING
Via FAX: (301) 594-0180
Hardcopy to Follow

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Attn: Sarah Kim, Project Manager

Dear Mr. Buehler:

This correspondence responds to a December 13, 2002 telephone inquiry from Sarah Kim of your office regarding the above-referenced ANDA. As a result of the recent change in marketing status of this drug product from Rx to OTC, Ms. Kim requested that IMPAX provide information regarding the tamper-evident packaging features used for this drug product, as required by 21 CFR 211.132. Ms. Kim also requested that IMPAX inform the Office of Generic Drugs as to any planned changes in the packaging configuration.

Tamper-Evident Feature

Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg will be initially marketed in 1000-count HDPE bottles as described in Section XIII, pages 4163-4251 of the original ANDA submission. The HDPE bottles are sealed with an inner liner that is imprinted, "Sealed For Your Protection." The immediate-container OTC labeling that IMPAX submitted in its December 4, 2002 correspondence contains a reference alerting the end-user to this tamper-evident feature. Please refer to the "Other information" section of the Drug Facts OTC label, submitted as Final Printed Labeling.

IMPAX will be marketing its 1000-count packaged product directly to a marketing partner; this product configuration will not be made available as a retail trade package.

(b) (4)

RECEIVED
DEC 19 2002
OGD / CDER

(b) (4)

[redacted]

Should you have questions or require additional information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 23, 2002

ORIG AMENDMENT

N/Am

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT –
FINAL APPROVAL REQUESTED

Attn: Sara Kim

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Dear Mr. Buehler:

This letter follows a December 20, 2002 telephone conversation with Sara Kim of your office regarding the above-referenced ANDA. Ms. Kim requested that IMPAX revise its Minor Amendment correspondence, dated October 11, 2002, to specifically state that no CMC changes have been made to the application since issuance of FDA's Tentative Approval of this application.

The text from the IMPAX's October 11 correspondence follows. The paragraph referring to "post-tentative approval changes" has been revised to explicitly state that no CMC changes have been made to the application since the date of the tentative approval. Rather than resubmitting the attachments accompanying the October 11 correspondence, IMPAX hereby incorporates them into this correspondence by reference, as annotated below:

Pursuant to Tentative Approval letter dated May 29, 2002, IMPAX is hereby requesting final approval of the above application.

Enclosed is the following information:

Attachment 1 – Copy of August 8, 2002 Court Decision. The court ruled in favor of IMPAX in declaring that Claims 1 and 3 of Schering's patent number 4,659,716 are invalid. This was the only patent upon which IMPAX was sued (*please refer to IMPAX's October 11, 2002 Minor Amendment correspondence*).

Attachment 2 – Final printed labeling (*please refer to IMPAX's October 11, 2002 Minor Amendment correspondence*).

Other than the minor "post-tentative approval changes" made to the labeling and fully described in this amendment, no *CMC* changes have been made to the application since the date of tentative approval.

RECEIVED
DEC 26 2002
OGD / CDER

It is IMPAX's opinion that the only barrier to full approval is the expiration of pediatric exclusivity for the 4,282,233 patent, which occurs on December 19, 2002.

IMPAX also notes and acknowledges in this correspondence that submission and FDA approval of OTC labeling is required before Final Approval can be granted. IMPAX is continuing to work with FDA to finalize the OTC labeling.

Should you have any questions regarding this correspondence, please contact me by telephone (*510-476-2018*) or by telefax (*510-476-2091*).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

December 27, 2002

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Sarah Kim, Project Manager

Re: ANDA 76-050: Loratadine and Pseudoephedrine Sulfate Extended Release Tablets, 5 mg/120 mg

Dear Mr. Buehler:

IMPAX has revised its OTC labeling, following telephone conversations between Michele Anderson of IMPAX and Labeling Reviewer Debra Catterson on December 18, 2002 and December 23, 2002. IMPAX also refers to email correspondence sent to Debra Catterson on December 20, 2002 and December 23, 2002.

Accompanying this letter are 12 copies of the final printed container label in the OTC Drug Facts format. A side-by-side comparison between the labels submitted on December 4, 2002 and the current IMPAX OTC label is provided.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Michele Anders for

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

RECEIVED
DEC 3 0 2002
OGD / CDER

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 471-3600 Fax (510) 471-3200

January 16, 2003

PATENT AMENDMENT
Via FAX: (301) 594-0183
(Hardcopy to Follow)

Gary Buehler

Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 76-050 (Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 5 mg/120 mg)

Attn.: Robert West

Dear Mr. Buehler:

This correspondence responds to a telephone request from Mr. Robert West of your office regarding the current legal status of the above-referenced ANDA.

On September 16, 2002, IMPAX submitted a copy of the court order granting IMPAX's Motion for Summary Judgment in Civil Action 01-520 (Schering Corporation v. IMPAX Laboratories, Inc., filed August 8, 2002). The court ruled in favor of IMPAX in declaring that Claims 1 and 3 of Schering's patent number 4,659,716 are invalid.

Chief Judge Bissel of the United States District Court For The District of New Jersey issued an August 8, 2002, decision finding U.S. Patent 4,659,716 invalid. On that same day, Schering Corporation appealed Judge Bissell's decision to the United States Court of Appeals for the Federal Circuit (Appeal Nos. 02-1540 through 1549 and 03-1021 through 03-1029).

Schering's appeal has been fully briefed according to the following schedule: October 15, 2002, Brief of Plaintiff-Appellant Schering Corporation; November 27, 2002, Brief of Defendants-Appellees including IMPAX Laboratories, Inc.; December 16, 2002, Reply Brief of Plaintiff-Appellant Schering Corporation. We expect the Appeal to be decided by the late spring or early summer of 2003.

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Senior Director, Regulatory Affairs and Compliance

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-050 Applicant ImPAX Laboratories, Inc.
Drug Loratadine and Pseudoephedrine Sulfate Strength 5 mg/120 mg (12 Hour Formulation)
Extended Release Tablets, 5mg/120 mg (12 Hour Formulation).

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Project Manager, Team 4 Sarah Kim Review Support Br	Date 12/10/02 Initials SKim	Date 1/13/03 Initials SKim

Application Summary:

Original Rec'd date 12/13/00
Date Acceptable for Filing 12/13/00
Patent Certification (type) III, IV
III 233 - 12/19/02 Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
IV 766 - 10/21/04 First Generic previously TA'ed Yes ☑ No ☐
731 - 3/15/09 (If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 2/21/01
Date of Office Bio Review 5/24/01
Date of Labeling Approv. Sum 1/06/03
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☑
Commitment Rcd. from Firm Yes ☐ No ☐
MV Satisfactory 3/18/02
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☑ Date 5/29/02
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Gregg Davis **PPIV ANDAs Only** Supv., Reg. Support Branch	Date 20-DEC-2002 Initials GD	Date 20-DEC-2002 Initials GD

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked previously granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD-Claritin-D 12 Hour Extended release tablets
Schering Corp. 5mg/120mg NDA 19-670

Comments:
ack. 12/13/00 w/ pIV - this is first loratadine/PSE citing Claritin D as RLD
sued by Schering on '716 only - found invalid 8/29/02 * post-Mylan
OK for full approval when labeling is resolved.

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:

Date 1/13
Initials R

OK for AP (from TA)

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Date _____
Initials _____
Comments: (First generic drug review)
N/A. This application was tentatively approved on 5/29/02.

5. Peter Rickman
Acting Director, DLPS
Date 1/16/03 Initials for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐
Comments: Acceptable EES dated 2/21/01 (Verified 1/16/03). No OAI clients noted. Refer to the administrative sign-off record completed at the time of the 5/29/02 tentative approval. IMPAX submitted a major amendment on 10/11/02 providing a copy of the 8/8/02 district court decision, FPL, and requesting final approval. Subsequent amendments dated 12/4, 12/23, and 12/27/2002 provided updated labeling. FPL (OTC) found acceptable 1/6/02. Labeling is presented in proper OTC format. CMC acceptable 1/13/03. Methods validation has been completed and found acceptable. First-generic CMC audit has been completed.

OR

5. Robert L. West
Acting Deputy Director, OGD
Date 1/30/2003 Initials for
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition:Yes☐ No☒
Comments: Following the Rx to OTC switch of the RLD the agency concluded that the generic applicants would not have to submit amended patent certifications to the new OTC RLD - see memo in file dated 11/21/02. This was based on the fact that Schering submitted no new patents in response to the change to OTC status. OGD issued a letter to ANDA applicants on 12/3/02 to this effect and requesting FPL in proper OTC format. In an 8/8/02 ruling the district court granted IMPAX's motion for summary judgement finding that claims 1 and 3 of the '216 patent are invalid (only 2 claims pursued by Schering). Schering has appealed this decision. This is a "post Hyatt" application - approval based upon district court decision. The '233 patent expires on 12/19/02. IMPAX was not sued on the '931 patent.
IMPAX is eligible for 180-day generic drug exclusivity (was first on both the '216 and '931 patents).
This application is recommended for approval.

6. Gary Buehler
Director, OGD
Date 1/30/03 Initials GB
Comments: for 12-Hr formulation.

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Sarah Kim
Review Support Branch
Date 1/30/03 Initials SSK

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:15pm Time notified of approval by phone 2:23pm Time approval letter faxed

FDA Notification:
1/30/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1/30/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

V:\...eports\approval\approvrou2.doc