CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75706

CORRESPONDENCE

75-706 (C.1)

ANDA (See Attachment)

Andrx Pharmaceuticals, L.L.C.
Attention: William Stahovec
4955 Orange Avenue
Ft. Lauderdale, FL 33314

Dear Sir:

We acknowledge receipt of your communications dated January 6, 2003, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the abbreviated new drug applications (ANDA) for the drug products listed in the attachment.

Your letter details the transfer of ownership of the ANDAs from Andrx Pharmaceuticals, Inc. to Andrx Pharmaceuticals, L.C.C.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the approved applications.

The material submitted is being retained as part of your applications.

Sincerely yours,

/S/

William P. Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

ANDA 75-706

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

We acknowledge receipt of your communication dated August 28, 2002, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the abbreviated new drug application (ANDA) for Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg.

Your letter details the transfer of ownership of the ANDA from Andrx Pharmaceuticals, L.L.C. to Andrx Pharmaceuticals, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/

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

ANDA 75-706

JUL 9 2002

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
U.S. Agent for: Andrx Pharmaceuticals, L.L.C.
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 21, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-hour formulation).

Reference is also made to your amendments dated January 23, and July 3, 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 24 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), March 15, 2009 (U.S. Patent No. 4,863,931, the '931 patent), and April 23, 2013 (U.S.

Patent No. 5,314,697, the '697 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,'931, or '697 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 Andrx Pharmaceuticals, L.L.C. (Andrx) for infringement of one or more of the patents that are the subject of the "paragraph IV certifications". This action must be brought against Andrx prior to the expiration of forty-five (45) days from the date the notice provided by Andrx under paragraph (2)(B)(I) is received. You have notified FDA that Andrx 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 and '697 patents (Schering Corporation v. Andrx Corporation, Andrx Pharmaceuticals, Inc., and Andrx Pharmaceuticals, L.L.C., Civil Action No. 00-1439 (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)], which has been interpreted by the agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

   c. the '233, '716 and '697 patents have all 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,

/S/

Gary Buehler 7/9/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

5.1

ANDA 75-706

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 21, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg (24-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,

/S/

12/3/02

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Claritin Labeling

ANDA 75-706

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

FEB -7 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to File" letter dated November 22, 1999 and your amendment dated December 14, 1999.

NAME OF DRUG: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

DATE OF APPLICATION: September 21, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 15, 1999

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 final order or judgement from which no appeal may be taken (which might not be the one from the District Court), 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 Nasser Mahmud, 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) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-706
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett

ANDA 75-706

Andrx Pharmaceutical, Inc.
Attention: Diane Servello
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314

NOV 22 1999

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated September 21, 1999, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Loratadine and Pseudoephedrine Hydrochloride Extended-release Tablets, 10 mg/240 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You are required to completely package your exhibit batch in containers intended for marketing. Partial packaging is not acceptable unless a protocol has been submitted and approved prior to submission of the application. For instance, your records show that the theoretical yield for your exhibit batch is tablets but you appear to have packaged only tablets, less than the minimum packaging required. Please refer to the letters to the industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. We also refer you to the CDER Manual of Policies and Procedures (MAPP) 5225.1.

The same standard operating procedures (SOPs) and controls as well as the same formulation and manufacturing procedures should be used on the test batch and on the full-scale production batches. As stated on page 397 of your submission, you propose to compress future batches of tablets with more compression force to produce harder tablets. This manufacturing change raises substantial questions regarding the comparability of the drug products proposed for production batches in contrast to the test batch used in your bioequivalence study. Please refer to

the Office of Generic Drugs' Policy and Procedure Guide #22-90, dated September 13, 1990.

The concentration of the inactive ingredient, in your proposed drug product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that this inactive ingredient in this concentration does not affect the safety of the proposed drug product.

The concentration of the inactive ingredient, in your proposed drug product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that this inactive ingredient in this concentration does not affect the safety of the proposed drug product.

Please note that DMF authorization and composition alone may not be sufficient to prove safety. If you choose to provide the composition instead of pharmacology and toxicology data, you must provide supporting data showing that **each** component and composition was used in an approved drug product.

In addition, please provide three additional copies of draft labels and labeling for the archival copy. To be in compliance with 21 CFR 314.94(a)(8)(ii), you must provide four copies of the draft labels and labeling in the archival copy of the application. In the future, please include four copies of the draft labels and labeling in both the archival and review copies of the application.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-706
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-615/MBennett

Andrx
PHARMACEUTICALS, INC.

VIA FEDERAL EXPRESS

September 21, 1999

RTF
11/12/99
Gregory

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Dear Sir:

In accordance with Section 505(j) of the FD&C Act and 21 CFR 314.94, Andrx Pharmaceuticals is submitting an original Abbreviated New Drug Application for approval to market its formulation of Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg. The reference listed drug is Claritin-D® 24 Hour (loratadine and pseudoephedrine sulfate, USP) Extended-release Tablets, manufactured by Schering Corp.

This application consists of 20 volumes and contains the necessary information to demonstrate that Andrx's generic product is both pharmaceutically equivalent and bioequivalent to the reference listed drug. Two copies of the application are provided - an archival copy and a review copy that is divided into a bioequivalence review section and a chemistry review section.

THIS APPLICATION CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA - The draft package insert is provided in Microsoft Word 97 format on a 3.5" diskette located with the four copies of the draft labeling in the Chemistry Review Copy. The data contained in the electronic submission is the same as in the hardcopy submission.

Andrx Pharmaceuticals commits to resolve any issues identified in the methods validation process after approval.

Please direct any questions regarding this application to Jacqueline Davis, Regulatory Affairs Manager, at (954) 321-5229 (tel.) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

This info addresses the inactive components but I am still waiting for a response to the first four RTF issues

NEW CORRESP

The safety of c/c of the have not been evaluated. This will be done when the response is complete.

12/16/99

December 13, 1999

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
Attention: Nasser Mahmud

RE: Andrx Pharmaceuticals ANDA 75-706 for Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg

Dear Mr. Mahmud:

We are providing the following information directly to the agency on the behalf of Andrx Pharmaceuticals, Inc. in support of the above referenced ANDA.

We understand that you had questions regarding the use of in Andrx's application pertaining to the levels of use of these materials compared to the levels listed in the Inactive Ingredients Guide (IIG).

I believe that there may have been some type of mix-up since these products are considered to be mixed excipient systems and are routinely used in many drug applications. Sometimes our customers will list these products in their applications as and sometimes they are listed using the individual components. The products are produced with commonly used excipient components that are typical to hundreds of drug products at similar levels. We feel that it is necessary to look at the potency range information in the IIG for both the listed products as well as the individual components to determine whether a formulated product such as an is being used within previously approved levels. The key is really the individual components since new formulated products such as are developed daily with different formula numbers that all contain well established excipients.

We have compiled the following tables which list the amount of each component actually present on the dosage form (based on Andrx's use levels and the percentages in our formula) along with the appropriate Potency Range information for oral applications to show that the levels being used in the And

1 pg

application fall well below the IIG Potency Range levels for each of the components of the

We see no reason why there should be any concern with the use of these products by Andrx at the levels they have proposed. We hope this information answers your questions concerning these products. If you have any further questions, please contact me

Sincerely,

Director of Global Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

December 14, 1999

NDA ORIG
N/AC

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-706; Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg

RESPONSE TO REFUSE-TO-FILE LETTER

Dear Mr. Sporn:

We refer to our abbreviated new drug application (ANDA) for the above-mentioned drug product dated September 21, 1999 and your letter dated November 22, 1999 providing reasons for refusing to file our ANDA. This response addresses each of the items listed in your letter. We request that OGD review this submission and reconsider the filing date of our ANDA based on the merits of the issues. *We are requesting that your refuse-to-file letter be rescinded, and that our ANDA be filed retroactively to the original date of submission, September 21, 1999.*

Andrx Pharmaceuticals, Inc. ("Andrx") believes that our ANDA, as submitted on September 21, 1999, was sufficiently complete to permit a substantive review as described in 21 CFR 314.101(b)(1). In general, the filing determination for an ANDA is based on an evaluation of completeness and acceptability to determine that all required components of the ANDA has been submitted. The reasons cited in your letter for refusing to file this ANDA appear to be more appropriately described as the type of deficiencies that are identified during an in depth technical review of the ANDA and not the type of issues that are raised during the filing determination. Andrx also believes that certain deficiencies cited in the refuse to file letter are incorrect and ask that the initial filing determination be reconsidered. These issues are described in detail in our responses to OGD's refuse to file comments.

This ANDA contains a paragraph IV patent challenge. Therefore, the filing date is critical for a successful outcome to our patent challenge. This issue aside, Andrx firmly believes that our original filing was substantially complete for filing. Additionally, OGD's December 24, 1996 letter to industry states that the agency will notify firms by telephone when it is believed that the firm can provide information within 10 days to address a refuse-to-file issue. If the requested information is provided within 10 days, the original filing date of the application will be applicable. We believe that this policy should have been applied to this submission. Had we

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 15 1999
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-585-[illegible]

been contacted by telephone, we would have been able to respond within 10 days to the items cited in your letter. If OGD deemed our response unacceptable, a refuse to file letter could have been issued at that time.

The following is an item-by-item response to the issues raised in your letter:

OGD Comment:

You are required to completely package your exhibit batch in containers intended for marketing. Partial packaging is not acceptable unless a protocol has been submitted and approved prior to submission of the application. For instance, your records shows that the theoretical yield for your exhibit batch is tablets but you appear to have packaged only tablets, less than the minimum packaging required. Please refer to the letters to the industry from the Director, Office of Generic Drugs, dated November 8, 19991, and August 4, 1999. We also refer you to the CDER Manual of Policies and Procedures (MAPP) 5225.1.

Andrx Response:

As explained below, we believe that this is an issue that is appropriately addressed in the technical review and not as a filing issue. It is not possible to fully understand the complete manufacturing/packaging operations without detailed review of the pertinent information. In compliance with OGD Policy and Procedure Guide #22-90, Andrx produced an ANDA exhibit batch with a theoretical batch size of tablets. The entire batch was processed through all the stages of the manufacturing procedure (blending, compression, immediate-release (IR) coating, and final color coating). Full testing was conducted on representative samples at each stage of manufacture, including the final color coating stage. At the final coated stage, cosmetic tablet defects were noted, causing a portion of the batch to be treated as rejects.

We believe that the tablets originally packaged were truly representative of our process since rejects are not packaged during commercial operations. While Andrx is aware of the guidance regarding packaging of the exhibit batch, we wish to point out that applicants may deviate from a guidance with proper justification. Therefore, even though OGD believed the batch was not packaged in complete accordance with the guidance it is clear that packaging is representative of the actual manufacturing procedures. We also believe that after technical review of the ANDA, the reviewer would have better understood the apparent deviation from recommendations outlined in the packaging guidance. However, in order to address the recommendations in MAPP 5225.1, "Guidance on the Packaging of Test Batches", the tablets with cosmetic coating defects from our ANDA exhibit batch were subjected to a packaging operation in order to provide packaging for more than tablets. The revised Packaging Reconciliation Summary table for lot #605R004 (the ANDA exhibit batch) and the packaging record for the additional packaging are enclosed in Exhibit 1.

Please note that for both the IR coating and final color coating steps, the entire ANDA exhibit batch was coated in a single coating pan. The pan rotation during the coating process provided further assurance that samples taken at these stages were representative of the entire batch. The representative samples from all manufacturing stages met each of the established specifications for identity, strength, quality and purity. After the cosmetic defects were observed after the final color coating stage, a physical inspection of the batch was conducted after the analytical testing was completed to sort out the defective tablets. The physical inspection was performed prior to the packaging operation. It should be noted that this same procedure would occur with a commercial batch having cosmetic coating defects. Therefore, our packaging process for the exhibit batch was entirely representative of a commercial production batch.

As a result of the higher than expected rate of rejects, an investigation was launched. This investigation is the same procedure that is followed when unexpected results are encountered during the production of a commercial batch. Therefore, the process, including the investigation, is typical of manufacturing procedures in the industry. In regard to our exhibit batch, the investigation revealed that

This problem will be eliminated in the future by

Please see Exhibit 2 for copies of memos describing the investigation of the tablet defects. An instruction has been added to the blank batch record for commercial batches to make sure that (See page 9 of the revised batch record in Exhibit 3.)

Please note that the corrective actions made to our batch record will prevent a recurrence of the tablet defects. These actions are limited to an optimization of the tablet with all in-process controls during the compression process remaining the same as those used for the ANDA exhibit batch. The tablet hardness specification will be unchanged from the ANDA exhibit batch, i.e., the target hardness will be kp. Therefore, while the tablet defects will not recur, the physical characteristics of the tablets will be the same as the ANDA exhibit batch. Since the hardness is unchanged, the dissolution rate will be unchanged. It should be noted that this product employs a as its extended-release (ER) mechanism. Once the tablet is imbibed with the surface of the tablet forms a continuous layer on the outside of the ER core. This continuous layer is the mechanism that controls the release of the drug. In fact, the edge defect disappears after of the tablets, and the subsequent formation of the layer.

Since the defective tablets were stored in bulk for more than 30 days, in order to comply with the retest requirements listed in the finished product specification submitted with our ANDA (page 000668), a representative sample of the tablets with physical defects was tested. The test results showed that the defective tablets were equivalent to the

previously packaged portions of the batch with respect to assay, related compounds, content uniformity and dissolution. . The data show that the minor tablet defects had no effect on the drug release, as supported by our comparison of dissolution rates for normal tablets and the tablets with minor defects. Please see Exhibit 4 for a table providing comparative test results.

As shown in the preceding paragraphs, the justification for the acceptability of our ANDA exhibit batch is more appropriately addressed as a chemistry review issue, rather than during the filing process for acceptance of the submission. Andrx is concerned that a pre-review of our ANDA was conducted rather than the traditional evaluation of completeness for filing purposes.

OGD Comment:
The same standard operating procedures as well as the same formulation and manufacturing procedures should be used on the test batch and on the full-scale production batches. As stated on page 397 of your submission, you propose

This manufacturing change raises substantial questions regarding the comparability of the drug products proposed for production batches in contrast to the test batch used in your bioequivalence study. Please refer to the Office of Generic Drugs' Policy and Procedure Guide #22-90, dated September 13, 1990.

Andrx Response:
This is clearly a chemistry review issue that is normally identified during the technical review process. It appears that a specific pre-review of the batch records was required to comment on this specific issue. However, we are providing a revised blank batch record for production size batches specifying the same hardness specification as was used for the ANDA test batch. Please see Exhibit 1 for the revised blank batch record.

OGD Comment:
The concentration of the inactive ingredient, in your proposed drug product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that this inactive ingredient in this concentration does not affect the safety of the proposed drug product.

The concentration of the inactive ingredient, in your proposed drug product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that

this inactive ingredient in this concentration does not affect the safety of the proposed drug product.

Please note that DMF authorization and composition alone may not be sufficient to prove safety. If you choose to provide the composition instead of pharmacology and toxicology data, you must provide supporting data showing that ***each*** *component and composition was used in an approved drug product*

Andrx Response:

We believe that the information provided in our original submission addresses the requirements of 314.94(a)(9)(ii) concerning the safety of inactive ingredients. We provided the qualitative composition of the formulations used in our product, listing the commonly used inactive ingredients from which they are composed. Since the maximum permitted amount of any of these inactive ingredients taken individually is at least three times greater than the total amount of the mixture in the tablets, no safety issues are present. Andrx does not believe that it is the intent of OGD to refuse to file based on the previous use of a particular proprietary preparation when that preparation is comprised of commonly used excipients. In the case of preparations, the actual components are commonly used excipients that are marketed commercially in specific proportions. However, the critical issue is whether the individual components of the commercial preparation exceed the amounts previously approved for that route of administration. For our product, it is clear that the individual components of the preparations could not have exceeded previously approved quantities.

The statement that these inactive ingredients exceed the maximum concentration previously approved by the Agency is not correct. As stated on the List of Components included in our ANDA (page 00080), these formulations are mixtures of commonly used inactive ingredients. Each of these individual inactive ingredients is listed in the 1996 Inactive Ingredient Guide with quantities for oral dosage forms that exceed the total amount of in our product. See the following table for illustration:

Formulation/ Quantity per tablet	*Inactive Ingredient Name*	*Maximum amount in oral drug product*
mg/tablet)	Hydroxypropyl methylcellulose	mg
	Polyethylene glycol	mg
	Polyethylene glycol	mg
ng/tablet)	Hydroxypropyl methylcellulose	mg
	Polyethylene glycol	mg
	Polysorbate	mg
	Titanium dioxide	mg

Since the quantitative composition of formulations is proprietary, the manufacturer of has submitted this information directly to the Office of Generic Drugs on December 13, 1999, on the behalf of Andrx. A copy of the cover letter accompanying their submission is attached as Exhibit 5. The information provided to the agency by gives the quantities of each of the inactive ingredients listed above on a "per tablet" basis.

In compliance with your request, three additional draft copies of our labels and labeling are enclosed as Exhibit 6. Although four copies were provided in the review copy of our ANDA, future submissions will include four sets of labeling in both the archival and review copies.

We believe this response satisfactorily addresses the issues raised in your letter. Should the agency not agree with our request to rescind the refuse-to-file letter, we may wish to avail ourselves to an informal conference in accord with 21 CFR 314.101(a)(3). If we decide to pursue this option, we will contact OGD to request that this ANDA be filed over protest.

Please do not hesitate to contact me at (954) 581-7500 Extension 1412 or (954) 327-4412 (direct line) if you have any questions concerning this response.

Sincerely,
ANDRX PHARMACEUTICALS, INC.

Diane Servello

Diane Servello,
Director of Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

February 11, 2000

NEW CORRESP
NC WF 2/27/03

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-706; Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg

Dear Mr. Sporn:

We refer to the abbreviated new drug application ("ANDA") listed above, which was accepted for filing on December 15, 1999. Pursuant to §314.72, Andrx Pharmaceuticals, Inc. is notifying the agency of a change in ownership for this ANDA. The change in ownership is effective as of February 11, 2000.

All rights to this ANDA have been transferred to:

Andrx Pharmaceuticals, L.L.C. ✓ OK
c/o LeClair Ryan
707 East Main Street, 11th Floor
Richmond, VA 23219

Please continue to address all correspondence regarding this ANDA to:

Andrx Pharmaceuticals, Inc.
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314
Attention: Diane Servello, Director of Regulatory Affairs
Phone: (954) 581-7500 Ext. 1412 or (954) 327-4412 (direct line)
Fax: (954) 587-1054

Andrx Pharmaceuticals, Inc. certifies that the new owner has a complete copy of this ANDA. A separate letter will be sent to your office by Andrx Pharmaceuticals, L.L.C. with a signed 356H form, containing (1) a commitment to abide by the agreements, promises and conditions contained in this application; (2) the date the change in ownership is effective; and (3) a statement that a complete copy of the application is in their possession.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 14 2000
OGD

Please do not hesitate to contact me at (954) 327-4412 if you require any additional information.

Sincerely,
ANDRX PHARMACEUTICALS, INC.

Diane Servello,
Director, Regulatory Affairs

Andrx Pharmaceuticals, L.L.C.
c/o LeClair Ryan
707 East Main Street, 11th Floor
Richmond, VA 23219

February 11, 2000

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-706; Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg

Dear Mr. Sporn:

We refer to a letter dated February 11, 2000 from Andrx Pharmaceuticals, Inc. notifying the agency of a change in ownership of the above referenced abbreviated new drug application ("ANDA"). The change in ownership is effective on February 11, 2000. All rights to this ANDA have been transferred to:

Andrx Pharmaceuticals, L.L.C.
c/o LeClair Ryan
707 East Main Street, 11th Floor
Richmond, VA 23219

Andrx Pharmaceuticals, L.L.C. certifies the following:

1. A commitment is made to abide by the agreements, promises and conditions contained in this ANDA

2. A complete copy of the ANDA is in the possession of Andrx Pharmaceuticals, L.L.C.

3. A signed application form is attached.

Please continue to address all correspondence regarding this ANDA to:

Andrx Pharmaceuticals, Inc.
4001 SW 47th Avenue
Ft. Lauderdale, FL 33314
Attention: Diane Servello, Director of Regulatory Affairs
Phone: (954) 581-7500 Ext. 1412 or (954) 327-4412 (direct line)
Fax: (954) 587-1054

Please do not hesitate to contact me at (954) 321-5214 if you require any additional information.

Sincerely,
ANDRX PHARMACEUTICALS, L.L.C.

Elliot F. Hahn, Ph.D.
Member of Andrx Pharmaceuticals, L.L.C.

Andrx Pharmaceuticals, L.L.C.
c/o LeClair Ryan
707 East Main Street, 11th Floor
Richmond, VA 23219

February 28, 2000

NEW CORRESP
NC
Notice of non-infringement
OK!
Express mail agreed to
prior to submission.
3/1/00

Douglas Sporn
Director, Office of Generic Drugs, HFD-600
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: PATENT AMENDMENT - ANDA 75-706
Loratadine & Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

Dear Sir:

Andrx Pharmaceuticals, L.L.C. is amending the above-referenced application to provide documentation of notification/receipt of notice of certification of invalidity/non-infringement of a patent (paragraph IV certification).

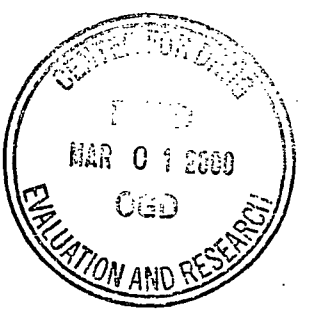
In accordance with 21 CFR 314.95(b), Andrx Pharmaceuticals, L.L.C.. certifies that: **(i)** notices of certification of non-infringement of a patent have been provided by U.S. express mail, return receipt requested, to each person identified under section 314.95(a), and **(ii)** the notices met the content requirements under section 314.95(c). The use of U.S. express mail as an alternate means of transmittal was agreed to by the agency in a telephone conversation between Nasser Mahmoud and Diane Servello on September 16, 1999.

In accordance with section 314.95(e), this submission includes a copy of the return receipt postcard as documentation of receipt of the notice by Schering-Plough Corp. on February 12, 2000. A copy of the notice is provided for informational purposes.

Please do not hesitate to contact me at (954) 327-4412 if you require any additional information.

Sincerely,

Diane Servello,
Director, Regulatory Affairs, Andrx Pharmaceuticals, Inc.
Agent for Andrx Pharmaceuticals, L.L.C.



Andrx
PHARMACEUTICALS, INC.

NEW CORRESP
NC

March 22, 2000

NAE 2/27/03

Nadine Warren
Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-706; Loratadine and Pseudoephedrine Sulfate ER Tablets, 10 mg/240 mg

Dear Ms. Warren,

As requested I am sending you additional copies of the two transfer letters (including the 356h forms) which were submitted to ANDA 75-706 on February 11, 2000.

Please do not hesitate to contact me at (954) 321-5229 if you need any additional information.

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 23 2000
OGD

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FACSIMILE: 44-171-495-3101

KUNSTLAAN 44 AVENUE DES ARTS
BRUSSELS 1040 BELGIUM
TELEPHONE: 32-2-549-5230
FACSIMILE: 32-2-502-1598

March 30, 2000

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
NC

NAE
4/27/2003

Re: ANDA No. 75-706
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 75-706;

(ii) The name of the ANDA applicant listed on the notice of Paragraph IV Certification is Andrx Pharmaceuticals LLC;

(iii) The established name of the drug is loratadine and pseudoephedrine sulfate extended release tablets, the strength is 10 mg of loratadine and 240 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. 00-1439 (JAG), was filed in an appropriate court (the United States District Court for the District of New Jersey) on March 27, 2000. A copy of the Complaint filed in that action is enclosed.

CENTER FOR DRUG EVALUATION AND RESEARCH
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Schering received notice of a Paragraph IV Certification alleging the noninfringement, invalidity and/or unenforceability of United States Patent Nos. 4,659,716, 4,863,931 and 5,314,697 on February 14, 2000. 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. 75-706 cannot be approved until the expiration of the thirty-month period beginning on February 14, 2000 and ending on August 14, 2002, or until such time as ordered by the Court.

Thank you for your attention to this matter.

Sincerely yours,

Christopher N. Sipes
Counsel for Schering Corporation

Enclosure

Enclosure

Andrx
PHARMACEUTICALS

NEW CORRESP
NC

VIA FEDERAL EXPRESS

April 12, 2000

N AE
O'Neal
2/27/2003

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-706; Loratadine and Psuedoephedrine Sulfate ER Tablets, 10 mg/240 mg

PATENT AMENDMENT

Dear Mr. Buehler:

Andrx Pharmaceuticals LLC ("Andrx") is amending the above referenced application to provide documentation of a complaint for patent infringement, as follows:

Schering Corporation filed an action for patent infringement (Case No. 00-1439) against Andrx alleging infringement of patents 4,659,716 and 5,314,687. The complaint was filed on March 28, 2000 in the United States District of New Jersey. A copy of the complaint is enclosed.

Please do not hesitate to contact me at (954) 327-4412 if you require any additional information.

Sincerely,

JMSavice / for
Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG
RECD
APR 13 2000
OGD
EVALUATION AND RESEARCH

ANDRX PHARMACEUTICALS, LLC; c/o LECLAIR RYAN; 707 EAST MAIN STREET, 11TH FLOOR, RICHMOND VA 23219

Andrx
PHARMACEUTICALS, L.L.C.

October 27, 2000

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

ORIG AMENDMENT
N/AB
BIOAVAILABILITY

RE: ANDA 75-706; Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets 10 mg/240 mg

BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler:

We refer to your facsimile dated June 5, 2000 (copy attached) providing ***Bioequivalence*** comments regarding our abbreviated new drug application submitted on December 14, 1999. Pursuant to 21 CFR 314.120, Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting an amendment responding to the comments included in your facsimile.

I. Bioequivalence response:

FDA Comment 1

Loratadine and descarboethoxy loratadine: Fasting study samples were analyzed using method whereas food study and multiple-dose study samples were analyzed using method Please provide method validation data like inter and intra day accuracy, precision, recovery, and stability of loratadine and descarboethoxy loratadine in extracted samples for method

Response:

A copy of the method validation and matrix stability data for method are enclosed. Please see Exhibit 1.

FDA Comment 2

The relative recovery of loratadine ranges from % and that of descarboethoxy loratadine ranges from % , method validation). Please explain such a variation in the recovery at three different concentrations. What were the concentrations of loratadine and descarboethoxy loratadine used in the recovery experiments? Please explain in detail how the relative recovery was calculated? Is this the response measured from the matrix (plasma) as a percentage of that measured from pure solvent? Please provide the absolute recovery of loratadine, descarboethoxy loratadine, and their internal standards. Recovery experiments should be performed by comparing

represent 100% recovery.

Response:

has provided the following response to this comment: (See Exhibit 2)

utilizes a form of sample extraction. The pertinent aspects of the method are briefly summarized as follows:

1. Internal standards are

FDA Comment 3
Please provide date of manufacture of bio-lot.

Response:
The bio-lot (lot #605R004) was manufactured in January 1999.

FDA Comment 4
Please provide SOPs for all analytical methods.

Response:

Since it is the policy of the Office of Generic Drugs to rely upon Field Investigators to review SOPs, we presume you are referring to the actual analytical methods, rather than SOPs. These documents are enclosed, as follows:

1. Method Report Analysis of Loratadine and descarboethoxy-loratadine in human plasma. (Exhibit 3)

2. Method Report Analysis of Loratadine and descarboethoxy-loratadine in human plasma. (Exhibit 4)
3. Method Analysis of Pseudoephedrine in Human Plasma – Amended (Exhibit 5)

FDA Comment 5:

The Division of Bioequivalence currently requests measurement of loratadine and descarboethoxy loratadine in all three bioequivalence studies. The 90% confidence intervals for loratadine LC_{max} in the multiple-dose study are outside the acceptable limits. Please note that subject #28 cannot be dropped from the analyses solely on the basis that this subject's plasma levels are high compared to other subjects. In the fasting study, subject #26 showed high loratadine levels in both periods compared to other subjects and this subject was not omitted from the analysis. You may retest subject #28 with some control subjects who did not have extremely high loratadine levels.

Response:

Upon further review of this matter, we noted that subject #28 of the multiple-dose study (P98-259) did not meet the study's inclusion criteria. Protocol number P98-259 (Exhibit 6) specifically excludes persons whose body weight was 10% more or less than the weight specified in the 1983 Metropolitan Height and Weight Table. Subject #28 was the only subject that did not meet the specified criteria of the study, which criteria is acceptable to FDA according to September 9, 1993 Guidance: *Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing*: Page 5, Selection of Subjects (Exhibit 7). Indeed, since our protocol specifically states that no modifications to the protocol may be made without our consent, which Andrx did not provide in this instance, subject #28 should never have been included in our ANDA report.

A statistical analysis (Dixon's test) performed on subject # 28 confirms that the extremely high loratadine levels for AUC and CMAX values are statistical outliers and therefore bias the statistical analysis of the data. (Exhibit 8).

We also note that the Agency is trending towards greater reliance upon the single-dose study and less reliance upon, or the elimination of, the multiple dose study; which we agree with. As the literature[1] demonstrates that loratadine exhibits highly variable pharmacokinetic behavior which will have no significant accumulation in a multiple dose study, we believe the need for, and significance of a multiple dose study for loratadine is highly questionable (Exhibit 9).

We also agree with your comment that since subject #28 was omitted from our analysis of the multiple-dose study (P98-259), we should also omit subject #26 from our analysis of the fasting study (P98-234). We have therefore performed a new statistical analysis for the fasting study without subject #26 (Exhibit 10). As shown in these tables, the PK parameters excluding subject

[1] Radanski E, Hilbert J, Symchowicz S, Zampaglione N; Loratadine: Multiple-Dose Pharmacokinetics, *J Clin Pharmacol* 1987; 27:530-533.

#26 are similar to those in our original data that included subject #26, and remain within the acceptable limits.

FDA Comment 6

The guidance 'Oral extended (controlled) release dosage forms: In vivo Bioequivalence and In Vitro Dissolution Testing' recommends dissolution testing using apparatus II (paddle) at 50 and 75 rpm for tablets. Based on your results in five dissolution media, you are requested to provide additional data on dissolution testing conducted using apparatus II (paddle) at 50 and 75 rpm and 900 mL of 0.1N HCL in the first hour and 900 mL of 0.1M phosphate buffer (pH 7.5) for additional 16 hours.

Response:

Per your request, we have generated additional dissolution data on the bio-lot and the reference product, as follows:

1. Apparatus II (paddles) at 50 rpm using 900 mL of 0.1N HCl in the first hour and 900 mL of 0.1M phosphate buffer (pH 7.5) for an additional 16 hours. (Exhibit 11)
2. Apparatus II (paddles) at 75 rpm using 900 mL of 0.1N HCl in the first hour and 900 mL of 0.1M phosphate buffer (pH 7.5) for an additional 16 hours. (Exhibit 12)

Please note that during the testing, it was observed that the tablets from Andrx's bio-lot were firmly sticking to the bottom of the dissolution vessels in both 0.1N HCl and pH 7.5 buffer media. This phenomenon was the cause for the low release rate of loratadine and pseudoephedrine when tested under these conditions. Our previous pH profile studies have confirmed that for the Andrx formulation of this product, a medium consisting of

is most suitable for complete release of both loratadine and pseudoephedrine.

A list of exhibits is included after the 356h form for the reviewer's convenience.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

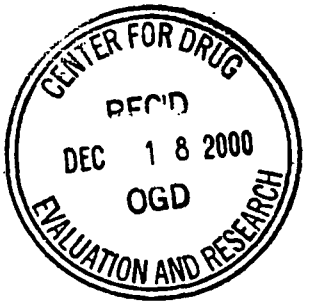
Diane Servello
Director of Regulatory Affairs

Andrx
PHARMACEUTICALS, L.L.C.

ANDA 75-706
Loratadine & Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg

December 14, 2000

ORIG AMENDMENT
N/AC



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

RE: MAJOR AMENDMENT: CMC AND LABELING

Dear Mr. Buehler:

Reference is made to your facsimiles dated July 10, 2000 (labeling comments) and July 31, 2000 (chemistry comments) for the above referenced application (copies attached). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. ("Andrx") is submitting a major amendment to this ANDA that provides a complete response to all the deficiencies listed in the facsimiles. This amendment consists of 1 volume.

Response To Chemistry, Manufacturing And Controls Deficiencies (July 31, 2000 Facsimile)

Section A

1. **The following pertains to the chipping and imprinting of the tablets:**

   a. **On page 000245 of the application, you specify "ANDA test batch tablets were not imprinted with the product code, however, all production batches will be imprinted". Please explain why the bio batches were not imprinted and how this bio batch is equivalent to production batch or listed drug product. Also, there was a significant loss of yield due to chipping of tablets (page 397).**

Response

Since the ANDA test batch is solely intended for testing purposes under controlled conditions and not intended for interstate commerce, Andrx did not provide an ink imprint for bio-batch with an identification code. However, as stated in the ANDA all post-approval commercial batches will be ink imprinted to permit unique identification of the drug product and its manufacturer as required by 21 CFR Part 206 (i.e. the commercial batches will be imprinted with the Andrx logo and '605' in black ink). All imprinting will be done at Andrx's Fort Lauderdale manufacturing facility, using the imprinting batch records provided in the ANDA.

The imprinting ink, has been approved for use in the CDER-approved product, Naproxen Sodium Extended-release Tablets (Andrx's ANDA 75-416, tentatively approved March 17, 2000). In addition, as indicated in Section VII, page 000084 of the original application, components of this ink have been used in previously approved products at levels that are much higher than the trace amounts that will be imprinted on each tablet. We therefore consider the addition of the ink

imprint to commercial batches a minor change, that is, one considered to have a minimal potential of causing an adverse effect on the identity, strength, quality, purity, or potency of the product.

Indeed, this change is classified as a minor change (suitable for submission in the annual report) in CDER's November 1999 *Guidance for Industry: Changes to an Approved NDA or ANDA*[1]. Andrx Pharmaceuticals commits to providing stability data for an imprinted commercial batch in the first annual report.

Andrx's release specification for the imprinting ink, a sample certificate of analysis, a sample manufacturer's certificate of analysis, and an organic volatile impurity statement from the ink manufacturer are provided under **Tab 1**.

There was a significant loss of yield due to chipping of tablets during the manufacture of the test batch, lot 605R004. This minor edge defect was observed after the batch was completely coated and the batch record reconciled. The defect was not noticeable during tablet compression. The entire batch was 100% inspected, and tablets with defective edges were manually removed and considered rejects. The defect was believed to have been due to the . Tablet edges often get less coating than the body and therefore are more susceptible to chipping while tumbling in the coating pan.

In an effort to eliminate this problem during the manufacture of future lots of the drug product, compression optimization studies were conducted **(Tab 2)**. From these studies, it was concluded that pre-compression is important during core tablet compression to prevent premature capping and help in manufacturing tablets with stronger edges. Tablets with softer edges resulted in tablets with chipped edges after drug layering. Studies also demonstrated that in order to attain coated tablets without defects, the hardness of core tablets should be greater than kp. Dissolution studies performed demonstrate that the dissolution profile of the tablets does not change with this increase in hardness.

Based on these findings, the batch record was updated and a new test batch of the drug product (lot 605R005) was manufactured by Additionally, due to our increased experience with the manufacturing process, the batch record for film coating was revised if the potency of the tablets from the previous drug is less than %. Please note that this was included in the bio-batch record but was inadvertently omitted from the proposed batch record submitted in the original application. Although the potency adjustment was not required in our original biobatch (lot # 605R004), a potency adjustment was necessary for the new test batch (lot # 605R005).

The new batch of the drug product, lot 605R005, had no rejects due to chipping.

The reconciliation of the finished product, lot 605R005, indicates that the weight of rejects was kg. Please note that this was due to samples taken after An in-process specification for the immediate release coating stage that will be used for commercial batches is provided under **Tab 3**.

b. Please manufacture a new batch reflecting the manufacture of a tablet with proper imprinting and provide a complete certificate of analysis for the batch. In addition,

[1] Please refer to Section VII. Manufacturing Process, subsection D. Minor Changes (Annual Report), which states "*Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form product when the ink is currently used on CDER-approved products.*"

please provide comparative content uniformity data on one hundred tablets for both batches, i.e. batch #605R004 and new batch with imprinted tablets.

Response

Andrx Pharmaceuticals has manufactured a new batch (Lot 605R005) of Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg, using batch records with the revisions indicated in the response to question 1. Also, as indicated in the above response, the batch was not imprinted as it is Andrx's intention to ink imprint the commercial batches and provide the required documentation (stability data) in the first annual report. The new batch was produced to demonstrate that the formulation and process included with our original ANDA is capable of producing tablets free from the defects seen in our original ANDA test batch.

The following are provided under the Tabs indicated:

- Executed batch record for lot 605R005 (**Tab 4**)
- Certificate of analysis for lot 605R005 (**Tab 5**)
- Comparative content uniformity data on one hundred tablets for the original bio-batch, Lot #605R004, and the new batch, Lot 605R005. (**Tab 5**)

c. Please provide friability data on the coated tablets to show stability of tablets.

Response

Friability testing was performed on the coated tablets for both lot 605R004 and lot 605R005. The testing was performed with 20 tablets, 200 drops in the friabilator. The results are as follows:
Lot 605R004: % Friability : %
Lot 605R005: % Friability

The friability of the tablets from both lots of the drug product is within the required specification limit of NMT %, thus confirming the quality of the tablets.

d. Since weight variation is affected by both the core tablets and active ingredient, content uniformity assay of coated tablet should be established as an in-process control.

Response

If the loratadine potency is less than % after drug layering, it may be necessary to adjust the potency . Thus, while content uniformity testing for pseudoephedrine sulfate in the intermediate tablets may be appropriate, and may be indicative of the pseudoephedrine sulfate levels in the final product, such testing for loratadine in the intermediate may not provide any useful information. We are therefore proposing to conduct content uniformity testing only on the finished product (waxed tablets), as part of the release requirement.

2. Both DMFs, for Loratadine and for Pseudoephedrine Sulfate USP, have been found deficient and the holders have been notified. Please provide the notification in your response that the DMF holders have responded to the deficiencies.

Response

Both DMF holders have acknowledged that they have responded to the DMF deficiencies. Please see **Tab 6** for notifications from ' (DMF # for loratadine) and (DMF for pseudoephedrine sulfate) indicating that the responses were submitted on June 9, 2000,