and September 15, 2000, respectively. Please note that (as stated in the letter from ownership of the DMF has been transferred from

3. **Please separate residual solvents from organic volatile impurities and provide a statement from the manufacturer indicating that per USP 24 <467>, no organic impurities other than are used in the manufacturing of drug substance, Loratadine.**

Response

We have revised the drug substance specifications for loratadine to separate the residual solvents from organic volatile impurities. Also, the manufacturer has provided a statement indicating that per USP 24 <467>, no organic volatile impurities (OVI) other than are used in the manufacture of loratadine. The revised specification and the OVI statement are provided under **Tab 7**.

4. **Please develop a more accurate and precise method for the analysis of Loratadine to replace assay and include a specification for the identification of Loratadine by method on the certificate of analysis.**

Response

We have adopted the drug substance manufacturer's assay method for the analysis of loratadine to replace the previously submitted method and will rely on the manufacturer's validation of the method. We have also included a specification for the identification of loratadine by on the certificate of analysis. A copy of a revised release specification and certificate of analysis for lot 9808015 of the drug substance, as well as the revised test method for loratadine which includes the assay method, are provided under **Tab 8.**

5. **Please identify each known impurity for Loratadine by its chemical name and tighten the impurities limits (individual known and total) based on the actual observed values and provide them on the revised certificate of analysis for Loratadine drug substance.**

Response

There are known impurities for loratadine. We have revised the release specification and the certificate of analysis for loratadine, lot 9808015, (**Tab 8**) to include the chemical names of these impurities and to tighten the specification limits for individual and total impurities.

6. **Please establish and include bulk loose and bulk tapped density specification for drug substance, Loratadine.**

Response

Physical parameters such as bulk loose and bulk tapped density are critical in manufacturing processes that involve compression of the active ingredient. Andrx's manufacturing process

Therefore, the bulk loose and bulk tapped density of loratadine will have no impact on the quality of the finished product and therefore should not be required.

7. **Please justify the need to test Loratadine for sulfate and report the result in actual numerical value.**

Response

Since is used in the synthesis of loratadine the sulfate test is performed to monitor the sulfate residue levels. As this is a limit test (USP<221>) it is not possible to report the actual numerical value, instead it is reported as 'Not more than' the stated limit – the limit being taken from the manufacturer's specifications.

8. **Please revise the Pseudoephedrine Sulfate specifications for ordinary impurities to as specified in the manufacturer's specifications (known, secondary and total). A method may be used for the identification and analysis of impurities. Actual numerical values should be reported on the certificate of analysis.**

Response

We have revised the specifications for pseudoephedrine sulfate to include known, secondary, and total impurities in the ordinary impurities test (see **Tab 9**). However, as pseudoephedrine sulfate is a compendial substance it is tested by the method specified in the current USP monograph and test results are reported accordingly. It is our intention to update the test method to comply with any changes in the compendial method.

9. **Please revise your re-testing schedule for active ingredients, Loratadine and Pseudoephedrine Sulfate, USP to state that the drug substance should be tested prior to its use, either one year after its original release date or its retest date and testing shall include all the analysis.**

Response

The active ingredients, loratadine and pseudoephedrine sulfate, have been assigned a retest period of 1 year from the date of the original release. The active ingredients will be tested prior to use, either one year after the original release date or the retest date.

Please note however, that retesting will include only those parameters deemed likely to be affected by storage, or affect the final product. Thus, re-testing of the loratadine and pseudoephedrine sulfate raw materials will include, at minimum, appearance, identification, loss on drying, impurities and assay.

10. **Please revise your re-testing schedule for inactive ingredients to state that the microbial testing for the inactives, where appropriate, should be conducted every year.**

Response

In accordance with Andrx's standard operating procedures for raw material testing all inactive ingredients (including those that require microbial testing such as magnesium stearate, talc, and lactose monohydrate) are retested every 2 years, unless a shorter expiration period is specified by the manufacturer. The tests will include appearance, identification, microbial limits (if applicable) and any other critical parameters.

11. You submitted the master and exhibit packaging record for tablets and capsules. Please provide the revised intended and exhibit batch packaging record for tablets only, which is the subject of this ANDA, packaged in 100's and 1000's.

Response

The template used to generate the packaging records in the original ANDA contained a non-specific header ("Master Packaging Record – Tablets and Capsules") to indicate that the template could be used for tablets or capsules. We do not intend to manufacture capsules for this product. We have therefore revised the exhibit packaging records to specify tablets as the dosage form (**Tab 10**).

12. Please provide the multiple internal reflectance data for 1500 HDPE bottle to meet the USP <661> requirements.

Response

The USP<661> multiple internal reflectance data for the 1500 cc HDPE bottle was previously provided on pages 486 and 487 of the original ANDA, copies of which are provided under **Tab 11**. The sample exhibited major absorption bands only at the same wavelengths as the spectrum of the USP HDPE RS lot F. Please note that at the time the testing was performed, the MIR analysis was done in-house at Andrx Pharmaceuticals. Subsequent lots will be tested by an outside firm,

13. Please establish a specification for tablet thickness based on the observed values and include it in the in-process controls.

Response

Based on the measurements made during the compression of the exhibit batch and four other experimental pilot batches we have established tablet thickness specifications of . The in-process controls summary table for post approval batches has been revised to include this information. A copy of the revised table is provided under **Tabs 12**. In addition, the proposed master batch records have been revised to incorporate this change. Tab 12 also includes the following revised proposed master batch records:

(i) Pseudoephedrine Sulfate Extended-Release Tablets, 240 mg (Core)
(ii) Loratadine And Pseudoephedrine Sulfate Extended-Release Tablets 10 mg/240 mg (Intermediate)
(iii) Loratadine And Pseudoephedrine Sulfate Extended-Release Tablets 10 mg/240 mg (Film Coated)
(iv) Loratadine And Pseudoephedrine Sulfate Extended-Release Tablets 10 mg/240 Mg (Imprinting)

Please note that the revised batch records include the changes described in the response to question 1, as well as the changes recommended by the Agency. The imprinting batch record was revised to indicate as was previously indicated, will be the solvents used for thinning the ink. A release specification for is also provided

under Tab 12. The change from was made based on recommendations from the manufacturer of the imprinting ink.

14. **testing should be performed as a routine in-process control for all production batches for this product. Between six to ten samples should be tested from each blend. Samples should be between 1 to 3 equivalent of tablet weight. The specifications for assay should be revised to be between % with an RSD of NMT %. Please modify your Master Batch Records to include this test as a routine in-process control.**

Response

We are proposing to perform testing on the first ten commercial production batches (inclusive of the three validation batches) of the pseudoephedrine sulfate blend. Blend samples will be taken that are representative of the entire batch. Between six to ten samples will be tested from each blend. The sample size shall not be greater than 3 times the tablet weight. The mean of the individual assay test results shall be between % with a relative standard deviation of not more than %. Since we are not proposing to perform this testing on an ongoing basis, we have not included it in our proposed manufacturing batch records.

15. **In-process specification for individual tablet weight is high. Please tighten to % of the theoretical tablet weight.**

Response

During the compression of the experimental and ANDA batches, the individual tablet weight specifications were frequently monitored and maintained at % of the tablet theoretical weight. These % specifications were treated as the upper and lower control limits. The upper and lower tolerance values were set at %. If any individual values fell between the upper control and upper tolerance value or between the lower control and lower tolerance value, the tablet press was adjusted to bring the weight back into the % range.

As recommended, the in-process individual weight specifications for future batches will be tightened to % of theoretical tablet weight and will be treated as the upper and lower control limits. The upper and lower tolerance limits will be maintained at % during the compression runs. This revision is reflected in the revised master production batch records provided under **Tab 12**.

16. **You submitted a copy of the blank batch record for the production size batches on December 14, 1999 in response to agency's comment, specifying the same in-process specification for hardness as listed for the ANDA batch kp). However, in-process specification for hardness submitted in the original application for post-approval production batches is kp). Please provide the revised in-process controls for the post-approval production batches reflecting the correct specification for hardness.**

Response

Please refer to the response to question 1. We have revised the hardness specification for production batches based on the results of compression optimization studies we conducted **(Tab 2)**. The studies demonstrated that could be avoided if tablet hardness is greater than kp. This increased hardness also helps in the attainment of coated tablets without defective edges. Based on these findings, the hardness specification was changed from the previously proposed acceptance

criteria of kp. The report provided under Tab 2 includes data demonstrating that the dissolution profile of tablets meeting both acceptance criteria is identical.

A revised in-process controls sheet for the post-approval production batches that reflects the change in specification limits for hardness (i.e. kp) is provided under **Tab 12**.

17. **Please revise your related compound specifications for the drug product release and stability to include limits for individual known, individual unknown and total impurities. Specifications reported for individual and total impurities are high. Please revise the impurity specifications to be closer to the actual observed values.**

Response

The drug product release and stability specifications have been revised to include limits for individual known, individual unknown, and total impurities. We have also lowered the impurities specification limits for individual and total impurities. The revised release and stability specifications are provided under **Tab 13**.

18. **Please establish a specification for moisture content in the stability controls.**

Response

As the drug product is not moisture-sensitive, we do not expect changes in moisture content during storage of the drug product. It is therefore our belief that inclusion of a specification for moisture content will not provide any useful information.

Section B

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

1. **Please update your specifications for all excipients and provide the revised certificate of analysis to refer to USP 24.**

Response

We have updated the specifications for all excipients to refer to USP 24. The revised specifications and corresponding certificates of analysis are provided under **Tab 14**.

2. **A satisfactory cGMP compliance evaluation of the firms referenced in the ANDA is required for approval.**

Response

We acknowledge that a satisfactory cGMP compliance evaluation of the firms referenced in the ANDA is required for approval.

3. **The FDA district office will be performing methods validation on the new drug substance and the finished dosage form after the related impurities issues are resolved.**

Response

We acknowledge your comment that the FDA district office will be performing methods validation on the new drug substance and the finished dosage form after the related impurities issues are resolved.

4. **Acceptance of your dissolution method and specifications for release and stability are contingent upon the results of the bio-equivalence review.**

Response

We acknowledge your comment that acceptance of our dissolution method and specifications for release and stability are contingent upon the results of the bioequivalence review.

5. **Your response must also address the labeling deficiencies.**

Response

A response to the labeling deficiencies outlined in your July 10, 2000, facsimile is provided in the following section.

6. **If the chipping issue is not resolved, we may not accept the previous batch 605R004 as the bio batch.**

Response

We acknowledge your comment that if the chipping issue is not resolved, the previous batch 605R004 may not be accepted as the biobatch. However, as demonstrated, no chipping occurred with the new batch, lot 605R005 which was produced using the same formulation and process as the original batch (please refer to the response to question 1 in Section A).

RESPONSE TO LABELING DEFICIENCIES (July 10, 2000 facsimile):

We have revised our labels and insert labeling as indicated (see attached facsimile from Debra Catterson, Labeling Reviewer). Please note the following:

1. We refer to the comment regarding the prominence of the established name and strength. The draft black-and-white labels provided in the original ANDA were for layout purposes only and were not representational with regard to the font sizes, prominence, etc. We have provided colored proofs that show the established name and strength as the most prominent information on the label. (OK) RC

2. As discussed in a telephone conversation between Jacqueline Davis, Regulatory Affairs Manager, Andrx Pharmaceuticals, and Debra Catterson, Labeling Reviewer, OGD, Andrx Pharmaceuticals uses the designation "extended-release" (hyphenated) on all its labels and labeling. With regard to the labeling comment to remove the hyphen between "extended" and "release", as is done on the labeling for the brand product, we prefer to retain the hyphen to maintain consistency throughout our product line. We note that the USP and other publications also use the designation "extended-release". This was agreed to by Ms. Catterson.

(OK) RC 1/3/02

3. This amendment contains four copies of the draft container labels and the package insert. In accordance with 21 CFR 314.94(a)(8)(iv), we have also provided a side-by-side comparison of our proposed labeling with our last submission with all differences annotated and explained.

Revised labels and labeling, as well as the side-by-side comparison are provided under **Tab 15**.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions or comments concerning this amendment, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

Diane Servello
Director Regulatory Affairs

Andrx
PHARMACEUTICALS, L.L.C.

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

December 15, 2000

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: General Correspondence

Dear Sir:

This letter is to inform you that the regulatory agent for the above referenced ANDA, Andrx Pharmaceuticals, Inc., has relocated to a new address. Please direct all future correspondences pertaining to the above ANDA to the following address and/or contact persons:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Fort Lauderdale, Florida 3331

Diane Servello, *Director of Regulatory Affairs*
Telephone: (954) 585-1412

Janet Vaughn, *Manager of Regulatory Affairs*
Telephone: (954) 585-1665

Facsimile: (954) 587-1054

Please note that the manufacturing site for the drug product has not changed. The new address for the administrative offices is contiguous with the manufacturing site.

Should you have any questions or comments concerning these changes, please contact Janet Vaughn at the above telephone number.

Sincerely,

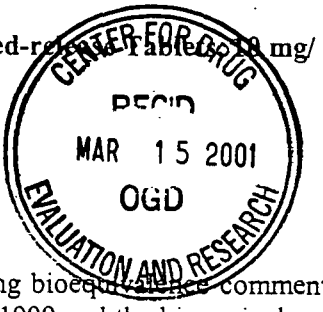
Diane Servello
Director, Regulatory Affairs

Andrx
PHARMACEUTICALS, L.L.C.

March 12, 2001

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



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 February 5, 2001 (copy attached) providing bioequivalence comments regarding our abbreviated new drug application submitted on December 14, 1999 and the bioequivalency data submitted on October 27, 2001. Pursuant to 21 CFR 314.96, Andrx Pharmaceuticals, Inc. ("Andrx") is herewith submitting an amendment responding to the comments included in your facsimile.

I. Bioequivalence response:

FDA Comment 1

You have resubmitted the validation data for method . instead of providing the data for method For method, you provided the data in your original submission from one pre-study validation run for each of the following:loratadine standards, loratadine QC samples, descarboethoxy loratadine standards and descarboethoxy loratadine QC samples (Appendix B, volume 1.6). You did not provide the following data: inter-day accuracy and precision, recovery of loratadine and descarboethoxy loratadine and stability of loratadine and descarboethoxy loratadine in extracted samples. Please provide the method validation data especially stability of loratadine and descarboethoxy loratadine in extracted samples for method. Also, for all three studies, provide the dates the samples were extracted and the dates the samples were analyzed to determine the storage duration.

Response:

A copy of the method validation report for method is provided under **Tab 1**. Stability data of loratadine and descarboethoxy loratadine in extracted samples is provided under **Tab 2**. The dates the samples were extracted and analyzed for all three studies are also provided under **Tab 2**.

FDA Comment 2

Several study samples were repeated due to poor recovery and only reassay values were reported. Please provide the original values, repeat values and a rationale for selecting the reported values for all reassays in the three studies. The relevant SOP for repeating the samples should be provided.

Response:
According to . rejection of samples is based on a predetermined internal standard peak area response criteria. Any unknown, calibration standard or quality control not meeting that criteria is rejected and therefore no result is obtained. In this case, the SOP requires the sample to be assayed again in order to obtain a reportable result. SOP entitled "Conduct of an Analytical Study", SOP #LP-PAL-3001, is also provided under **Tab 3**.

FDA Comment 3
Please provide the SOPs for accepting/rejecting a run.

Response:
SOP # LP-PAL-1003, "Criteria for Data Acceptance" is provided under **Tab 4**.

FDA Comment 4
We suggest that the dissolution testing should be conducted in
The following interim specifications are suggested:

Loratadine
Pseudoephedrine

Response:
Andrx has conducted dissolution testing using the dissolution medium suggested by the Agency. Results of this testing was submitted previously in the original ANDA and are again provided under **Tab 5**. The data indicates a slow release rate of loratadine from the Andrx formulation when the dissolution is conducted in For this reason, Andrx is proposing

Loratadine recovery studies performed in have been conducted using the

The results were as follows:

I. Loratadine Recovery Data

Concentration Level	V*# 1	V# 2	V# 3	V# 4	V# 5	V# 6	Average
50%							85.8%
100%							89.3%

II. Loratadine Recovery Data

Concentration Level	V# 1	V# 2	V# 3	V# 4	V# 5	V# 6	Average
50%							95.8%
100%							99.9%

* V: Vessel

The above results confirm that is not a suitable dissolution medium. is more suitable for Andrx's drug product as it provides an accurate measure of the release of both loratadine and pseudoephedrine sulfate from the drug product.

Andrx is proposing to conduct the dissolution in with following dissolution limits:

Loratadine
Pseudoephedrine

The proposed limits are based on actual observed data.

Should you have any questions concerning this submission, please do not hesitate to contact Janet Vaughn 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

April 19, 2001

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

[redacted] AMEND
N/AB

RE: Bioequivalence Telephone Amendment
Additional Comparative *In-vitro* Dissolution Data

Dear Mr. Buehler:

Please refer to Andrx Pharmaceuticals Abbreviated New Drug Application for Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets, 10 mg/240 mg, ANDA 75-706. Reference is also made to my April 9, 2001 telephone conversation with Dr. Nina Nwaba of the Division of Bioequivalence.

As requested, please find attached, additional comparative *in-vitro* dissolution data for Andrx's Loratadine and Pseudoephedrine Sulfate Extended-release Tablets versus the reference listed drug, Claritin-D® 24. The dissolution data was generated in
under the following conditions:

Should you have any questions or comments concerning this amendment, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

Diane Servello
Director Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 20 2001
OGD

Andrx
PHARMACEUTICALS, L.L.C.

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

July 17, 2001

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: MINOR AMENDMENT: CMC AND BIOEQUIVALENCE

ORIG AMENDMENT
N/Am

Dear Mr. Buehler:

Reference is made to your facsimiles dated June 13, 2001 (chemistry and bioequivalency comments) for the above referenced application (copy attached). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, L.L.C. is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the facsimile.

Response To Chemistry, Manufacturing And Controls Deficiencies

Section A

1. **Please note that DMF for Pseudoephedrine Sulfate, USP has been found deficient and the holder, has been notified of the DMF deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactory response to the Agency's deficiency letter has been submitted.**

Response

The holder of DMF has indicated that a response to the deficiency letter dated February 7, 2001 was submitted to the FDA on June 3, 2001 (Tab 1).

2. **Your response to deficiency 5 in the amendment dated December 14, 2000 regarding impurities specification is not satisfactory. The proposed impurity specifications for the loratadine drug substance are high. Please lower the acceptance criteria for individual known and total impurities for loratadine to be closer to the actual observed values.**

Response

The release specification for the loratadine drug substance has been revised to lower the acceptance criteria for individual known and total impurities as follows:

7-23-01

Test	Previously Proposed acceptance criteria	Current proposed acceptance criteria
	Not More Than %	Not More Than %
	Not More Than %	Not More Than %
	Not More Than %	Not More Than %
	Not More Than %	Not More Than %
	Not More Than %	Not More Than %
	Not More Than %	Not More Than %
Total impurities	Not More Than %	Not More Than %

The revised acceptance criteria are based upon actual observed data. A limit of NMT 0.1% is consistent with the International Conference on Harmonization (ICH) guideline for impurities in new drug substances. The guideline does not require identification of those impurities that do not exceed a level of 0.1%.

In addition, we have updated the procedure used for assay and chromatographic purity. Formerly, the standard and system suitability solutions contained impurities In the revised method, the standard solution contains only loratadine, while the system suitability solution contains loratadine and impurity V. Thus, the percentage of each impurity is determined by the total area of the peaks found in the sample. Provided under **Tab 2** are the revised release specification, revised certificate of analysis for loratadine lot 9808015, revised standard test method for the drug substance and an addendum to the method validation report.

3. **Please reduce the specification for heavy metals for loratadine drug substance to NMT ppm.**

Response

The specification for heavy metals for the loratadine drug substance has been reduced from ppm. A copy of the revised release specification is provided under **Tab 2**.

4. **Your response to deficiency 10 in the amendment dated December 14, 2000 regarding microbial test for inactive is not satisfactory. Please revise your re-testing schedule for inactive ingredients to specify that the microbial test should be performed every year for the inactive ingredients requiring microbial testing.**

Response

The re-testing schedule for inactive ingredients has been revised to specify that the microbial test will be performed every year for the inactive ingredients requiring microbial testing. Copies of the relevant release specifications indicating this change in re-testing (testing for the extension of release) schedule are provided under **Tab 3**.

5. **Your response to deficiency 14 in the amendment dated December 14, 2000 regarding testing is not satisfactory. It is recommended that testing for pseudoephedrine sulfate must be performed as a routine in-process control for all production batches for this product. Please modify the in-process controls in your Master Batch Records accordingly.**

Response

testing for the pseudoephedrine sulfate will be performed as a routine in-process control for all production batches for this product. A revised summary of in-process controls for post-approval production batches is provided under **Tab 4**. Please note that the batch record for the blend and the core tablets, code 115, has been separated and a new code number assigned to the blend, that is, code 119. A copy of and the revised proposed commercial batch records for the blend and the core tablets, as well as an in-process blend specification, are also provided under Tab 4.

6. **Your response to deficiency 17 in the amendment dated December 14, 2000 regarding impurity specification for drug product release and stability is not satisfactory. The proposed specifications for known, unknown and total impurities for drug product release and stability are high. Please lower the limit for impurities close to the actual observed values.**

Response

The drug product release and stability specifications have been revised to tighten the limits for individual known, individual unknown, and total impurities as follows:

The new limits are based on actual observed data. The revised release and stability specifications are provided under **Tab 5**. The procedure used to determine the percent of each impurity has also been

revised. The percentages are based on the total peak area in the sample rather than the concentration of each impurity standard. The revised test method, and an addendum to the method validation package are also provided under Tab 5.

7. **The dissolution testing should be incorporated into your stability and quality control program as recommended by the Division of Bio-equivalence:**

   The dissolution testing should be conducted in ' The test product should meet the following in interim specifications:

   Loratadine
   Pseudoephedrine

   Please provide the revised specifications accordingly.

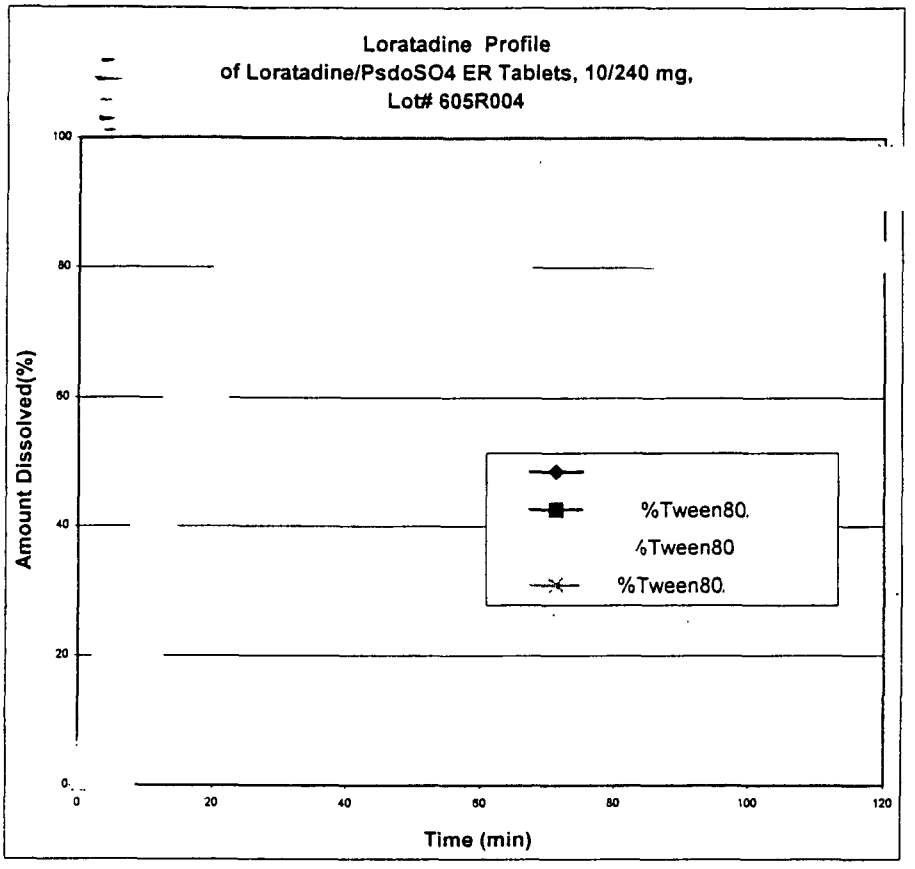
Response

Dissolution testing has been conducted using However, based on the data observed and recovery studies conducted in three concentrations of Tween 80 , Andrx is proposing The recovery studies show that while testing conducted in each of the three media provides results that can meet the proposed interim specifications, 100% recovery of the loratadine can only be achieved in

% Recovery of Loratadine in Different Dissolution Media

% Loratadine Dissolved in Different Media (n=12)

Time Point	Dissolution Medium			
Minutes		%Tween 80	Tween 80/	%Tween 80/
0	0	0	0	0
5	6	6	7	11
15	56	61	64	63
30	78	87	92	92
60	82	90	96	97
120	82	91	97	98



We believe that it is more appropriate to conduct the testing in a medium in which full recovery of the drug and thus accurate results can be achieved. We are therefore proposing to conduct the dissolution test . The product will be required to meet Andrx's proposed interim specifications as follows:

Loratadine
Pseudoephedrine

These limits are based on actual observed data using Andrx's test method. A copy of the drug product release and stability specification is provided under **Tab 5**.

8. **Your response to deficiency 18 in the amendment dated December 14, 2000 regarding moisture testing for drug product stability is not satisfactory. Please revise the stability protocol to state that moisture content for the drug product packaged in the marketed container will be monitored for the first three production batches and establish a specification for moisture content in the stability controls.**

Response

The stability protocol has been revised to state that moisture content for the drug product packaged in the marketed container will be monitored for the first three production batches and a specification for

moisture content will be established as a stability control. The revised protocol and stability initiation form are provided under **Tab 6**. The revised test method provided under Tab 5, includes a procedure for moisture determination.

9. **Please provide the full term (24 months) controlled room temperature stability data for both lots #605R004 (previous) and #605R005 (new) packaged in marketed container/closure systems for approval of this drug product.**

Response

Up to 24 months controlled room temperature stability data for lot# 605R004 (previous) and 6 months room temperature and 3 months accelerated stability data for lot #605R005 (new) in the container/closure systems intended for commercial lots, are provided under **Tab 7**. Based on the results of the accelerated stability studies from these two lots, and the 24 months data obtained for lot #605R004, Andrx is proposing a tentative expiration dating period of 24 months. Full term stability data (24 months) for lot #605R005 will be provided once it becomes available.

Section B

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

1. **Request to perform the methods validation for the new drug substance, Loratadine and the finished dosage form has been submitted to the FDA district office. Please submit samples promptly when requested.**

Response

Per the agency's request, samples of the drug substance and the finished dosage form were provided to the US Food & Drug Administration in Atlanta, Georgia, on June 15, 2001 for method validation.

2. **Your response to the labeling deficiencies is pending review. Any comment, if found will be communicated in a separate letter.**

Response

We acknowledge that our response to the labeling deficiencies is pending review and that any comment, if found, will be communicated to us in a separate letter.

Response to Bioequivalency Comments

We note that the Division of Bioequivalence has completed its review and has no further questions at this time.

We also note that the Division of Bioequivalence recommends that the following dissolution testing be incorporated into the stability and quality control programs:

The dissolution testing should be conducted
The test product should meet the
following interim specifications:

Loratadine
Pseudoephedrine

Andrx has conducted dissolution testing using However, based on the data observed and recovery studies conducted in three concentrations of Tween 80 Andrx is proposing to continue conducting the dissolution test The studies show that while testing conducted in each of the three media provides results that can meet the proposed interim specifications, 100% recovery of the loratadine can only be achieved in (Please refer to the response to comment #7).

We believe that it is more appropriate to conduct the testing in a medium in which full recovery of the drug and thus accurate results can be achieved. We are therefore proposing to conduct dissolution testing using The product will be required to meet the proposed interim specifications.

The release specifications and test methods for the drug product have been revised accordingly and are provided under **Tab 5**.

We acknowledge that the bioequivalency comments provided in the facsimile are preliminary and that the comments are subject to revision after review of the entire application.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions or comments concerning this amendment, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

Diane Servello
Director Regulatory Affairs

Andrx
PHARMACEUTICALS, L.L.C.

Via Facsimile to 301-594-0181

September 21, 2001

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

NEW CORRESP
NC/610

RE: Request for Teleconference
ANDA 75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

Dear Dr. Nwaba:

As discussed by telephone yesterday, Andrx Pharmaceuticals is requesting a teleconference to discuss the dissolution method and specifications for the above-referenced product, particularly in relation to the agency's September 6, 2001 letter.

As we would like to resolve this matter as expeditiously as possible, we are requesting the teleconference for next week at a mutually convenient date and time, possibly the morning of Tuesday, September 25, 2001. The meeting should take approximately 45 minutes.

We are requesting that the meeting be attended by yourself, as well as the team leader and reviewer from Bioequivalence.

The following Andrx representatives will be participating:

- Diane Servello, Regulatory Affairs Director
- Francisco Alvarez, Ph.D., Analytical Research Director
- Zhengjian (Jack) Chen, Analytical Research Manager
- Janet Vaughn, Regulatory Affairs Manager

I will be contacting you shortly to confirm the date and time for the teleconference. Thank you for your assistance in this matter. If you have any questions please contact Janet Vaughn at (954) 585-1665 (phone) or (954) 587-1054 (facsimile).

Sincerely,

Diane Servello
Director Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 25 2001

Andrx
PHARMACEUTICALS, L.L.C.

ORIG AMENDMENT
N/A'S

ANDA 75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets
10 mg/ 240 mg

September 26, 2001

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

RE: BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler:

Reference is made to your facsimile dated September 6, 2001 (bioequivalence comments) for the above referenced application (facsimile attached). Reference is also made to our September 25, 2001 telephone conference with Dr. Nina Nwaba (Project Manager), Dr. Nerrkar (Team Leader) and Dr. Vhariwal (Bioequivalence Reviewer) of your office. In accordance with 21 CFR 314.96, Andrx Pharmaceuticals, L.L.C. is submitting a complete response to the deficiencies listed in the facsimile.

1. **You have submitted loratadine recovery information in this amendment. The dissolution data in this amendment are identical to the dissolution data submitted earlier (March 12 and April 19, 2001). The recovery data do not justify change of dissolution medium from especially in light of the fact that in the former medium loratadine (immediate release component) dissolution testing passes specification at Moreover, the lowest concentration of the detergent is recommended for the dissolution testing because there is no significant difference in the dissolution at the three concentrations of Tween 80 used in the dissolution medium. The variability is less when is used compared Therefore; your request for change of dissolution medium is denied.**

   Response:
   As revealed in the September 25, 2001 teleconference, the July 17, 2001 amendment did in fact include additional dissolution data for samples of the bio-lot, lot # 605R004, stored for up to 24 months under controlled room temperature, as well as, data for samples from a second test batch, lot #605R005, stored for up to 6 months under controlled room temperature and 3 months under accelerated conditions.

   We agree with the Agency that the test results provided in the March 12 and April 19, 2001 amendments did not indicate any significant difference in the dissolution at the three concentrations of Tween 80 and that the variability appears to be less when % Tween 80 is used compared to)%. We also agree with the Agency that a lower concentration of the surfactant would be preferable. However, we believe that:

   (a) The recovery data from the various concentrations of Tween 80 cannot be overlooked. The accuracy of an analytical method is defined as the closeness of test results obtained by that

method to the true value. Accuracy is calculated as the percentage of recovery by the assay of the known added amount of analyte in the sample. Our current acceptance criterion, as defined in our method validation report provided in the original ANDA, is a percent recovery of not greater than %. This acceptance criterion is generally required and expected for a chemistry review of an application. Thus, we fear that a dissolution medium of % Tween 80 will not allow us to meet the required standards for accuracy of our drug release method as we can only obtain a recovery of %.

(b) Dissolution in a medium from which 100% recovery cannot be obtained presents difficulty in interpreting test data, particularly in the case of borderline results. As we know 100% recovery cannot be achieved, it will be difficult to determine whether failing and even passing results are in fact an accurate measure of the amount of drug released from the tablet.

(c) The variability observed in the various dissolution media is due to variability in the drug product (tablet to tablet) in addition to the variability of the analytical method. Recovery studies provide a better prediction of accuracy in an analytical procedure, as they are not influenced by product variability.

Please note, that it is our desire to cooperate with the agency, but we would also like to provide the agency with data we believe to be most accurate.

2. **Besides the change in dissolution medium, you have also requested change in the loratadine dissolution specification from NLT % (Q) in 30 minutes to NLT % (Q) in 60 minutes. The resubmitted dissolution data do not support the change requested by you. Therefore, request for change in loratadine specification is denied.**

Response:
As indicated in the September 26 teleconference, the Division was not provided with the stability data included in the July 17, 2001 minor amendment to the ANDA and thus, the agency believed that Andrx lacked sufficient justification for our proposed specification limits. In fact, the limits proposed by the Division were based on the limited data previously provided.

We are therefore providing up to 24 months controlled room temperature stability data for the first test batch of the drug product, lot #605R004, and up to 6 months room temperature and 3 months accelerated stability data for a second batch of the drug product, lot # 605R005 for the Agency's review (Tab 1). This data provides the basis for our proposal. As it shows, the drug product would fail to meet the Agency's proposed specification limit of NLT than % (Q) in 30 minutes at various time points for each test batch (Tab 2). In fact, at 24 months RT, lot #605R004 would fail to meet the Agency's proposed criteria, even at the level. The possibility of failure would be even greater in a dissolution medium in which 100% recovery cannot be attained.

3. **You also requested to widen the dissolution specification ranges for pseudoephedrine. The resubmitted data do not justify your request. The request is therefore denied.**

Response:
Andrx's proposed specification limits are based on the data provided under Tab 1, which indicate that our drug product would have difficulty meeting the Agency's proposed limits. It should be noted that all dissolution results presented in this amendment were generated using % Tween 80 in the dissolution medium. It is not possible for us to predict what the dissolution results would be using Tween 80 at the % level.

Lot #605R004

Up to 24 months controlled room temperature and 3 months accelerated data

Timepoint	Min %	Max %
1 hr		
2 hr		
4 hr		
8 hr		
16 hr		

Lot #605R005

Up to 6 months controlled room temperature and 3 months accelerated data

Timepoint	Min %	Max %
1 hr		
2 hr		
4 hr		
8 hr		
16 hr		

*At this timepoint, up to 4 vessels would not meet the Agency's proposed limits of %.

4. **The initial dissolution specifications are set on the basis of the dissolution data of the bio-lot. Please refer to the criteria for setting dissolution specifications outlined in the FDA Guidance for Industry, "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997."**

Response:
Please note that Andrx's proposed dissolution specifications are based on dissolution data obtained for the bio-lot at initial release and up until the proposed expiration dating period for the drug product (24 months). However, as the Agency recommends, we will continue to refer to the criteria for setting dissolution specifications outlined in the FDA Guidance for Industry.

5. **The Agency may consider your request for change in the specifications if you can provide justifiable dissolution data on three production lots of this drug product.**

Response:
As we indicated in the September 26, 2001 teleconference, we have provided the agency with data from two test batches, lot #605R004 and lot #605R005. We believe the data from these lots provide sufficient justification for our proposed specifications. We are concerned that if the test batches, particularly the lot used for our bioequivalence study (lot #605R004), are unable to meet the Agency's proposed specifications, then it will most likely be very difficult for commercial batches to conform.

6. **The following dissolution testing will need to be incorporated into your stability and quality control programs:**

The dissolution testing should be conducted . The test product should meet the following interim specifications:

Loratadine
Pseudoephedrine

Response:
Based on recovery data and the stability data obtained for two lots of the drug product, we are once more proposing to conduct the dissolution test in
. with the following specifications:

Loratadine
Pseudoephedrine

We understand that the Division of Bioequivalence did not receive all the data included with our July 17, 2001 amendment. We are requesting that our proposed dissolution specification be evaluated against the data included in this amendment.

Should you have any questions concerning this submission, please do not hesitate to contact Janet Vaughn 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 and Pseudoephedrine Sulfate Extended-release Tablets
10 mg/ 240 mg

October 16, 2001

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

FA

RE: FAX AMENDMENT – CHEMISTRTY COMMENTS ORIG AMENDMENT

Dear Mr. Buehler:

Reference is made to your facsimile dated September 18, 2001 (chemistry comments) for the above referenced application (facsimile attached). In accordance with 21 CFR 314.96, Andrx Pharmaceuticals, L.L.C. is submitting a complete response to the deficiencies listed in the facsimile.

A. Deficiencies:

1. **Your response to deficiency 2 in the amendment dated July 17, 2001 is not satisfactory. Please lower the acceptance limit for total impurities for loratadine drug substance or provide justification for the proposed limit %).**

Response:
The release specification for the loratadine drug substance has been revised to lower the acceptance limit for total impurities to %. The revised specification is provided under **Tab 1**.

2. **Please correct the assay specification for loratadine drug substance, tab 2, amendment dated July 17, 2001 and provide the revised specifications.**

Response:
The acceptance criteria for assay specifications have been revised to the following:

Test	Previously proposed acceptance criteria	Current proposed acceptance criteria
Assay (dried basis)	%	%

The revised specification can be found under **Tab 1**.

3. **Your response to deficiency 6 in the amendment dated July 17, 2001 is not satisfactory. Please lower the acceptance limit for total impurities for drug product release and stability or provide justification for the proposed limit %).**

Response:

The release specification for the drug product, Loratadine and Pseudoephedrine Sulfate Extended-release (ER) Tablets, 10 mg/240 mg, has been revised to lower the acceptance limit for total impurities to ≤ %. The revised specification is provided under **Tab 2**. A revised stability initiation form is also provided under this tab.

4. **It is noted that there is a significant drop in the stability assay value for loratadine at 24 months test point time, lot #605R004, page 0111. Up and down trend is also observed for loratadine assay for room temperature and accelerated stability studies, lot #605R005, pages 0121, 0123, and 0125. However, no increase in degradation of the drug product is observed. Please provide explanation and justify that the analytical method for determining the assay and degradation for this drug product is stability indicating.**

Response:

Based on information provided by the manufacturer of each drug substance, as well as the results of forced degradation studies (stress studies) performed on the drug product, the following related substances are monitored as possible degradation products:

As demonstrated in the method validation report provided in the original ANDA, Andrx's standard test method is able to detect and quantify each of the above degradation products, and is therefore stability indicating.

The variability of the loratadine assay values observed during the stability is attributed to the inherent variability of loratadine in the product, rather than degradation of the active ingredient.

The manufacturing process

Content uniformity testing performed on 100 tablets of each test batch of the drug product, lot numbers 605R004 and 605R005 demonstrates this variability:

Lot #	LORATADINE				PSEUDOEPHEDRINE SULFATE			
	Av. (% LC)	Min. (% LC)	Max. (% LC)	%RSD	Av. (% LC)	Min. (% LC)	Max. (% LC)	%RSD
605R004	96.5			6.5	99.2			1.8
605R005	100.4			6.4	99.7			1.7

As shown, the pseudoephedrine sulfate component of the drug product remained within the range of % with a % RSD of less than %. However, the range of values for the loratadine component was outside of % with % RSD greater than .

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

1. **Review of your response to deficiency 7 in amendment dated July 17, 2001 will not be completed until the issues on dissolution specifications are resolved with the Division of Bioequivalence. Please submit the final dissolution specifications after the issues are resolved toward drug product release and stability in order to complete the chemistry review.**

Response:

We note and acknowledge that the review of our response to deficiency 7 in the amendment dated July 17,2001 will not be completed until the results on dissolution specifications are resolved with the Division of Bioequivalence. Final dissolution specifications will be submitted after the issues are resolved toward drug product release and stability in order to complete the chemistry review.

2. **A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.**

Response:

We note and acknowledge that a review of the labels and labeling is pending and that deficiencies found will be sent to us under separate cover.

Should you have any questions concerning this submission, please do not hesitate to contact Janet Vaughn at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

Andrx
PHARMACEUTICALS, L.L.C.

ANDA 75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets
10 mg/ 240 mg

January 23, 2002

N/AM

ORIG AMENDMENT

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

RE: MINOR AMENDMENT – CHEMISTRTY AND BIOEQUIVALENCY COMMENTS

Dear Mr. Buehler:

Reference is made to your facsimile dated December 13 2001 (chemistry and bioequivalence comments) for the above referenced application (facsimile attached). In accordance with 21 CFR 314.96, Andrx Pharmaceuticals, L.L.C. is submitting a complete response to the deficiencies listed in the facsimile.

Chemistry Comments:

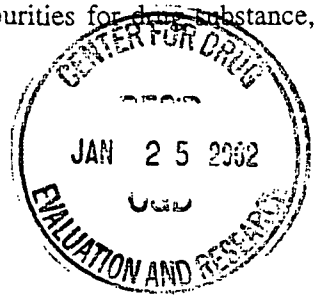
A. Deficiencies:

1. DMF **for Loratadine drug substance has been found inadequate and the DMF holder, has been informed. Please provide notification in your response that the DMF holder has responded to the Agency's deficiency letter.**

Response:
Tab 1 includes a letter from the holder of DMF indicating that a response to the deficiencies was submitted to the agency on December 20, 2001.

2. **You have been requested twice previously to tighten the acceptance limit for total impurities for drug substance, drug product release, and stability to reflect the actual observed test values obtained for the ANDA batch. However, your revised specification in the amendment dated October 16, 2001 (deficiency 1 & 3) is still high. Please lower the specification further to more accurately reflect the results obtained for the ANDA batch.**

Response:
The acceptance limit for total impurities for drug substance, drug product release, and stability has been tightened as follows:



	Previously Proposed acceptance criteria	Current proposed acceptance criteria
Drug Substance	Not more than %	Not more than %
Drug Product	Not more than %	Not more than %

The proposed acceptance criteria reflects the actual observed test values obtained for the ANDA batch. Revised specifications are provided under **Tab 2**.

3. **Please revise and provide the final dissolution acceptance criteria for Loratadine /Pseudoephedrine Sulfate Extended Release Tablets according to as recommended by the Division of Bioequivalence for release and stability. Please provide the room temperature stability data and if possible, accelerated stability data to support the revised dissolution specifications.**

Response:
The release and stability specifications for the drug product have been revised to include the dissolution acceptance criteria recommended by the Division of Bioequivalence. The revised release specification, stability initiation forms and standard test method is provided under **Tab 2**.

4. **Please provide data to justify that the three other synthetic impurities found in the Loratadine drug substance (impurities are not degradants of the drug product.**

Response:
Based on information provided by the manufacturer of the drug substance, the following related compounds may be present in the loratadine raw material as a result of the method of manufacture used:

As part of method development, the drug product was subjected to various stress conditions, the results of which are documented in the original ANDA (page 687). Based on this study, only (related compounds A (and B) are monitored in the drug product as degradation products. were not detected in the stress study.

Table 1 summarizes results of the forced degradation studies performed on the drug product (the Loratadine component).

Table 1. Summary of Loratadine forced degradation study (D24)

Observed Impurity	Condition				
	Acid	Base	Oxidation	Light	Heat
	No	No	No	No	No
	No	No	No	No	No
	No	No	No	No	No
	No	Yes	No	No	No
	No	No	No	No	No

is formed as a result of oxidation of Loratadine at the (refer to *page iv* - Pathway B. b) while the formation of may occur under basic conditions (*page iv* - Pathway B. d).

In theory, the formation of , is virtually impossible considering the nature of the reactions that would be required.

Formation of requires

. This is supported and confirmed by the forced degradation studies documented in the original ANDA.

Formation of requires

into the final product.

The formation of

It should also be noted that our current standard test method is capable of detecting and quantifying all impurities, as shown in the sample chromatogram provided under **Tab 3**. This chromatogram was derived using our current test procedure. In addition, as shown in the sample chromatogram of samples stored for up to 24 months RT (also provided under Tab 3), none of the above impurities have been detected in the drug product. (Stability data for lot numbers 605R004 (24 months) and 605R005 (12 months) is provided under **Tab 4**).

Both theoretical and empirical evidence sufficiently demonstrate that impurities are not degradation products but are a consequence of the synthetic route used in the manufacture of the Loratadine raw material.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

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

1. Labeling comments, if any, will be sent to you under separate cover.

Response:
We note and acknowledge that the labeling comments, if any, will be sent to us under separate cover.

Bioequivalency Comments:

1. **Loratadine: Your stability results do not meet the acceptance criteria at stage 1 testing (each unit is not less than Q- %) at some storage time points. However, the results meet the criteria at stage 2 testing. The acceptance criteria for stage 2 testing is average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q %. Therefore, a specification of NLT % (Q) in 60 minutes is not recommended.**

Response:
The drug product specification has been changed to NLT % (Q) in 30 minutes for the loratadine component of the drug product. The revised drug product specification, stability initiation form and standard test method are provided under **Tab 2**.

2. **The following dissolution testing will need to be incorporated into your stability and quality control programs:**

   The dissolution testing should be conducted in 900 mL of 0.10% Tween 80 in SGF at 37°C using USP Apparatus 1 (basket) at 100 rpm. The test product should meet the following interim specifications:

Loratadine	**NLT**	**% (Q) in 30 minutes**
Pseudoephedrine	**1h**	**%**
	2h	**%**
	4h	**%**
	8h	**%**
	16h	**NLT %**

Response:
Dissolution testing will be conducted in 900 mL of 0.10% Tween 80 in SGF at 37°C using USP Apparatus 1 (basket) at 100 rpm, as recommended by the Division of Bioequivalence. The test product will be required to meet the recommended interim specifications. The revised release specification, stability initiation form and standard test method are provided under **Tab 2**.

We acknowledge that the bioequivalency comments provided in the facsimile are preliminary and that the 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.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions concerning this submission, please do not hesitate to contact Janet Vaughn at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

Andrx
PHARMACEUTICALS, L.L.C.

ANDA 75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets
10 mg/ 240 mg

July 3, 2002

NC

NEW CORRESP

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: Patent Certification

Dear Sir:

Please refer to our abbreviated new drug application (ANDA) for the above-mentioned drug product. We are amending the application by providing revised patent certifications that reflect the expiration dates of the patents based on their assigned pediatric exclusivities.

Should you have any questions regarding this amendment, or if additional information is required, please do not hesitate to contact Janet Vaughn at (954) 358-6125 *(Tel.)* or (954) 358-6350*(Fax)*. All written communication regarding this ANDA may be directed to the above address.

Sincerely,

Diane Servello
Senior Director, Regulatory Affairs

RECEIVED
JUL 0 5 2002
OGD / CDER

Andrx™
PHARMACEUTICALS, INC.

NEW CORRESP

August 29, 2002

NC

Gary Buehler
Director, Office of Generic Drugs, HFD-600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

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

Dear Mr. Buehler:

We refer to the above-referenced abbreviated new drug application ("ANDA"). Pursuant to §314.72 Andrx Pharmaceuticals, L.L.C. is notifying the agency of a change in ownership for this ANDA. In June 2002, Andrx Pharmaceuticals, L.L.C. was merged into Andrx Pharmaceuticals, Inc.

Accordingly, all rights to this ANDA have been transferred to:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Ft Lauderdale, Fl 33314
Attention: Diane Servello, Senior Director of Regulatory Affairs
Phone: (954) 358-6100 or (954) 358-6114 (direct line)
Fax: (954) 358-6350

Andrx Pharmaceutical, L.L.C. certifies that the new owner has a complete copy of this ANDA. Enclosed is a signed 356H form executed by Andrx Pharmaceuticals, LLC and a signed 356H form executed by Andrx Pharmaceuticals, Inc. will be sent to you separately, together with its (1) commitment to abide by the agreements, promised and conditions contained in the ANDA; (2) statement regarding the effective date of the change; and (3) statement that a complete copy of the application is in their possession.

Please do not hesitate to contact me at (954) 581-7500 if you require additional information.

Sincerely,

Scott Lodin,
Member, Andrx Pharmaceuticals, L.L.C.

Enclosure: Signed Form 356H

RECEIVED
AUG 30 2002
OGD / CDER

9-10-02

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS INC.

NEW CORRESP

NC

August 28, 2002

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

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

Dear Mr. Buehler:

We refer to a letter dated August 28, 2002 from Andrx Pharmaceuticals, Inc. notifying the agency of a transfer of ownership of the above referenced abbreviated new drug application ("ANDA). The transfer of ownership was effective as of June 2002.

Accordingly, all rights to this ANDA have been transferred to:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Ft Lauderdale, Fl 33314
Attention: Diane Servello, Senior Director of Regulatory Affairs
Phone (954) 358-6100 or (954) 358-6114 (direct line)
Fax: (954) 358-6350

Andrx Pharmaceuticals, Inc. certifies the following:

1. A commitment is made to abide by the agreement, promises and conditions contained in this ANDA
2. A complete copy of the ANDA is in the possession of Andrx Pharmaceuticals, Inc.
3. A signed application form is attached

Please continue to address all correspondence regarding this ANDA to the above address.

If you require additional information, please do not hesitate to contact me ant (954) 358-6114.

Sincerely,

Diane Servello,
Senior Director, Regulatory Affairs
Andrx Pharmaceuticals, Inc.

RECEIVED
AUG 3 0 2002
OGD / CDER

Andrx™
PHARMACEUTICALS INC.

ANDA 75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg

September 30, 2002

ORIG AMENDMENT
N/AM FPL

Gary Buehler,
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: MINOR AMENDMENT – Final Approval Requested

Dear Mr. Buehler:

Please refer to your July 9, 2002 tentative approval letter for the above referenced ANDA. Andrx Pharmaceuticals, Inc. is requesting final approval of this ANDA. The ANDA was originally submitted on September 21, 1999 and accepted for filing on December 15, 1999. It included both paragraph III (for patent # 4,282,233) and paragraph IV (for patent #'s 4,659,716; 4,863,931 and 5,314,697) certifications. The NDA and patent holders for the reference-listed drug were notified on February 12, 2000 of the submitted paragraph IV certification, and an action was brought against Andrx within the 45 day period specified in section 505(j)(5)(B)(i) of the Act.

We believe the application will be entitled for final approval on or after December 19, 2002 for the following reasons:

- The pediatric exclusivity for patent #4,282,233 will expire on December 19, 2002
- The 30 month period since the date of receipt of the paragraph IV notification required under Section 505(j)(5)(B)(iii) expired on August 12, 2002.

No changes in the labeling or the chemistry, manufacturing and controls data have been made to the application since the date of the tentative approval. Enclosed please find twelve copies of the final printed labels (six copies are included with the archival copy and six copies are included with the review copy).

Should you have any questions concerning this submission, please contact Diane Servello (954) 358-6114 (telephone) or (954) 358-6350 (fax).

Sincerely,

Diane Servello
Senior Director, Regulatory Affairs

RECEIVED
OCT 0 2 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS, INC.

December 26, 2002

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

RE: ANDA #75-706; Loratadine and Pseudoephedrine Sulfate Extended-release Tablets, 10 mg/240 mg
Amendment

Dear Mr. Buehler:

Reference is made to your facsimile dated December 3, 2002 providing for the over-the-counter (OTC) use of Claritin® D24 (copy attached). As Claritin® D24 will no longer be marketed with prescription labeling, we are amending the application to provide a revised Form FDA 356h to indicate the correct reference listed drug (RLD). In addition, we are requesting the withdrawal of all previously submitted labeling and we are providing final printed labeling which is consistent in content and format with that which provides for the OTC use of the RLD.

In this regard, we have enclosed the following:

1. Twelve copies of container labels for 100's and 1000's bottle counts. (Six copies are included with the archival copy and six copies are included with the review copy.)
2. In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison, annotating the revisions to our labeling is included.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6125.

Sincerely,
ANDRX PHARMACEUTICALS, INC.

Janet Vaughn
Sr. Manager Regulatory Affairs

RECEIVED
DEC 27 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS, INC.

ANDA 75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets
10 mg/ 240 mg

January 6, 2003

Sent via fax to Sarah Kim at
(301) 594-0180
Hard copy to follow

NEW CORRESP
NC

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

RE: TAMPER-EVIDENT PACKAGING METHODOLOGY

Dear Mr. Buehler:

Reference is made to your facsimile dated December 3, 2002 providing for the over-the-counter (OTC) use of Claritin® D24. Reference is also made to our December 26, 2002 labeling amendment to the above-referenced ANDA in which we provided a revised Form FDA 356h to indicate the correct reference listed drug (RLD) and requested the withdrawal of all previously submitted labeling. Final printed labeling which is consistent in content and format with that which provides for the OTC use of the RLD was also provided.

As the labeling indicates, Andrx's drug product will be supplied is tamper-evident packaging as required by 21 CFR §211.132. Tamper-evidence is provided by the use of a safety-seal under the closure. This safety seal is paper-backed aluminum foil coated with a clear heat-sealable coating blend of high molecular weight ethylene and vinyl acetate copolymers. It is applied by heat induction to the plastic container and offers a high degree of tamper-resistance. Proper application of the seal is verified during each packaging operation. It must be torn or broken to open the container and remove the product. It cannot be removed and reapplied without leaving visible evidence of entry. The seal is imprinted, "SEALED for YOUR PROTECTION".

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions concerning this submission, please do not hesitate to contact the undersigned at (954) 358-6125 (telephone) or (954) 358-6350 (fax).

Sincerely,

Janet Vaughn
Senior Manager of Regulatory Affairs

RECEIVED
JAN 07 2003
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS, INC.

January 7, 2003

NEW CORRESP

NC

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

Re: ANDA 75-706; Loratadine & Pseudoephedrine ER Tablets, 10 mg/240 mg

Dear Mr. Buehler:

We refer to the abbreviated new drug application ("ANDA") listed above. 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 December 13, 2002.

All rights to this ANDA have been transferred to:

Andrx Pharmaceuticals L.L.C.
4955 Orange Avenue
Ft Lauderdale, FL 33314
Attention: Janet Vaughn, Senior Manager of Regulatory Affairs
Phone: (954) 358-6100 or (954) 358-6125 (direct line)
Fax: (954) 358-6350

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.

Please do not hesitate to contact me at (954) 585-1751 if you require additional information.

Sincerely,

Scott Lodin
Executive Vice President and General Counsel

RECEIVED
JAN 0 9 2003
OGD / CDER

Andrx
PHARMACEUTICALS
LLC

ANDA #75-706
Loratadine and Pseudoephedrine Sulfate Extended-release Tablets
10 mg/240 mg

ORIG AMENDMENT

N/A

January 29, 2003

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

Amendment – OTC Labeling

Dear Mr. Buehler:

Reference is made to the January 8, 2003 telephone conversation with Debbie Catterson, Label Reviewer, Office of Generic Drugs. We have revised the label as instructed and revised final printed labels are being submitted as follows:

1. Twelve copies of container labels for 100's and 1000's bottle counts. (Six copies are included with the archival copy and six copies are included with the review copy.)
2. In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison, annotating the revisions to our labeling is included.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6125.

Sincerely,

Janet Vaughn
Sr. Manager Regulatory Affairs

RECEIVED
JAN 30 2003
OGD / CDER