Table 7. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg in pH 4.2 Acetate Buffer

'doephedrine Sulfate

.od: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														1	7.1
0.25														8	6.9
0.5														14	4.6
1														23	4.1
2														36	3.7
4														53	3.4
8														75	3.3
12														89	3.4
16														96	3.3
20														101	3.4

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														1	44.5
0.25														8	2.1
0.5														14	2.2
1														23	1.6
2														35	1.1
4														52	0.6
8														75	0.6
12														88	0.6
16														96	0.6
20														100	0.7

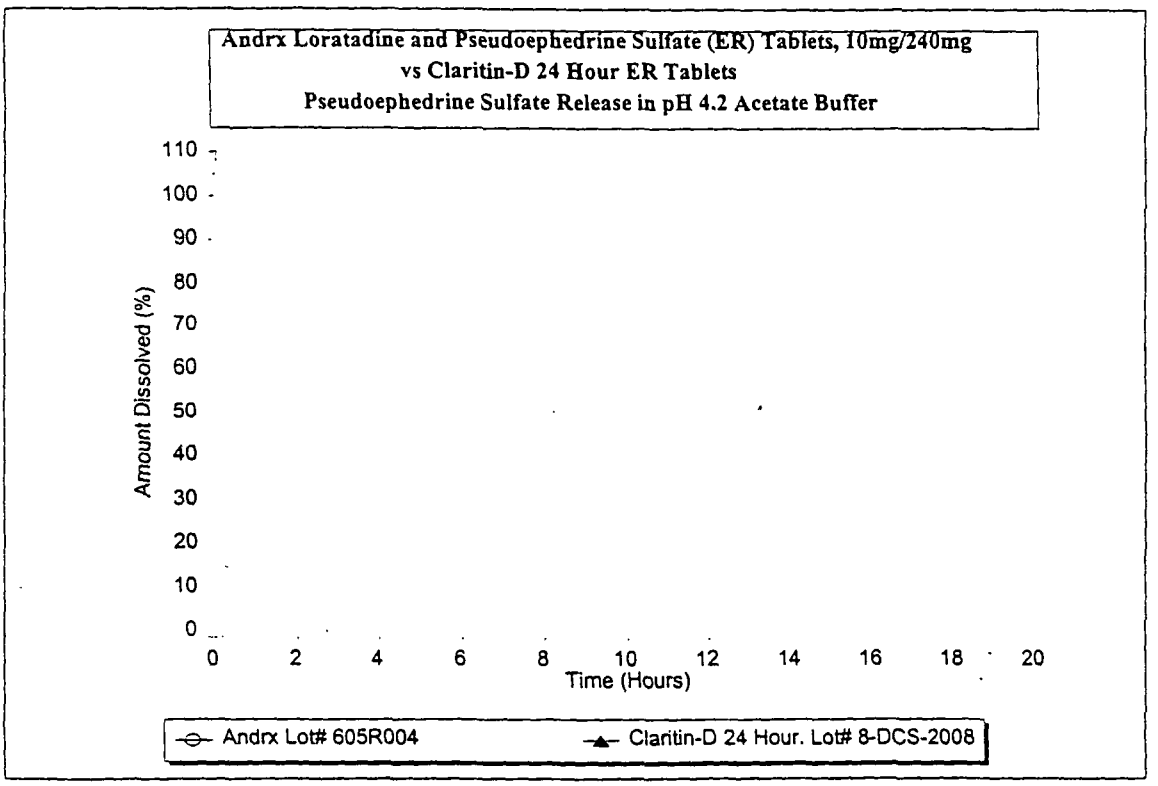

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Table 8. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg in pH 6.5 Phosphate Buffer

adine

Method: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														6	28.0
15														10	11.4
30														12	5.6
60														14	4.1
120														15	5.2

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														4	8.7
15														9	6.7
30														13	6.1
60														15	4.9
120														16	3.2

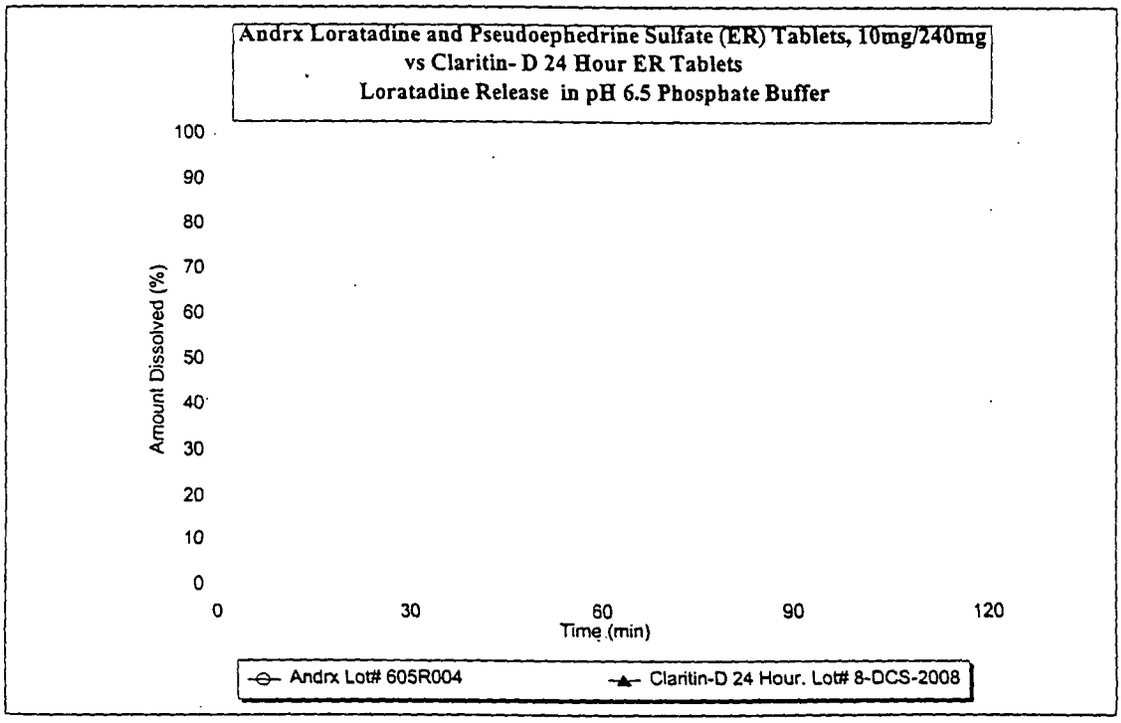

Table 9. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg in pH 6.5 Phosphate Buffer

doephedrine Sulfate

d: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														0	ERR
0.25														3	27.3
0.5														12	5.8
1														22	2.4
2														35	1.7
4														52	1.8
8														74	1.7
12														87	1.4
16														94	1.2
20														98	1.0

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0				0	0	0	0	0	0	0	0	0	0	0	0
0.0833														0	346.4
0.25														5	10.2
0.5														10	5.2
1														17	2.9
2														29	1.4
4														45	1.2
8														66	0.7
12														79	0.9
16														86	1.0
20														89	0.8

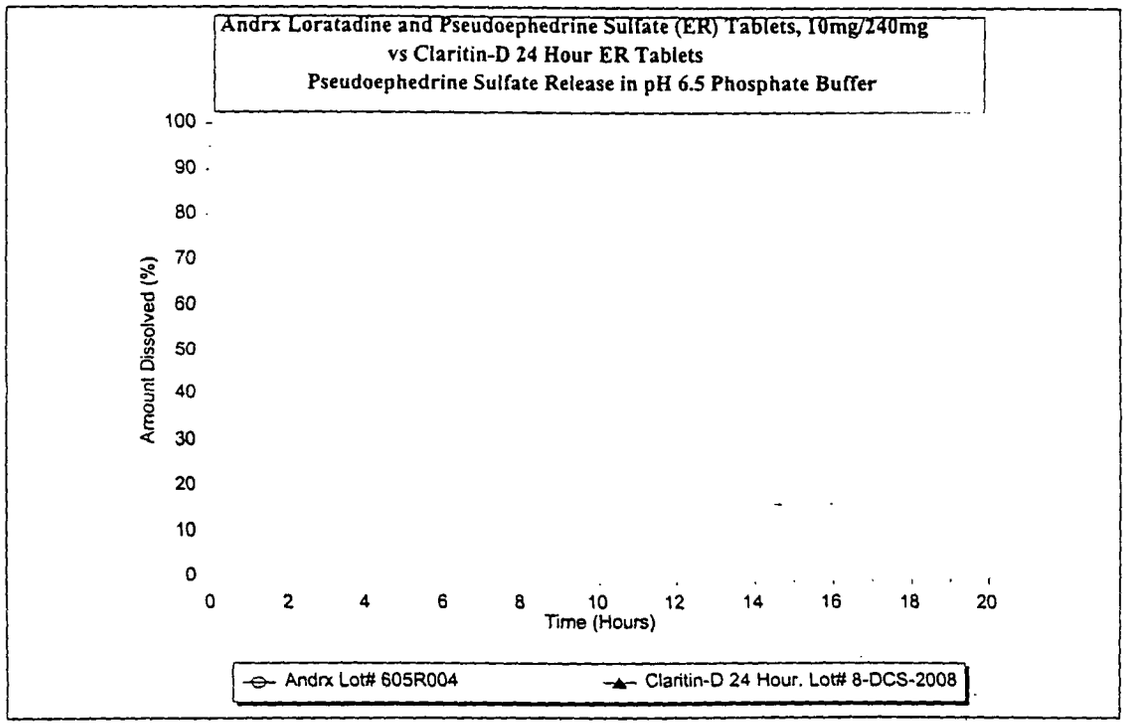

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Table 10. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg in pH 7.5 Phosphate Buffer

tadine

d: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														4	16.3
15														8	11.0
30														8	14.7
60														9	8.3
120														11	4.6

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														3	52.8
15														7	14.3
30														10	22.9
60														12	19.8
120														13	16.9

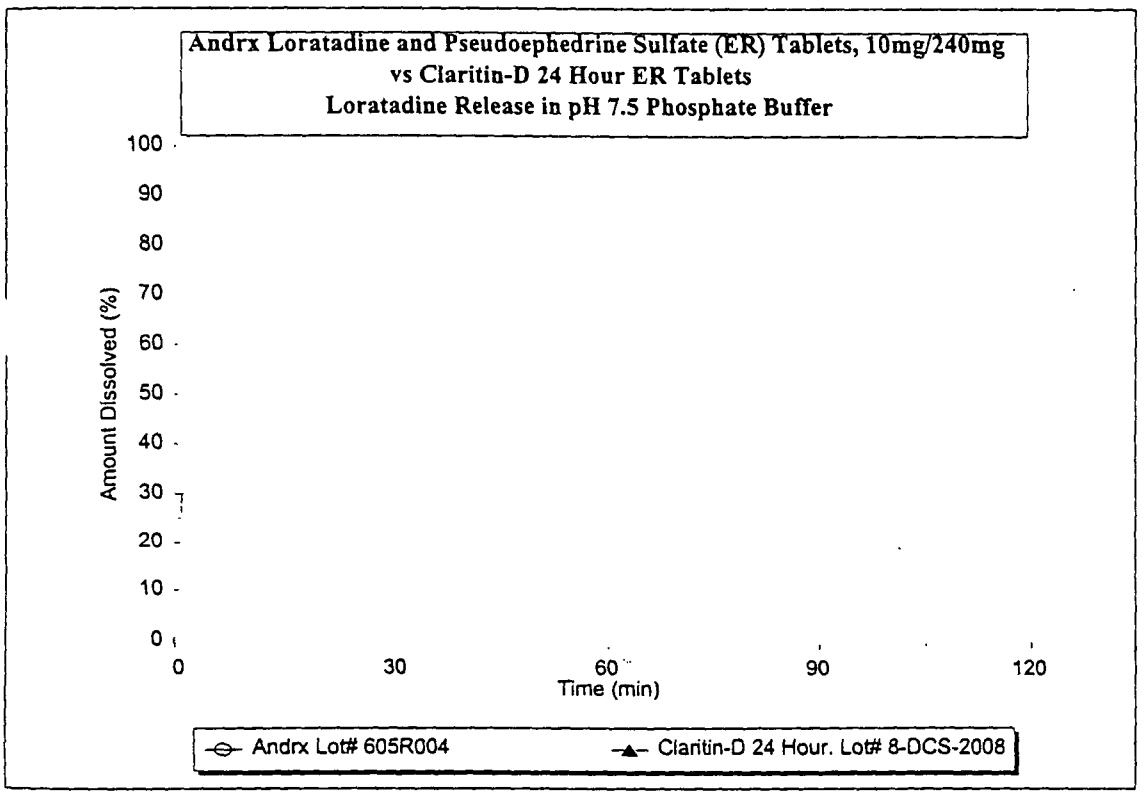


Table 11. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg in pH 7.5 Phosphate Buffer

ɔudoephedrine Sulfate

ɹ: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

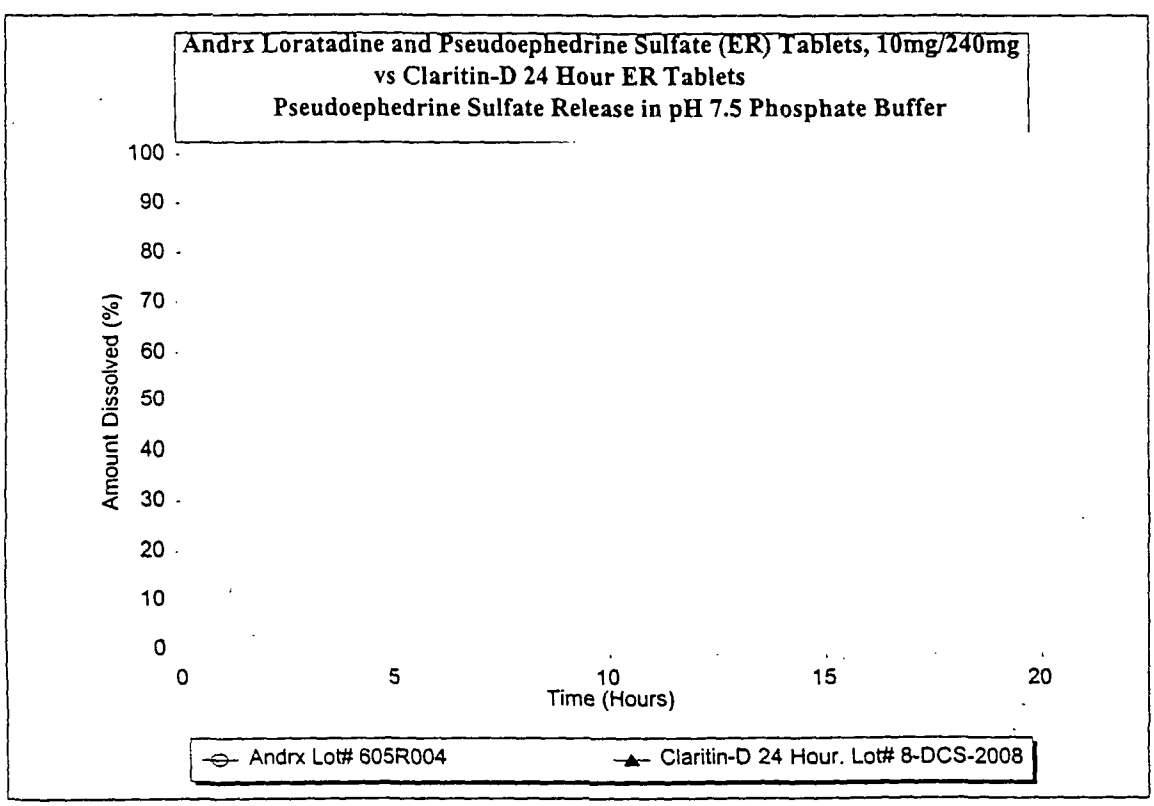
Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														0	346.4
0.25														2	16.1
0.5														11	7.4
1														21	4.7
2														34	7.0
4														51	2.2
8														72	2.3
12														84	2.5
16														91	2.5
20														96	2.3

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														1	28.8
0.25														8	5.8
0.5														12	2.5
1														20	2.3
2														32	1.5
4														48	1.1
8														70	1.0
12														83	0.9
16														91	0.8
20														95	0.8



JUN 5 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-706 - APPLICANT: Andrx Pharmaceuticals

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

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

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
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 three 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 the analytical results for extracted samples at three concentrations with unextracted standards that represent 100% recovery).
3. Please provide date of manufacture of bio-lot.
4. Please provide SOPs for all analytical methods.
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.

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 first hour and 900 mL of 0.1M phosphate buffer (pH 7.5) for additional 16 hours.

Sincerely yours,

/S/

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

CC: ANDA 75-706
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Dhariwal 3/20/99
HFD-655/Nerurkar 3/27/00
HFD-617/J. Fan
HFD-650/Dale Conner 5/8/00

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 12/14/1999

1. **FASTING STUDY** (STF)
Clinical:
Analytical:
Statistical:
Strengths: 10 mg/240 mg
Outcome: IC

2. **FOOD STUDY** (STP)
Clinical:
Analytical:
Statistical:
Strengths: 10 mg/ 240 mg
Outcome: IC

3. **MULTIPLE DOSE STUDY** (STM)
Clinical:
Analytical:
Statistical:
Strengths: 10 mg/240 mg
Outcome: UN

Outcome Decisions:
IC - Incomplete

WinBio Comments:

FEB

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-706 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate
Extended Release Tablets, 10 mg/240 mg

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

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.

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.

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

4. We suggest that the dissolution testing should be conduced in 900 mL of SGF using apparatus I (basket) at 100 rpm. The following interim specifications are suggested:

Sincerely yours,

/S/

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

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA #75-706
Reviewer: Kuldeep R. Dhariwal
File name: 75706SD.O00

Andrx Pharmaceuticals
4001 S.W. 47th Ave.
Ft. Lauderdale
Florida 33314
Submission Date:
October 27, 2000

Review of an Amendment

Andrx submitted fasting, non-fasting, and multiple-dose studies on December 14, 1999. This reviewer reviewed the submission and the deficiencies were communicated to the firm (file name: 75706SD.D99). This amendment is a response to those deficiencies.

Deficiency 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

Firm's response: The firm states that the method validation data for are provided in the attachment.

Reviewer's comments: Instead of providing the data for the firm has resubmitted the validation data for method

Fasting study samples were analyzed from April 12 to April 28, 1999 using method. A modification to the extraction procedure was made in May 1999 and the samples from food and multiple dose studies were analyzed using this The firm provided method validation report for

For method, the firm provided data 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). The firm did not provide the following data:

a. inter-day accuracy and precision

b. recovery of loratadine and descarboethoxy loratadine and
c. stability of loratadine and descarboethoxy loratadine in extracted samples for method

The inter-day accuracy and precision obtained during the analysis of study samples are acceptable.

The recovery of loratadine and descarboethoxy loratadine is discussed under deficiency #2.

The duration for which the extracted study samples were stored is not known. The firm provided the stability of loratadine and descarboethoxy loratadine in the extracted samples for the revised method (3 days) but not the original method. The difference between the original method and the revised method is in the extraction procedure. It is not known that if the samples extracted using the original method were as stable as samples extracted using the modified method. The firm should provide method validation data especially stability of loratadine and descarboethoxy loratadine in extracted samples for method. The firm should also provide the dates the samples were extracted and the dates the samples were analyzed to determine the storage duration.

Deficiency #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 three 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 the analytical results for extracted samples at three concentrations with unextracted standards that represent 100% recovery.

Firm's response: method utilizes Determining the analyte recovery in this type of method is difficult. The approach taken in this validation was intended to provide a relative comparison of the absolute analyte responses obtained from fully processed (i.e. precipitated human plasma quality

controls with those from "external" recovery standards carried process. The external recovery standards were prepared in the 20:80 methanol/aqueous 10 mM ammonium formate reconstitution solvent with half the analyte concentrations of the corresponding plasma QC samples to account for the 1:2 dilution factor between the original matrix sample volume and the final prepared sample 'extract' volume.

Reviewer's comments: Determining the analyte recovery method is difficult. As per draft guidance 'Bioanalytical method validation' recovery is information that is "nice to know", but is not necessary for bioanalytical method validation.

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

Deficiency #3. Please provide date of manufacture of bio-lot.

Firm's response: The bio-lot (lot #605R004) was manufactured in January 1999.

Reviewer's comments: The response is satisfactory.

Deficiency #4. Please provide SOPs for all analytical methods.

Firm's response: The firm has provided the analytical methods and not SOPs.

Reviewer's comments: The firm should provide the SOPs for accepting/rejecting a run and for repeat analyses of the samples.

Deficiency #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.

Firm's response: Upon further review of this matter, we noted that subject #28 of the multiple-dose study did not meet the study inclusion criteria. The study Protocol specifically excludes persons whose body weight was 10% more or less than the weight specified in the 1983 Metropolitan Weight and Height Table. Subject #28 was the only subject that did not meet the specified criteria of the study. 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 C_{max} values are statistical outliers and therefore bias the statistical analysis of the data.

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 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.

Reviewer's comments: Please see the comments in attachment 1.

Deficiency #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 first hour and 900 mL of 0.1M phosphate buffer (pH 7.5) for additional 16 hours.

Firm's response: The firm has generated additional dissolution data as requested. The firm observed that the test tablets were firmly sticking to the bottom of the dissolution vessels in both 0.1N HCl and pH 7.5 buffer media, which led to the low release rate of loratadine and pseudoephedrine. The firm suggests that a medium consisting of is the most suitable for its product.

Reviewer's comments: The dissolution data were discussed with the DBE dissolution focal point, Nhan Tran. The DBE discourages the use of detergents in the dissolution medium and therefore the firm should be recommended to use as the medium. The following interim specifications are to be suggested:

General comments:

1. The fasting study is incomplete because the firm did not provide method validation data especially the stability of

loratadine and descarboethoxy loratadine in extracted samples.

2. The firm did not provide the original values, repeat values and a rationale for selecting the reported values for all reassays. The relevant SOPs for accepting/rejecting a run and for repeating the samples should be provided. Therefore, all three bioequivalence studies are incomplete.
3. The multiple-dose study data will be accepted as per discussion in the DBE management meeting. (see attachment 1).
4. The reference listed drug, Claritin-D 24 hour tablet was originally approved as a round tablet. Several adverse events related to esophageal obstructions (and some cases of esophageal perforations) were reported with this product. The tablet adhered to the esophagus and in some cases required esophageal endoscopy for removal. The manufacturer (Schering) reformulated the round tablet to an oval shaped tablet with an added sugar coating and an outer wax polish. Andrx is stating that its test product was firmly sticking to the bottom of the dissolution vessels in 0.1N HCl and pH 7.5 phosphate buffer. This sticking of the test tablet in a dissolution vessel may be different than the sticking observed with the original reference listed drug. However, keeping this information in mind, the Division of Chemistry may be advised to critically review the formulation of the test product.

Recommendations:

1. The fasting, non-fasting and multiple-dose bioequivalence studies conducted by Andrx Pharmaceuticals on its loratadine/pseudoephedrine sulfate 10/240 mg.ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering have been found incomplete by the Division of Bioequivalence.
2. The dissolution testing should be conduced in 900 mL of SGF using apparatus I (basket) at 100 rpm. The test product should meet the following interim specifications:

3. The Division of Chemistry may be advised to critically review the formulation of the test product as per general comment #4.

/S/ - 1/9/01

Kuldeep R. Dhariwal
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 1/22/2001

Concur: /S/ Date 1/30/2001

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

CC: ANDA 75-706
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Dhariwal 1/9/01
HFD-655/Nerurkar
HFD-617/Nwaba
HFD-650/Dale Conner for 1/30/2001

BIOEQUIVALENCY -DEFICIENCIES Submission Date: 10/27/00

1. STUDY AMENDMENT (STA)

Strengths: 10 mg/ 240 mg
Outcome: IC

Outcome Decisions:

IC - Incomplete

WinBio Comments

In Vitro Dissolution Testing

Drug (Generic Name):	Loratadine and Pseudoephedrine Sulfate Extended-release (ER) Tablets, 10 mg/240 mg
Dose Strength:	10 mg Loratadine 240 mg Pseudoephedrine Sulfate
Firm:	Andrx Pharmaceuticals, Inc.

I. Conditions for Dissolution/Release Testing:

Method Ref:

USP 24 Apparatus:	Paddle	Medium:	pH 7.5 Buffer
RPM:	75	Volume:	900 mL
No. Units Tested:	12	Tolerance(Q):	N/A

Reference Drug: Claritin D-24®Hour (10 mg loratadine/240 mg pseudoephedrine sulfate) ER Tablets

Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times	Test Product: Loratadine and Psdo. SO_4* ER Tablets, 10 mg/ 240 mg Lot # : 605R004A Exp. Date: N/A Strength: 10 mg Loratadine 240 mg Psdo. SO_4*			Ref. Product: Claritin D-24®Hour ER Tablets Lot # 0-DCS-2010 Exp. Date: 3/01 Strength: 10 mg Loratadine 240 mg Psdo. SO_4*		
Loratadine (hours)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
1	0		N/A	0		N/A
2	1		24.4	0		N/A
4	2		18.0	0		N/A
8	1		16.1	0		N/A
12	1		18.3	0		N/A
16	1		29.0	0		181.0
20	1		40.4	0		181.4
Psdo SO_4* (hours)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
1	10		4.7	10		2.0
2	17		4.1	17		1.5
4	29		4.5	28		1.5
8	48		3.3	44		1.7
12	59		3.0	57		1.3
16	66		3.4	66		1.0
20	71		3.4	72		1.1

*Psdo SO_4: Pseudoephedrine Sulfate

In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate Extended-release (ER) Tablets, 10 mg/240 mg
Dose Strength: 10 mg Loratadine
240 mg Pseudoephedrine Sulfate
Firm: Andrx Pharmaceuticals, Inc.

I. Conditions for Dissolution/Release Testing:

Method Ref:
USP 24 Apparatus: Paddle
RPM: 75
No. Units Tested: 12
Medium: 0.1N HCl
Volume: 900 mL
Tolerance(Q): N/A
Reference Drug: Claritin D-24®Hour (10 mg loratadine/240 mg pseudoephedrine sulfate) ER Tablets
Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times	Test Product: Loratadine and Psdo. SO_4* ER Tablets, 10 mg/ 240 mg Lot # : 605R004A Exp. Date: N/A Strength: 10 mg Loratadine 240 mg Psdo. SO_4*			Ref. Product: Claritin D-24®Hour ER Tablets Lot # 0-DCS-2010 Exp. Date: 3/01 Strength: 10 mg Loratadine 240 mg Psdo. SO_4*		
Loratadine (min)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
5	9		26.0	52		5.0
15	51		11.3	76		4.5
30	70		8.4	82		4.8
60	72		8.1	85		4.9
Psdo SO_4* (min)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
5	0		N/A	1		13.7
15	4		12.6	6		4.7
30	11		5.0	12		2.7
60	19		6.4	19		1.9

*Psdo SO_4: Pseudoephedrine Sulfate

In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate Extended-release (ER) Tablets, 10 mg/240 mg
Dose Strength: 10 mg Loratadine
240 mg Pseudoephedrine Sulfate
Firm: Andrx Pharmaceuticals, Inc.

I. Conditions for Dissolution/Release Testing:

Method Ref:
USP 24 Apparatus: Paddle
Medium: pH 7.5 Buffer
RPM: 50
Volume: 900 mL
No. Units Tested: 12
Tolerance(Q): N/A
Reference Drug: Claritin D-24®Hour (10 mg loratadine/240 mg pseudoephedrine sulfate) ER Tablets
Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times	Test Product: Loratadine and Psdo. SO_4* ER Tablets, 10 mg/ 240 mg Lot # : 605R004A Exp. Date: N/A Strength: 10 mg Loratadine 240 mg Psdo SO_4*			Ref. Product: Claritin D-24®Hour ER Tablets Lot # 0-DCS-2010 Exp. Date: 3/01 Strength: 10 mg Loratadine 240 mg Psdo SO_4*		
Loratadine (hours)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
1	0		N/A	0		N/A
2	1		82.9	0		346.4
4	2		43.1	0		346.4
8	2		46.8	1		213.3
12	3		49.0	1		191.0
16	3		49.2	1		138.9
20	3		55.5	1		19.1
Psdo SO_4* (hours)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
1	10		3.5	11		9.0
2	17		3.2	17		8.7
4	29		2.4	29		7.3
8	47		3.9	45		6.0
12	59		3.7	55		4.6
16	66		3.0	64		4.4
20	71		2.4	70		2.4

*Psdo SO_4: Pseudoephedrine Sulfate

In Vitro Dissolution Testing

Drug (Generic Name):	Loratadine and Pseudoephedrine Sulfate Extended-release (ER) Tablets, 10 mg/240 mg
Dose Strength:	10 mg Loratadine 240 mg Pseudoephedrine Sulfate
Firm:	Andrx Pharmaceuticals, Inc.

I. Conditions for Dissolution/Release Testing:

Method Ref:

USP 24 Apparatus:	Paddle	Medium:	0.1N HCl
RPM:	50	Volume:	900 mL
No. Units Tested:	12	Tolerance(Q):	N/A

Reference Drug: Claritin D-24®Hour (10 mg loratadine/240 mg pseudoephedrine sulfate) ER Tablets

Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times	Test Product: Loratadine and Psdo. SO_4* ER Tablets, 10 mg/ 240 mg Lot # : 605R004A Exp. Date: N/A Strength: 10 mg Loratadine 240 mg Psdo. SO_4*			Ref. Product: Claritin D-24®Hour ER Tablets Lot # O-DCS-2010 Exp. Date: 3/01 Strength: 10 mg Loratadine 240 mg Psdo. SO_4*		
Loratadine (min)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
5	4		33.6	45		6.5
15	38		17.9	75		7.1
30	58		11.4	83		7.6
60	65		8.7	86		7.9
Psdo SO_4* (min)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
5	0		N/A	0		105.4
15	3		21.1	6		3.7
30	9		10.5	12		3.1
60	18		5.7	19		3.9

*Psdo SO_4: Pseudoephedrine Sulfate

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA #75-706
Reviewer: Kuldeep R. Dhariwal

Andrx Pharmaceuticals
4001 S.W. 47th Ave.
Ft. Lauderdale
Florida 33314
Submission Dates:
March 12, 2001
April 19, 2001

Review of an Amendment

Andrx submitted fasting, non-fasting, and multiple-dose studies on December 14, 1999. This reviewer reviewed the submission and the deficiencies were communicated to the firm (file name: 75706SD.D99). The firm submitted the response on October 27, 2000. The amendment was reviewed and the deficiencies were communicated to the firm on February 5, 2001. This amendment is a response to those deficiencies.

Deficiency 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.

Firm's response: A copy of method validation report for method stability data of loratadine and descarboethoxy loratadine in extracted samples and the dates the samples were extracted and analyzed for all three studies are provided.

Reviewer's comments: The firm has provided following validation data for method

Loratadine and Descarboethoxy loratadine (DL):
Std curve range:

QC samples:

Inter-day accuracy:

Inter-day precision:

Intra-day accuracy:

Intra-day precision:

Absolute recovery:

Stability:
1. Unextracted samples: 4 hours at room temperature
2. Extracted samples: 9 days at room temperature

Stability of loratadine and descarboethoxy loratadine in extracted samples: The firm has conducted stability experiments and the data suggest that loratadine and descarboethoxy loratadine are stable in extracted samples for at least 9 days.

The firm has also provided the dates the samples were extracted and the dates the samples were analyzed. None of the extracted samples were stored for more than 9 days.

The response is satisfactory.

Deficiency 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.

Firm's response: According to rejection of samples is based on predetermined internal standard peak area response criteria. In each case shown in the reassay tables there is no original value because the analysis is rejected a priori for analytical reasons. Therefore, there is no reportable value for the initial assay attempt. The samples were reprocessed in order to obtain an analytically acceptable, reportable value.

Reviewer's comments: The response is satisfactory.

Deficiency 3: Please provide the SOPs for accepting/rejecting a run.

Firm's response: The SOP is provided.

Reviewer's comments: The response is satisfactory.

Deficiency 4: We suggest that the dissolution testing should be conduced in
The following interim specifications are suggested:

Firm's response: The data indicate a slow release rate of loratadine from the Andrx formulation when the dissolution is conducted in For this reason, Andrx is proposing a medium

Reviewer's comments: The reviewer discussed the dissolution data with the DBE dissolution focal point, Nhan Tran. As per this discussion, the DBE requested the firm to conduct dissolution testing using lower concentrations
The firm submitted the results on April 19, 2001. There is no significant difference in the dissolution of loratadine and pseudoephedrine at the three concentrations of Tween 80 (Tables 1-3). The firm should therefore use as dissolution medium. The following interim specifications are suggested:

General Comments:

1. The firm has satisfactorily responded to all the deficiencies. The fasting and fed studies are acceptable.
2. The multiple-dose study is acceptable as per discussion in the DBE management meeting (see review dated January 30, 2001, file name: 75706SD.000).
3. The reference listed drug, Claritin-D 24 hour tablet was originally approved as a round tablet. Several adverse events related to esophageal obstructions (and some cases of esophageal perforations) were reported with this product. The tablet adhered to the esophagus and in some cases required esophageal endoscopy for removal. The manufacturer (Schering) reformulated the round tablet to an oval shaped tablet with an added sugar coating and an outer wax polish. Andrx is stating that its test product was firmly sticking to the bottom of the dissolution vessels in 0.1N HCl and pH 7.5 phosphate buffer. This sticking of the test tablet in a dissolution vessel may be different than the sticking observed with the original reference listed drug. However, keeping this information in mind, the Division of Chemistry may be advised to critically review the formulation of the test product.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Andrx Pharmaceuticals on its loratadine/pseudoephedrine sulfate 10 mg/240 mg ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering is acceptable to the Division of Bioequivalence. The study demonstrates that Andrx's loratadine/pseudoephedrine sulfate 10 mg/240 mg ER tablet is bioequivalent to the reference product, Claritin-D 24 hour ER tablet manufactured by Schering.
2. The bioequivalence study conducted under non-fasting conditions by Andrx Pharmaceuticals on its loratadine/ pseudoephedrine sulfate 10 mg/240 mg ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting

conditions, the bioavailability of Andrx's loratadine/pseudoephedrine sulfate 10 mg/240 mg ER tablet is similar to the reference product, Claritin-D 24 hour ER tablet manufactured by Schering.

3. The multiple-dose bioequivalence study conducted by Andrx Pharmaceuticals on its loratadine/pseudoephedrine sulfate 10 mg/240 mg ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering is acceptable to the Division of Bioequivalence.
4. The dissolution testing conducted by the firm on its loratadine/pseudoephedrine sulfate 10 mg/240 mg ER tablet is acceptable. The dissolution testing should be incorporated into manufacturing controls and stability programs. The dissolution testing should be conducted in

   The test product should meet the following interim specifications:
   Loratadine
   Pseudoephedrine

5. The Division of Chemistry may be advised to critically review the formulation of the test product as per general comment #3.

/S/ 4/26/01
Kuldeep R. Dhariwal
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 4/25/2001

Concur: /S/ Date 5/1/01
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate ER Tablet
Dose Strength: 10 mg/240 mg
ANDA No.: 75-706
Firm: Andrx
Submission Date: March 12 and April 19, 2001
File Name: 75706SD.301

I. Conditions for Dissolution Testing:

USP XXIV Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium:
Specifications: see text
Reference Drug: Claritin-D 24 hour
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (hour)	Test Product: Loratadine Lot #605R004 Strength(mg) 10			Ref. Product: Loratadine Lot #8-DCS-2008 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	6		20.6	53		7.4
0.25	61		6.9	88		5.0
0.50	87		5.6	94		4.9
1.00	90		5.3	97		5.0
2.00	91		5.0	99		4.8
4.00	92		5.3	101		4.8

Sampling Times (hour)	Test Product: Pseudoephedrine Lot #605R004 Strength(mg) 240			Ref. Product: Pseudoephedrine Lot #8-DCS-2008 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	0		0	1		88.3
0.25	5		17.7	7		4.1
0.50	13		6.8	13		3.0
1.00	22		3.9	21		2.4
2.00	35		2.5	33		2.3
4.00	51		2.4	51		1.2
8.00	73		2.9	75		1.1
12.00	86		2.5	88		1.0
16.00	94		2.6	95		1.1

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate ER Tablet
Dose Strength: 10 mg/240 mg
ANDA No.: 75-706
Firm: Andrx
Submission Date: March 12 and April 19, 2001
File Name: 75706SD.301

I. Conditions for Dissolution Testing:

USP XXIV Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium:
Specifications: see text
Reference Drug: Claritin-D 24 hour
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (hour)	Test Product: Loratadine Lot #605R004 Strength(mg) 10			Ref. Product: Loratadine Lot #8-DCS-2008 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	7		12.2	52		6.6
0.25	64		7.0	90		4.3
0.50	92		5.6	95		4.5
1.00	96		6.5	97		4.4
2.00	97		6.7	99		4.5
4.00	98		6.8	100		5.1

Sampling Times (hour)	Test Product: Pseudoephedrine Lot #605R004 Strength(mg) 240			Ref. Product: Pseudoephedrine Lot #8-DCS-2008 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	0		-	1		88.3
0.25	4		15.1	8		7.0
0.50	13		4.5	13		2.2
1.00	22		2.7	22		2.4
2.00	35		2.0	34		1.3
4.00	51		2.0	51		0.9
8.00	72		1.9	74		0.9
12.00	86		1.7	88		0.7
16.00	94		1.8	94		0.4

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate ER Tablet
Dose Strength: 10 mg/240 mg
ANDA No.: 75-706
Firm: Andrx
Submission Date: March 12 and April 19, 2001
File Name: 75706SD.301

I. Conditions for Dissolution Testing:

USP XXIV Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium:
Specifications: see text
Reference Drug: Claritin-D 24 hour
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (hour)	Test Product: Loratadine Lot #605R004 Strength(mg) 10			Ref. Product: Loratadine Lot #8-DCS-2008 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	8		21.4	53		4.2
0.25	68		8.8	88		4.8
0.50	91		7.8	94		5.4
1.00	94		7.3	96		5.7
2.00	94		7.1	98		5.7

Sampling Times (hour)	Test Product: Pseudoephedrine Lot #605R004 Strength(mg) 240			Ref. Product: Pseudoephedrine Lot #8-DCS-2008 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	0		346.4	0		346.4
0.25	5		50.0	8		4.4
0.50	12		12.0	14		2.5
1.00	22		7.0	22		1.7
2.00	34		5.4	35		1.2
4.00	50		4.5	52		1.3
8.00	73		3.4	76		1.1
12.00	85		1.9	89		1.4
16.00	94		1.9	95		1.1

CC: ANDA 75-706
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 4/26/2001

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 4/26/01
HFD-655/ Nerurkar
HFD-650/ D. Conner 5/1/01

4/26/01

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: March 12, 2001
April 19, 2001

1. **STUDY AMENDMENT** (STA)
March 12, 2001
Strengths: 10 mg/240 mg
Outcome: AC

2. **STUDY AMENDMENT** (STA)
April 19, 2001
Strengths: 10 mg/240 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

SEP - 6 01

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-706 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate ER Tablet, 10 mg/240 mg

The Division of Bioequivalence has completed its review and provides the following comments:

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 S1 level. 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 % Tween is used compared to % Tween. Therefore, your request for change of dissolution medium is denied.
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.
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.
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."*

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.
6. 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

   The test product should meet the following interim specifications:

   Loratadine
   Pseudoephedrine

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

Sincerely yours,

/S/

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

Loratadine and Pseudoephedrine Sulfate
Extended Release Tablets
10 mg/240 mg
ANDA #75-706
Reviewer: Kuldeep R. Dhariwal

Andrx Pharmaceuticals
4001 S.W. 47th Ave.
Ft. Lauderdale
Florida 33314
Submission Date:
July 17, 2001

Review of an Amendment

Andrx submitted fasting, non-fasting, and multiple-dose studies on December 14, 1999. This reviewer reviewed the submission and the deficiencies were communicated to the firm (file name: 75706SD.D99). The firm submitted the response on October 27, 2000. The amendment was reviewed and the deficiencies were communicated to the firm on February 5, 2001. The firm satisfactorily responded to all bioequivalence deficiencies in its amendments dated March 12 and April 19, 2001.

The dissolution testing was conducted in containing different concentrations of Tween 80: %. There was no significant difference in dissolution of loratadine and pseudoephedrine at the three concentrations of Tween 80. Therefore % Tween 80 in was recommended for dissolution testing. The following interim specifications were suggested:

Loratadine
Pseudoephedrine

In this amendment, the firm is proposing to conduct the dissolution testing in

Loratadine
Pseudoephedrine

To support its argument, the firm has provided the following recovery data (details of the recovery experiments are not given):

% Recovery of loratadine in different dissolution media

The firm states that 100% recovery of loratadine can only be achieved in and therefore it is appropriate to conduct the dissolution testing in this medium.

Comments:

1. In this amendment, the firm has submitted loratadine recovery information. The dissolution data in this amendment are identical to the dissolution data submitted earlier (see review dated May 1, 2001; submission dates 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 S1 level. 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 % Tween is used compared to % Tween (see ranges at different dissolution time points in the two media). Therefore, the change of dissolution medium is unacceptable.
2. Besides the change in dissolution medium, the firm has 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 the firm. Therefore, the requested change in loratadine specification is not acceptable.
3. The firm also requested to widen the dissolution specification ranges for pseudoephedrine. The resubmitted data do not justify the firm's request. The request is therefore denied.
4. The initial dissolution specifications are set on the basis of the dissolution data of the bio-lot. The FDA Guidance for Industry-Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997 suggests a number of considerations when setting dissolution criteria for extended release oral dosage forms, including:
   - Recommended range at any dissolution time point specification is % deviation from the mean dissolution profile.
   - In certain cases, reasonable deviations from the % range can be accepted provided that the range at any time point does not exceed %.
   - Specifications should be established on clinical/bioavailability lots.
   - Specifications should be established based on average dissolution data for each lot under study, equivalent to USP stage 2 testing.
5. A change in the specifications can be considered if the firm provides justifiable dissolution testing data on three production lots of this drug product.

Recommendations:

The dissolution testing should be conducted in :

The test product should meet the following interim specifications:

Loratadine

Pseudoephedrine

/S/

Kuldeep R. Dhariwal
Review Branch II
Division of Bioequivalence

/S/

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR Date 7/31/2001

/S/

Concur: Date 8/30/01

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate ER Tablet
Dose Strength: 10 mg/240 mg
ANDA No.: 75-706
Firm: Andrx
Data from submissions: March 12 and April 19, 2001
File Name: 75706SD.701

I. Conditions for Dissolution Testing:

USP XXIV Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium:
Specifications: see text
Reference Drug: Claritin-D 24 hour
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (hour)	Test Product: Loratadine Lot #605R004 Strength(mg) 10			Ref. Product: Loratadine Lot #8-DCS-2008 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	6		20.6	53		7.4
0.25	61		6.9	88		5.0
0.50	87		5.6	94		4.9
1.00	90		5.3	97		5.0
2.00	91		5.0	99		4.8
4.00	92		5.3	101		4.8

Sampling Times (hour)	Test Product: Pseudoephedrine Lot #605R004 Strength(mg) 240			Ref. Product: Pseudoephedrine Lot #8-DCS-2008 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	0		0	1		88.3
0.25	5		17.7	7		4.1
0.50	13		6.8	13		3.0
1.00	22		3.9	21		2.4
2.00	35		2.5	33		2.3
4.00	51		2.4	51		1.2
8.00	73		2.9	75		1.1
12.00	86		2.5	88		1.0
16.00	94		2.6	95		1.1

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate ER Tablet
Dose Strength: 10 mg/240 mg
ANDA No.: 75-706
Firm: Andrx
Data from submissions: March 12 and April 19, 2001
File Name: 75706SD.701

I. Conditions for Dissolution Testing:

USP XXIV Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium:
Specifications: see text
Reference Drug: Claritin-D 24 hour
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (hour)	Test Product: Loratadine Lot #605R004 Strength(mg) 10			Ref. Product: Loratadine Lot #8-DCS-2008 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	7		12.2	52		6.6
0.25	64		7.0	90		4.3
0.50	92		5.6	95	1	4.5
1.00	96		6.5	97	3	4.4
2.00	97		6.7	99	5	4.5
4.00	98		6.8	100	6	5.1

Sampling Times (hour)	Test Product: Pseudoephedrine Lot #605R004 Strength(mg) 240			Ref. Product: Pseudoephedrine Lot #8-DCS-2008 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	0		-	1		88.3
0.25	4		15.1	8		7.0
0.50	13		4.5	13		2.2
1.00	22		2.7	22		2.4
2.00	35		2.0	34		1.3
4.00	51		2.0	51		0.9
8.00	72		1.9	74		0.9
12.00	86		1.7	88		0.7
16.00	94		1.8	94		0.4

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate ER Tablet
Dose Strength: 10 mg/240 mg
ANDA No.: 75-706
Firm: Andrx
Data from submissions: March 12 and April 19, 2001
File Name: 75706SD.701

I. Conditions for Dissolution Testing:

USP XXIV Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium:
Specifications: see text
Reference Drug: Claritin-D 24 hour
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (hour)	Test Product: Loratadine Lot #605R004 Strength(mg) 10			Ref. Product: Loratadine Lot #8-DCS-2008 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	8		21.4	53		4.2
0.25	68		8.8	88		4.8
0.50	91		7.8	94		5.4
1.00	94		7.3	96		5.7
2.00	94		7.1	98		5.7

Sampling Times (hour)	Test Product: Pseudoephedrine Lot #605R004 Strength(mg) 240			Ref. Product: Pseudoephedrine Lot #8-DCS-2008 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
0.08	0		346.4	0		346.4
0.25	5		50.0	8		4.4
0.50	12		12.0	14		2.5
1.00	22		7.0	22		1.7
2.00	34		5.4	35		1.2
4.00	50		4.5	52		1.3
8.00	73		3.4	76		1.1
12.00	85		1.9	89		1.4
16.00	94		1.9	95		1.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-706 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate ER Tablet, 10 mg/240 mg

The Division of Bioequivalence has completed its review and provides the following comments:

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 S1 level. 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 % Tween is used compared to % Tween. Therefore, your request for change of dissolution medium is denied.
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.
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.
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."*

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

   The dissolution testing should be conducted in

   The test product should meet the following interim specifications:

   Loratadine
   Pseudoephedrine

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

Sincerely yours,

/S/

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

CC: ANDA 75-706
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 7/26/2001

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 7/31/01
HFD-655/ Nerurkar 7/31/01
HFD-650/ D. Conner 8/30/01

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: July 17, 2001

1. **STUDY AMENDMENT** (STA)

Strengths: 10 mg/240 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

Loratadine and Pseudoephedrine Sulfate
Extended Release Tablets
10 mg/240 mg
ANDA #75-706
Reviewer: Kuldeep R. Dhariwal

Andrx Pharmaceuticals
4001 S.W. 47th Ave.
Ft. Lauderdale
Florida 33314
Submission Date:
September 26, 2001

Review of an Amendment

Andrx submitted fasting, non-fasting, and multiple-dose studies on December 14, 1999. This reviewer reviewed the submission and the deficiencies were communicated to the firm (file name: 75706SD.D99). The firm submitted the response on October 27, 2000. The amendment was reviewed and the deficiencies were communicated to the firm on February 5, 2001. The firm satisfactorily responded to all bioequivalence deficiencies in its amendments dated March 12 and April 19, 2001.

The dissolution testing was conducted in containing different concentrations of Tween 80: %. There was no significant difference in dissolution of loratadine and pseudoephedrine at the three concentrations of Tween 80. Therefore % Tween 80 in was recommended for dissolution testing. The following interim specifications were suggested:

Loratadine
Pseudoephedrine

In the amendment dated July 17, 2001, the firm proposed to conduct the dissolution testing in 900 mL of % Tween 80 (instead of % Tween 80) in using apparatus 1 (basket) at 100 rpm. The firm proposed the following interim specifications:

Loratadine ates
Pseudoephedrine

To support its argument, the firm provided the following recovery data:

% Recovery of loratadine in different dissolution media

The firm stated that 100% recovery of loratadine can only be achieved in
and therefore it is appropriate to conduct the dissolution testing in this medium.
The dissolution data submitted in the amendment were identical to the dissolution data submitted earlier. The DBE did not accept change of dissolution medium and change in specifications for loratadine and psudoephedrine.

This amendment is a response to the DBE comments.

Comment #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 S1 level. 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 Tween is used compared to % Tween. Therefore, your request for change of dissolution medium is denied.

Firm's response: We agree with the Agency that the test results provided in the March 12 and April 19, 2001 amendments did not indicate any significant differences 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 criteria, as defined in our method validation report provided in the original ANDA, is a % 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.

Comment 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.

Firm's response: We are 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. This data provides the basis of our proposal. As it shows, the drug product would fail to meet the Agency's proposed specification limit of NLT % (Q) in 30 minutes at various time points for each test batch. In fact, at 24 months RT, lot #605R004 would fail to meet the Agency's proposed criteria, even at the L2 level. The possibility of failure would be even greater in a dissolution medium in which 100% recovery cannot be attained.

Comment 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.

Firm's response: Andrx's proposed specification limits are based on the data provided here, 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.

Comment 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.*"

Firm's response: 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.

Comment 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.

Firm's response: We are providing the 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 (605R004), are unable to meet the Agency's proposed specifications, then it will most likely be very difficult for commercial batches to conform.

Reviewer's comments:

1. The reviewer discussed the recovery and dissolution data with the DBE dissolution focal point, Dr. Tran and the recommendations are made as per this discussion.
2. Concentration of Tween 80 in the dissolution medium: The firm has shown that the recovery of loratadine is nearly 100% in % Tween 80 and is only % in % Tween 80. Therefore, the firm used % Tween 80 for dissolution testing of the bio-lot stored for up to 24 months. We do not know what the dissolution results would be using % Tween 80. Since, the recovery of loratadine is better in % Tween 80 compared to % Tween 80 and all dissolution data were generated in % Tween 80, use of % Tween 80 is acceptable.
3. Change in specifications: The initial dissolution specifications are set on the basis of the dissolution data of the bio-lot. The FDA Guidance for Industry-Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997 suggests a number of considerations when setting dissolution criteria for extended release oral dosage forms, including:
   - Recommended range at any dissolution time point specification is % deviation from the mean dissolution profile.
   - In certain cases, reasonable deviations from the % range can be accepted provided that the range at any time point does not exceed %.
   - Specifications should be established on clinical/bioavailability lots. Widening specifications based on scale-up, stability, or other lots for which bioavailability data are unavailable is not recommended.
   - Specifications should be established based on average dissolution data for each lot under study, equivalent to USP stage 2 testing.

   The dissolution method and the specifications proposed by the firm are the same it proposed in its original submission dated December 14, 1999. In other words, the firm is not proposing the new specifications after seeing the stability data. The DBE's recommendations were based on the dissolution data generated on fresh bio-lot. The firm has now submitted the stability data on the bio-lot and is requesting that the DBE should accept the original specifications it proposed. The specifications proposed by the DBE can be revised because they are based on the stability data on the bio-lot (#605R004A).
4. Loratadine specifications: The firm wants that the DBE should revise the specifications from % in 30 minutes to % in 60 minutes based on the following results:

Lot #605R004A	Dissolution at 30 minutes
6 months RT	
24 months RT	

Lot#605R004B
2 months AC
3 months AC
24 months RT
Lot#605R005A
2 months AC

Lot#605R005B
3 months AC

From these results, the firm concludes that the drug product would fail to meet the Agency's proposed specification limit of NLT % (Q) in 30 minutes at various time points for each test batch and at 24 months RT, lot#605R004 would fail to meet the specifications even at the L2 level. It is true that it would not meet the criteria at stage 1 testing (each unit is not less than Q %). However, it would 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 %. The firm would comfortably meet this criterion at all storage time points given above. If at any point, S1 criterion is not met, the firm can test 12 tablets for S2 stage. A specification of NLT % (Q) in 60 minutes is not necessary.

5. Pseudoephedrine specifications: The firm also wants the DBE to revise the pseudoephedrine specifications and recommend % range at every time point. After reviewing the stability data, the DBE would make the following changes in the specifications:

Time	Old recommendation	New recommendation
1h		
2h		
4h		
8h		
16h		

A range of % at each time point is not necessary.

Recommendations:

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

Loratadine
Pseudoephedrine

/S/ 10/11/01

Kuldeep R. Dhariwal
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 11/15/2001

Concur: /S/ Date 11/15/01

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 10/11/2001

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 10/11/01
HFD-655/ Nerurkar 10/15/01
HFD-650/ D. Conner 11/15/01

BIOEQUIVALENCY - ACCEPTABLE

Submission date: September 26, 2001

1. **STUDY AMENDMENT** (STA)

Strengths: 10 mg/240 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75706 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate ER
Tablet, 10 mg/240 mg
Amendment date: September 26, 2001

The Division of Bioequivalence has completed its review and provides the following 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.
2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in

   The test product should meet the following interim specifications:

   Loratadine
   Pseudoephedrine

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency

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

Sincerely yours,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-706 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Loratadine and Pseudoephedrine Sulfate ER Tablet
10 mg/240 mg

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

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:

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

Sincerely yours,

/S/

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