CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-625 /S008
20-786/S004

Trade Name: Allegra Capsules
Allegra-D Extended Release Tablets

Generic Name: fexofenadine hydrochloride
fexofendadine hydrochloride and pseudoephedrine hydrochloride

Sponsor: Hoechst Marion Roussel, Inc.

Approval Date: January 21, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-625 /S008

20-786/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-625 /S008

20-786/S004

APPROVAL LETTER

NDA 20-625/S-008
NDA 20-786/S-004

Aventis Pharmaceuticals
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: J. Michael Nicholas, Ph.D.
Director, US Drug Regulatory Affairs

Dear Dr. Nicholas:

Please refer to your supplemental new drug applications dated July 23, 1998, received July 24, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Capsules and Allegra-D (fexofenadine hydrochloride and pseudoephedrine hydrochloride) Extended-release Tablets.

Reference is also made to your submissions dated October 15, 1998, February 26, July 15, and September 10, 1999.

These supplements propose the following changes: an alternative starting material for the manufacture of fexofenadine hydrochloride drug substance at your Frankfurt, Germany facility, an alternative synthesis of the [redacted] and process modifications in steps for the manufacture of fexofenadine hydrochloride at the Midland, Michigan Facility only, and an additional primary packaging materia. [redacted] for the fexofenadine hydrochloride drug substance.

We have completed the review of these supplemental applications, as amended, and they are approved effective on the date of this letter. We also make reference to your supplements 20-625/S-009 and 20-786/S-006 supporting the use of the Frankfurt, Germany site for manufacture of fexofenadine hydrochloride.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products,
HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-625, 20-786
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Poochikian
HFD-095/DDMS-IMT
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: GST/January 14, 2000
Initialed by: Jani/1-18-00
Rogers/1-18-00
Poochikian/1-18-00
final: GTrout/1-21-00
filename: c:\draft\my documents\20625ap

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-625 /S008

20-786/S004

APPROVABLE LETTER

NDA 20-625/S-008
NDA 20-786/S-004

Hoechst Marion Roussel
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: Dhiren N. Shah, Ph.D.
Director - CMC, US Drug Regulatory Affairs

Dear Dr. Shah:

Please refer to your supplemental new drug applications dated July 23, 1998, received July 24, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Capsules and Allegra-D (fexofenadine hydrochloride/pseudoephedrine hydrochloride) Tablets.

We acknowledge receipt of your amendments dated September 10, 1999. Your amendments of September 10, 1999 constituted complete responses to our August 3, 1999 action letters.

These supplements propose the following changes: an alternative starting material for the manufacture of fexofenadine hydrochloride drug substance, an alternative synthesis of the [redacted] and process modifications in some [redacted] synthesis steps for the manufacture of fexofenadine hydrochloride, and an additional primary packaging materia[redacted] for the fexofenadine hydrochloride drug substance. We note that the modified fexofenadine hydrochloride manufacturing process applies only to your Frankfurt, Germany facility.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit, and receive approval for a supplement supporting the use of your Frankfurt, Germany facility for manufacture of fexofenadine hydrochloride.

We remind you of the following agreements pertaining to the drug substance.

1. You will submit [redacted] months of stability data for three commercial scale batches of fexofenadine hydrochloride drug substance produced in Frankfurt, Germany in the forthcoming supplements.

2. You will submit data from the six-month time point as soon as they become available.

NDA 20-625/S-008
NDA 20-786/S-004

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-625, 20-786
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Poochikian
DISTRICT OFFICE

Drafted by: GST/October 14, 1999
Initialed by: Schumaker/10-14-99
Rogers/10-14-99
Poochikian/10-14-99

final: Trout/10-14-99
filename: n:\staff\troutg\20625ae

APPROVABLE (AE)

NDA 20-625/S008

Hoechst Marion Roussel
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: Dhiren N. Shah, Ph.D.
Director - CMC, US Drug Regulatory Affairs

Dear Dr. Shah:

Please refer to your supplemental new drug application dated July 23, 1998, received July 24, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Capsules.

We acknowledge receipt of your submission dated July 15, 1999. Your submission of February 26, 1999, constituted a complete response to our January 22, 1999, action letter.

This supplement proposes the following changes: an alternative starting material for the manufacture of fexofenadine hydrochloride drug substance, an alternative synthesis of the [redacted] and process modifications in some [redacted] synthesis steps for the manufacture of fexofenadine hydrochloride at the Midland, MI facility only, and an additional primary packaging materia[redacted], for the fexofenadine hydrochloride drug substance.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following. Note that the number in parentheses refers to a comment from our July 1, 1999, information request letter.

1. As discussed with you and Faraneh Attarchi via teleconference on July 22, 1999, the specification for *Total Related Substances* for release of the drug substance is not justified by the data provided. The specification should be tightened to NMT [redacted] (comment 2).

2. Provide an updated Raw Material Specification for fexofenadine hydrochloride.

In addition, we remind you of the following agreements.

3. For the forthcoming supplement to support manufacture of fexofenadine hydrochloride drug substance at your Frankfurt, Germany facility, you will submit [redacted] months of stability data for three ~~c~~ommercial-scale batches produced in Frankfurt, and you will submit the six-month time point data as soon as they become available.

4. You will not use [redacted] instead of [redacted] in the [redacted] process leading to [redacted] in the Frankfurt production facilities.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-625
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Bertha
HFD-570/Poochikian
HFD-95/DDMS
DISTRICT OFFICE

Drafted by: GST/July 29, 1999
Initialed by: Schumaker/8-2-99
Rogers/8-2-99
Schroeder (for Poochikian)/8-2-99
final: Trout/8-3-99
filename: n:\staff\troutg\20625ae

APPROVABLE (AE)

NDA 20-625/S-008

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: Dhiren N. Shah, Ph.D.
Director-CMC, US Drug Regulatory Affairs

Dear Dr. Shah:

Please refer to your supplemental new drug application dated July 23, 1998, received July 24, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine HCl) Capsules 60 mg.

We acknowledge receipt of your submission dated October 15, 1998.

This supplement proposes an alternative starting material for the manufacture of fexofenadine HCl drug substance, an alternative synthesis of the ——— and process modifications in synthesis steps for the manufacture of drug substance at Midland, MI, and an additional packaging materia — for the drug substance.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). We have the following comments and requests for information.

1. The following comments pertain to in-process testing specifications:

   a. The specification for the level of ——— is not justified by the data provided and should be tightened to NMT —

   b. The specification for the levels of ——— in ——— are not justified by the data provided and should be tightened to NMT — and NMT —, respectively.

   c. The specification for the level of ——— is not justified by the data provided and should be tightened to NMT —

2. Since the levels of [redacted] and [redacted] are higher using your proposed process, while the [redacted] ratio of [redacted] lower as [redacted] you should reinstate the current [redacted] or optimize the modified process to minimize [redacted] in [redacted] At this time we recommend that these levels not exceed those found in current production batches of [redacted]

3. Provide available comparative data on [redacted] in the drug substance manufactured with current and proposed manufacturing method including Limits of Quantitation and Limits of Detection of the methods utilized.

4. The specification for *Total Related Substances* for release of the drug substance is not justified by the data provided. The specification should be tightened to NMT [redacted] to reflect the levels seen in the current production batches. In addition, we recommend that the other individual impurities be reduced to reflect levels seen in recent production batches.

5. Prior to approval of the proposed process change, you should provide [redacted] months stability data, both long-term and accelerated. [redacted] production-scale batch of the fexofenadine hydrochloride drug substance. [redacted]

6. We advise you that fexofenadine hydrochloride manufacturing experience at the commercial scale at your Midland, Michigan site is necessary to justify submission of a *Changes-Being-Effected* supplement to support Frankfurt, Germany as a manufacturing site for the drug substance.

7. Adequate stability data must be submitted to support your proposed alternative packaging material for the drug substance.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary Drug Products (HFD-570)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-625
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Rogers
HFD-570/Poochikian
HFD-870/Uppoor
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE
HFR-SW300/Kansas District Office/AMehl

Drafted by: kd/01-21-99
Initialed by: Schumaker/1-22-99
Rogers/1-21-99
Poochikian/1-21-99

Final: Campbell/1-22-99

filename: n:\staff\troutg\20625let

NOT APPROVABLE (NA)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-625 /S008

20-786/S004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-625
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER: SCS-008 DATE: 7/23/98
6. NAME OF DRUG Allegra 60 mg Capsules	7. NONPROPRIETARY NAME fexofenadine hydrochloride 60 mg capsules	
8. SUPPLEMENT PROVIDES FOR: 1. An alternative starting material for the manufacture of fexofenadine hydrochloride drug substance at their Frankfurt, Germany facility. 2. An alternative synthesis of the _____ and process modifications in synthesis steps for the manufacture of fexofenadine hydrochloride at Midland, MI facility only. 3. An additional packaging materia _____ or the fexofenadine hydrochloride drug substance.		9. AMENDMENT(S), REPORT(S), ETC. SCS-008 BC 10/15/98 SCS-008 BC 2/26/99 SCS-008 BC 7/15/99 SCS-008 AC* 9/10/99 *Subject of this review
10. PHARMACOLOGICAL CATEGORY Histamine H_1-receptor antagonist for treatment of seasonal allergic rhinitis	11. HOW DISPENSED RX X OTC _	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Immediate-release capsule	14. POTENCY 60 mg immediate-release fexofenadine HCl	
15. CHEMICAL NAME AND STRUCTURE (±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl (for structure see USAN)		16. RECORDS AND REPORTS CURRENT YES_ NO_ REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-625
HFD-570/div. File
HFD-570/BRogers/10/13/99
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by:_____
F/T by: B. Rogers/10/13/99
doc # 20625.c08.DOC

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is APPROVABLE. The PM should send the comments in the *Draft Letter to the Applicant* portion of this review to the applicant in the AE letter. It should be made clear in all correspondence that this supplement does not support the use of the Frankfort site for manufacture of fexofenadine HCl.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.		10/13/99

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-625 5008

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-625

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627		SCS-008	7/23/98

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Allegra 60 mg Capsules	fexofenadine hydrochloride 60 mg capsules

8. SUPPLEMENT PROVIDES FOR:
1. An alternative starting material for the manufacture of fexofenadine hydrochloride drug substance.
2. An alternative synthesis of the f[redacted] and process modifications in synthesis steps for the manufacture of fexofenadine hydrochloride at Midland, MI facility only.
3. An additional packaging material [redacted] for the fexofenadine hydrochloride drug substance.

9. AMENDMENT(S), REPORT(S), ETC.
SCS-008 BC 10/15/98
SCS-008 BC 2/26/99
SCS-008 BC* 7/15/99

*Subject of this review

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Histamine H_1-receptor antagonist for treatment of seasonal allergic rhinitis	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
Immediate-release capsule	60 mg immediate-release fexofenadine HCl

15. CHEMICAL NAME AND STRUCTURE
(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl (for structure see USAN)

16. RECORDS AND REPORTS
CURRENT YES_ NO_
REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-625
HFD-570/div. File
HFD-570/BRogers/7/28/99
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by:_____
F/T by: B. Rogers/7/28/99
doc # 20625.B08.DOC

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is APPROVABLE. The PM should send the comments in the *Draft Letter to the Applicant* portion of this review to the applicant in the AE letter. It should be made clear in all correspondence that this supplement does not support the use of the Frankfort site for manufacture of fexofenadine HCl.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.		7/28/99

13 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 26625 / 500B

CHEMIST'S REVIEW

1. ORGANIZATION HFD-570 DPDP		2. NDA NUMBER 20-625
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER: SCS-008 DATE: 7/23/98
6. NAME OF DRUG Allegra 60 mg Capsules	7. NONPROPRIETARY NAME fexofenadine hydrochloride 60 mg capsules	
8. SUPPLEMENT PROVIDES FOR: 1. An alternative starting material for the manufacture of fexofenadine hydrochloride drug substance. 2. An alternative synthesis of the [redacted] and process modifications in synthesis steps for the manufacture of fexofenadine hydrochloride at Midland, MI facility only. 3. An additional packaging material [redacted] for the fexofenadine hydrochloride drug substance.		9. AMENDMENT(S), REPORT(S), ETC. SCS-008 BC 10/15/98 SCS-008 BC* 2/26/99 *Subject of this review
10. PHARMACOLOGICAL CATEGORY Histamine H_1-receptor antagonist for treatment of seasonal allergic rhinitis	11. HOW DISPENSED RX X OTC _	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Immediate-release capsule	14. POTENCY 60 mg immediate-release fexofenadine HCl	
15. CHEMICAL NAME AND STRUCTURE (±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl (for structure see USAN)		16. RECORDS AND REPORTS CURRENT YES_ NO_ REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-625
HFD-570/div. File
HFD-570/BRogers/6/29/99
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by:_____
F/T by: B. Rogers/6/29/99
doc # 20625.A08.DOC

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is NOT APPROVED. The PM should include the comments in the *Draft Letter to the Applicant* portion of this review in the NA letter.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.		6/29/99

14 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-625 SOOC

CHEMIST'S REVIEW

	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-625
3. NAME AND ADDRESS OF APPLICANT (City and State) Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER: SCS-008 DATE: 7/23/98
6. NAME OF DRUG Allegra 60 mg Capsules	7. NONPROPRIETARY NAME fexofenadine hydrochloride 60 mg capsules	
8. SUPPLEMENT PROVIDES FOR: 1. An alternative starting material for the manufacture of fexofenadine hydrochloride drug substance. 2. An alternative synthesis of the ——— and process modifications in synthesis steps for the manufacture of fexofenadine hydrochloride at Midland, MI facility only. 3. An additional packaging material ——— for the fexofenadine hydrochloride drug substance.		9. AMENDMENT(S), REPORT(S), ETC. SCS-008 BC 10/15/98
10. PHARMACOLOGICAL CATEGORY Histamine H_1-receptor antagonist for treatment of seasonal allergic rhinitis	11. HOW DISPENSED RX X OTC _	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Immediate-release capsule	14. POTENCY 60 mg immediate-release fexofenadine HCl	
15. CHEMICAL NAME AND STRUCTURE (±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl (for structure see USAN)		16. RECORDS AND REPORTS CURRENT YES_ NO_ REVIEWED YES_ NO_

17. COMMENTS: See attached

cc:
Orig. NDA #20-625
HFD-570/div. File
HFD-570/BRogers/1/21/99
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by:_____
F/T by: B. Rogers/1/21/99
doc # 20625.S08.DOC

18. CONCLUSIONS AND RECOMMENDATIONS: The supplement is NOT APPROVED. The PM should include the comments in the *Draft Letter to the Applicant* portion of this review in the NA letter.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.		1/21/99

17 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-625 5008

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPADP	20-786 and 20-625

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
Hoechst Marion Roussel, Inc. PO Box 9627 Kansas City, MO 64134-0627		20-786/SCS-004 20-625/SCS-008	7/23/98 7/23/98

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Allegra-D™ Extended-release Tablets and Allegra Capsules	fexofenadine hydrochloride and pseudoephedrine hydrochloride extended-release tablets and fexofenadine hydrochloride capsules

8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC.	
1. An alternative starting material for the manufacture of fexofenadine hydrochloride drug substance at their Frankfurt, Germany facilitv.	SCS-004 BC	10/15/98
	SCS-008 BC	10/15/98
2. An alternative synthesis of the ~~——~~ and process modifications in synthesis steps for the manufacture of fexofenadine hydrochloride at Midland, MI facility only.	SCS-004 BC	2/26/99
	SCS-008 BC	2/26/99
3. An additional packaging material ~~——~~ for the fexofenadine hydrochloride drug substance.	SCS-004 BC	7/15/99
	SCS-008 BC	7/15/99
	SCS-004 AC	9/10/99
	SCS-008 AC	9/10/99

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Histamine H_1-receptor antagonist/decongestant for treatment of symptoms associated with seasonal allergic rhinitis	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
Extended-release Tablet and Immediate release tablets	60 mg immediate-release fexofenadine HCl and 120 mg extended-release pseudoephedrine HCl

15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS	
(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-dimethylbenzeneacetic acid HCl and [S-(R*,R*)]- -[1-(Methylamino)ethyl]-benzenemethanol HCl (for structures see USAN)	CURRENT	YES_ NO_
	REVIEWED	YES_ NO_

17. COMMENTS: See attached

and

cc:
Orig. NDA #20-786
Orig. NDA #20-625
HFD-570/div. File
HFD-570/BRogers/1/12/99
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by:_____
F/T by: B. Rogers/1/12/99
doc # 20786.d04.DOC

18. CONCLUSIONS AND RECOMMENDATIONS: These supplements are APPROVED. These supplements had previously been made approvable pending approval of supplements 20-786/SCM-006 and 20-625/SCM-009. These supplements have been approved (see reviews dated 1/4/00). It should be stated in the approval letter that these supplements do not support the use of the Frankfurt site for manufacture of fexofenadine HCl.

19. REVIEWER NAME	20. SIGNATURE	21. DATE COMPLETED
Brian D. Rogers, Ph.D.		1/12/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-625 /S008

20-786/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-625/S-008

Hoechst Marion Roussel
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Attention: Dhiren N. Shah, Ph.D.
Director – CMC, U.S. Drug Regulatory Affairs

Dear Dr. Shah:

Please refer to your pending July 23, 1998, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine HCl) Capsules.

We also refer to your submission dated February 26, 1999.

We have completed our review of your submission and have the following comments and information requests.

1. As stated in our letter dated January 22, 1999, the following comments pertain to in-process testing specifications. Tightening of intermediate specifications to reflect current capabilities is considered a relevant part of process evaluation (comment 1).

   a. The specification for the level of [redacted] is not justified by the data provided and should be tightened to NMT [redacted]

   b. The specifications for the levels of [redacted] in [redacted] are not justified by the data provided and should be tightened to NMT [redacted] and NMT [redacted], respectively.

   c. We acknowledge your change in specification, submitted in your Annual Report dated September 25, 1998, for the [redacted] in [redacted] to NMT [redacted]

2. As stated in our letter dated January 22, 1999, the specification for *Total Related Substances* for release of the drug substance is not justified by the data provided. The specification should be tightened to NMT — to reflect the levels seen in the current production batches. In addition, we recommend that the other individual impurities be reduced to reflect levels seen in recent production batches (comment 4).

3. Since HMR is — Midland, provide — months long-term and accelerated conditions stability data from at least — commercial-scale batch from the Frankfurt site in the supplement to support manufacture of fexofenadine hydrochloride in Frankfurt (comment 6).

4. In reference to the change submitted as — in Exhibit 5, and on pages 31 to 34 in your September 25, 1998, Annual Report, provide a commitment that you will not use the proposed alternative process with — at your Frankfurt facility.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

Guirag Poochikian, Ph.D.
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DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-625
HFD-570/Div. Files
HFD-570/G.Trout
HFD-570/Reviewers and Team Leaders
HFD-820/DNDC Division Director (only for CMC related issues)
DISTRICT OFFICE

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Poochikian/6-30-99

final: Trout/7-1-99
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INFORMATION REQUEST (IR)