CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201373Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

To: File for NDA 201-613 and NDA 201-373

From: Terrance Ocheltree, Ph.D., R.Ph.
Director, Division New Drug Quality Assessment, ONDQA

Date: 21-Jan-2011

Re: ONDQA Recommendation on Approvability for NDAs 201-613 and 201-373

I fully concur with the ONDQA recommendations for "Approval" of NDAs 201-613 and 201-373 based on the findings in the reviews and the Overall Establishment Recommendation of "Acceptable" dated 21-Jan-2011 by the Office of Compliance.

During the review process for NDAs 201-613 and 201-373, but after the completion of the initial ONDQA reviews, the status on the drug substance manufacturing site, Sanofi Aventis Deutschland GmbH, was changed to "OAI pending" due to an anticipated Warning Letter associated with the sterile drug manufacturing operations at this site. This resulted in the Overall Establishment Recommendation changing from "Acceptable" to "Withhold" on 19-Jan-2011. However, following discussions involving OC, DNCE and ONDQA the status of the Overall Establishment Recommendation was changed to "Acceptable" on 21-Jan-2011 because the violations cited in the anticipated Warning Letter are not associated with the non-sterile drug substance manufacturing operations and therefore should not affect the quality of the drug substance in the products described in these NDAs.

Therefore, the ONDQA approvability recommendation for NDAs 201-613 and 201-373 remains "Approval".

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/s/

TERRANCE W OCHELTREE
01/21/2011

NDA 201-373

Children's Allegra
(Fexofenadine Hydrochloride) Oral Suspension
6 mg/mL

sanofi-aventis

Minerva Hughes, PhD, RAC
Review Chemist

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 201-373
For the Division of Nonprescription Clinical Evaluation

Table of Contents

CMC Review Data Sheet

1. NDA 201-373

2. REVIEW #: 2

3. REVIEW DATE: 22 Dec 2010

4. REVIEWER: Minerva Hughes, PhD, RAC

5. PREVIOUS DOCUMENTS: Quality Review #1, 22 Nov 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	26 Mar 2010
Amendment (BC) – CMC establishment information	7 May 2010
Amendment (BC) – Labeling	24 June 2010
Amendment (BC) – Quality information response	30 Jul 2010
Amendment (BC) – Labeling	27 Aug 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	sanofi-aventis U.S. LLC
Address:	55 Corporate Drive Bridgewater, NJ 08807
Representative:	Mary Beth Wigley, Assistant Director RR&DP
Telephone:	610-889-6792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Children's Allegra Hives (proposed)
Children's Allegra Allergy (proposed)
Allegra (approved)

b) Non-Proprietary Name (USAN): fexofenadine hydrochloride

c) Code Name/# (ONDQA only): none

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 8
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 6 mg/mL

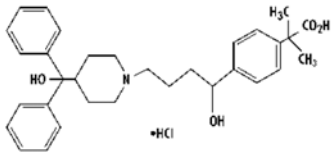
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____Rx __√__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:	(±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride
CAS Registry No.:	153439-40-8
Structural formula:	
Molecular formula:	$C_{32}H_{39}NO_4 \cdot HCl$
Molecular weight:	538.13 g/mol

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4	(b) (4)	3	Adequate	12 Aug 2004 S. Pope	Same configuration as Rx product. No component changes since Rx approval.
	III			3	Adequate	12 Aug 2003 R. Frankewich	Same configuration as Rx product. The updated DMF LOA referenced a 28 July 2009 amendment. This amendment is an annual report with updated access information. A follow-up review is not needed.
	III			3	Adequate	9 June 2003 D. Klein	Same configuration as Rx product. No component changes since Rx approval.
	III			4	Adequate	-	Adequate information in NDA. DMF not reviewed.
	III			4	Adequate	-	Adequate information in NDA. DMF not reviewed.
	III			7	Adequate	-	Cross referenced to NDA 21-963/S-004. Accepted based on PAS approval of 12 Feb 2010 (by Edwin Jao). No supplier or component changes are proposed. No major amendments to DMF since approval, so DMF was not reviewed.
	III			7	Adequate	-	Same as above.
	III			7	Adequate	-	Same as above.
	III		(b) (4)	7	Adequate	-	Same as above.

Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CMC Review Data Sheet

B. Other Documents: *Relevant previous submissions by applicant*

Document	Date (Original Application)	Status
IND-43573	5 Oct 1993	Active IND for fexofenadine HCl solution
NDA-20872	17 July 1998	Allegra tablet (30, 60, and 180 mg fexofenadine HCl) approved for Rx use
NDA-21909	28 Sept 2006	Allegra Orally Disintegrating Tablet (30 mg fexofenadine HCl), approved for Rx use
NDA-21963	15 Dec 2005	Allegra Oral Suspension (6 mg/mL fexofenadine HCl), approved for Rx use
NDA-20786	20 Dec 1996	Allegra-D 12 hour (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg), approved for Rx use
NDA-21704	19 Dec 2003	Allegra-D 24 (fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg), approved for Rx use
NDA-20625	31 July 1995	Allegra capsule (fexofenadine HCl 60 mg), approved for Rx use

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	-	-
EES*	Acceptable	20 Dec 10	Office of Compliance
Pharm/Tox	Not applicable	-	-
Biopharm	Not applicable	-	-
Labeling (DNRD for OTC)	-		Labeling review is managed by OTC. Final labeling is pending; however, there are no CMC issues.
Methods Validation	N/A, according to the current ONDQA policy	-	-
DMEPA (Proprietary Review)	Acceptable		
Environmental Assessment*	No significant Impact	30 Nov 10	Raanan Bloom
Microbiology	Not applicable	-	-

***** The Office of Compliance's assessment of the manufacturing facilities and the environmental assessment review were pending when Quality Review #1 was finalized. This addendum provides the recommendation from these reviews and the final quality review recommendation for NDA 207-373.

The CMC Review for NDA 201-373

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided adequate information to assure identity, strength, purity, and quality of the drug product. All outstanding CMC issues at the finalization of Quality Review # 1 have been adequately addressed.

An acceptable site recommendation from the Office of Compliance has been made, and no adverse environmental effects have been identified for the proposed action of a partial switch to nonprescription use.

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations on Phase 4 commitments. The applicant has committed to post-approval stability testing of the new bottle sizes.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Reference is made to approved NDA 20-625 for details on fexofenadine HCl drug substance. No new information on the drug substance is provided in this application.

(2) Drug Product

Allegra (fexofenadine HCl 6 mg/mL) oral suspension is an immediate-release (b) (4), white, aqueous, raspberry cream flavored suspension intended for twice-a-day oral dosing in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria (hives). NDA 201-373 was submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for a partial switch from prescription to over-the-counter (OTC) use. Fexofenadine HCl suspension for children younger than 6 years with CIU will not be switched from prescription to nonprescription status. The applicant will maintain NDA 21-963 for the prescription use of fexofenadine HCl, and incorporates much of the drug product information in NDA 201-373 by cross reference to NDA 21-963. There were no changes to the approved manufacturing process, process controls

and product specification with the exception of a change in packaging for two new bottle sizes for the OTC market: 150 mL bottles (4 oz with approx. 120-mL suspension) and 300 mL bottles (8 oz with approx. 240 mL suspension). Bottles are closed using a 24-mm child-resistant cap and packaged with a dosing cup.

One full scale lot was manufactured for each bottle size and placed on stability in accordance with ICH guidelines. Stability data were submitted through 9 months storage at 25°C/40% RH. There were no significant differences in product quality overtime. The stability data and the physical and chemical comparability of the bottles to the prescription product packaging support the acceptability of the new bottle sizes. An expiration dating period of 24 months is granted.

Carton and container labeling are adequate from a CMC perspective. Additional labeling comments from the OTC labeling review team is addressed in their respective reviews.

The partial switch to OTC is expected to increase the use of fexofenodine HCl. An environmental assessment was submitted and a finding of no significant environmental impact was assessed by FDA, Raanan Bloom review of 30 November 2010.

B. Description of How the Drug Product is Intended to be Used

Fexofenadine HCl oral suspension is intended for the treatment of seasonal allergic rhinitis in adults and children 2 years or older and for the treatment of hives and the relief of itching due to hives in adults and children 6 years or older. The product is administered orally, twice-a-day, for the relief of symptoms.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Minerva Hughes, Ph.D., R.A.C., Review Chemist, Branch IV, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DARRTS

CMC Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE

Refer to Quality Review #1 dated 22 November 2010.

P DRUG PRODUCT

Note: Relevant CMC changes from approved NDA 21-963 include new bottle sizes, inclusion of a dosing cup as an administrative device, and compliance with child resistant and tamper evident requirements for over-the-counter products.

Refer to Quality Review #1 dated 22 November 2010.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Drug Facts

Refer to Quality Review #1 dated 22 November 2010.

B. Environmental Assessment Or Claim Of Categorical Exclusion

An environmental assessment was submitted and reviewed by Ranaan Bloom, review dated 30 November 2010. Bloom's review concluded that an increased use of fexofenadine HCl from an approval action of this NDA is not expected to have a significant impact on the environment.

III. List Of Deficiencies to be Communicated

There are no deficiencies to be communicated to the applicant.

IV. Attachments

Attachment 1 – Abbreviated EES Report

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MINERVA HUGHES
12/22/2010

MARIE KOWBLANSKY on behalf of MOO JHONG RHEE
12/22/2010

NDA 201-373

Children's Allegra
(Fexofenadine Hydrochloride) Oral Suspension
6 mg/mL

sanofi-aventis

Minerva Hughes, PhD, RAC
Review Chemist

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 201-373
For the Division of Nonprescription Clinical Evaluation

Table of Contents

CMC Review Data Sheet

1. NDA 201-373

2. REVIEW #: 1

3. REVIEW DATE: 22-November-2010

4. REVIEWER: Minerva Hughes, PhD, RAC

5. PREVIOUS DOCUMENTS: Not applicable.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	26 Mar 2010
Amendment (BC) – CMC establishment information	7 May 2010
Amendment (BC) – Labeling	24 June 2010
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7. NAME & ADDRESS OF APPLICANT:

Name:	sanofi-aventis U.S. LLC
Address:	55 Corporate Drive Bridgewater, NJ 08807
Representative:	Mary Beth Wigley, Assistant Director RR&DP
Telephone:	610-889-6792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Children's Allegra Hives (proposed)
Children's Allegra Allergy (proposed)
Allegra (approved)

b) Non-Proprietary Name (USAN): fexofenadine hydrochloride

c) Code Name/# (ONDQA only): none

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 8
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 6 mg/mL

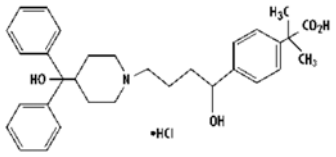
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____Rx __√__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:	(±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride
CAS Registry No.:	153439-40-8
Structural formula:	
Molecular formula:	$C_{32}H_{39}NO_4 \cdot HCl$
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CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

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	III			7	Adequate	-	Same as above.
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *Relevant previous submissions by applicant*

Document	Date (Original Application)	Status
IND-43573	5 Oct 1993	Active IND for fexofenadine HCl solution
NDA-20872	17 July 1998	Allegra tablet (30, 60, and 180 mg fexofenadine HCl) approved for Rx use
NDA-21909	28 Sept 2006	Allegra Orally Disintegrating Tablet (30 mg fexofenadine HCl), approved for Rx use
NDA-21963	15 Dec 2005	Allegra Oral Suspension (6 mg/mL fexofenadine HCl), approved for Rx use
NDA-20786	20 Dec 1996	Allegra-D 12 hour (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg), approved for Rx use
NDA-21704	19 Dec 2003	Allegra-D 24 (fexofenadine HCl 180 mg/pseudoephedrine HCl 240 mg), approved for Rx use
NDA-20625	31 July 1995	Allegra capsule (fexofenadine HCl 60 mg), approved for Rx use

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	-	-
EES	Pending*	N.A	Not specified.
Pharm/Tox	Not applicable	-	-
Biopharm	Not applicable	-	-
Labeling (DNRD for OTC)	-		Labeling review is managed by OTC. Final labeling is pending; however, there are no CMC issues.
Methods Validation	N/A, according to the current ONDQA policy	-	-
DMEPA (Proprietary Review)	Acceptable		
Environmental Assessment	Pending**	N.A.	Not specified
Microbiology	Not applicable	-	-

*A compliance rating for manufacturing facilities is pending.

**The applicant has concluded that the increased use of fexofenadine HCl after approval of NDA 201-373 presents no significant risk to the environment based on microbial inhibition testing through Tier 2, in accordance with FDA Guidance for Industry- Environmental Assessment of Human Drug and Biologics Applications. The Environmental Assessment group was consulted to review the Tier 2 assessment data and assess the environmental impact; however, a recommendation is pending.

The CMC Review for NDA 201-373

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. However, an assessment of the environmental impact is pending, and a recommendation from the Office of Compliance on the acceptability of manufacturing facilities has not been made as of the date of this review.

From the CMC perspective, this NDA is not recommended for approval until the acceptability of the manufacturing facilities is established.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations on Phase 4 commitments. The applicant has committed to post-approval stability testing of the new bottle sizes.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Reference is made to approved NDA 20-625 for details on fexofenadine HCl drug substance. No new information on the drug substance is provided in this application.

(2) Drug Product

Allegra (fexofenadine HCl 6 mg/mL) oral suspension is an immediate-release (b) (4), white, aqueous, raspberry cream flavored suspension intended for twice-a-day oral dosing in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria (hives). NDA 201-373 was submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for a partial switch from prescription to over-the-counter (OTC) use. Fexofenadine HCl suspension for children younger than 6 years with CIU will not be switched from prescription to nonprescription status. The applicant will maintain NDA 21-963 for the prescription use of fexofenadine HCl, and incorporates much of the drug product information in NDA 201-373 by cross reference to NDA 21-963. There were no changes to the approved manufacturing process, process controls and product specification with the exception of a change in packaging for two new bottle sizes for the OTC market: 150 mL bottles (4 oz with approx. 120-mL

suspension) and 300 mL bottles (8 oz with approx. 240 mL suspension). Bottles are closed using a 24-mm child-resistant cap and packaged with a dosing cup.

One full scale lot was manufactured for each bottle size and placed on stability in accordance with ICH guidelines. Stability data were submitted through 9 months storage at 25°C/40% RH. There were no significant differences in product quality overtime. The stability data and the physical and chemical comparability of the bottles to the prescription product packaging support the acceptability of the new bottle sizes. An expiration dating period of 24 months is granted.

Carton and container labeling are adequate from a CMC perspective. Additional labeling comments from the OTC labeling review team is addressed in their respective reviews.

The partial switch to OTC is expected to increase the use of fexofenodine HCl and a finding of no significant environmental impact was claimed based on microbial testing through tier 2. A concurrence finding of no significant impact from the Office of Pharmaceutical Science's Environmental Assessment group is pending (consult requested on 16 Jul 2010).

B. Description of How the Drug Product is Intended to be Used

Fexofenadine HCl oral suspection is intended for the treatment of seasonal allergic rhinitis in adults and children 2 years or older and for the treatment of hives and the relief of itching due to hives in adults and children 6 years or older. The product is administered orally, twice-a-day, for the relief of symptoms.

C. Basis for Approvability or Not-Approval Recommendation

A recommendation from the Office of Compliance on the site acceptability has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability is established.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Minerva Hughes, Ph.D., R.A.C., Review Chemist, Branch IV, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

MINERVA HUGHES
11/22/2010

MOO JHONG RHEE
11/22/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	201373
Applicant:	Sanofi-aventis U.S. LLC
Stamp Date:	March 25, 2010
PDUFA Date	Jan. 25, 2011
Trademark:	Allegra®
Established Name:	Fexofenadine HCl
Dosage Form:	Suspension, 30 mg/5 mL
Route of Administration:	Oral
Indication:	Relief of symptoms associated with allergic rhinitis in adults and children 2 years of age and over, and hives in adults and children 6 years of age and over
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

A. Summary

Sanofi-aventis is submitting a 505(b) (2) New Drug Application (NDA) for the nonprescription use of Allegra (fexofenadine HCl) oral suspension, 30 mg/5 mL for the treatment of allergic rhinitis in adults and children 2 years of age and over, and hives in adults and children 6 years of age and over. This is a partial switch of NDA 21-963 Allegra (fexofenadine HCl) oral suspension, approved 1n Y2006. Allegra oral suspension for pediatric patients younger than 6 years of age with chronic idiopathic urticaria will remain under the prescription NDA 21-963.

The applicant references to NDA 20-625 Allegra capsules and all its applicable supplements/annual reports for the CMC information of the drug substance, fexofenadine HCl. NDA 20-625 was approved in Y1996.

CMC information of the drug product is referenced to the approved prescription NDA 21-963 and all applicable amendments, supplements and Annual Reports made to NDA 21-963. With the exception of a change in fill volume and bottle size, no changes are in formulation composition, manufacturing, container/closure system, and drug product specification.

The proposed OTC packaging configurations are 120 mL fill in 150 mL amber, (b) (4) bottles, and 240 mL fill in 300 mL amber, (b) (4) bottles. Both fill sizes are equipped with a child resistant, white, opaque, (b) (4) 24 mm closure with foam liner and aluminum foil induction innerseal. Although two fill sizes are proposed, only the 120mL fill size is intended for commercialization.

To support the proposed 24 month expiration dating period when stored at 25ºC, the applicant provides for each packaging configuration 3 months of long term and accelerated stability data from one full-scale batch (upright and inverted). Additional 12-36 months supporting stability data are also provided from other packaging configurations with a similar head-space to volume ratio.

B. Critical issues for review

Drug Product Stability

- Although 3 months of stability data are provided, the data cover only one stability time point (3 month). One data point does not allow evaluation of stability trend. An update in stability should, therefore, be requested.

Measuring Cup

- The cup needs to be validated for volume measurements. This cup was not approved under the prescription NDA 21-963.

Labels

- Two fill sizes are proposed for this OTC NDA but only the one intended for commercialsiztion is provided with container/carton labels. The reviewer in the CMC review should clearly state the configuration whose Container/carton labels are not included in the review/approval of the NDA.

Environmental Assessment

- An Environmental Assessment report is included in the NDA. A consult should be sent by ONDQA to Environmental Assessment group.

C. Comments for 74-Day Letter:

None.

D. Comments/Recommendation:

The application is fileable from CMC perspective. The major CMC review issues with this NDA are stability and environmental assessment.

The drug substance manufacturing site is located in Germany. The drug product manufacturing site is located in U.S. GMP inspection requests are being processed.

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch III

NDA Number: 201373	**Supplement Number and Type:**	**Established/Proper Name: Allegra (fexofenadine HCl) oral suspension**
Applicant: sanofi-aventis	**Letter Date: 3/26/10**	**Stamp Date: 3/25/10**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			n/a

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		x	
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		A report is included in the NDA.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	Referenced to NDA 20-625.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced toNDA 20-625.
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to NDA 20-625.
15.	Does the section contain controls for the DS?		x	Referenced to NDA 20-625.
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to NDA 20-625.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?		x	Referenced to NDA 21-963
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?		x	Referenced to NDA 21-963
21.	Is there a batch production record and a proposed master batch record?		x	Referenced to NDA 21-963
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		x	Referenced to NDA 21-963
23.	Have any biowaivers been requested?		x	Not applicable
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?		x	Referenced to NDA 21-963
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		x	Referenced to NDA 21-963

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	1/12/2010	
	III			1/21/2010	
	III			1/14/2010	
	III			12/3/2009	
	III			11/4/2009	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 2 of IQA.

{See appended electronic signature page}

Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201373	ORIG-1	SANOFI AVENTIS US LLC	FEXOFENADINE HCL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHULIN DING
05/12/2010

MOO JHONG RHEE
05/12/2010
Chief, Branch IV