	Last Subject Completed: October 4, 2004	Fax (816) 767-7361

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by May 25, 2007. We intend to issue an action letter on this application by July 27, 2007.

Should you require any additional information, please contact Lori Garcia, at (301) 796-1212.

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From: Al Habet, Sayed
Sent: Tuesday, December 19, 2006 2:52 PM
To: Fadiran, Emmanuel O
Cc: Garcia, Lori
Subject: RE: BE Inspection: NDA 21-909 (Allegra Fexofenadine HCL ODT 30 mg)

Lori,

Yes both studies are conducted at the same clinical and analytical sites. See our filing memo (Page 3 of the filing form, attached). The clinical site is Bio-Kinetic in Springfield, MO and the analytical site is [redacted] b(4)

Sam

FilingMemo.doc (2 MB)

From: Fadiran, Emmanuel O
Sent: Tuesday, December 19, 2006 11:17 AM
To: Al Habet, Sayed
Cc: Garcia, Lori
Subject: FW: BE Inspection: NDA 21-909 (Allegra Fexofenadine HCL ODT 30 mg)

Sayed,

Please respond to Lori's questions.

Thanks.

Tayo

Emmanuel Olutayo Fadiran, R.Ph., Ph.D.
Team Leader, Pulmonary & Allergy Products
Division of Clinical Pharmacology 2, OCP, FDA
Building 21, Room 4672
10903 New Hampshire Avenue, Silver Spring, MD 20993-0002
Phone: 301-796-1529
Fax: 301-796-9741
E-mail: emmanuel.fadiran@fda.hhs.gov

From: Garcia, Lori
Sent: Tuesday, December 19, 2006 11:15 AM
To: Fadiran, Emmanuel O
Subject: RE: BE Inspection: NDA 21-909 (Allegra Fexofenadine HCL ODT 30 mg)

are the clinical and analytical sites the same for both studies??

From: Fadiran, Emmanuel O
Sent: Friday, December 15, 2006 10:15 AM
To: Garcia, Lori
Cc: Al Habet, Sayed; Himaya, Amalia; Skelly, Michael F; Yau, Martin K
Subject: RE: BE Inspection: NDA 21-909 (Allegra Fexofenadine HCL ODT 30 mg)

Lori,

Please change the DSI consult to include both studies 1007 and 1008.

Thanks.

Tayo

Emmanuel Olutayo Fadiran, R.Ph., Ph.D.
Team Leader, Pulmonary & Allergy Products
Division of Clinical Pharmacology 2, OCP, FDA
Building 21, Room 4672
10903 New Hampshire Avenue, Silver Spring, MD 20993-0002
Phone: 301-796-1529
Fax: 301-796-9741
E-mail: emmanuel.fadiran@fda.hhs.gov

From: Yau, Martin K
Sent: Friday, December 15, 2006 10:12 AM
To: Fadiran, Emmanuel O
Cc: Al Habet, Sayed; Himaya, Amalia; Skelly, Michael F
Subject: BE Inspection: NDA 21-909 (Allegra Fexofenadine HCL ODT 30 mg)

Taro:

As a follow-up to our phone conversation this morning, please ask the project manager (Lori Garcia) to send us a new DSI Consult requesting that the clinical and analytical portions of both Studies 1007 and 1008 be inspected by DSIBE. Please note that the Nov 28, 2006 Consult we received earlier from HFD-570 requested inspection of Study 1007 only.

Thanks.
Martin

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

/s/

Lori Garcia
12/19/2006 04:05:05 PM

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Garcia

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 2006

TO: Director, Investigations Branch
Kansas City District Office
11630 West 80th Street
Lenexa, KS 66214-3338

FROM: C.T. Viswanathan, Ph.D. CTV
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2007, **High Priority CDER User Fee NDA**, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-909
DRUG: Allegra (fenofenadine HCl) Orally Disintegrating Tablets (ODT) 30 mg
SPONSOR: Sanofi Aventis Pharmaceuticals Inc.
Bridgewater, NJ

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence studies.

Because of Review Division deadlines, the inspections should be completed by May, 2007.

Study MO16455H/1007: Two-way Crossover, Randomized, Open-label Pivotal Bioequivalence Study Comparing the Fexofenadine Hydrochloride Orally Disintegrating Tablet (ODT) Formulation (30 mg) to the Marketed Allegra Tablet (30 mg) in Healthy Adult Subjects.

Study MO16455H/1008: Two-way Crossover, Randomized, Open-label Study Comparing the Bioequivalence of the Fexofenadine Hydrochloride Orally Disintegrating Tablet (ODT) Formulation (30 mg) Given with and without Water to Healthy Adult Subjects.

[redacted] **Effective October 1, 2006, [redacted] would only continue** b(4)

[redacted] **The analytical source records and documentation of Studies M016455H/1007 and M016455H/1008 were transferred back to the sponsor, Sanofi-Aventis Phamraceuticals Inc. at Kansas City, MO. The sponsor contact person is Gerry Choc, Ph.D., Head, Bioanalytics and Preclinical Pharmacokinetics, Sanofi-Aventis Pharmaceuticals, Inc. (tel: 908-231-4667; fax: 908-231-2697; e-mail: Gerry.Choc@sanofi-aventis.com)**

Subject plasma samples obtained in Studies M016455H/1007 and M016455H/1008 were analyzed for fexofenadine using the same LC-MS/MS method. All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigators, background material will be forwarded directly. A member of the Bioequivalence Team from the Division of Scientific Investigations will participate in the inspection of the analytical portions of Studies M016455H/1007 and M016455H/1008.

Headquarters Contact Person: Martin K. Yau, Ph.D.
301-827-5458

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cc:
HFD-45/RF
HFD-48/Yau(2)/Himaya/CF
DPAP/Garcia (NDA 21-909)
DCP2/Fadiran/Al Habet
HFR-SE300/Montgomery (Please FAX to 913-752-2413)
Draft: MKY 12/15/06
DSI 5741; O:\BE\assigns\bio21909.doc
FACTS [redacted] b(4)

[redacted] b(4)

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REGULATORY PROJECT MANAGER REVIEW

PLR Format Review of Proposed Labeling

Application Number: NDA 21-909

Name of Drug: Allegra (fexofenadine HCl) ODT, 30mg

Applicant: Sanofi-aventis

Material Reviewed:

Submission Date(s): September 28, 2006 (.doc)
November 10, 2006 (.xml)

Receipt Date(s): September 29, 2006
November 13, 2006

Background and Summary

On September 28, 2006, Sanofi-aventis US LLC submitted a New Drug Application for Allegra Orally Disintegrating Tablets, 30mg, for the twice-daily treatment of seasonal allergic rhinitis (SAR) and uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in children 6 to 11 years of age.

The proposed labeling text for Allegra ODT, 30 mg, was provided in PDF format (.pdf). Draft labeling text was provided in Word format (.doc) as a review aid. PLR-compliant labeling, formatted in Structured Product Labeling (SPL), was not submitted, although the cover letter for the NDA submission stated that it was included. PLR-compliant SPL was requested and submitted by the sponsor on November 10, 2006.

Review

Primary reviewer: Lori Garcia, R.Ph., Regulatory Project Manager
Division of Pulmonary and Allergy Products
OND, ODE II, CDER

Secondary reviewer: Jeanne Delasko, RN, MS, Labeling Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

The .xml version of the proposed labeling in the new PLR format was reviewed using the Label Review Tool provided by SEALD. The following is a list of revisions, comments and recommendations for the proposed labeling that should be conveyed to the applicant in the 74-

day letter.

General Comments:

- Highlights and Contents must each be limited in length to one-half page, in 8 point type, two-column format. In addition, all labeling information, headings and subheadings must be a minimum of 8 points. [See 21 CFR 201.57(d)(6) and (d)(8)].

- The Word version (.doc) of the labeling submitted on September 28, 2006, does not match the SPL version (.xml) submitted on November 10, 2006. The formatting and text of these 2 versions should be the same.

Highlights:

- Delete the white space between the **Highlights of Prescribing Information** heading and the Highlights limitation statement.

- The drug names must be followed by the drug's dosage form(s) and route of administration. Please correct and include all dosage forms that are provided for by this labeling. [See 21 CFR 201.57(a)(2)]

- The phrase '[redacted] after "Allegra (fexofenadine hydrochloride) Tablet, Orally Disintegrating" can be omitted. It is only necessary to include the route of administration if it is not typical for the dosage form. b(4)

- The revision date is missing from Highlights and will be the month/year that the supplement is approved. [See 21 CFR 201.57(a)(15)] Also, delete "Revised" at the end of the FPI. The revision date at the end of Highlights replaces this information.

- Under RECENT MAJOR CHANGES, the heading, and if appropriate, the subheading of the labeling section affected by the change must be listed together. Do not include the type of change [See 21 CFR 201.57(a)(5)]. In addition, the corresponding new or modified text under the sections in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]

- Delete the bolded lines before and after the list of major changes.

- Under RECENT MAJOR CHANGES, add the date 10/2006 for Allegra Oral Suspension now that it approved.

- Under Dosage and Administration, do not use the asterisk (*) to footnote information in tables in Highlights since this symbol is used in the Table of Contents (i.e., *Sections or subsections omitted from the full prescribing information are not listed). Use a different symbol.

- Regarding Contraindications, "theoretical" possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]

- If the WARNINGS AND PRECAUTIONS section is present in Highlights, then it must also be included in the Contents and in the Full Prescribing Information (FPI).

- [redacted] b(4)

Full Prescribing Information (FPI) Contents:

- Under DRUG INTERACTIONS, list only the names of the foods and/or drugs that interact with Allegra. Delete the preceding phrase ' [redacted] b(4)

- The footnote "*Sections of subsections omitted from the full prescribing information are not listed" should be right-justified. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

Full Prescribing Information (FPI):

- You refer to adverse reactions as " [redacted] Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your adverse reactions section accordingly. b(4)

- Indent all paragraphs, headings, subheadings throughout the FPI. For overall FPI formatting, refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

- The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. For example, *[see Clinical Pharmacology (12)]*, not (See CLINICAL PHARMACOLOGY). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use bold print. Do not use all capital letters. Please fix all cross-references throughout the labeling. [See Implementation Guidance]

- Avoid using "trailing" zeros after whole numbers (e.g., see 12.3 Pharmacokinetics). Please refer to the Institute for Safe Medication Practices website at http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.

- In the DOSAGE FORMS AND STRENGTHS section, include the identifying characteristics of the dosage forms, such as shape, color, coating, scoring, and imprinting when applicable. [See 21 CFR 201.57(c)(4)(ii)]

- Under How Supplied/Storage and Handling, you refer to [See USP Controlled Room Temperature]. Please provide a temperature range for controlled temperature. [See 21 CFR 201.57(c)(17)]

- In the PATIENT COUNSELING INFORMATION section, use an active voice instead of passive voice, e.g., [redacted] instead of [redacted] b(4)

Lori Garcia, R.Ph.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

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Drafted: LGarcia/December 6, 2006
Revised/Initialed: SBarnes/12.8.06
Finalized: LGarcia/December 12, 2006
Filename: Document2

CSO PLR FORMAT LABELING REVIEW

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/s/

Lori Garcia
12/13/2006 04:15:53 PM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-909

Sanofi-aventis
200 Crossing Blvd, PO Box 6890
Bridgewater, NJ 08807-0890

Attention: Lori Birkenberger, Ph.D.
Associate Director, Regulatory Development

Dear Dr. Birkenberger:

Please refer to your September 28, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra (fexofenadine hydrochloride) Orally Disintegrating Tablets (ODT), 30mg.

We also refer to your submission dated November 10, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 28, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. As indicated in the EOP2 and PreNDA meetings, the proposed acceptance criteria for disintegration and the size of the tablet in relation to the performance and nomenclature of an Orally Disintegrating Tablet (ODT) will be potential review/policy issues. The current Office of New Drug Quality Assessment (ONDQA) policy does not consider your tablet to have met the requirements of an Orally Disintegrating Tablet (ODT).

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

2. Provide the fate of the remaining [redacted] fexofenadine [redacted] that are not used in the fina[redacted] process. Provide the shelf-life and stability data for these [redacted]

b(4)

3. Identify the differences between the [redacted] blister foil obtained from the [redacted] sites located in [redacted] and [redacted]. Indicate which blisters were employed during the registration stability batches. b(4)

4. Provide graphical summaries of stability data for each parameter to better assess the shelf-life.

5. Provide samples of drug product.

The following comments pertain to the Physician's Labeling Rule (PLR) format of your proposed labeling and are based on Title 21 of the Federal Code of Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

General Comments:

6. Highlights and Contents must each be limited in length to one-half page, in 8 point type, two-column format. In addition, all labeling information, headings and subheadings must be a minimum of 8 points. [See 21 CFR 201.57(d)(6) and (d)(8)].

7. The Word version (.doc) of the labeling submitted on September 28, 2006, does not match the SPL version (.xml) submitted on November 10, 2006. The formatting and text of these 2 versions should be the same.

Highlights:

8. Delete the white space between the **Highlights of Prescribing Information** heading and the Highlights limitation statement.

9. The drug names must be followed by the drug's dosage form(s) and route of administration. Please correct and include all dosage forms that are provided for by this labeling. [See 21 CFR 201.57(a)(2)]

10. The phrase [redacted] after "Allegra (fexofenadine hydrochloride) Tablet, Orally Disintegrating" can be omitted. It is only necessary to include the route of administration if it is not typical for the dosage form. b(4)

11. The revision date is missing from Highlights and will be the month/year that the supplement is approved. [See 21 CFR 201.57(a)(15)] Also, delete [redacted] at the end of the FPI. The revision date at the end of Highlights replaces this information. b(4)

12. Under RECENT MAJOR CHANGES, the heading, and if appropriate, the subheading of the labeling section affected by the change must be listed together. Do not include the type of change [See 21 CFR 201.57(a)(5)]. In addition, the corresponding new or modified text under the sections in the Full Prescribing Information (FPI) must be marked

with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]

13. Delete the bolded lines before and after the list of major changes.

14. Under RECENT MAJOR CHANGES, add the date 10/2006 for Allegra Oral Suspension now that it approved.

15. Under DOSAGE AND ADMINISTRATION, do not use the asterisk (*) to footnote information in tables in Highlights since this symbol is used in the Table of Contents (i.e., *Sections or subsections omitted from the full prescribing information are not listed). Use a different symbol.

16. Regarding CONTRAINDICATIONS, "theoretical" possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the CONTRAINDICATIONS section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]

17. If the WARNINGS AND PRECAUTIONS section is present in Highlights, then it must also be included in the Contents and in the Full Prescribing Information (FPI).

18. Do not include pregnancy category in Highlights. [See comment #34 Preamble]

Full Prescribing Information (FPI) Contents:

19. Under DRUG INTERACTIONS, list only the names of the foods and/or drugs that interact with Allegra. Delete the preceding phrase "[redacted]" b(4)

20. The footnote "*Sections of subsections omitted from the full prescribing information are not listed" should be right-justified. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

Full Prescribing Information (FPI):

21. You refer to adverse reactions as "adverse experiences." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your adverse reactions section accordingly.

22. Indent all paragraphs, headings, subheadings throughout the FPI. For overall FPI formatting, refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

23. The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. For example, *[see Clinical Pharmacology (12)]*, not (See CLINICAL PHARMACOLOGY). The cross-reference should be in brackets. Because

cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use bold print. Do not use all capital letters. Please fix all cross-references throughout the labeling. [See Implementation Guidance]

24. Avoid using "trailing" zeros after whole numbers (e.g., see 12.3 Pharmacokinetics). Please refer to the Institute for Safe Medication Practices website at http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.

25. In the DOSAGE FORMS AND STRENGTHS section, include the identifying characteristics of the dosage forms, such as shape, color, coating, scoring, and imprinting when applicable. [See 21 CFR 201.57(c)(4)(ii)]

26. Under HOW SUPPLIED/STORAGE AND HANDLING, you refer to [See USP Controlled Room Temperature]. Please provide a temperature range for controlled temperature. [See 21 CFR 201.57(c)(17)]

27. In the PATIENT COUNSELING INFORMATION section, use an active voice instead of passive voice, e.g., "Advise patients to take the Allegra Tablets with water' instead of [redacted] b(4)

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 796-1212.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
12/12/2006 02:55:59 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Office/Division): Division of Drug Marketing, Advertising and Communications	FROM (Name, Office/Division, and Phone Number of Requestor): Lori Garcia, R.Ph., Regulatory Project Manager Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 28, 2006		NDA 21-909	Original NDA	September 28, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Allegra	standard	3	May 25, 2007

NAME OF FIRM: sanofi aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please perform DDMAC review of new NDA 21-909 for Allegra (fexofenadine) ODT. This is a new formulation to the fexofenadine product-line. The entire NDA is available in the EDR.
If you have any questions, please contact me at 301-796-1212.
PDUFA goal: July 27, 2007

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Lori Garcia	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Lori Garcia
11/29/2006 03:28:00 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
WO22, RM 4447

FROM:
Lori Garcia, R.Ph., Regulatory Project Manager
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 28, 2006		NDA 21-909	Original NDA	September 28, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Allegra (fexofenadine) ODT	S	3	May 25, 2007

NAME OF FIRM: sanofi aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please perform DMETS review of new NDA 21-909 for Allegra (fexofenadine) ODT. This is a new formulation to the fexofenadine product-line. The entire NDA is available in the EDR. If you have any questions, please contact me at 301-796-1212.

PDUFA DATE: July 27, 2007
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 21-909
HFD-570/Division File
HFD-570/RPM
HFD-570/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Lori Garcia	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/
Lori Garcia
11/29/2006 03:25:51 PM

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Request for Biopharmaceutical Inspections

DATE: November 28, 2006

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Lori Garcia, Regulatory Project Manager, HFD-570

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-909
Allegra (fexofenadine HCl) ODT 30mg
Sanofi aventis

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	**Clinical Site:**	**Analytical Site:**
M016455H/1007	Bio-Kinetic Clinical Applications 1816 West Mount Vernon Springfield, MO 65802 PI: Dr. Dennis N. Morrison, DO Dates: August 31, 2004 Last Subject Completed: October 4, 2004	[redacted] Study Manager: [redacted] Phone [redacted] Fax [redacted]

b(4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by May 25, 2007. We intend to issue an action letter on this application by July 27, 2007.

Should you require any additional information, please contact Lori Garcia, at (301) 796-1212.

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Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-909**	**Brand Name**	**N/A**
OCP (I, II, III)	**II**	**Generic Name**	**Fexofenadine**
Medical Division	**DPADP**	**Drug Class**	Anti Allergy
OCPB Reviewer	Sayed (Sam) Al Habet, RP.h, Ph.D.	**Indication(s)**	Seasonal Allergic Rhinitis and Chronic Idiopathic Urticaria
OCPB Team Leader	**Emmanuel (Tayo) Fadiran, RP.h., Ph.D.**	**Dosage Form**	**Oral Disintegrating Tablets**
PM Reviewer		**Dosing Regimen**	**Once or Twice daily in children 6 to 11 years of age**
Date of Submission	**September 28, 2006**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**April 28, 2007**	**Sponsor**	**Sanofi-Aventis**
PDUFA Due Date	**July 28, 2007**	**Priority Classification**	Standard
Division's Due Date	May 28, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	X			
Patients-				
single dose:	x			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**No Comments at this time.**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. NONE at this time
QBR questions (key issues to be considered)	**The sponsor conducted adequate PK/BE studies (see attached filing slides for detisl). The three main studies are:**	
	1) BE study with ODT and marketed allegro 30 mg. **2) Effect of food study** **3) Effect of water (ODT with and without water)**	

Clinical Pharmacology Filing Meeting
(November 17, 2006)

Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

11/21/2006 12:42 PM 1

Product Summary

NDA#:	21-909
Date of Submission:	September 28, 2006
Generic Name:	Fexofenadine
Trade Name:	ALLEGRA® Orally Disintegrating Tablet (ODT)
Formulation:	30 mg ODT
Route of Administration:	Oral
Indications:	Seasonal Allergic Rhinitis (SAR) Chronic Idiopathic Urticaria (CIU)
Type of Submission:	NDA
Sponsor:	Sanofi-Aventis Pharmaceuticals
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

11/21/2006 12:43 PM 2

What Studies Were Submitted in the Current NDA?

In vitro Dissolution:

- Two lots of ODT
- Two lots of reference

Clinical Pharmacology Studies:

- Pilot/Formulation development study and food effect study (#1004)
  - Four prototypes
  - Fed/fasted on one prototype (formulation II)
- Pivotal BE study (#1007):
  - 30 mg single dose of ODT vs 30 mg reference Allegra
- Effect of water:
  - ODT with and without water

Pilot Study (Formulation Development and Food Effect) Study # 1004

Crossover in 35 healthy subjects:

Treatment A: 30 mg reference (Allegra)
Treatment B: 30 mg ODT prototype I (fasting)
Treatment C: 30 mg ODT prototype I (fed)
Treatment D: 30 mg ODT prototype II (fasting)
Treatment E: 30 mg ODT prototype II (fed)
Treatment F: 30 mg ODT prototype I (without water)
Treatment G: 30 mg ODT prototype IV (fasting)
Treatment H: 30 mg ODT prototype V (fasting)

Results of the Pilot Study (#1004)

Summary of analysis of variance of pharmacokinetic parameters

Parameter		Treatment[a]	N	Mean	CV (%)	Adjusted Mean[b]	Pair[c]	Pairwise comparison[c] Ratio (%)[b]	90% Confidence Interval[b]
AUC(0-∞)	⇨	A	33	672.0	29.9	615.5	Reference		
(ng•hr/mL)		B	17	707.2	29.8	674.9	B/A	109.65	(97.04, 123.89)
		C	16	391.4	27.6	386.3	C/B	57.24	(50.27, 65.18)
Fasted ➡		D	17	655.4	34.4	630.4	D/A	102.42	(90.92, 115.37)
Fed ➡		E	16	390.8	38.7	393.6	E/D	60.37	(53.02, 68.74)
		F	12	581.3	32.5	657.1	F/B	97.36	(83.29, 113.81)
		G	11	600.6	38.9	583.4	G/A	91.53	(79.47, 105.42)
		H	11	571.2	29.9	560.6	H/A	91.08	(79.08, 104.92)
C_{max}		A	35	100.05	47.76	89.13	-	-	-
(ng/mL)		B	17	98.99	23.48	97.46	B/A	109.35	(92.44, 129.35)
		C	17	36.56	32.29	35.45	C/B	36.37	(30.38, 43.52)
	➡	D	17	96.59	39.27	89.11	D/A	99.97	(84.57, 118.18)
	➡	E	17	38.11	31.29	36.51	E/D	40.97	(34.24, 49.03)
		F	12	103.12	56.72	98.29	F/B	98.79	(79.34, 122.94)
		G	11	82.64	39.76	75.68	G/A	85.11	(69.93, 103.58)
		H	11	85.36	37.42	80.01	H/A	89.77	(73.91, 109.18)

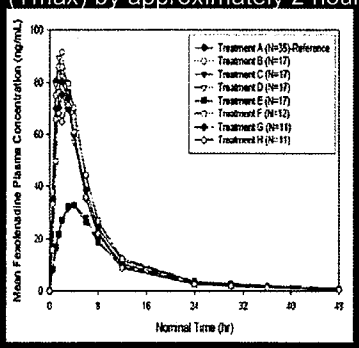
[a] Treatment A: 30 mg marketed lactose-free small tablet (fasted conditions), lot number 1045761
Treatment B: 30 mg prototype fast-disintegrating formulation I (fasted conditions); lot number C0067D
Treatment C: 30 mg prototype fast-disintegrating formulation I (fed conditions), lot number C0067D
Treatment D: 30 mg prototype fast-disintegrating formulation II (fasted conditions); lot number RA0206
Treatment E: 30 mg prototype fast-disintegrating formulation II (fed conditions); lot number RA0206
Treatment F: 30 mg prototype fast-disintegrating formulation I (fasted conditions with no water), lot number C0067D
Treatment G: 30 mg prototype fast-disintegrating formulation IV (fasted conditions); lot number C0070D
Treatment H: 30 mg prototype fast-disintegrating formulation V (fasted conditions); lot number C0071D

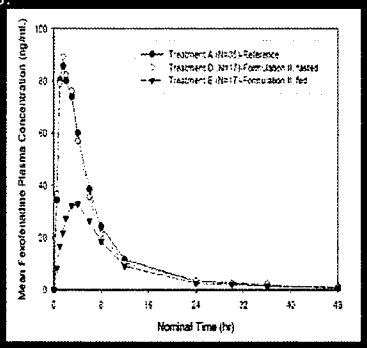
[b] Natural-log transformed results for the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

[c] Relative bioavailability is assessed by the comparison of Treatment A (reference) to Treatments B, D, G, and H (test). The effect of food is assessed by comparison of Treatments B and D (references) to Treatments C and E (tests), respectively. The effect of the coadministration of water is assessed by comparison of Treatment B (reference) to Treatment F (test).

Conclusions from Study #1004

- Formulation II goes forward for further development
- Food reduce exposure by approximately 50% and delays Cmax (Tmax) by approximately 2 hours.





Pivotal BE Study (#1007)

Crossover in 54 healthy subjects:

Treatment A: 30 mg reference (Allegra) (fasting)

Treatment B: 30 mg ODT prototype II (fasting)

Note: A and B were given in fasted condition with 240 ml water.

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Results of Pivotal BE Study (#1007)

Parameter (unit)	Treatment [a]	Arithmetic Mean (CV%) [b]	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	637 (29.2)	612	98.9	92.3 - 106
	B	635 (31.2)	606		
Cmax (ng/mL)	A	93.8 (33.3)	88.9	93.2	85.3 - 102
	B	88.0 (35.5)	82.9		
AUC(0-last) (ng·h/mL)	A	607 (30.7)	582	99.4	92.3 - 107
	B	608 (32.9)	579		
Tmax [f] (h)	A	2.0 (1.0-4.0)	-	-	-
	B	2.0 (0.5-6.0)	-		
t1/2 (h)	A	11.6 (27.8)	-	-	-
	B	11.8 (31.8)	-		
CLpo (L/h)	A	47.4 (27.4)	-	-	-
	B	48.3 (32.2)	-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.

[a] Treatment A: single dose of 30 mg fexofenadine HCl as marketed tablet (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet (test).

[b] Arithmetric mean calculated from all subjects with evaluable data; N = 52 for all Treatment B parameters and AUC(0-last), Cmax, and Tmax for Treatment A; N = 51 for Treatment A AUC(0-∞) t1/2, and CLpo.

[c] Geometric mean calculated from balanced pair data; N = 52 for AUC(0-last) and Cmax; N = 51 for AUC(0-∞).

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

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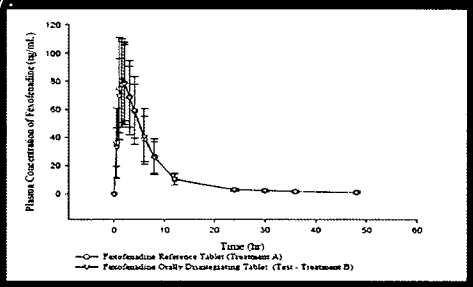
Comments on Pivotal Study (#1007)

- ODT is bioequivalent to the reference when given with water under fasting condition.
- ODT should have been administered without water in this study.



Effect of Water (Study #1008)

Crossover in 54 healthy subjects:

Treatment A: ODT 30 mg (fasting with 240 ml water) (reference)

Treatment B: ODT 30 mg (fasting without water) (Test)

Results Summary of Effect of Water (Study # 1008)

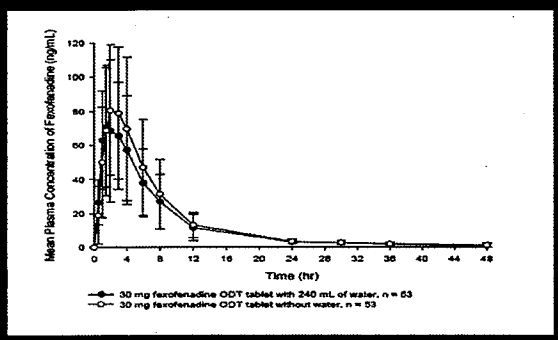
Results - Pharmacokinetics and pharmacodynamics

Parameter (unit)	Treatment [a]	N	Arithmetic Mean (CV%) [b]	N	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng-h/mL)	A	52	628 (34.3)	51	601	112	102 - 122
	B	53	699 (40.5)	51	671		
Cmax (ng/mL)	A	53	86.3 (50.9)	52	78.5	113	100 - 127
	B	53	96.5 (46.7)	52	88.5		
AUC(0-last) (ng-h/mL)	A	53	589 (38.4)	52	552	113	103 - 125
	B	53	668 (42.7)	52	625		
Tmax [f] (h)	A	53	2.0 (1.0-8.0)		-	-	-
	B	53	2.0 (1.0-8.0)		-		
t1/2 (h)	A	52	12.8 (52.9)		-	-	-
	B	53	12.0 (54.6)		-		
CLpo (L/h)	A	52	49.5 (31.8)		-	-	-
	B	53	46.8 (42.8)		-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.
[a] Treatment A: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet with 240 mL water (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet without water (test).
[b] Arithmetic mean calculated from all subjects with evaluable data.
[c] Geometric mean calculated from balanced pair data.
[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.
[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).
[f] Tmax reported as median (range) values.

Comments On Effect of Water (Study # 1008)

- Cmax was slightly outside 80-125%
- Wide variability in the data



General Comments

- The sponsor conducted adequate studies to characterize the PK of Allegra ODT product.
- It is noted that in the pivotal BE study ODT was administered with 240 ml water. The study should have been conducted without water. Alternatively, the sponsor should have conducted the study as three arms with and without water.
- Water appears to have some effect on the Cmax, but not on AUC. The Cmax was slightly outside the 80-125% (100-127%).
- Considering the variability in the data with both products, ODT is considered bioequivalent to the reference.

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Recommendation

Fileable

(from OCP Perspective)

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/s/

Sayed Al-Habet
11/21/2006 02:40:33 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
11/21/2006 02:46:42 PM
BIOPHARMACEUTICS
I concur.

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/s/

Lori Garcia
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MEMORANDUM OF E-MAIL COMMUNICATION

DATE: November 9, 2006
November 10, 2006

APPLICATION NUMBER: NDA 21-909

BETWEEN:

Name:	Lori Birkenberger
e-mail address:	Lori.Birkenberger@sanofi-aventis.com
Representing:	sanofi aventis

AND

Name:	Lori Garcia, R.Ph., Regulatory Project Manager Division of Pulmonary and Allergy Products

SUBJECT: Lack of submission of SPL-formatted PLR labeling with this NDA. See e-mail (attached).

Lori Garcia, R.Ph.
Regulatory Project Manager

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E-MAIL ATTACHMENT

From: Lori.Birkenberger@sanofi-aventis.com [mailto:Lori.Birkenberger@sanofi-aventis.com]
Sent: Friday, November 10, 2006 8:52 AM
To: Garcia, Lori
Subject: RE: NDA 21-909

Hello Lori,

Thank you for the note and time to reply with the required SPL PLR labeling. I am confident we will be able to provide the SPL formatted document as required by regulation ensuring the file-ability of NDA21-909.

If I have any questions – I'll be sure to contact you.

lori

-----Original Message-----
From: Garcia, Lori [mailto:lori.garcia@fda.hhs.gov]
Sent: Thursday, November 09, 2006 3:43 PM
To: Birkenberger, Lori PH/US
Subject: NDA 21-909

Hi Lori,

We are currently conducting the filing review for this application and we have noted that PLR-compliant labeling formatted in SPL has not been submitted, although your cover letter states that it has been provided. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. During the initial implementation phase of the PLR (until the end of 2006), FDA advises applicants to make a good faith effort to provide PLR-compliant SPL with their marketing applications or efficacy supplements. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance. Also, please submit evidence of your good faith effort to provide PLR-compliant SPL by the filing date, November 28, 2006. Failure to submit PLR-compliant SPL by the filing date may result in a refuse-to-file action.

I have followed up with the electronic document room staff to determine if there was an error on our end and the information was not uploaded into the electronic document room, and I have been informed that the CD submitted did not contain SPL.

Please look into this and respond back to me at your earliest convenience.

Thanks,

LCDR Lori Garcia, R.Ph.
Regulatory Project Manager
FDA/CDER/OND/DPAP
Bldg. 22, Rm. 3343
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Phone: (301) 796-1212
lori.garcia@fda.hhs.gov

Important: The Information in this e-mail belongs to Sanofi-Synthelabo Inc., is intended for the use of the individual or entity to which it is addressed, and may contain information that is privileged, confidential, or exempt from disclosure under applicable law. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or use of, or reliance on, the contents of this e-mail is prohibited. If you have received this e-mail in error, please notify us immediately by replying back to the sending e-mail address, and delete this e-mail message from your computer.

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/s/

Lori Garcia
11/13/2006 11:00:41 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-909

NDA ACKNOWLEDGMENT

sanofi-aventis
200 Crossing Blvd, PO Box 6890
Bridgewater, NJ 08807-0890

Attention: Lori Birkenberger, Ph.D.
Associate Director, Regulatory Development

Dear Dr. Birkenberger:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Allegra (fexofenadine hydrochloride) Orally Disintegrating Tablets, 30mg
Review Priority Classification:	Standard (S)
Date of Application:	September 28, 2006
Date of Receipt:	September 29, 2006
Our Reference Number:	NDA 21-909

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 28, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 29, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call LCDR Lori Garcia, Regulatory Project Manager, at (301) 796-1212.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
10/13/2006 06:34:56 PM
signed for Sandy Barnes

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sanofi aventis

Because health matters

September 28, 2006

Federal Drug Agency
120 North Center Drive
Building C
North Brunswick, NJ 08902

NEW DRUG APPLICATION
NDA 21-909
ALLEGRA® (fexofenadine hydrochloride) Orally Disintegrating Tablet

Dear Ms. Rolli,

ALLEGRA® NDA 21-909 will be submitted as an electronic e-NDA/CTD hybrid submission. In accordance with 21CFR 314.71(b), sanofi-aventis U.S. LLC, certifies that this a true and complete copy of the cover letter to the (September 28, 2006) ALLEGRA Orally Disintegrating Tablet (NDA 21-909), FDA 356h along with the corresponding CMC sections. Most of the CMC information provided in this application is provided by cross-reference to approved ALLEGRA Applications. Sections 4.A and 4.B of the CMC section explain this cross-referencing strategy.

Sincerely,

Lori Birkenberger Ph.D.
Associate Director Regulatory Development

cc: Minneapolis Regional Staff (MIN-DO)
212 3rd Ave. South, Minneapolis, MN 55401

Enclosures
FDA 356h
Cover Letter NDA 21-909
Section 4

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200 Crossing Boulevard, PO Box 6890, Bridgewater, NJ 08807-0890
Tel: (908) 304-7000 - www.sanofi-aventis.com

sanofi aventis

Because health matters

September 28, 2006

Federal Drug Agency
Minneapolis Regional Staff (MIN-DO)
212 3rd Ave. South
Minneapolis, MN 55401

NEW DRUG APPLICATION
NDA 21-909
ALLEGRA® (fexofenadine hydrochloride) Orally Disintegrating Tablet, 30mg

To whom it may concern,

ALLEGRA® NDA 21-909 will be submitted as an electronic e-NDA/CTD hybrid submission. In accordance with 21CFR 314.71(b), sanofi-aventis U.S. LLC,, certifies that this a true and complete copy of the cover letter to the (September 28, 2006) ALLEGRA Orally Disintegrating Tablet (NDA 21-909), FDA 356h along with the corresponding CMC sections. Most of the CMC information provided in this application is provided by cross-reference to approved ALLEGRA Applications. Sections 4.A and 4.B of the CMC section explain this cross-referencing strategy.

Sincerely,

Lori Birkenberger

Lori Birkenberger Ph.D.
Associate Director Regulatory Developement

cc: Field Office (NWJ-DO),
120 North Center Drive, Building C, North Brunswick, NJ 08902

Enclosures
FDA 356h
Cover Letter NDA 21-909
Section 4

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200 Crossing Boulevard, PO Box 6890, Bridgewater, NJ 08807-0890
Tel: (908) 304-7000 - www.sanofi-aventis.com

DUPLICATE

N-000

sanofi aventis

Because health matters

September 28, 2006

Badrul Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Drug Products (HFD-570)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705

RECEIVED
SEP 29 2006
CDER CDR

NEW DRUG APPLICATION
NDA 21-909
ALLEGRA® Orally Disintegrating Tablet, 30 mg
(fexofenadine hydrochloride)

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OCT 02 2006
CDER White Oak CR 1

Dear Dr. Chowdhury,

In accordance with 21 CFR §314.50, sanofi-aventis US LLC hereby submits a New Drug Application for ALLEGRA® Orally Disintegrating Tablet, 30 mg a twice-daily treatment of seasonal allergic rhinitis (SAR) and uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in children 6 to 11 years of age.

Fexofenadine hydrochloride, the active ingredient of ALLEGRA®, is a non-sedating antihistamine with selective H_1-receptor antagonist activity. ALLEGRA 60 mg capsules and tablets administered twice daily (BID) have previously been approved for the relief of symptoms associated with SAR and the treatment of uncomplicated skin manifestations of CIU in adults and children 12 years of age and older. ALLEGRA 30 mg BID is currently approved for the treatment of SAR and CIU in children 6 to 11 years of age.

In addition, reference is made to IND 62,912 (Fexofenadine Hydrochloride) Orally Disintegrating Tablet. References are made to the most recent correspondences with the Agency regarding this filing. Reference is made to the Pre-NDA meeting briefing package (submitted February 3, 2005) and Agency responses received via fax communication on March 7, 2005. Reference is also made to former Aventis' request to gain further Agency comment on two reformatted pre-NDA briefing package questions submitted on March 18, 2005 followed by Agency response on April 12, 2005.

Reference is made to the January 27, 2006 submission transferring corporate ownership of IND 62,912 from Aventis Pharmaceuticals Inc. to sanofi-aventis U.S. Inc. FDA acknowledgement of this transfer was received June 20, 2006. Within this NDA dossier, references to Aventis Pharmaceuticals Inc. should be recognized to be the same as sanofi-aventis U.S. LLC.

Structure and Format of this Submission

This application is submitted as a New Drug Application (NDA 21-909) for ALLEGRA (fexofenadine HCl) 30 mg Orally Disintegrating Tablet to obtain approval for its use for the treatment of symptoms associated with SAR and CIU in children 6 to 11 years of age. This NDA is submitted as an Electronic Submission in accordance with the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). Data are provided in SAS transport format (.xpt).

All applicable Items are submitted here within as an electronic archival copy (e-NDA) in accordance with current Guidances for Industry[1],[2], as well as recent Draft Guidance[3]. Paper copies of this cover memo and Form 356h, as well as the certifications included in Items 13, 16, 17, 18 and 19 that contain original signatures, are included here per guidance.

Details on the format of each item and the medium for this electronic submission are appended to this correspondence. A brief description of each item in this application is provided here.

Labeling

The proposed labeling text for ALLEGRA (fexofenadine HCl) Orally Disintegrating Tablet, 30 mg is provided in PDF format (.pdf) within Item 2. The annotated proposed labeling is located within Item 3.A. The draft labeling text is provided in Word format (.doc) as a review aid for editing purposes during review. The Structured Product Labeling (SPL), format in XML, is also provided, as outlined in the new Physician Labeling Rule. Coding for medical terms in the "Highlights" section for which we were unable to find corresponding SNOMED terms are listed in the labeling history (history.pdf) file.

ALLEGRA (fexofenadine HCl) ODT, 30 mg is indicated for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in children 6 to 11 years of age. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat and itchy/watery/red eyes associated with SAR and in CIU subjects it significantly reduces pruritus and the number of wheals.

CMC

ALLEGRA (fexofenadine HCl) is a marketed product in the US (NDA 20-625 and NDA 20-872), and all Chemistry, Manufacturing and Controls (CMC) information on the drug substance (fexofenadine HCl) exists in approved ALLEGRA applications. CMC information related to the drug substance is provided in this application by cross-reference to the approved ALLEGRA Application, NDA 20-625, submitted July 31, 1995, approved July 25, 1996.

This submission provides CMC information on a new orally disintegrating tablet formulation that is bioequivalent to the currently marketed tablet product. This new formulation provides a convenient alternative dosage form to the currently approved pediatric product/dosage strength. The tablets are pleasant tasting and disintegrate within a few seconds in the oral cavity. The orally disintegrating tablet is shown to be physically and chemically stable with acceptable organoleptic properties.

The CMC section is organized in Common Technical Document (CTD) format in line with ICH M4: The CTD -- Quality.

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[1] Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations, January 1999

[2] Guidance for Industry: Providing Regulatory Submission in Electronic Format – NDAs, January 1999

[3] Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions, August 2003

Establishment description is included in Item 20.
A Field Copy Certification has been included in Item 17.

Nonclinical Pharmacology, Toxicology and Metabolism
Reference is made to NDA 20-625 and NDA 20-872 for previously submitted and reviewed information pertaining to nonclinical pharmacology, toxicology and metabolism. No new nonclinical pharmacology, toxicology or metabolism studies were performed for this NDA. Information from previously submitted studies and relevant to the determination of the relationship between nonclinical and human exposure at therapeutic doses of fexofenadine HCl are summarized in Item 5. These data support the safety margin data referenced in the proposed ALLEGRA package insert.

Human Pharmacokinetics and Bioavailability
The pharmacokinetic profile of fexofenadine has been described previously in NDA 20-625 and NDA 20-872. Three new Clinical Pharmacology studies are presented in this submission. The pivotal studies for this application are a single-dose fasting bioequivalence study in which study medication has been administrated with water (study M016455H/1007), a single-dose bioavailability study with and without water (study M016455H/1008), and a single-dose food effect study (study M016455H/1004). Relevant studies, including special population and drug-drug interaction information, from previous NDAs applicable to fexofenadine HCl are summarized in Item 6 of this NDA. Full reports for these studies with details on pharmacokinetics and bioavailability are not included in this NDA as they have been previously submitted in NDAs 20-625 and 20-872. Synopses of these study reports are included in this submission.

Clinical Data Section
Background information and summaries of the studies relevant for the assessment of the efficacy and safety of fexofenadine HCl are provided in Item 8, Sections 8.A to 8.F.

The Integrated Summary of Efficacy (ISE) focuses on the results from the combined pivotal study PJPR0066/77, which evaluated the efficacy of fexofenadine HCl 15, 30 and 60 mg BID in comparison to placebo over an observation period of 2 weeks in pediatric subjects 6 to 11 years of age with SAR. This study has previously been submitted in NDA 20-872; the studies have not been re-analyzed for this NDA. However, excerpts of the relevant sections of the original NDA 20-872 have been electronically linked from this document for reference. Since study PJPR0066/77 did not conclusively demonstrate the efficacy of fexofenadine HCl in pediatric subjects, efficacy in this population was deducted from the proven efficacy of fexofenadine HCl 60 mg BID in subjects 12 years of age and older with SAR and CIU. Results of the relevant efficacy studies for SAR (PJPR0009, PJPR0010, PJPR0023 and PJPR0024) and CIU (PJPR0039 and PJPR0067) are briefly summarized in the ISE for reference and in support of the efficacy. In addition, the results of a supportive study administering fexofenadine HCl 30 mg in pediatric subjects 6 to 11 years of age (study M016455C/3212) is briefly summarized. Synopses of the study reports of all referenced studies are provided in this NDA

The safety data for the pivotal clinical pharmacology studies have been integrated for adverse events, including serious adverse events and adverse events leading to discontinuation, clinical laboratory evaluations, electrocardiogram (ECG) data, and vital signs. Following recommendations from the Agency, and because no label changes other than to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections are being sought, safety information for the pivotal efficacy and safety study PJPR0066/77 and the supportive efficacy and safety study M016455C/3212 are not integrated for this ISS. For pivotal efficacy and safety study PJPR0066/77, excerpts from the original

NDA 20-872 have been electronically linked from this document for convenient reference. The safety conclusions for supportive efficacy and safety study M016455C/3212 are summarized briefly for completeness. For the other studies included in this ISS, safety conclusions are also summarized and, if the study had been submitted previously in an NDA, the locations of the safety results of these studies in the previous NDAs are provided for reference. Synopses of the study reports of all referenced studies are provided in this NDA; complete reports are available upon request.

Studies PJPR0009, PJPR0010, PJPR0023, and PJPR0024 in adult subjects with SAR, and studies PJPR0039 and PJPR0067 in adult subjects with CIU have been included in this NDA as supportive studies for the efficacy of fexofenadine HCl 60 mg for the SAR and CIU indications, respectively. The studies also support the safety of fexofenadine HCl. However, these studies are not discussed in this ISS, as the safety data from those studies have been analyzed in detail in the respective approved NDAs.

Supporting tables with the results of the analyses of the integrated safety data from the pivotal clinical pharmacology studies M016455H/1004, M016455H/1007, and M016455H/1008 are provided in *clinstat\iss\isstables.pdf.*

Adverse events from sources other than clinical studies are discussed in Item 8, Section 8.H.6.

Reports from literature are included in Item 8, Section 8.F.4. The referenced publications can be accessed from this section or the publication folder.

Case Report Tabulations and Case Report Forms

In accordance with 21 CFR §314.50(f), this application contains case report tabulations (datasets and data definition information) in Item 11 and case report forms from the pivotal Clinical Pharmacology studies (for subjects that discontinued as a consequence of an adverse event and experienced serious adverse events) in Item 12. Annotated case report forms are also provided in support of the PK datasets for the pivotal Clinical Pharmacology studies.

Pediatric Assessment and Request for Deferral

This NDA summarizes data in support of the efficacy and safety of fexofenadine HCl 30 mg BID for the relief of symptoms of SAR and CIU in children 6 to 11 years of age. The 30 mg BID is the approved dose of fexofenadine HCl for the treatment of SAR and CIU in children 6 to 11 years. The approved package insert states that the safety and effectiveness of fexofenadine HCl in pediatric patients under 6 months of age have not been established.

In line with Section 505B of the Pediatric Research Equity Act, sanofi-aventis is requesting a deferral for the submission of data for pediatric patients younger than 6 years for ALLEGRA orally disintegrating tablets, as part of Item 20. Sanofi-aventis has developed an appropriate formulation, ALLEGRA Oral Suspension 30mg/ mL (fexofenadine HCl) for pediatric patients 6 months to 11 years, thus, including the age group of younger than 6 years. The approval of NDA 21-963 is pending.

Sanofi-aventis US certifies that all electronic media are free from computer virus. The virus scan was performed using Symantec's Norton Antivirus Corporate Edition, Program version 8.1.1.336, Scan Engine Version 4.2.0.7, with the virus Definition File Version issued 09/20/06, rev.52.

A list of reviewers from the Division Pulmonary and Allergy Drug Products (HFD-570) who should be provided access to this electronic submission on their desktops may be obtained from Ms. Lori Garcia, Regulatory Project Manager, Division of Pulmonary and Allergy Drug Products (HFD-570).

Sanofi-aventis US LLC considers the information included in this submission to be confidential and proprietary, and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Sanofi-aventis US according to 21 CFR §312.130 and 21 CFR §314.430.

On behalf of Sanofi-aventis US we look forward to continuing to work with the Division to facilitate the review of this application. If you have any questions or need additional information during the review, please contact the undersigned Lori Birkenberger, Ph.D., at (908) 231-3126.

Sincerely,

Lori Birkenberger

Lori Birkenberger Ph.D.
lori.birkenberger@sanofi-aventis.com
Associate Director
Regulatory Development

Enclosures:
Electronic archival copy: 1 CD-ROM labeled
1 paper copy of Cover Letter, Form FDA356h and certifications in Items 13, 16, 17, 18 and 19 with original signatures.

cc: Ms. Lori Garcia, Regulatory Project Manager (Cover letter and Form FDA 356h only)

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NDA 21-909 Electronic Submission Information

Description Format (Electronic/Paper)

The following identifies the primary sections included in this submission. Each section has been identified with an "X" if presented in paper or electronically.
(n/a = Not Applicable)

Item	Description	Electronic	Paper
	Cover memo	X	X
	Form 356h	X	X
1	Index	X	
2	Labeling	X	
3	Application Summary	X	
4	Chemistry	X	
5	Nonclinical Pharmacology and Toxicology	X	
6	Human Pharmacokinetics and Bioavailability	X	
7	Clinical Microbiology	n/a	
8	Clinical Data Section	X	
9	Safety Update Report	n/a	
10	Statistical Section*	X	
11	Case Report Tabulations	X	
12	Case Report Forms	X	
13	Patent Information	X	X
14	Patent Certification	n/a	
15	Establishment Description	n/a	
16	Debarment Certification	X	X
17	Field Copy Certification	X	X
18	User Fee Cover Sheet	X	X
19	Financial Information	X	X
20	Pediatric Assessment &Request for Deferral; Establishment Description	X	

*This information is identical to Item 8.

Electronic Submission Summary

Media Type:	CD-Rom
Number of Media	1 CD-Rom
File Formats:	Portable Document Format (.pdf)
	SAS Transport (.xpt)
	Microsoft Word (.doc) (proposed labeling only)
Total Size:	Electronic Submission - Approximately 250 MB

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-909

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
sanofi-aventis US, LLC.	9/28/06
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
908-231-3126	908-541-5274
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
300 Somerset Corporate Boulevard Bridgewater, NJ 08807	sanofi-aventis U.S. 200 Crossing Boulevard Bridgewater, NJ 08807

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PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-909

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Fexofenadine Hydrochloride	ALLEGRA

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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
(±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride	MDL 16,455

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION
Oral Disintegrating Tablets	30 mg	oral

(PROPOSED) INDICATION(S) FOR USE:
asonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU)

PLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Establishment Information - see Item 20

ss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 43,573 fexofenadine HCl	DMF
IND 62,912 fexofenadine HCl, orally disintegrating tablet	DMF
IND 51,709 fexofenadine HCl pediatric formulation	DMF
NDA 20-625 ALLEGRA® (fexofenadine HCl) capsules	DMF
NDA 20-872 ALLEGRA® (fexofenadine HCl) tablets	DMF
	DMF

b(4

This application contains the following items: *(Check all that apply)*

☐	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Pediatric Assessment and Deferral & Establishment Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Lori Birkenberger	Lori Birkenberger, Ph.D. Associate Director Reg. Dev.	9/28/06
ADDRESS *(Street, City, State, and ZIP Code)* 00 Crossings Blvd, Bridgewater, NJ 08807	Telephone Number (908) 231-3126	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Submission Detail

20-Jul-2007 12:07:58PM

Application: N-021909
Division: 570
CSO: GARCIA,LO
Drug Class:
Potential: S
Chemical Type: 3
R/C:

Drug Name: ALLEGRA (FEXOFENADINE HCL)
Generic Name: FEXOFENADINE HCL
Sponsor: SANOFI AVENTIS US
Status: PN **Status Date:** 29-Sep-2006
Indication: SEASONAL ALLERGIC RHINITIS (SAR) AND CHRONIC IDIOPATHIC URTICARIA

Document Type	SEQ	MOD	Letter Date	Stamp Date	Decision Code	Decision Date	Status Code	Status Date
N	000		28-Sep-2006	29-Sep-2006	DP	29-Sep-2006	PN	29-Sep-2006
N	000	FG	28-Sep-2006	29-Sep-2006	FI	12-Dec-2006		
N	000	BL	10-Nov-2006	13-Nov-2006	DP	13-Nov-2006		
N	000	BC	18-Jan-2007	19-Jan-2007	DP	19-Jan-2007		
N	000	SU	25-Jan-2007	26-Jan-2007	DP	26-Jan-2007		
N	000	BC	08-Feb-2007	09-Feb-2007	DP	09-Feb-2007		
N	000	US	25-Apr-2007	25-Apr-2007	DR	25-Apr-2007		
N	000	BC	07-May-2007	08-May-2007	DP	08-May-2007		
N	000	BL	21-Jun-2007	22-Jun-2007	DP	22-Jun-2007		
N	000	BL	29-Jun-2007	02-Jul-2007	DP	02-Jul-2007		

Jan 11
April 4

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NDA 21-209 GRMP worksheet

PDUFA date 7/29/2007

Timeline	Activity		Comments/Dates
Day 0	**Application Receipt**		9/29/06
Days 0 – 14	**Assign RPM - CPMS**		
	Begin Regulatory Filing Review- RPM		
By Day 14	Acknowledge application receipt in writing		10/13/06
	Assign Review Team- Team Leaders		
	Schedule Filing Meeting- RPM		(by 11/13/06 = 45 days)
Days 0 – 45	**Request Consults**		
	Identify Inspection Actions		
	Submit EER and request inspections (for NDA)		
	Request investigation of clinical, nonclinical, and biopharmaceutics research sites		
	Designate Priority or Standard Review Status		S
	Conduct Filing Review- decide if AC necessary		
	Convey Potential RTF Issues to Applicant		
	Identify Signatory Authority		Batch chemistry
By Day 45	**Hold Filing/Planning Meeting** ~ 11/13/06		scheduled for 11/17/06
By Day 60	**Inform Applicant of a Priority Designation in Writing**		11/28/06
	Communicate Filing Determination to Applicant, if RTF (for DPADP, via letter)		
By Day 74	**Communicate Filing Review Issues to Applicant**		12/12/06
> Day 74	**Continue Review**		
	Team meetings		
	Issue IR Letter or faxes, as needed		
By End of Month 5	**Mid-Cycle Meeting**		2/28/07-mtg
	Update on reviews, consults, and inspections, consider need for center level input (Regulatory Briefing)		
	Define need for additional interaction with applicant related to labeling, risk management, PMCs		
	Revise review plan, if needed ***ie, internal consults***		
By End of Month 8	***Complete Primary Review***		5/29/07-mtg
Variable	**Issue DR Letters, as appropriate**		
	Wrap-Up Meeting		
	Integrate outcomes of reviews, consults, inspection reports, and AC input		
6 Weeks Before Action	***Complete Secondary reviewer memo***		6/17/07
	Labeling Discussions (for AP and AE)		
	6-5 weeks before action fax proposed labeling		
4 weeks before Action	**Labeling telecon with applicant, Negotiation of PMC, Risk Mgmt**		7/1/07
	Action Package readiness		
	Draft Action Letter with Conditions of Approval		
	Draft Action Letter with Comprehensive List of Deficiencies (for Actions Other than Approval)		
	Pre-AP Safety Conference (for NMEs in CDER)		
	Circulate and Review Action Package and Letter		
	Division level sign off	***Office level sign off***	
4 weeks before action		***DD memo complete***	
3 Weeks Before actn	Package to DD	Package to OD	7/8/07
By PDUFA GD	**Action**		7/29/07

Birkenberger, Lori PH/US

From: Foldes, Csilla PH/US
Sent: Monday, September 11, 2006 3:35 PM
To: Birkenberger, Lori PH/US; Gural, Richard Sanofi; Cumiskey, Wayne Sanofi
Cc: Parker, James A (USRA) PH/US
Subject: Allegra ODT Wire Transfer - Completed

The Allegra application user fee payment of US $ 383,700.00 has been wired to the FDA for NDA 21-909.
Below is a "visual capture" copy available from the wire transfer system - in case you want to retain with your FDA files. Please note the new format of the wire transfer due to new system capture reporting.

Please share this information with others within CRA as needed.

Best regards,
Csilla

Csilla Földes, M.S.
Director, Regulatory Submissions
US RAMP - Medical Affairs
sanofi-aventis U.S. Inc.
300 Somerset Corporate Blvd.
Bridgewater, NJ 08807-0977
Mail Stop: SC3-615A
ph: 908-243-7438
fx: 908-243-6017
cell: 908-510-4755
mail: csilla.foldes@sanofi-aventis.com

-383,700.00 WIO 8/31/2006
FOOD & DRUG ADMINISTRATION
9116309
FurRef:SAME DAY DR TRANSFER Dtl:NDA*21_909**USER*FEE*ID*PD3006705
BenAcct:9116309 Ben:FOOD & DRUG ADMINISTRATION
BenBk:043000261 MELLON BANK NA ATTN DUE FROM BANKS MGMT UNIT 3
MELLON BANK CTR _ROOM 2523 PITTSBURGH, PA. 15259_0003
ConfRef:20060831B1Q8023C006777 ByOrderOf:40552555 AVENTIS
PHARMACEUTICALS

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3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

AVENTIS PHARMACEUTICALS INC
Lori Birkenberger
300 Somerset Corperate Blvd
Bridgewater NJ 08807
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-909

2. TELEPHONE NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
ALLEGRA (fexofenadine HCl)

6. USER FEE I.D. NUMBER
PD3006705

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$383,700.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

ACTION PACKAGE CHECKLIST

Application Information		
~~BLA #~~ NDA # 21-909	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Allegra ODT Established Name: fexofenadine HCl Dosage Form: orally disintegrating tablet		Applicant: sanofi-aventis
RPM: Lori Garcia	Division: 570	Phone # 301-796-1212

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	July 29, 2007
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

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❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	DD memo: 7/26/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	July 25, 2007
• Original applicant-proposed labeling	November 10, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	N/A
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	N/A
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	November 10, 2006
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 3/21/07 ☐ DSRCS ☒ DDMAC 3/8/07 ☒ SEALD 7/16/07 ☒ Other reviews 12/13/06 ☒ Memos of Mtgs 7/25/07

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	1/3/07 RPM filing review
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Ackn. Letter: 10/13/06 Email: 11/13/06 74-day letter: 12/12/06 Fax: 6/14/07 Fax: 7/18/07
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 3/17/05
• EOP2 meeting *(indicate date)*	☐ No mtg 3/24/03
• Other (e.g., EOP2a, CMC pilot programs)	2/16/07
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	11/17/06; 4/17/07; 6/7/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☒ Review & FONSI *(indicate date of review)*	4/27/07 & 4/29/07
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 11/2/06 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11/22/06; 5/21/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	11/17/06; 5/29/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	MO review 5/29/07
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
Safety Update review(s) *(indicate location/date if incorporated into another review)*	MO review 5/29/07
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	n/a
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	5/15/07
❖ Statistical Review(s) *(indicate date for each review)*	☒ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/21/06 & 5/21/07

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Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 12, 2005

To: Lori Birkenberger, Ph.D. Regulatory Liaison, USRA	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6318	**Fax number:** 301-827-1271
Phone number: 908-231-3126	**Phone number:** 301-827-1051

Subject: IND 62,912 Fexofenadine ODT post preNDA meeting communication
Responses to submission dated March 18, 2005

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ **YES** √ **NO**

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-1050. Thank you.

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We refer to IND 62,912 for fexofenadine orally disintegrating tablets, and to your submission dated March 18, 2005, which contained your revised Table of Contents for the clinical and CMC data section of the proposed NDA for fexofenadine HCl orally disintegrating tablets, 30 mg. We have the following comments and recommendations:

1. Summaries or synopses for studies PJPR0066, PJPR0077, PJPR0031, and PJPR0027 without the full study reports would be adequate for this NDA submission.
2. A full report for study M016455C/3212 would be necessary only if labeling changes to sections of the label other than INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION are being sought, otherwise, a study summary or synopsis would be adequate for this NDA submission. A full user fee may be required if a full report for study M016455C/3212 must be reviewed.
3. The ISE that you have proposed would be necessary only if you are seeking changes to sections of the label other than INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.
4. If you are not planning to seek changes to sections of the label other than INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION, the only information that is required for the Integrated Summary of Safety (ISS) for this application would be:
   - Safety information from the three pivotal clinical pharmacology studies, M016455H/1004, M016455H/1007, and M016455H/1008.

Additionally, your revised format for the CMC section of the NDA is acceptable as proposed in the March 18, 2005, submission.

If you have questions about the contents of this facsimile, please contact Christine Yu at 301-827-1051.

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Memorandum of Telephone Facsimile Correspondence

Date: March 17, 2005

To: Lori Birkenberger, Ph.D.
U.S. Regulatory Affairs

Fax: 908-304-6318

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: IND 62,912 for fexofenadine ODT
Minutes of March 8, 2005

Reference is made to the meeting/teleconference held between representatives of your company and this Division on March 8, 2005. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

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TELECONFERENCE MINUTES

DATE:	March 8, 2005
TIME:	2:30 PM - 3:30 PM
APPLICATION:	IND 62,912
DRUG NAME:	Fexofenadine 30 mg orally disintegrating tablets (ODT)
INDICATION:	Relief of symptoms associated with SAR and CIU in adults and children 6 years of age and older
IMTS#:	14569
SPONSOR:	Aventis Pharmaceuticals, Inc.
Represented by:	Lori Birkenberger, Ph.D., Regulatory Liaison Daniel BollagMadhu, Ph.D., Regulatory Liaison Rosemary Crew, M.S., Regulatory Operations Prafulla Agrawala, Ph.D., Global Project Development Rajiv Haribhakti, M.S., Pharmaceutical Sciences Kazimierz Chrzan, M.S., Analytical Sciences Barbara Kittner, M.D., Clinical Development Jessica Collis, Regulatory CMC Denise Dennie, Pharm.D., Project Director Denise Flanagan, Ph.D., Regulatory CMC Dan Howard, Ph.D., Biopharmaceutics Yongtao (Christine) Li, Ph.D., Biopharmaceutics Marie Parrish, Ph.D., CMC Documentation Srikumar Sahasranaman, Ph.D., Biopharmaceutics Derek Moe, Ph.D., Pharmaceutical Sciences (CIMA Labs, Inc.) Adepeju Odunusi, Ph.D., Analytical Sciences (CIMA Labs, Inc.) Phil Simonson, Ph.D., Regulatory Affairs
FDA attendees:	Division of Pulmonary & Allergy Drug Products, HFD-570 Craig Bertha, Ph.D., CMC Reviewer Rik Lostritto, Ph.D., CMC Team Leader Charles Lee, M.D., Medical Officer Badrul Chowdhury, M.D., Ph.D., Director Christine Yu, R.Ph., Regulatory Project Manager

A pre-NDA meeting with Aventis was scheduled for March 8, 2005, to discuss the NDA submission strategy for the fexofenadine ODT product. The Division's responses to the questions in the briefing package were faxed to Aventis on March 7, 2005 (attached at end of these minutes). Aventis determined that a face-to-face meeting was not necessary, however, requested further teleconference discussion on questions 12, 17, and 18.

Format of the minutes

Aventis' questions, followed by the Division's faxed responses are in Italics font. Teleconference discussions are captured in normal font.

Question 12

ODT Nomenclature: Does the Agency concur with the proposed Orally-Disintegrating Tablet (ODT) nomenclature to be used for this product? (p. 017)

Criteria for ODT are as follows:

- *disintegrate rapidly in the oral cavity.*
- *eliminate the need for use of water or chewing.*
- *recommended tablet weight to be less than 500 mg for compliance reasons, especially for children (if too big, dosage form may be partially spit out).*
- *in vitro disintegration with USP <701> to be less than 30 seconds.*

Application of the ODT dosage form nomenclature to your product is a review issue.

Aventis noted that the recommended weight cutoff is less than 500 mg, but their product is [redacted] b(4) They requested suggestions for approaching this problem so that it does not become a major review issue when the NDA is submitted, since reformulation is not feasible at this time. There would also be taste masking issues to be addressed if reformulation would be required.

The Division responded that the criteria listed above reflect the Agency's current thinking in defining an ODT. This is a multi-disciplinary issue, currently under discussion in the Agency. Decisions would be made on a case-by-case basis for products that have already been submitted or close to being submitted to the Agency for review as an ODT. The Division cannot definitively say at this time that Aventis' product is not an ODT. It is a review issue and would be answered at the end of the NDA review cycle.

Question 17

Control of [redacted] Does the Agency concur with the approach to test for residual solvents on the [redacted] and to include the results with the COA for the finished product? (p. 019) b(4)

The approach is reasonable but the finished product should have acceptance criteria for residual solvents reflective of data. As discussed at the EOP2 meeting, the specification for the product can indicate that this test is done on the [redacted] in-process.

ICH Q3C limits are for safety considerations and are not necessarily limits for quality control.

The Division provided clarification that although the testing for residual solvents would be conducted at the [redacted] stage, the final drug product should include acceptance criteria for residual solvents reflective of the data. The specification can specify that the test was conducted in process on the [redacted] b(4)

Question 18

Holding Time Study: Does the Agency concur with this proposed strategy for hold time and does the Agency confirm that the stability data amendment three months prior to the action date will be considered a "minor amendment?" (p. 020)

- *Hold times for intermediates longer than [redacted] during the drug product manufacturing process are strongly discouraged.*
- *If the [redacted] hold period is longer than [redacted] the expiration dating period of the drug product must be calculated from the beginning of drug product [redacted] production.* b(4)

- *The hold times of the [redacted] used in preparing the stability batches supporting the application should be indicated in the submission. The [redacted] hold periods that have been used will determine the hold period that can be allowed.* b(4)
- *Alternatively, you should submit the limited stability data supporting the [redacted] hold period either at the time of submission of the application or as a post-approval supplement.*

The Division clarified that the stability clock starts at the time the drug substance is added to begin manufacturing. All times after that point must be accounted for, and the resulting data should support the proposed expiry.

Dr. Lostritto gave the following scenario as an example. If there is a [redacted] maximum hold time for the [redacted] (supported with stability data) and an additional [redacted] of stability data for the drug product manufactured with those aged [redacted], then [redacted] could be the acceptable expiry for the final drug product. However, the storage condition of the [redacted] b(4) should be the same or worse (i.e., warmer and/or more humid) than the tablet storage conditions. In this manner, less than the maximum hold time storage of [redacted] could be accounted for in the total shelf life scenario (i.e., [redacted] time plus tablet time = total shelf life which is [redacted] in this example).

Dr. Bertha added that if the primary stability batches with [redacted] stability data had [redacted] hold periods that are significantly shorter than the proposed [redacted] (Aventis confirmed they were between [redacted], [redacted] of supporting stability data on the drug b(4) product with [redacted] hold time for the [redacted] would not support the requested expiry based on the primary stability batch data.

The Division noted that although the Agency would like to see more than [redacted] batch on stability, [redacted] batch may be sufficient in the future depending on the observed stability of the product. b(4) Aventis should propose the number of stability batches and provide appropriate supportive data and justification.

The Division also noted that with the implementation of the Good Review Management Practices (to be issued sometime in the future by the Agency), the application should be complete at the time of NDA submission. Review practices will be changing so that primary reviews will be expected to be complete by the eighth month of the review cycle. This reduces the possibility that data or information submitted late in the review cycle will be reviewed in that cycle.

Aventis indicated that this bulk storage hold time scenario is similar to their marketed drug product Abilify. Dr. Lostritto agreed to investigate this for the sake of clarity and consistency.

Aventis thanked the Division for the clarifications provided. They stated that they will be submitting revised formats in response to the Division's comments to Questions 2 and 10.

The teleconference was adjourned at this time.

POST MEETNG NOTES

The approved stability protocol for Aventis' Abilify drug product provides for a Hold Time for finished tablets, not intermediate granules. Therefore, the cases are directly comparable.

We encourage you to make your PROPOSED granule hold time as short as feasible.

********** *Attachment* **********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2005

To: Lori Birkenberger, Ph.D. Regulatory Liaison, USRA	**From:** Christine Yu, R.Ph. Regulatory Project Manager
Company: Aventis Pharmaceuticals, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 908-304-6318	**Fax number:** 301-827-1271
Phone number: 908-231-3126	**Phone number:** 301-827-1051

Subject: IND 62,912 Fexofenadine ODT pre-NDA meeting
Responses to briefing package questions

Total no. of pages including cover: 6

Comments:

Document to be mailed: ☐ YES √ NO

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We refer to IND 62,912 for fexofenadine orally disintegrating tablets, and to your submission dated February 3, 2005, which contained the briefing package for the pre-NDA meeting currently scheduled for March 8, 2005. We are providing our responses to your questions from the briefing package. Your questions are noted in Italics font, followed by the Division's response in normal font.

Question 1

As discussed at the EOP2 meeting, Aventis regards the following pharmacokinetic studies as sufficient to support the submission and approval of the fexofenadine HCl ODT formulation for ages 6 to 11 years of age:

- *M106455H/1004*
- *M106455H/1007*
- *M106455H/1008*

Does the Agency concur?

The studies are sufficient to support the submission of an application for the new fexofenadine HCl formulation for ages 6 to 11 years of age. Whether the data is sufficient to support the approval of the application is a review issue.

Question 2

The proposed Table of Contents for the NDA is included in the pre-NDA meeting information package. The Table of Contents shows the cross-referencing strategy for NDA sections 5, 6, and 8. Examples of the cross-referencing tables can be found in Table 8 of Section 6, and in Table 12 of Section 8.1.

Does the Agency agree with the proposed Table of Contents and cross-referencing strategy?

Your proposed Table of Contents is not acceptable. Include a clinical data section and a safety update. Include the post-marketing adverse events for fexofenadine, covering the period of time since the approval of Allegra-D 24 Hour Tablets, in the Integrated Summary of Safety (ISS) as part of the clinical data section.

Additionally, include a review of information from the published medical literature relevant to the safety of fexofenadine in the ISS. The review should cover the period of time since the approval of Allegra-D 24 Hour Tablets. The Integrated Summary of Safety should also address the safety of fexofenadine in subgroups, including children and the elderly, by gender, by race, and in patients with renal and hepatic impairment.

We also recommend that you consult the following FDA Guidances for Industry available at (http://www.fda.gov/cder/guidance/index.htm):

- Format and Content of the Clinical and Statistical Sections of an Application (Issued 7/1988, posted 5/21/97)
- Providing Regulatory Submissions in Electronic Format—NDAs (Issued 1/1999, posted 1/27/99)

In addition, reference the format of similar Aventis applications, such as NDA 21-704 for Allegra-D 24 Hour Extended Release Tablets.

Question 3

Aventis proposes to submit a separate original NDA for fexofenadine HCl ODT for the treatment of SAR and CIU in pediatric patients 6 to 11 years of age. The foundation of this submission is based on a "change in composition of an approved product" without new clinical data as defined in the Guidance for Industry Submitting Separate Marketing Applications and Clinical Data for the Purposes of Assessing User Fees.

3a: Based on the above mentioned Guidance for Industry, fexofenadine HCl ODT will be filed as a separate original NDA. Does the Agency concur?

Yes, we concur that a separate original NDA should be submitted. The Agency considers the orally disintegrating tablet a different dosage form than the approved fexofenadine capsules or tablets. Therefore, a separate original NDA should be submitted in accordance with the Guidance referenced above.

3b: Under the fee schedule provided in the Prescription Drug User Fee Act (1992) and subsequent amendments, the fexofenadine HCl ODT NDA qualifies for "approximately one-half the NDA user fee." Does the Agency concur?

Based on the information submitted, a fee of $336,000 (a half-fee) appears to be appropriate if you submit your NDA in FY 2005. When the NDA is submitted, we will review the application to see if clinical data (study reports or literature reports), other than bioavailability or bioequivalence, are required for approval with respect to safety or effectiveness. We will consult with CDER's User Fee Staff and contact you if a full fee is required.

3c: Aventis proposes a stand alone package insert for fexofenadine HCl ODT, separate from the approved Allegra package insert, which covers multiple dose strengths and dosing recommendations. It is Aventis' intention to avoid consumer confusion among Allegra products. Does the Agency concur?

Yes, this is acceptable. The choice of a stand-alone package insert or a combined package insert is your prerogative.

Sections of the Package Insert for other Allegra products will be applicable to your proposed product. Examples of such sections include information on special populations, drug interactions, overdose, among others. The language of all applicable sections of the package inserts for Allegra products should be consistent with each other.

Question 4

In an effort to reduce confusion between Allegra family products and differentiate this pediatric formulation from Allegra Tablets, Aventis wishes to retain the proprietary name Allegra as the primary lead name, but provide a secondary identifier for its pediatric ODT formulation. The tentative proprietary name for Allegra fexofenadine HCl ODT 30 mg is [redacted]

Aventis proposes forgoing an application to the United States Adopted Names (USAN) because fexofenadine HCl is a registered entity (Allegra®), and to instead interact directly with the Division of Pulmonary and Allergy Drug Products for approval of the Allegra ODT's proprietary name. Does the Agency agree with this approach?

The primary lead name, Allegra, is acceptable. However, we have serious concerns about the promotional connotations of the proposed secondary identifier and strongly recommend that you consider an alternative identifier. We advise you that a proprietary name consisting of a lead name and a secondary identifier is considered to be a single entity, for example [redacted] b(4)

When the NDA is submitted, various divisions within the Agency will review the proposed name for your drug product, including the Division of Medication Errors and Technical Support and the Division of Drug Marketing, Advertising, and Communications.

Question 5

This NDA will be submitted as an electronic submission utilizing CTD module presentation for CMC sections and Form 356h format with an eNDA backbone for the remaining sections in accordance with Form 356h NDA format and the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs (January 1999). Does the Agency concur?

Yes, we concur.

Question 6

Study M016455H/1004 provides information about the bioavailability of fexofenadine HCl ODT under fed conditions. Since the formulation evaluated in this study is the final formulation, no additional studies to evaluate the effect of food on the bioavailability of fexofenadine HCl ODT will be conducted. Does the Agency concur?

Yes, we concur.

Question 7

Copies of individual case report forms will be provided for any subject who meets DDOS criteria (death, discontinuations due to adverse events, and other serious adverse events) in the relevant phase 1 studies (M106455H/1004, M106455H/1007, and M106455H/1008). Does the Agency agree with this approach?

Yes, we agree.

Question 8

A data correction form will be provided in the front of each Case Report Form (CRF). There will be a bookmark for the Data Correction Form; however, no hyperlink will be utilized for Data Correction Form items to the corresponding CRF corrected item. Does the Agency concur?

Yes, this is acceptable.

Question 9

Referring to FDA Guidance for Industry: Providing Regulatory Submission in Electronic Format-NDA (January 1999), no patient profiles will be provided. Does the Agency concur?

Yes, we concur.

Question 10

Format and Content of CMC Documentation: Does the Agency find this proposed format and content acceptable for the CMC section? (pp. 016, 043)

Providing only the summary to the NDA and cross-referencing the remaining drug substance information to NDA 20-625 is acceptable.

Additionally, provide a clarification of why there are so many subsections for the compendial excipients. Why not just one section simply stating that compendial methods and monograph specifications are applied? If compendial methods are used, validation data are not necessary for inclusion in the NDA.

Question 11

PAT-Related Information for DS: Does the Agency agree with the proposed strategy for reporting Process Analytical Technology (PAT) related information for the DS via N20-625? (pp. 017)

Yes, we agree.

Question 12

ODT Nomenclature: Does the Agency concur with the proposed Orally-Disintegrating Tablet (ODT) nomenclature to be used for this product? (p. 017)

Criteria for ODT are as follows:

- disintegrate rapidly in the oral cavity.
- eliminate the need for use of water or chewing.
- recommended tablet weight to be less than 500 mg for compliance reasons, especially for children (if too big, dosage form may be partially spit out).
- in vitro disintegration with USP <701> to be less than 30 seconds.

Application of the ODT dosage form nomenclature to your product is a review issue.

Question 13

In-Process Control for DP: Does the Agency concur with the approach to test hardness as an in-process test during manufacturing and not as a test on the finished tablets? Is our approach acceptable to demonstrate, through shipping studies, that friability testing is not applicable? (pp. 018, 037)

The approach is acceptable for performing hardness testing as an in-process test instead of at release. However, there should be in-process acceptance criteria proposed that are reflective of supportive hardness data provided in the application.

Additionally, we highly recommend that you collect the hardness data for the NDA primary stability batches [redacted], and report these in the NDA. b(4)

Your approach for justifying of the omission of friability testing is acceptable.

Question 14

Analytical Specifications/Tests (release): Does the Agency maintain that the testing regimen for the release of the finished drug product is appropriate and adequate for the control of this product? (p. 018)

Yes, assuming we agree with your justification for not performing the quantitative color measurements at release.

Question 15

Analytical Specifications/Tests (stability): Does the Agency concur that the proposed testing regimen for the stability of the finished drug product is appropriate and adequate for the control of this product.? (p. 019)

Whether or not hardness and quantitative color measurements are to be performed routinely during stability studies will depend on the data submitted for these parameters.

The data provided from shipping studies will need to be evaluated prior to a decision on whether or not friability testing is appropriate for the routine stability studies.

Question 16

Does the Agency concur with the proposal to submi[redacted](Batch) Record [redacted] for [redacted] of the registration stability batches [redacted] commercial manufacturing site, used in pivotal clinical studies)? (p. 019) b(4)

No. Provide the [redacted] for each primary stability batch and the bioavailability/bioequivalence study batch(es).

Question 17

Control of [redacted] Does the Agency concur with the approach to test for residual solvents on the [redacted] and to include the results with the COA for the finished product? (p. 019) b(4)

The approach is reasonable but the finished product should have acceptance criteria for residual solvents reflective of data. As discussed at the EOP2 meeting, the specification for the product can indicate that this test is done on the [redacted] in-process. b(4)

ICH Q3C limits are for safety considerations and are not necessarily limits for quality control.

Question 18

Holding Time Study: Does the Agency concur with this proposed strategy for hold time and does the Agency confirm that the stability data amendment three months prior to the action date will be considered a "minor amendment?" (p. 020)

Hold times for intermediates longer than [redacted] during the drug product manufacturing process are strongly discouraged. b(4)

If the [redacted] hold period is longer than [redacted] the expiration dating period of the drug product must be calculated from the beginning of drug product [redacted] production.

The hold times of the [redacted] used in preparing the stability batches supporting the application should be indicated in the submission. The [redacted] hold periods that have been used will determine the hold period that can be allowed. b(4)

Alternatively, you should submit the limited stability data supporting the [redacted] hold period either at the time of submission of the application or as a post-approval supplement. b(4)

If you have questions about the contents of this facsimile, please contact Christine Yu at 301-827-1051.

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/s/

Christine Yu
3/17/05 05:36:24 PM

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Memorandum of Telephone Facsimile Correspondence

Date: March 24, 2003

To: Eric Floyd, Ph.D.
Sr. Director, Drug Regulatory Affairs

Fax: 908-541-5274

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: IND 62,192 Fexofenadine orally disintegrating tablet
Minutes of January 10, 2003, EOP2 meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on January 10, 2003. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

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MEETING MINUTES

DATE:	January 10, 2003
TIME:	11:00 am - 12:30 pm
LOCATION:	Parklawn Conference Room C
TYPE:	End of Phase 2 (EOP2)
APPLICATION:	IND 62,912
DRUG NAME:	Fexofenadine orally disintegrating tablet
IMTS#:	9309
SPONSOR:	Aventis Pharmaceuticals, Inc.

Represented by:
Praful Agrawala, Pharmaceuticals Sciences
Jeffrey Barrett, Biopharmaceutics
Kazimierz Chrzan, Analytical Sciences
Jessica Collis, Regulatory CMC
Ian, Davidson, Project Leader
Eric Floyd, Sr. Director, Drug Regulatory Affairs
Sanjay Jalota, Drug Regulatory Affairs
Barbara Kittner, Clinical Development
Sriram Krishnaswami, Biopharmaceutics
Derek Moe, Pharmaceuticals Sciences (CIMA Labs, Inc.)
Peju Odunussi, Analytical Sciences (CIMA Labs, Inc.)
Abdul Sankoh, Biostatistics
Donna Taneja, Project Management
Marie Parrish, Analytical Sciences

FDA participants: Division of Pulmonary & Allergy Drug Products, unless noted otherwise

Craig Bertha, CMC Reviewer
Guirag Poochikian, CMC Team Leader (TL)
Lawrence Sancilio, Pharmacology/Toxicology Reviewer
Joseph Sun, Supervisor, Pharmacology/Toxicology
Emmanuel Fadiran, Clinical Pharmacology & Biopharmaceutics (CPB) TL
Charles Lee, Medical Officer
Lydia Gilbert-McClain, Acting Medical TL
Marianne Mann, Deputy Director
Badrul Chowdhury, Acting Director
Christine Yu, Regulatory Project Manager
Eric Duffy, Director, Division of New Drug Chemistry II

Background

Aventis requested an End-of-Phase II (EOP2) meeting to discuss their bioequivalence (BE) and Chemistry, Manufacturing, and Controls (CMC) program to support a NDA for fexofenadine HCl 30 mg orally disintegrating tablet. Prior to the meeting, the Division had requested that samples of the product be brought to the meeting, so that the Division could get a better idea of

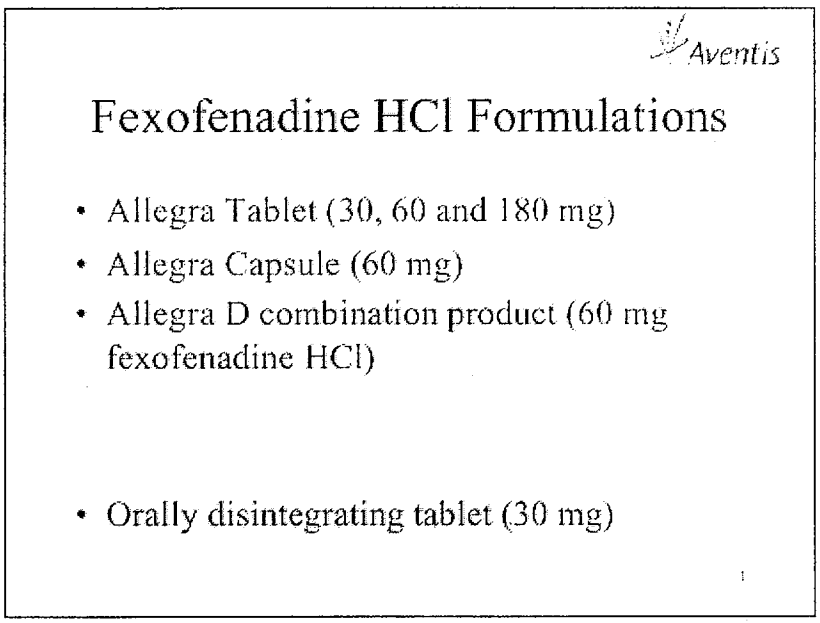
the tablet size and appearance. The Division had also requested that Aventis give a brief presentation on comparative food effect data for the approved Allegra products and the fexofenadine orally disintegrating tablet.

Aventis' questions from the briefing package served as the agenda for the meeting.

Attachment (following the minutes)
Aventis' additional overheads that included data and information about the NDA batch lots.

Minutes

Aventis presented the following slides and information on comparative food effect data for the approved Allegra products and the fexofenadine orally disintegrating tablet.



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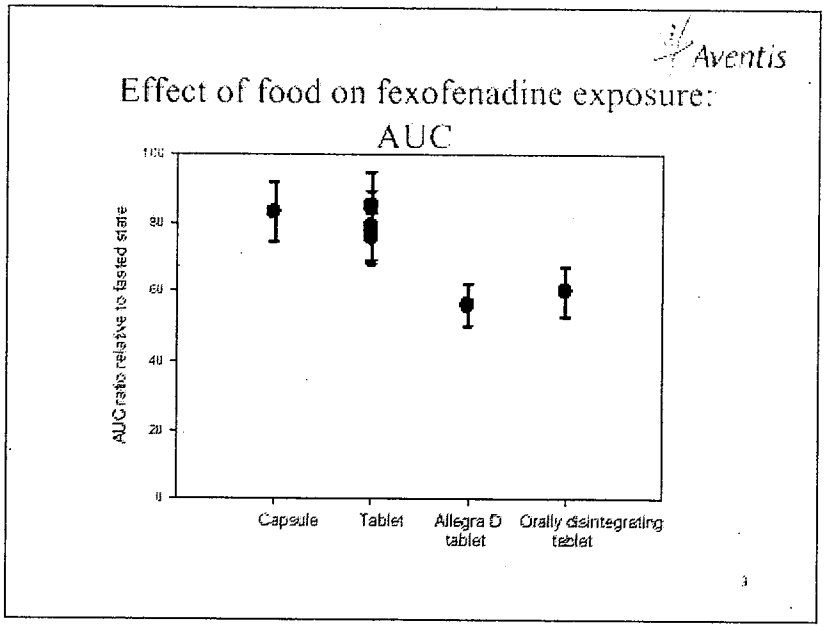
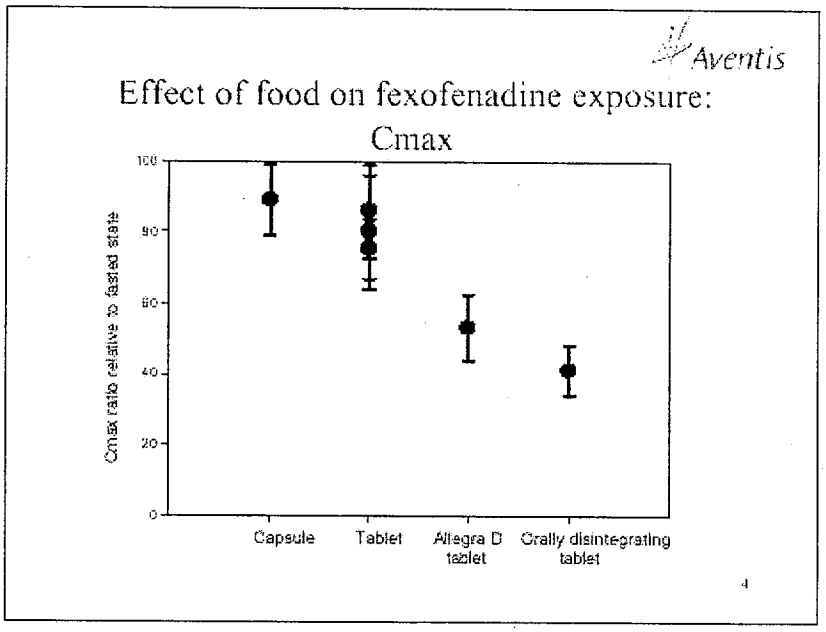

Aventis
Effect of food on fexofenadine exposure:
AUC
AUC ratio relative to fasted state
100
80
60
40
20
0
Capsule
Tablet
Allegra D tablet
Orally disintegrating tablet
3


Aventis
Effect of food on fexofenadine exposure:
Cmax
Cmax ratio relative to fasted state
100
80
60
40
20
0
Capsule
Tablet
Allegra D tablet
Orally disintegrating tablet
4

Aventis

Conclusions

- Fexofenadine exhibits formulation-dependent food effect characteristics
- The reduction in exposure in the presence of food is similar between marketed capsules and tablets and is not clinically relevant
- The magnitude of food effect is similar between Allegra D and the orally disintegrating tablet
- Aventis is therefore seeking comparable labeling for the orally disintegrating tablet as for Allegra D

5

Aventis

Allegra D Label

DOSAGE AND ADMINISTRATION
The recommended dose of ALLEGRA-D is one tablet twice daily for adults and children 12 years of age and older. ***It is recommended that the administration of ALLEGRA-D with food should be avoided.*** A dose of one tablet once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY and PRECAUTIONS.)

6

The Division expressed concern about calling this product an "orally disintegrating tablet (ODT)" based on CMC data already submitted in the briefing package and to IND 62,912.

In other approved products labeled ODT, **disintegration** occurs within a few seconds and **dissolution** occurs within a few minutes. Another major concern is the mass of the tablet which is relatively for an ODT and particularly for use in children. b(4)

Aventis responded that they had submitted to the IND information about batches They presented data on the product they plan to continue development of fexofenadine ODT with, see Attachment at end of minutes. Aventis expected that size would be greater than ranging from b(4)

Upon inquiry from the Division, Aventis replied that placebo formulation acceptability testing has not been performed in the 2-5 year old subjects but the fexofendine ODT is the same size as the currently marketed b(4)

The Division reiterated their concerns about labeling the proposed product as an ODT based on its physical characteristics, such as the data presented on the disintegration and dissolution rate (Q= in 20-30 minutes). Such properties are similar to conventional tablets, and do not justify ODT nomenclature. The Division also expressed concern about the size of the tablet particularly when the target population includes children. Aventis can submit a rationale for calling this product an ODT b(4)

CMC Questions

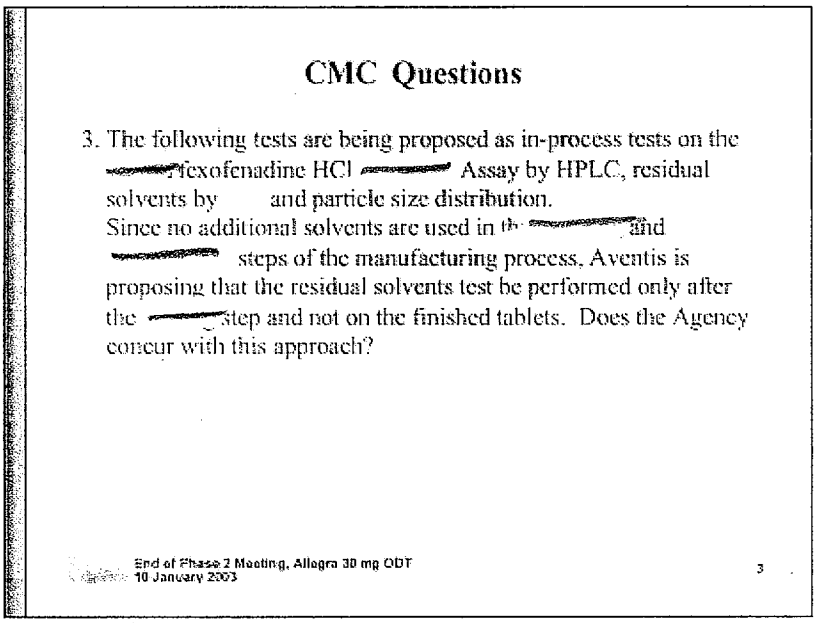
1. Does the Agency confirm (as per our August 20, 2002 discussion with the Agency) that of stability data (ICH conditions) on NDA stability batches and at least of data on the pilot clinical batch of the to-be-marketed formulation would be sufficient to support the submission of the NDA? b(4)

2. Does the Agency concur that the stability data (ICH conditions) on NDA stability batches could be provided approximately 3 months after the initial NDA submission with no impact on the review timetable? b(4)

End of Phase 2 Meeting, Allegra 30 mg ODT
10 January 2003 2

The Division, in response to questions 1 and 2, stated that the proposals are acceptable, but Aventis should consider that expiry dating is determined by available and analyzable data. Additionally, given that reviewers have competing assignments, Aventis may choose to submit

12-month data a time period after submission of the original NDA, but Aventis should be aware that the Division may not be able to review the data submitted *during* the review cycle. Normally, based on the depth and extent of available data and observed trends, the maximum expiry date cannot extend more than [redacted] beyond the provided stability data. b(4)



b(4)

b(4)

The Division referred Aventis to ICH Guidance for Industry, "Q3C Impurities: Residual Solvents." Methods should also be appropriately validated. (If the organic volatile impurities (OVI) test is performed as an in-process test then the specifications sheet for the drug product should include this test and appropriate acceptance criteria, with an asterisk to indicate that this test is being performed at the in-process stage.)

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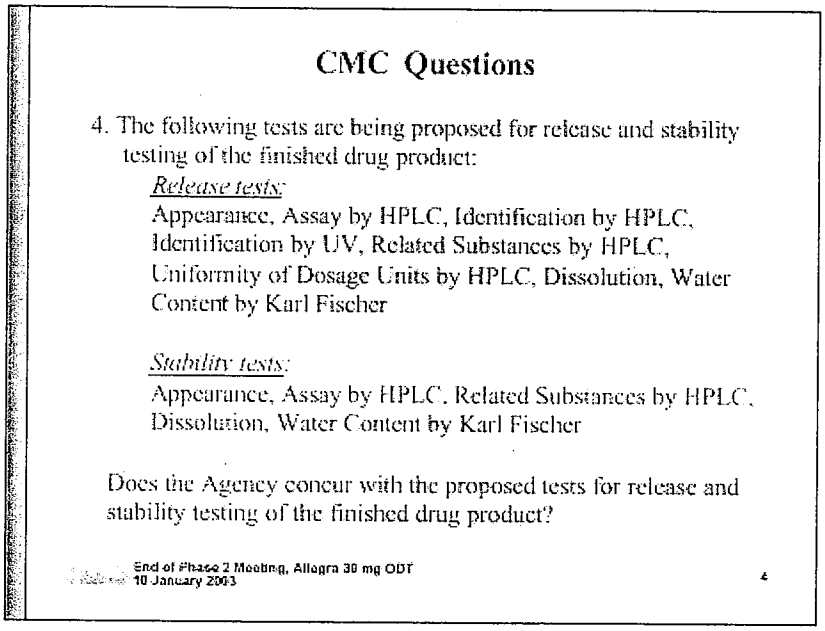

CMC Questions

4. The following tests are being proposed for release and stability testing of the finished drug product:

Release tests:
Appearance, Assay by HPLC, Identification by HPLC, Identification by UV, Related Substances by HPLC, Uniformity of Dosage Units by HPLC, Dissolution, Water Content by Karl Fischer

Stability tests:
Appearance, Assay by HPLC, Related Substances by HPLC, Dissolution, Water Content by Karl Fischer

Does the Agency concur with the proposed tests for release and stability testing of the finished drug product?

End of Phase 2 Meeting, Allegra 30 mg ODT
10 January 2003

The Division stated that color (if applicable), disintegration, hardness and friability tests should be performed at release and stability.

Aventis responded that hardness and friability testing may not be applicable with this product.

The Division replied that Aventis can submit alternative proposals for hardness and friability of tablets to address concerns about the product remaining intact and stable during manufacturing, packaging and shipping.

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Fexofenadine HCl
30-mg Orally Disintegrating Tablet (ODT)
IND 62,912

Emmanuel Fadiran, Ph.D., Team Leader
Clinical Pharmacology & Biopharmaceutics
Division of Pulmonary and Allergy Drug Products

10 January 2003
End-Of-Phase 2 Meeting

Center for Drug Evaluation and Research

Clinical Pharmacology

Question 1

Does the Agency concur that the proposed bioequivalence program will support approval of the new NDA for the orally disintegrating tablet in the pediatric age group 6-11 years?

Response:

Yes, we concur (refer to chemistry comments).

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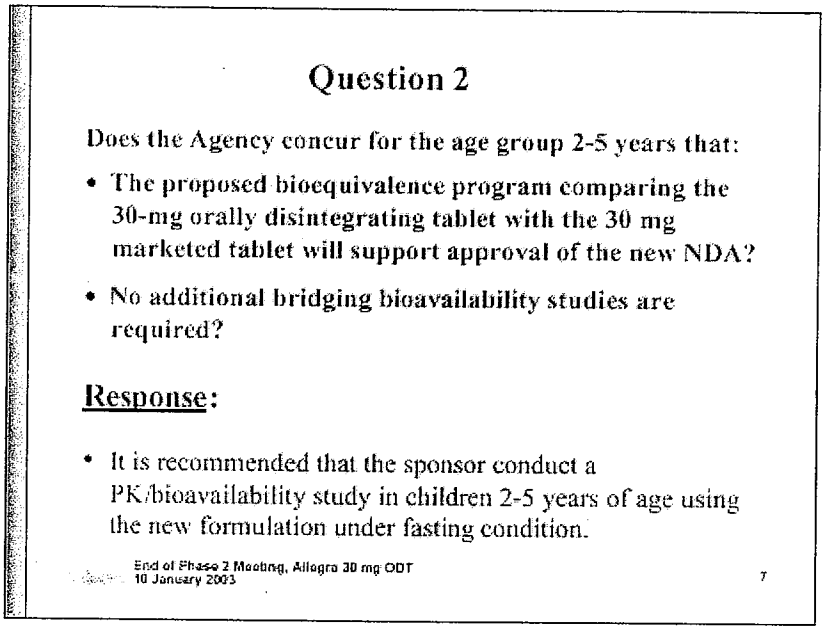
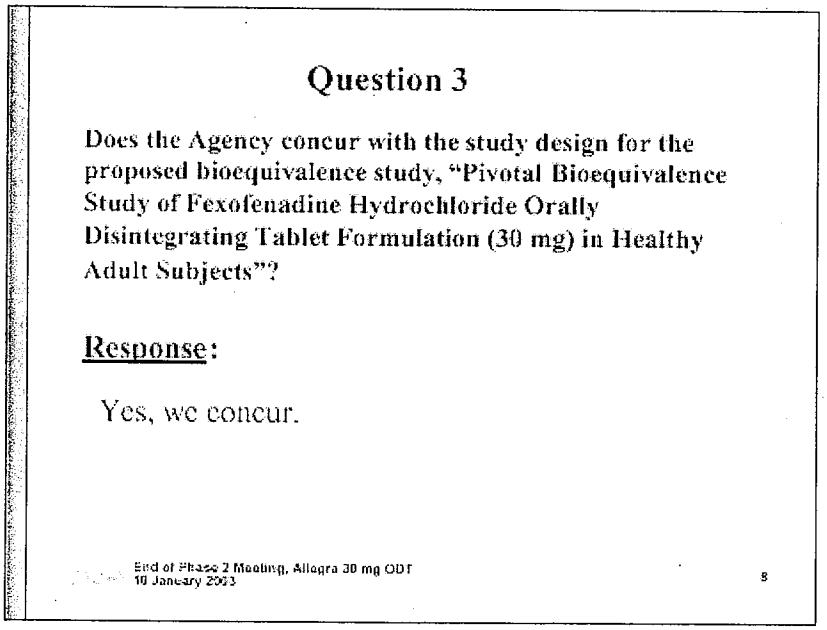
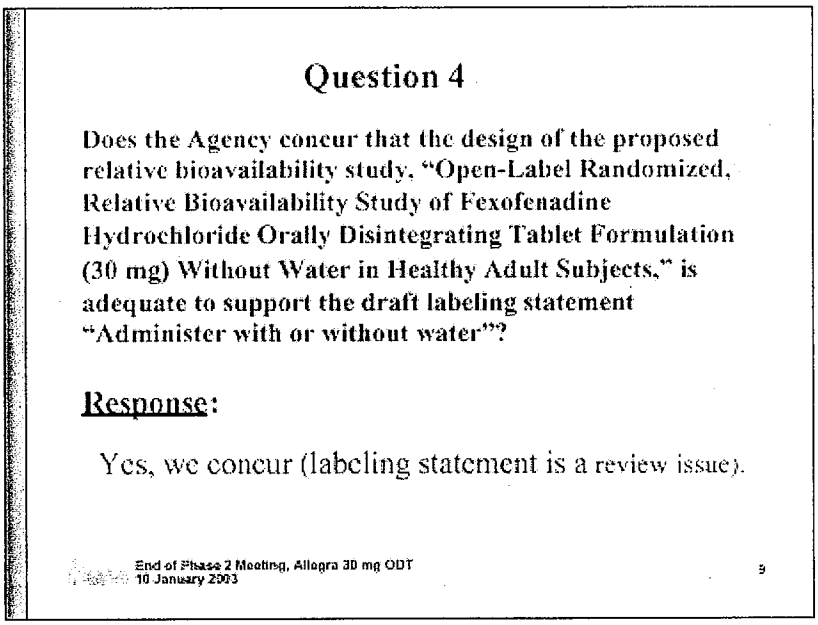
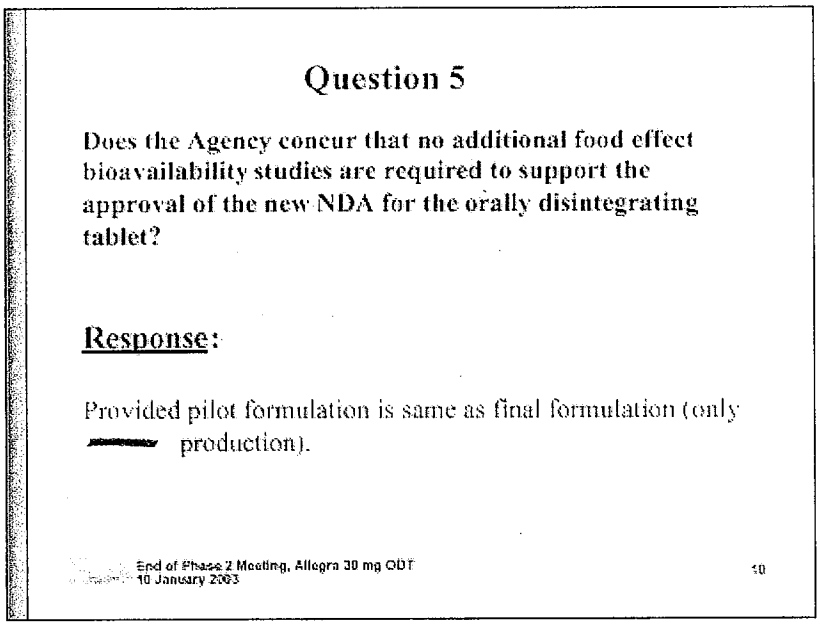


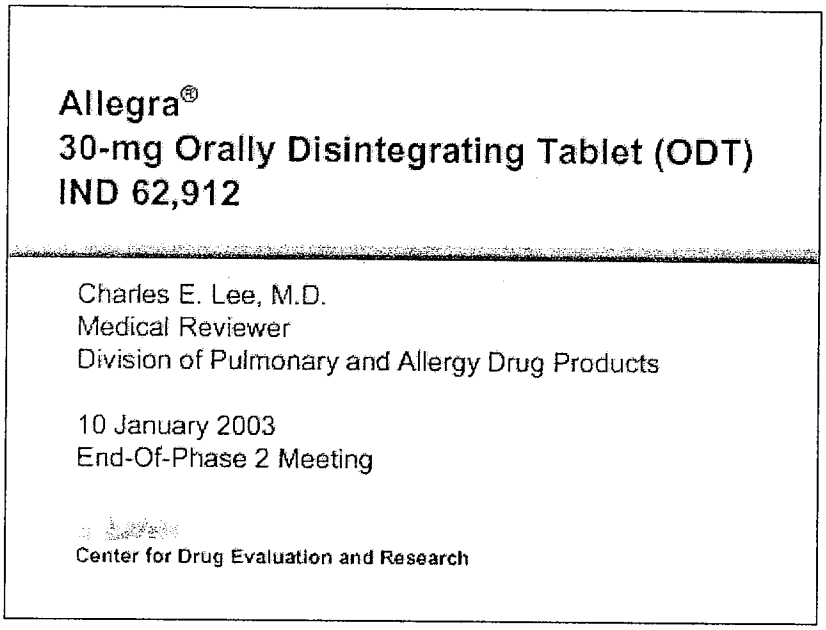
The Division noted that no pharmacokinetic study has been conducted in children without the use of applesauce. (The applesauce link is in adults.)

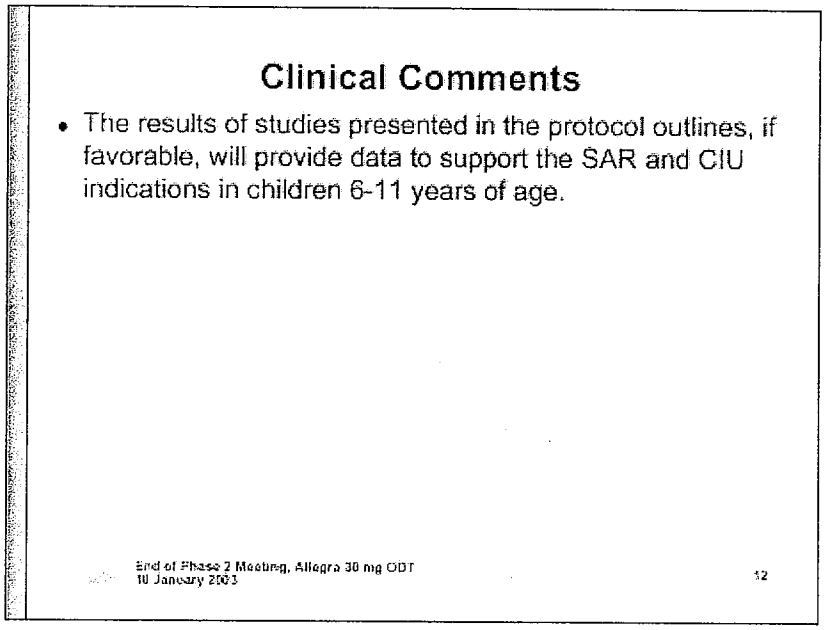




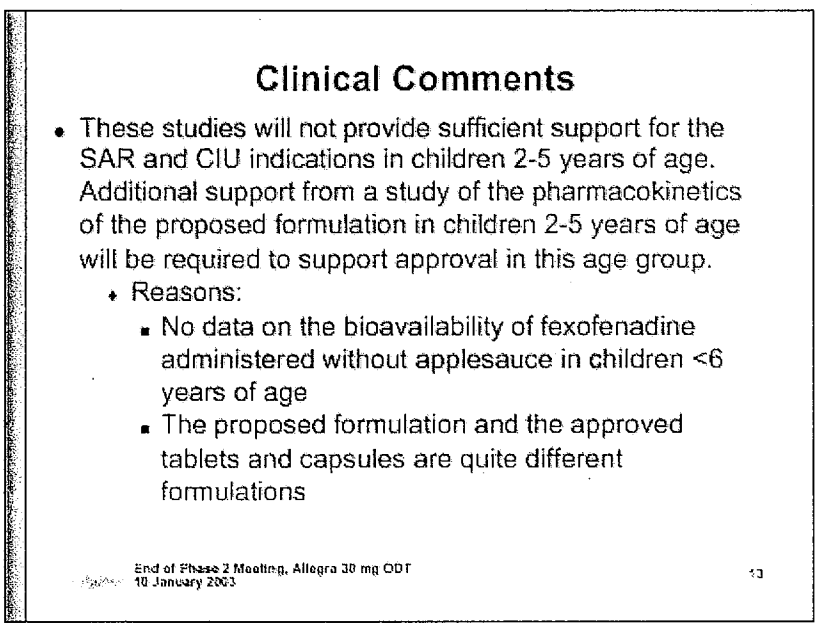


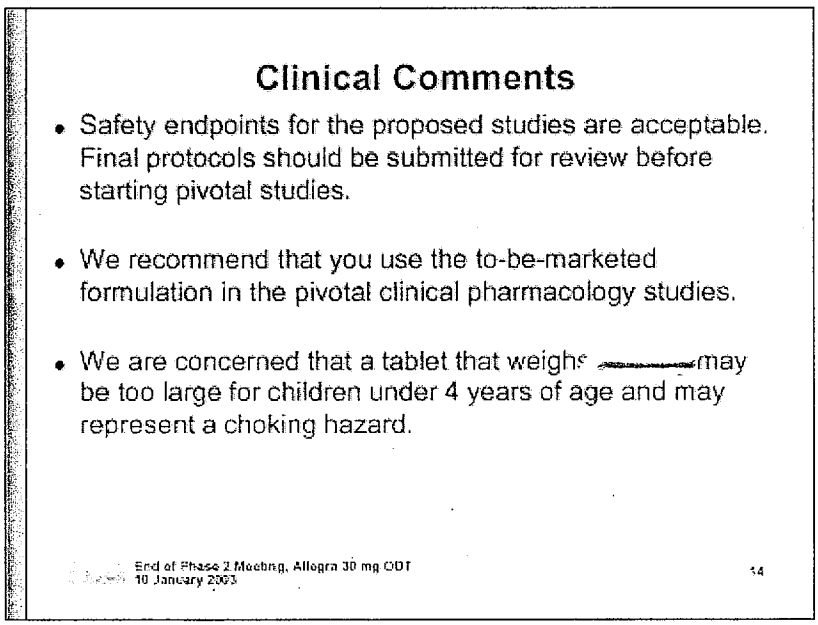
Aventis responded that the composition of the pilot formulation used for the food effect study is the same as the final formulation.





The Division noted that these clinical comments are applicable for a true ODT formulation. If the formulation is different, study requirements may vary.





b(4)

The Division added that after looking at the samples brought to the meeting, there is less concern with choking.

Aventis asked if the Division would find the 6-11 year olds acceptable as the proposed age group for this product. The Division stated that Aventis should determine what would be the most appropriate dosage form for the age group in light of their clinical development plans. The Division also questioned the advantage of having another 30 mg tablet in the market for 6-11 year olds- is it not the purpose of developing the new product to provide a marketable formulation of Allegra for the younger children (age 2-5).

Clinical Development Plan

- Children 2-5 years of age
  - Proposed 30-mg ODT linked to 30-mg of the capsule formulation in applesauce
    - 30-mg ODT to marketed 30-mg tablet (M106455H/1007)
    - Marketed 30-mg tablet has same [redacted] as the marketed 60-mg tablet
    - Marketed 60-mg tablet is bioequivalent to marketed 60-mg capsule (PJPR0094)
    - 60-mg capsules with applesauce bioequivalent to 60-mg capsules without applesauce (PJPR0076)
      - AUC is OK; Cmax is not but is close
    - PK and safety data for children 2-5 years of age for 30 mg fexofenadine from the capsules given with applesauce (M106455I/1114, M106555I/3112)

End of Phase 2 Meeting, Allegra 30 mg ODT
10 January 2003 22

Fexofenadine PK, Different Age Groups

Age	2-5 years	6-12 years	Adults	Adults
N	21	13	46	47
Source of data	M106455I/1114	Allegra label	PJPR0076	PJPR0076
Dose	30 mg capsule contents with applesauce	30 mg tablet no applesauce	Normalized data 30 mg capsule no applesauce	Normalized data 30 mg tablet no applesauce
AUC_{INF}	633	1091	460	487
C_{max}	146.6	183.5	65.5	71.0

End of Phase 2 Meeting, Allegra 30 mg ODT
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Clinical Question

- Aventis does not plan to conduct any additional clinical safety and efficacy studies in support of this new formulation. Does the Agency concur?

Clinical Question

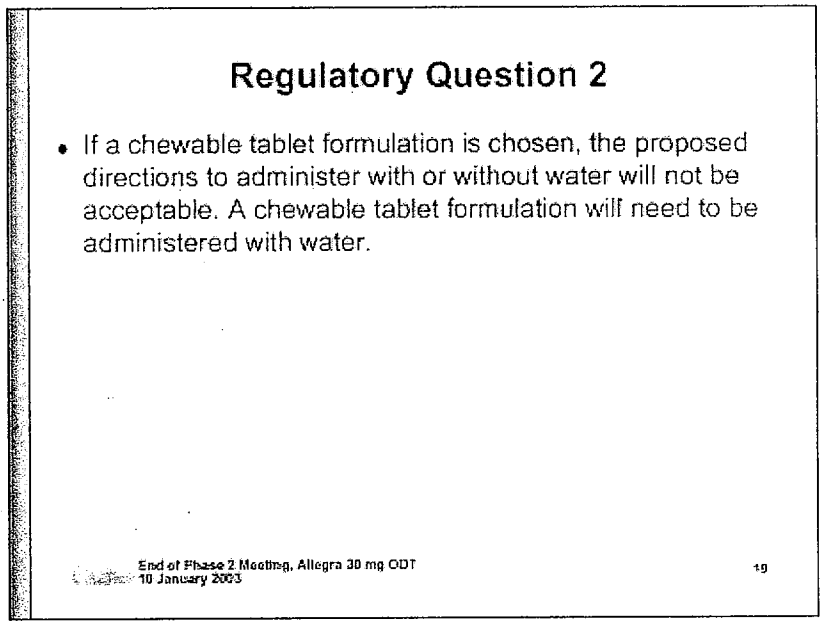
- No additional clinical safety and efficacy studies in support of the new formulation in children 6-11 years of age will be required if the results of the pivotal clinical pharmacology studies are favorable.
- If a pharmacokinetics study of the proposed formulation in children 2-5 years of age demonstrates exposures that are similar to those noted in previous studies in this age group (M106455I/1114 and M106455I/3112), no additional clinical safety and efficacy studies of the new formulation in children 2-5 years of age will be required.

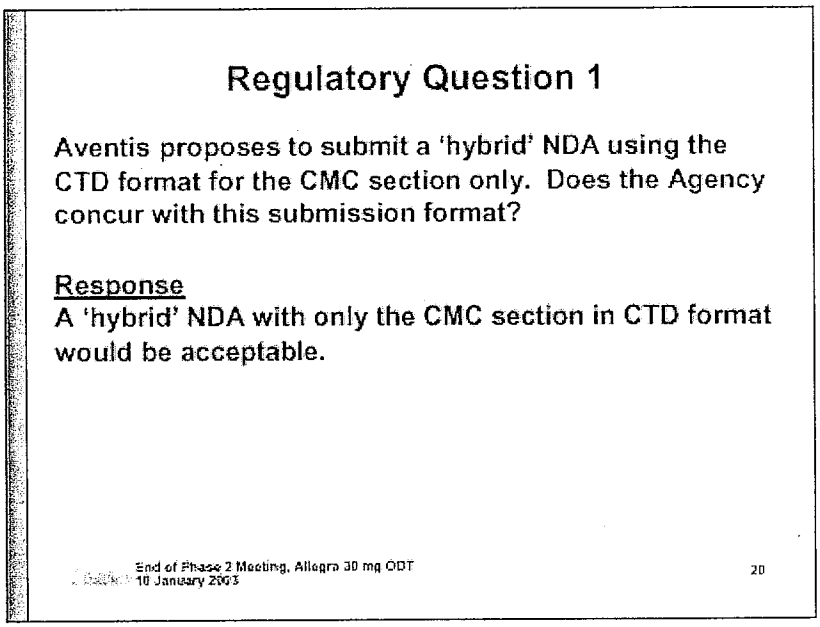
Regulatory Question 2

- Aventis proposes the following wording for the Dosage and Administration section of the Allegra package insert. Does the Agency concur?
  - Children 6 to 11 years of age. The recommended dose of Allegra as a tablet or orally disintegrating tablet is 30 mg twice daily. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see CLINICAL PHARMACOLOGY).
  - Children 2 to 5 years of age. The recommended dose of Allegra as a tablet or orally disintegrating tablet is 30 mg twice daily. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see CLINICAL PHARMACOLOGY).
  - Administration of Allegra Orally Disintegrating Tablet. Place Allegra Orally Disintegrating Tablet on the tongue. Tablet disintegration occurs rapidly. Administer with or without water. It is recommended that the administration of Allegra Orally Disintegrating Tablet with food should be avoided.

Regulatory Question 2

- In principle, it is acceptable for you to address the food effect with labeling instructions. However, in addition to proposed labeling that states that co-administration with food is not recommended, you also will need to describe the food effect and the period of time before and after meals that the drug should be taken. The exact language to be used in the labeling will be negotiated when the application has been submitted.





The meeting adjourned at this time.

Post-meeting Addendum

The appropriateness of designating and labeling your proposed product as an "orally disintegrating tablet" is currently under discussion at the Agency. You will be informed of any decisions made.

Aventis

DisIntegration Time Data on NDA Lots at Release

	Batch No.		
	720290	**720291**	**720583**
Time (sec)	[redacted]	[redacted]	[redacted]
Mean	**34**	**34**	**36**
Range (Min – Max)	[redacted]	[redacted]	[redacted]

b(4)

Aventis Pharmaceuticals

Aventis

Fexofenadine HCl Orally Disintegrating Tablets - Formulation

•The tablet combines taste masked Fexofenadine HCl with a fast disintegrating, low effervescence excipient system

- taste masking is performed by [redacted] b(4)
- all inactive ingredients used are compendial/GRAS materials for solid dosage forms

•Manufacturing process includes [redacted] b(4)

•Formulations developed using similar active ingredient/excipient matrix have been previously reviewed and approved by FDA (*e.g.* Zomig-ZMT™, Remeron® SolTab™, Alavert™), and have also been developed for OTC monograph products Triaminic™ Soft Chews and Tempra™ Tablets

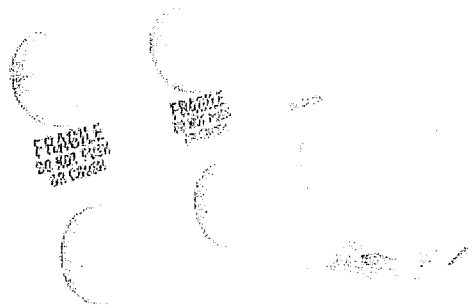
Attachment Page 19

Aventis Pharmaceuticals

Aventis

Fexofenadine HCl Orally Disintegrating Tablets - Packaging

- The tablets are packaged in [redacted] foil blisters specially designed to protect these tablets during shipping and handling **b(4)**
- The packaging system is light and moisture proof
- The packaging system is identical to other marketed products with successful worldwide shipping history



- Packaging is child resistant as per 16 CFR Part 1700.15 (b) (1) and Part 1700.20 (a) (2) (ii).
- Tablets are packaged using a [redacted] system immediately after [redacted] **b(4)**
- The tablets cannot be shipped in bulk

Aventis Pharmaceuticals

Aventis

Quantitative Comparison of Composition

Component	Amount in Developmental Batch	Amount in NDA Batches
Fexofenadine		
Fexofenadine HCl		
Microcrystalline Cellulose		
Sodium starch glycolate		
Povidone		
Magnesium stearate		
Alcohol anhydrous		
Fexofenadine HCl Orally-disintegrating Tablets, 30 mg		
Fexofenadine		
Mannitol[2]		
Mannitol		
Crospovidone		
Microcrystalline cellulose		
Sodium bicarbonate		
Citric acid, anhydrous		
Aspartame		
Magnesium stearate		
Cream flavor, Artificial		
Orange flavor, Natural and Artificial		
Total		

b(4)

b(4)

[1]Removed during processing
[2]Amount adjusted based on the assay of the Fexofenadine

b(4)

Attachment
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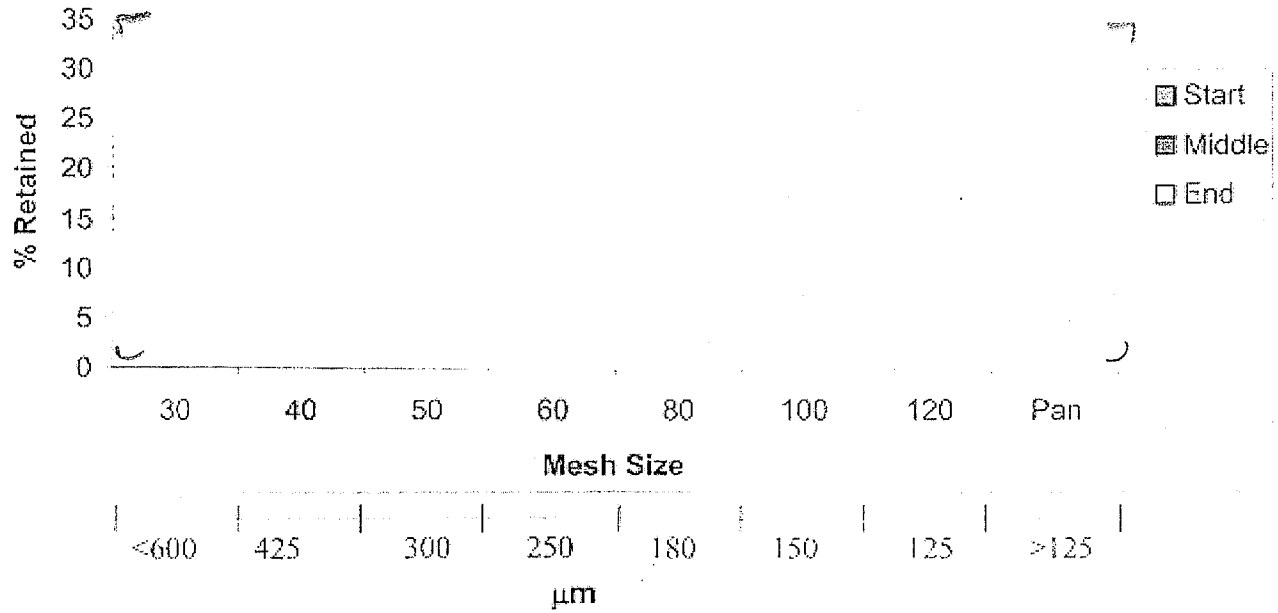
Aventis Pharmaceuticals

Aventis

Particle Size Distribution of [redacted] Fexofenadine HCl

[redacted]

[redacted], Lot 720287

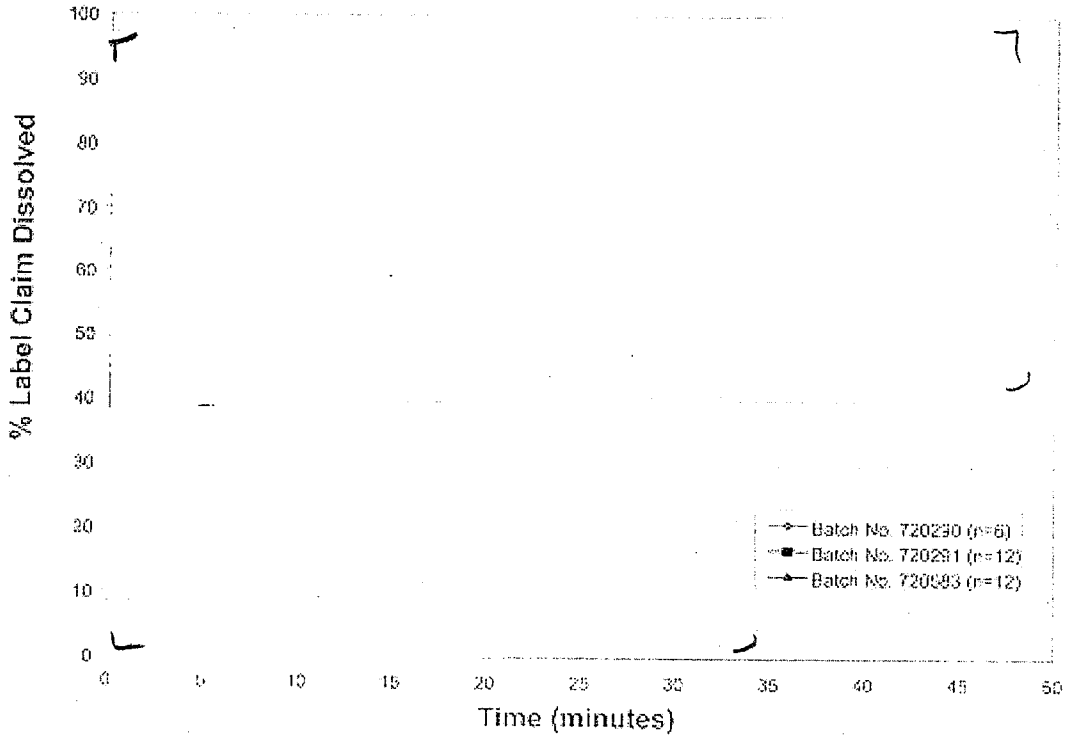


Aventis Pharmaceuticals

Aventis

Dissolution Profile at pH =3.0 Medium

NDA Batches Release Data (Mean, Min, Max)



b(4)

USP Apparatus II at 50 RPM
Dissolution Medium: 0.001N HCL (pH 3.0)
Sample Volume: 500 mL

Sampling times: 5, 10, 15, 30 and 45 min
Sample Analysis: HPLC (UV detection @ 220 nm)

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/s/

Christine Yu
3/24/03 02:30:30 PM

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