DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-150

Pfizer Pharmaceuticals
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Attention: John Tomaszewski, M.S.
Director, Regulatory Affairs

Dear Mr. Tomaszewski:

As requested on July 20, 2001, please find attached an MS Word version of the draft Zyrtec-D label faxed to your firm on July 20, 2001.

If you have any questions, you may contact me at 301-827-5585.

Sincerely,

{*See appended electronic signature page*}

Craig Ostroff, Pharm.D.
Regulatory Management Officer
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachment

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Craig Ostroff
7/23/01 11:02:09 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-150

Pfizer Pharmaceuticals
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Attention: John Tomaszewski
Director, Regulatory Affairs

Dear Mr. Tomaszewski:

We acknowledge receipt on February 12, 2001, of your February 12, 2001, resubmission to your new drug application (NDA) for Zyrtec-D 12 Hour (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets.

This resubmission contains additional Chemistry, Manufacturing, and Controls (CMC) and revised labeling information submitted in response to our January 17, 2001 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is August 12, 2001.

If you have any questions, call Dr. Craig Ostroff, Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

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

/s/

Craig Ostroff
3/1/01 02:34:26 PM
Craig Ostroff for Sandy Barnes

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Number of Pages Redacted 16 + 14 = 30

❖❖❖

Draft Labeling
(not releasable

REQUEST FOR INFORMATION

November 27, 2000

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FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: **John Tomaszewski**

Phone Number: (212) 733-6295

Fax: **212-573-1563**

From: **Vicky Borders-Hemphill**
Project Manager

Subject: **NDA 21-150**

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857
PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 2

Date: November 27, 2000

The following request pertains to NDA 21-150, study 143-007, page 14 of the final study report of this study (page 6319 of the NDA):

You stated that standardized breakfasts were provided during the inpatient part of the study. Please provide more detailed information about the following:

1. The content of the breakfast.

2. The exact time period between the completion of the breakfast and the dosing of the drug. Currently, the report states only "that subjects were to complete their meals at least one hour prior to dosing".

/s/

(Brenda) Vicky Borders
12/8/00 02:46:59 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

9 pages

NDA ACKNOWLEDGEMENT LETTER

May 25, 2000

Trout
570

NDA 21-150

MAY 25 2000

Pfizer Pharmaceuticals
235 East 42nd Street
New York, NY 10017-5755

Attention: Rita Wittich
Director/Team Leader, Regulatory Affairs

Dear Ms. Wittich:

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: Zyrtec-D (cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg)
Extended Release Tablets

Therapeutic Classification: Standard (S)

Date of Application: January 18, 2000

Date of Receipt: January 19, 2000

Our Reference Number: NDA 21-150

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 19, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 19, 2000, and the secondary user fee goal date will be January 19, 2000.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1058.

Sincerely yours,

Gretchen Trout
Project Manager
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-150
HFD-570/Div. Files
HFD-570/G.Trout

DISTRICT OFFICE

Drafted and final by: GST/May 25, 2000

filename: c:\draft\my documents\21150ac

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

INFORMATION REQUEST

March 10, 2000

APPEARS THIS WAY
ON ORIGINAL

TROUT

Memorandum of Telephone Facsimile Correspondence

Date: March 10, 2000

To: Stephen Cristo
Director
Regulatory Affairs
(212) 573-1563

From: LCDR James Lindsay Cobbs
Regulatory Project Manager

Subject: Information Request

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

/S/

LCDR James Lindsay Cobbs
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

1. Please provide multi-point dissolution profiles for both active ingredients in the bilayer tablet for the different media investigated (water, 0.1N HCl, pH 4.5 buffer and pH 7.4 buffer) and provide the individual and mean values of the percentage dissolved for each sampling time in a table format. Also, include multi-point dissolution profiles and tables, for both active ingredients, using the dissolution medium that was selected (0.1N HCl), for the same batch as used in study 143-007.

2. Please provide the following items in electronic format (disk, zipdisk or CD-ROM).

   a. The Human Pharmacokinetics and Bioavailability Overview (Vol. 12, pages 6-5 through 6-23).

   b. Study 143-006: the Final Study Report (Vol. 12, pages 6-24 through 6-45), the Summary Tables (Vol. 12, pages 6-46 through 6-81), the Figures (Vol. 12, pages 6-82 through 6-87) and the Subject Data Listings under Section 13 (Vol. 12, pages 6-285 through 6-305).

   c. Study 143-007: the Final Study Report (Vol. 12, pages 6-306 through 6-332), the Summary Tables (Vol. 12, pages 6-333 through 6-401), the Figures (Vol. 12, pages 6-402 through 6-413) and the Subject Data Listings under Section 13 (Vol. 13 pages 6-875 through 6-907).

3. Please clarify whether Sudafed LA 120 mg caplets (Warner Lambert), that were used in study 143-007, are identical to Sudafed 12 hour tablets (Warner Lambert) that are referenced in the PDR.

CC: ORIGINAL NDA 21-150
DIVISION FILE
HFD-570/TROUT
HFD-570/UPPOOR/3-10-00
HFD-570WAKELKAMP-BARNES/3-10-00

DRAFTE BY:LCOBBS/3-10-00

MY DOCUMENTS/ZYRTECDFAX00-03-10.DOC

APPEARS THIS WAY
ON ORIGINAL

PFIZER CMC COMMITMENTS

July 2001

APPEARS THIS WAY
ON ORIGINAL

Groton Laboratories
Pfizer Inc
Eastern Point Road
Groton, CT 06340-5146
Tel 860 441 4100 Fax 860 441 7961

Pfizer

Global Research & Development

Regulatory CMC

Facsimile Message to: Dr. Prasad Peri
Division of Pulmonary and Allergy Drug Products

CC to: [redacted]

Location: [redacted]

Number of Pages (including cover sheet): 2 FAX # 301-827-~~1271~~ 5586

Acknowledgment of Receipt Required: No

Sent by: J. Blumenstein Ext. 860-441-0429 Secretary: J. French 860-441-4472

Date: 7/24/2001

FACSIMILE PHONE NO.
(860) 441-7961

If you do not receive all of the pages, please call sender.

Comments:
Dr. Peri,
As discussed on the telephone earlier today, please find attached wording describing our commitments for your comment.
Thanks
Jeff Blumenstein

Commitment 1:
As noted in our Feb 12, 2001 response to the Agency's comment #7, Pfizer commits to provide a new HPLC purity method to address the Agency's concerns with method P187.21. This new method will be submitted as a supplement to the approved NDA on or before Aug 12, 2001.

Commitment 2:
As noted in our Feb 12, 2001 response to the Agency's comment #11, Pfizer commits to attempting to identify any new degradation products observed at levels equal to or greater than the threshold for the identification of impurities for this dose listed in the ICH guideline Q3b of 0.5% or 20µg TDI. This corresponds to a limit of 0.2% vs. cetirizine hydrochloride.

Commitment 3:
Pfizer commits to providing a summary to the Agency of our production and stability experience regarding individual and total unspecified degradants after 1 year. We acknowledge the Agency's desire to tighten the limits for individual and total unspecified degradants to be more consistent with the ICH identification threshold of 20µg TDI, corresponding to 0.2% vs. cetirizine hydrochloride. The evaluation of that 1 year experience will be with the goal of meeting the Agency's desire for a tightened specification, should the data support it. While Pfizer accumulates the 1 year experience and provides the update to the Agency noted above, the specifications will remain as stated in our Feb 12, 2001 response to the Agency's comment #11.

APPEARS THIS WAY
ON ORIGINAL

CMC TELECON

March 15 2001

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: March 15, 2001

APPLICATION NUMBER: NDA 21-150, Zyrtec-D Extended Release Tablets

BETWEEN:

Name: Jeff Blumenstein, Ph.D., Director, Regulatory Affairs (CMC)
Michael Cohen, Ph.D., Associate Director, Pharmaceutical Sciences
John Tomaszewski, M.S., Director, Regulatory Affairs
Phone: 212-733-6295
Representing: Pfizer, Inc.

AND

Name: Craig Ostroff, Pharm.D. Project Manager
Prasad Peri, Ph.D., CMC Reviewer
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Changes to specifications, labeling for drug product

- The Moisture Release specification should be set to 4% at release and at 6% upon stability testing. The data show that the drug product is gaining moisture while on stability study. Pfizer responded that the stability specification might already be present as an IPC but that they agreed on making the revision.

- The Division requested an updated Methods Validation Package be submitted that incorporated all revisions as reflected in Pfizer's Feb 12, 2001 response.

- We advised that they change the storage statement in all labeling to include, at the minimum, the following statement, "Store at 20°- 25°C (68°- 77°F)". For additional information on excursion statements, Pfizer should refer to the draft CMC guidance issued June 5, 2001, entitled, "Stability Testing of Drug Substance and Drug Products." The sponsor was concerned that excursions ranging in temperatures of 15°- 30°C be permitted, as they have generated stability data in those ranges.

Craig Ostroff, Pharm.D.
Project Manager

/s/

Craig Ostroff
4/5/01 10:01:02 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

CMC TELECON

March 12 2001

MEMORANDUM OF TELECON

DATE: March 12, 2001

APPLICATION NUMBER: NDA 21-150, Zyrtec-D Extended Release Tablets

BETWEEN:

Name: Jeff Blumenstein, Ph.D., Director, Regulatory Affairs (CMC)
Michael Cohen, Ph.D., Associate Director, Pharmaceutical Sciences
Gail Farfel, Ph.D., Director, Clinical Research
Greg Stieno, Statistician
John Tomaszewski, M.S., Director, Regulatory Affairs
Debra Webb, Scientist, Regulatory Affairs (CMC)

Phone: 212-733-6295

Representing: Pfizer, Inc.

AND

Name: Craig Ostroff, Pharm.D., Project Manager
Prasad Peri, Ph.D., CMC Reviewer
Feng Zhou, M.S., BioStatistics Reviewer
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Resolution of Statistical questions with Stability data submitted 2/28/01

The discussion focused on data missing from the SAS Transport files that was originally present in the original Excel tables. It was found that wherever the Excel tables listed "LOQ" or something similar the SAS Transport conversion technique inserted in its place a null field.

The Division determined that there was no need for a further response from the sponsor on the issue at this time.

Craig Ostroff, Pharm.D.
Project Manager

/s/

Craig Ostroff
4/5/01 04:37:21 PM
CSO

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ON ORIGINAL

TELECON:
Comments on CMC Section of NDA

December 22, 2000

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: 12-22-00

APPLICATION NUMBER:
NDA 21-150, Zyrtec-D 12 H (cetirizine/pseudoephedrine) extended release tablet

BETWEEN:

Name:	Jeff Blumenstein, Director, CMC Regulatory Affairs
	Kevin Phelan, Director, Regulatory Affairs
	John Tomaszewski, Director, Regulatory Affairs
	Debra Webb, Scientist, CMC Regulatory Affairs
Office Phone:	212-733-6295
Representing:	Pfizer, Inc.

AND

Name:	Craig Ostroff, Pharm.D., Project Manager
	Prasad Peri, Ph.D., Chemistry Reviewer
	Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Comments on CMC section of NDA

BACKGROUND:

Dr. Prasad has been reviewing the October 11, 2000 major CMC amendment as part of the NDA package. This review generated some questions for the sponsor that needed to be addressed prior to the end of the review period.

DISCUSSION:

The Agency requested S2/S3 data for batches 8104, 8105, 8107 for where S1 level testing failed. The distributions and 18-month stability are already in the file (p 43). On p 25 of the submission in reference to the retention time ephedrine data, Pfizer needs to provide chromatographic conditions for each of the retention time point extremes listed on that page.

The Agency asked about the DMF authorization letter for [redacted] regarding packaging component PEC 11805 that had been requested by the Division on 12-20-00. Pfizer responded that it had just recently been faxed over to the Agency.

Pfizer mentioned that they would soon request a dialog with the agency on the impurity specifications for the compound.

Craig Ostroff, Pharm.D.
Project Manager

CONCUR:

Prasad Peri, Ph.D.
Chemistry Reviewer

APPEARS THIS WAY
ON ORIGINAL

/s/

Craig Ostroff
12/27/00 02:29:46 PM
CSO

Prasad Peri
12/28/00 07:10:38 PM
CHEMIST

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Number of Pages Redacted 53

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Confidential,
Commercial Information

DIVISION DIRECTOR'S MEMO

August 2001

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DIVISION DIRECTOR'S MEMORANDUM

Date:	2 August, 2001
NDA:	21-150
Proprietary Name:	Zyrtec-D (cetirizine with pseudoephedrine) tablets
Sponsor:	Pfizer
Due Date:	8/10/01

Introduction: This is the second cycle for this first combination product for the Zyrtec product line. Zyrtec-D has cetirizine as the antihistamine, a second-generation antihistamine with some sedative properties (but less sedating that many first generation antihistamines). The agency already accepts the combination of a decongestant (pseudoephedrine) and an antihistamine as rational. So this program was largely based on biopharmaceutics to show that this combination product gives comparable levels of exposure to its respective single ingredients (from approved products) and that there is no significant interaction between the two drug moieties, nor any problematic pharmaceutic properties of the formulation (i.e., food effects on the sustained relief properties).

CMC: See Dr. Peri's review for details. The CMC issues have largely been addressed, though there are some remaining issues in terms of identifying an unknown that occurs just above the 0.2% threshold and some test methods to delineate pseudoephedrine better from ephedrine hat Pfizer has agreed to address through post-approval supplements.

Pharmacology/toxicology: No new issues, as these drug substances are both approved and there are no new significant degradants or impurities.

Biopharmaceutics: No new issues.

Clinical / Stastical: The safety update was scant and does not contribute to the decision on approvability.

Labeling: Satisfactory PI and carton and container labeling has been agreed to by the sponsor.

Recommended Action: Approval

/S/

Robert J. Meyer, MD
Director, Division of Pulmonary and Allergy Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DIVISION DIRECTOR'S MEMORANDUM

Date:	2 August, 2001
NDA:	21-150
Proprietary Name:	Zyrtec-D (cetirizine with pseudoephedrine) tablets
Sponsor:	Pfizer
Due Date:	8/10/01

Introduction: This is the second cycle for this first combination product for the Zyrtec product line. Zyrtec-D has cetirizine as the antihistamine, a second-generation antihistamine with some sedative properties (but less sedating that many first generation antihistamines). The agency already accepts the combination of a decongestant (pseudoephedrine) and an antihistamine as rational. So this program was largely based on biopharmaceutics to show that this combination product gives comparable levels of exposure to its respective single ingredients (from approved products) and that there is no significant interaction between the two drug moieties, nor any problematic pharmaceutic properties of the formulation (i.e., food effects on the sustained relief properties).

CMC: See Dr. Peri's review for details. The CMC issues have largely been addressed, though there are some remaining issues in terms of identifying an unknown that occurs just above the 0.2% threshold and some test methods to delineate pseudoephedrine better from ephedrine hat Pfizer has agreed to address through post-approval supplements.

Pharmacology/toxicology: No new issues, as these drug substances are both approved and there are no new significant degradants or impurities.

Biopharmaceutics: No new issues.

Clinical / Stastical: The safety update was scant and does not contribute to the decision on approvability.

Labeling: Satisfactory PI and carton and container labeling has been agreed to by the sponsor.

Recommended Action: Approval

Robert J. Meyer, MD
Director, Division of Pulmonary and Allergy Drug Products

APPEARS THIS WAY
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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/

Robert Meyer
8/2/01 04:42:57 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DIVISION DIRECTOR'S MEMO

January 2001

Division Director's Memorandum

Date:	Wednesday, January 17, 2001
NDA:	21-150
Sponsor:	Pfizer
Proprietary Name:	Zyrtec-D (cetirizine HCl 5 mg and pseudoephedrine 120 mg) extended release tablets
From:	Robert J. Meyer, MD, Director, Division of Pulmonary and Allergy Drug Products.

Introduction: This is the first cycle for this extended release combination product containing the antihistamine – cetirizine and pseudoephedrine (PSE) as a decongestant. The product is a bilayer tablet with immediate-release cetirizine and 12-hour extended release pseudoephedrine. Since the combination of an effective antihistamine with pseudoephedrine is already established as rational, and since the 10 mg daily dose of cetirizine was previously shown to be effective (including the twice-daily administration in children), this program is mainly based on pharmacokinetics. The PK program was intended to show that PSE and cetirizine do not interact, and that the tablet provides equivalent exposures to approved and marketed formulations of the two active ingredients.

CMC: The are a variety of outstanding CMC issues with the drug substance and product, including a deficient DMF for the PSE drug substance, that have not been satisfactorily addressed (see CMC review and action letter for details). These outstanding issues will lead to an approvable action.

Pharm/Tox: No new pharm-tox data were needed for this application to date.

Biopharmaceutics: While there were questions related to data integrity that were answered to FDA's satisfaction (see Dr. Wakelkamp-Barnes' review and Dr. Chowdhury's team leader memo), the sponsor has shown what they intended with their biopharmaceutics program (including generating single and multiple dose bioequivalence data and food effects data). Essentially, this product gives equivalent exposure to cetirizine and PSE as provided by the referenced marketed, approved formulations and the two components do not have a pharmacokinetic interaction. Therefore, Zyrtec-D should be an effective antihistamine-decongestant combination product.

Clinical / Stastical: The medical review largely focused on an ISS of safety for cetirizine and pseudoephedrine from the PK studies and other studies both US and non-US. See Dr. Nicklas' review of 1/3/2001 for details. Essentially, no new safety issues – including cardiac safety – were identified. Interestingly, since we have no substantive controlled data for safety, the label will be based primarily on the experience with the individual components. Since Zyrtec is a sedating product, it is not clear from any data whether the combination product would be less sedating (as one might suspect). In any case, the labeling will contain the sedation reporting rate for cetirizine alone.

Note that although not overtly stated in Dr. Nicklas' review, all safety data (including updates) were reviewed and formed the basis of his approval recommendation.

Labeling: A few outstanding issues remain for the labeling of fairly minor consequence and be will a part of the action letter. By and large, the label is consistent with other such combination products and with the Zyrtec label. However, some of the changes in this label reflect the evolution of the division's thinking since Zyrtec was approved and will necessitate amending the approved label for the single ingredient Zyrtec product to achieve harmony between the two.

Conclusions: This product is clinically approvable. Once satisfactory labeling and the resolution of the remaining CMC issues are achieved, we can approve this product for twice-daily administration for the treatment of seasonal and perennial allergic rhinitis in patients where decongesting properties are needed.

MEDICAL TEAM LEADER'S MEMO

January 2001

APPEARS THIS WAY
ON ORIGINAL

MEDICAL TEAM LEADER MEMORANDUM

DATE: January 5, 2001

TO: NDA 21-150

FROM: Badrul A. Chowdhury, MD, PhD
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

SUBJECT: Secondary medical review of Zyrtec-D

CC: HFD-570: Meyer, Nicklas, Wakelkamp

Administrative

NDA 21-150 was submitted by Pfizer, Inc. on January 18, 2000. The extended user fee goal date for action on this application is January 19, 2001. The user fee goal date was extended because the sponsor submitted a major amendment during review of this application. Zyrtec-D is a combination of cetirizine, an H1 receptor antagonist, and pseudoephedrine, a sympathomimetic agent, for the symptomatic treatment of seasonal and perennial allergic rhinitis including nasal congestion, in patients 12 year and older. The proposed product contains 5 mg of cetrizine HCl in an immediate release form, and 120 mg of pseudoephedrine HCl in sustained-release form, in a bilayer tablet. The product is proposed for twice daily administration, giving a total daily dose of 10 mg of cetirizine and 240 mg of pseudoephedrine. The recommended doses of the Zyrtec-D do not exceed the recommended daily doses for the approved cetirizine or pseudoephedrine. Twice daily dosing of cetirizine is currently approved for Zyrtec syrup (5 mg cetrizine HCl/5 ml), at a 2.5 mg dose strength in children 2 to 5 years of age.

Chemistry and Manufacturing

Zyrtec-D bilayer tablet consists of two distinct layers. The first layer contains pseudoephedrine and other excepients in a matrix of release-controlling polymer containing hydroxypropyl methylcellulose. Pseudoephedrine is released by diffusion from and erosion of the hydroxypropyl methylcellulose matrix. The second layer contains cetirizine and other excepients. The formulation is to be manufactured and packaged by UCB S.A. in Belgium. The sponsor plans to submit an amendment to the NDA at a later date to add [redacted] The bilayer tablet formulation used in the pivotal pharmacokinetic studies is identical to the to-be-marketed formulation. The proposed in vitro dissolution specification and method, and the impurity specifications of the formulations are being evaluated and may need to be tightened.

Pharmacology and toxicology

No new preclinical studies were submitted with this application. There are no outstanding pharmacology and toxicology issues in this submission.

Clinical studies

The sponsor submitted two pivotal in vivo pharmacokinetic studies (143-006 and 143-007) addressing the comparative bioavailability between the proposed combination product and the co-administration of the individual active ingredients separately, and issues of possible interaction of the bilayer tablet with food. No efficacy and safety studies were done with the new formulation. Two other pharmacokinetic studies (9817 and 9831) were also done with the same formulation but are considered supportive because they did not contain a reference approved US product for comparison. To support safety of the product the sponsor submitted results from a total of 24 studies using a combination of cetirizine and pseudoephedrine. Biopharmaceutics reviewer Dr. Wakelkamp reviewed the pharmacokinetic studies and has concluded that (a) Zyrtec-D is bioequivalent to the co-administration of the separate active ingredients with regards to both cetirizine and pseudoephedrine, (b) twice-daily dosing of 5 mg cetirizine in adults is expected to be as safe and efficacious as is the once-daily dosing of 10 mg of cetirizine, and (c) Zyrtec-D can be administered with or without food. Medical reviewer Dr. Nicklas reviewed the safety database and has concluded that there is no unique safety concern with Zrytec-D.

In the subsequent section, the two pivotal pharmacokinetic studies and the safety database are briefly reviewed. Detailed review of the studies can be found in Dr. Wakelkamp's and Dr. Nicklas's —— reviews.

Protocol 143-007: Single and multiple dose comparative bioavailability study

This was an open label, multiple-dose, two-way, two-period cross-over study with a seven-day washout between treatment periods. The two treatments were a single dose of Zyrtec-D bilayer tablet (5 mg cetrizine/120 mg pseudoephedrine) followed by every 12 hour dosing for 7 days, or concomitant administration of a single dose of 5 mg Zyrtec tablet and 120 mg pseudoephedrine caplet (Sudafed LA 120 mg, Warner Lambert) followed by every 12 hour dosing for 7 days. The days of single morning dose were days 1, 9, 17, and 25; and days for every 12 hour dosing were days 3-8 for one period, and days 19-24 for the other period. The study enrolled 24 healthy subjects 20 to 41 years of age of both genders in a single center. All enrolled subjects completed the study.

The clinical part of the study was done at ——— , and analytical part was done at ——— Pfizer apparently noted some anomalies in the original analyses of the samples by ——— personnel, and instructed an initial re-analyses of a subset of samples, and subsequently complete re-analysis of all samples. Pfizer's original submission included a mixture of data from the two analyses. This raised a question on the reliability of the data. DSI conducted an audit of the ——— facilities and concluded that there were no clinical or analytical reasons to suggest that the original data were inaccurate. On our request, Pfizer later submitted results separately based on both the original and on the repeat assays. The resubmission was a major amendment to the NDA, and therefore the review clock was extended.

Plasma cetirizine and pseudoephedrine concentrations after single and multiple dosing following administration of the bilayer tablet and co-administration of the active ingredients, utilizing both the original and repeat analyses are presented in Table 1. The findings, based on either set of data, indicate that the Zyrtec-D bilayer tablet is bioequivalent to the co-administration of a cetirizine tablet and pseudoephedrine caplet, after single-dose administration and at steady-state. This study was not conducted under strict fasting conditions, which is generally preferred. This is not expected to influence the results, because the food effect would influence both treatment periods, and is likely to increase the hurdle of showing bioequivalence because of variability due to any potential food effect.

Table 1. Single and multiple dose comparative bioavailability results

	Bilayer Tablet*		Co-administration*	
	Original assay	**Repeat assay**	**Original assay**	**Repeat assay**
Cetirizine, single-dose				
C_{max} (ng/ml)	122 ± 28	144 ± 22	118 ± 22	113 ± 25
T_{max} (h)	2.0	2.0	2.0	2.0
AUC $_{(0\text{-tlast})}$ (h.ng/ml)	1154 ± 251	1208 ± 226	1174 ± 197	1230 ± 204
Cetirizine, multiple-dose				
C_{max} (ng/ml)	185 ± 27	178 ± 32	195 ± 32	195 ± 33
T_{max} (h)	2.0	2.0	2.0	2.0
AUC $_{(0\text{-}12\ hr)}$ (h.ng/ml)	1396 ± 221	1370 ± 204	1433 ± 217	1423 ± 218
Pseudoephedrine, single-dose				
C_{max} (ng/ml)	332 ± 66	309 ± 63	316 ± 92	284 ± 54
T_{max} (h)	4.0	4.0	5.0	4.0
AUC $_{(0\text{-tlast})}$ (h.ng/ml)	4055 ± 926	3924 ± 968	3949 ± 845	3719 ± 683
Pseudoephedrine, multiple-dose				
C_{max} (ng/ml)	543 ± 134	526 ± 144	536 ± 153	475 ± 100
T_{max} (h)	4.0	4.0	3.0	3.0
AUC $_{(0\text{-}12\ hr)}$ (h.ng/ml)	4961 ± 1269	4786 ± 1210	4816 ± 1090	4561 ± 1013
* Data presented as mean ± SD for all except T max. Tmax presented as mean and range				
Source: Biopharma review				

Protocol 143-006: Food effect study

This was an open, single dose, two-way, two-period cross-over study with a seven-day washout between treatment periods. The two treatment sequences were administration of a single dose of Zyrtec-D bilayer tablet under fasting condition, and after a standardized high fat content meal. The study enrolled 24 healthy subjects 18 to 43 years of age of both genders in a single center. All enrolled subjects completed the study. The study was conducted at [redacted]

Plasma cetirizine and pseudoephedrine concentrations under fasting and fed conditions after single dose of the Zyrtec-D bilayer tablet are presented in Table 2. Food had no significant effect on cetrizine AUC, but decreased the C_{max} and T_{max} significantly. These findings are consistent with the food effect data on the regular Zyrtec tablet. There was no significant food effect on pseudoephedrine AUC, C_{max} and T_{ma}. Regular Zyrtec tablet is labeled to be taken with or without food. Based on the similarity of food effect on cetirizine bioavailability between Zyrtec tablet and Zyrtec-D bilayer tablet, and the lack of food effect

on pseudoephedrine, the Zyrtec-D bilayer tablet may also be administered either with or without food.

Table 2. Food effect study results

	Fasting*	Fed*
Cetirizine, single-dose		
C_{max} (ng/ml)	153 ± 36	107 ± 28
T_{max} (h)	1.0 ± 0.8	2.8 ± 1.4
$AUC_{(0\text{-}tlast)}$ (h.ng/ml)	1360 ± 348	1253 ± 326
Pseudoephedrine, single-dose		
C_{max} (ng/ml)	325 ± 69	339 ± 78
T_{max} (h)	5.3 ± 1.7	5.3 ± 1.4
$AUC_{(0\text{-}tlast)}$ (h.ng/ml)	4837 ± 1249	4222 ± 1070
* Data presented as mean ± SD		
Source: Biopharma review		

Safety data:

The sponsor's integrated summary of safety includes data from 2161 patients in 24 studies conducted in US and Europe, including the two pharmacokinetic studies reviewed above. In four studies the bilayer formulation was used. In other studies, other combination formulations were used, or cetirizine and pseudoephedrine were administered concurrently. In studies using the bilayer formulation involving 80 patients who received the formulation, there were no deaths, serious adverse events, or safety related discontinuations. No clinically significant changes in vital signs, ECGs, and laboratory values were noted in this study population. Other studies also support safety of the combination of cetirizine and pseudoephedrine. The types of adverse events reported in the studies were those generally associated with administration of either cetirizine or pseudoephedrine.

Data integrity

[redacted] were audited by the DSI. These centers were involved in conducting the two pivotal pharmacokinetic studies. As discussed above, the reliability of study 143-007 was questioned because Pfizer analyzed the same samples more than once and initially submitted results based on a mixture of data from these analyses. DSI on a memo dated August 18, 2000, also questioned the reliability of the study for the same reason. However, DSI could not identify any reason to suggest that the original analyses or the repeat analyses were inaccurate. DSI also did not identify any other major irregularities. Therefore, the study was accepted and a conclusion based on one set of analyses was relied upon.

Pediatric plan

Pfizer requests waiver for patients under 12 years of age in accordance with 21 CFR 314.55(c)(3)(iii), because the fixed concentration of pseudoephedrine in this formulation is higher than the recommended dose for this age group, and there are existing treatments containing either cetirizine or pseudoephedrine down to the age of 2 years. Pfizer's request for waiver for this formulation is reasonable and it is recommended that the waiver be granted.

Recommendation

From a clinical standpoint, an APPROVABLE action is recommended for this NDA. The sponsor has satisfied the scientific and regulatory requirement for this combination product.

The product label is generally consistent with the current labeling of cetirizine and other second-generation antihistamine and pseudoephedrine combination products. There are two labeling issues that will need to be resolved. First, the sponsor is proposing Zyrtec-D as the proprietary name of the product. The name may potentially be confusing as the sponsor is also developing another cetirizine and pseudoephedrine combination product that will have once-a-day dosing recommendation. Further, the current Zyrtec-D tablet is proposed for twice daily dosing whereas original Zyrtec tablet is dosed once daily. The words "12" or "12 hour" should be made part of the proprietary name to avoid confusion with dosing frequency. Second, the clinical trials section of the label contains a new paragraph dealing with onset of action of cetirizine that is not present in the current labeling for cetirizine. Since this data was not part of this NDA, this paragraph should be deleted.

APPEARS THIS WAY
ON ORIGINAL

[redacted]

/s/

Badrul Chowdhury
1/5/01 08:57:38 AM
MEDICAL OFFICER
Medical Team Leader Memorandum

APPEARS THIS WAY
ON ORIGINAL

DSI REPORT FOR STUDY 143-007

August 24, 2000

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR DSI INVESTIGATION FOR STUDY 143-007

May 15, 2000

MEMORANDUM

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

DATE: May 12, 2000

TO: Director, Investigations Branch
Cincinnati District Office
6751 Steger Drive
Cincinnati, OH 45237-3097

and

Director, Investigations Branch
Dallas District Office
3310 Live Oak Street
Dallas, TX 75204

FROM: C.T. Viswanathan, Ph.D. CTV 5/15/00
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2000 **For Cause**, High Priority CDER **User Fee NDA**, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-150
DRUG: Zyrtec-D 12 Hour Extended Release Tablets
(Cetirizine HCl/Pseudoephedrine HCl)
SPONSOR: Pfizer Pharmaceuticals

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence study. **Due to the user fee deadline, the inspections must be completed by July 15, 2000.**

Protocol #: 143-007
Title: "A Comparative Single and Multiple Dose Bioavailability Study of Cetirizine (5 mg)/ Pseudoephedrine (120 mg) Bilayer Tablet BID Versus Co-administration of Cetirizine (5 mg) and Pseudoephedrine (120 mg) BID"

Clinical Site: _____

_____

Clinical Investigator: Roderick Malone, M.D.

This inspection is designated FOR CAUSE because one of the sub-investigators was unwilling to provide Part 54 financial disclosure information to the sponsor. Please check the batch numbers of both the test and the reference drug formulations used in the study with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site: [redacted]

e

Analytical Investigator: Melvin Tan

Instrumentation: HPLC-MS

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, Q.C., 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 may participate in the inspections.

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301) 827-5457

cc:
HFD-45/Lepay
HFD-48/Fujiwara/Skelly(3)/CF
HFD-570/Trout/NDA 21-150
HFD-870/Uppoor/Wakelkamp-Barnes
HFR-CE450/Grelle
HFR-SW1540/Martinez
Draft:MFS 5/12/00
Edits:JAO 5/12/00
DSI:5332; O:\BE\assigns\bio21150.doc