CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-150

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021150
Trade Name: ZYRTEC-D 12 HOUR(CETIRIZINE HCL 5MG/PSEU
Generic Name: CETIRIZINE HCL 5MG/PSEUDOEPHEDRINE 120MG
Supplement Number. 000 **Supplement Type**: N
Dosage Form:
Regulatory Action: AE **Action Date**: 1/17/01
COMIS Indication: SEASONAL ALLERGIC RHINITIS/PERENNIAL ALLERGIC RHINITIS WITH NASAL CONGESTION

Indication #1: ZYRTEC-D 12 HOUR should be administered when both the antihistaminic properties of cetirizine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.

ZYRTEC-D 12 HOUR is indicated for the relief of nasal and non nasal symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older.

Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: No new formulation is needed
Comments (if any) acceptable. 1/5/01: Proposed label mentions use for patients 12 and above, which is

Lower Range	Upper Range	Status	Date
0 years	11 years	Waived	8/12/01

Comments: A partial waiver for pediatric patients under the age of 12 years was requested and granted because the fixed concentration of pseudoephedrine in this dosage formulation (120 mg) is higher than the recommended dose for this age group.

12 years	Adult	Completed	8/12/01

Indication #2: ZYRTEC-D 12 HOUR should be administered when both the antihistaminic properties of cetirizine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.

ZYRTEC-D 12 HOUR is indicated for the relief of nasal and non nasal symptoms associated with perennial allergic rhinitis in adults and children 12 years of age and older.

Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: No new formulation is needed
Comments (if any) acceptable 1/5/01: Proposed label mentions use for patients 12 and above, which is

Lower Range	Upper Range	Status	Date
0 years	11 years	Waived	8/12/01

Comments: A partial waiver for pediatric patients under the age of 12 years was requested and granted because the fixed concentration of pseudoephedrine in this dosage formulation (120 mg) is higher than the recommended dose for this age group.

12 years	Adult	Completed	8/12/01

This page was last edited on 8/9/01

Signature /S/ [illegible]

8-10-01
Date

APPEARS THIS WAY
ON ORIGINAL

The request for a partial pediatric waiver is found to be acceptable (p 16, medical officer's review).

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR PARTIAL PEDIATRIC WAIVER

October 6, 1999

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7827 Fax 212 573 1563

DESK COPY

Pfizer Pharmaceuticals

Stephen Cristo
Director
Regulatory Affairs

October 6, 1999

Robert J. Meyer, M.D., Director
Division of Pulmonary and Allergy
Drug Products (HFD-570)
Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: [redacted] Cetirizine HCl/Pseudoephedrine HCl Extended Release Tablets
REQUEST FOR PARTIAL PEDIATRIC WAIVER FOR NDA 21-150

Dear Dr. Meyer,

Reference is made to Pfizer's [redacted] and to our imminent submission of a New Drug Application for a cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg Extended Release Tablet (assigned NDA 21-150). We anticipate filing this application in November 1999. Reference is also made to our meeting with the Agency on April 23, 1999 to discuss the clinical development program and chemistry, manufacturing and controls section for the subject NDA.

During this meeting, Pfizer presented a Pediatric Plan for this NDA. The NDA will support labeling for pediatric patients 12 years and older. A partial waiver in accordance with 21CFR314.55 was requested for pediatric patients under the age of 12 years because the fixed concentration of pseudoephedrine in this dosage formulation is higher than the recommended dose for this age group. The Agency advised they would take this proposal under consideration. In a telephone conversation in August with Ms. Gretchen Trout, Project Manager, Division of Pulmonary Drug Products, a request was made by FDA to formally submit Pfizer's Pediatric Plan to the Agency for evaluation.

Attached please find Pfizer's Pediatric Plan for NDA 21-150. Pfizer requests a waiver be granted in accordance with 21CFR314.55(c)(3)(iii) for pediatric patients under 12 years

of age and commits to appropriately addressing pediatric use in the labeling for this product. This Plan is consistent with pediatric labeling for prescription antihistamine/decongestant combination drug products currently available.

If you have any questions or comments, please contact me at (212) 573-7827.

Sincerely,

Stephen Cristo

Stephen Cristo

Attachment

Cc: R. Nicklas, MD, Medical Reviewer, FDA
G. Trout, Project Manager, FDA (3 copies)

APPEARS THIS WAY
ON ORIGINAL

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR	2. DATE OF SUBMISSION
PFIZER INC	10/6/99
3. ADDRESS *(Number, Street, City, State, and Zip Code)*	**4. TELEPHONE NUMBER** *(Include Area Code)*
235 EAST 42ND STREET NEW YORK, NY 10017-5755	(212) 573-2323
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*	**6. IND NUMBER** *(If previously assigned)*
Cetirizine/Pseudoephedrine Sustained Released Tablets	

7. INDICATION(S) *(Covered by this submission)*

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. *IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." the next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 043

11 THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☐ INITIAL WRITTEN REPORT
- ☐ FOLLOW UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

☒ OTHER Pediatric Waiver Request *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
	[illegible] 1999	DIVISION ASSIGNMENT:

PEDIATRIC USE SECTION 21CFR314.50(d)(7)

The NDA for the Zyrtec-D Bilayer tablet supports labeling for the pediatric population 12 years of age and older.

For pediatric patients less than 12 years of age, Pfizer requests a partial waiver pursuant to 21 CFR 314.55 (c)(3)(iii). In this pediatric population, the Zyrtec-D Bilayer tablet is likely to be unsafe due to the higher than recommended amount of pseudoephedrine contained in this fixed dose combination product. In addition, existing treatments containing either cetirizine or pseudoephedrine are adequately labeled and readily available for the pediatric population from 2 to less than 12 years of age. The information supporting this rationale and request for a partial waiver is presented below.

Cetirizine and pseudoephedrine are each indicated for use in adults and children two years of age and older. For both cetirizine and pseudoephedrine, the recommendations for dosage and administration vary with age. The dosing recommendations for cetirizine and pseudoephedrine are as follows:

Patient Population	Maximum Total Daily Dose (mg)	
	Cetirizine	Pseudoephedrine
Adult	10	240
≥ 12 Years of Age	10	240
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The Zyrtec-D Bilayer Tablet contains 5 mg cetirizine/120 mg pseudoephedrine, administered bid (10 mg cetirizine/240 mg pseudoephedrine per day). The cetirizine and pseudoephedrine contents of the Zyrtec-D Bilayer Tablet are consistent with the dosing guidelines for adults and pediatric patients greater than or equal to 12 years of age (adolescents). Therefore, this NDA addresses the adolescent segment of the pediatric population.

The Zyrtec-D Bilayer Tablet contains a fixed dose of 120 mg of pseudoephedrine in each extended release tablet. Administered as a single dose, this is higher than recommended for patients less than 12 years of age and is explicitly not recommended in the product labeling because this amount of pseudoephedrine is likely to be unsafe in this age group.

Cetirizine is available as a single ingredient syrup formulation for the treatment of seasonal and perennial allergic rhinitis in pediatric patients from 2 to less than 12 years of age. Pseudoephedrine is also available in multiple liquid and solid dosage forms for the relief of nasal congestion in this 2 to less than 12 year old patient population. Therefore, this pediatric population is currently served by existing treatments that are adequately labeled.

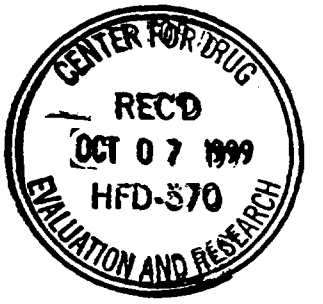
Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7827 Fax 212 573 1563

DESK COPY

Pfizer Pharmaceuticals

Stephen Cristo
Director
Regulatory Affairs

October 6, 1999



Robert J. Meyer, M.D., Director
Division of Pulmonary and Allergy
Drug Products (HFD-570)
Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: Cetirizine HCl/Pseudoephedrine HCl Extended Release Tablets
REQUEST FOR PARTIAL PEDIATRIC WAIVER FOR NDA 21-150

Dear Dr. Meyer,

Reference is made to Pfizer's [redacted] and to our imminent submission of a New Drug Application for a cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg Extended Release Tablet (assigned NDA 21-150). We anticipate filing this application in November 1999. Reference is also made to our meeting with the Agency on April 23, 1999 to discuss the clinical development program and chemistry, manufacturing and controls section for the subject NDA.

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If you have any questions or comments, please contact me at (212) 573-7827.

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Stephen Cristo

Stephen Cristo

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G. Trout, Project Manager, FDA (3 copies)

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ON ORIGINAL

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

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10/6/99

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NEW YORK, NY 10017-5755

4. TELEPHONE NUMBER *(Include Area Code)*
(212) 573-2323

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Cetirizine/Pseudoephedrine Sustained Released Tablets

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*

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FOR FDA USE ONLY

CDR/OBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
	RECEIVED OCT 7 1999	DIVISION ASSIGNMENT:

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Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7827 Fax 212 573 1563

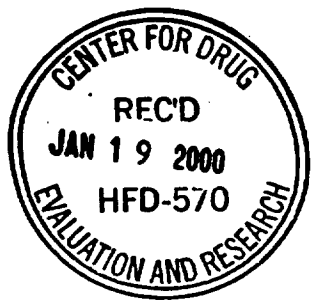
/S/

DESK COPY

Pfizer Pharmaceuticals

Stephen Cristo
Director
Regulatory Affairs

January 18, 2000



Robert J. Meyer, MD, Director
Division of Pulmonary Drug Products (HFD-155)
Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: NDA 21-150
Zyrtec-D™ 12 Hour (cetirizine HCl 5mg/pseudoephedrine HCl 120mg)
Extended Release Tablets

Dear Dr. Meyer:

Pursuant to 21CFR 314.50, Pfizer is herewith submitting a New Drug Application (NDA 21-150) for Zyrtec-D™ 12 Hour (cetirizine HCl 5mg/pseudoephedrine HCl 120mg) Extended Release Tablets. This combination product contains 5 mg of cetirizine HCl and 120 mg of pseudoephedrine HCl in an extended release tablet formulation. The proposed indications for use are for seasonal and perennial allergic rhinitis with nasal congestion for patients 12 years of age and older.

Reference is made to our meeting of April 23, 1999 ("Meeting") where the clinical development plan and proposed structure of the subject NDA were discussed. Industry Meeting Minutes were issued by the Agency (Pfizer, ——— Zyrtec-D Tablets, April 23, 1999 ———, and were supplemented by Pfizer in correspondence dated July 19, 1999. Reference is also made to Pfizer's NDA 19-835 for Zyrtec Tablets containing the active ingredient cetirizine HCl.

As was agreed with the Agency in our Meeting, the clinical development plan for this NDA is based on establishing the bioequivalence of the combination product to the co-administration of the individual ingredients. To support this clinical development plan, two pharmacokinetic studies were conducted. The first study, a single and multiple-dose study, compares the combination tablet to the co-administration of a commercial 5 mg Zyrtec (cetirizine HCl) tablet plus a standard pseudoephedrine product (Sudafed LA, 120 mg). The main objective of this study was to demonstrate bioequivalence with respect to AUC, Cmax and Cmin after a single

dose and at steady state. The second study was conducted to examine the effect of food on the combination product.

This NDA also contains supporting documentation from clinical studies evaluating the co-administration of cetirizine and pseudoephedrine as single ingredients and in various combination formulations. These studies were conducted by Pfizer or UCB Pharma, S.A., Belgium. Pfizer licenses cetirizine HCl from UCB Pharma and they have evaluated the combination of cetirizine and pseudoephedrine in numerous studies.

Based on the agreement reached with the Agency, the safety data presented in the integrated safety summary include deaths, serious adverse events and discontinuations due to medical reasons.

Submission Contents

As mentioned above, the effectiveness of Zyrtec-D™ 12 Hour Extended Release Tablets is based on establishing the bioequivalence of the combination product to the co-administration of the individual ingredients. The single/multiple dose bioequivalence study and the food effect study are contained in the Human Pharmacokinetics and Bioavailability Section of the NDA (Item 6).

A safety evaluation is provided in the Clinical Data Section (Item 8) as well as study reports for various clinical studies evaluating the co-administration of cetirizine and pseudoephedrine. Also provided in this section is Pfizer's Pediatric Plan.

The Nonclinical Pharmacology and Toxicology Section (Item 5) contains studies conducted by UCB Pharma.

A Chemistry, Manufacturing and Controls (CMC) Section is provided in this application (Item 4) describing the manufacturing and control process for the combination product. The manufacturing and packaging site specified in this application is UCB S.A., Pharma Sector, Belgium. [redacted] Based on 12 month stability data, a 24 month expiration dating period is proposed for the product. Finished product samples and applicable reference standards for validation studies are available and will be provided upon the Agency's request. As requested by the Agency in our Meeting, a review copy of the CMC section is also provided on CD-ROM. Please see details below describing the electronic submission.

Labeling

The Package Insert for Zyrtec-D™ 12 Hour is based on the existing labeling for Zyrtec (cetirizine HCl) Tablets 5 and 10 mg (NDA 19-835) and on labeling currently available for pseudoephedrine HCl products. The Precautions Section contains labeling in the Carcinogenesis, Mutagenesis and Impairment of Fertility, Pregnancy Category, and Nursing Mothers sections based on the information contained in the Nonclinical Pharmacology and Toxicology Section (Item 5).

An annotated Draft Package Insert is provided in the Application Summary (Item 3). A Draft Package Insert and draft component labeling (bottle, blister and carton labels) are provided in the Labeling Section (Item 2) of the Archive copy. Draft labeling is also provided in the chemistry, pharmacology, and clinical review sections of the application.

Electronic Submission

NDA 21-150 is submitted in total as a paper copy.

As requested by the Agency in our Meeting, a review copy of the CMC section is also provided on CD-ROM. This is a true copy of the paper CMC section. The CD-ROM has been scanned for viruses and is virus free. The scanning software used was McAfee Virus Scan Version 4.0.3.

Administrative Items

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this application, Pfizer certifies that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act (Item 16).

The user fee number obtained for this application is 3822 and the application fee was submitted according to standard procedure. An executed User Fee Cover Sheet (Form FDA 3397) is provided in this application.

Financial Disclosure information is contained in Item 19. There is one covered study contained in this NDA.

In accordance with 21CFR314.50(k)(3), a complete Field Copy of the Chemistry, Manufacturing and Controls (CMC) technical section [21CFR314.50(d)(1)] of this NDA has been provided to the FDA New York District Office in Brooklyn, NY under separate cover. Also included in this Field Copy is a copy of the application form and Application Summary section [21CFR314.50(c)] of the NDA (Item 3). Pfizer certifies that the Field Copy is a true copy of the CMC technical section as described in the archival and review copies of NDA 21-150.

If you have any questions regarding this New Drug Application, please contact me at (212) 573-7827.

Sincerely,

Stephen Cristo

Stephen Cristo

Desk Copy Cover letter and application summary:
Ms. G. Trout

APPEARS THIS WAY
ON ORIGINAL

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, 314 & 601)

Form Approved : OMB No. 0910-0338 ,
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pfizer	01/18/00
TELEPHONE NO. *(Include Area Code)* 212 - 573- 3414	FACSIMILE (FAX) Number *(Include Area Code)* (212) 573 - 1563
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 235 E 42nd St. New York, NY 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-150

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
cetirizine HCl 5mg/pseudoephedrine HCl 120mg	Zyrtec - D 12 Hour

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (±) [2-[4-((4 chlorophenyl)phenylmethyl)-1 piperazinyl] ethoxy] acetic acid dihydrochloride / (1S,2S)-2-methylamino-1-phenyl-1-propanol hydrochloride

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	5mg / 120mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Seasonal Allergic Rhinitis and Perennial Allergic Rhinitis with nasal congestion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
- ☒ NEW DRUG APPLICATION (21 CFR 314.50)
- ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
- ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
- ☐ 505 (b) (1)
- ☐ 505 (b) (2)
- ☐ 507

IF AN ANDA, OR AADA, 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 A PENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ SUPAC SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

REASON FOR SUBMISSION
New Drug Application

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

NUMBER OF VOLUMES SUBMITTED 45

THIS APPLICATION IS
- ☒ PAPER
- ☐ PAPER AND ELECTRONIC
- ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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.

Please see attached document

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

see attached sheet for references

FORM FDA 356h - Attachment

Provide location of all manufacturing, packaging and control sites for drug substance and drug product. 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.

Cetirizine HCl/Pseudoephedrine HCl 5/120mg bi-layer tablet

Name/Address of Site	Contact/ Telephone	Registration Number	DMF Number	Manufacturing, Packaging or Testing Responsibilities	Date of Inspection Readiness
UCB S.A., Chemin du Foriest, 1420 Braine-l' Alleud, Belgium	Cromlin Christian 32 2 386 3200	36998		Drug Substance Manufacturing Drug Substance Packaging Drug Substance Stability Testing	2/01/00
					2/01/00
UCB S.A., Chemin du Foriest, 1420 Braine-l' Alleud, Belgium	Cromlin Christian 32 2 386 3200	36998		Drug Product Manufacturing Drug Product Packaging Drug Product Stability Testing	2/01/00
Pfizer Inc Eastern Point Rd Groton, CT 06340-5146	Kerry Hertenstein (860) 441-3204	1211022		Drug Product Stability Testing	2/01/00
Pfizer Inc 630 Flushing Ave Brooklyn, NY 11026	Maria Guazzaroni (718) 780-6486	2410924-NYK		Drug Product Packaging Drug Product Approval Testing	2/01/00

APPEARS THIS WAY
ON ORIGINAL

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

1 page

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

APPLICANT'S NAME AND ADDRESS

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

3. PRODUCT NAME: Zyrtec D 12 Hour (cetirizine HCL 5mg/ pseudoephedrine HCL 120 mg) extended release tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? 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 _____ (APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER *(Include Area Code)*

(212) 572-2323

5. USER FEE I.D. NUMBER

3822

6. LICENSE NUMBER / NDA NUMBER

N021150

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 *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Stephen Cristo FOR RITA WITTICH	Director, Group Leader Regulatory Affairs	01/18/00

ZYRTEC-D™ 12 HOUR
(cetirizine HCl 5mg/pseudoephedrine HCl 120mg)
Extended Release Tablets
NDA-21-150

FINANCIAL DISCLOSURE COVER NOTE

Section 19.1

Reference in made to a teleconference between Pfizer and the Food and Drug Administration, Regulatory Policy, of August 6, 1999 and correspondence sent to the Division of Pulmonary Drug Products dated August 18, 1999 (attached). During the teleconference, it was established that there is a single covered study for this NDA, and Pfizer's cut-off date of May 25, 1999 for data to be included in the NDA would serve as the Date of Completion for the covered study. The covered study is Protocol 143-007, entitled:

> A Comparative Single and Multiple Dose Bioavailability Study of Cetirizine (5mg)/Pseudoephedrine (120mg) Bilayer Tablet BID Versus Co-administration of Cetirizine (5mg) and Pseudoephedrine (120mg)

Information regarding Pfizer Efforts to Eliminate Bias in this study are described in NDA Section 19.2.

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7827 Fax 212 573 1564

Pfizer Pharmaceuticals

August 18, 1999

Stephen Cristo
Director
Regulatory Affairs

Robert J. Meyer, M.D., Acting Director
Division of Pulmonary Drug Products (HFD-155)
Document Control Room 17B-20
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: ——— Cetirizine HCl/Pseudoephedrine HCl Extended Release Tablets
Financial Disclosure for NDA 21-150

Dear Dr. Meyer,

Reference is made to Pfizer ——— and to our imminent submission of a New Drug Application for a cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg Extended Release Tablet (assigned NDA 21-150). We anticipate filing this application in November 1999.

Reference is also made to a telephone conference held on August 6, 1999 with Ms. Linda Carter, Regulatory Policy, Food and Drug Administration (FDA) and Dr. Stephen Sasson, Senior Director Regulatory Affairs and myself, Stephen Cristo, Director Regulatory Affairs, of Pfizer. We discussed the new Financial Disclosure regulations (21 CFR 54) as they pertain to the subject NDA.

The subject NDA will contain one covered study. It was established in this conversation that Pfizer's cut-off date of May 25, 1999 for data to be included in the NDA would serve as the Date of Completion for the covered study. Financial Disclosure information for this study through May 25, 1999 will be included in the NDA. It was also agreed that any significant changes in investigator financial status requiring reporting pursuant to the Financial Disclosure regulation would be reported to the FDA until May 25, 2000, one year after the Date of Completion.

If you have any questions or comments, please contact me at (212) 573-7827.

Sincerely,

Stephen Cristo

Stephen Cristo

Cc: L. Carter, Regulatory Policy, FDA
R. Nicklas, MD, Medical Reviewer, FDA
G. Trout, Project Manager, FDA
S. Sasson, Ph.D., Pfizer

Steps Taken to Minimize the Potential for Bias

Protocol # 143-007

Study 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

During the course of processing, analyzing and reporting data from clinical trials the Pfizer Biometrics Department applies many procedures designed to ensure that errors are eliminated. Some of these procedures and their results may indicate aberrant data.

Most of our trials are randomized double blind studies conducted under strict scientific principles. Our standard operating procedure is to follow the current ICH Good Clinical Practices. And, we always check the current FDA listing:

"DISQUALIFIED/RESTRICTED/ASSURANCES LIST
FOR CLINICAL INVESTIGATORS"
www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm.

Other processes we use to minimize potential bias are as follows:

[Those used for this study have been checked.]

Used	Technique
✔	Randomized
	Blinded
✔	Frequent monitor individual sites
✔	Individual site audits
	Analyses
	Stratified efficacy data by site or included site in the analysis
	Stratified safety data by site or included site in the analyses
	Investigated distribution of base line values by site
	Tables and Displays
	Produced tables of safety data by site
	Produced tables of efficacy data by site
	Produced tables of base line values by site
	Other

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

NDA-21-150

FORM FDA 3454 (3/99)

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Applicable check box is marked.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Investigators (See attached.)

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Investigators (See attached.)

NAME JOHN J. REGAN	TITLE DIRECTOR - MEDICAL FINANCE
FIRM / ORGANIZATION PFIZER INC.	
SIGNATURE John J. Regan	DATE 12-1-99

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

PPLICANT'S NAME AND ADDRESS

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

3. PRODUCT NAME: Zyrtec D 12 Hour (cetirizine HCL 5mg/ pseudoephedrine HCL 120 mg) extended release tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? 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 _____ (APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER *(Include Area Code)*

(212) 572-2323

5. USER FEE I.D. NUMBER

3822

6. LICENSE NUMBER / NDA NUMBER

N021150

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 *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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200 Independence Avenue, S.W.
Washington, DC 20201

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Stephen Cristo FOR RITA WITTICH	Director, Group Leader Regulatory Affairs	01/18/00

FORM FDA 3397 (5/98)

ORIGINAL

Regulatory Affairs
Pfizer Inc
235 East 42nd Street 150/7/5
New York, NY 10017
Tel 212 733 6295 Fax 212 857 3558
Email tomasj@pfizer.com

N... DL

ORIG AMENDMENT
ORIGINAL

Pfizer Pharmaceuticals Group

John Tomaszewski
Director
Worldwide Regulatory Strategy

July 26, 2001

Robert J. Meyer, MD, Director
Division of Pulmonary and Allergy Drug Products (HFD-570)
Document Control Room 10B-03
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

RE: NDA 21-150
Zyrtec-D 12 Hour™ (cetirizine hydrochloride 5mg and pseudoephedrine hydrochloride 120 mg)
Extended Release Tablets

Dear Dr. Meyer:

Please refer to the above referenced NDA submitted on January 18, 2000; FDA's Discipline Review Letter dated July 28, 2000; Pfizer's responses to that letter dated October 11 and November 21, 2000; FDA's "approvable letter" dated January 17, 2001, Pfizer's response to the "approvable" letter dated February 12, 2001, and Pfizer's submission dated March 27, 2001 responding to FDA's labeling comments.

Per Dr. Ostroff's request of July 24, 2001 this submission includes a complete copy of all labeling, including the Package Insert, revised per the agency's comments communicated via fax from Craig Ostroff dated July 20, 2001.

This submission consists of the following:

1) Package Insert

The Package Insert (PI) has been revised to reflect all comments made by the agency in its 7/20/01 fax. The PI is identical in wording and content to FDA's 7/20/01 version with the following exception (which is made for clarifying the specific cross- reference):

Page 5, **CONTRAINDICATIONS** section, second paragraph, line 4: The parenthetical statement "(see **Drug Interactions** section)" has been changed to read "(see **PRECAUTIONS, Drug Interactions** section)". The revised wording accurately reflects the specific section to which one should be referred.

Aside from this one substantive change several minor editorial adjustments have been made to correct typographical and grammatical errors. These are as follows:

• Page 2, "**CLINICAL PHARMACOLOGY**" section, "**Pharmacokinetics**" heading, "**Absorption**" sub-heading, paragraph 2, line 1: the hyphen between the words "single" and "dose" was removed.

• Page 2, "**CLINICAL PHARMACOLOGY**" section, "**Pharmacokinetics**" heading, "**Absorption**" sub-heading, paragraph 3, line 2: a hyphen was added between the words "steady" and "state".

• Page 2, "**CLINICAL PHARMACOLOGY**" section, **Pharmacokinetics**" heading, **Metabolism**" sub-heading, paragraph 2, line1: the words "per cent" was changed to "percent".

• Page 3, "**CLINICAL PHARMACOLOGY**" section, **Pharmacokinetics**" heading, "**Elimination**" sub-heading, paragraph 2, line 3: hyphens were added after "2 " and "3". The corrected version now reads "... 2- to 3- fold higher..."

• Page 4, "**Pharmacodynamics**" sub-heading, paragraph 1, line 1: the word "ages" was changed to "aged". This change was made to be consistent with other sections of the PI where age ranges are defined, e.g., same section paragraph 3, line 1.

• Page 4, "**Pharmacodynamics**" sub-heading, paragraph 1, line 3: a hyphen was added after the number "10", revised copy reads "... 10-mg dose..."

• Page 9, "**ADVERSE REACTIONS**" section, "**Cetirizine Hydrochloride**" heading, "**Body as a Whole**" sub-heading, paragraph 3, line 1: the word "potential" was changed to "potentially". This was changed to be consistent with the base Zyrtec Tablets PI.

• Page 9, "**ADVERSE REACTIONS**" section, "**Pseudoephedrine hydrochloride**" heading: the word "hydrochloride" has been capitalized and now reads "Hydrochloride".

• Page 10, "**DOSAGE AND ADMINISTRATION**" section, paragraph 2, line 3: the period was moved to the end of the parenthetical statement that concludes the paragraph.

• Page 10, "**HOW SUPPLIED**" section, paragraph 1, line 5: a hyphen was added after the word "child", revised copy reads "child-resistant".

Additionally, on a global basis all parenthetical references to other section of the PI have been bolded and all mentions of the trade name "Zyrtec-D 12 Hour" have been made all capital letters. These changes were made to be consistent with PI formatting convention for all Pfizer products.

2) 2 Count Sample Blister Foil – identical to 3/27/2001 submission

3) 100 Count Bottle Label – identical to 3/27/2001 submission

4) 14 Count Bottle Label – identical to 3/27/2001 submission

5) Sample Bin – identical to 3/27/2001 submission.

Thank you for your consideration of this submission. Please call me directly with any questions you may have.

Sincerely,

John Tomaszewski

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. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA #21-150

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pfizer	07/26/01
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
212-573-3414	(212) 857-3558
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 235 E 42nd Street, New York, NY 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-150

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
cetirizine HCl 5mg/pseudoephedrine HCl 120mg	**Zyrtec - D 12 Hour**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
(±) [2-[4-((4 chlorophenyl)phenylmethyl)-1 piperazinyl] ethoxy] acetic acid dihydrochloride / (1S,2S)-2-methylamino-1-phenyl-1-propanol hydrochloride	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	**5mg / 120mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE: Seasonal Allergic Rhinitis and Perennial Allergic Rhinitis with nasal congestion

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (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 A PENDING 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
Response to FDA request

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

NUMBER OF VOLUMES SUBMITTED _____ 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.

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

Number of Pages Redacted 103

❖❖❖

Draft Labeling
(not releasable

13. PATENT AND EXCLUSIVITY INFORMATION

1.	Active Ingredients:	(+/-)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride/[S-(R*,R*)]-alpha-[1-(methylamino)ethyl]-benzene methanol hydrochloride.
2.	Strength:	5 mg cetirizine HCL/120 mg pseudoephedrine HCL
3.	Trade Name:	Zyrtec – D
4.	Dosage Form/Route of Administration:	Tablets/Oral
5.	Application Firm Name:	Pfizer Inc.
6.	NDA Number:	21-150
7.	Exclusivity Period:	Not Applicable
8.	Applicable Patent Numbers And Expiration Dates:	4,525,358 June 25, 2007

TIME SENSITIVE PATENT INFORMATION
PURSUANT TO 21 C.F.R. § 314.53
for
NDA No. 21-150 – ZYRTEC® D

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZYRTEC® D
Active Ingredient(s):	cetirizine dihydrochloride and pseudoephedrine hydrochloride
Strength(s):	5.00 mg and 120.00 mg, respectively
Dosage Form:	film-coated bilayer tablet (aqueous coating)

A. Information for Each Individual Patent

U.S. Patent Number: 4,525,358

Expiration Date: June 25, 2007

Type of Patent:

1. Drug Substance (Active Ingredient) √ Y ___ N
2. Drug Product (Composition/Formulation) √ Y ___ N
3. Method of Use √ Y ___ N

The above-identified patent claims method(s) of use; accordingly, the specific method(s) of use for which approval is being sought that are covered by said patent are the following: seasonal/perennial allergic rhinitis.

Name of Patent Owner: UCB Pharmaceuticals, Inc., Dover, Delaware.

B. Declaration Statement for Patents Having Composition/Formulation or Method of Use Claims

The undersigned declares that the above-stated United States Patent Number 4,525,358 covers the composition, formulation and/or method of use of the drug product cetirizine and pseudoephedrine. This product is the subject of this application for which approval is being sought.

Signed: _____

Raymond M. Speer, Esq.

Date: June 17, 1999

Title: Senior Patent Counsel

Telephone Number: 212-733-4606

EXCLUSIVITY SUMMARY for NDA # 21-150 SUPPL # _____

Trade Name Zyrtec-D 12 Hour Extended Release Tablets
Generic Name Cetirizine HCL 5 mg and Pseudoephedrine HCl 120 mg
Applicant Name Pfizer HFD-570
Approval Date August 10, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /___/ NO / X /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-835	Zyrtec Tablets
NDA # 20-346	Zyrtec Syrup
NDA # 13-483	Drixoral / Disophrol
NDA # 18-191	Afrinol
NDA # 18-397	Chlor-Trimeton
NDA # 18-506	Trinalin
NDA # 19-279	Dimetane-DX
NDA # 19-428	Pseudoephedrine HCl, Chlorpheniramine Maleate
NDA # 19-453	Drixoral Plus
NDA # 19-670	Claritin-D
NDA # 19-672	Efidac 24 Pseudoephedrine HCl / Brompheniramine Maleate
NDA # 19-771	Advil Cold and Sinus
NDA # 19-806	SEMPREX-D
NDA # 19-899	Sine-Aid IB
NDA # 20-021	Efidac 24 Pseudoephedrine HCl
NDA # 20-470	Claritin-D 24 Hour
NDA # 20-786	Allegra-D
NDA # 21-076	Aleve Cold and Sinus
NDA # 21-082	Tavist Allergy/ Sinus/Headache
NDA # 21-128	Children's Motrin Cold

NDA #	72-758	Pseudoephedrine HCl, Triprolidine HCl
NDA #	73-585	Sudafed 12 Hour
NDA #	74-567	Ibuprohm Cold and Sinus
NDA #	75-153	Pseudoephedrine HCl
NDA #	88-193	Pseudoephedrine HCl, Triprolidine HCl
NDA #	88-515	Trilitron
NDA #	88-578	Triprolidine HCl, Pseudoephedrine HCl
NDA #	88-602	Corphed
NDA #	88-704	Triacin-C
NDA #	88-722	Bromanate DM
NDA #	88-811	Myphetane DX
NDA #	88-833	Triprolidine HCl, Pseudoephedrine HCl, Codeine Phosphate
NDA #	89-116	Brompheril
NDA #	89-681	Bromfed-DM

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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ON ORIGINAL

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to

support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new"

to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

_____ 8-10-01

Signature of Preparer Date

Title: Regulatory Management Officer

Signature of Office or Division Director

Date

CC:
Archival NDA 21-150
HFD-570/Division File
HFD-570/Ostroff
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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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/

Marianne Mann
8/13/01 12:09:18 PM
Dr. Mann [Acting Director] is signing for Dr. Meyer in his absence.

APPEARS THIS WAY
ON ORIGINAL

16. DEBARMENT CERTIFICATION

Pfizer Inc hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Financial Disclosure is discussed on p 15 of the Medical Officer's review.

APPEARS THIS WAY
ON ORIGINAL

ZYRTEC-D™ 12 HOUR
(cetirizine HCl 5mg/pseudoephedrine HCl 120mg)
Extended Release Tablets
NDA-21-150

FINANCIAL DISCLOSURE COVER NOTE

Section 19.1

Reference in made to a teleconference between Pfizer and the Food and Drug Administration, Regulatory Policy, of August 6, 1999 and correspondence sent to the Division of Pulmonary Drug Products dated August 18, 1999 (attached). During the teleconference, it was established that there is a single covered study for this NDA, and Pfizer's cut-off date of May 25, 1999 for data to be included in the NDA would serve as the Date of Completion for the covered study. The covered study is Protocol 143-007, entitled:

> A Comparative Single and Multiple Dose Bioavailability Study of Cetirizine (5mg)/Pseudoephedrine (120mg) Bilayer Tablet BID Versus Co-administration of Cetirizine (5mg) and Pseudoephedrine (120mg)

Information regarding Pfizer Efforts to Eliminate Bias in this study are described in NDA Section 19.2.

Pfizer has examined its financial data regarding significant payments of other sorts made to investigators in this study and equity information as provided by the investigators, as defined in 21 CFR 54.2, and has determined that there were no such significant payments or equity to report. The details of the reporting of this information is provided in the enclosed **Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators** (NDA Section 19.3). As there is nothing to report, form 3455 has not been included.

APPEARS THIS WAY
ON ORIGINAL

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7827 Fax 212 573 1564

Pfizer Pharmaceuticals

August 18, 1999

Stephen Cristo
Director
Regulatory Affairs

Robert J. Meyer, M.D., Acting Director
Division of Pulmonary Drug Products (HFD-155)
Document Control Room 17B-20
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: [redacted] Cetirizine HCl/Pseudoephedrine HCl Extended Release Tablets
Financial Disclosure for NDA 21-150

Dear Dr. Meyer,

Reference is made to Pfizer's [redacted] and to our imminent submission of a New Drug Application for a cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg Extended Release Tablet (assigned NDA 21-150). We anticipate filing this application in November 1999.

Reference is also made to a telephone conference held on August 6, 1999 with Ms. Linda Carter, Regulatory Policy, Food and Drug Administration (FDA) and Dr. Stephen Sasson, Senior Director Regulatory Affairs and myself, Stephen Cristo, Director Regulatory Affairs, of Pfizer. We discussed the new Financial Disclosure regulations (21 CFR 54) as they pertain to the subject NDA.

The subject NDA will contain one covered study. It was established in this conversation that Pfizer's cut-off date of May 25, 1999 for data to be included in the NDA would serve as the Date of Completion for the covered study. Financial Disclosure information for this study through May 25, 1999 will be included in the NDA. It was also agreed that any significant changes in investigator financial status requiring reporting pursuant to the Financial Disclosure regulation would be reported to the FDA until May 25, 2000, one year after the Date of Completion.

If you have any questions or comments, please contact me at (212) 573-7827.

Sincerely,

Stephen Cristo

Stephen Cristo

Cc: L. Carter, Regulatory Policy, FDA
R. Nicklas, MD, Medical Reviewer, FDA
G. Trout, Project Manager, FDA
S. Sasson, Ph.D., Pfizer

Steps Taken to Minimize the Potential for Bias

Protocol # 143-007

Study 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

During the course of processing, analyzing and reporting data from clinical trials the Pfizer Biometrics Department applies many procedures designed to ensure that errors are eliminated. Some of these procedures and their results may indicate aberrant data.

Most of our trials are randomized double blind studies conducted under strict scientific principles. Our standard operating procedure is to follow the current ICH Good Clinical Practices. And, we always check the current FDA listing:

"DISQUALIFIED/RESTRICTED/ASSURANCES LIST
FOR CLINICAL INVESTIGATORS"
www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm.

Other processes we use to minimize potential bias are as follows:

[Those used for this study have been checked.]

Used	Technique
✔	Randomized
	Blinded
✔	Frequent monitor individual sites
✔	Individual site audits
	Analyses
	Stratified efficacy data by site or included site in the analysis
	Stratified safety data by site or included site in the analyses
	Investigated distribution of base line values by site
	Tables and Displays
	Produced tables of safety data by site
	Produced tables of efficacy data by site
	Produced tables of base line values by site
	Other

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

NDA-21-150

FORM FDA 3454 (3/99)

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Applicable check box is marked.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Investigators (See attached.)

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Investigators (See attached.)

NAME	TITLE
JOHN J. REGAN	DIRECTOR - MEDICAL FINANCE
FIRM / ORGANIZATION: PFIZER INC.	
SIGNATURE: John J. Regan	DATE: 12-1-99

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages Redacted 2

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Confidential,
Commercial Information