CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-155

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER: 20-346 Rx-to-OTC Supp.

NAME OF APPLICANT / NDA HOLDER: Pfizer Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): ZYRTEC

ACTIVE INGREDIENT(S)	STRENGTH(S)
cetirizine HCl	5mg/5ml

DOSAGE FORM: Syrup

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number: 4525358	b. Issue Date of Patent: 6/25/1985	c. Expiration Date of Patent: 6/25/2007
d. Name of Patent Owner: UCB Inc. Legal Department	Address *(of Patent Owner)*: 1950 Lake Park Drive	
	City/State: Smyrna, GA	
	ZIP Code: 30080	FAX Number *(if available)*
	Telephone Number: (770) 970-7500	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☑ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

FORM FDA 3542a (7/03)

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b)?	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ?	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ?	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ?	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☑ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 23-31	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* The "Indications and Usage" section of the proposed labeling describes seasonal and perennial allergic rhinitis symptoms as well as chronic urticaria, all of which indications are covered by the cited claims that encompass achieving an antiallergic (claim 23) or antihistaminic (claims 23-27) effect and treating allergic symptoms (claims 28-31), by administration of the product for which approval is being sought.		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Bruce A. Pokras	11/29/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Bruce A. Pokras	
Address 201 Tabor Road	City/State Morris Plains, NJ
ZIP Code 07950	Telephone Number (973) 385-5399
FAX Number *(if available)* (973) 385-7330	E-Mail Address *(if available)* bruce.a.pokras@pfizer.com

EXCLUSIVITY SUMMARY

NDA # 22-155 SUPPL # HFD # 560

Trade Name Children's Zyrtec syrup

Generic Name cetirizine HCl

Applicant Name McNeil (agent for Pfizer)

Approval Date, If Known November 16, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 ☐

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 ☒ 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 ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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:

Studies in-house from the original Rx application, NDA 20-346 were re-reviewed for this OTC NDA

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☐

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

Investigations SAR-1, SAR-2, SAR-3, SAR-4, L-0362, L-0364, PAR-1, PAR-3, PAR-4, L-0352, URT-2, URT-3 from NDA, 20-346, McNeil Rx Zyrtec syrup

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 ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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"):

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 ☐ ! NO ☐

Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! 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:

==========

Name of person completing form: Elaine Abraham
Title: RPM
Date: 11/16/07

Name of Office/Division Director signing form: Andrea Leonard-Segal
Title: Director, DNCE

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Andrea Segal
11/16/2007 12:38:38 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-155 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: January 16, 2007 **PDUFA Goal Date:** November 16, 2007

HFD ONP/DNCE **Trade and generic names/dosage form:** Zyrtec (cetirizine HCl 1 mg/mL) syrup

Applicant: McNeil (Agent for Pfizer) **Therapeutic Class:** Antihistamine

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☐ **Yes. Please proceed to the next question.**
- X **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): _____

Indication #1: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Elaine Abraham
11/30/2007 01:49:10 PM

20.0 OTHER

20.1 PEDIATRIC ASSESSMENT

Pediatric Use Information: No waiver is requested

This application provides for the over-the-counter use of Zyrtec Chewable Tablets (cetirizine HCl) for relief of symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older and for the relief of symptoms of chronic idiopathic urticaria in adults and children 6 years of age and older. The age range proposed for the over-the-counter product is more restrictive than that of the current prescription product which allows dosing for perennial allergic rhinitis and chronic idiopathic urticaria for adults and children 6 months of age and older and for seasonal allergic rhinitis in adults and children 2 years of age and older. Accordingly, no new pediatric studies are included in this application and no pediatric waiver is requested.

20. OTHER

20.1 Pediatric Assessment

Pediatric Use Information: No waiver is requested

This application provides for the over-the-counter use of Zyrtec Tablets (cetirizine HCl) for relief of symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older and for the relief of symptoms of chronic idiopathic urticaria in adults and children 6 years of age and older. The age range proposed for the over-the-counter product is more restrictive than that of the current prescription product which allows dosing for perennial allergic rhinitis and chronic idiopathic urticaria for adults and children 6 months of age and older and for seasonal allergic rhinitis in adults and children 2 years of age and older. Accordingly, no new pediatric studies are included in this Supplemental New Drug Application and no pediatric waiver is requested.

20.0 OTHER

20.1 PEDIATRIC ASSESSMENT

Pediatric Use Information: No waiver is requested

This application provides for the over-the-counter use of Zyrtec Syrup (cetirizine HCl) for relief of symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older and for the relief of symptoms of chronic idiopathic urticaria in adults and children 6 years of age and older. The age range proposed for the over-the-counter product is more restrictive than that of the current prescription product which allows dosing for perennial allergic rhinitis and chronic idiopathic urticaria for adults and children 6 months of age and older and for seasonal allergic rhinitis in adults and children 2 years of age and older. Accordingly, no new pediatric studies are included in this application and no pediatric waiver is requested.

NDA 22-155: Zyrtec Syrup (cetirizine HCl 1 mg/ mL)
Over-the-Counter (OTC) Use
Item 9 -Safety Update

ITEM 16. DEBARMENT CERTIFICATION [FD&C Act 306(K)(1)]

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

Hans Knapp
Director, Global Regulatory Affairs
McNeil Consumer Healthcare

May 10, 2007
May 10, 2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration **CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS**	**Form Approved: OMB No. 0910-0396** **Expiration Date: April 30, 2009** **NDA Number : 169-835, 20-346**
TO BE COMPLETED BY APPLICANT	

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) 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).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) 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).

Clinical 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 (attach list of names to this form) 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 (attach list of names) 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.

Clinical investigators (See attached.)

NAME John J. Regan	TITLE Sr. Director-Medical Finance
FIRM/ORGANIZATION Pfizer Inc	
SIGNATURE John J. Regan	DATE November 8, 2006

Paperwork Reduction Act Statement

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

FORM FDA 3454 (4/06)

44 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

OTC Drug Labeling Review

Office of Nonprescription Products

Center for Drug Evaluation and Research • Food and Drug Administration

NDA 2nd Addendum Labeling Review

1. **NDA # 19-835; SE6 (022) - Submission Date: 11/06/07** **Review Date : 11/13/07**
2. **NDA # 21-621; SE6 (005) - " " : 11/07/07**
3. **NDA # 22-155; N (000) - " " : 11/08/07**

Applicant: McNeil Consumer Healthcare Inc.
201 Tabor Road
Morris Plains, New Jersey 07950

Applicant's Representative: Hans Knapp
Director, Global Regulatory Affairs
215-273-7000; 973-385-7250

Drug:
1. **Zyrtec Tablets (cetirizine HCl 5 mg and 10 mg)** (NDA #19835)
2. **Zyrtec Chewable Tablets (Grape flavor) (cetirizine HCl 5 mg and 10 mg)** (NDA #21621)
3. **Zyrtec Syrup (cetirizine HCl 1 mg / 1 mL)** (NDA #22155)

Pharmacological Category: Antihistamine

Submitted: Revised Draft labeling with annotated Drug Facts specifications for the following:

NDA # 19-835

10 mg tablet	**5 mg tablet**
Tablet blister: 1-count (common to hives relief & allergy)	Tablet blister: 1-count (common to hives relief & allergy)
Shrink wrap bottle label: 30-count (allergy)	Clamshell: 14-count (allergy)
Bottle induction seal	
Clamshell: 5-count (allergy)	
Clamshell: 14-count (allergy)	
Clamshell: 30-count (allergy)	
Clamshell: 45-count (allergy)	
Bottle: 45- count	
Clamshell: 75-count (allergy)	
Blister pouch: 1-count (allergy)	
Pouch dispenser: 50-count (allergy)	

NDA # 21-621

10 mg chewable tablet	**5 mg chewable tablet**
Blister card: 6-count (common to hives relief and allergy)	Blister card: 5-count (common to hives relief and allergy)
Carton: 12-count (allergy)	Carton: 5-count (allergy)
Carton: 24-count (allergy)	
Clamshell: 24-count (allergy)	

NDA # 22-155 (Syrup)

Bottle label: 4 fl oz (allergy) – 2 yrs and older	Sample tray: 12 bottles at 15 ml each (allergy)
Carton: 4 fl oz (allergy) – 2 yrs and older	Dosing cup schematic – "Hives"
Twin pack retail carton (allergy)	Dosing cup schematic – "Allergy"
Bottle label: 15 ml (allergy) - sample	Bottle neckband

Background:

The sponsor submitted revised draft labeling for all Zyrtec Tablets, Chewable Tablets (5 and 10 mg), and Syrup "Allergy" SKUs on November 6, 2007, November 7, 2007 and November 11, 2207, respectively. These revised draft labeling are in response to the Agency's Information Request Letter dated October 25, 2007. In the November 11, 2007, Zyrtec Syrup submission, the sponsor submitted schematics for separate "allergy" and "hives" dosing cups.

In each of the submissions noted above, the sponsor certified that no changes have been made to the Drug Facts label since that submitted in its previous October 9, 2007 (Tablets), October 15, 2007 (Chewable Tablets), and October 11, 2007 (Syrup) submissions.

Reviewer Comments:

1. The sponsor has revised the labeling for all Zyrtec "Allergy" SKUs (Tablets, Chewable Tablets, and Syrup) and the 1-count Tablet and Chewable blister card labeling (5 and 10 mg) as requested in the Agency's Information Request Letter dated October 25, 2007. The labeling is acceptable.

2. The sponsor has revised the 15 mL sample bottle dispenser carton by adding the complete Drug Facts labeling to the carton. The sponsor states that the content of the Drug Facts label on the dispenser carton did not change from that submitted on October 11, 2007. The labeling is acceptable.

3. In each submission noted above, the sponsor has certified that it has not made any changes to the Drug Facts content since that submitted in its previous October 9, 2007 (Tablets), October 15, 2007 (Chewable Tablets), and October 11, 2007 (Syrup) submissions. This is acceptable.

4. **Dosing Cup**: The sponsor has resubmitted separate dosing cups for the allergy and hives products. Each dosing cup is unique to the product in which it is packaged and its labeling includes the brand name, product descriptor (i.e., "Allergy" or "Hives Relief"), and only the dosing gradations that are consistent with the dosing instruction for that product. The labeling of these cups is acceptable.

Recommendations:

1. An approval letter can be issued to the sponsor requesting final printed labeling for the following:
   a. Zyrtec Tablets "Allergy":
      i. Clamshell: 5-, 14-, 30-, 45-, and 75-count (10 mg)
      ii. Clamshell: 14-count (5 mg)
      iii. 30- and 45-count bottle (10 mg)
      iv 1-count individual blister card (5 and 10 mg)
      v. 1-count blister pouch (10 mg)
      vi. 50-count Pouch Dispenser (10 mg)

      These final printed labeling must be identical to the labeling submitted on November 6, 2007.

   b. Zyrtec Chewable Tablets "Allergy":
      i. 5-count blister card (5 mg)
      ii. 6-count blister card (10 mg)
      iii. 5-count carton (5 mg)
      iv. 12- and 24-count carton (10 mg)
      v. 24-count clamshell (10 mg)

      These final printed labeling must be identical to the labeling submitted on November 7, 2007.

c. Zyrtec Syrup "Allergy":
   i. 4 fl. oz. bottle
   ii. 4 fl. oz. carton
   iii. Twin pack retail carton
   iv. 15 mL bottle (sample)
   v. Sample tray (12-count sample bottle)
   vi. "Allergy" dosing cup
   vii. "Hives" dosing cup

These final printed labeling must be identical to the labeling submitted on November 8, 2007.

2. Inform the sponsor that the flag "NEW!", wherever it appears in the labeling of all acceptable SKUs, needs to be deleted 6 months after introduction into the OTC market.

Cazemiro R. Martin
IDS: Reg. Review Chemist

Concur: Matthew Holman, Ph.D.
Team Leader

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

/s/

Cazemiro Martin
11/13/2007 02:00:39 PM
INTERDISCIPLINARY

Matthew Holman
11/13/2007 02:03:46 PM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-835/S-022
NDA 21-621/S-005
NDA 22-155

INFORMATION REQUEST LETTER

McNeil Consumer Healthcare
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
U.S. Agent for Pfizer, Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl 5 and 10 mg) tablets [NDA 19-835/S-022] and Zyrtec (cetirizine HCl 5 and 10 mg) chewable tablets [NDA 21-621/S-005], and your January 15, 2007 new drug application for Zyrtec (cetirizine HCl 1 mg/mL) syrup [NDA 22-155].

We also refer to your following submissions dated October 9, 2007 (NDA 19-835), October 15, 2007 (NDA 21-621), and October 11, 2007 (NDA 22-155).

We have reviewed the labeling section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The draft labeling submitted for all Zyrtec "Hives Relief" cartons and bottles SKUs (tablets, chewable tablets, and syrup) is acceptable. See comments on "Hives Relief" dosing cup below.

2. Revise and resubmit draft labeling as follows (i.e., SKUs, blister cards, and dosing cups):

   a. ***Zyrtec Syrup "Allergy" 15 ml sample bottle SKU:*** The labeling for this SKU is not in compliance with 21 CFR 201.66, and therefore is not acceptable. Either the 15 ml immediate bottle label or the sample tray must include the full *Drug Facts* labeling as set forth in 21 CFR 201.66. If you elect to include the full Drug Facts on the immediate container label, the title "*Drug Facts*" must be included to introduce this information. The title "*Drug Facts (continued)*" must be added on top of each subsequent panel containing such information.

If you elect to include the full *Drug Facts* information (i.e., in compliance with 21 CFR 201.66) on the *sample tray*, the current labeling on the *15 ml sample bottle* would be acceptable.

b. ***Zyrtec Syrup 4 fl. oz. SKU draft carton labeling***: Delete the text "*Also try these other Children's ZYRTEC products*" and the graphics referring to other Zyrtec products (i.e., Zyrtec Syrup for "*Hives Relief*" and Zyrtec Chewable Tablets for "*Allergy*") that appear on the side panel, and wherever such similar multiple drug product promotions appear in the labeling of any of the other Zyrtec products. To help avoid possible consumer medication error, labeling of any Zyrtec SKU should exclusively focus the consumer's attention on the safe and effective use of the particular drug product and not on any of your other Zyrtec products.

c. ***All Zyrtec "Allergy" SKUs*** [*pouches, immediate containers, cartons, and clamshells*]: For labeling accuracy and clarity, the following revisions are necessary:

1) Revise the phrase "Indoor & Outdoor" [redacted] wherever it appears in the labeling (italic is added for emphasis only).
2) Relocate the revised phrase "*Indoor & Outdoor Allergies*" on the PDP and side panels, wherever it appears in the labeling, to appear either above the product's proprietary name, or beneath the "statement of identity" section. This revised phrase must be distant from the promotional phrase "*24 hour Relief of • Sneezing • Runny Nose • Itchy, Watery Eyes • Itchy Throat or Nose* ".
3) Revise the phrase "24 hour" that is not in direct proximity to the listed symptoms [redacted] wherever it appears in the labeling.

d. **Blister Cards** [*5 mg and 10 mg*]: Increase the prominence and distinguish the two different blister card dosage strengths available (i.e., "5 mg" and "10 mg") by using a different type color or other print feature, wherever this information appears in the labeling.

e. **Zyrtec Syrup Dosing Cup** [*"Allergy" and "Hives Relief" SKUs*]: To avoid possible medication error, provide a separate dosing cup for each SKU indication with the following revised labeling:

- Include only the measuring gradations on the dosing cup that are consistent with the dosing instruction in the *Directions* section of the respective label.
- Include the indication descriptor of the product (i.e., "Allergy" or "Hives Relief") on the respective dosing cup.

3. You do not need to resubmit" Drug Facts" annotated specifications if you certify that there are no changes to these specifications, except for the Zyrtec Syrup "Allergy" 15 ml sample bottle SKU or sample tray depending on your choice of revision (see point 2a above).

4. Your revised labeling should include only the changes described above and no additional changes.

In addition to sending the revised labeling of these SKUs to your NDA, you should email or fax a copy to Elaine Abraham. These should be received by us at least one week prior to the action due date, that is by November 9, 2007, in order to allow time for our review.

If you have any questions, call Elaine Abraham, Regulatory Project Manager, at 301-796-0843.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
10/25/2007 02:25:21 PM

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Addendum Labeling Review

1. **NDA # 19-835; SE6 (022) - Submission Date: 10/09/07** **Review Date : 10/24/07**
2. **NDA # 21-621; SE6 (005) - " " : 10/15/07**
3. **NDA # 22-155; N (000) - " " : 10/11/07**

Applicant: McNeil Consumer Healthcare Inc.
201 Tabor Road
Morris Plains, New Jersey 07950

Applicant's Representative: Hans Knapp
Director, Global Regulatory Affairs
215-273-7000; 973-385-7250

Drug:
1. **Zyrtec Tablets (cetirizine HCl 5 mg and 10 mg)** *(NDA #19835)*
2. **Zyrtec Chewable Tablets (Grape flavor) (cetirizine HCl 5 mg and 10 mg)** (NDA #21621)
3. **Zyrtec Syrup (cetirizine HCl 1 mg / 1 mL)** (NDA #22155)

Pharmacological Category: Antihistamine

Submitted: Revised Draft labeling with annotated Drug Facts specifications for the following:

NDA # 19-835

10 mg tablet	**5 mg tablet**
Tablet blister: 1-count (common to hives relief & allergy)	Tablet blister: 1-count (common to hives relief & allergy)
Shrink wrap bottle label: 30-count (allergy)	Carton: 14-count (hives relief)
Bottle induction seal	Clamshell: 14-count (allergy)
Carton: 14-count (hives relief)	
Clamshell: 5-count (allergy)	
Clamshell: 14-count (allergy)	
Clamshell: 30-count (allergy)	
Clamshell: 45-count (allergy)	
Bottle: 45- count	
Clamshell: 75-count (allergy)	
Blister pouch: 1-count (allergy)	
Pouch dispenser: 50-count (allergy)	

NDA # 21-621

10 mg chewable tablet	**5 mg chewable tablet**
Blister card: 6-count (common to hives relief and allergy)	Blister card: 5-count (common to hives relief and allergy)
Carton: 12-count (hives relief)	Carton: 15-count (hives relief)
Carton: 12-count (allergy)	Carton: 5-count (allergy)
Carton: 24-count (allergy)	
Clamshell: 24-count (allergy)	

NDA # 22-155

Bottle label: 4 fl oz (hives relief) – 6 yrs and older	Bottle label: 15 ml (allergy) - sample
Bottle label: 4 fl oz (allergy) – 2 yrs and older	Sample tray: 12 bottles at 15 ml each (allergy)
Carton: 4 fl oz (allergy) – 2 yrs and older	Dosing cup schematic
Carton: 4 fl oz (hives relief) – 6 yrs and older	Bottle neckband
Twin pack retail carton (allergy)	

Background:

In this submission, the sponsor has submitted revised draft labeling for Zyrtec Tablets and Chewable Tablets (5 and 10 mg), and Zyrtec Syrup for "Allergy" and "Hives Relief" indications. The revised labeling is based on the Agency's Information Request Letter dated August 31, 2007, which requested changes to the sponsor's proposed labeling submitted on July, 10, 2007. The sponsor has also indicated that it has decided to not include a package insert with any of the Zyrtec products, including the proposed package inserts for the Zyrtec Syrup ("Allergy" and "Hives Relief") and the Zyrtec Chewable Tablets ("allergy") products.

At the request of the sponsor, a telephone conference call on September 12, 2007 was held during which the Agency discussed the proposed labeling changes included in its Information Request Letter. During the discussion, the Agency agreed that the statement "*A 5 mg product may be appropriate for less severe symptoms*" did not need to be bolded, as it had previously proposed. The Agency further mentioned that it would provide further comment at a later date regarding the statement in the Drug Facts "***Uses***" section

Additional new SKUs with draft labeling included in this submission are as follows:

- Zyrtec Tablets – 10 mg (Allergy): 45-count immediate container and clamshell
- Zyrtec Chewable Tablets – 10 mg (Allergy): 24-count carton and clamshell
- Zyrtec Syrup (Allergy): Twin Pack carton (two 4 oz bottles; grape syrup)

Reviewer Comments:

1. The sponsor indicates that the brand name for thee products is "Zyrtec" with the descriptors "Allergy" or "Hives Relief" to distinguish the two different indications. According to the sponsor, the descriptors are located adjacent to the brand name "Zyrtec" and are different in color to distinguish the "Allergy" and "Hives Relief" products.

   This is acceptable.

2. **Zyrtec "Hives Relief"** (all carton and bottle SKU labeling): The revised draft labeling included in these submissions are acceptable.

3. **Drug Facts labeling**: The sponsor has revised the Drug Facts section of all Zyrtec SKUs as indicated in the Agency Information Request letter, dated August 31, 2007. These revisions are acceptable.

4. **Drug Facts Annotated Specifications**:

   The Drug Facts annotated specifications for all Zyrtec SKUs are acceptable, **except** for the following:

   - ***Zyrtec Syrup "Allergy" 15 ml sample bottle***:
     The labeling for this SKU is not in compliance with 21 CFR 201.66, and therefore is not acceptable. Either the 15 ml immediate bottle label or the sample tray must include the full *Drug Facts* labeling as set forth in 21 CFR 201.66. If the sponsor elects to include the full Drug Facts on the immediate container label, it must include the title "*Drug Facts*" to introduce this information and add the title "*Drug Facts (continued)*" on top of each subsequent panel containing such information.

     If the sponsor elects to include the full *Drug Facts* information (i.e., in compliance with 21 CFR 201.66) on the *sample tray*, the current labeling on the *15 ml sample bottle* would be acceptable.

5. **Zyrtec "Allergy" Syrup 4 fl. oz. [*carton labeling*]**:
The labeling for this SKU is not acceptable. The sponsor has added to the side panel [redacted] Labeling of any SKU should exclusively focus the consumer's attention on the safe and effective use of the particular OTC drug product and not on any other product, regardless of brand name or therapeutic category. Accordingly, to help avoid possible medical error, the sponsor needs to delete the text "*Also try these other Children's Zyrtec products*" and the graphics referring to these other Zyrtec drug products in the labeling of this SKU, and wherever such similar multiple drug product promotions appear in the labeling of any of its other Zyrtec products.

6. [redacted]

b. For labeling accuracy and clarity, the sponsor needs to revise the labeling [*for All "Allergy" SKUs including pouches, immediate containers, cartons, and clamshells*] as follows:

1. Revise the phrase "Indoor & Outdoor" to read [redacted] wherever it appears in the labeling.
2. Relocate the revised phrase [redacted] on the PDP and side panels, wherever it appears in the labeling, to appear either above the product's proprietary name, or beneath the "statement of identity" section. This revised phrase must be distant from the promotional phrase "*24 hour Relief of • Sneezing • Runny Nose • Itchy, Watery Eyes • Itchy Throat or Nose* ".
3. Revise the phrase "24 hour" that is not in direct proximity to the listed symptoms to read "*24 hour symptom relief*", wherever it appears in the labeling.

7. **Blister Card [*5 mg and 10 mg*]** -- *Tablets and Chewable Tablets*: The labeling is unacceptable. To avoid possible medication error, the sponsor must increase the prominence and distinguish the two different blister card dosage strengths available (i.e., "5 mg" and "10 mg") by using a different type color or other print feature, wherever this information appears in the labeling."

8. **Zyrtec Syrup Dosing Cup** ["*Allergy" and "Hives Relief*" SKUs]: A common dosing cup for the syrup "Allergy" and "Hives Relief" SKUs is not acceptable. To avoid possible medication error, the sponsor must provide a separate dosing cup for each SKU indication with the following revised labeling:
   - Include no other measuring gradations but the gradations that are consistent with the dosing instruction in the *Directions* section of the label.
   - Include the indication descriptor of the product (i.e., "*Allergy*" or "*Hives Relief*") on the respective dosing cup.

9. **Package insert**: The sponsor indicated in this submission that it has decided to not include a package insert with any of the Zyrtec products, including the previously proposed package inserts. This is acceptable.

Recommendations:

1. An approval letter can be issued to the sponsor requesting final printed labeling for the following:
   - All Zyrtec "Hives Relief" cartons and bottle SKUs [Tablets, Chewable Tablets, and Syrup]

These final printed labeling must be identical to the labeling submitted in this submission.

2. Inform the sponsor to further revise the labeling as follows (i.e., SKUs, blister cards, and dosing cups) and resubmit revised labeling for our review and comment prior to the Action Due date. The sponsor does not need to resubmit "Drug Facts" annotated specifications if it certifies that there are no changes to these specifications.

a. ***Zyrtec Syrup "Allergy" 15 ml sample bottle SKU:***
The labeling for this SKU is not in compliance with 21 CFR 201.66, and therefore is not acceptable. Either the 15 ml immediate bottle label or the sample tray must include the full *Drug Facts* labeling as set forth in 21 CFR 201.66. If the sponsor elects to include the full Drug Facts on the immediate container label, it must include the title "*Drug Facts*" to introduce this information and add the title "*Drug Facts (continued)*" on top of each subsequent panel containing such information.

If the sponsor elects to include the full *Drug Facts* information (i.e., in compliance with 21 CFR 201.66) on the *sample tray*, the current labeling on the *15 ml sample bottle* would be acceptable.

b. ***Zyrtec Syrup 4 fl. oz. SKU draft carton labeling***: Delete the text "*Also try these other Children's ZYRTEC products*" and the graphics referring to other Zyrtec products (i.e., Zyrtec Syrup for "*Hives Relief*" and Zyrtec Chewable Tablets for "*Allergy*") that appear on the side panel, and wherever such similar multiple drug product promotions appear in the labeling of any of its other Zyrtec products. To help avoid possible consumer medical error, labeling of any Zyrtec SKU should exclusively focus the consumer's attention on the safe and effective use of the particular drug product and not on any of the sponsor's other Zyrtec products.

c. ***All Zyrtec "Allergy" SKUs*** [*pouches, immediate containers, cartons, and clamshells*]: For labeling accuracy and clarity, the following revisions are necessary:

1. Revise the phrase "Indoor & Outdoor" [redacted] . wherever it appears in the labeling.
2. Relocate the revised phrase [redacted] on the PDP and side panels, wherever it appears in the labeling, to appear either above the product's proprietary name, or beneath the "statement of identity" section. This revised phrase must be distant from the promotional phrase "*24 hour Relief of • Sneezing • Runny Nose • Itchy, Watery Eyes • Itchy Throat or Nose* ".
3. Revise the phrase "24 hour" that is not in direct proximity to the listed symptoms to read "*24 hour symptom relief*", wherever it appears in the labeling.

d. **Blister Cards** [*5 mg and 10 mg*]: Increase the prominence and distinguish the two different blister card dosage strengths available (i.e., "5 mg" and "10 mg") by using a different type color or other print feature, wherever this information appears in the labeling."

e. **Zyrtec Syrup Dosing Cup** [*"Allergy" and "Hives Relief" SKUs*]: To avoid possible medication error, provide a separate dosing cup for each SKU indication with the following revised labeling:
- Include only the measuring gradations on the dosing cup that are consistent with the dosing instruction in the *Directions* section of the respective label.
- Include the indication descriptor of the product (i.e., "Allergy" or "Hives Relief") on the respective dosing cup.

4. Inform the sponsor that the flag "NEW!", wherever it appears in the labeling of all acceptable SKUs, needs to be deleted 6 months after introduction into the OTC market.

Cazemiro R. Martin
IDS: Reg. Review Chemist

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
10/24/2007 01:12:32 PM
INTERDISCIPLINARY

Marina Chang
10/24/2007 02:19:46 PM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-155

INFORMATION REQUEST LETTER

McNeil Consumer Healthcare
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl) Syrup 1 mg/mL.

We also refer to your submissions dated March 2, May 4, May 15, and June 25, 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the procedures of the test methods for [redacted] **Dosing Cups** release tests stated in your amendment dated May 4, 2007, p-6.

2. Verify that the dose accuracy tests described in your amendment dated June 25, 2007 will be performed for each incoming batch of [redacted] **Dosing Cups.**

3. Provide information to support the change in stability protocols stated in your amendment dated May 15, 2007. Otherwise, due to the primary container change, revise the stability plan to be consistent with the existing stability plan approved under NDA 20-346, described in your amendment dated March 2, 2007.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Moo-Jhong Rhee
9/12/2007 10:01:58 AM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-835/S-022
NDA 21-621/S-005
NDA 22-155

INFORMATION REQUEST LETTER

McNeil Consumer Healthcare
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
U.S. Agent for Pfizer, Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl 5 and 10 mg) tablets [NDA 19-835/S-022] and Zyrtec (cetirizine HCl 5 and 10 mg) chewable tablets [NDA 21-621/S-005], and your January 15, 2007 new drug application for Zyrtec (cetirizine HCl 1 mg/mL) syrup [NDA 22-155].

We also refer to your following submissions dated July 10, 2007 (NDA 19-835), July 16, 2007 (NDA 21-621), and July 19, 2007 (NDA 22-155).

We are reviewing the labeling section of your submission and have the following preliminary comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Revise and submit revised labels with annotated Drug Facts specifications for our review as follows:

   A. **General Comment: [All submitted Zyrtec SKUs, 1-count blister card, and package inserts]** The proprietary name for these Zyrtec products is not clear. You need to inform us of the intended proprietary name for the various Zyrtec dosage forms intended as relief from symptoms associated with allergy and hives. If you intend to distinguish the two different labeling indications by using the flags "Allergy" and "Hives Relief", the flags must be relocated to appear adjacent to the word "Zyrtec" and preferably in the same color as the brand name "Zyrtec".

   B. **PDP:**
      i. Tablet/Chewable Tablets: Delete the promotional flags "*Full Prescription Strength*" and "*Full Prescription Strength...Now OTC!*" These flags must be deleted or revised to read "*Original Prescription Strength*", wherever they appear in the labeling of these dosage forms.
      ii. Syrup: Delete the promotional flags "*Full Prescription Strength*" and "*Full Prescription Strength...Now OTC!*" wherever they appear in the labeling of any Zyrtec Syrup. These

flags should not appear on any syrup SKU because there continues to be a prescription product for the population group 6 months to 2 years of age.

iii. Chewable Tablet – 5 mg Allergy SKU

a. Delete the flag "*2 yrs. & older*". This flag is not accurate because the dosage direction for this OTC SKU does not provide for an initial dose of 2.5 mg for children 2 years to under 6 years of age as noted in the prescription labeling.

b. Delete the graphic of a child under 6 years of age. This graphic is misleading because this proposed OTC drug product should be intended only for children 6 years and older. See comment B. iii. a. above.

C. **Other Panel (All submitted SKUs):** Provide for lot number and expiration date.

D. **Drug Facts**: For all SKUs, revise as per attached prototype "Drug Facts" labeling.

2. **Consumer Information Leaflet:** Revise the Consumer Information Leaflet (CIL) as follows:

A. Under the heading "*What is Zyrtec?*", delete the phrase in the last sentence of the first paragraph "*so you can go anywhere life takes you*". This phrase is unrelated to the intended purpose of the drug product.

B. Under the heading "*Who Should Not Take Zyrtec?*", revise the information in this section as follows:

i. Delete the bulleted phrase "*If you are pregnant or breast-feeding, ask your doctor or pharmacist before using Zyrtec*".

ii.

C. For the Hives CIL only: In addition to the previous CIL comments, under the heading "*When Should Zyrtec be Taken*?", revise the second bulleted statement

3. We recommend the following:

A. The established name of the active ingredient, dosage form, dosage strengths, and pharmacological category need to appear more prominently. We strongly recommended that the following:

i. Change the color contrast lettering of the *statement of identity* (established name of the active ingredient, dosage form, and pharmacological category) and increase the print size of this statement, wherever this information appears in the labeling. This revision will make the information easier to read and understand and help to avoid medication error.

ii. Increase the prominence and distinguish the two different dosage strengths available (i.e., "5 mg" and "10 mg") by using a different type color or other print feature wherever this information appears in the labeling.

B. Consumer Information Leaflet (CIL):

i. under the heading "*SAFETY PROFILE: Caution*", revise the bulleted data entries in plain language to make such information more consumer friendly.

ii. under the heading "*DIRECTIONS FOR USE*", include the dosage directions for the specific SKU (allergy or hives) in a table format.

iii. Consider providing a CIL for all the Zyrtec SKUs as is provided for the Syrup (Allergy & Hives) and the Chewable Tablets (Allergy) SKUs.

4. We remind you to submit 24-count chewable tablet carton label and the 45-count tablet immediate container and clamshell draft labels for our review as you stated in your August 9, 2007 email.

If you have any questions, call Elaine Abraham, Regulatory Project Manager, at 301-796-0843.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure:
- Prototype A: Drug Facts labeling - *Allergy* [tablet/chewable tablet]
- Prototype B: Drug Facts labeling - *Hives* [tablet/chewable tablet]
- Prototype C: Drug Facts labeling - *Allergy* [syrup]
- Prototype D: Drug Facts labeling - *Hives* [syrup]

7 Page(s) Withheld

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0 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

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/s/

Leah Christl
8/31/2007 02:33:40 PM

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Supplement Labeling Review

1. **NDA # 19-835; SE6 (022) - Submission Date: 1/15/07 & 7/11/07** **Review Date : 8/27/07**
2. **NDA # 21-621; SE6 (005) - " " : " & 7/16/07**
3. **NDA # 22-155; N (000) - " " : " & 7/19/07**

Applicant: McNeil Consumer Healthcare Inc.
201 Tabor Road
Morris Plains, New Jersey 07950

Applicant's Representative: Robert Kohler
Senior Director, Global Regulatory Affairs
215-273-7000; 973-385-7250

Drug:
1. Zyrtec Tablets (cetirizine HCl 5 mg and 10 mg) *(NDA #19835)*
2. Zyrtec Chewable Tablets (cetirizine HCl 5 mg and 10 mg) *(NDA #21621)*
3. Zyrtec Syrup (cetirizine HCl 1 mg / 1 mL) *(NDA #22155)*

Pharmacological Category: Antihistamine

Submitted: Draft labeling for the following:

NDA # 19-835

10 mg tablet	**5 mg tablet**
Tablet blister - 1 count (common to hives relief & allergy)	Tablet blister -1 count (common to hives relief & allergy)
Shrink wrap bottle label – 30 count (allergy)	Carton- 14 count (hives relief)
Bottle induction seal	Clamshell - 14 count (allergy)
Carton – 14 count (hives relief)	
Clamshell – 14 count (allergy)	
Clamshell – 30 count (allergy)	
Clamshell – 75 count (allergy) **[note: 45-count immediate container and clamshell draft labels not included]**	
Blister pouch – 1 count (allergy)	
Pouch dispenser – 50 count (allergy)	

NDA # 21-621

10 mg chewable tablet	**5 mg chewable tablet**
Blister card - 6 count (common to hives relief and allergy)	Blister card - 5 count (common to hives relief and allergy)
Carton – 12 count (hives relief)	Carton – 15 count (hives relief)
Carton – 12 count (allergy)	Carton – 5 count (allergy)
[note: 24-count (allergy) draft carton label not included]	Package Insert: 5mg & 10 mg SKUs - Allergy

NDA # 22-155

Bottle label – 4 fl oz (hives relief) – 6 yrs and older	Bottle label – 15 ml (allergy) - sample
Bottle label – 4 fl oz (allergy) – 2 yrs and older	Sample tray – 12 bottles at 15 ml each (allergy)
Carton – 4 fl oz (allergy) – 2 yrs and older	Package insert Allergy
Carton – 4 fl oz (hives relief) – 6 yrs and older	Package insert Hives

Background:

As a prescription drug product, Zyrtec was approved as follows:

- Zyrtec Tablets on December 8, 1995
- Zyrtec Chewable Tablets on March 16, 2004
- Zyrtec Syrup on September 27, 1996

The sponsor is requesting Rx-to-OTC switch for the above mentioned Zyrtec (antihistamine) drug products. These proposed OTC Zyrtec products will be indicated for the temporary relief of symptoms due to hay fever or other upper respiratory allergies for adults and children down to 2 years of age for syrup and down to 6 years of age for tablets and chewable tablets. As separately labeled, these products will also be indicated for relief of itching due to hives (urticaria) for adults and children down to 6 years of age.

In a 74 day filing letter dated March 23, 2007, the agency identified the following labeling issues:

1. Based on our preliminary review of the labeling, the package insert and all other labeling included should specifically address in its entirety either allergy relief information or hive relief information. No SKU labeling should include both allergy and hives information.
2. Based on the proposed OTC dosing for the 5 mg and 10 mg (Allergy and Hives) formulations (tablets and chewable tablets), we noted that the consumer does not have the option of using the lowest effective dose as is available in the prescription dosing information. We asked the sponsor to address this dosing discrepancy.
3.

Subsequent to the issuance of the 74-day filing letter, the sponsor requested a telephone conference call with the agency to discuss FDA's concerns about the dosing information provided in the proposed labeling of the OTC Zyrtec 5 mg and 10 mg SKUs (tablet and chewable tablet dosage forms). During the teleconference call on May 22, 2007, the sponsor argued the appropriateness of the proposed dosing information for these SKUs. At the conclusion of the telephone conference call, FDA expressed its continued concerns regarding this labeling/dosing issue and asked the sponsor to reconsider the concerns FDA expressed in its 74 day filing letter. (See Record of Teleconference dated May 23, 2007.) The issue of a single universal dosing device for the Zyrtec syrup was also discussed.

The sponsor resubmitted revised labeling for Zyrtec tablet, chewable tablets, and syrup on July 11, 2007, July 16, 2007, and July 19, 2007, respectively. The sponsor indicated that the Zyrtec Chewable Tablets (5 and 10 mg) for "Allergy" and the Zyrtec Syrup for "Allergy" and "Hives" will include a package insert. Further, the sponsor proposed that for the syrup SKU, only a dosing cup with gradations equal to the dosing amounts described in the direction section of the labeling would be provided.

Not included in the resubmission of draft labeling are the following:

- Chewable Tablets 10 mg (Allergy): 24-count draft carton labeling
- Tablet 10 mg (Allergy): 45-count draft immediate container (bottle) and clamshell labels.

Reviewer Comments:

1. All submitted SKUs including 1-count blister card and package inserts:

A. General comments:

(i) The proprietary name for these Zyrtec products is not clear. The sponsor needs to inform the agency of the intended proprietary name for the various Zyrtec dosage forms intended as relief from symptoms associated with allergy and hives. If the sponsor intends to distinguish the two different labeling indications by using the flags "Allergy" and "Hives Relief", the flags must be relocated to appear adjacent to the word "Zyrtec" and preferably in the same color as the brand name "Zyrtec".

(ii) The established name of the active ingredient, dosage form, and pharmacological category need to appear more prominently. It is strongly recommended that the sponsor:

a. change the color contrast lettering and print size of established name of the active ingredient, dosage form, and pharmacological category, wherever this information appears in the labeling. This revision will make the information easier to read and understand and help to avoid medication error.

b. increase the prominence and distinguish the two different dosage strengths available (i.e., "5 mg" and "10 mg") by using a different type color or other print feature wherever this information appears in the labeling.

B. PDP:

(i) Promotional Flags:

a. *Tablet/Chewable Tablet*: The flags "*Full Prescription Strength*" and "*Full Prescription Strength...Now OTC!*" are not acceptable. These flags must be deleted or revised to read , wherever they appear in the labeling of these dosage forms.

b. *Syrup*: The flags "*Full Prescription Strength*" and "*Full Prescription Strength...Now OTC!*" are not acceptable and must be deleted wherever they appear in the labeling of any Zyrtec Syrup labeling. There continues to be a prescription product to treat allergy symptoms for the population group 6 months to 2 years of age.

c. *Chewable Tablet – 5 mg Allergy* SKU

1. The flag "*2 yrs. & older*" must be deleted. This flag is not accurate because the dosage direction for this SKU does not provide an initial dose of 2.5 mg for children 2 to under 6 years of age as noted in the Rx labeling.
2. The graphic of a child under 6 years of age must be deleted. The graphic is misleading because this proposed OTC drug product should only be intended only for children 6 years and older. See comment B(i)(c)(1) above.

d. The flag "*New*" wherever it appears in the labeling of the Zyrtec products must be deleted after 6 months in the OTC market place.

C. Other Panel (All submitted SKUs): Provision for lot number and expiration date is needed.

D. Drug Facts:

(i) Zyrtec Syrup only: After the heading "*Active ingredients (in each 5 mL)*", the sponsor needs to revise the parenthetical expression to read for accuracy and labeling consistency.

(ii) Uses: The second bulleted statement under this heading should be revised to read as follows:

This revision helps avoid consumer confusion concerning the relief of symptoms associated with other allergens not mentioned in this section.

(iii) Add the following Drug Facts Warning subheading and subsequent text: '. This information must be included to alert consumers of the potential for drowsiness when these medications are taken concurrently.

(iv) The **"If pregnant or breast-feeding"** warning must be revised to reflect the Rx labeling that recommends nursing mothers not use this product. The **"If pregnant or breast-feeding"** warning is revised as follows: "

(v) **Directions**:

a. *[5 mg tablets and chewable tablets; and syrup]*:

1. Need to add the population group "adults 65 years and over" followed by the text:

The Rx labeling recommends that elderly adults should take 5 mg once a day.

2. [*5 mg chewable tablet* only]: The sponsor needs to revise the directions for "*children 2 to 6 years of age: 1 chewable tablet once daily*" to read as follows:

The dosage strength of this product does not provide an initial 2.5 mg dose for children 2 to under 6 years of age as instructed in the Rx labeling directions.

b. [*10 mg tablets/chewable tablets* (allergy and hives SKUs)]:

1. The bulleted statement "*A 5 mg product may be appropriate for less severe symptoms*" that appears immediately after the heading "*Directions*" should be relocated to appear in bold type in the dosing directions section corresponding to the population group "adults and children 6 years and over"
2. The sponsor needs to add the population group followed by the text . The Rx labeling recommends that elderly adults should not take more than 5 mg once a day.

c. *[Syrup SKU - Dosing Cup]:* To provide clearer understanding of the use of the dosing cup, the sponsor needs to relocate and revised the phrase "*use dosing cup provided*" as follow:

1. revise the phrase "use dosing cup provided" to read " ".
2. relocate the revised the phrase as stated in (c)(1) above to appear as the first bulleted statement after the heading "*Directions*".

2. **Package Inserts** - *Zyrtec Chewable Tablets for Allergy (5 and 10 mg) and Zyrtec Syrup for Allergy and Hives*:

A. Under the heading "*What is Zyrtec?*", the phrase in the last sentence of the first paragraph "*so you can go anywhere life takes you*" should be deleted. This phrase is unrelated to the intended purpose of the drug product.

B. Under the heading "*Who Should Not Take Zyrtec?*", revise the information in this section as follows:

1. Delete the bulleted phrase "*If you are pregnant or breast-feeding, ask your doctor or pharmacist before using Zyrtec*".
2. Add the following bulleted phrases:

C. Under the heading *"SAFETY PROFILE: Caution"* section, it is recommended that the sponsor revise the bulleted data entries in plain language to make such information more consumer friendly.

D. Under the heading *"DIRECTIONS FOR USE"*, it is recommended that the sponsor include in each allergy and hives package insert the specific SKU dosage directions in a table format.

E. **For the Hives Package Insert**: In addition to the previous package insert comments, under the heading "When Should Zyrtec be Taken?", the second bulleted statement needs to be revised for clarity as follows:

F. It is recommended that the sponsor provide a package insert for all the Zyrtec SKUs as is provided for the Syrup (Allergy & Hives) and the Chewable Tablets (Allergy) SKUs.

Recommendations:

1. This application is not approvable. Inform the sponsor to revise the labeling as follows and resubmit revised labels with annotated Drug Facts specifications for our review and comment prior to the Action Due date:

   A. **General comment: [All submitted Zyrtec SKUs, 1-count blister card, and package inserts]**
   The proprietary name for these Zyrtec products is not clear. The sponsor needs to inform the agency of the intended proprietary name for the various Zyrtec dosage forms intended as relief from symptoms associated with allergy and hives. If the sponsor intends to distinguish the two different labeling indications by using the flags "Allergy" and "Hives Relief", the flags must be relocated to appear adjacent to the word "Zyrtec" and preferably in the same color as the brand name "Zyrtec".

   B. **PDP : *Promotional Flags*:**
   (i) *Tablet/Chewable Tablets*: Delete the flags "*Full Prescription Strength*" and "*Full Prescription Strength...Now OTC!*" These flags must be deleted or revised to read ' ... wherever they appear in the labeling of these dosage forms.
   (ii) *Syrup*: Delete the flags *"Full Prescription Strength"* and "*Full Prescription Strength...Now OTC!*" wherever they appear in the labeling of any Zyrtec Syrup. These flags should not appear on any syrup SKU because there continues to be a prescription product for the population group 6 months to 2 years of age.
   (iii) *Chewable Tablet – 5 mg Allergy* SKU
   a. Delete the flag "*2 yrs. & older*". This flag is not accurate because the dosage direction for this SKU does not provide an initial dose of 2.5 mg for children 2 to under 6 years of age as noted in the Rx labeling.
   b. Delete the graphic of a child under 6 years of age. This graphic is misleading because this proposed OTC drug product should only be intended only for children 6 years and older. See comment B(iii)(a) above.

   C. **Other Panel (All submitted SKUs):** Provide for lot number and expiration date.

   D. **Drug Facts**: Revise as per attached prototype "Drug Facts" labeling.

2. **Package Inserts:** Inform the sponsor to revise the package inserts as follows:
   A. Under the heading "*What is Zyrtec?*", delete the phrase in the last sentence of the first paragraph "*so you can go anywhere life takes you*". This phrase is unrelated to the intended purpose of the drug product.
   B. Under the heading "*Who Should Not Take Zyrtec?*", revise the information in this section as follows:
   i. Delete the bulleted phrase "*If you are pregnant or breast-feeding, ask your doctor or pharmacist before using Zyrtec*".
   ii. Add the following bulleted phrases:

   C. For the Hives insert only: In addition to the previous package insert comments, under the heading "*When Should Zyrtec be Taken*?", revise the second bulleted statement as follows:

3. **Inform the sponsor that the agency recommends the following**:
   A. The established name of the active ingredient, dosage form, dosage strengths, and pharmacological category need to appear more prominently. It is strongly recommended that the sponsor:

i. change the color contrast lettering of the *statement of identity* (established name of the active ingredient, dosage form, and pharmacological category) and increase the print size of this statement, wherever this information appears in the labeling. This revision will make the information easier to read and understand and help to avoid medication error.

ii. increase the prominence and distinguish the two different dosage strengths available (i.e., "5 mg" and "10 mg") by using a different type color or other print feature wherever this information appears in the labeling.

B. Package Inserts:

i. under the heading *"SAFETY PROFILE: Caution"* section, revise the bulleted data entries in plain language to make such information more consumer friendly.

ii. under the heading *"DIRECTIONS FOR USE"*, include the dosage directions for the specific SKU (allergy or hives) in a table format.

iii. consider providing a package insert for all the Zyrtec SKUs as is provided for the Syrup (Allergy & Hives) and the Chewable Tablets (Allergy) SKUs.

4. Delete the flag "*New*" wherever it appears in the labeling of the Zyrtec products 6 months after introduction into the OTC market place.

5. Drug Facts annotated specifications are acceptable.

6. **Project Manager**:

a. The review chemist for Zyrtec tablets (NDA # 19-835) and Zyrtec chewable tablets (NDA # 21-621) has indicated in an e-mail dated August 27, 2007 that all of these SKUs will be child-resistant packages.

The review chemist for Zyrtec Syrup (NDA #22-155) has indicated that the container closure system for these SKUs are in child-resistant packaging.

b. This review may be further revised based on the completion of the *clinical and chemistry reviews*. However, prior to the completion of these reviews, this review can be forwarded to the sponsor as our preliminary labeling comments.

c. Remind the sponsor of its e-mail dated August 9, 2007 regarding its intention to submit at a later date the draft 24-count chewable tablet carton label and the 45-count tablet immediate container and clamshell draft labels for review and comment.

d. Please forward the attached "*Drug Facts*" prototype labels to the sponsor.

Cazemiro R. Martin
IDS: Reg. Review Chemist

Concur: Marina Chang, R.Ph.
Team Leader

Enclosure:
- Prototype A: Drug Facts labeling - *Allergy* [tablet/chewable tablet]
- " B: " " " - *Hives* "
- " C: " " " - *Allergy* [syrup]
- " D: " " " - *Hives* "

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6 Draft Labeling

_____ Deliberative Process

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/s/

Cazemiro Martin
8/27/2007 01:38:08 PM
INTERDISCIPLINARY

Marina Chang
8/27/2007 01:51:43 PM
INTERDISCIPLINARY

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

REQUEST FOR CONSULTATION

TO (*Office/Division*): Director
OSE/Division of Drug Risk Evaluation

FROM (*Name, Office/Division, and Phone Number of Requestor*):
Elaine Abraham, RPM
Division of Nonprescription Clinical Evaluation/ONP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 9, 2007		22-155	Safety eval request	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zyrtec (cetirizine)	High	antihistamine	August 31, 2007

NAME OF FIRM: Pfizer/McNeil

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Applications for the Rx-to-OTC switch of Zyrtec (cetirizine) are currently being reviewed in CDER (NDA 22-155, NDA 19-835/S-022, and NDA 21-621/S-005). Please review all domestic postmarketing data for single-ingredient cetirizine and seizure/convulsion adverse events in comparison with loratadine. We would like to know if there is a significant difference in crude counts of seizure/convulsion reports between cetirizine and loratadine use. If there is such a difference, please conduct a complete safety assessment.

SIGNATURE OF REQUESTOR
Elaine Abraham, RPM, (301) 796-0843

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

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/s/

Elaine Abraham
7/9/2007 02:23:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-155

INFORMATION REQUEST LETTER

McNeil Consumer Healthcare
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
U.S. Agent for Pfizer, Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl) Syrup 1 mg/mL.

We also refer to your submissions dated March 2, May 4 and May 15, 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your proposed timeline of August 31 for the submission of [redacted] accuracy results is not acceptable. This information needs to be received by July 31, 2007.

2. Your proposed timeline of June 30, 2007 for a complete DMF list is unacceptable. Please submit the list by June 15, 2007.

3. Confirm that the NDA applicant of NDA 22-155 is McNeil Consumer Healthcare not Pfizer. Form 356h and the letters of authorization submitted to-date under this NDA indicate that Pfizer is the NDA applicant. If McNeil Consumer Healthcare is the applicant of NDA 22-155 as stated in your amendment dated May 15, 2007, please correct Form 356h, and re-submit all letters of authorization for DMFs, by June 15, 2007, with the correct NDA applicant name to reflect this change.

4. Confirm that the referenced DMF for newly proposed dosing cup is DMF [redacted]. The DMF list to be submitted as requested in this IR letter (item 2) should include this information.

5. The establishment list provided in your response dated March 2, 2007 to CMC IR letter is incomplete because —— facility information is missing. Check the list for completeness and accuracy, and re-submit the revised list by June 15, 2007.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager, at 301-796-2096.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
6/4/2007 12:56:51 PM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-155

INFORMATION REQUEST LETTER

McNeil Consumer Healthcare
Division of McNeil-PPC, Inc.
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
For Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZYTREC (cetirizine HCL).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please confirm that the closure(s) for OTC Zyrtec oral solution is child resistant. Child resistant container/closure system is required for the OTC drug products.

3. Regarding [redacted], please clarify as to when you plan to introduce them.

4. We have noticed many changes in DMFs since the approval of NDA 20-346 in 1996. For ease of review, please provide a complete and updated list of DMFs for NDA 22-155, and the components for which those DMFs are referenced. Also should be provided, is a copy of Letter of Authorization for each referenced DMF.

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/s/

Moo-Jhong Rhee
4/2/2007 02:54:49 PM
Chief, Branch III

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

FILING COMMUNICATION

NDA 22-155

McNeil Consumer Healthcare
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
U.S. Agent for Pfizer, Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl) Syrup 1 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 17, 2007, in accordance with 21 CFR 314.101(a).

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

1. You provided the results of the AERS DataMart database search, but did not include the search criteria used for the search.

2. The basis of Categorical Exclusion claim for Environment Assessment may not be correct. You claim Categorical Exclusion for Environment Assessment citing 21 CFR 25.31(a) as the basis for the claim. 21 CFR 25.31(a) states that "action on an NDA, abbreviated application for marketing approval of a biological product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety."

   In addition to NDA 22-155, which is filed for the partial switch of Zyrtec Syrup 1 mg/mL from Rx to OTC, you have recently filed the following three Rx to OTC switch supplements:

   Zyrtec tablets 5 & 10 mg (NDA 19-835/S-022)
   Zyrtec-D Tablets 5 mg/120 mg pseudoephedrine (NDA 21-150/S-007)
   Zyrtec Chewable Tablets 5& 10 mg (NDA 21-621/S-005)

   These four Rx to OTC switches may collectively increase the use of the active moiety.

3. You did not identify if you will have a non-child resistant closure.

4. Based on our preliminary review of the labeling, the package insert and all other labeling should specifically address in its entirety either allergy relief information or hives relief information. No SKU labeling should include both allergy and hives information.

5. Multiple dosing devices can create consumer confusion and medication error. We believe that there is no need for different devices for different populations. We strongly recommend that you provide only one universal dosing device

6. Your NDA submission did not include a debarment certification.

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

We request that you submit the following information:

1. The search criteria used for the AERS DataMart database search or indicate where the criteria appear in the submission.

2. Submit EIC (Expected Introduction Concentration for use) calculation to support your claim of categorical exclusion of Environment Assessment. Include the active moiety use data for all dosage forms and indications. The calculation should be based on the highest quantity of the active moiety (cetirizine) expected to be produced for direct use in any of the next five years.

3. Identify which SKU, if any, will have a non-child resistant closure. If there is a non-child resistant closure SKU, you are reminded that the SKU needs to comply with 16 CFR 1700.

4. Revise the package insert and all other labeling that includes both allergy relief and hives relief information so that allergy relief and hives relief are not included in the same labeling. Submit revised labeling for each indication for our review and comment.

5. Select one dosing device for your application or justify the need for multiple dosing devices.

6. Debarment certification in accordance with section 306(k) of the Federal Food, Drug and Cosmetic Act.

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

If you have any questions, call Elaine Abraham, Regulatory Project Manager, at (301) 796-0843.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
3/23/2007 12:46:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-155

NDA ACKNOWLEDGMENT

McNeil Consumer Healthcare
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
U.S. Agent for Pfizer, Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

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 (cetirizine HCl) Syrup 1mg/mL
Review Priority Classification:	Standard (S)
Date of Application:	January 15, 2007
Date of Receipt:	January 16, 2007
Our Reference Number:	NDA 22-155

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 17, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 16, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the requirement for pediatric studies for this application in children less than 6 months of age for the relief of itching due to hives and in children less than 2 years of age for the relief of symptoms due to hay fever and other upper respiratory allergies. We note that you have fulfilled the pediatric study requirement for this application for children 6 months of age and older for the relief of itching due to hives and for children 2 years of age or older for the relief of symptoms due to hay fever and other upper respiratory allergies.

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

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

If you have any questions, call Elaine Abraham, Regulatory Project Manager, at (301) 796-0843.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
3/12/2007 11:37:02 AM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Medication Errors and Technical ...port (DMETS)

FROM: Elaine Abraham, RPM
Div. of Nonprescription Clinical Evaluation, WO22, Rm. 5410

...TE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 15, 2007		22-155		January 15, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Children's Zyrtec Allergy (cetirizine HCl syrup)	Med	8S Antihistamine	August 15, 2007

NAME OF FIRM: Pfizer

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We are requesting a trade name review of the name "**Children's Zyrtec Allergy**". The labeling can be found in the electronic document room (EDR). Please limit your review to consideration of the trade name only. ONP is reviewing all other aspects of the label (principal display panel, Drug Facts content and format etc.). The PDUFA date for this NDA is November 16, 2007. Please contact me at 796-0843 if you have any questions.

...TURE OF REQUESTER	METHOD OF DELIVERY (Check one)
...e appended electronic signature page}	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Medication Errors and Technical Support (DMETS)

FROM: Elaine Abraham, RPM
Div. of Nonprescription Clinical Evaluation, WO22, Rm. 5410

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 15, 2007		22-155		January 15, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Children's Zyrtec Hives Relief (cetirizine HCl syrup)	Med	8S Antihistamine	August 15, 2007

NAME OF FIRM: Pfizer

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
We are requesting a trade name review of the name "**Children's Zyrtec Hives Relief**". The labeling can be found in the electronic document room (EDR). Please limit your review to consideration of the trade name only. ONP is reviewing all other aspects of the label (principal display panel, Drug Facts content and format etc.). The PDUFA date for this NDA is November 16, 2007. Please contact me at 796-0843 if you have any questions.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
{See appended electronic signature page}	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Elaine Abraham
2/16/2007 11:52:43 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-155

INFORMATION REQUEST LETTER

McNeil Consumer Healthcare
Division of McNeil-PPC, Inc.
Attention: Robert Kohler
Senior Director, Global Regulatory Affairs
For Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950

Dear Mr. Kohler:

Please refer to your January 15, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZYTREC (cetirizine HCL).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a side-by-side comparison of NDA 22-155 with NDA 20-346 according to CDT format, indicating all differences between the two NDAs.

2. Provide a complete establishment list, including names, addresses, contact information, CFN#, the function of each facility, and a statement of readiness for inspection. Additionally, state if the facilities involved in the NDA 222-155 have been approved under NDA 20-346.

3. Provide the current specifications for the drug product and drug substance, including their test procedures.

4. Provide formulation composition table for the drug product. Clarify if the formulation is the same as that approved under NDA 20-346.

5. Provide Post-approval Stability Protocol and Stability Commitment for the drug substance and drug product.

6. Clarify if the 15 ml sample size container has been approved under NDA 20-346.

7. Clarify why the proposed dosage form for NDA 22-155 is "oral solution." Note that the dosage form approved for NDA 20-346 is "syrup."

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
2/13/2007 11:07:59 AM
Chief, Branch III

MEMORANDUM OF TELECON

DATE: February 9, 2007

APPLICATION NUMBER: NDA 22-155

BETWEEN:

Name: Hans Knapp
Susan Beavis
Beverly Zaber
Phone: 866-714-4882
Representing: Pfizer

AND

Name: Shulin Ding, Ph.D., Pharmaceutical Assessment Lead
Yubing Tang, Ph.D., Chemist
Linda Athey, Regulatory Health Project Manager for Quality
ONDQA, Division of Pre-Marketing Assessment II

SUBJECT: Comparison of NDA 22-155 (Zytrec OTC) with NDA 20-346 (Zytrec Rx)

Pfizer submitted NDA 22-155 on January 16, 2007 with a full cross reference to NDA 20-346. FDA requested the following information for ease of review:

1. Provide a side-by-side comparison of NDA 22-155 with NDA 20-346 according to CDT format, indicating all differences between the two NDAs.

2. Provide a complete establishment list, including names, addresses, contact information, CFN#, the function of each facility, and a statement of readiness for inspection. Additionally, state if the facility has been approved under NDA 20-346.

3. Provide the current specifications for the drug product and drug substance, including their test procedures.

4. Provide formulation composition table for the drug product. Clarify if the formulation is the same as that approved under NDA 20-346.

5. Provide Post-approval Stability Protocol and Stability Commitment for the drug substance and drug product.

6. Clarify if the 15 ml sample size container for Children's Zyrtec Allergy has been approved under NDA 20-346.

7. Clarify why the proposed dosage form for NDA 22-155 is "oral solution." Note that the dosage form approved for NDA 20-346 is "syrup."

Pfizer stated in the telecon that the CMC information in NDA 22-155 is identical to that of NDA 20-346 in every regard with the exception of the inclusion of a measuring cup [redacted] in the secondary packaging of Zyrtec OTC . Pfizer agreed to provide all the requested information in about three weeks.

Chair, Shulin Ding, Ph.D.
Pharmaceutical Assessment Lead

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/s/

Linda D Mullins-Athey
2/12/2007 09:16:58 AM
PROJECT MANAGER FOR QUALITY

Shulin Ding
2/12/2007 09:23:01 AM
CHEMIST

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 22-155 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Zyrtec Syrup
Established Name: cetirizine HCl
Strengths: 5mg/5mL

Applicant: Pfizer
Agent for Applicant (if applicable): McNeil

Date of Application: January 15, 2007
Date of Receipt: January 16, 2007
Date clock started after UN:
Date of Filing Meeting: March 7, 2007
Filing Date: March 17, 2007
Action Goal Date (optional): September 16, 2007 User Fee Goal Date: November 16, 2007

Indication(s) requested: Allergic rhinitis, hives (CIU)

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 8
Other (orphan, OTC, etc.) OTC

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☒

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☒
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?

  Age range is more restrictive than current approved Rx product, so no new pediatric studies are included and no pediatric waiver is requested.

  YES ☐ NO ☒

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.) Copy of original. See N 19-835 S-022 for original.
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: I 74,262 & N 20-346

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 27, 2006 (PIND) NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☐ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☐ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☒ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☒ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 7, 2007

NDA #: 22-155

DRUG NAMES: cetirizine HCl

APPLICANT: Pfizer

BACKGROUND: Zyrtec (cetirizine HCl) Syrup was approved as a prescription product for SAR, PAR and CIU (6 yrs and above) on September 27, 1996 under NDA 20-346. In subsequent supplemental approvals, Zyrtec was allowed for SAR (> 2 yrs. - S-002), PAR and CIU (> 6 mos - S-008). This NDA is for the Rx-to-OTC switch of Zyrtec syrup for SAR (> 2 yrs), PAR (> 2 yrs), and CIU (> 6 yrs). PAR (6 mos - 2 yrs) and CIU (6 mos - 6yrs) will remain as prescription indications under NDA 20-346. Pfizer is the innovator of cetirizine. The Division of Nonprescription Clinical Evaluation is the lead divison for this NDA and the Division of Pulmonary and Allergy Products is reviewing clinical efficacy.
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Andrea Leonard-Segal, Joel Schiffenbauer, Daiva Shetty, Marina Chang, Sally Seymour, Tayo Fadiran, Shulin Ding in addition to assigned reviewers

ASSIGNED REVIEWERS (including those not present at filing meeting) : see below

Discipline/Organization	**Reviewer**
Medical:	Susan Limb
Secondary Medical:	Lolita Lopez
Statistical:	
Pharmacology:	Wafa Harrouk
Statistical Pharmacology:	
Chemistry:	Yubing Tang
Environmental Assessment (if needed):	
Biopharmaceutical:	Partha Roy
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Tejashri Purohit-Sheth
OPS:	
Regulatory Project Management:	Elaine Abraham
Other Consults:	Cazemiro Martin (labeling)

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☒	FILE	☐	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX	N/A	☐	FILE	☒	REFUSE TO FILE	☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY			FILE	☒	REFUSE TO FILE	☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional): Numerous including labeling - hives and allergy on same container, chemistry - environmental assessment

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Elaine Abraham
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

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

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

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

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

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

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

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

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Elaine Abraham
5/8/2007 08:46:35 AM
CSO

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 22-155	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Zyrtec Established Name: cetirizine HCl Dosage Form: Syrup		Applicant: McNeil (agent for Pfizer)	
RPM: Elaine Abraham		Division: DNCE	Phone # (301) 796-0843

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

❖ User Fee Goal Date ❖ Action Goal Date (if different)	11/16/07
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

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

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

☐ Orphan drug designation

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

NDAs and NDA Supplements:
- ☒ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action

❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

notice of certification?

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

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

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

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

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

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

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

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

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

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

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

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

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

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	11/8/07, 11/13/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	1/15/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	10/11/07
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	11/8/07
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 11/7/07 ☐ DSRCS ☐ DDMAC ☐ SEALD ☒ Other reviews 8/27/07, 10/24/07, 11/13/07 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	5/8/07
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	2/13/07, 3/23/07, 4/2/07, 6/4/07, 9/12/07
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	11/2/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/2/07
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 10/15/07 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9/10/07, 10/2/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	incl
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☐ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	10/2/07
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☐ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☒ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☒ None

Appendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Store: PDUFA CoverSheet

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

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

1. APPLICANT'S NAME AND ADDRESS

PFIZER INC
Hans Knapp
201 Tabor Road
Morris Plains NJ 07950
US

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

22-155

2. TELEPHONE NUMBER
973-385 7250

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

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

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

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

20-346

3. PRODUCT NAME
Zyrtec Syrup (Cetirizine hydrochloride)

6. USER FEE I.D. NUMBER
PD3007004

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

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

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

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

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

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

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

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

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

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robert G Kohler	SR DIRECTOR REGULATORY AFFAIRS	1/11/07

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$448,100.00

Form FDA 3397 (12/03)

Close Print Cover sheet