fasted state. The results of these studies showed that the Zyrtec 10 mg chewable tablet taken with or without water is bioequivalent to the already approved Zyrtec immediate release tablet (90% CI for the ratio of AUC_t, AUC_{inf} and C_{max} for the CT/commercial tablet was within the 80 -125% limits). The requirement for bioequivalence studies for the 5 mg chewable tablet was waived because the composition of the 5 mg tablet was proportionally similar to the 10 mg tablet and had a similar dissolution profiles (*f2* >50). The study conducted in the fed and fasted state showed that a meal high in fat and calories decreased the C_{max} by 38% and increased the t_{max} by about 3 hours but these findings do not appear to be of clinical relevance.

Review of the safety data in the clinical pharmacology studies did not reveal any new safety signals with this product. A total of 124 healthy adult subjects aged 18 -55 years participated in the single-dose clinical pharmacology studies. Of these, 80 subjects were exposed to the 10 mg CT. There were no deaths, serious adverse events or withdrawals due to adverse events and the two most commonly reported adverse events were headache and somnolence. Previous post-marketing safety reviews conducted by the Division of Drug Risk Evaluation I (DDRE I) in the Office of Drug Safety noted that psychiatric, emotional and behavioral disturbances and seizures were reported in association with the use of Zyrtec®. In the case of seizures, the etiologic role of cetirizine was uncertain. During this NDA review cycle, DDRE I was consulted to review reports of suicide in association with cetirizine. DDRE I concluded that cases of suicide and suicidal ideation were probably causally related to cetirizine and should be included in the product label. During the review cycle, the applicant submitted a revised label to add seizures, and aggressive reactions to the list of events occurring in the post marketing experience.

During the review cycle, the concern for interaction of betacylodextrin ——— ——— contained in the formulation with other drugs. Betacyclodextrin (Betadex) is included in the formulation in a molar ratio of — Each 10 mg Zyrtec® chewable tablet contains ——— of Betadex. Published articles have reported the potential for Betadex to interact with certain poorly water-soluble drugs, such as some vitamins. However, not all drugs interact with Betadex and the degree of interaction depends on [among other factors], the size of the molecule and the amount of BCD in the formulation. The Agency has not previously approved drugs containing BCD however, BCD has been declared GRAS for oral use. The Pharm/Tox team indicated that the amount of BCD that a subject would be exposed to in the CT is well below the recommended dose of 5 mg/kg/day (equivalent to 300 mg/day for a 60 kg person) The Division concluded that the BCD contained in the drug product does not pose a clinical concern and it is unlikely that BCD with interact with other drugs taken in close proximity with Zyrtec® CT.

Interdisciplinary Issues

Chemistry, Manufacturing and Controls

The original application contained only six months of stability data for the primary stability batches (Belgium site) and no stability data from the site-specific batches manufactured at the intended commercial site in [redacted]. The sponsor was issues a deficiency letter on November 14, 2003. The sponsor subsequently submitted an amendment containing [redacted] of stability data (under long and intermediate term conditions) and [redacted] of stability data for [redacted] site-specific batches. These stability data were deemed adequate and the drug product can be given an expiry to 24 months by extrapolation. With respect to the use of Betadex in the formulation, from a CMC perspective it was noted that [redacted] is used [redacted]. The applicant agreed to control the residue solvent at NMT [redacted]. Based on [redacted] of Betadex per chewable tablet a [redacted] ppm concentration of [redacted] is equivalent to a maximum daily exposure of [redacted]. In consultation with the pharm/tox team it was concluded that this level should not pose a safety concern considering the fact that the EPA allowable limit of [redacted] is [redacted] of drinking water.

Non-clinical Pharmacology and Toxicology

The Agency did not require the sponsor to conduct nonclinical safety studies and none were submitted with this application.

Pediatric Considerations

No additional pediatric studies are required for the chewable tablet since this program is based entirely on establishment of bioequivalence. The sponsor has approved indications for cetirizine down to age 6 months.

Ethical and Statistical Integrity Issues:

There were no ethical and statistical integrity issues with this application. The clinical studies were conducted in accordance with all good clinical practice standards and protection of human subjects according to regulatory requirements and the declaration of Helsinki. The biopharm team concluded that a DSI audit was not warranted and none was conducted for this NDA.

Nomenclature:

The trade name "Zyrtec" is an established trade name for the product and this name will be maintained and this is acceptable. During the review process a consult was sent to the Division of Medication Errors and Technical Support (DMETS). The Division indicated that they had previously conducted a root cause analysis of Zantac and Zyrtec medication errors and had recommended that the manufactures of both products highlight the different portions of their proprietary names (e.g. zYRtEc vs. zANtAc) or emphasize the established names by placing them before the proprietary names and by increasing their font sizes. The Division (DPADP) after review of the medication error cases noted that the errors were (in almost all cases) a result of an error with Zantac (i.e. zantac being prescribed incorrectly as Zyrtec) and decided that we should not ask the manufacturer of Zyrtec to change their proprietary name because of this. The DMETs consult for this

Zyrtec application made recommendations on the label and packaging and the Division has accepted all but one of these recommendations. [redacted]

[redacted] The Division disagrees with this interpretation.

Summary

The sponsor has adequately established bioequivalence of the Zyrtec chewable tablet to the commercially available Zyrtec tablet and have addressed the CMC issues sent in the DR letter. The Applicant will be asked to tighten some specifications for some impurities and make a few changes to the label that include the addition of suicide and suicide ideation to the post marketing section of the label, and dose adjustment in elderly patients > 77 years of age (because of decreased clearance of the drug stated in the current label). The recommended changes from DMETs for the product packaging will be incorporated with the one exception noted above.

Recommended Regulatory Action

Approval

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

/s/

Lydia McClain
2/23/04 02:24:25 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: February 18, 2004

APPLICATION NUMBER: NDA 21-621/Zyrtec Chewable Tablet

PFIZER PARTICIPANTS:

Thomas Garcia, Ph.D., Associate Director, CMC
Debra Webb, Senior Scientist, CMC
Stephen Brune, Associate Director, Project Analyst
Gregory Steeno, Manager, Statistician
Denise Andrews, Director, US Regulatory Affairs
Samantha Wolfe, Director, US Regulatory Affairs
Antonio Benvenuti, Package and Design Development Team

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS, HFD-570

Edwin Jao, Ph.D., Chemistry Reviewer
Richard Lostritto, Ph.D., Chemistry Team Leader
Colette Jackson, Project Manager

SUBJECT: Pfizer's clarifying questions listed in the February 17, 2004, facsimile in response to the Agency's February 12, 2004, CMC facsimile.

The FDA responded to the following questions, in bold italics, listed in the February 17, 2004, facsimile.

FDA Comment 1: Your currently proposed acceptance criteria for impurities are not reflective of the data provided (including an appropriate statistical analysis towards a projected ——— expiry) nor are they reflective of impurity limits for your marketed drug products containing this API. Therefore, tighten the regulatory acceptance criteria of the drug product specifications. The recommended "e.g." revisions, which are supported by the statistical analyses (extrapolating of your 12 months data to 24 months through linear regression and taking mean and 95% upper confidence limit into account), are provided in the Table below.

Attribute	Proposed criteria	Recommended "e.g." criteria	Criteria for Zyrtec Extended Release Tablet
———	NMT ———	NMT ———	Na
Total Specified Degradants	NMT ———	NMT ———	LT ———
Individual Unspecified Degradant	NMT ———	NMT ——— each	LT ——— each

Total Unspecified Degradants	**NMT**	**NMT**	**LT**
Total Degradants	**NMT**	**NMT**	**LT**

In order for your response to be used in the current review cycle, your response should be received by us no later than COB February 20, 2004. In the interest of expediting these issues regarding final specifications, we remain available for a teleconference.

Pfizer Clarifying Questions:

1. ***The two degradants, , are not listed in the table above. We plan to list them on the specifications with the originally proposed acceptance criteria of NMT for each.***

2. ***Pfizer agrees with the FDA's evaluation based on the statistical analyses of the currently available stability data (12-months data from ICH lots manufactured by UCB), Per ICH guidance Q3B(R), when there is no safety concern, the acceptance criteria for degradation products should allow sufficient latitude for normal manufacturing and analytical variation. Thus Pfizer is proposing the acceptance criteria listed on the next page for commercial lots manufactured at the commercial manufacturing site at***

Attribute	Initial Pfizer Proposed Criteria	Revised Pfizer Proposed Criteria	FDA Recommended "e.g." criteria	Approved Criteria for Zyrtec D Tablet
	NMT	NMT		LT
	NMT	NMT		LT
	NMT	NMT	NMT	NA
Total Specified Degradants	NMT	NMT	NMT	LT
Individual Unspecified Degradant	NMT	NMT each	NMT each	LT ; each
Total Unspecified Degradants	NMT	NMT	NMT	LT
Total Degradants	NMT	NMT	NMT	LT 0.7%

The FDA referred to Pfizer's revised proposed criteria and noting that the originally proposed is NMT where the FDA proposed is a new impurity specific to this drug product and the Agency's proposed was devised using a statistical model with extrapolation out to 24 months and upper 95% confidence interval. The Agency then used an additional calculation just to round up to This is reflective of manufacturer capability and a valid scientific method. The FDA questioned Pfizer's rationale and calculation for their newly proposed limit of NMT Pfizer stated they applied the same statistical calculations and confidence

intervals, and noted that their limit incorporates their desire to expand the shelf life to [redacted] months. [redacted] is acceptable for the currently proposed [redacted] shelf life. Pfizer would like to expand to a [redacted] shelf life and if the limit goes down to [redacted] they would lose that option. Also, Pfizer noted that the ICH batches used in the calculation are pilot scale, and they have little information on the commercial batches. One plot Pfizer devised shows data close to the [redacted] limit, and this puts them on the edge of failure. The FDA asked if this information was submitted for review. Pfizer referred to the [redacted] at 25°C, lot# 11361, where there was a point at 0.5% and they are concerned that the application of 95% confidence intervals may increase their chance for failure. The FDA noted that these are only projected figures. Pfizer requested the option to increase the limit to [redacted] in case of variability at the commercial scale. The FDA stated that we will take this into consideration with our review.

Pfizer questioned the FDA's concern since [redacted] or [redacted] is below ICH specification qualification. The FDA informed Pfizer that this is a quality control issue so the acceptance criteria for the drug product are in line with performance within reasonable tolerance for variability. The FDA proposed the use of [redacted] as an interim specification for [redacted], with re-examination after an additional 12-months of data. Pfizer would then tighten the specification if supported by data. Pfizer agreed to the FDA's proposal of [redacted] NMT [redacted] interim specification to be re-visited after the first [redacted] commercial batches. By then, data would be available for the [redacted] ICH batches. Pfizer indicated that the [redacted] data would not be available at the same time, with approximately an [redacted] lag behind. The FDA indicated that we prefer to go with [redacted] month data on the ICH batches plus [redacted] data on the commercial batches. As an alternative, wait for the [redacted] data and make a projection out to [redacted]. The FDA and Pfizer agreed that the interim criterion will be revisited when the stability data from either the [redacted] ICH batches or from the 12 months commercial batches are available. Pfizer questioned if this planning could apply to the total degradants as well. The FDA agreed, and Pfizer agreed to submit their proposal in writing in the very near future.

The Division raised the labeling issue of the blister packs. FDA requested to obtain blister pack samples, but was informed by Pfizer that they are unavailable. The FDA needs to evaluate friability with the tablets in the blister. The hardness range is too broad and even though the friability range is acceptable, the FDA would prefer to physically see and touch the blister pack. Pfizer noted they would have to get back with us for comment since they have no product currently manufactured. Pfizer noted that the ICH package foil is slightly different than the commercial and the labeling is currently being commissioned. They will let the agency know when the product is available. Pfizer informed the FDA that a compression study was performed and the friability ranges confirmed. The FDA questioned the difference between the ICH stability batches without the label and the commercial batches to be manufactured. Pfizer stated that the packaging is the same except for the "peel and push" feature to be commercially manufactured. The FDA expressed concern for friability since the "peel and push" packaging has not been tested and therefore the friability limits established are not indicative of commercial use. The FDA is concerned with the possibility of reports of

broken tablets with the product post approval. Pfizer stated they would look into the earliest timeframe they could have the blister available. When the product is available, Pfizer stated they would perform an in-use study with various hardness to see if there is an issue. The FDA agreed, but would then also consider Pfizer's proposed hardness specification as an interim specification. Pfizer agreed and committed to having the data to the FDA 12-months post-approval.

Pfizer summarized the following agreements as a result of this teleconference:

1. The impurity specifications for ——— and total impurities would be interim until either option could be provided to the FDA:

   a. ———: of ICH data.

   b. 12 month data for the first three commercial batches.

2. Within 6-months post-approval, Pfizer will submit their in-use study to verify or change the hardness specifications.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

APPEARS THIS WAY
ON ORIGINAL

cc:

HFD-570/Division Files
HFD-570/Jao
HFD-570/Lostritto

Drafted: February 27, 2004
Initialed:

Jao/March 2, 2004
Lostritto/March 3, 2004

Finalized: CCJ/March 3, 2004

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

/s/

Colette Jackson
3/3/04 11:01:45 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 12, 2004

To: Samantha Wolfe	**From:** Colette Jackson
Company: Pfizer	Division of Pulmonary and Allergy Drug Products
Fax number: 212-857-3558	**Fax number:** 301-827-1271
Phone number: 212-573-2241	**Phone number:** 301-827-9388
Subject: NDA 21-621	
Total no. of pages including cover: 3	
Comments:	

Document to be mailed: YES xNO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-621
Zyrtec Chewable Tablets

Please refer to your May 15, 2003, new drug application (NDA) for Zyrtec (cetirizine HCl) Chewable Tablets, 5 mg and 10 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission dated May 15, 2003, and amendments dated September 19, September 30, October 13, October 31, December 17, and December 24, 2003. We have identified the following deficiencies which need to be resolved. A prompt response to these deficiencies will facilitate a timely resolution of these issues.

1. Your currently proposed acceptance criteria for impurities are not reflective of the data provided (including an appropriate statistical analysis towards a projected 24 month expiry) nor are they reflective of impurity limits for your marketed drug products containing this API. Therefore, tighten the regulatory acceptance criteria of the drug product specifications. The recommended "e.g." revisions, which are supported by the statistical analyses (extrapolating of your 12 months data to 24 months through linear regression and taking mean and 95% upper confidence limit into account), are provided in the Table below.

Attribute	Proposed criteria	Recommended "e.g." criteria	Criteria for Zyrtec Extended Release Tablet
—	NMT —	NMT —	Na
Total Specified Degradants	NMT —	NMT —	LT —
Individual Unspecified Degradant	NMT —	NMT — each	LT —, each
Total Unspecified Degradants	NMT —	NMT —	LT —
Total Degradants	NMT —	NMT —	LT —

In order for your response to be used in the current review cycle, your response should be received by us no later than COB February 20, 2004. In the interest of expediting these issues regarding final specifications, we remain available for a teleconference.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

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

/s/

Colette Jackson
2/12/04 11:57:29 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: December 09, 2003	**DESIRED COMPLETION DATE:** February 28, 2004 **PDUFA DATE:** March 16, 2004	**ODS CONSULT #:** 03-0319

TO: Badrul Chowdhury, MD
Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Collette Jackson
Project Manager
HFD-570

PRODUCT NAME: **Zyrtec** (Cetirizine Hydrochloride Tablets) Chewable 5 mg and 10 mg **NDA# 21-621**	**NDA SPONSOR:** Pfizer Inc.

SAFETY EVALUATOR: Linda M. Wisniewski, RN

DMETS RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: January 05, 2004

NDA#: 21-621

NAME OF DRUG: Zyrtec (Cetirizine Hydrochloride Tablets) Chewable 5 mg and 10 mg

NDA HOLDER: Pfizer Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570), for assessment of the proposed labels and labeling for Zyrtec Chewable Tablets. The sponsor is currently marketing Zyrtec in 5 mg and 10 mg tablets, 5 mg/5 mL syrup, and as a 12-hour combined product containing Cetirizine Hydrochloride 5 mg and Pseudoephedrine 120 mg known as Zyrtec-D 12 hour. These products were approved on: 12/8/95, 9/27/96, and 8/10/01 respectively. Thus, DMETS did not conduct the standard proprietary name review for this proposed name. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION:

Zyrtec (Cetirizine hydrochloride) is an orally active and selective H_1-receptor antagonist. Zyrtec chewable tablets are formulated as purple round tablets for oral administration and are available in 5 mg and 10 mg strengths. The dose is one tablet daily. The tablets are packaged in blister cards as follows:

5 mg tablets are engraved with "Zyrtec C5" on one side in boxes of 3 blister cards of ten tablets each.
10 mg tablets are engraved with "Zyrtec C10" on one side in boxes of 3 blister cards of ten tablets each.

II. RISK ASSESSMENT:

Zyrtec Chewable Tablets is an addition to the Zyrtec product line. Thus, the Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports concerning medication errors associated with Zyrtec. The MEDDRA Preferred Terms (PT): "medication error", "accidental overdose", and "overdose nos" (not otherwise specified) and the term "Zyrtec" were used as search criteria. The AERS search revealed a total of 88 medication error reports concerning confusion between Zyrtec and Zantac (41), and Zyrtec and Zyprexa (47).

1. The Division of Medication Errors and Technical Support conducted a root cause analysis of the Zantac and Zyrtec errors (See ODS Consults 01-0014-1 and 01-0014-2) and provided the findings to the Division of Pulmonary and Allergy Drug Products (HFD-570). These consults addressed factors that may have contributed to the medication errors between Zantac and Zyrtec. DMETS recommended that both manufacturers highlight the different portions of their proprietary names (e.g.zYRtEc vs. zANtAc) or emphasize the established names by

placing them before the proprietary names and by increasing their font sizes. To date there has been no action taken on DMETS post-marketing recommendations.

2. The Division of Medication Errors and Technical Support conducted a root cause analysis of the Zyprexa and Zyrtec errors (See ODS Consult 01-0233) and provided the recommendations to the Division of Neuropharmacological Drug Products (HFD-120). This consult addressed factors that may have contributed to the medication errors between Zyprexa and Zyrtec. DMETS recommended differentiating the labels of the two products and dissemination of appropriate educational materials. The manufacturer of Zyprexa has revised the name so that it is represented as ZyPREXA with the PREXA portion of the name back-highlighted in yellow. HFD-120 has also asked the sponsor to institute an educational program.

3. DMETS has no safety concerns with regard to the dosage form description "Chewable". The modifier will likely minimize the possibility for confusion with other drugs or other Zyrtec formulations.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Zyrtec Chewable Tablets, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. PROFESSIONAL SAMPLE BLISTER (5 mg and 10 mg) One Count

1. Front panel:

   a. [ ]

   b. Relocate the strength so that it appears in conjunction with the established name and increase its prominence.

   c. Because this is a chewable tablet, revise to read '**chew**' rather than 'take…'

2. Back panel:

   The product name and website obscure the readability of the stamped lot number and expiration date. Revise accordingly.

B. PROFESSIONAL SAMPLE CARTON (5 mg and 10 mg) 30 cards X 1 tablet

See comments under A1.

C. INDIVIDUAL FOLDING CARTON-PROFESSIONAL SAMPLE (10 mg) Ten count

See Comments under A1.

D. PROFESSIONAL SAMPLE SHIPPING CARTON (Early Experience Kit 10 mg) (10 x 10)

1. See comments A1.

2. DMETS notes that this carton contains 10 professional sample cartons of 10 tablets each and is referred to as the 'Early Experience Kit'. Please explain what is meant by this terminology.

E. BLISTER LABEL (5 mg and 10 mg) 10 count

We note that the labels and labeling were submitted in black and white. Thus, DMETS did not have the opportunity to evaluate and comment on the use of colors, color fonts and/or graphics, etc. Additionally, we are unable to determine if the strengths are differentiated by color. Because there are multiple strengths available, we recommend differentiating them with the use of contrasting color, boxing or some other means.

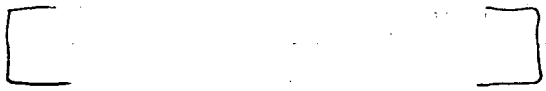
F. INDIVIDUAL FOLDING CARTON (5 mg and 10 mg) 3 x 10 count

1. The numbers 5 and 10 inside the blue circle have no designation. DMETS recommends deleting the blue circle. The blue circle (containing the numbers 5 and 10) are distracting especially since the strength is prominently displayed below.

2. Revise the net quantity to read "30 chewable tablets – 3 X 10 tabs/card".

3. Increase the prominence of the statement "Tablet not recommended for children under the age of 2 years old".

G.



H. INSERT LABELING

APPEARS THIS WAY
ON ORIGINAL

IV. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Linda Wisniewski
2/17/04 10:25:21 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/17/04 12:36:29 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/17/04 02:28:45 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECONFERENCE

DATE: December 16, 2003

APPLICATION: NDA 21-621/ Zyrtec Chewable Tablets/Pfizer

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Craig Bertha, Ph.D., Acting Chemistry Team Leader
Edwin Jao, Ph.D., Chemistry Reviewer
Lori Garcia, Project Manager
Colette Jackson, Project Manager

PFIZER ATTENDEES AND TITLES:

Denise Andrews, Regulatory Affairs
Debra Webb, Senior Scientist, Regulatory, CMC, PGRD
Thomas Garcia, Associate Director, Regulatory CMC, PGRD

BACKGROUND: The purpose of this meeting is to discuss comment 2.b. of the cetirizine hydrochloride chewable tablets Discipline Review Letter dated November 14, 2003.

DISCUSSION:

Pfizer requested the Division clarify the factors contributing to the decision regarding the acceptability of Betadex NF, besides what is available in the compendia. The Division indicated that the acceptability of the currently proposed CMC controls for Betadex are dependent upon the manufacturing methods utilized. The Division has not been provided information on the manufacturing process. Pfizer stated that the compendia information is usually sufficient, therefore eliminating the need to submit additional information. Pfizer also noted that Betadex is generally regarded as safe (GRAS). The Division informed Pfizer that even though Betadex is an excipient in the National Formulary (NF), it has not been used to our knowledge as an excipient or as part of an oral drug product that is approved for use in the United States. The acceptability of this excipient for use in this drug product will also have to be evaluated by our Pharmacological/Toxicological team. An NF listed excipient does not necessarily equate acceptance by the Agency for use in drug products. Furthermore, pending more complete information describing the manufacturing process for preparation of the Betadex, there may be other parameters that should be evaluated or controlled during manufacturing or on the final material itself. Until this additional information is provided it is not possible for the Agency to be more specific with regard to potential additional controls for this excipient.

Pfizer expressed its concern with establishing a drug master file (DMF). Pfizer would like the flexibility to utilize multiple suppliers. The Division indicated that if the suppliers have similar

manufacturing methods and procedures, it would be acceptable, but there may be potential issues if they differ. All DMF's would be evaluated for safety and quality control.

Pfizer asked how they could add a supplier to their NDA without commitment to one supplier. It is doubtful that the vendors would supply the necessary information and they would need letters of authorization (LOA's) from each of their suppliers. The Division stated that multiple DMF's are required if the manufacturer will not supply the information. Alternately, the manufacturing process could be submitted to the NDA, providing the DMF holder commits to no changes in the manufacturing process and also commits to report any changes directly to Pfizer. The Division asked why Pfizer is hesitant in committing to one or two suppliers. Pfizer stated that they are unsure of the commercial outcome and the manufacturer may have preferred vendors. The Agency indicated that if the applicant includes sufficient additional controlling specifications for the Betadex that will take into consideration the manufacturing process (e.g., isomeric purity, residual solvents), the NDA could be reviewed without the DMFs from the Betadex manufacturers. Pfizer noted that they would need to discuss this issue internally and get back with the Agency

Colette Jackson, Minutes Preparer

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Colette Jackson
1/14/04 02:24:22 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 4, 2003		21-621	N	May 15, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zyrtec (cetirizine HCl) Chewable Tablet	Standard	Antihistamine	February 28, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for a nomenclature consult to evaluate the acceptability of Zyrtec Chewable Tablet.
This submission is electronic only and is located in the EDR in the submission dated May 15, 2003.

PDUFA DATE: March 16, 2004

CC:
Archival NDA 21-621
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Colette Jackson
12/4/03 02:20:20 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-621

DISCIPLINE REVIEW LETTER

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

Attention: Rita A. Wittich
Vice President, Worldwide Regulatory Strategy

Dear Ms. Wittich:

Please refer to your May 15, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl) Chewable Tablets, 5 mg and 10 mg.

Our review of the Chemistry, Manufacturing and Controls section of your submission dated May 15, 2003, is complete, and we have identified the following deficiencies. Additional comments will be forthcoming pending our review of your amendments.

1. The following comment pertains to the Manufacturing and Packaging of the drug product:

   a. Revise the Master Production Record to include information regarding the storage procedure for the bulk tablets prior to final packaging.

2. The following comments pertain to the Specifications and Methods for the excipients:

   a. Include a test and acceptance criteria for residual solvent(s) in the Betadex acceptance specifications.

   b. Provide a letter of authorization from the manufacturer of Betadex to a Drug Master File (DMF). The DMF should include all the pertinent CMC information with appropriate acceptance criteria including residual solvent. Further review of the Betadex manufacture information may result in the need to add additional attributes in the acceptance specifications.

   c. Provide certificate of analyses (COA) for representative batches of Betadex.

   d. Additional comments from Pharmacology/Toxicology may be forthcoming regarding the usage of the Betadex as a drug product excipient.

   e. DMF ——was found to be inadequate to support your application. A deficiency letter dated October 22, 2002 was forwarded to the holder.

3. The following comments pertain to the Regulatory Specifications and Methods for the drug product:

   a. Tighten the acceptance criteria of the drug product (e.g., individual and total degradants) to reflect the available data provided on pilot scale batches in the original application. Additional comments on the drug product specification acceptance criteria will be forthcoming following an evaluation of your updated stability data.

   b. Provide sampling information in terms of sampling for analytical procedures. The information should describe the number of samples selected for a determination, how they are used (i.e., individual or composite), and if replicate analysis is done.

   c. Revise the Standard Test Procedure —— to include information about the type of the —— plate.

   d. Specify the extraction procedure in the sample preparation part of method ——

   e. Revise the method —— such that the system suitability requirements are presented as limits, e.g., Precision —— , and Tailing Factor ——

   f. Provide the method for testing dosage form hardness ——, e.g., model of the instruments, sampling procedure, and analysis protocols.

   g. Additional comments may be forthcoming regarding your proposed acceptance criteria for the drug product specifications pending our review of your updated stability data.

4. The following comment pertains to the Container/Closure System:

   a. Provide representative certificate of analyses from the manufacturers of —— Blister Material (supplier# ——) and Blister Foil Backing (supplier# ——) to support the suitability and quality control of this container/closure system. The COAs should clearly indicate the type of the —— alloy used in both top and bottom layers.

5. The following comments pertain to the stability data provided with the original NDA submission. Additional comments may be forthcoming pending review of your updated stability data.

   a. Revise the post approval stability protocol to include annual testing for microbial content.

   b. Revise the post approval stability protocol for annual batches to increase the testing frequency (e.g., 0, 3, 6, 9, 12, 18, 24 etc.) due to the currently limited manufacture and stability experience with this product from the intended commercial site.

   c. Provide more evidence (e.g. description of the methods, the typical chromatograms run by two stability indicating methods) to substantiate the claim that the two sets of stability testing methods (UCB and Pfizer) listed in 3.2.P.8.2., p269 are "functionally equivalent,

differing in style and format only".

d. Provide data for mannitol ester of cetirizine and lactose ester of cetirizine in the stability testing for — primary stability batches and ——— batches.

e. Monitor mannitol and lactose esters of ceterizine in the stability testing of the first — commercial and annual production batches of each strength in each container closure system according to the post-approval stability protocol.

f. Provide an explanation for the mass balance discrepancies observed during your stability studies as illustrated in the table below. Revise the assay and stability-indicating methodology accordingly to address this issue.

Batch #	configuration	conditions	Assay Loss after 6 month	Total degradants increase after 6 month
11631	—			
11631	—			
11631				
11628	blister			
11628	—			

6. The following comment pertains to expiry dating:

a. Expiry dating will be evaluated following review of your updated stability data.

7. The following comments pertain to labeling:

a. [redacted]

b. Clarify the intended usage of cartons ZYRCH-10-0001 and ZYRCH-10-0002. If they are the cartons for blister packaging systems, clearly indicate the inside packaging configurations.

c. Indicate the exact location of lot number and expiration date on cartons ZYRCH-10-0001 and ZYRCH-10-0002.

d. Provide information about the cartons for the 5mg and 10 mg ———————

e. Provide information about the front portion of the 5mg and 10 mg blister packaging systems.

f. Improve the legibility of the labels for 5mg and 10 mg ——————— by either increasing the dimensions of the labels or rearrangement of the contents on the labels.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Colette Jackson, Project Manager, at 301-827-5584.

Sincerely,

{See appended electronic signature page}

Craig Bertha, Ph.D.
Acting Chemistry Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Craig Bertha
11/14/03 03:31:45 PM

APPEARS THIS WAY
ON ORIGINAL

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	2680
CONNECTION TEL	912128573558
SUB-ADDRESS	
CONNECTION ID	
ST. TIME	09/04 13:45
USAGE T	00'22
PGS.	3
RESULT	OK

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 4, 2003

To: Denise Andrews	**From:** Colette Jackson
Company: Pfizer	Division of Pulmonary and Allergy Drug Products
Fax number: 212-857-3558	**Fax number:** 301-827-5586
Phone number: 212-573-3865	**Phone number:** 301-827-5584

Subject: NDA 21-621

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

NDA 21-621
Zyrtec Chewable Tablets

As indicated in our July 28, 2003, filing review letter, information from published literature has shown that the co-administration of formulations containing betacyclodextrins (BCD) with some oral formulations may change the oral bioavailability of the co-administered drug (drug in formulation not containing BCD). Here are some references related to Zyrtec and betacyclodextrins.

1. A.Z.M. Abosehmah-Albidy, et al. (1997). Improved bioavailability and clinical response in patients .....J. Clin. Pharmacol, 44, 35-39.

2. H.O. Ammar et al. (1996). Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation. Part 6. Ampicillin. Pharmazie, 51(8): 568-570.

3. H.O. Ammar et al. (1995). Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation. Part 5. Theophylline. Pharmazie, 51(1): 42-46.

4. H.O. Ammar et al. (1995). Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation. Part 4. Chlorpromazine hydrochloride. Pharmazie, 50(12): 805-808.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-5584.

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

/s/

Colette Jackson
9/4/03 01:10:55 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-621

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

Attention: Rita A. Wittich
Vice President, Worldwide Regulatory Strategy

Dear Ms. Wittich:

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

Name of Drug Product: Zyrtec® (cetirizine HCl) Chewable Tablets

Review Priority Classification: Standard (S)

Date of Application: May 15, 2003

Date of Receipt: May 16, 2003

Our Reference Number: NDA 21-621

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 July 15, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 16, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Colette Jackson
7/29/03 09:46:59 AM
Signed for S. Barnes.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-621

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

Attention: Rita A. Wittich
Vice President, Worldwide Regulatory Strategy

Dear Ms. Wittich:

Please refer to your May 15, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl) Chewable Tablets, 5 mg and 10 mg.

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 July 15, 2003, in accordance with 21 CFR 314.101(a).

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

1. Information from published literature has shown that the co-administration of formulations containing betacyclodextrins (BCD) with some oral formulations may change the oral bioavailability of the co-administered drug (drug in formulation not containing BCD). Provide information related to this issue with Zyrtec chewable tablets.

2. Submit an Integrated Summary of Safety (ISS) for cetirizine HCl. This should include a summary of adverse events that have occurred in any ongoing trials and the postmarketing experience.

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.

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Badru A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
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/

Badrul Chowdhury
7/28/03 04:10:05 PM

APPEARS THIS WAY
ON ORIGINAL

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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
235 East 42nd Street
New York, New York 10017

2. TELEPHONE NUMBER (*Include Area Code*)
(212) 573-7291

3. PRODUCT NAME.
Zyrtec (cetirizine HCl) chewable tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 21-621

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ 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.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4516

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

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

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (*See item 7, reverse side before checking box.*)

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

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

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

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Rita Wittich, Vice President, Vice President, Worldwide Regulatory Strategy	May 15, 2003

Created by: PSC Media Arts (301) 443-2454 EF

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-621	Efficacy Supplement Type SE-	Supplement Number	
Drug: Zyrtec (cetirizine HCl) Chewable Tablet		Applicant Pfizer	
RPM: Colette Jackson		HFD- 570	Phone 7-9388
Application Type: (x) 505(b)(1) () 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	4/7/2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	March 3, 2004
• Most recent applicant-proposed labeling	March 8, 2004
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS- March 17, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	March 3, 2004
• Applicant proposed	March 8, 2004
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Division Director Medical Team Leader 2/23/04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	1/15/04 and 7/21/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	January 13, 2004
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	January 18, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	3/12/03 and 10/23/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	CMC review 10/23/03
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	10/17/03 **(x)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**()** Completed **( )** Requested **(x)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2/10/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A