CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-464

21-466

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-464 and 21-466 SUPPL # N/A

Trade Name VFEND® Generic Name Voriconazole

Applicant Name Pfizer, Inc. HFD-590
Approval Date November 14, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

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

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

      YES /_x_/ 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 /_x_/

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

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

YES /___/ NO /_x_/

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

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

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_x_/

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

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

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates

or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x_/ NO /___/

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

NDA # 21-266 VFEND (voriconazole) Tablets

NDA # 21-267 VFEND IV (voriconazole) for Injection

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 /___/ N/A /_x_/

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 9. IF "YES," GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.)

   If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_X_/ NO /___/

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

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

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

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

YES /_x_/ NO /___/

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

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

YES /___/ NO /_x_/

(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 /___/ N/A /_x_/

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 /_x_/

If yes, explain:

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

Investigation #1, Study # 305

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 /_x_/

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

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

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

   Investigation #1 YES /___/ NO /_x_/

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

   NDA # _____ Study #

NDA # _____ Study #

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

Investigation # 1 : Study # 305

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 # 305 YES /x/ NO /___/ Explain:

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

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

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

YES /___/ NO /_x_/

If yes, explain: _____

_____

_____

Rebecca D. Saville
Signature of Preparer Date
Title: Regulatory Project Manager

Renata Albrecht
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Rebecca Saville
11/14/03 03:51:52 PM
NDAs 21-464/21-466 Exclusivity Summary VFEND EC

Renata Albrecht
11/14/03 05:04:12 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-464 & 21-466 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: November 17, 2000 Action Date: December 17, 2001
Class I Resubmission/Stamp Date: May 14, 2003 Action Date: November 14, 2003 HFD 590
Trade and generic names/dosage form: VFEND® (voriconazole) Tablets and VFEND® IV (voriconazole for infusion)

Applicant: Pfizer, Inc. Therapeutic Class: Antifungal
Indication(s) previously approved:
(1) Invasive aspergillosis
(2) Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, in patients intolerant of or refractory to other therapy

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Esophageal candidiasis

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

__ Yes: Please proceed to Section A.

X No: Please check all that apply: ____Partial Waiver __X__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:

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:

2-18 years of age deferred
0-2 years of age deferred

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**
- **X Adult studies ready for approval**
- **X Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 12/31/2004

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

ection D: Completed Studies

Age/weight range of completed studies:

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

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

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

Indication #2: _____

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:

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:

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:

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

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Rebecca Saville
11/13/03 05:38:43 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-464 NDA 21-466	Efficacy Supplement Type: n/a	Supplement Number: n/a	
Drug: **VFEND (voriconazole) Tablets and IV (voriconazole for infusion)**		Applicant: Pfizer, Inc.	
RPM: Rebecca Saville		HFD-590	Phone # 301-827-2127
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): n/a	

❖ Application Classifications:	
• Review priority	( ) Standard ( ) Priority (x) Resubmission
• Chemical class (NDAs only)	n/a
• Other (e.g., orphan, OTC)	n/a
❖ User Fee Goal Dates	November 14, 2003
❖ 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 (NDA 21-266 and 21-267)
• 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)	n/a
• OC clearance for approval	n/a
❖ 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 (see NDA 21-266 and NDA-21-267)
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified (see NDA 21-266 and NDA-21-267)
• 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	x (11-14-03)
• 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)	AE December 17, 2001
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes, via approvals email ( ) N/A
• 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)	n/a
• Most recent applicant-proposed labeling	x (with minor spelling corrections)
• Original applicant-proposed labeling	x
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	n/a
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	x
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	n/a
• Reviews	n/a
❖ 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	n/a
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	n/a (see NDA 21-266 and 21-267)
• Pre-NDA meeting (indicate date)	n/a (see NDA 21-266 and 21-267)
• Pre-Approval Safety Conference (indicate date; approvals only)	n/a (see NDA 21-266 and 21-267)
• Other	n/a (see NDA 21-266 and 21-267)

❖ Advisory Committee Meeting	
• Date of Meeting	October 14, 2001 (see NDA 21-266/21-267)
• 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)*	n/a
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	11/10/2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	11/06/2003
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	11/13/2003
❖ Demographic Worksheet *(NME approvals only)*	n/a
❖ Statistical review(s) *(indicate date for each review)*	11/09/2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11/07/2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	n/a
• Bioequivalence studies	n/a
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	n/a
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	n/a
• Review & FONSI *(indicate date of review)*	n/a
• Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	n/a
❖ Facilities inspection (provide EER report)	Date completed: **n/a** ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed **n/a** ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	n/a
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

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/s/

Rebecca Saville
11/14/03 05:42:31 PM
NDA 21-464/21-466 Action Package Checklist for VFEND

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-464
NDA 21-466

Pfizer Inc.
Attention: Maureen Garvey, Ph.D.
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Dr. Garvey:

We acknowledge receipt on May 14, 2003 of your May 13, 2003 resubmissions to your new drug applications for VFEND® (voriconazole) Tablets, NDA 21-464 and VFEND® (voriconazole for injection), NDA 21-466. You will recall that, as Renata Albrecht, M.D., explained by telephone on December 11, 2001, NDA numbers 21-464 (Tablets) and 21-466 (for Injection) have been assigned to the indication of esophageal candidiasis for our administrative purposes. Once a final action is taken on this indication, NDA numbers 21-464 and 21-466 will be retired and all future correspondence should refer to NDAs 21-266 and 21-267, respectively.

We consider this a complete, class 2 response to our December 17, 2001 action letter. Therefore, the user fee goal date is November 14, 2003.

If you have any question, call Jouhayna Saliba, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Frank
6/2/03 04:17:27 PM
NDA 21-464 and NDA 21-466

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 5, 2002

To: Maureen Garvey	**From:** Jouhayna Saliba
Company: Pfizer	Division of Special Pathogen and Immunologic Drug Products
Fax number: 212-573-7314	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2387

Subject: Response to submission dated July 18, 2002

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

Dear Dr. Garvey:

We refer to your submission dated July 18, 2002 for protocol A1501041 "A multi-centre, randomized, single-blind, single dose, placebo-controlled, 5-way crossover study to investigate the effect of 3 oral doses of voriconazole (800mg, 1200mg, and 1600mg) and active comparator (oral ketoconazole 800mg) on QTc interval in healthy subjects aged 18-65 years."

We have the following response to your request to use only Fridericia's correction factor (QTcF) in the analysis of the QT data from study A1501041.

The Division is in agreement that Fridericia's formula should be used in the primary data analysis as it appears to correct the baseline QT data for heart rate more appropriately than Bazett's formula, as evidenced by the shallower slope of the linear regression line obtained by plotting lnQTc versus lnRR. Please note final determination of the appropriateness of the analysis will be made at the time the final study report is reviewed. Additional calculations using Bazett's correction formula (QTcB) may be requested at that time as a supportive analysis.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2387.

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/s/

Jouhayna Saliba
8/5/02 03:03:04 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 16, 2002

To: Maureen Garvey	**From:** Jouhayna Saliba
Company: Pfizer	Division of Special Pathogen and Immunologic Drug Products
Fax number: 212-573-7314	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2387

Subject: Comment regarding QTc Study

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-266 and 21-267
Voriconazole

Dear Dr. Garvey:

The following are comments regarding the oral QTc study protocol submitted on December 17, 2001 with a latest draft submitted on January 14, 2002.

The protocol (A150104) states that the QT baseline to be used will be described in the "Analysis and Reporting plan". Since we cannot locate this information, we are resubmitting our request to calculate baseline using multiple methods. Similar information was previously communicated to you as part of the comments related to Protocol A1501021.

Baseline QTc determination should be defined as:

- The mean QTc for all ECG readings obtained on Day 0 (Run-in Day) for each respective treatment period
- The mean QTc for all ECG readings obtained from the placebo arm, and
- The mean QTc for ECG readings obtained on Day 0 of all treatment periods at times corresponding to each subject's C_{max}.

  An example for the third definition is as follows:

  For a given subject, if the drug C_{max} is achieved at 1 hour, then the change in QTc will be the difference between the QTc value at C_{max} and the mean of the QTc values obtained at 1 hour on Day 0 of all five treatment periods. This method will minimize the possible effect of time-of-day, if any, on the variability of the QTc parameter.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2387.