CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-266

21-267

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266
NDA 21-267

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

Dear Dr. Garvey:

We acknowledge receipt on March 27, 2002 of your March 26, 2002 resubmission to your new drug applications for VFEND™ (voriconazole) tablets and VFEND™ I.V. (voriconazole) for infusion.

We consider this a complete, class 1 response to our December 17, 2001 action letter. Therefore, the user fee goal date is May 24, 2002.

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

Sincerely,

{See appended electronic signature page}

Ellen 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
4/29/02 05:22:55 PM
NDA 21-266 and NDA 21-267

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266
NDA 21-267

Pfizer Inc.
Attention: Maureen Garvey, Ph.D.
50 Pequot Avenue
New London, CT 06320

Dear Dr. Garvey:

Please refer to your submission dated January 31, 2002, requesting an extension of the deferral date for submission of the pediatric oral formulation of VFEND (voriconazole).

We have reviewed the submission and agree that an extension of the deferral date is justified for submission of the pediatric oral formulation of VFEND (voriconazole) because stability problems with the current formulation have been encountered.

Accordingly, submission of the pediatric oral formulation of VFEND (voriconazole) is deferred under 21 CFR 314.55 until December 31, 2003.

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

Sincerely

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Renata Albrecht
3/28/02 11:49:38 AM

WorldWide Regulatory Affairs
Pfizer Inc
50 Pequot Avenue
New London, CT 06320

Global Research & Development

May 23, 2002

Mark Goldberger, M.D., Director ODE IV
Renata Albrecht, M.D., Director
Division of Special Pathogen and Immunologic
Drug Products HFD #590
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM
9201 Corporate Boulevard
Rockville, MD 20850

Dear Drs. Goldberger and Albrecht:

RE: NDA-21-266 -VFEND™ - (voriconazole) tablets
NDA-21-267 -VFEND™ I.V. - (voriconazole) for infusion (cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

We refer to the May 17, 2002 request, shared via telephone call from Ms. Jouhayna Saliba, for the protocol submission, study initiation, and final study report submission dates for the studies recommended in the December 17, 2001 approvable letter.

As indicated in an email to Ms. Jouhayna Saliba on May 21, 2002, the requested target dates for the agreed studies are as follows:

	Protocol Submission	Study Initiation	Report Submission
Interaction Studies			
Ritonavir	July 2002	August 2002	August 2003
Efavirenz	October 2002	November 2002	November 2003
Methadone	1Q2003	1Q2003	1Q2004
Dog Cardiac Contractility Study	October 2002	January 2003	End 1Q2003

As discussed with Ms. Saliba, we are considering another rifabutin interaction study but we may choose not to perform such a study although we recognize that the rifabutin contraindication would then remain in the label.

We also continue to feel that an oral contraceptive study should not be a requirement for voriconazole. The Division has agreed that a metabolic interaction between oral contraceptives and voriconazole will not occur. The rationale for a potential pharmacodynamic interaction is not clear. The interaction between antibiotics and ethinylestradiol is thought to be mediated by an effect on enterohepatic recirculation. Since it is not possible to predict which women may be in the very small subset who are susceptible to enterohepatic recirculation of ethinylestradiol, we would have no means for recruiting such women for an interaction study.

If you have any questions regarding this submission, please feel free to call me at (212) 733-5688.

Please include this information in our files for NDA 21-266 and NDA 21-267.

Sincerely,

for Maureen H. Garvey, Ph.D.
Director
Regulatory Strategy, Policy and Registration
Worldwide Regulatory Affairs

cc: Ms Jouhayna Saliba, Project Manager

NDA 21-266 Submission #158
NDA 21-267 Submission #158

NDA 21-266 & 21-267
Voriconazole tablets and IV

Dear Dr. Garvey:

In preparation for our teleconference on Thursday March 14, 2002, following are a list of items to be addressed with regard to the clinical pharmacology section of the label submitted on February 25, 2002.

1. The sentence [redacted] s not acceptable since it is a qualitative and not quantitative statement.

2. A range for oral bioavailability, in addition to the 96% point estimate, needs to be included. We propose reporting the range as 60 to 100% (and not up to 122% as the label indicated), since we recognize that this may be confusing to clinicians.

3. Coadministration of voriconazole and rifabutin needs to remain contraindicated. We are willing to revisit this issue if Pfizer performs an additional study evaluating a dose of voriconazole 350 mg orally Q12 hours and rifabutin 300 mg QD (see Approvable Letter). The data submitted investigating this regimen in 3 patients is not sufficient.

4. [redacted] should remain in Table 7. We are willing to revisit this issue if Pfizer performs an additional study evaluating the effect of oral contraceptives on voriconazole (See Approvable Letter).

5. Dihydropyridine Calcium Channel Blockers should remain in Table 8, however we agree to delete [redacted]

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

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/s/

Jouhayna Saliba
3/13/02 09:06:28 AM
CSO

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.

Dear Dr. Garvey:

In preparation for our meeting Friday May 25, 2001, We would like to request the following information regarding NDAs 21-266 and 21-267 for voriconazole.

1. Please prepare a graphical representation of the change in QTcB from baseline against voriconazole concentration after receiving single and multiple doses at 4 hours after the last dose. These graphs would be similar to the ones in the Cardiac Safety Report, except it would be the 4-hour data and not the 1-2 hour data.

2. Please present the adverse event profile and any available EKG data from the Phase II/III studies, including only those subjects above the 75th quartile of plasma concentrations. This would include subjects with plasma concentrations in the range of ~~~~~~~~~~~~~~~~~~~~

3. What was the overall incidence of QT prolongation and torsades de pointes in the comparator arms in the Voriconazole NDA?

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

Dear Dr. Garvey:

We would like to request the following regarding NDAs 21-266 and 21-267 for voriconazole:

Re: New Aspergillosis data

In addition to the datasets similar to those already submitted, we would like analysis datasets that contain all of the variables used to perform the primary and secondary efficacy analysis. Preferably, these datasets should have one row per patient. If multiple rows per patient are necessary, for example one row per visit, the visit variable should be complete with no empty cells. The variables we would like to have included in the datasets are:

- The standard- patient id, protocol, treatment, center, country, demographic (sex, age, race)
- Baseline neutropenic status
- Site of infection
- Diagnosis (definite, probable)
- Underlying disease
- Global response (data review committee and investigator assessments), primary analysis
- Duration of therapy (both methods as calculated by Pfizer)
- Indicator as to whether the patient switched from IV to oral therapy during treatment
- Day of switch to oral, if applicable
- Indicator as to whether the patient is eligible to be included in the evaluable analysis
- For the secondary time to event analysis, the time of the event and associated censoring variables
- any additional variables used in the primary and secondary efficacy analysis not stated above

This information can be provided in multiple datasets; one for the primary analysis and one or more for the secondary analysis.

The following are Questions to consider before submitting the new datasets for the new aspergillosis data:

1. How many patients on amphotericin discontinued this drug for intolerance or elevated creatinine? How many days had they been on amphotericin? What was their baseline creatinine going into the trial?

2. Of the patients who discontinued amphotericin--how many of these were on concomitant drugs such as aminoglycosides, diuretics, cyclosporine, tacrolimus?

3. How many patients in the trial were treated with antihistamines, steroids?

4. Of the patients who developed "rash", what percentages were on steroids, antihistamines or other immunosuppressant therapy?

5. How many patients had flushing, rash, skin exanthemas? Were they receiving IV or PO voriconazole and how many days of therapy had they received? Was there any particular/unique concomitant drug that all of these patients, who developed rash, may have been taking in addition to voriconazole.

6. In what percentage of patients:

   - Was the study drug stopped completely because of the rash and how long does it take for the rash to resolve once the drug is stopped---did these patients require specific therapy for the rash?

   - Was the study drug stopped and restarted and what was the outcome? How many days were they off the drug before it was restarted?

7. Did anyone continue on the drug, despite the rash, and what was the outcome?

8. How many patients had normal liver function (LFT's = transaminases, t bili , alkphos) going into the trial?

9. What percentage developed elevated LFT's (at 7 days –14 days- 30 days of therapy, etc)? Was the study drug discontinued and did the LFT's return to normal---how long did it take for this laboratory abnormality to resolve? Any particular combination of concomitant therapies that surfaces in these patients with elevated LFT's any underlying disease besides GVHD (hepatitis C?)

10. Please inform us as to how the duration of neutropenia prior to randomization was calculated.

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

Dear Ms. Garvey:

We would like to request the following information regarding NDAs 21-266 and 21-267 for voriconazole.

1. Please provide any available information to help characterize the biopharmaceutics classification of voriconazole. Please refer to the Guidance for Industry: "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System."

2. Please provide the number (and percent) of patients enrolled in Phase III clinical trials who received the N6117 and N8175 formulations of oral voriconazole. In addition, please provide comparative safety data for patients treated with these formulations.

3. Please provide dissolution profile comparisons for formulations N6117 and N8175.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2423.

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266
NDA 21-267

Pfizer Global Research & Development
Attention: Maureen H. Garvey, Ph.D.
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Garvey:

Please refer to your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vfend™ Tablets and Vfend™ I.V. Solution.

On November 14, 2001, we received your November 13, 2001 major amendment to these applications. The receipt date is within 3 months of the secondary user fee goal date. Therefore, we are extending the goal date to provide time for a full review of the submissions. The user fee goal date is December 17, 2001.

If you have any questions, 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
11/16/01 12:40:40 PM
NDA 21-266 and NDA 21-267

J. Saliba

Food and Drug Administration
Rockville MD 20857

DMF —

JUL 9 2001

Dear Mr. [redacted]

Your letter dated May 13, 1999, authorizes us to reference Drug Master File (DMF) — for information applicable to the manufacturing of [redacted] in support of Pfizer, Inc.'s drug product application (NDA).

Your communication dated July 31, 1998 was reviewed in support of this NDA and the following additional information is requested.

Please identify all [redacted], and the ratio of all components used to manufacture [redacted] as supplied to Pfizer, Inc.

Please cite specific references to applicable [redacted] regulations for — contact for all components of the —

Please provide criteria and specifications for the use of —

Please provide a copy of your release specifications. Please provide results of testing according to USP <661> and <671>, if performed by [redacted]

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Pfizer, Inc. will be notified that information has been requested for your DMF. When you amend your DMF — please notify Pfizer, Inc. in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that your DMF has been amended. Do not provide a copy of the amendment to the review chemist.

Gene W. Holbert, Ph.D.
FDA
5600 Fishers Lane, HFD-590
Rockville, MD 20857

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

Sincerely,

/S/

Norman R. Schmuff, Ph.D.
Chemistry Team Leader for the
Division of Special Pathogen and Immunologic
Drug Products, HFD-590
DNDC 3, Office of New Drug Chemistry
Center for Drug Evaluation and Research

CC:
Original DMF (2 copies) —
HFD-590/Division File for NDA 21-266
HFD-590/Chemist/G.Holbert
HFD-590/Chemistry Team Leader/Norman R. Schmuff, Ph.D.
HFD-590/RPM/J.Saliba
HFD-590/Team Leaders and Reviewers

Drafted by: gwh/June 24, 2001
Initialed by: names of draft letter reviewers
Final: initials/date
filename: C:\Data\My Documents\DMF\PACKAGING\DMF — IR.doc

DMF INFORMATION REQUEST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND ——
IND ——

Pfizer Global Research and Development
Attention: Maureen H. Garvey, Ph.D.
Director, Regulatory Affairs Department
Eastern Point Road
Groton, CT 06340

Dear Dr. Garvey:

Reference is made to your correspondence dated September 29, 2000 requesting a deferral for certain requirements under the Pediatric Final Rule pursuant to 21 CFR 314.55(c)(3).

This request consisted of three parts as follows:

1. A deferral until June 30, 2001 for submission of Study A1501007, "An open, intravenous multiple dose, multi-centre study to investigate the pharmacokinetics, safety and toleration of voriconazole in children aged 2-12 years who require treatment for the prevention of systemic fungal infection."

2. A deferral for submission of the pediatric oral suspension formulation until March 31, 2002.

3. A deferral for submission of data in pediatric subjects 0-2 years of age. You state that you plan to convert this request for a deferral to a request for a waiver by December 1, 2002.

We have reviewed the information you have submitted and agree that a deferral as requested in items 1 and 2 above is justified for voriconazole for the pediatric population.

We also refer to your January 18, 2001 facsimile transmission that requested a waiver for children under 2 years of age. As communicated to you in the February 5, 2001 teleconference, we have determined that a deferral for submission of data in pediatric subjects 0-2 years of age is justified for voriconazole for the pediatric population.

Accordingly, a deferral for pediatric studies for this application is granted under 21 CFR 314.55(b) at this time.

If you have questions, please contact Diana Willard, Regulatory Project Manager, at (301) 827-2387.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D.
Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Mark Goldberger
3/8/01 04:36:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-266
NDA 21-267

Pfizer Global Research & Development
Attention: Maureen Garvey, Ph.D.
Director, Regulatory Affairs Department
Eastern Point Road
Groton, CT 06340

Dear Dr. Garvey:

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 Products: Vfend (voriconazole) Tablets (50 and 200mg)
Vfend (voriconazole) Intravenous (200mg/vial)

Review Priority Classification: Standard (S)

Date of Application: November 17, 2000

Date of Receipt: November 17, 2000

Our Reference Number: NDA 21-266 and NDA 21-267

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 16, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 17, 2001 and the secondary user fee goal date will be November 17, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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

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

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

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

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

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

Sincerely,

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

/s/

Ellen Frank
1/16/01 06:53:49 PM
NDA 21-266 and NDA 21-267

JAN 9 1997

IND

Pfizer Inc.
Attention: Martha A. Brumfield, Ph.D.
Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Brumfield:

Please refer to your Investigational New Drug application submitted pursuant to section 505(I) of the Federal Food, Drug, and Cosmetic Act for voriconazole tablets and voriconazole lyophilized powder.

Please also refer to the February 26, 1996 and March 5, 1996 telephone conferences between you and Albinus D'Sa, Ph.D. of our division regarding your amendment dated June 11, 1996. In addition, please refer to the August 14, 1996 telephone conference between you and Mary Ann Jarski, Ph.D. regarding your amendment dated September 12, 1996.

The telephone conferences and amendments outlined above relate to the synthesis of the intermediate [redacted] as their starting material. The [redacted] is consistent with all tests described in the USP/NF official monograph for fluorouracil. The [redacted] that is produced will then be used by Pfizer, Inc. in the synthesis of voriconazole.

The [redacted] is currently being held by US Customs in Boston.

The information provided in the telephone conversations and amendments is acceptable from a chemistry, manufacturing and controls standpoint.

A copy of this communication is being forwarded to the Boston District FDA Office to allow for the release of the [redacted] from US Customs. A copy of this letter is also being forwarded to [redacted] to allow for their acceptance of the [redacted] from US Customs.

The material submitted is being retained in our files.

Should you have any further questions, please contact Ms. Vikki Kinsey, Consumer Safety Officer at (301) 827-2335.

Sincerely,

/S/ 1-7-99

Donna J. Freeman, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:

/S/ 3Jan97

HFD-530/Chikam
HFD-530/Miller /S/ 12/13/96
HFD-530/Jarski 12/24/96
HFD-530/Decicc 12.26.96

cc:
Original IND's
Divison files
HFD-530/Jarski
HFD-530/Miller
HFD-530/Kinsey

Richard Midwood
Food and Drug Administration
Boston NE Region
One Montvale Ave.
Stoneham, MA 02180

Address: C:\wpfiles\48735ltr

DIV

IND —
IND —

JUL 25 1996

Pfizer Inc.
Attention: Martha Brumfield, Ph.D, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Brumfield:

Please refer to your Investigational New Drug application submitted pursuant to section 505(I) of the Federal Food, Drug, and Cosmetic Act for voriconazole oral and intravenous.

Please also refer to your May 1, 1996, submission to IND — requesting an End of Phase II meeting. The meeting was held on June 24, 1996, with the following participants:

Representatives of the Division of Antiviral Drug Products
David Feigal, Division Director
Donna Freeman, Deputy Director
Steve Gitterman, Team Leader (Clinical)
Teresa Wu, Medical Officer
Mary Ann Jarski, Chemistry Reviewer
Owen McMaster, Pharmacology Reviewer
Shukal Bala, Microbiology Reviewer
Lisa Kammerman, Team Leader (Biostatistics)
Liji Shen, Biostatistics Reviewer
Barbara Davit, Biopharmaceutics Reviewer

Representatives of Pfizer
Martha Brumfield, Regulatory
Peter Coates, Pharmacokinetics
Al Lodola, Toxicology
Guy Paulus, Toxicology
Rebecca Rosenstein, Statistics
Gary Ryan, Director
Nicos Sarantis, Clinical
Haran Schlamm, Clinical
Robert Swanson, Clinical
Konrad Tomaszewski, Clinical Safety
Steve Wicks, Chemistry

In accordance with the Manual of Policies and Procedures (MAPP) 4512.1, we are providing you with a list of the issues and resolutions discussed during the June 24, 1996 End of Phase II meeting.

Should you have any questions concerning this letter, please contact Vikki Kinsey, Consumer Safety Officer at (301) 827-2335.

Sincerely yours,

Anthony W. DeCicco, R.PH
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:

HFD-530/TL/Gittermar 7/.1/96
HFD-530/MO/WuT 7/22/96
HFD-530/Chem/Jarski 7/22/96
HFD-530/Pharm/McMaste 7/22/96
HFD-530/Micro/Bala 7/22/96
HFD-530/TL/Kammerman 7/22/96
HFD-530/Stat/Shen 7/22/96
HFD-530/Biopharm/Davit 7/23/96

CC:
Orig IND's
Division File
HFD-530/DivD/DFeigal
HFD-530/DD/DFreeman
HFD-530/MO/WuT
HFD-530/CHem/Jarski
HFD-530/Pharm/McMaster
HFD-530/Micro/Bala
HFD-530/Biopharm/Davit
HFD-530/Stat/Shen
HFD-530/SCSO/ADecicco
HFD-530/CSO/Kinsey

Address: a:\minlet.3

AUG 1 4 19

IND
IND

Div

Pfizer Inc.
Attention: Martha Brumfield, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Brumfield:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505 (I) of the Federal Food, and Cosmetic Act for voriconazole oral and intravenous.

Please also refer to the June 24, 1996 End-of-Phase-2 meeting between members of this division and representatives of your company. In reference to that meeting, we have the following comments and recommendations for your consideration:

1. You may initiate dosing at 3 mg/kg/day. Additional clinical data (from studies in which higher doses of drug were used) are needed to justify dosing at the higher doses, for the proposed duration.

2. Among the toxic effects associated with intravenous voriconazole administration in animals are changes in the liver, heart, thyroid gland, eyes, pituitary gland and adrenal glands. Continued monitoring of these organs is important, even if these changes have not been reproduced in early human trials, since this particular dose and treatment duration have not been previously tested in man.

3. This drug is teratogenic and induces cleft palates in rats. While women should be encouraged to enter this trial, it should be clearly explained that there is a risk to the unborn child if she should become pregnant, and that effective contraception be used for the duration of the study.

4. Regarding your proposed indication for aspergillosis, you agreed to provide a detailed description of the mechanism of conducting the two clinical trials of aspergillosis in parallel and outlining how the results of both studies will be pooled.

5. With respect to your proposed indication for the empiric treatment of fungal infections, we recommend that you include incidence of fungal infection as a secondary endpoint.

6. Your proposed indication for systemic candidiasis will be supported by two randomized comparative multi-center clinical trials of treatment of esophageal candidiasis and by documented cases of candidiasis from the empiric therapy trials. This approach seems adequate, however, we will provide additional comment upon receipt and subsequent review of the data.

7. With respect to your proposed indication for patients who are intolerant of and or refractory to current therapies, we recommend that you include a closely monitored follow-up of patients after completion of the study.

8. We recommend that you include the FDA in the process of determining the dissolution specifications for this drug product.

9. The use of the complexing agent cyclodextrin will need to be addressed.

We will continue to work with you and look forward to the continued clinical development of this drug product.

Should you have any further questions, please contact Ms. Vikki Kinsey, Consumer Safety Officer at (301) 827-2335.

Sincerely,

/S/ 8/15/96

Donna J. Freeman, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:

HFD-530/TL/Gitterman 8/2/96
HFD-530/MO/WuT 8/2/96
HFD-530/TL/Farrelly 8/5/96
HFD-530/Pharm/McMaster 8/5/96
HFD-530/TL/Jenkins 8/5/96
HFD-530/Biopharm/Davit 8/5/96
HFD-530/SCSO/DeCicco 8-12-96

cc:
Original IND's
Division File
HFD-530/MO/WuT
HFD-530/Chem/Jarski
HFD-530/Pharm/McMaster
HFD-530/Micro/Bala
HFD-530/Biopharm/Davit
HFD-530/Stat/Shen
HFD-530/CSO/Kinsey

Action: End of Phase 2 letter

Address: O:\finals\voriep2.ltr

January 4, 1996

TO WHOM IT MAY CONCERN

[redacted] a fine chemical manufacturing company, located in [redacted] manufactured by:

[redacted]

[redacted] is used by us to manufacture an advanced intermediate for the Phase III clinical drug substance, Voriconazole - an Anti-fungal - for Pfizer, Sandwich, UK.

The imported [redacted] is used entirely for our manufacturing and no part is re-distributed or re-sold.

Please feel free to contact me if I can answer any further questions.

Sincerely,

[redacted]

[redacted]

[redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-465
NDA 21-467

Pfizer Global Research & Development
Attention: Maureen H. Garvey, Ph.D.
Director, U.S. Regulatory Strategy and Registration
Eastern Point Road
Groton, CT 06340

Dear Dr. Garvey:

Please refer to your new drug applications (NDAs) dated November 17, 2000, received November 17, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VFEND™ (voriconazole) Tablets, NDA 21-266, and VFEND™ (voriconazole for injection), NDA 21-267. Please note, as Renata Albrecht, M.D., explained by telephone on December 11, 2001 to Maureen Garvey, Ph.D., of Pfizer, that NDA numbers 21-465 (Tablets) and 21-467 (Injection) have been assigned to the indication of empiric antifungal therapy in febrile neutropenic patients for our administrative purposes. Once a final action is taken on this indication, NDA numbers 21-465 and 21-467 will be retired and all future correspondence should refer to NDAs 21-266 and 21-267, respectively.

We acknowledge receipt of your submissions dated:

November 22, 2000
December 15, 2000
December 20, 2000
January 15, 2001 (NDA 21-465)
January 18, 2001
February 1, 2001
February 6, 2001
February 7, 2001
February 14, 2001
March 2, 2001
March 14, 2001
March 27, 2001
March 28, 2001 (2)
March 29, 2001 (2)
March 30, 2001
April 3, 2001
April 6, 2001
April 9, 2001
April 12, 2001 (NDA 21-465)
April 16, 2001
April 30, 2001
May 2, 2001
June 5, 2001
June 7, 2001
June 12, 2001
June 19, 2001
June 21, 2001 (4)
June 27, 2001 (2)
June 28, 2001
June 29, 2001
July 9, 2001
July 13, 2001 (2)
July 16, 2001
July 17, 2001
July 18, 2001
July 19, 2001
July 20, 2001 (2)
July 24, 2001 (3)
July 25, 2001
July 31, 2001
August 8, 2001
August 10, 2001
August 13, 2001
August 22, 2001 (2)
September 6, 2001 (3)
September 7, 2001 (4)
September 19, 2001 (2)
September 26, 2001
October 2, 2001
October 3, 2001
October 15, 2001 (2)
October 17, 2001 (5)
October 23, 2001
October 24, 2001
October 25, 2001
October 26, 2001
October 30, 2001
October 31, 2001
November 5, 2001 (2)
November 9, 2001
November 13, 2001
November 14, 2001 (2)
November 20, 2001
November 28, 2001
November 30, 2001 (2)
December 3, 2001

May 10, 2001 (2)	August 24, 2001	December 7, 2001
May 16, 2001	August 27, 2001	December 10, 2001 (3)
May 17, 2001 (2)	August 31, 2001 (2)	December 11, 2001 (2)
May 18, 2001 (3)	September 4, 2001 (2)	
May 31, 2001	September 5, 2001 (6 for NDA	
June 4, 2001 (2)	21-266; 5 for NDA 21-267)	

We completed our review of these applications for the indication empiric antifungal therapy in febrile neutropenic patients and find the information presented is inadequate. Therefore, the applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. During a recent inspection of the manufacturing facility for VFEND™ (voriconazole for injection), our field investigator conveyed deficiencies to the facility's representative(s). The methods to be used in, and the facility and controls proposed for, the manufacture, processing, packing, or holding of the drug product by ——————————————— facility, do not comply with the current good manufacturing practice regulations in 21 C.F.R. § 210 and 211 (2001). Satisfactory resolution to these deficiencies is required before these applications may be approved.

2. The one study submitted in support of empiric antifungal therapy in febrile neutropenic patients (Study 150-603, A Randomized, Open Label, Comparative, Multicenter Trial of Voriconazole vs. Liposomal Amphotericin B for Empirical Antifungal Therapy in Immunocompromised Patients with Persistent Fever and Neutropenia) failed to meet the statistical definition of non-inferiority as specified in the analysis plan. It will be necessary to conduct a further study of empiric antifungal therapy in febrile neutropenic patients. We strongly recommend that you consult with the Division of Special Pathogen and Immunologic Drug Products in the design of such a trial.

In addition, prior to approval for empiric antifungal therapy in febrile neutropenic patients, a drug product should demonstrate activity in the treatment of documented invasive *Candida* and *Aspergillus* infections. Although you have demonstrated efficacy in esophageal candidiasis, your applications would be strengthened by demonstration of efficacy in more severe, invasive *Candida* infections. Such data may be provided by the ongoing Study 608, "A Randomized, Open Label, Comparative Multicenter Study of Voriconazole Versus Conventional Amphotericin B Followed by Fluconazole in the Treatment of Candidemia in Non-Neutropenic Subjects," when completed. Alternatively, you may be able to show an advantage in favor of voriconazole with breakthrough *Candida* infections in the additional study of empiric antifungal therapy in febrile neutropenic patients described above.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as major amendments nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Special Pathogen and Immunologic Drug Products to discuss what further steps need to be taken before these applications may be approved.

These drug products may not be legally marketed until you have been notified in writing that these applications are approved.

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

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Acting Director
Office of Drug Evaluation IV
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/

Mark Goldberger
12/17/01 04:32:49 PM