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**Minutes of Second Voriconazole End-of-Phase II Meeting  
Division of Special Pathogen and Immunologic Drug Products**

February 25, 1998

**Attendees:**

**FDA**

Shukal Bala, PhD- Microbiology  
Marc Cavaille-Coll, Actg. Med. Team Leader  
Aloka Chakravarty, PhD-  
Actg. Stat. Team Leader  
Cheryl Dixon, PhD- Statistical Reviewer  
Ellen Frank RPh- Regulatory Mgt. Officer  
Mark Goldberger, MD- Director, DSPIDP  
Linda Gosey, Microbiology Reviewer  
Marianne Mann, MD- Medical Officer  
Owen McMaster, PhD- Pharm/Tox Reviewer  
Kellie Reynolds-  
Rev. Clin. Pharm. and Biopharmaceutics Officer  
Rigoberto Roca, MD- Medical Officer  
Teresa Wu, MD- Medical Officer

**Pfizer**

Reinhard Baildon, MD- Clinical UK  
Maureen Garvey, PhD- Regulatory  
Michael Leeming, PhD- Clinical UK  
Gary Muirhead, PhD- PK  
Alain Romero, PhD- Clinical US  
Rebecca Rosenstein, PhD-Statistics  
Haran Schlamm, MD- Clinical US  
Robert Swanson, PhD- Clinical US  
Konrad Tomaszewski, PhD-  
Clinical Safety UK

**Summary**

Our proposal to support the empirical therapy indication with a single large global trial (603) (instead of two separate trials) together with results of the esophageal candidiasis study (305), the candidemia study (608) and the aspergillosis program was accepted.

Our proposal to support the candidiasis (esophageal and invasive) indication with one completed study in esophageal candidiasis (305) and one study in candidemia (608) which may be filed with an interim analysis if the study is not complete at NDA cutoff was accepted in principle. The quality of the data available from the candidemia trial will determine if an interim analysis will be sufficient. Since the esophageal candidiasis and candidemia trials are both in non-neutropenic patients, the data from the complete NDA database will also determine if the indication will be allowed for both neutropenic and non-neutropenic patients.

Our proposal to support the aspergillosis indication with a non-comparative Phase II study in 137 patients and documented cases of aspergillosis from the Phase III program was accepted in principle. The "strength" of the data, including confirmed diagnosis in a substantial proportion of patients with complete/partial response, will determine if the data package is sufficient.

Whether the indication will be first line or second line will depend on the numbers of patients receiving voriconazole as primary or secondary therapy in 304 and in the total NDA database. The appropriate historical control data must be provided for either first or second line therapy.

Our proposal to support the indication for rare and refractory fungal infections with 5-10 cases for each pathogen was accepted.

Our position that the pathogenesis of serious fungal infections is similar in children and adults and that the pediatric program will consist of single and multiple dose pharmacokinetic studies was accepted. Also accepted was our proposal that the pharmacokinetic data together with data from the Phase III program (over 12 years) and the compassionate use program (no age restriction) will support inclusion of pediatric information in the Clinical Pharmacology, Clinical Studies and Dosing and Administration sections of the labeling.

Our position that the dosing regimen in the pediatric pharmacokinetic studies and dosing recommendations in the labeling will be limited to the intravenous formulation was accepted.

Our position that we will not have an oral suspension available at the time of NDA filing was accepted on the basis of technical difficulties encountered in the ongoing development of an oral formulation. This would not have been an acceptable position based on commercial reasons.

Our position that the difference in Cmax (outside the standard 80-125% bioequivalence range) between the regular-flo lactose tablet used in the esophageal candidiasis study (305) and the fast-flo lactose tablet intended for commercialization is not of clinical significance was accepted pending the clinical data. There is no biopharmaceutics issue with this difference in Cmax.

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## MINUTES

### General

The pre-meeting package identified six Items for Consideration to be covered during the meeting. During their internal pre-meeting, FDA made three additional requests. These were answered:

1. The method used to calculate the level of Type 1 error ( $\alpha$ ) on which the sample size for the candidemia protocol, 608, was based, was provided by Pfizer biometrician Dr. Rebecca Rosenstein to the FDA biometrician, Dr. Cheryl Dixon in a teleconference prior to the meeting.
2. Preliminary data from the aspergillosis study 304 was offered for insertion into the Pfizer agenda during the discussion of the aspergillosis indication.
3. Information about the dose relatedness, description and reversibility of the visual experiences was offered for addition to the end of the Pfizer agenda.

Overheads were faxed to FDA prior to the meeting. These did not include the overheads offered and accepted for showing by R. Baildon and K. Tomaszewski, although they are included with these minutes for information.

Items for Consideration (bold/italics in the following minutes) were discussed following R. Swanson's presentation of each indication and agreements/ positions were recorded.

### Empirical Therapy

***The indication for empirical therapy will be supported by:***

- ***a large, comparative, open label trial in immunocompromised patients (603)***
- ***a comparative, double-blind trial in the treatment of esophageal candidiasis (305)***
- ***data from a comparative candidemia trial (608)***
- ***data from the aspergillosis program***

FDA asked a few questions regarding projected enrollment in the esophageal candidiasis and aspergillosis trials which would support the empirical therapy claim. They were told that the esophageal candidiasis trial will be complete (n= 160 patients on voriconazole), the candidemia trial will be at least 50% complete (n= 78 patients on voriconazole), and the non-comparative aspergillosis trial will be complete (n=137 patients). Dr. Goldberger stressed the importance of the supportive data because:

1. FDA also needs a demonstration of effect in the treatment of at least one specific pathogen, in this case, *Candida and/or Aspergillus*.
2. Results of empirical trials can vary.

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Dr. Goldberger said he appreciated that the studies in the voriconazole clinical program support each other. He said FDA needs to look at the pattern of breakthrough infections in the empirical study; this will affect how FDA will look at other indications.

It was agreed that the data package to support the empirical therapy indication is very reasonable, especially supported by the double-blind, comparative esophageal candidiasis trial 305.

**APPEARS THIS WAY  
ON ORIGINAL**

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

## Aspergillosis

*The aspergillosis indication will be supported by:*

- *an open-label label, non-comparative study in immunocompromised, acute invasive aspergillosis patients*
- *documented cases of aspergillosis from the Phase III program*

FDA accepted R. Swanson's offer to have R. Baildon share some preliminary data from Study 304. (See attached overheads.) During his presentation, R. Baildon stressed, and it was repeated by other Pfizer persons, that we wish to discuss the 304 data, analyses and optimal presentation when the final study report is available. Dr. Wu asked if Protocol 304 had been filed to the IND adding that 304 is the pivotal study in aspergillosis. We acknowledged that it has not been submitted to the IND, but that a report is expected to be produced around mid 1998.

In response to a question from Dr. Wu, R. Baildon said 45% of the patients received voriconazole as first line therapy. In response to a question from Dr. Mann, he said the majority of the patients in 304 were neutropenic.

Dr. Wu asked what indication Pfizer intends to pursue. R. Swanson said that if the data is strong we would expect an indication for first line therapy. Dr. Goldberger said FDA would want to see a significant proportion of patients on voriconazole as initial therapy in the "complete" and "partial" response categories. In his concluding remarks regarding this indication, he said that the decision to grant a first or second line indication would be based on the data, and added that to have enough patients for a first line indication, support may come from the rest of the program. He suggested that we have outside experts review the data and score the patients based on clinical and radiological data, while blinded to outcome as assessed by investigator and previous expert review. He said the complete/partial responders who received voriconazole as primary therapy would form the basis of the approval for aspergillosis.

Dr. Wu said the aspergillosis package is a little weaker than the candidiasis package. She observed that 304 is a mixture of first line and second line treated patients. She said FDA highly encourages sponsors seeking a first line indication to conduct comparative trials. She recommended that we think about the appropriate historical control database. She said the historical control database would be different for a first line claim and a second line claim and recommended we investigate both.

It was agreed that the proposed data package to support the aspergillosis indication is acceptable in concept. Dr. Goldberger stressed again that what is considered adequate will depend on the strength of the data. A decision regarding first or second line therapy will also depend on the data.

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ON ORIGINAL**

### **Rare and Refractory Fungal Infections**

***The indications for rare and refractory fungal infections will be supported by documented cases from the Phase III program.***

Dr. Goldberger commented that we might be seeking to say voriconazole is a "broad spectrum anti-fungal agent" in the labeling. He asked what pathogens we expect to see and was told *Pseudoallescheria*, *Scedosporium*, *Fusarium spp.* He said FDA would want to see efficacy against such pathogens as *Cryptococcus* if such a claim is to be considered. Dr. Wu said we should anticipate many questions if we seek "broad spectrum" labeling. Dr. Goldberger said something will be allowed in the labeling but there may be some decisions regarding how the results are described. He said we should seek out the rare pathogens and complimented the conduct of studies 309 and 604, saying conducting trials such as these is the best way to proceed.

It was agreed that the proposed data package to support the rare and refractory indications, is acceptable.

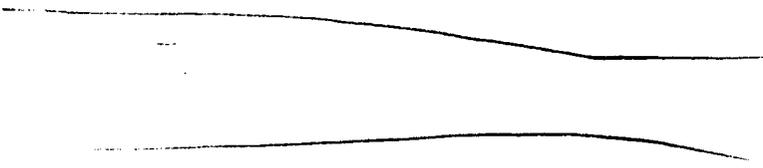
### **Pediatric Program**

***Pediatric information in the voriconazole labeling will be based on single and multiple dose pharmacokinetic studies in appropriate pediatric age groups and data from the compassionate use program.***

***Pediatric dosing using the intravenous formulation is acceptable***

There was a brief discussion regarding dosing in the planned pharmacokinetic studies with the intravenous formulation only. M. Leeming described the limitations imposed upon pediatric dosing by the availability of only two tablet strengths: 50 mg and 200 mg. Dr. Goldberger said it is probably reasonable to proceed with only an intravenous formulation since we have encountered technical difficulties in developing an oral formulation. He said this would not have been an acceptable position if based on commercial reasons. He said FDA would like an update on Pfizer's efforts in this area when we meet with FDA again later this year to discuss the aspergillosis study 304.

**APPEARS THIS WAY  
ON ORIGINAL**



### Visual Experiences

In response to the FDA request, K. Tomaszewski gave a brief presentation addressing the three points of FDA interest: description of the events, relationship to dose, reversibility. He stressed that a 'position paper' had been prepared for submission to FDA which contained data from an electroretinographic study as well as the results of a workshop of external consultants who had reviewed the visual experiences issue.

Dr. Goldberger suggested we consider similar assessments to those conducted by the Trovan team for the analysis of dizziness. Dr. Wu said the evaluation of the visual disturbances would probably involve an internal FDA consult. Dr. Wu said as a last comment that we can also look at discontinuations due to visual AEs in the empirical study.

### Conclusion

The meeting ended with a review by M. Garvey of the agreements and conclusions reached regarding the Items for Consideration.

### Action Items

M. Garvey to submit the position paper on the visual experiences in March.

FDA to request a teleconference with Pfizer following FDA review of protocol 608.

Pfizer to submit, and FDA/Pfizer to discuss, proposal for presentation of data in aspergillosis Study 304 report, which would serve as a model for reports of other pivotal studies in the NDA.

# VORICONAZOLE TARGET LABELING

## INDICATIONS

1. Empirical therapy for fungal infections
2. Treatment of serious candidal infections, including candidemia and esophageal candidiasis
3. Treatment of aspergillosis
4. Treatment of fungal infections for which there is no standard treatment (list of organisms as per clinical trial results)
5. Treatment of fungal infections in patients intolerant of and/or refractory to current therapies

## PEDIATRIC INFORMATION

- Clinical Pharmacology, Clinical Studies, Dosing and Administration

## **SPECIFIC ITEMS FOR CONSIDERATION (CONT.)**

3. The aspergillosis indication will be supported by:
  - an open-label label, non-comparative study in immunocompromised,
  - acute invasive aspergillosis patients (304)
  - documented cases of aspergillosis from the Phase III program
  
4. The indications for rare and refractory fungal infections will be supported by documented cases from the Phase III program (309, 604)

# VORICONAZOLE CURRENT CLINICAL PROGRAM

## INDICATION

*Treatment of aspergillosis*

## NDA PACKAGE

Aspergillosis noncomparative study 304; 137 pts  
Documented cases of aspergillosis from empirical  
study 603

Refractory/rare fungal infection studies 604 and 309

## NOTE

Umbrella analysis of 307/602 filed subsequently

**To:** FDA Log

**Date:** August 21, 1997

**Re:** August 15, 1997 teleconference to discuss the proposal for the combined analysis of Studies 150-307 and 150-602. Prior to the teleconference we requested that an additional related item be added to the agenda if possible: enrollment criteria for studies in patients with invasive aspergillosis.

**FDA Participants:**

Cheryl Dixon, Statistician, Ellen Frank, CSO, Mark Goldberger, Division Director, Brad Leissa, Supervisory Medical Reviewer, Nancy Silliman, Supervisory Statistician, Theresa Wu, Medical Reviewer

**Pfizer Participants:**

NY: M. Garvey, R. Rosenstein, H. Schlamm, R. Swanson, D. Wilson (visiting from Sandwich)  
UK: M. Leeming, P. Troke

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**EXECUTIVE SUMMARY**

FDA wished to discuss the proposed combined analysis, the parent protocol, 150-602 and if time permitted, enrollment criteria.

**Statistical issues-** The combined analysis is acceptable; the Week 12 analysis is the primary analysis. The End-of-Therapy (EOT) time point might be of some value. The sample size is adequate but there would need to be an adjustment to the alpha if we have 2 primary objectives. Asked what we will do if the outcomes of the two trials are different at the time of the umbrella analysis, R. Rosenstein replied that it is unlikely that we will have statistically significantly different results from the two studies.

**Labeling-** Following M. Leeming's comment that we would hope to get a claim for the successful variable (in the event that both endpoints were not successful), Dr. Wu stressed that the data would determine the labeling, that results may suggest other labeling. Success at the EOT would support "Voriconazole is superior to Amphotericin B regarding efficacy." If there is success at the Week 12 timepoint, the wording will be quite a challenge. When told that we would expect wording stating that voriconazole is indicated for the treatment of aspergillosis, Dr. Wu said the labeling may not be as straightforward as we hope.

**Other protocol design issues-** FDA asked for a list of the lab/AEs which will be withheld from the blinded expert panel to avoid un-blinding. There was discussion whether or not the Week 6 assessment constituted a midpoint analysis. Pfizer responded that it is a secondary analysis in the parent protocol. FDA will agree to radiologic diagnosis of aspergillosis by the "halo" sign. They agreed that a "halo" sign on CT scan of the chest would be sufficient to support a diagnosis of "probable" aspergillosis.

**NDA -** FDA expects the results of the umbrella analysis will be the basis of the NDA submission. The NDA will get a priority review.

**Item from Previous Teleconference (March 31, 1997)-** Dr. Wu and H. Schlamm discussed her desire for two positive sputums for entry as "probable" aspergillosis. Dr. Wu accepted the Pfizer position that a requirement for two sputums will seriously hamper enrollment.

**Discussions with Other Regulatory Authorities-** FDA expressed willingness to discuss the combined analysis proposal with other regulatory bodies in order to agree on a global protocol.

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## **TELECONFERENCE**

Following my introductory remarks which included an inquiry regarding the willingness of FDA to participate in a discussion with other regulatory authorities if necessary to achieve a single global combined analysis plan for pooling the data from Studies 150-307 and 150-602, R. Rosenstein described our interest in providing voriconazole, a promising new therapy, as soon as possible to a seriously ill patient group. She reviewed the original brief discussion of a combined analysis that occurred at the End-of-Phase II meeting on June 24, 1996. We handed the teleconference over to FDA.

Dr. Wu said the FDA had comments on the proposed combined analysis and wished to revisit the parent protocol. If time permitted they were willing to discuss enrollment criteria. She said that overall, the concept of the combined analysis is fine. FDA wishes us to consider other scenarios and possibly develop contingency plans. She allowed that we may not be prepared to answer during the teleconference.

### **Combined Analysis Proposal**

#### **Statistical Issues:**

Dr. Wu asked which analysis is the primary analysis: Week 12 which demonstrates equivalence to standard therapy or End-of-Therapy (EOT) which demonstrates superiority to conventional Amphotericin B.

R. Rosenstein explained how the two parent protocols, one "US" and the other "ex-US", were developed to respond to different climates and that the Week 12 timepoint in the US protocol represented the US and FDA preference. However, use of the combined analysis as a single global analysis, acceptable to other regulatory authorities, necessitates the inclusion of a second end point: EOT.

Dr. Wu affirmed that the type of analysis for primary consideration for a submission is the Week 12 analysis. She continued with additional comments on the EOT time point: She thinks the EOT is a moving target and there may be a difference in the overall picture in the two study arms because voriconazole can be used for a much longer duration than Amphotericin B. Also, she feels that evaluability criteria which exclude data from patients on concomitant medications that can lower voriconazole levels may introduce a bias.

Dr. Dixon said there would need to be an adjustment to the alpha if we have 2 primary objectives. Dr. Dixon interpreted that the sample size had been based on calculations showing superiority, but it is also acceptable for equivalence. Although Dr. Wu asked what Pfizer will do if the outcomes of the two protocols are different or if one study is inconclusive at completion, the brief ensuing discussion addressed the idea that the combined analysis might be considered an interim analysis. R. Rosenstein explained that there would be no combined analysis at the completion of the protocols and therefore the combined analysis was not an interim analysis. When Dr. Dixon asked if we will mention, in the final study reports for the two completed studies, that a portion of the data had been analyzed elsewhere, R. Rosenstein deferred an answer to a later time.

**Action: This issue will be discussed further.**

Dr. Dixon returned to a variation of Dr. Wu's question later in the teleconference, asking what we will do if the outcomes of the two trials are different at the time of the umbrella analysis. R.

Rosenstein deferred to a degree, saying that it is unlikely that we will have statistically significantly different results from the two studies considering the similarity of their design. What we will do if we see something like a slight trend which is different in the two studies will take more thought.

#### Labelling-

There was some discussion regarding the possibility that only one of two primary variables might be successful. Dr. Wu felt a need to qualify M. Leemings comment that we would hope to get a claim for the successful variable. She stressed that the data would determine the labeling and that FDA may have to change its thoughts about labeling, that results may suggest other labeling. She repeated that she was not saying that the EOT is definitely not suitable.

Although Dr. Wu reiterated that the primary endpoint should be Week 12, Dr. Goldberger interjected that results of the Week 12 timepoint may be difficult to interpret because patients will have been on other follow-on therapies including itraconazole. On the other hand, Dr. Goldberger said there may be some advantage to looking at EOT.

Dr. Wu said the phraseology for the labeling will depend on the results. Success at the EOT would support "Voriconazole is superior to Amphotericin B regarding efficacy." If there is success at the Week 12 timepoint, the wording will be quite a challenge. When I said we would expect wording stating that voriconazole is indicated for the treatment of aspergillosis, Dr. Wu said the labeling may not be as straightforward as we hope.

#### Other protocol design issues-

Dr. Wu asked that we send FDA a more final list of the lab/AE data such as LFTs, visual disturbances, infusion related AEs, which will be withheld from the blinded expert panel to avoid unblinding.

There was discussion of the Week 6 assessment and whether it constituted a midpoint analysis. R. Rosenstein stated that it is a secondary analysis as in the parent protocol; it is a fixed point analysis on the Intent-to-Treat population, and D. Wilson added that the EOT for Amphotericin B is generally expected to be at Week 6.

FDA would like the Expert Review Panel to be truly one global panel because of the potential for bias and because there are only 278 patients. R. Rosenstein and M. Leeming described the planned dual review of several initial cases as a QC measure, and ongoing sharing of difficult diagnoses and cases for which there was disagreement between the investigator and initial expert panel review. FDA suggested that we assure a systematic dual review of a number of cases on an ongoing basis.

**Action :** The requested list of lab/AE data to be withheld from the Expert Panel will be created in cooperation with the Data Review Committee of experts in the area of aspergillosis and submitted to FDA. A specific plan will be designed for the dual review of cases on an ongoing basis in addition to the initial dual review of a number of cases and the ongoing dual review of difficult cases.

**NDA**

Dr. Wu said FDA expects the results of the umbrella analysis will be the basis of the NDA submission. She asked if there were any plans to update the safety and efficacy data during the later part of the review. I told her we would provide a safety update but there would be no efficacy update because there would be no further formal analysis until the completion of the two studies. R. Rosenstein added that enrollment for the two studies is expected to be nearly complete around the time of the NDA filing; however, treatment of those final patients, data cleanup, statistical analyses and report generation would take almost another year.

Dr. Leissa said whenever we submit, the NDA will get a priority review. R. Rosenstein repeated that there would not be additional efficacy data submitted during the review.

**Action-** Further clarification will be sought from FDA regarding the review status of the non-aspergillois indications- priority or standard- following internal discussion of the optimal approval packages/approval timelines.

#### Protocol 150-602 Items

Dr. Wu requested clarification of the different descriptions of Con Meds in Section 5.3.2 and 4.2.1. She she feels that evaluability criteria which exclude data from patients on concomitant medications that can lower voriconazole levels may introduce a bias. D. Wilson and R. Rosenstein explained the role of the Expert Panel in deciding the impact of con meds on evaluability.

There were brief Q and A discussions about the meaning of "licensed anti-fungal therapy", FDA's desire to see if there is any effect by strata and the outcomes research purpose of the Week 16 timepoint in the follow-up period.

**Action:** The phraseology of Sections 5.3.2 and 4.2.1 will be reviewed for clarity.

#### Inclusion Criteria for Aspergillois Trials

Dr. Wu said since everyone agrees on "that sign" (radiologic diagnosis by the "halo" sign), FDA will also agree to it. She added that the assignment of patients to the "probable" aspergillois on the basis of the halo alone is appropriate. FDA does not want to see "Halo" diagnoses with no other tests done. Dr. Wu said physicians should be encouraged to perform BAL. H. Schlamm described the protocol wording which strongly encourages physicians to make every effort to obtain histological confirmations. He added that the data from the "probable" and "definite" patients would be pooled for the analysis.

#### Item from previous teleconference

Dr. Wu and H. Schlamm discussed her desire for two positive sputums for entry as "probable" aspergillois. H. Schlamm described the investigators' view that a requirement for two sputums will seriously hamper enrollment. Dr. Wu accepted this position, but she stressed that a complete diagnostic workup of a patient should include continuous culturing for aspergillois. Dr. Goldberger suggested that we consider using one sputum for entry but require a second sputum for confirmation of the diagnosis of aspergillois. In turn, Dr. Wu suggested that we have the Endpoints Committee review the Inclusion Criteria and the diagnostic criteria for invasive aspergillois for each patient.

#### Discussions with other Regulatory Authorities

I returned to this question at the end of the teleconference. Dr. Goldberger said the FDA would have no difficulty discussing the combined analysis proposal with other regulatory bodies in

order to agree on a global protocol which would satisfy FDA and others. He added, however, that how each Authority assesses approvability may be different, based on a different view of the same analyses, or a different perspective on which analysis is truly primary.

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To: Ms. Vikki Kinscy, DAVDP

From: Dr. Martha Brumfield, Pfizer

*Martha C. Brumfield*

Date: June 27, 1996

RE: Slides presented at End of Phase II meeting on Voriconazole IND \_\_\_\_\_

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Vikki,

Attached please find the overheads that Pfizer presented at the End of Phase II meeting held on June 24, 1996. Most of these were in the package sent prior to the meeting; however, slight modifications were made to a few so I enclose the entire package presented.

These will be officially submitted to the INDs along with Pfizer generated meeting minutes in a couple of weeks.

Thanks for arranging everything.

Martha

## VORICONAZOLE END OF PHASE II MEETING

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### TARGET LABELING: INDICATIONS AND USAGE

- PRIMARY TREATMENT OF INVASIVE INFECTIONS DUE TO ASPERGILLUS
- PRIMARY TREATMENT OF CANDIDA INFECTIONS (INCLUDING INVASIVE OR SYSTEMIC AND ESOPHAGEAL CANDIDIASIS)
- EMPIRIC TREATMENT OF FUNGAL INFECTIONS
- PRIMARY TREATMENT OF FUNGAL INFECTIONS FOR WHICH THERE IS NO LICENSED TREATMENT (LIST OF ORGANISMS AS PER CLINICAL TRIAL RESULTS)
- TREATMENT OF FUNGAL INFECTIONS IN PATIENTS INTOLERANT AND/OR REFRACTORY TO CURRENT THERAPIES

## VORICONAZOLE END OF PHASE II MEETING

### STUDIES SUPPORTING GLOBAL CLAIM STRUCTURE

Planned Phase III studies					
Protocol #	Site	Indication	Comparator	# patients	# patients on voriconazole
602	US	Acute invasive aspergillosis	Amphotericin B	248	124
307	Europe	Acute invasive aspergillosis	Amphotericin B	266	133
603	US	Empiric therapy	Amphotericin B	436	218
308	Europe	Empiric therapy	Amphotericin B	436	218
604	US	Refractory fungal infections	None	100	100
309	Europe	Refractory fungal infections	None	100	100
605	US	Esophageal candidiasis	Fluconazole	300	150
305 (in progress)	Europe	Esophageal candidiasis	Fluconazole	320	160

ALL STUDIES WITH VORICONAZOLE TABLET AND/OR IV LYOPHILE IN SBECB

## VORICONAZOLE END OF PHASE II MEETING

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**REGISTRATION OF INVASIVE ASPERGILLOSIS MAY BE BASED ON POOLED DATA FROM U.S., EUROPEAN STUDIES**

- **SAMPLE SIZE FOR STUDY 602 INCREASED TO PER ARM BASED ON DELTA OF**
- **REGISTRATION MAY REQUIRE POOLING OF DATA FROM STUDIES 602 AND 307**
- **GLOBAL DATA SAFETY MONITORING BOARD BEING CONSIDERED TO OVERSEE BOTH PROTOCOLS**
- **ASSESSMENT OF PATIENT RECRUITMENT AND MECHANISMS FOR POOLING DATA (UMBRELLA PROTOCOL) TO BE DISCUSSED WITH AGENCY WITHIN 1 YEAR AFTER INITIATION OF TRIALS**

## VORICONAZOLE END OF PHASE II MEETING

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**OVERALL DESIGN OF EMPIRIC PROTOCOL  
SUPPORTS PROPOSED LABELING**

### **SAMPLE SIZE**

#### **BASED ON:**

- **PRIMARY ANALYSIS: EQUIVALENCE IN RATE OF RESOLUTION OF FEVER (RATE FOR AMPHOTERICIN B = 0.70)**
- **POWER = 0.90**
- **$\Delta = 0.15$**
- **10% OF ENROLLED PATIENTS EXCLUDED FROM EFFICACY EVALUABLE SUBGROUP ANALYSIS**

#### **SAMPLE SIZE:**

- **N = 218 PATIENTS ENROLLED IN EACH TREATMENT GROUP**

## VORICONAZOLE END OF PHASE II MEETING

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OVERALL DESIGN OF REFRACTORY INFECTIONS PROTOCOL SUPPORTS PROPOSED LABELING.

- **SUPPORTING DATA**

- **WORLDWIDE PROGRAM INCLUDING 2 IDENTICAL NONCOMPARATIVE PROTOCOLS**
- **DOCUMENTED INVASIVE INFECTIONS ONLY**
- **NDA DATABASE TO INCLUDE 200 PTS**
- **REGISTRATION BASED ON SUCCESSFUL TREATMENT OF LIMITED # PATIENTS WITH INFECTIONS DUE TO EACH PATHOGEN (*FUSARIUM*, *PSEUDOALLESCHERIA*, ETC.)**

## VORICONAZOLE END OF PHASE II MEETING

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### OTHER STUDIES

- IV/PO DOSE ESCALATION
- HEPATIC/RENAL IMPAIRMENT (SD)
- BIOBATCH BE
- ABSOLUTE BA
- MENSTRUAL CYCLE



## Record of Industry Meeting

**Meeting Date:** June 24, 1996    **Time:** 1:30    **Location:** S400

**IND Numbers:**    — Voriconazole Oral  
                          — Voriconazole I.V.

**Sponsor:** Pfizer Inc.

**Type of Meeting:** End of Phase II meeting

**Meeting Chair:** Steve Gitterman    **Sponsor Chair:** Martha Brumfield

**Regulatory Management Officer:** Vikki S. Kinsey

### **FDA Attendees, Titles, and Offices:**

David Feigal, Division Director  
Donna Freeman, Deputy Director  
Steve Gitterman, Team Leader (Clinical)  
Teresa Wu, Medical Officer  
Mary Ann Jarski, Chemistry Reviewer  
Shukal Bala, Microbiology Reviewer  
Lisa Kammerman, Team Leader (Biostatistics)  
Liji Shen, Biostatistician  
Barbara Davit, Biopharmaceutics Reviewer

**External Constituent and Titles:**  
(See attached)

### **Meeting Objectives:**

1. To provide comments to the sponsor regarding the development program for voriconazole and proposed Phase III clinical studies.

**Discussion Point:** The proposed indication for the treatment of invasive aspergillosis:

1. The FDA concurred with the sponsors proposal to support this indication with at least one randomized comparative clinical trial, however, there was concern expressed with the pooling the analysis of the two proposed clinical trials.

interaction studies with protease inhibitors.

2. Dr. Davit requested that the sponsor include the FDA in the process of determining the dissolution specifications for this drug product.

**Discussion Points: Chemistry**

1. Dr. Jarski reminded the sponsor that the use of the complexing agent cyclodextrin will need to be addressed. The sponsor responded that they will provide a justification for using cyclodextrin and will meet with the division at a later date to discuss this issue further. The sponsor added that they plan to present their justification to Dr. Schwab's committee.

**Discussion Points: Pharmacology**

1. Dr. McMaster stated that 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 the proposed regimen has not been previously tested in man.
2. Dr. McMaster stated that the drug is teratogenic and induces cleft palates in rats. However, women should be encouraged to enter this trial, although 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.
3. Dr. McMaster stated that the doses proposed for the animal carcinogenicity study seem to be adequate but the regimen needs to be approved by the Carcinogenicity Committee of the FDA.

**Unresolved Issues or Issues Requiring Further Discussion:**

1. The proposed population pharmacokinetic analysis in Protocol 150-602 will be reviewed by the Office of Clinical Pharmacology and Biopharmaceutics staff and comments will be provided to the sponsor.

Signature, minutes preparer: IS/ Date: 7/19/96  
Conference Chair (or designated signatory): IS/ Date: 7/17/96

**Attachment/Handouts:**

List of Pfizer attendees and copies of slides presented during the meeting.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services  
Food and Drug Administration  
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

**DATE:** October 17, 2001

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs

**ADDRESS:** Eastern Point Road  
Groton, CT 06340

**TELEPHONE:** 212-733-5688

**FAX:** 212-573-7314

**FROM:** Jouhayna Saliba, R.Ph.

**APPLICATION:** NDA 21-266 and 21-267

**SUBJECT:** CMC comments and requests

The Division has the following comments and requests:

**General:**

- With respect to release and stability data, in the future we would prefer to see actual values, reported to an appropriate number of significant figures, instead of 0.0% for impurity levels above the limit of quantitation but below 0.1%.

**For the Drug Substance:**

- ~~\_\_\_\_\_~~ Please also provide a rationale for choosing one purification option over the other options listed.
- ~~\_\_\_\_\_~~ Please also provide a rationale for the optional purification steps listed and explain under what circumstances they are applied.
- ~~\_\_\_\_\_~~ Please also provide a rationale for the optional purification procedure(s) and explain under what circumstances they are applied.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services  
Food and Drug Administration  
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

**DATE:** October 16, 2001

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs

**ADDRESS:** Eastern Point Road  
Groton, CT 06340

**TELEPHONE:** 212-733-5688

**FAX:** 212-573-7314

**FROM:** Jouhayna Saliba

**APPLICATION:** INDs \_\_\_\_\_

**SUBJECT:** Protocol 150-606: "An Open Label, Non-Comparative Protocol for the Emergency Use of Voriconazole (UK-109,496) in Patients with Life-threatening, Invasive Mycosis Who Are Failing on Currently Available Antifungal Agents", (serial #269, IND \_\_\_\_\_ and serial #252, IND \_\_\_\_\_).

We refer to your submission dated July 24, 2001, where an amendment to the above mentioned protocol was submitted. The Division has the following comment:

On page 19 of your submission, you discuss drug interactions of voriconazole with cyclosporine and tacrolimus. There was no discussion of the drug interaction between voriconazole and sirolimus. The label states that voriconazole increased sirolimus  $C_{max}$  and AUC by 556% and 1014% respectively and therefore coadministration of voriconazole and sirolimus is contraindicated. Please include in your protocol information on the drug interactions with sirolimus.

If you have any questions, please contact me at (301) 827-2387.

  
Jouhayna S. Saliba, R.Ph.  
Regulatory Health Project Manager  
Division of Special Pathogen and Immunologic Drug Product



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Services  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**DATE:** August 24, 2001

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs

**ADDRESS:** Eastern Point Road  
Groton, CT 06340

**TELEPHONE:** 212-733-5688

**FAX:** 212-573-7314

**FROM:** Jouhayna Saliba

**APPLICATION:** NDAs 21-266 and 21-267

**SUBJECT:** FDA recommendations to the Sponsor's Advisory Committee briefing document

As a follow-up to our teleconference on August 22, 2001, the following are FDA's recommendations regarding the microbiology and clinical pharmacology section of the Advisory Committee briefing package:

**Microbiology Section:**

The microbiology section should be organized such that pre-clinical in vitro data should first be discussed followed by in vivo studies. Information regarding only *Aspergillus* species and *Candida* species should be discussed in this section.

The in vitro susceptibility data obtained from the clinical trials should be discussed in the clinical efficacy section of the package. MIC data from the MITT patient populations should only be shown and correlated with the global response rates. The *Aspergillus* tables should clearly show how many patients had single pathogens versus multiple fungal species recovered from clinically relevant sites. Again, MICs for amphotericin B, fluconazole, itraconazole and voriconazole should be shown in one table. MICs from fluconazole resistant isolates should be separated out from fluconazole susceptible isolates.

**In vitro section:**

Aspergillus should first be discussed. Tables should contain MICs for amphotericin B, fluconazole, itraconazole and voriconazole. The susceptibility testing method used to obtain the MICs should be described in detail along with established breakpoints for the approved drugs. MIC ranges and MIC90 values should only be shown. MIC50 values are not relevant. Fluconazole resistant strains should be shown separate from fluconazole susceptible fungal strains. In addition, please delete the comments regarding the in vitro cidal activity of voriconazole.

In vitro studies assessing the activity of voriconazole against the various Candida species should be shown using similar criteria used to discuss voriconazole MICs against Aspergillus strains.

Tables and figures showing clinical data from Aspergillus studies 307/602 and Candida study 305 should be taken out of this section and placed in the clinical efficacy section of the package. Only clinical microbiology data from the MITT patients should be discussed and correlated with clinical outcome.

**In vivo section:**

Again, studies evaluating the in vivo activity of voriconazole against Aspergillus infections in animals should be discussed first. It is important to include in this section the reason for using the guinea pig model versus the mouse model which was used for assess the activity of fluconazole and itraconazole. It should be clearly stated that voriconazole is rapidly metabolized in mice and that is why this animal model was not used initially to assess the in vivo activity of voriconazole.

In vivo data assessing the activity of voriconazole against fluconazole susceptible and resistant strains of Candida albicans should be shown. If there are studies employing *C. glabrata* that should also be included. Data from studies using both normal and immunosuppressed animals should be shown.

**Clinical Pharmacology Section:**

1. Please limit the Clinical Pharmacology portion (Section 7) to a total of 8-10 pages. Please summarize and abbreviate so as to limit the discussion to major points only.
2. Please include Dose Justification (Section 10) as a subsection of Section 7. This subsection should be renamed "Rationale for Dose Selection". In this subsection please summarize the sections currently numbered 10.1 through 10.2.3 and 10.3 in 1-2 pages. As stated above, the entire Section 7 should be limited to 10 pages or less.
3. The new section on "Rationale for Dose Selection" should include a summary of the exposure-response data in terms of both efficacy and safety.
4. Section 10.2.4 contains ROC curves that were not part of the NDA submission. Please delete reference to these curves in the briefing document.
5. As mentioned in our teleconference, you may delete Appendix 2. There is no need to include summary tables of the studies conducted as part of the Clinical Pharmacology development program.

NDA 21-266 and 21-267  
Voriconazole Tablets and IV  
August 24, 2001

If you have any questions, please contact me at (301) 827-2387.

**/S/**

Jouhayna S. Saliba, R.Ph.  
Regulatory Health Project Manager  
Division of Special Pathogen and Immunologic Drug Product



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services  
Food and Drug Administration  
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

**DATE:** July 25, 2001

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs

**ADDRESS:** Eastern Point Road  
Groton, CT 06340

**TELEPHONE:** 212-733-5688

**FAX:** 212-573-7314

**FROM:** Jouhayna Saliba

**APPLICATION:** NDA 21-266

**SUBJECT:** Voriconazole Tablets

The Division has the following comments:

For the drug substance:

- Please clearly specify reaction completion and other in-process tests (other than testing done on the isolated intermediates themselves).
- Please provide a DMF reference (or source) and CFR reference for the \_\_\_\_\_ bags. What testing is performed other than the acceptance tests?
- Concerning the drug substance stress testing studies, please clarify the meaning of the phrase \_\_\_\_\_ found on page 5 of section VDS-19-EF.

For the drug product:

- Please provide a rationale for the decrease in dissolution rate with the increased granulation time for batch N6117 (Section VTB-48-F).

NDA 21-266  
Voriconazole Tablets  
July 25, 2001

- Please verify that there are no reprocessing operations proposed.
- 
- There is not sufficient data available to warrant a — month expiry period. The available data, — months long-term and —months accelerated) point to an expiry period of —months.

If you have any questions, please contact me at (301) 827-2387.

---

Jouhayna S. Saliba, R.Ph.  
Regulatory Health Project Manager  
Division of Special Pathogen and Immunologic Drug Product

## MEMORANDUM OF TELECON

DATE: 12/14/00

APPLICATION NUMBERS: NDA 21-266, Vfend (Voriconazole) Tablets

NDA 21-267, Vfend (Voriconazole) IV

**BETWEEN:**

Name: Maureen Garvey Ph.D., Director, Regulatory Affairs Department  
Phone: [REDACTED]  
Representing: [REDACTED]

**AND**

Name: Jouhayna Saliba, R.Ph., Regulatory Project Manager  
Marc Cavaille-Coll, M.D., Ph.D., Medical Officer/ Team Leader  
Division of Special Pathogen and Immunologic Drug Products, HFD-590

**SUBJECT:** Inform the Sponsor of the Division's concern regarding their timeline submission of supplemental information during the review period.

[REDACTED] 17, 2000 letter from Pfizer, the timeline submission of their ongoing studies during the review period. We informed Pfizer of our concern regarding the late submission of these studies during the review period. We requested from Pfizer a written commitment to confirm that the final study reports will be submitted no later than April 17, 2000. Failure to submit these studies in the requested time may result in an approvable action. Pfizer agreed to provide us with a written letter which will have the revised timelines for the submission of the studies to reflect the date agreed upon. A revised timeline was sent via telefacsimile on December 15, 2000.

---

Jouhayna Saliba  
Regulatory Project Manager

/s/

-----  
Jouhayna Saliba  
12/19/00 12:18:43 PM  
CSO



**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

**DATE:** November 2, 2000

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department

**ADDRESS:** Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017-5755  
Phone: (212) 733-5688  
Fax: (212) 573-7314

**FROM:** Jouhayna Saliba, R.Ph.

**INDs:** (serial # 219, 221) (serial # 202, 204)

**SUBJECT:** Response to submissions to both INDs dated September 19, 2000 and September 29, 2000

In response to your submissions dated September 29, 2000, requesting a pediatric deferral, the Agency has the following comments:

1. It is acceptable to provide the final study reports for the multiple dose pediatric study and population pharmacokinetic analysis after the NDA has been submitted. Assuming a standard 10 month review, the study reports should be received no later than 5 months after the date of submission.
2. Please note that the pediatric population pharmacokinetic analysis involves collaboration with another team within the Office of Clinical Pharmacology and, therefore, the Agency would require adequate time for review and collaboration.

In addition, the Agency would like to summarize the agreements that has been made with you regarding the submissions of various pharmacokinetic study reports.

- The Agency agrees to accept the drug interaction studies with sirolimus and mycophenolate mofetil during the first quarter of the year 2001.
- The renal impairment, dialysis, pediatric multiple dose, and pediatric population pharmacokinetic studies must be submitted no later than 5 months into a standard 10 month review. If the NDA is given priority status, the review clock will not begin until the final study report has been received.

If you have any further questions, please contact me at (301) 827-2423.

*JS*  
Jouhayna Saliba, R.Ph.  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

IND \_\_\_\_\_  
November 2, 2000

page 2

DFS Keywords:  
admin memo  
class antifungal  
indic aspergillosis

Concurrence:  
HFD-590/MO TL/Cavaille-Coll/Sy/BL/50  
HFD-590/Biopharm TL/Ajayi  
HFD-590/Biopharm/Meyer

HFD-590/PM/Saliba/drafter/10-17-2000

Distribution:  
HFD-590/MO TL/Cavaille-Coll  
HFD-590/Biopharm TL/Ajayi  
HFD-590/Biopharm/Meyer  
HFD-50-/MO/Tierman

HFD-590/Division file  
HFD-590/PM/Saliba

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to DFS  
faxed to sponsor w/o this page

**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

**DATE:** November 2, 2000

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department

**ADDRESS:** Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017-5755  
Phone: (212) 733-5688  
Fax: (212) 573-7314

**FROM:** Leo Chan, R.Ph., for Jouhayna Saliba, R.Ph.

**INDs:** \_\_\_\_\_

**SUBJECT:** Response to submissions — (serial # 212) . — (serial #195)

Please refer to our fax of June 23, 2000, which contained our follow-up comments from the CMC pre-NDA videoconference for voriconazole. Please also refer to your submissions dated July 25, 2000, in which you provided some responses to our fax. We have provided the following comments below:

1. We accept your proposal to submit bioequivalence results based on multiple dose data because of:
  - a) the non-linearity in the pharmacokinetics of voriconazole
  - b) the voriconazole dosing regimen requires a loading dose
2. Because of our request in (1), we would also like to request that you provide comparisons of  $C_{max}$  and  $AUC_{0-12}$  following the first dose.

If you have any further questions, please contact me at (301) 827-2423.

/s/

\_\_\_\_\_  
Leo Chan, R.Ph., Regulatory Project Manager for  
Jouhayna Saliba, R.Ph., Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

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



**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

**DATE:** April 12, 2000  
**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department  
**ADDRESS:** Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017-5755  
Phone (212) 733-5688  
Fax (212) 573-7314  
**FROM:** Leo Chan, R.Ph.  
**IND:** \_\_\_\_\_  
**SUBJECT:** Comments on Protocol: A1501007

Please refer to your letter dated March 16, 2000, received March 17, 2000, containing protocol A1501007 entitled "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."

We have reviewed this protocol and have provided the following comments with respect to section 5.8 :

1. Please clarify what criteria the ophthalmologist will use to determine if a subject is able and willing to cooperate in these ophthalmological tests. We agree that that some children will be unable to cooperate in an exam using the Snellen chart, but we still require indirect funduscopy.
2. We recommend using the distance visual acuity testing rather than using the near visual acuity testing. We believe the former will be easier for children to complete; however, either test is acceptable.
3. For all subjects participating in the ophthalmological examination, each eye should be tested separately.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

\_\_\_\_\_  
Leo Chan, R.Ph.  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

DFS Keywords:  
admin memo  
class antifungal  
indic aspergillosis

Concurrence:  
HFD-590/MO TL/Cavaille-Coll  
HFD-590/MO/Tiernan  
HFD-550/SMO/Chambers

Distribution:  
HFD-590/MO TL/Cavaille-Coll  
HFD-590/MO/Tiernan  
HFD-550/SMO/Chambers

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HFD-590/Division file  
HFD-590/PM/Chan

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**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

**DATE:** January 20, 2000  
**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department  
**ADDRESS:** Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017-5755  
Phone (212) 733-5688  
Fax (212) 573-7314  
**FROM:** Leo Chan, R.Ph.  
**IND:** \_\_\_\_\_  
**SUBJECT:** Comments on Protocol: A1501004

Please refer to your letter dated January 12, 2000, received January 13, 2000, requesting confirmation that:

- 1) Beta testing of SIRIUS will occur separately from the voriconazole submission.
- 2) It is acceptable to the review division that pharmacokinetic data will be provided in electronic filing guidance compliant format, SAS transport files with associated descriptor documents to provide variable definitions.

We have reviewed your requests and agree to your proposals.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

\_\_\_\_\_  
Leo Chan, R.Ph.  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

DFS Keywords:  
admin memo  
class antifungal  
indic aspergillosis

Concurrence:  
HFD-590/MO TL/Cavaillé-Coll  
HFD-590/Biopharm/Meyers

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HFD-590/Biopharm/Meyers

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HFD-590/Division file  
HFD-590/PM/Chan

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file**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

**DATE:** September 22, 1999

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department  
Pfizer, Inc.  
(212) 733-5688  
(212) 573-7314 (fax)

**FROM:** Matthew A. Bacho, Regulatory Project Manager

**THROUGH:** Sheryl Lard-Whiteford, Ph.D., Microbiology Team Leader  
Linda L. Gosey, Microbiology Reviewer  
Funmilayo O. Ajayi, Ph.D., FCP, Clin. Pharm. & Biopharmaceutics Team Leader  
Joette Meyer, Pharm.D., Clin. Pharmacology & Biopharmaceutics Reviewer

**IND:** \_\_\_\_\_ (Voriconazole)

**SUBJECT:** Comments on Protocol Amendment (Serial No. 133 and 116, respectively)

With reference to the protocol amendment submitted to IND \_\_\_\_\_ and \_\_\_\_\_ our clinical pharmacologist and microbiologist have some comments to make:

- 1) Please provide any information available on the in vivo interconversion of the proposed isomeric form (UK 109,496) to the other isomer \_\_\_\_\_ which is considered to be an impurity in the drug substance.
- 2) What proportion of a given voriconazole dose is metabolized to each of the 3 major metabolites? Has it been determined whether any of the major metabolites is a substrate, inhibitor, or inducer of P-450 enzymes?
- 3) Please refer back to a memo dated July 19, 1996 that contains comments on the population pharmacokinetic sampling scheme for Protocol 150-602. These comments still apply to Study 602 and also pertain to Study 604.
- 4) We would be willing to discuss the clinical pharmacology program for voriconazole with you in late November or early December.
- 5) Please provide the details of the laboratory protocols that will be used for microbiological measurements, which include the collection and transport of clinical samples for fungal culture, the processing of specimens for the recovery of fungi and the identification of fungal isolates obtained from clinical samples taken during these clinical trials.

- 6) When these clinical trials are complete please provide the voriconazole MIC values for the particular fungal species isolated and a copy of the susceptibility testing method. These data may be used to help determine if voriconazole resistance develops while patients are receiving therapy.
- 7) Please consider conducting fluconazole and itraconazole susceptibility testing on all fungal isolates recovered from patients enrolled in these clinical trials to determine if cross-resistance occurs between voriconazole and fluconazole and itraconazole.
- 8) Please clarify what Aspergillus diagnostic assay will be employed in these clinical trials. Submit a copy of the Aspergillus diagnostic assay procedure/methodology.
- 9) Please clarify what will be done with the Aspergillus diagnostic assay results obtained from these clinical trials. Test results from non-FDA approved methods can not be used in support of the NDA.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

---

Matthew A. Bacho  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

**Concurrence:**

HFD-590/Micro-TL/Lard/e-mail/092099  
HFD-590/Micro/Gosey/e-mail/092199  
HFD-590/Biopharm-TL/Ajayi/e-mail/092099  
HFD-590/Biopharm/Meyer/e-mail/092099  
HFD-590/RPM/Bacho/drafter/092099

**Distribution:**

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HFD-590/Micro/Gosey  
HFD-590/Biopharm-TL/Ajayi  
HFD-590/Biopharm/Meyer  
HFD-590/RPM/Bacho  
HFD-590/Division file

IND \_\_\_\_\_

IND \_\_\_\_\_

To DFS

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**DFS Keywords:**

Admin memo  
Class antifungal  
Indic aspergillosis



in Div file

**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

**DATE:** September 20, 1999

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department  
Pfizer, Inc.  
(212) 733-5688  
(212) 573-7314 (fax)

**FROM:** Matthew A. Bacho, Regulatory Project Manager

**THROUGH:** Marc Cavallé-Coll, M.D., Ph.D., Medical Officer Team Leader  
Rosemary Tiernan, M.D., Medical Officer  
Joette Meyer, Pharm.D., Clin. Pharmacology & Biopharmaceutics Reviewer

**IND:** — (Voriconazole)

**SUBJECT:** Comment on Protocol Amendment (SN-136) and Contact Information

With reference to the protocol amendment submitted to IND ~~SN-136~~, our medical officer has one comment to make:

You require the correction of clinically significant hypokalemia prior to the initiation of voriconazole administration for all protocols except 150-606, a compassionate use study. Please provide the rationale for this exception.

In addition, during our last teleconference (September 17, 1999), we proposed beta-testing a new pharmacokinetic software package called ~~---~~ in anticipation of your electronic regulatory submission for voriconazole. If you are still interested in doing this, please contact John Lazor, Pharm.D., Director of the Division of Pharmaceutical Evaluation III at (301) 827-2010.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Matthew A. Bacho  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

**Concurrence:**

HFD-590/MO-TL/Cavaillé-Coll/e-mail/092099  
HFD-590/MO/Tiernan  
HFD-590/Biopharm/Meyer/e-mail/092099  
HFD-590/RPM/Bacho/drafter/092099

**Distribution:**

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HFD-590/MO/Tiernan  
HFD-590/Biopharm/Meyer  
HFD-590/RPM/Bacho  
HFD-590/Division file

IND ———

IND ———

To DFS

Faxed to sponsor without this page

**DFS Keywords:**

Admin memo  
Class antifungal  
Indic aspergillosis



Division of Special Pathogen and  
Immunologic Drug Products  
Food and Drug Administration  
Rockville MD 20850

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**DATE:** April 8, 1999

**TO:** Maureen Garvey, Ph.D.  
Director, Regulatory Affairs Department  
(212) 733-5688  
(212) 573-7314 (FAX)

**COMPANY:** Pfizer, Inc.  
235 East 42<sup>nd</sup> Street  
New York, N.Y. 10017-5755

**FROM:** Laurie Bernato, R.N., M.N.  
Regulatory Project Manager

**THROUGH:** Marc Cavaille-Coll, M.D., Ph.D., Medical Officer Team Leader  
Rosemary Tiernan, M.D., Medical Officer  
Joette Meyer, Pharm. D., Bio-Pharmaceutical Reviewer

**IND:** \_\_\_\_\_

**SUBJECT:** Voriconazole Serious Event.

This memo refers to the teleconference that took place on Wednesday, April 6, 1999 that discussed the issues surrounding the voriconazole serious event that was reported on March 15, 1999.

**Comments:**

To date, you estimate that 964 subjects have received voriconazole with 7/964(0.73%) episodes of life-threatening arrhythmia. We concur with your plan to send a "Dear Investigator" letter to all investigators and their respective IRB's. This letter will include an addendum to the consent form outlining the potential for cardiac rhythm disturbances. FDA believes it is premature to use wording such as "remote" and "more likely" in paragraph three on page 2 of your March 22, 1999 report. While one cannot exclude that other factors may have contributed to this adverse event, one can no more exclude the possibility that this event was related to the voriconazole infusion.

Voriconazole  
Serious Event  
April 8, 1999

**This trial may proceed with implementation of the changes outlined below:**

1. All patients will be appraised of the risk for sudden cardiac death during intravenous voriconazole infusion. Should a patient with a prior history of cardiac arrhythmia still desire to enroll in this study, they should be continuously monitored with telemetry until the completions of intravenous voriconazole therapy. Depending on the course of intravenous voriconazole therapy, this might encompass several days or weeks.
2. Patients must have stable electrolytes prior to voriconazole infusion. Hypokalemia should be corrected prior to voriconazole infusion.
3. Until this current issue of fever and arrhythmia is further clarified, infusion of blood products and electrolyte supplementation should not occur simultaneously with voriconazole infusion.

In addition you agreed to provide the following information:

4. This 52 y.o. Canadian patient had a past medical history of cardiac arrhythmia. Please clarify the nature of this rhythm disturbance including details of her cardiac evaluation.
5. In the voriconazole IND safety report, you included case synopses on ten additional patients who had cardiac dysrhythmia while enrolled in the febrile neutropenia/voriconazole trial (Study 150-603). There have been two cases of ventricular fibrillation and five cases of cardiac arrest without a clear precipitating factor. Three cases of cardiac arrest occurred in patients on study but they were receiving the comparator drug. Nine of the ten patients died. Please collect the following information on these ten patients and submit this material for our review:
  - a. All concomitant medications including their dosages and duration of therapy
  - b. Assessment of patient's renal and liver function prior to and while on study drug
  - c. Electrolyte status prior to and while on study drug
  - d. Prior cardiac history and evaluation including EKG's prior to initiation of study drug.

Finally, FDA pharmacokinetics and chemistry staff will review this case for voriconazole drug interactions. FDA pharmacology-toxicology staff will review the pre-clinical pharmacology -toxicology data and re-assess for evidence of cardiotoxicity.

We are providing the following information via telephone facsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

  
\_\_\_\_\_  
D. Laurie Bernato  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

Voriconazole  
Serious Event  
April 8, 1999  
D. Laurie Bernato  
Regulatory Project Manager  
Division of Special Pathogen and Immunologic Drug Products

cc:

HFD-590/MTL/Cavaillé-Coll /S/ 4/8/99  
HFD-590/MO/Tierman  
HFD-590/Bio-Pharm/Meyer

Distribution:

Original File IND \_\_\_\_\_

Div file

HFD-590/MTL/Cavaillé-Coll

HFD-590/MO/Tierman

HFD-590/Bio-Pharm/Meyer

HFD-590/Pharm/McMaster

HFD-590/Chem/Holbert

HFD-590/PM/Bernato

## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** March 11, 1999

**TO:** Maureen Garvy, Ph.D.  
Director  
Regulatory Strategy and Registration

**ADDRESS:** Pfizer, Inc.  
235 East 432<sup>nd</sup> Street  
New York, NY 10017-5755

**FROM:** Laurie Bernato  
Project Manager

**THROUGH:** Norman Schmuff, Ph.D., Chemistry Team Leader  
Gene Holbert, Ph.D., Chemistry Reviewer

**IND:** \_\_\_\_\_

**SUBJECT:** Meeting Minutes-February 3, 1999  
Discussion of Chemical Issues

### FDA Attendees:

Bonnie Dunn, Ph.D., Dep.Div. Dir., DNDC III  
Norman Schmuff, Ph.D., Chemistry Team Leader  
Gene Holbert, Ph.D., Chemistry Reviewer  
Funmilayo Ajayi, Ph.D., Clinical Pharmaceutical and Biopharmaceutic  
Joette Meyer, Pharm.D., Clinical Pharmaceutical and Biopharmaceutic Reviewer  
Laurie Bernato, RN, MN, Project Manager

### Pfizer Attendees:

John Berridge, Ph.D., Developmental Research, UK  
Val Harding, Ph.D., Developmental Research, UK  
Allastair Coupe, Ph.D., Developmental Research, UK  
Mike Butlers, Ph.D., Developmental Research, UK  
Peter Jones, Ph.D., Developmental Research, UK  
Dennis Casey, Ph.D., Developmental Research, US  
Maureen Garvey, Ph.D., Regulatory Affairs

## CHEMISTRY COMMENTS

1. Synthesis, Starting Materials and Proposed Control Strategy- The quality of the starting materials will be closely monitored used a control strategy where the routes of synthesis will be known. Are our proposals acceptable to the FDA?

*The proposals are acceptable.*

2. Strategy for qualification of commercial manufacturing sites for drug substance and drug product- Pfizer presented their proposed strategy for qualification of commercial manufacturing sites. Is this plan acceptable to the FDA?

*The FDA is in agreement with your plans.*

3. Strategy for particle size and endotoxin testing- Pfizer asked for Agency input as to the acceptability of their specification and control strategy for particle size and endotoxin testing.

*This proposal is acceptable.*

4. Strategy and rationale for the proposed choice of dissolution methods- Pfizer proposed a Q value of — at 45 minutes utilizing USP apparatus 2 at 50 rpm in water.

*The Biopharmaceutical reviewers said that they preferred a Q value of — in forty-five minutes using — HCL.*

5. Rationale for enantiomeric control-To be controlled at the drug substance stage.

*This rationale is acceptable to the FDA*

6. Bracketing approach for stability program to support bottle count/bottle size options-

*This approach is acceptable.*

7. Overall approach to testing and controls for the lyophile for intravenous injection-Pfizer presented their proposals to tests and controls to ensure drug specifications.

*This was also acceptable. Dr.Schmuff indicated that we would be following the lead of the Neuropharmacology Division with respect to sulfobutylether beta-cyclodextrin.*

**8. Strategy and Rationale for the Proposed Stability Program for the Pediatric Suspension-**

*This program was acceptable.*

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**D. Laurie Bernato**  
**Regulatory Project Manager**  
**Division of Special Pathogen and Immunologic Drug Products**

IND \_\_\_\_\_  
Chemistry Issues Meeting  
February 3, 1999

cc:

HFD-590/Schmuff/Chem.T.L.  
HFD-590/Holbert/Chem.Rev.  
HFD-590/Dunn/Dep.Div.Dir., DNDCII

Distribution:

HFD-590/MTL/Cavaillé-Coll  
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HFD-590/Holbert/Chem. Rev.  
HFD-590/Ajayi/BioPharm.TL  
HFD-590/Meyer/BioPharm. Rev.  
HFD-590/Dunn/Dep.Dir., DNDCIII  
HFD-590/Bernato/PM/Drafter

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HFD-530/R. Behrman  
HFD-530/M. Truffa