**Infusion Related Reactions in Study A1501021**

Dr. Garvey stated that two occurrences of infusion related reactions occurred in Study A1501021 at the same site on the same day. The study has been suspended at all four active sites and this will affect the timeline for submission of study results by May 31, 2001 as outlined in a December 15, 2000 letter to the Division. Before the study can be re-initiated, new volunteers will need to be enrolled, time re-scheduled with the study sites, and an ethics committee will need to review these two events. Pfizer estimates that the data from this study could be submitted to the NDAs by the end of November 2001.

Dr. Purkins stated that the February 2, 2001 FAX summarized what is currently known about these two events. Both of these events occurred in young, healthy females. One subject was receiving 8 mg/kg intravenous voriconazole and the other subject was receiving 64 mg/kg SBECD placebo. To date, Pfizer has been unable to identify a specific causative factor for these 2 events.

Dr. Goldberger recommended that Pfizer submit a summary of these two reactions to the voriconazole NDAs. As the Division continues the review of these NDAs, discerning both efficacy and safety, how important the data from Study A1501021 are to decision-making for this drug as well as what impact the data could have on the final decision will be determined. Information from Study A1501021 may be sufficiently important that it could impact on whatever decision is made. Pfizer noted that Section 11 of the ISS contains a report summarizing safety concerns, including QT, for voriconazole.

Dr. Goldberger stated that as the review progresses, it might be useful at a later date to discuss with Pfizer the importance of the data from Study A1501021 for decision-making purposes. If Pfizer decides to revise the protocol for Study A1501021, the Division would like the opportunity to review the revised protocol as it may impact on the importance of the study to decision-making.

**Other**

Pfizer stated that they are very aggressively pushing to complete the aspergillosis database. The last patient visited occurred about one week ago. Dr. Goldberger questioned how useful these data would be in making a regulatory decision absent the usual level of detail.

**Summary**

The Division discussed with Pfizer the reasoning for a deferral rather than a waiver of voriconazole studies in the under 2 years of age pediatric population.

Two infusion related reactions in Study A1501021 and how these reactions may impact the review of the voriconazole NDAs were also discussed.

**Minutes Preparer:** _____
**Diana Willard**

**Concurrence, Meeting Chair:** _____
**Mark J. Goldberger, M.D., M.P.H.**

/s/
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Diana Willard
4/6/01 07:45:07 AM
CSO

Mark Goldberger
4/16/01 12:22:46 PM
MEDICAL OFFICER

# MEMORANDUM OF TELECONFERENCE MINUTES

**Meeting Date:** November 3, 2000
**Time:** 11:00 a.m.
**Location:** U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S400
Rockville, MD 20850

**Application:** INDs ———————

**Type of Meeting:** Type C

**Meeting Recorder:** Jouhayna Saliba, Regulatory Project Manager

**FDA Attendees, titles, and Office/Division:**

Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader and Meeting Chairperson
Rosemary Tiernan, M.D., Medical Officer
Funmilayo Ajayi, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer Team Leader
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Karin Higgins, Ph.D., Statistics Reviewer Team Leader
Cheryl Dixon, Ph.D., Statistics Reviewer
Leo Chan, R.Ph., Regulatory Project Manager
Jouhayna Saliba, R.Ph., Regulatory Project Manager

**External Constituent Attendees and titles:**

Maureen Garvey, Regulatory Affairs (NY)
Reinhard Baildon M.D., Clinical Leader (UK)
Peter Troke Ph.D., Clinical (UK)
Haran Schlamm M.D., Clinical

**Background:** Pfizer informed the Division by phone call and by facsimile of their decision to terminate recruitment of patients into their aspergillosis trials for voriconazole: Study 602 and Study 307

**Meeting Objective:** The Division requested additional details regarding the circumstances that prompted termination of these two randomized, controlled aspergillosis trials.

**Discussion Points:**

1. **The Division asked for clarification regarding the reasons that prompted Pfizer's decision to stop Study 602 and Study 307.**

   *Pfizer had various recruitment issues in both of these Studies ranging from changes in patient treatment options to the reluctance of investigators to*

*randomize patients to the amphotericin B arm. The end-result was the unsuccessful enrollment of the original target number of study patients.*

2. **Pfizer indicated that 276 evaluable patients were required for the original "Umbrella Protocol" analysis. The Division and the sponsor had agreed to using this " Umbrella Protocol" analysis and the early termination of studies 307 and 602 would not compromise the total number of evaluable study patients.**

3. **The Division asked Pfizer for additional details regarding the "Umbrella Protocol" analysis.**

   *Pfizer stated that they would be performing a blinded review assessment. Three hundred ninety patients will have been recruited globally for the aspergillosis studies. The most recent group of study patients will have data available in February 2001 with initial assessment complete in March 2001. The final data review committee analysis should be completed by June 2001.*

4. **The Division asked how much extensive and complete the safety data base would be for the voriconazole NDA.**

   *Pfizer believes that greater than 90% of patients would be included in the safety update as well as in the NDA submission. Pfizer stated that the last piece of data would not be received until March 2001.*

5. The Division reiterated to Pfizer, as had been done in the pre-NDA meeting, that 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. The Division explained that the pediatric population pharmacokinetic analysis involves collaboration with another team within the Office of Clinical Pharmacology. Therefore, the Division requires adequate time to review the information.

6. The Division expressed concern regarding Pfizer's plans for submitting additional studies after filing the NDA. Untimely submission of these studies could compromise the review team's ability to adequately evaluate all data. The Division reserves the right to grant an "Approvable" letter instead of an "Approval" letter pending the review of all final study reports.

**Action Items Agreed Upon Prior To the NDA Filing of Voriconazole**

1. Pfizer will provide a comprehensive written narrative explaining their rationale for discontinuing Study 602 and Study 307.

2. Pfizer will provide a written plan detailing exactly what will be submitted to the NDA as well as a **timeline (in weeks from the date of the NDA submission)** for the submission of any additional studies.

3. Pfizer will provide a written plan of what information will be provided in the 120 day safety update.

4. Pfizer will provide a detailed description of the revised "Umbrella Protocol" analysis for studies 602 and 307.

Minutes Preparer: /S/ 11/20/00

Meeting Chairperson: /S/ 11/20/00

DFS Keywords:
Admin minutes
Class antifungal
Indic aspergillosis
Indic candidiasis, esophagus

Concurrence:
HFD-590/MO-TL/Cavaillé-Coll/
HFD-590/MO/Tiernan/
HFD-590/Stat/Dixon/
HFD-590/Biopharm/Meyer/
HFD-590/RPM/Chan
HFD-590/RPM/drafter/Saliba

Distribution:
HFD-590/MO-TL/Cavaillé-Coll
HFD-590/MO/Tiernan
HFD-590/Stat/Dixon
HFD-590/Biopharm/Meyer
HFD-590/RPM/Chan
HFD-590/Division File
HFD-590/RPM/Saliba
IND —
IND —

**In DFS**

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Draft

## Record of Meeting

**Date of Meeting:** July 26, 2000

**IND:** [redacted] DRAFT

**Drug:** Voriconazole

**Sponsor:** Pfizer, Inc

**Subject:** General Pre-NDA meeting

**FDA Attendees, Titles, and Officers:**

Renata Albrecht, M.D., DSPIDP Acting Division Director
Mark Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
Wiley Chambers, M.D., DAAOD Deputy Director
Funmilayo Ajayi, Ph.D., FCP, Clin. Pharm. & Biopharm. Team Leader
Joette Meyer, Pharm D., Clin. Pharm. & Biopharm Reviewer
Karen Higgins, Sc.D., Statistical Team Leader
Cheryl Dixon, Ph.D., Statistical Reviewer
Norman Schmuff, Ph.D., Chemistry Team Leader
Gene Holbert, Ph.D., Chemistry Reviewer
Brad Leissa, M.D., Medical Officer Team Leader
Ed Cox, M.D., Medical Officer
John Powers, M.D., Medical Officer
Eileen Navarro, M.D., Medical Officer
Ellen Frank, R.Ph., Chief Project Manager Staff
Leo Chan, R.Ph., Project Manager

**External Constituents and Titles:**

Reinhard Baildon, M.D., Clinical
Alice Baruch, M.D., Ph.D., Clinical
Nigel Brayshaw, M.D., Clinical
Steve Felstead, M.D., Clinical
Maureen Garvey, Ph.D., Regulatory
Andrew Grieve, Ph.D., Biometrics
Mike Hodges, M.D., Clinical
Elina Srulevitch-Chin, B.S., Regulatory
Konrad Tomaszewski, Ph.D., Clinical Safety

**Background:**
On August 28, 1995, Pfizer Inc. formally submitted an application for voriconazole in the treatment of patients suffering from key opportunistic fungal infections including aspergillosis. A background package was sent on July 11, 2000, which served as the agenda for this meeting.

**Objective:**
Pfizer Inc. requested this meeting to seek FDA concurrence on their proposed NDA submission plan.

**Discussion Points:**

[The statements in bold were taken from the agenda for this meeting.]

1. Based on the preliminary safety and efficacy data which was presented for study 603, what indications would the Division consider to be supported by this empirical therapy trial?

   *After presenting the preliminary safety and efficacy data, the sponsor informed the Division that they were no longer going to pursue an indication for empirical therapy. The Division shared the sponsor's concern about the failure of voriconazole to meet the study's primary endpoint. However, the Division strongly encouraged the sponsor to submit the final study report since study 603 was a large study that would provide valuable safety information. In addition, the Division believed it would be important to review the results of study 603 and analyze the circumstances where the drug was successful and where it failed. Although the Division stated it would be premature to discuss the indications that could be supported by this study, the Division informed the sponsor that filing for empirical therapy could still be an option.*

2. **We wish to discuss the acceptability of the pooled aspergillosis data to support a first-line indication for voriconazole in the treatment of patients with acute invasive aspergillosis?**

   *The Division asked for clarification from the sponsor on pooled data. Pfizer responded that any patients enrolled in one study but later discovered to actually possess another fungal infection would not be included in the per protocol analysis of the study the patient was enrolled but would be included in the analysis of the fungal infection pooled across studies.*

   *Due to the fact that only a historical control study will be submitted for the treatment of acute invasive aspergillosis at the time of filing, the Division pointed out that it would be difficult for the sponsor to show significant improvement over what is currently available.*

3. **We wish to discuss the acceptability of the pooled data to support a first-line indication for voriconazole in the treatment of subjects with serious *Candida* infections.**

   *The Division informed the sponsor that a blanket indication of "serious Candida infection" to a study drug which may show efficacy by pooling results from patients who harbor Candida infections in different body sites would NOT be granted. The Division will review the data from studies 303, 304, 603, 604 and 608 and will consider the patient's underlying disease, prior treatment (primary or salvage therapy), species of Candida and grant a site-specific indication if warranted.*

**4. We wish to discuss the acceptability of study 305 and the pooled data to support the first-line indication for voriconazole in the treatment of subjects with esophageal candidiasis.**

*The Division stated that the analysis from study 305 will be the primary analysis. Pooled data from other studies may be considered supportive.*

*The Division further pointed out that they would review the study reports and thereafter make a decision on whether the data supports a first line indication for voriconazole.*

**5. We wish to discuss the acceptability of pooled data indicating successful outcomes in subjects for whom these infections were previously uniformly fatal or in the case of eye infections, disfiguring to support an indication for voriconazole in the treatment of subjects with specific rare pathogens and subjects with infections refractory to other treatments.**

*The Division stated they would review the data from the various studies where patients received treatment for rare and refractory fungal infections. The Division requested from the sponsor data from the literature that reflects the natural history of such rare infections. The Division would review these studies taking into account the patient's prior anti-fungal therapy, underlying disease and immune status, and ascertain whether the Division could grant voriconazole an indication that will be pathogen and site-specific. The sponsor agreed to accommodate the Division's request.*

**6. Pediatric Use Information**

*Once the sponsor had presented their plans for satisfying the Pediatric Rule, the Division informed the sponsor that an NDA application submitted after December 2, 2000, would require a letter submitted to the IND outlining their pediatric development plan (including any request for deferral 60 days prior to submitting the NDA application.*

**8. Sample NDA Tables**

*The Division agreed to the sponsor's proposal as outlined in the background package.*

**9. Miscellaneous Items**

- *The Division informed the sponsor that the review team would first examine the controlled trials before studying the open trials. Once the open trials were reviewed, the Division would study the compassionate use as a whole. Lastly, the Division would consider all the studies together with respect to the given infection.*
- *The Division informed the sponsor that the decision of granting any indication a priority review would be made at the time of filing. The decision of granting a priority review would come from the fact that the sponsor has an oral formuation, the effectiveness of the studies versus placebo, and the efficacy of voriconazole against severe infections.*
- *The Division reiterated (from the Clinical Pharmacology Pre-NDA meeting held on July 14, 2000 ) that the Division would accept the final study reports for the multiple dose pediatric study report, population pediatric pharmacokinetic analysis, renal impairment, and dialysis studies **NO LATER than 5 months from the date of submission assuming a standard 10***

***month review.*** *Should the NDA be granted priority review status, the review clock would not begin until the final study report had been received. The sponsor acknowledged the Division's reiteration of the final study reports timeline.*

Signature, minutes preparer:_____ Date:_____

Leo Chan, R.Ph.

Conference Chair :_____ Date:_____

Renata Albrecht, M.D.

DFS Keywords:
admin minutes
class antifungal
indic

Concurrence:
HFD-590/MO Acting Div. Dir./Albrecht

HFD-590/MO TL/Cavaillé-Coll/
HFD-590/MO/Tiernan/
HFD-590/Biopharm TL/Ajayi/
HFD-590/Biopharm/Meyer/
HFD-590/Micro/Gosey/
HFD-590/Stat/Dixon/
HFD-590/PM/Chan/drafter/10-30-2000

Distribution:
HFD-590/MO Acting Div. Dir./Albrecht
HFD-590/MO TL/Cavaillé-Coll
HFD-590/MO/Tiernan
HFD-590/Biopharm TL/Ajayi
HFD-590/Biopharm/Meyer
HFD-590/Micro/Gosey
HFD-590/Stat/Dixon
HFD-590/PM/Chan

HFD-590/Division file

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to DFS
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IND —— Voriconazole (intravenous)
IND —— Voriconazole (oral)

**Voriconazole Pre-NDA Meeting**

**July 26, 2000**

**Attendees**

| **FDA participants:** | **Pfizer participants:** |
|---|---|
| Renata Albrecht, MD - Acting Division Director<br>Funmilayo Ajayi, PhD, Biopharmaceutics Team Leader<br>Marc Cavaille-Coll, MD, Team Leader<br>Wiley Chambers, MD, Division of Ophthalmological Drug Products<br>Leo Chan, RPh, Project Manager<br>Cheryl Dixon, PhD, Biometrics reviewer<br>Ellen Frank, RPh, Senior Project Manager<br>Linda Gosey, Microbiology reviewer<br>Karen Hager, PhD, Acting Statistical Team Leader<br>Kenneth Hasting, PhD, Pharmacology Team Leader<br>Owen McMaster, PhD, Pharmacology reviewer<br>Joette Meyer, PhD, Biopharmaceutics reviewer<br>Dave Roeder, Regulatory<br>Rosemary Tieman, MD, Medical reviewer | Alice Baruch, MD, Clinical<br>Reinhard Baildon, MD, Clinical<br>Nigel Brayshaw, MSc, Biometrics<br>Steve Felstead, MD, Clinical<br>Maureen Garvey, PhD, Regulatory<br>Andy Grieve, PhD, Biometrics<br>Mike Hodges, MD, Clinical<br>Elina Srulevitch-Chin, BS, Regulatory<br>Konrad Tomaszewski, PhD, Clinical Safety |



**MINUTES**

Specific Attachments to our pre-meeting package included data from the empirical therapy trial, 603, the aspergillosis/historical control study comparison, Studies 304/1003, the candidiasis program and the rare and refractory fungal infections program. Other Attachments contained information about the voriconazole efficacy response assessment tool (VERA), summary safety data and draft Tables of Contents for the NDA, ISE and ISS. We planned brief presentations to allow maximum time for discussion. Prior to the meeting, we were requested to address the pooled analyses that would be used to demonstrate effectiveness against specific pathogens in subjects from across all protocols.

**VERA and Pooled Data**

After introductions, M. Garvey described plans for the meeting, encouraged discussion and questions from FDA and shared the Pfizer questions which would be posed during the presentations.

R. Baildon addressed the FDA inquiry about pooling as part of a review of overall voriconazole patient disposition. He used overheads shown at the March 10, 1999 meeting with FDA to review VERA [called SAT (Sponsor Assessment Tool) in 1999] and described the pooling of subjects from across protocols. In response to a series of questions from Dr. Albrecht, R. Baildon clarified how protocols differed, which patients were evaluated by VERA and entered into the pooled analyses, the role of Data

Review Committees and how VERA assessments were made. He confirmed that only patients with documented fungal infection were evaluated in VERA, but that all subjects would be considered in the final reports for the study into which they were enrolled.

There was discussion about the subjects with multiple documented fungal infections, sometimes at multiple sites. Dr. Albrecht asked that we state explicitly what those pathogens are. Dr. Cavaille-Coll interjected that they would want the CRFs of these subjects. Dr Albrecht asked that we document the decision process for subjects with multiple pathogens: how subjects with more than organism were assigned and evaluated.

**Empirical Therapy/ Priority Review**

R. Baildon described the empirical therapy trial, Study 603, its design and composite endpoint. He described how the finding of non-equivalence was driven by the component endpoint: defervesence during the period of neutropenia. He described the benefit of voriconazole in high risk subjects such as subjects with allogeneic bone marrow transplant and the similar efficacy of voriconazole and AmBisome® in low-risk subjects: those with autologous transplants or other neoplasms.

Dr. Cavaille-Coll asked if the statistical analysis plan contained any pre-defined comments about superiority. A. Grieve answered no, there was only a lower margin of the Confidence Interval, this was a non-inferiority trial.



R. Baildon continued with a description of the difference in the results of 603 compared to the earlier AmBisome® trial. He addressed the defervescence during the period of neutropenia component and why the duration of this period was shorter in the voriconazole trial (5 days) compared to the earlier AmBisome® trial (10 days), allowing less time for recovery from fever in 603. More than 90% of patients who failed, failed because of this component. Dr. Albrecht asked if this was true of both treatment groups and was told yes.

R. Baildon described the effectiveness of voriconazole in specific populations. He mentioned the opinions of participating investigators including Dr, Tom Walsh, the Principal Investigator, that voriconazole's efficacy in breakthrough infections is very important.

R. Baildon described the differences in managing patients and possible instances of investigator bias toward the approved drug, AmBisome®, over the investigational drug, voriconazole:

- Discontinuations for Lack of Efficacy- more on voriconazole
- Protocol- allowed dose escalations- fewer on voriconazole

Dr. Albrecht asked about other reasons for discontinuation. R. Baildon answered that there were discontinuations due to adverse events, primarily elevated Liver Function Tests (LFTs).

R. Baildon projected the following *Question*:

IND _____ oriconazole (intravenous)
IND _____ oriconazole (oral)

- *The empirical therapy trial, 603, did not demonstrate equivalence of voriconazole to AmBisome®. We seek input regarding the appropriate description of the results of this study in the label to guide prescribers in the use of voriconazole.*

R. Baildon sought discussion regarding the best way to describe the beneficial effects of voriconazole to guide prescribers. Discussion of priority review was interspersed throughout the discussion of Study 603 and an empirical therapy claim.

In response to Dr. Albrecht's questions, R. Baildon said that Pfizer does plan to submit the 603 data; and that prevention of breakthrough infections was not a pre-defined endpoint.

Dr. Albrecht commented that the data are not what was expected and asked how these findings modify Pfizer's view regarding priority review. R Baildon answered that the possibility of a priority review was based also on the oral formulation and M. Garvey added that the priority review designation had also been considered in association with a primary therapy indication in aspergillosis. Dr.Cavaille-Coll said the review designation decision would be made at the time of filing. Later in the discussion, in response to general comments about priority review, M. Garvey clarified that priority review does not depend on a demonstration of superiority. Dr. Albrecht answered that the guidelines for priority review call for a significant improvement over existing therapies and Dr. Cavaille-Coll added that a significant improvement is more difficult to demonstrate without randomized controlled trials.

Returning to Study 603, Dr. Cavaille-Coll stated that, to meet the evidence standard, voriconazole needs to have been better than placebo. He asked what is the contribution of AmBisome® compared to a contribution by a placebo? He asked what would be the results of an analysis between voriconazole and placebo; would the results indicate that voriconazole would have 'beaten' placebo? He concluded that this is a reviewable issue.

In response to R. Baildon's question about submitting an empirical therapy claim, Dr. Cavaille-Coll affirmed that Pfizer can submit for an empirical therapy indication, adding that, for approval, a drug does not need to be the best, a drug needs to be safe and effective. Dr. Cavaille-Coll added that efficacy in empirical therapy must be supported by a demonstration of efficacy in the treatment of serious fungal infections.

Dr. Albrecht concluded this discussion, suggesting that Pfizer submit for empirical therapy. If the data are not available to demonstrate a significant improvement (priority review standard), FDA will review the data under a standard review clock (10 month review).

**Aspergillosis**

M. Hodges summarized the data from Study 304. He recalled FDA's request that Pfizer conduct an historical control study and he described the results of the Study 304/ Study 1003 comparison. Briefly, he described why it was necessary to use US sites for historical control subjects and the difference detected between the EU and US populations in the historical control study. He projected the following *Question:*

IND —— Voriconazole (intravenous)
IND —— Voriconazole (oral)

- *Does the Division consider Study 304/ Study 1003 and the pooled aspergillosis data appropriate to support an indication for voriconazole as primary therapy for patients with invasive aspergillosis.*

Dr. Cavaille-Coll recalled the FDA recommendation that Pfizer conduct an historical control study as well as earlier discussions during which FDA recommended controlled trials, such as Studies 307/ 602. He asked about the status of those studies and when FDA would see that data.

R. Baildon answered that the umbrella analysis is to be conducted when the number of *evaluable* subjects reaches 276. He said the last subjects expected to be enrolled for this number of *evaluable* subjects will be enrolled in September-October 2000, have a four-month treatment period, and their data will undergo review by the Data Review Committee. A final study report is expected near the end of 2001.

Dr. Cavaille-Coll described FDA's dilemma. Not knowing the conclusion of the ongoing controlled trials is difficult for FDA. Whether those trial will reach the same conclusion as 304/1003 is unknown. In response to R. Baildon's inquiry regarding early submission of available data, Dr. Cavaille-Coll said that would be helpful; it is important to know of any concerns prior to approval.

R. Baildon answered several questions from Dr. Albrecht. He explained that recruitment into 307/602 is difficult because of earlier treatment of presumed fungal infections whereas our protocols require documented fungal infection.

Drs. Albrecht and Cavaille-Coll said FDA will review 304 and will look at all the data. Dr.Cavaille-Coll said the ongoing trials will also be a consideration with regard to a primary vs salvage indication. He referred to earlier meetings with FDA, including meetings with Drs. Teresa Wu and Mark Goldberger in which they stated that randomized controlled trials are a better way to a primary therapy indication. Dr. Albrecht acknowledged the Division's agreement with the fileability of Study 304, together with 1003, and said they would adhere to that agreement.

IND — Voriconazole (intravenous)
IND — Voriconazole (oral)

[redacted]



**Rare Fungal Pathogens**

R. Baildon briefly described our experience in treating rare fungal pathogens. He said we will apply for indications in specific rare fungal infections as we think are appropriate and are adequately supported, such as *Scedosporium* spp. and *Fusarium* spp. He mentioned 10-20 subjects as having been considered appropriate in earlier discussions. Dr. Albrecht said FDA would like to see the data, adding that FDA is always interested in seeing data on new therapies.

**Pediatric Final Rule**

M. Garvey reviewed the interactions with the Division regarding closure of the single dose pediatric pharmacokinetic study and initiation of the multiple dose study. She repeated what she had told the Biopharmaceutics reviewers on July 14: Pfizer had anticipated that by July 2000 we would have had an enrollment record upon which to project study conduct and completion. However, we have just enrolled our second subject into the multiple dose study and projections regarding availability of data are not possible.

She informed FDA that we would submit the single dose pediatric pharmacokinetic study and the compassionate use experience in pediatric subjects in the NDA. As discussed with FDA during the clinical pharmacology meeting on July 14, 2000, Pfizer proposes that dosing recommendations for pediatric subjects should follow the adult dosing recommendations on a weight-adjusted basis. We promised to inform FDA when ≥6 pediatric subjects had completed 8 days of therapy and had plasma samples analyzed in order to learn their preference for sharing/submission of the data. She told FDA that Pfizer will seek:

IND —— Voriconazole (intravenous)
IND —— Voriconazole (oral)

- a deferral for the multiple dose pediatric pharmacokinetic study.
- a deferral for the pediatric oral suspension.
- a waiver for children <2 years old.

FDA agreed with our plans except that Dr. Albrecht asked that Pfizer consider a request for deferral for subjects <2 years old rather than a waiver. M. Garvey answered that this waiver was discussed with FDA as early as the End-of-Phase II meeting. She said we anticipated very limited use in children less than two years old and that we thought we might have seen all such cases in our compassionate program. She said conduct of a study in children under 2 years might be impossible. R. Baildon added that the waiver request was also based on the fact that aspergillosis is rare in this age group; the more typical infection in the under- two years age group is *Candida* for which there is an approved therapy.

Dr. Albrecht acknowledged the reasons given for the waiver request and repeated her own request for a deferral. She said FDA would like more time to make a request in the event a relevant need arises soon after approval. M. Garvey stressed the difficulties encountered by the Pfizer Clinical Pharmacology group in getting as far as we have with the multiple dose study. She described Pfizer's sincere attempts to be compliant with the Pediatric Final Rule from its earliest days and said that Pfizer would continue to make labeling changes as might become appropriate. Dr. Albrecht responded that a deferral need not be indefinite; a timeframe could be specified in the deferral request and the deferral could be converted to a waiver.



**Clinical Pharmacology Studies**

Dr. Ajayi summarized certain discussions from the July 14 meeting for the benefit of those who had not been present. She identified four clinical pharmacology studies which Pfizer hoped to submit post-NDA filing: two in 1Q01 and two in 2Q01. There was some clarifying discussion regarding what type of study would cause the start of a priority review clock to be reset to zero if the study was submitted post-filing: viz, a study which is essential to the review and without which FDA could not review the drug and approve appropriate instructions for use. The FDA attendees concluded that the Clinical Pharmacology studies under discussion would not be essential for review although they would have an impact on the label. Therefore they would not need to be present in the first submission for the NDAs to be fileable.

**Safety Summary/ Safety Update**

K. Tomaszewski summarized the voriconazole safety database briefly. He described the difficulties in defining a single comparator safety profile. He referred to the Table of Contents for the Integrated Summary of Safety to explain the many cuts of the safety data that would be included in the ISS. He also pointed out that the ISS would contain discussions of specific safety topics as requested by FDA: cardiac function, visual function and liver function. In response to a question, K. Tomaszewski said there would be safety assessments within individual study reports.

IND —— Voriconazole (intravenous)
IND —— Voriconazole (oral)

Dr. Tiernan asked about the hallucinations reported in Study 305. K. Tomaszewski responded that the increased hallucinations in Study 603 were visual; these are being examined. He offered that we will be providing narratives of these patients.

Dr. Cavaille-Coll asked about Pfizer plans for the Safety Update. Dr. Albrecht said that the timing of the Safety Update will depend on whether the review is priority or standard. M. Garvey offered to be in further contact with FDA about the Safety Update.

**Microbiology**

Ms. Linda Gosey asked for hard copies of the microbiology references. She also recollected that mycology samples had not always been analyzed by the mycology reference laboratories in ———————————— She said she would need to see the laboratory procedures for those reference labs to assure that methodologies were consistent. She asked about testing isolates for antifungal activity of approved therapies such as itraconazole.

M. Garvey told Ms. Gosey that hard copies of the mycology references would be sent to her as soon as possible. She also told Ms. Gosey that we had responded to her question about Standard Operating Procedures and copies of the requested SOPs had been submitted. M. Garvey offered to confirm receipt of this submission off-line.

**NDAs/ Tables of Contents**

FDA expressed satisfaction with the planned NDAs as described by the ToCs.

**QTc Study**

Dr. Cavaille-Coll asked about the timeframe for completion of this study, which had been discussed during the Cardiac Safety teleconference, June 9, 2000. S. Felstead responded that Pfizer was waiting for FDA comments on the QTc protocol synopsis which was submitted July 7. In a conversation after the meeting, S. Felstead repeated to Dr. Cavaille-Coll that Pfizer could not finalize the protocol until we received FDA comments. Dr. Cavaille-Coll offered to follow up this issue.

IND- —— Voriconazole (Oral)
IND- —— Voriconazole (Intravenous)

# FDA- Pfizer Pre-NDA Meeting
# Voriconazole Triazole Antifungal Agent

## July 26, 2000

**Pfizer attendees:**

**Reinhard Baildon MD, Clinical**

**Alice Baruch MD, Clinical**

**Nigel Brayshaw PhD, Biometrics**

**Steve Felstead MD, Clinical**

**Maureen Garvey PhD, Regulatory**

**Andrew Grieve PhD, Biometrics**

**Mike Hodges MD, Clinical**

**Elina Srulevitch-Chin BS, Regulatory**

**Konrad Tomaszewski PhD, Clinical Safety**

# Agenda

- **Introduction with review of program history and plans for NDAs**
- **Discussion of data from the empirical therapy trial.**
- **Discussion of data from the aspergillosis study and the aspergillosis study- historical control comparison.**
- **Discussion of data from our clinical experience in subjects with serious *Candida* infections.**
- **Discussion of data from our clinical experience in subjects with rare infections and infections that are refractory to other therapy.**
- **Review of safety database and plans for ISS.**
- **Review of plans for presentation of pediatric information in the NDA and the label.**
- **Review of technical aspects and the Table of Contents of the planned NDAs.**

# Questions

## Proposed Indications

- ***The empirical therapy trial, 603, did not demonstrate equivalence of voriconazole to AmBisome. We seek input regarding the appropriate description of the results of this study in the label to guide prescribers in the use of voriconazole.***

- ***Does the Division consider Study 304/ Study 1003 and the pooled aspergillosis data appropriate to support an indication for voriconazole as primary therapy for patients with invasive aspergillosis.***

- ***Does the Division consider the pooled candidiasis data appropriate to support an indication for voriconazole as primary therapy for patients with systemic Candida infections?***

- ***Does the Division consider Study 305 appropriate to support an indication for voriconazole as primary therapy for patients with esophageal candidiasis.***

- ***Does the Division consider the pooled data appropriate to support an indication for voriconazole in the treatment of patients with Scedosporium spp. and Fusarium spp. infections.***

## NDA: Table of Contents/ Technical Aspects

- ***Is the draft Table of Contents, developed to be compliant with recent FDA guidances regarding electronic submissions, appropriate to enable a smooth and efficient review?***

## Priority Review

- ***Does the Division continue to consider that the voriconazole NDAs are appropriate for priority review.***

- ***Does the Division anticipate that an NDA Safety Update should be planned for submission earlier than the standard four-months post-NDA filing?***

DW file

**Minutes of a Meeting**
**June 9, 2000**

| | |
|---|---|
| **Applications:** | IND [redacted]<br>Voriconazole (triazole antifungal agent) oral |
| | IND [redacted]<br>Voriconazole (triazole antifungal agent) I.V. |
| **Sponsor:** | Pfizer Central Research |
| **Indication:** | Treatment of patients suffering from key opportunistic fungal infections including aspergillosis |
| **Purpose of Meeting:** | Discuss cardiac adverse event/how to address concerns regarding potential for future cardiac events |

**Attending:**

**Pfizer:**

| | |
|---|---|
| Reinhard Baildon, M.D. | Clinical Development |
| Maureen Garvey, Ph.D. | Regulatory Affairs |
| Bradley Marchant, M.D. | Clinical Development |
| Christopher Peters, Ph.D. | Toxicology |
| Keith Tan, Ph.D. | Clinical Pharmacology |
| Konrad Tomaszewski, Ph.D. | Clinical Safety |
| Rob Wallis, Ph.D. | Pharmacology |

**FDA:**

| | |
|---|---|
| Marc Cavaillé-Coll, M.D., Ph.D. | Team Leader/Medical Officer, HFD-590 |
| Rosemary Tiernan, M.D. | Medical Officer, HFD-590 |
| Owen McMaster, Ph.D. | Pharmacologist, HFD-590 |
| Funmilayo Ajayi, Ph.D., F.C.P. | Team Leader/Clinical Pharmacologist & Biopharmaceutist, HFD-880 |
| Joette Meyer, Pharm.D. | Clinical Pharmacologist & Biopharmaceutist, HFD-880 |
| Diana Willard | Regulatory Health Project Manager, HFD-590 |

| | |
|---|---|
| **Meeting Chair:** | Marc Cavaillé-Coll, M.D., Ph.D. |
| **Meeting Recorder:** | Diana Willard |

**Background:** Following a cardiac adverse event resulting in death in a voriconazole clinical trial, Pfizer instituted protocol changes in a letter to investigators and in a subsequent amendment to all voriconazole protocols. Included in the protocol changes was a requirement that patients identified to be at risk for cardiac events undergo continuous cardiac monitoring for the course of their intravenous infusion. In addition, during communications between Pfizer and the Division following the cardiac death, an additional ECG study in dogs was suggested by the Division to address concerns regarding any correlation between administration of voriconazole and QT prolongation.

A May 16, 2000 submission from Pfizer provided all relevant currently available data regarding cardiac events. A June 6, 2000 facsimile transmission (FAX) from the Division to Pfizer contained questions based on the Division's review of the May 16, 2000 submission. A June 9, 2000 FAX from Pfizer to the Division addressed several of the questions in the Division's June 7, 2000 FAX. Pfizer noted that questions from the June 7, 2000 FAX not addressed in their June 9, 2000 FAX would be addressed in the NDA.

This teleconference was arranged to address concerns regarding the potential for future cardiac events and to discuss studies that may address those concerns.

**Meeting**

**Pfizer Summary of Human Data**

Pfizer noted that several of the questions in the Division's June 7, 2000 FAX had been addressed in a June 9, 2000 FAX from Pfizer to the Division. Questions from the June 7, 2000 FAX not addressed by Pfizer's June 9, 2000 FAX will be addressed in writing in the NDA.

Pfizer summarized the information provided in the May 16, 2000 submission. A recent study referred to in this submission demonstrates that ketoconazole blocks HERG expression in Xenopus oocytes, indicating that ketoconazole may have a direct effect on prolonging the QT interval. Based on this study, Pfizer stated the possibility that QT prolongation may be a class effect.

Study 150-603, the longest controlled voriconazole study, has been reviewed for all cardiac related events. The incidence of cardiac events in patients receiving voriconazole was similar to the incidence of cardiac events in patients receiving AmBisome, the comparator in this study.

Blinded analyses of 12 lead ECGs from four single dose and three multiple dose Phase 1 studies were conducted. In measuring the QT interval, Bazett's formula was used to correct for heart rate. In cases where treatment was associated with an increase in heart rate, Fridericia's correction was also used to assess the corrected QT interval. Analyses were performed on measurements taken closest to the expected $T_{max}$ in order to maximize the probability of detecting an increase in $QT_c$. These analyses showed that no dose

response relationship was observed with either IV or oral treatment across the dose range studied. There was, however, a mean increase of 14 msec in $QT_c$ in the highest dose group, 8 mg/kg, in 6 subjects receiving IV voriconazole.

**Pfizer Summary of Dog Studies**

Pfizer stated that the following three general pharmacology studies were conducted in anaesthetized dogs:

1. In a 5 escalating dose study the range of plasma $C_{max}$ observed was from 10 to 220 ug/ml. Nodal premature contractions were observed in 1 out of 3 dogs following administration of 86 ug/ml.

2. In a 3 dose escalating dose study the range of plasma $C_{max}$ observed was from 8 to 24 ug/ml. A dose related QT increase up to 7% at peak plasma concentrations of 24 ug/ml, with no change in heart rate, was observed.

3. In a single dose study the range of plasma $C_{max}$ observed was from 5 to 20 ug/ml. At 30 mg/kg, QT increased by 33% and 21% in 2 out of 2 dogs and heart rate decreased by 27% in 1 out of 2 dogs. Plasma concentrations were 17 and 20 ug/ml.

In addition, four intravenous injection and three oral toxicology studies were conducted in dogs. In the one month oral toxicology study, ECG abnormalities were observed at the high dose, 24 mg/kg. This dose level was lethal and led to the sacrifice of this group after two weeks. Toxicity at this dose level was due to high plasma voriconazole concentrations following drug accumulation.

**Planned Studies**

Pfizer proposed the following to further characterize QT prolongation:

1. Conduction of [$^3$H]-dofetilide binding to study the potential of voriconazole to inhibit $I_{Kr}$.

2. Conduct *in vitro* inhibition of HERG current in a patch-clamp study to analyze the potential of voriconazole to inhibit $I_{Kr}$.

3. Conduct dog isolated purkinje fiber recordings with voriconazole using ketoconazole as an active control.

**FDA Concerns**

Although the sponsor seems to believe otherwise, the Division believes that the currently available human data are not sufficient to address the concern of the potential cardiotoxicity of voriconazole. Dr. McMaster had proposed a dog study in which unanaesthetized dogs would be dosed repeatedly with voriconazole and then examined

for cardiac toxicities. Holter monitors would allow for extended recording of the electrocardiogram and this recording would last for 24 hours on selected days. The sponsor asked if, rather than an animal study, a clinical trial would be useful in addressing this issue. The Division replied that if Pfizer can design a clinical study that clarifies the relationship, if any, between voriconazole administration and the observed QT changes, then there would be no need to do further animal studies.

It must be underscored that further consideration of an animal study was postponed to give the sponsor a chance to propose a clinical study to address the potential cardiac toxicities. If an acceptable clinical study cannot be performed, the issue of the animal study will again be discussed. These studies are to be completed before drug approval.

**Clinical Pharmacology and Biopharmaceutics Issues**

Dr. Meyer recommended that Pfizer conduct the following clinical pharmacology studies with voriconazole:

1. A single dose, dose escalation study with the highest dose being three to four times the proposed human dose.

2. A single dose comparator study using a positive control, a negative control, and a placebo where the highest dose is two times the proposed human dose.

3. A multiple dose study using the proposed human dose for the proposed regimen.

Each of these three studies should have a minimum of 32 evaluable subjects. In addition, each study should enroll both female and male subjects. Dr. Meyer noted that these studies have been recommended to other sponsors.

**Discussion**

Pfizer believes that investigational work conducted to date, both clinical and non-clinical, provides sufficient information to obviate the need for an additional ECG study in the dog. Their preference is to pursue clinical studies rather than further dog studies to address the Divisions concerns regarding voriconazole and QT prolongation.

One concern with conducting *in vitro* studies only is that some questions, such as the role of metabolites, will not be address by *in vitro* studies. The Division recommended that *in vivo*, as opposed to *in vitro*, studies be conducted.

The Division further recommended that Pfizer think about how the studies they conduct could be written into the label. It is not clear that information from *in vitro* studies would be written into the label.

Pfizer stated that a proposal to address the QT prolongation concern would be submitted to the Division, possibly by the middle of July 2000.

**Summary**

The need to understand whether voriconazole has the potential to cause the observed adverse cardiac event in the patient population that would use this drug was discussed. Potential studies to determine this potential were also discussed. Pfizer will submit to the Division a proposal to address concerns regarding voriconazole administration and potential for QT prolongation.

Signature, Minutes Preparer /S/ Diana Willard

Concurrence, Meeting Chair /S/ Cavaillé-Coll, M.D., Ph.D.

cc: Division Files
HFD-590/DWillard

Drafted: 7/7/00; Final: 7/24/00

| | | |
|---|---|---|
| RD: | Tiernan | 7/11/00/E-mail |
| | McMaster | 7/24/00/E-mail |
| | Meyer | 7/10/00/E-mail |
| | Ajayi | 7/7/00/E-mail |

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

## Record of Meeting

| | |
|---|---|
| **Date of Meeting:** | December 4, 1999 |
| **IND:** | [redacted] |
| **Drug:** | Voriconazole |
| **Sponsor:** | Pfizer, Inc |
| **Subject:** | Pediatric program and clinical pharmacology of voriconazole |
| **FDA Attendees, Titles, and Officers:** | Mark Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader<br>Rosemary Tiernan, M.D., Medical Officer<br>Tom Hassall, R.Ph., M.S., Associate Director of Regulatory Affairs ODE IV<br>Funmilayo Ajayi, Ph.D., FCP, Clin. Pharm. & Biopharm. Team Leader<br>Joette Meyer, Pharm D., Clin. Pharm. & Biopharm Reviewer<br>Linda Gosey, Microbiology Reviewer<br>Cheryl Dixon, Ph.D., Statistical Reviewer<br>Leo Chan, R.Ph., Project Manager |
| **External Constituents and Titles:** | Reinhard Baildon, M.D., Clinical UK<br>Alice Baruch, M.D., Ph.D., Clinical US<br>Maureen Gafvey, Ph.D., Regulatory US<br>Scott Hopkins, M.D., Clinical US<br>Irja Lutsar, M.D., Clinical UK<br>Keith Tan, Ph.D., Clinical Pharmacology UK<br>Konrad Tomaszewski, Ph.D., Clinical Safety UK |

**Discussion Points:**

[The statements in bold were taken from the agenda for this meeting.]

1. **Pfizer proposes that the safety and pharmacokinetic information available to date from the Phase III and compassionate use programs provide adequate support for the initiation of the multiple dose pharmacokinetic study in 18 pediatric subjects age 2-12 years, concurrent with closure of the single dose pediatric pharmacokinetic study at this time.**

Safety Concerns:

1. The Division expressed concern about the visual changes observed with voriconazole and how very young children would be able to communicate these problems. The Division recommended that the sponsor incorporate into the multiple dose study protocol information on how the sponsor would plan to monitor and evaluate eye changes. Pfizer agreed to the Division's suggestion of the monitoring system and noted that protocol revisions would be made after consulting with a pediatric ophthalmologist.
2. The Division recommended that the pediatric patients be monitored by a dermatologist instead of relying exclusively on a biopsy. Pfizer agreed to the Division's recommendation.
3. The Division recommended the inclusion of a cardiac monitoring program into the protocol. Pfizer agreed to the Division's recommendation.

Pharmacokinetic Concern:

The Division advised the sponsor that it was difficult to draw conclusions regarding the relationship between the pharmacokinetics of voriconazole in children and adults from the data presented. The Division requested submission of the data from the six pediatric subjects enrolled in the single-dose pharmacokinetic study prior to beginning the multiple dose study. The Division noted that they would accept the data in draft format and would not require Pfizer to wait for the final study report before submitting the data. Pfizer agreed to submit the data.

2. **Pfizer proposes that the Pediatric Use information in the NDA and the proposed label will be supported by the Phase III pediatric experience, the single dose study, an ongoing multiple dose study, population (NONMEM) simulations based on pooled data from these studies, and the compassionate use experience in pediatric subjects, projected to be approximately 110 subjects, 0-16 years of age, at the time of NDA filing.**

   The Division advised Pfizer that they would not be able to provide an answer at this time.

3. **Pfizer proposes that the information available to date from the compassionate use program provides adequate support for the initiation of the multiple dose pharmacokinetic study in 18 pediatric subjects age 2-12 years, concurrent with closure of the single dose pediatric study at this time.**

   See the Division's response in question #1.

4. **Pfizer would like FDA's concurrence that the proposed "Pediatric Use" sections in the NDA and the label will fulfill the requirements of the Pediatric Final Rule.**

   The Division provided the following summary:

   > There are two different regulatory factors to consider for pediatrics. One is the pediatric rule of 1998 and the other is the pediatric study provisions of FDAMA (now section 505A of the FD&C Act) which provides pediatric exclusivity. The rule is mandatory. Exclusivity under FDAMA is an incentive program and is completely voluntary.

The pediatric rule requires a sponsor to include a "pediatric assessment" (meaning pediatric studies) in the NDA for those adult conditions that also exist in certain pediatric populations. This requirement can be deferred until a later date or can be satisfied with pediatric studies. For pediatric populations that are not subject to these diseases, a sponsor can request a waiver of the study requirement.

The two provisions work together to provide FDA the opportunity to seek pediatric information about a product that may not be required under the rule. Section 505A is the chance to "fill in the blanks" left by the required studies under the rule. The studies the Division ask for in a written request may be different from the ones required under the rule.

A sponsor does not have to be anxious about submitting a Proposed Pediatric Study Request (PPSR) early to obtain a Written Request for pediatric studies and qualify for pediatric exclusivity. Pediatric exclusivity will extend any market protection that is still in existence upon completion of the studies required by the Written Request. It is not necessary to have the PPSR submitted or the WR in place before submitting the NDA or before its approval.

Studies required by the rule will "count" towards fulfilling requirements for exclusivity. Any Written Request that the Division issues will seek studies to answer questions about pediatric use that remain after the required studies are complete.

The Division advised Pfizer that it is not possible to state unequivocally whether the sponsor's proposals would satisfy the requirements of the pediatric rule at this time because of the issues described above and the information currently available for review. The Division advised Pfizer that until more is known about the drug and the indications that the sponsor will seek for its adult population it is also not possible to state whether a Written Request would be forthcoming for this program or whether the Division may use the incentive of exclusivity to seek studies in additional age groups or for additional infections.

5. **The Proposed Pediatric Study Request will include a single dose Pharmacokinetic study in 6 subjects, age 2-12 years and a multiple dose pharmacokinetic study in 18 pediatric subjects, age 2-12 years. Pfizer would like to discuss this Proposed Pediatric Study Request and its appropriateness as the basis for a Written Request.**

   See the Division's response in question #4.

6. **The current Phase III oral or intravenous dosing strategy involves a twice daily loading dose regimen on the first day followed by a twice daily maintenance dose regimen. With consideration of the non-linear pharmacokinetics of voriconazole, provision is made for dose increase if there is a lack of response and dose reduction if tolerability issues arise. Pfizer proposes the above dosing regimen and seeks your concurrence on the dosage strategy in view of the genetic polymorphism in CYP2C19-mediated metabolism.**

   The Division asked Pfizer the rationale for not genotyping patients enrolled in the Phase III trials. The sponsor responded that in Europe an informed consent is necessary prior to genotyping patients and many of these patients have died. In addition, US and European

patients are on multiple concomitant medications and the effect of genotype on the pharmacokinetics of voriconazole would be difficult to separate out. Therefore, the sponsor proposed using genotype as a covariate in the NONMEM model for all Phase 1 subjects, but not Phase III patients. The Division accepted this proposal.

7. **Pfizer seeks the Division's concurrence that drug interactions with voriconazole has been adequately studied for registration and that the current in vitro and in vivo data is sufficient basis for labeling on drug interactions.**

Pfizer was asked to quantify the amount of voriconazole metabolized to the N-oxide and other metabolites. In addition, the Division expressed interest in the microbiologic and toxicological activity of the major metabolites.

[Pfizer had been asked previously to provide information on the metabolism of voriconazole in a fax dated September 22, 1999.]

Pfizer replied that 72% of voriconazole is metabolized to the N-oxide metabolite, which is primarily renally eliminated. It has the same elimination half-life as voriconazole. The other minor metabolites of voriconazole are glucuronide conjugates. These data come from a completed radiolabeled study that has not yet been submitted to the Division. The N-oxide metabolite has 65-fold lower antifungal activity than the parent drug. In rats and dogs exposed to high doses of voriconazole, and presumably high metabolite concentrations, there have been no adverse effects.

The Division expressed concern about the drug interaction studies previously conducted by Pfizer since these studies have only measured changes in the parent compound, voriconazole, which amounts to < 2% of the circulating drug. Therefore, the Division advised the sponsor that it may be necessary to investigate the effect of co-administered drugs on the N-oxide and other metabolites. Also, if the metabolites are inhibitors or substrates of the cytochrome P-450 enzyme system, Pfizer may need to investigate the effect of voriconazole metabolite(s) on co-administered drugs.

The Division requested that Pfizer perform drug interaction studies with sirolimus and mycophenolate mofetil. These are transplant immunosuppressive drugs that will be used clinically with voriconazole. Neither drug requires therapeutic drug monitoring, so effects of voriconazole on these drugs will not be readily apparent.

Pfizer stated that they did not plan on doing drug interaction studies with CYP 2C19 substrates since these drugs have a wide therapeutic index. The Division suggested that the sponsor select a prototypical 2C19 substrate and perform an in vivo drug interaction study to quantify the effect of voriconazole and the N-oxide metabolite on the co-administered drug.

The Division also requested that the in vitro microbiology data generated with the N-oxide metabolite be submitted for review.

**8. FDA provided the following comments on the multiple dose pediatric pharmacokinetic study.**

- Enrollment within each age category should be evenly distributed.
- A minimum of 8 subjects should be enrolled in each age group (i.e. 24 subjects total). The data can be analyzed using age as a continuous variable, as Pfizer has proposed. However, data should also be analyzed using the three specified age categories.
- Additional blood samples (2-3) should be added on Day 1 after the second 6 mg/kg IV loading dose.
- Safety monitoring should be added which is similar to the Phase III studies (i.e. daily potassium levels, no concurrent infusion with blood products, etc.).
- Data should be collected on the pharmacokinetics of the N-oxide metabolite.
- Genotype should be used as a covariate for children in the NONMEM model.

Pfizer agreed to take these comments into consideration, modify, and then resubmit the protocol. They also agreed to submit the data from the single dose pharmacokinetic study in draft, prior to initiating this study.

9. The Division recommended that Pfizer perform a multiple dose study of voriconazole in subjects with hepatic impairment and measure concentrations of voriconazole and the N-oxide metabolite, since the drug exhibits non-linear pharmacokinetics and the single dose data previously collected may not reflect changes that occur at steady state. Pfizer was encouraged to study subjects with moderate impairment (Child-Pugh Class B) and advised that the data collected could be extrapolated to patients with mild disease (Child-Pugh Class A).
10. Pfizer has conducted a single oral dose pharmacokinetic study of voriconazole in subjects with varying degrees of renal impairment and found no significant effect. The Division noted that the IV formulation of voriconazole contains cyclodextrin and accumulation of cyclodextrin has been seen in other IV drug formulations when given to patients with renal impairment. Pfizer acknowledged the potential for toxicity due to cyclodextrin accumulation in renal impairment. In current Phase III studies, a serum creatinine of > 2.5 is exclusion from receiving the IV formulation and such patients may receive oral voriconazole only. Pfizer has already studied cyclodextrin in animal toxicity studies. They are planning an IV study in humans with renal impairment, which will not be ready at the time of NDA submission. They are also planning toxicokinetic studies in animals.
11. The Division reminded Pfizer of interest in the interconversion of the administered voriconazole enantiomer to the opposite enantiomer. They responded that they have completed a multiple dose study in humans. The results showed that in plasma obtained around the time of $C_{max}$ there was no interconversion of the administered product to the other enantiomer.

Signature, minutes preparer: /S/ Date: 2/3/00
Leo Chan. R.Ph.

Conference Chair : /S/ Date: 2/03/00
Marc Cavaillé-Coll, M.D., Ph.D.

IND On File

# MEMORANDUM OF TELECONFERENCE MINUTES

**Meeting Date:** September 17, 1999
**Time:** 11:00 a.m.
**Location:** U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S400
Rockville, MD 20850

**Application:** INDs [redacted]

**Type of Meeting:** Electronic Regulatory Submission (ERS) Formatting Issues/Type C

**Meeting Recorder:** Matthew A. Bacho, Regulatory Project Manager

**FDA Attendees, titles, and Office/Division:**
Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader and Meeting Chairperson
Rosemary Tiernan, M.D., Medical Officer
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Cheryl Dixon, Ph.D., Statistics Reviewer
John Mahoney, Regulatory Health Project Manager
Leo Chan, Regulatory Project Manager
Matthew A. Bacho, Regulatory Project Manager

**External Constituent Attendees and titles:**
Paul Burke, Information Technology (UK)
Simon Dundas, Electronic Submissions-Biometrics (UK)
Maureen Garvey, Regulatory Affairs (NY)
Anthony Gazikas, Information Technology (Groton, CT)
Ian Miller, Biometrics (UK)
Philip Ross, Information Technology (Groton, CT)
Konrad Tomaszewski, Clinical Safety and Submissions (UK)

**Background:** Pfizer requested, and was granted, a meeting to discuss the ERS for their anticipated new drug application for voriconazole.

**Meeting Objective:** Pfizer wanted concurrence from the FDA on their proposed ERS and to confirm its compliance with the Agency's guidance document regarding electronic NDA submissions.

**Discussion Points:**

1. Pfizer stated that a demonstration of the voriconazole ERS could be done and inquired about when would be a good time to do this. They also asked for a contact who could provide guidance on issues regarding the archival copy of their submission. *The FDA noted that the demonstration should be close to the actual date of submission, with enough time to make any necessary corrections, and John*

*Mahoney would be able to help Pfizer with any concerns they may have with the archival copy of the NDA.*

2. Pfizer inquired about the nature and origins of a program that the FDA was interested in beta-testing in anticipation of the proposed NDA. *The FDA noted that this piece of software was developed by to analyze clinical pharmacological data. The Agency agreed to provide the name and number of the biopharmaceutics division director, who would be able to provide more information about this program.*

3. As for the organization of adverse events, Pfizer noted that the datasets would include the patient identification number, date that the event took place, and any subsequent findings that pertain to that specific event. They then pointed out that reviewers would be able to search the datasets by specific adverse event, which would allow an analysis to be performed on any subset desired by the reviewer. Pfizer had also addressed the 25-megabyte file size limit specified by the Agency's guidance document and asked if they should submit the whole SAS datasets as well. *The FDA accepted Pfizer's proposal for adverse events and concurred on the submission of the large, uncut SAS datasets.*

4. Pfizer confirmed that the efficacy and safety data would be organized by study and added that the time fields utilize numeric variables, which would allow the FDA to easily manipulate them. In response to a request from a reviewer, they wished to confirm that the FDA would like the Phase I study reports to be submitted in the Microsoft Word format. *The Agency noted that individual divisions could not request documents to be submitted in this format.*

   As an alternative to Microsoft Word, Pfizer noted that these study reports could be submitted as PDF files for Adobe Acrobat 4.0. *The FDA agreed that this would be an adequate format for the Phase I study reports.*

5. Pfizer supported the FDA's need to see datasets with individual pharmacokinetic variables for each patient, which would include plasma concentration data and the relevant timepoints. *The Agency acknowledged Pfizer's statement and then asked if these pharmacokinetic variables could be submitted in Microsoft Word tables, which would allow reviewers to manipulate the data using ISI Graph (a plug-in tool that allows one to copy a graph from a PDF file to a Microsoft Word document without changing its format).*

   Pfizer agreed to look into this and get back to the FDA at a later date.

6. Pfizer inquired about whether the FDA still wanted pharmacokinetic data to be submitted in ASCII format. *The FDA noted that internal discussions on this subject resulted in their inability to ask for data in this format, leaving SAS transport and archival portable data files as the only viable options. However, the Agency would look into using this format for the reviewer's aid.*

7. Pfizer agreed to submit electronic and paper copies of all published articles and in-house experiments that evaluate the microbiologic activity and mechanism of action of voriconazole against fungi. *The Agency acknowledged Pfizer's statement and inquired about making MIC (minimally inhibiting concentration) and resistance data available through Microsoft Access or SAS so that reviewers could manipulate it.*

   Pfizer agreed to look into this and get back to the FDA at a later date.

8. The FDA inquired about when Pfizer planned on submitting their NDA for voriconazole. *Pfizer noted that the NDA would probably be submitted sometime during the fourth quarter of 2000.*

**Action Items:**

1. Pfizer agreed to explore submitting the pharmacokinetic variables in a Microsoft Word table format and look into making MIC and resistance data available through either Microsoft Access or SAS.

2. The Agency agreed to provide more information concerning the biopharmaceutics program Sirius and look into accepting alternative data file formats for the reviewer's aid.

Minutes Preparer: /S/ 3/6/00

Meeting Chairperson: /S/ 3/6/00

DFS Keywords:
Admin minutes
Class antifungal
Indic aspergillosis
Indic candidiasis, esophagus

Concurrence:
HFD-590/MO-TL/Cavaillé-Coll/e-mail/111799
HFD-590/MO/Tiernan/e-mail/111799
HFD-590/Stat/Dixon/e-mail/111799
HFD-590/Biopharm/Meyer/e-mail/111899
HFD-104/RHPM/Mahoney/e-mail/111799
HFD-590/RPM/Chan
HFD-590/RPM/drafter/Bacho/102199

Distribution:
HFD-590/MO-TL/Cavaillé-Coll
HFD-590/MO/Tiernan
HFD-590/Stat/Dixon
HFD-590/Biopharm/Meyer
HFD-104/RHPM/Mahoney
HFD-590/RPM/Chan
HFD-590/Division File
IND
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To DFS
Faxed to sponsor w/o this page 3/10/00

# MEMORANDUM OF MEETING MINUTES

**Meeting Date:** July 7, 1999
**Time:** 11:30 a.m.
**Location:** U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S300
Rockville, MD 20850

**Application:** INDs [redacted]

**Type of Meeting:** Visual Adverse Phenomena and Liver Function Data Presentation/Type C

**Meeting Recorder:** Matthew A. Bacho, Regulatory Project Manager

**FDA Attendees, titles, and Office/Division:**
Mark J. Goldberger, M.D., M.P.H., DSPIDP Director and Meeting Chairperson
Wiley A. Chambers, M.D., DAAODP Deputy Director
Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
Rigoberto Roca, M.D., Medical Officer
Owen G. McMaster, Ph.D., Pharmacology/Toxicology Reviewer
Matthew A. Bacho, Regulatory Project Manager

**External Constituent Attendees and titles:**
Reinhard Baildon, M.D., Clinical (U.K.)
Alice Baruch, M.D., Ph.D., Clinical (U.S.)
Suresh Chahwala, Ph.D., Safety Pharmacology (U.K.)
Maureen Garvey, Ph.D., Regulatory Affairs (N.Y.)
Scott Hopkins, M.D., Clinical (U.S.)
Konrad Tomaszewski, Ph.D., Clinical Safety (U.K.)

**Background:** Pfizer requested, and was granted, a meeting to respond to FDA concerns about several aspects of the visual adverse phenomena associated with voriconazole and to discuss the presentation of the liver function data in the upcoming NDA.

**Meeting Objective:**

1. Pfizer presented new data from the ophthalmological testing conducted as part of the clinical evaluation of voriconazole and their proposals for additional investigation.

2. Pfizer brought up their proposal for presenting the liver function test data in the voriconazole NDA.

**Discussion Points:**

1. Pfizer briefly discussed the status of their various studies and then presented the preliminary results from Study 150-305 (a double blind, comparative study of voriconazole versus fluconazole in the treatment of oesophageal candidiasis). In

summary, and keeping in mind that these data could only be studied qualitatively, no systematic change from baseline, comparing the three visual function tests (Pelli-Robson chart, funduscopy, and City University Color Vision test) between the two groups at the end of therapy, could be detected. Pfizer then stated that their other study, 95CK39-0673 (dose escalation study of voriconazole, with active control of fluconazole, in patients at risk of fungal infection), also presented no differences between the two treatment groups (ETDRS chart series, photostress recovery time, Humphrey or Goldmann visual fields, intra-ocular pressure, slit lamp exams, and the three mentioned above). *The FDA acknowledged these statements and reminded Pfizer to submit the types of visual tests to be performed as part of any future study they may wish to conduct. With reference to the background package submitted by Pfizer, the FDA cautioned against relying on the confrontation perimetry for visual fields and use of the City University Color Vision test because it will not consistently pick up acquired eye disturbances. The FDA advocated the use of the ETDRS chart series to check visual acuity and warned Pfizer that the design of Study 95CK39-0673 could allow a few patients with abnormal baselines to undermine its ability to detect anything significant.*

2. Pfizer summarized the effects of voriconazole on the electroretinogram (ERG) in the anesthetized dog. In short, the results supported what was observed in the human subjects of Study 150-231 and suggest voriconazole can effect phototransduction in the retina. Contrary to the clinical studies, which showed voriconazole to have a predominant effect on the a-wave, the dog actually uncovered effects to the b-wave as well. *The FDA acknowledged the data from the dog study.*

3. Pfizer presented its multiple-dose ERG study, which was designed to address the FDA's concerns about voriconazole's potential cumulative effects, as well as their reversibility, on the visual function of patients. The preliminary protocol would involve 36 healthy volunteers receiving either voriconazole or placebo for 4 weeks. In addition to the multiple ERG assessments, which would compose the primary endpoint, Pfizer would also include electro-oculograms, visually evoked potential, color vision testing using the Farnsworth-Munsell 100 hue test, and other functional tests. Finally, Pfizer proposed initiating multiple dose pediatric studies if reversibility of the visual effects could be demonstrated in this study. *The FDA noted that the visual evoked potential test and EOG might yield less-than-satisfactory data because of the possible difficulties with drop out rate and lack of compliance. The FDA noted that Pfizer would be better served by using the Farnsworth-Munsell 100 hue test, automated Humphrey visual field test, and the ETDRS chart series (keeping in mind that the chart should have an equal number of letters/line and equal spaces between lines) instead of these other two tests. The FDA also noted that a 20% difference in ERG from baseline might not be significant, however, there was no problem powering this study to look at changes greater than that. The FDA then commented that the dog study ERG data would help to support any future multiple dose pediatric studies Pfizer would like to initiate prior to the completion of this clinical study in adults.*

4. The FDA inquired about how the funduscopy would be done and who would perform the test. *The investigating physician would perform the direct funduscopy unless he or she felt insecure about it and then an ophthalmologist would take care of it.*

5. The FDA advised Pfizer to drop the direct funduscopy unless the indirect and visual acuity tests were performed as well. *Pfizer acknowledged the advice.*

6. In addition to the multiple-dose ERG study described above, Pfizer would gather additional visual effects data from the Aspergillosis studies (307 and 602) as well. Pfizer inquired about whether looking at the long-term visual adverse events of voriconazole in patients as part of a Phase III study would be advised. *The FDA noted that any study designed to look at the visual effects of voriconazole should be at least two weeks in length. In addition, the FDA reminded Pfizer to include indirect funduscopy, the Humphrey automated visual field test, and the slit lamp examination in any future studies of this nature. With reference to Protocol A1501004, the FDA noted that subjects with a visual acuity of 20/15 should not be ignored (they compose approximately 50% of the population), that the order of tests was important (e.g., funduscopy should precede the ERG), and that patients should be dark-adapted at least 20 minutes prior to the ERG. Finally, the FDA asked Pfizer to submit the visual field raw data in a format similar to what was done for the product Viagara®.*

7. Pfizer turned the discussion to the hepatic issues concerning voriconazole and proposed to define clinically significant liver functions tests (LFTs) using the method published by Walsh et al. (NEJM 1999;340:764). *The FDA accepted Pfizer's plan to use Walsh's method to define clinically significant LFTs. The FDA then noted that the clinical significance of increases in transaminase and direct bilirubin were not known. It would be important to look for other subtle signals (e.g., adverse events occurring late in the trial, slight LFT accumulations over a long period of time, etc.) that might indicate hepatotoxicity risk over time, even if the LFTs seem to be similar between the voriconazole and comparator arms.*

8. Pfizer acknowledged the FDA's comments and noted that they would like to have a pre-NDA meeting sometime during the first quarter of 2000. They would also like to discuss their plans for electronically submitting their NDA with the Division as well. *The FDA acknowledged Pfizer's statements.*

**Action Items:**

Pfizer will submit a revised protocol that incorporates the recommendations made by the FDA at this meeting.

Minutes Preparer: _____ _____

Meeting Chairperson: _____ _____

DFS Keywords:
Admin minutes
Class antifungal
Indic aspergillosis
Indic candidiasis, esophagus

Concurrence:
HFD-590/DSPIDP-Dir/Goldberger/
HFD-590/MO-TL/Cavaillé-Coll/080699
HFD-590/MO/Tiernan/
HFD-550/DAAODP/Chambers/072899
HFD-590/MO/Roca/
HFD-590/PharmTox/McMaster/
HFD-590/RPM/Bacho/drafter/081199

:
Distribution:
HFD-590/DSPIDP-Dir/Goldberger
HFD-590/MO-TL/Cavaillé-Coll
HFD-590/MO/Tiernan
HFD-550/DAAODP/Chambers
HFD-590/MO/Roca
HFD-590/PharmTox/McMaster
HFD-590/RPM/Bacho
HFD-590/Division File
IND ~~~~
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**In DFS**
**Faxed to sponsor w/o this page**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

# MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** April 7, 1999

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

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

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

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

**IND:** [redacted]

**SUBJECT:** Voriconazole Serious Event.

**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.

**This trial will be allowed to proceed with implementation of the changes outlined below:**

1. 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.

2. 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 completion of intravenous voriconazole therapy. Depending on the course of intravenous voriconazole therapy, this might encompass several days or weeks.

3. Patients must have stable electrolytes prior to voriconazole infusion. Hypokalemia should be corrected prior to voriconazole infusion.

4. 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.

5. 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.

6. In the voriconazole IND safety report, you included case synopses on ten additional patients who had cardiac dysrhythmia while enrolled in the febrile neutropenia/vhoriconazole 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.



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 7, 1999

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**Date:** March 25, 1999
**To:** FDA Log
**From:** Maureen. H. Garvey PhD
**Subject:** IND ___ Voriconazole (intravenous)
IND ___ Voriconazole (oral)
Minutes of March 10, 1999 FDA Meeting to discuss final data from the aspergillosis trial 150-304 and other issues (Overheads shown at the meeting are attached)

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| FDA Attendees: | Pfizer Attendees: |
|---|---|
| Mark Goldberger MD, Div. Director | Reinhard Baildon MD, Clinical UK |
| Joyce Korvick MD, Act. Team Leader | Alice Baruch MD PhD, Clinical US |
| Rosemary Tiernan MD, Medical Officer | Nigel Brayshaw CSc Biometrics UK |
| Nancy Silliman PhD, Stat. Team Leader | Don Costello PhD, Reg. Affairs NY |
| Cheryl Dixon PhD, Stat. Reviewer | Maureen Garvey PhD, Reg. Affairs NY |
| Funmilayo Ajayi PhD, Bioph.Team Leader | Scott Hopkins MD, Clinical US |
| Joette Meyer PharmD, Bioph. Reviewer | Robert Swanson PhD, Clinical US |
| Laurie Bernato RN MN, Project Manager | Konrad Tomaszewski PhD, Clin. Safety UK |

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**Executive Summary:**

The meeting was very cordial. After M. Garvey described the agenda and goals of the meeting, R. Swanson gave a brief review of the status of the voriconazole clinical program, R. Baildon presented the final data from Study 304 and D. Costello presented Pfizer plans for the Integrated Summary of Effectiveness. In conclusion, M. Garvey reviewed the discussions and agreements and asked if the Division could share their current view of the possibility of a priority review.

Dr. Goldberger led the discussion for FDA with a few questions coming from the Medical Reviewer and Biopharmaceutics Team Leader. Dr. Goldberger said there is a more than reasonable chance that the voriconazole NDA will go before an Advisory Committee.

Following are the agreements/understandings reached:

**Re: First line indication for aspergillosis.**
Dr. Goldberger said there is probably a sufficient number of patients in Study 304 to file for a first line indication; approval will depend on the final data. This was said in the context of allowing a maximum of 96 hours prior therapy with another agent for a patient to still be considered a first line voriconazole patient. (Ninety-six hours is the most conservative approach to classifying a patient as having received first vs second line treatment and is the duration used for inclusion in the ongoing aspergillosis trials.) The 304 protocol-permitted duration of prior therapy is 10 days. Alternative allowable durations of prior therapy were discussed and Dr. Goldberger made suggestions regarding what would strengthen the case for a first line indication.

**Re: Table set for Study 304 as a template for principal study reports in the NDA.**
Dr. Tiernan, Medical Team Leader, speaking for the microbiological reviewer, who was not present, requested that mycology data and MICs be part of the tabulated data in the final report. There were no other requests.

**Re: Pfizer plans for presentation of the Integrated Summary of Effectiveness (ISE) and utilization of the Sponsor Assessment Tool (SAT).**
The SAT is a mechanism for standardizing the description and evaluation of patients from across the NDA database to allow appropriate assignment of patients to specific pooled analyses. The Division found our plans for the ISE and SAT acceptable. Dr. Goldberger suggested additional descriptors of patients which would enhance the SAT for this NDA and for later submissions such as the combined analysis of the Phase III aspergillosis trials 602 and 307.

**Re: Priority review for the voriconazole NDAs.**
Dr. Goldberger confirmed that the NDA has the potential for priority review, referring in particular to the oral formulation. The review designation will also depend on the outcome of the empirical therapy trial. He added that the only available therapy is liposomal Amphotericin B.

**Re: Outstanding Items.**
M. Garvey identified the visual adverse events and the pediatric program as outstanding items in need of further discussion (The latter was identified as needing discussion in the context of Dr. Wiley Chambers' concerns regarding development of the retina, the timetable for conducting pediatric PK studies and the need to begin the process of obtaining a Written Request. The pediatric program of PK studies was accepted at the February 25, 1998 End-of-Phase II meeting.) She informed FDA that we will submit a response to the FDA facsimile soon which will include our proposal for additional investigation of the visual adverse events, and that we will request a meeting to discuss the proposal. Dr. Goldberger suggested that Pfizer come to the visual adverse events meeting prepared to discuss liver function abnormalities as well. He stressed that his suggestion was a wish to begin discussion of an issue that will need to be addressed in the NDA.

M. Garvey told FDA that we are anxious to have the visual AEs discussion ASAP. We agreed that we will not delay discussions of the visual AEs in order to discuss liver function abnormalities simultaneously. If Pfizer is not prepared to discuss LFT changes when the visual AEs meeting is scheduled, we will meet separately re LFTs.

Note:
At the February 3 End-of-Phase II CMC meeting, Dr. F. Ayaji, the Biopharmaceutics Team Leader, had asked about the metabolism of the enantiomers. M. Garvey's interpretation was that Dr. Ayaji wanted to see the topic addressed in the NDA. Dr. Ayaji raised the question again at the 304 meeting, commenting that she had not received a response yet. M. Garvey apologized, explained the misinterpretation, and committed to a response to Dr. Ayaji.

**Action:** M. Garvey, with voriconazole team members from Clinical Pharmacology and Developmental Research, will prepare response to Dr. Ayaji.

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**Minutes:**

**Introduction**

M. Garvey thanked the FDA attendees for the opportunity to continue the sharing of voriconazole data which we began last year at the End-of-Phase II meeting. She introduced the possibility of future meetings to discuss other aspects of the voriconazole program such as pharmacokinetics and candidiasis. She confirmed that the current program and plans for the NDAs are as was described to FDA at the February 25, 1998 End-of-Phase II meeting. She indicated that there would be later submissions, *viz* the combined analysis for the two large aspergillosis trials, the pediatric oral suspension and final study reports for certain trials. She continued with a description of the goals of the meeting:

- present status of voriconazole clinical program
- share final data from Study 304 and discuss proposal for the aspergillosis historical control study
- elicit FDA input regarding sample study tables included in the pre-meeting package
- present proposal for ISE and Sponsor Assessment Tool
- elicit current FDA position regarding priority review for voriconazole
- continue discussion of first line indication for voriconazole in the treatment of aspergillosis
- identify Outstanding Items: visual AEs and pediatric program

**Status of Voriconazole Clinical Program**

R. Swanson gave a brief review of the status of the voriconazole clinical program. Dr. Goldberger asked if there would be any efficacy data from the aspergillosis trials 307 and 602 in the NDA. In his response that there would not be any efficacy data from those trials, R. Swanson cited agreements with the EORTC and US investigators that Pfizer wanted to maintain the integrity of the data and would not perform any other analyses than those described in the protocols. Dr. Goldberger asked if there are any other planned analyses of these trials, *eg*, for the Data Safety Monitoring Board. R. Swanson described the combined analysis which will be conducted when the total number of patients in Studies 307 and 602 reaches approximately 300. In response to Dr. Goldberger's next question about timing of the submission of the combined analysis, R. Swanson said the combined analysis would be submitted approximately one year after the initial NDA.

When Dr. Goldberger asked if Pfizer would be seeking an indication for initial therapy or for patients who failed other therapies, M. Garvey referred to the meeting objective to discuss this issue. She said Pfizer hoped to receive an indication for initial therapy in aspergillosis in the initial NDA, based on Study 304 and cases from the rest of the clinical program, together with the historical control study.

**Study 304**

R. Baildon presented the final data from Study 304.

Dr. Goldberger said it is important for the third party reviewer to determine the really refractory cases in Study 304. This would make a much stronger case for voriconazole. If a patient becomes intolerant to his initial therapy and the patient is treated with voriconazole as second line, the patient may actually have been doing well prior to switch, be almost cured, and any therapy would have produced a cure. R. Swanson commented that the Principal Investigator distinguished between intolerant and refractory patients. Dr. Goldberger stressed the point of demonstrating efficacy in truly refractory patients. He said, "If the synthesis of all cases will make a case for initial therapy for aspergillosis, a good effect in refractory patients makes a strong case for the drug overall."

Dr. Tiernan asked how Pfizer considered patients with neutrophil counts >550 but absolute counts <1000. She said this group may be relevant if recovering neutrophil counts are contributing to the response. R. Baildon said it is likely that a fair number of patients in Study 304 had been immunosuppressed for some time prior to entry into the study. However, these data were not collected

Dr. Goldberger said Pfizer should be ready to discuss liver function abnormalities when we come back to discuss visual adverse events. There is increased interest in Liver Function Test across drugs at the Agency. He acknowledged that voriconazole was seeking approval for the treatment of systemic and life threatening fungal infections, and that an assessment of toleration over risk would be a factor. He concluded that there may be better ways to present these LFT data in the NDA.

R. Baildon said that one of the issues he wished to discuss with FDA was the assessment of response when a patient died subsequent to End Of Therapy. This raises the issue that there will be a patient assessed as 'partial response' by the investigator at End Of Therapy but the patient died at End Of Therapy or shortly thereafter. This was the case for some patients in study 304 , some of these had been treated for over 100 days. Our preference is to present crude mortality only. Assessment of attributable mortality has been very difficult in those trials where we use an external data review committee. We suggested that we will use the investigator assessment at End of Therapy, although one of our experts says a death may be a success.

Dr. Tiernan asked to see the data presented where death is classified as a failure and an analysis where death is attributed according to the expert's attribution. Dr. Tiernan asked what Pfizer thought of a patient who was assessed as cured but died while still on voriconazole therapy at Day 144. R. Baildon gave the example of cerebral aspergillosis for which investigators are afraid to stop voriconazole therapy. Patients remain on therapy for a long time and some die of various causes while still on voriconazole therapy.

R. Baildon suggested that the NDA would include a presentation of outcome as "favorable" or "unfavorable". "Favorable" would include *complete* cures and *partial* cures; the latter would include ten patients who died on therapy, such as the patient who died at Day 172. "Unfavorable" would include patients assessed as *stable* or *failure*.

Dr. Tiernan sought clarification regarding the number of days of therapy at "End of Therapy". R. Baildon said it varied, all the way up to 140 days or 177 days for example among the ten patients who died.

Dr. Goldberger said some of these issues may be settled by the historical control data. When discussing underlying diseases, Dr. Goldberger raised the issue whether some of the positive responses could be due to recovery of patients from their underlying disease, eg recovery from neutropenia. Distinguishing between a drug effect and recovery of neutrophil count is difficult; however, with the Sponsor Assessment Tool we hope to be able to identify special patient populations where a distinction is possible.

There was an extended discussion of primary vs secondary therapy. R. Baildon described the 304 protocol definition of primary therapy: <10 days of prior anti-fungal therapy, and the ongoing aspergillosis trials definition: < 4 days of prior anti-fungal therapy. Dr. Tiernan asked why Pfizer chose the second definition. R. Baildon explained that 4 days is used in the current aspergillosis trials as a means to ensure entry of primary cases only and that this is considered to be a very narrow definition by the external experts.

Dr. Goldberger asked what is the most liberal definition of allowable prior therapy. R. Baildon answered ten days, but that most people are most comfortable with five days as the cutoff. He described Pfizer's discussions with outside experts who vary in their definitions of primary vs salvage treatment, but most of whom think four days is too short and ten days is too long. Dr. Goldberger acknowledged that the "n" of patients who qualify as primary treatment patients is sensitive to the definition of the cutoff. He said five days might be a reasonable approach. He asked how the pattern of response varies with different numbers of days for the cutoff.

Dr. Goldberger raised the Pfizer meeting objective: "Do you have enough patients for a primary indication?" He answered "Probably yes." The issue will be how do the voriconazole data compare to the historical control data. He added (repeating an earlier point) that data from salvage patients will be helpful.

Dr. Goldberger asked which parameters would be matched between Study 304 patients and historical control patients. He assumed (correctly) that the CRO conducting the historical control study will not know the outcome of the patients, just the demography of the historical patients. He indicated his wish to see the proposed protocol.

In response to Dr. Goldberger's question about analysis of the Study 304 and historical control data, R. Baildon said the analyses will be descriptive at a minimum. Additional analyses will depend on the homogeneity of the two populations; this is currently under discussion. There was further discussion regarding the number of patients required for the historical control study. Dr. Goldberger commented that 80 patients would be required for a 2:1 match (historical control patients : 304 patients) if the number of days of prior therapy is <4 days and therefore the number of primary treatment patients is 39. If five days of prior therapy are allowed, the number of historical control patients will be >80. He suggested we match historical control patients for different cutoffs for prior anti-fungal therapy. He also suggested that we address the basis of our classification in a

narrative summary. We should describe how Pfizer discussed first line and salvage treatment with outside experts.

There was a discussion of what data would be available for the historical control patients and how these patients would be assessed. R. Baildon said we will probably present the data with the treating physician assessment as far as outcome is concerned. Access to radiology and further data for outside expert assessment would be very difficult due to the elapsed time (we want patients who were treated in the same time period as 304) and data protection issues.

Dr. Goldberger raised another issue: Does the assignment of patients to "probable" or "definite" aspergillosis categories account for the efficacy findings in primary *vs* secondary patients? This comment referred to an earlier discussion during R. Baildon's presentation when it was noted that the relative cure rates for primary *vs* secondary patients were not what would have been expected. R. Baildon's suggestion was that the cutoff of four days of prior anti-fungal therapy for consideration as a primary treatment patient may be inappropriate. Dr. Goldberger suggested Pfizer look at other studies in the voriconazole database which contribute salvage patients and see how their cure rates compare to primary cases.

Dr. Goldberger offered that it will be helpful if the narrative also discusses partial cures; since in this patient population a partial cure means something good. It is not quite what we think of when we think of anti-infective therapy.

Switching subjects, Dr. Goldberger asked about formulations and bioavailability. R. Baildon answered that the bioavailability of the oral formulation is above 80%.

As a final point regarding 304, M. Garvey asked if there were any comments regarding the sample tables which were included in the pre-meeting package. Dr. Tiernan spoke for the absent microbiology reviewer and requested tables with mycology data and MICs. Dr. Baildon commented that these data will be included. However, as follow-up is difficult (requiring repeat biopsies), these data are sparse.

Dr. Goldberger summarized the discussions of Study 304. Voriconazole is clearly a drug that addresses an important medical need. There is a more than reasonable chance this NDA will go to an Advisory Committee. What adds greatly to the credibility of the NDA is that there are carefully crafted processes for patient identification, assignment and evaluation.

**Biopharmaceutics**

Dr. Ayaji, the biopharmaceutics reviewer, asked if Pfizer employed an —— assay for voriconazole in plasma samples. She asked if Pfizer has information regarding interconversion among metabolites. She said the metabolism appears to be complex. She said even if a metabolite is inactive regarding efficacy, it may not be inactive regarding toxicity. Dr. Ayaji said she had asked about the metabolism of the enantiomers at the CMC meeting (February 3, 1999) and that she had not received a response yet. M. Garvey apologized, explaining that she thought Dr. Ayaji wanted to see the topic addressed in the NDA.

Action: M. Garvey, with voriconazole team members from Clinical Pharmacology and Developmental Research, will prepare a response to Dr. Ayaji.

Integrated Summary of Effectiveness (ISE) and the Sponsor Assessment Tool (SAT).

D. Costello presented Pfizer plans for the ISE and SAT. The SAT is a mechanism for standardizing the description and evaluation of patients from across the NDA database to allow appropriate assignment of patients to specific pooled analyses. The Division found our plans for the ISE and SAT acceptable.

Dr. Goldberger suggested additional descriptors of patients which would enhance the SAT for this NDA and for later submissions such as the combined analysis of the Phase III aspergillosis trials 602 and 307. He suggested that we include "Outcome of Fungal Infection" and "Outcome of Underlying Disease" in the SAT. With regard to resolution of disease, he suggested "neutropenia' might be helpful in the assessment.
R. Baildon cautioned about the limits to which we can analyze the data and offered "no change", "improved", or "worsened" as possibly the best classification we can obtain.
Dr. Goldberger understood, agreed it may be the best Pfizer can do, and said neutropenia may have to be classified as "resolved"/ "not resolved". Dr. Goldberger suggested we include primary vs secondary patients in the SAT. He said it would improve the value of the SAT.

R. Baildon said there is an SOP for the SAT. He asked if it is appropriate to pool the data from several protocols if the response rates vary across the protocols? He added that the SAT probably offers a tool which explains why the response might be different among groups and thus allow pooling to take place. Dr. Goldberger said pooling would be possible because we are merging by demography and risk factors and these should explain any differences in response rates observed in the different studies.

In response to his questions, Dr. Goldberger was told which studies will be in the NDA and that the NDA will include US and non-US (mostly European) patients. He suggested we identify US and non-US patients in the NDA.

Conclusion

M. Garvey reviewed the discussions, agreements and outstanding items as described in the Executive Summary. She asked if the Division could share their current view of the possibility of a priority review.
Dr. Goldberger confirmed that the NDA has the potential for priority review, referring in particular to the oral formulation. The review designation will also depend on the outcome of the empiric therapy trial. He added that the only available therapy is liposomal Amphotericin B.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

# MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

**DATE:** October 9, 1998

**TO:** Maureen Garvey
Regulatory Affairs

**ADDRESS:** Pfizer
235 East 42nd Street
New York, NY 10017-5755
(212) 733-5688
(212) 573-7314 (fax)

**FROM:** Ellen C. Frank, R.Ph., Chief, Project Management Staff

**THROUGH:** Marc Cavaillé-Coll, M.D., Ph.D., Clinical Team Leader
Wiley Chambers, M.D., Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products

**IND:** [redacted]

**SUBJECT:** Submissions 077/060 and 087/070
Position Paper on Voriconazole and Altered Vision

Please refer to your submissions dated May 8, 1998 and July 28, 1998, containing the Pfizer Position Paper on Voriconazole and Altered Vision. Your cover letter requested FDA concurrence with your plan to address visual disturbances. For your convenience, the specific areas in which you requested concurrence are duplicated below (in *italics*) with our comments following. Our comments incorporate our consultation with a CDER ophthalmologist.

1. *Additional mechanistic investigations would not likely further elucidate the mechanism of action of these visual events.*

   We do not agree. We do not know if further mechanistic investigations would elucidate the mechanism of action of these visual effects.

2. *The long term ocular safety of voriconazole is comprehensively addressed by the combination of visual function tests performed to date, the bedside monitoring of patients in forthcoming studies and detailed animal histopathology of the eye.*

We do not agree. Ocular testing performed to date has had numerous problems; we recommend additional testing. All patients should have full ophthalmological examinations including best corrected distance visual acuity accurately measured, a slit lamp examination, direct and indirect funduscopy, and the Farnsworth-Munsell 100 hue testing. If the testing is not available during hospitalization, we recommend these ophthalmologic examinations be conducted when the patient is ambulatory. Patients who are treated for an extended period of time (>28 days) should have automated visual field testing in addition to the aforementioned tests. The utility of the animal histopathology studies is questionable.

3. *With the completed investigations and the proposed monitoring programme, the visual disturbances will have been adequately addressed in our planned NDA.*

   We do not agree, see our comments above. The effects observed to date appear to be clinically significant and are potentially sight threatening. It is not possible to conclude that the visual cortex is not affected. It is also not possible to conclude that the ERG changes are fully reversible. We disagree with your position that voriconazole's effect on vision is a minor side effect and that these issues have been adequately addressed by your company. The proposed dosing is in the range where visual adverse events have been reported. You should attempt to identify a way voriconazole may be dosed without decreasing visual function. If this is not found, it is possible that a labeled WARNING (possibly boxed warning) of potential visual loss may be warranted.

4. *The completed investigations and the proposed monitoring programme will support the use of voriconazole in adult and pediatric patients as proposed in the End-of-Phase II meeting.*

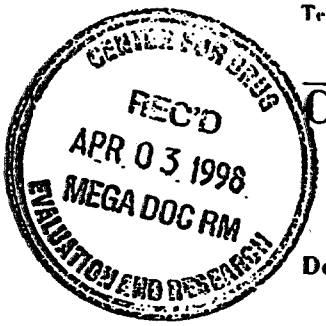
   Without further investigation, it is possible that voriconazole's potential visual loss may warrant a WARNING (possibly a boxed warning) in the label. Because irreversible ERG changes cannot be ruled out, use of voriconazole in children less than 9 years of age (when the retina is still developing) may be highly questionable.

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

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products

Eastern Point Road
Groton, CT 06340
Tel 860 441 4100




# Central Research

Department of Clinical Research

April 1, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



Dear Doctor Goldberger:

RE: IND- ——— VORICONAZOLE - Oral (Triazole Antifungal Agent)
Serial #071

IND- ——— VORICONAZOLE - I.V. (Triazole Antifungal Agent)
Serial #*054 (Cover letter only)

**MINUTES: END-OF-PHASE II MEETING**

We refer to the pre-meeting package submitted on February 11, 1998 in which we identified the topics for consideration at the second End-of-Phase II meeting for voriconazole. We refer also to a telephone conversation between Ms. Ellen Frank of FDA and M. Garvey on February 17 during which Ms. Frank informed Pfizer of three additional items which FDA wished to address. Lastly, we refer to a February 20 telephone conversation between Drs. Cheryl Dixon and Aloka Chakravarty of FDA and Rebecca Rosenstein and myself of Pfizer during which Dr. Rosenstein explained how the value for alpha was selected in Protocol 150-608, in response to the statistical question communicated by Ms. Frank on February 17.

Enclosed are the Pfizer minutes of the voriconazole End-of-Phase II meeting on February 25, 1998 together with the overheads shown at the meeting. Included are the overheads submitted in advance of the meeting and the overheads describing the aspergillosis Study 150-304 and the visual phenomena which were shown at FDA's request.

We wish to stress that the data from the aspergillosis Study 150-304 is preliminary; analysis of this study is ongoing. As we said during the meeting, we look forward to a discussion of the Study 150-304 results and their presentation in the final study report around mid 1998. We will contact FDA to arrange that discussion.

If you have any questions regarding these minutes, please feel free to call me at (212) 733-5688. We would appreciate receipt of the FDA minutes of this meeting as soon as they are available.

Please include this information in our files for IND- ———

Sincerely yours,

for Maureen H. Garvey, Ph.D.
Director
Regulatory Affairs Department

map/enclosures