

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 5, 2001

NDA NUMBER: 21-266/21-267

NAME OF DRUG: VFEND and V-FEND
(Voriconazole)
50 mg and 200 mg Film-coated Tablets;
Powder for Solution for Infusion

NDA HOLDER: Pfizer, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), for assessment of the tradenames "VFEND and V-FEND", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

VFEND/V-FEND is the proposed proprietary name for voriconazole, a broad-spectrum, triazole antifungal agent, indicated for the treatment of the invasive aspergillosis, serious Candida infections, serious fungal infections, and empirical treatment of presumed fungal infections in febrile immunocompromised patients. VFEND/V-FEND Film-Coated Tablets (50 mg and 200 mg) should be taken at least one hour before, or one hour following, a meal. VFEND/V-FEND I.V. for Infusion requires reconstitution and dilution prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours. VFEND/V-FEND I.V. for infusion is supplied in a single use vial as a sterile lyophilized powder equivalent to 200 mg voriconazole. See chart below for dosing information.

	INTRAVENOUS	ORAL	
		Patients 40 kg and above	Patients less than 40 kg
Loading Dose Regimen (1st 24 hrs)	Two doses of 6 mg/kg 12 hrs apart	Two doses of 400mg 12 hrs apart	Two doses of 200 mg 12 hrs apart
Maintenance Dose (after 1st 24 hrs)	3 mg/kg every 12 hrs	200 mg every 12 hrs	100 mg every 12 hrs

II. RISK ASSESSMENT

look alike to _____ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database⁵ and data provided by Thomson & Thomson's SAEGIS™ Online Service⁶ were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "_____. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel had concerns with the "vor" ending of _____, which may sound-alike and look-alike to names ending in "cor" and "clor". Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with '_____. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1

Zocor	Simvastatin (HMG-CoA Reductase Inhibitor – Rx) Tablet: 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg	Initial: 20 mg once a day in the evening. Dose range: 5 to 80 mg/day.	S/A, L/A per OPDRA
Asacol	Mesalamine (Gastrointestinal – Rx) Tablet: 400 mg (delayed-release)	800 mg three times a day for 6 weeks.	S/A, L/A per OPDRA

(Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

⁴ The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ WWW location <http://www.thomson-thomson.com>.

Cozaar	Losartan Potassium (Angiotensin II Receptor Antagonists - Rx) Tablet: 25 mg, 50 mg, 100 mg	Initial: 50 mg once daily. Can be given once or twice daily with total dose range from 25 mg to 100 mg.	L/A per OPDRA
Azmacort	Triamcinolone Acetonide (Corticosteroid - Rx) Aerosol: 100 mcg per actuation from mouthpiece	2 inhalations (200 mcg) 3 to 4 times a day or 4 inhalations (400 mcg) twice daily.	S/A per OPDRA
		*Frequently used, not all-inclusive	**S/A(Sound-alike), L/A (Look-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

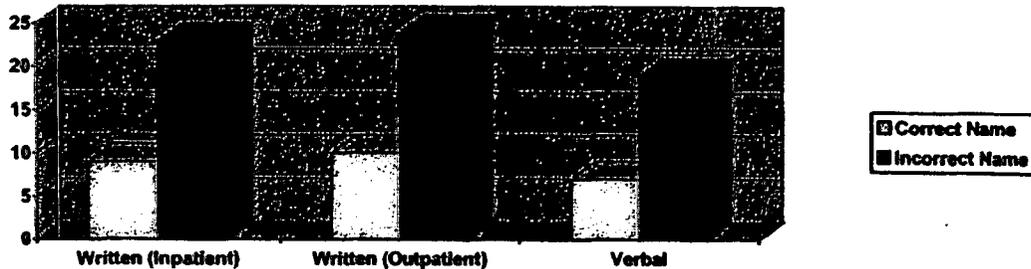
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of ' _____' and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 117 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for _____ (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

Inpatient: _____ 200 mg over 1-2 hr q 12h Outpatient: _____ 50 mg Sig: ii po q 12 ^o #60	Outpatient: _____ 50 mg Take 2 by mouth every 12 hours. #60
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2. Results:

Results of these exercises are summarized below:

	39	32 (82%)	9 (28%)	23 (72%)
	39	34 (87%)	10 (29%)	24 (71%)
	39	26 (67%)	7 (27%)	19 (73%)
	117	92 (79%)	26 (28%)	66 (72%)



Among the written inpatient prescriptions, 23 (72%) out of 32 respondents interpreted _____ incorrectly. Interpretations included *Azanor*, *Azavron*, *Aganor*, *Aravon*, *Avavor*, *Azarron*, *Aprovor*, *Ajovron*, *Avarron*, *Azonor*, *Avanor*, *Afaron*, *Afavor*, *Azaror*, *Azaron*, *Aravvor*, *Azavro*, *Azanor*, and *Ajavor*.

Among the written outpatient prescriptions, 24 (71%) out of 34 respondents interpreted _____ incorrectly. Twenty (59%) respondents interpreted _____ as *Azacor*. Two (6%) respondents interpreted _____ as *Cozaar*. Other interpretations included *Azacol* (3%) and *Azavoi* (3%).

Among the verbal outpatient prescriptions, 19 (73%) out of 26 respondents interpreted _____ incorrectly. Interpretations included *Effavor*, *Efavor*, *Esavor*, *Azavar*, *Affayfor*, *Evasor*, *Evaphor*, *Avavor*, *Azevor*, *Azabor*, *Azavon*, *Azafor*, *Evavior*, *Ezaphor*, *SS4*, *Afavore*, and *Eefavor*.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name _____, the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such drug proprietary names include *Azmacort*, *Zocor*, *Asacol*, and *Cozaar*.

Azmacort is the proprietary name for triamcinolone acetate inhaler and is indicated for the maintenance of asthma as prophylactic therapy. *Azmacort* sounds similar to _____ since the "azma" and "aza" and also the "cor" and "vor" sound alike, respectively. However, *Azmacort* is supplied as an inhaler where it administers 100 mcg per actuation while _____ is available as a 50 mg and 200 mg tablet and 10 mg/mL (20 mL) vial. The dosage forms of these two drug products are different (aerosol vs. tablet vs. injection), different administration directions ("Take 2 puffs 3 to 4 times a day" vs. "Take 1 tablet (200 mg) every 12 hours" vs. "3 mg/kg every 12 hours"), and the strengths are different. These differences may decrease the potential risk of a medication error occurring between these two drug products.

Zocor is the proprietary drug name for simvastatin and is indicated in patients with coronary heart disease, hypercholesterolemia, and hyperlipidemia. *Zocor* and "_____ " do sound alike due to the similarities in pronunciation with "zocor" and "zavor", respectively. A practitioner may prescribe "an _____ prescription" where the practitioner dispensing the prescription may misinterpret it as "a *Zocor* prescription". Even when scripted, the "A" and the "z" in _____ can resemble an uppercase, scripted "Z" and the "v" can look like a "c" so that _____ ' would look similar to *Zocor*. (See below) *Zocor* is available as a 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg tablet where _____ is available in a 50 mg and 200 mg tablet as well as a 200 mg lyophilized powder. Even though there are no exactly overlapping strengths, the 5 mg and 20 mg may be written as 5.0 mg and 20.0 mg with a trailing zero where the decimal point can be missed when reading the prescription. Both drug products have the same dosage form (tablet), the same route of administration (oral), and the same numbers in their strengths (50 mg and 200 mg vs. 5.0 mg and 20.0 mg). If a patient was given _____ instead of *Zocor*, the patient's coronary heart disease, hypercholesterolemia, and hyperlipidemia would not be adequately treated. Also, the patient would be exposed to unnecessary adverse effects such as hepatic toxicity, photophobia and/or blurring, color vision change, and rash. If the mistake was later discovered after administering the _____ and the problem was corrected by administering the *Zocor* to the patient before the " _____ " was out of the patient's system, a drug-drug interaction can occur between *Zocor* and the _____ *Zocor* belongs to a particular drug category, the *Statins*, where _____ is likely to increase the plasma concentration of statins that are metabolized by CYP3A4. An increased level of statins have been associated with myopathy. If *Zocor* was dispensed instead of _____ then the patient's serious fungal infection would not be treated. Also, the patient would experience unnecessary side effects such as abdominal pain, constipation, headaches, and asthenia. The patient would also be at risk for myopathy. *Zocor* is also rated as Pregnancy Category X. The fetus of a pregnant woman would be harmed if *Zocor* was inadvertently administered to a pregnant woman.

Writing Sample:

The image shows two handwritten prescriptions. On the left, a prescription is written as "50mg Zocor" with "50 mg" printed below it. On the right, a prescription is written as "5.0mg Zocor" with "Zocor 5.0 mg" printed below it. The handwriting is cursive and somewhat stylized, illustrating the potential for confusion between the two dosages.

Asacol is the proprietary drug name for mesalamine and is indicated for the remission and treatment of mildly to moderately active ulcerative colitis. *Asacol* sounds quite similar to _____, but slightly resembles _____ when scripted. The "Asa" and "Aza" sound alike as well as the "ol" and "or", respectively. Both drug products are also available in tablet form. *Asacol* is only available in 400 mg while _____ is available in 50 mg and 200 mg. Even though the strengths are different, a practitioner may disregard the strengths and dispense the wrong medication, especially when the names are similar and the practice setting is chaotic. For example, Cerebryx and Celebrex do not share the same strengths or dosage form; however, there have been reported cases of the name confusion. A practitioner may also adjust the amount of tablets given to satisfy the prescribed dosage. For example, a physician may prescribe "Asacol 400 mg; 2 tablets 3 times a day" where a practitioner may dispense " _____ 200 mg; 4 tablets 3 times a day" giving the patient an overdose of _____ as well as the wrong medication. According to the written outpatient portion of the OPDRA study, 20 (59%) out of 34 respondents

interpreted _____ as *Azacor*. One respondent (3%) interpreted _____ as *Azacol*, which when phonetically said is *Asacol*. Another respondent who interpreted _____ correctly commented that ' _____ can be confused with *Asacol*. If a nurse gave a prescription over the phone to a pharmacist, the pharmacist can easily mistaken it for *Asacol*. If *Asacol* was given instead of _____, then the patient's fungal infection would not be treated. Also, the patient would experience unnecessary side effects such as headaches, bloody diarrhea, abdominal pains, and conjunctivitis. If _____ was given instead of *Asacol*, then the patient's ulcerative colitis would not be treated. Also, the patient would be exposed to unnecessary adverse effects such as hepatic toxicity, photophobia and/or blurring, color vision change, and rash.

Writing Sample:

Asacol
Asacol

Cozaar is proprietary drug name for losartan potassium and is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents. Even though there are no sound-alike properties between *Cozaar* and ' _____ except for the "ar" and "or", respectively, they do look similar when scripted. (See below.) Like ' _____', *Cozaar* is available as a 50 mg tablet (also available in 25 mg and 100 mg) and can be dosed twice a day. These two drug products share the same route of administration (oral), the same dosage form (tablet), the same strength (50 mg), and the same dosing schedule (twice a day). Also, from the written outpatient portion of the OPDRA study, 2 (6%) out of 34 respondents interpreted _____ as *Cozaar*. Although there are limitations to the predictive value of the OPDRA studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretations with these drug products. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. If *Cozaar* was dispensed instead of _____, then the patient's fungal infection would not be treated. Also, the patient would be exposed to unnecessary side effects such as a persistent dry cough, hypotension, dizziness, fatigue, abdominal pain, chest pain, nausea, and headache. Also, *Cozaar* is rated in Pregnancy Category C (first trimester) and D (second and third trimesters). The fetus would be harmed if *Cozaar* was mistakenly given to a pregnant female. If _____ was given instead of *Cozaar*, then the patient's hypertension would not be controlled. Also, the patient would be exposed to unnecessary adverse effects such as hepatic toxicity, photophobia and/or blurring, color vision change, and rash.

Writing Sample:

_____ 50mg Cozaar 50mg

_____ 50 mg

Cozaar 50 mg

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Please refer to OPDRA Consult 00-0318 for labeling and packaging recommendations.

IV. RECOMMENDATIONS:

OPDRA does not recommend the use of the proprietary name _____

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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

/s/

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8/20/01 10:29:28 AM
PHARMACIST

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CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: November 11, 2000

DUE DATE:
February 28, 2001

OPDRA CONSULT #: 00-0318

TO: Renata Albrecht, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH: Jouhayna Saliba, Project Manager
HFD-590

PRODUCT NAME:

VFEND and V-FEND
(Voriconazole)
50 mg and 200 mg Film-coated Tablets;
Powder for Solution for infusion

DISTRIBUTOR: Pfizer, Inc.

NDA #: 21-266/21-267

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), OPDRA conducted a review of the proposed proprietary name "VFEND and V-FEND" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "VFEND" or "V-FEND".

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**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 5, 2001

NDA NUMBER: 21-266/21-267

NAME OF DRUG: VFEND and V-FEND
(Voriconazole)
50 mg and 200 mg Film-coated Tablets;
Powder for Solution for Infusion

NDA HOLDER: Pfizer, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), for assessment of the tradenames "VFEND and V-FEND", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

VFEND/V-FEND is the proposed proprietary name for voriconazole, a broad-spectrum, triazole antifungal agent, indicated for the treatment of the invasive aspergillosis, serious Candida infections, serious fungal infections, and empirical treatment of presumed fungal infections in febrile immunocompromised patients. VFEND/V-FEND Film-Coated Tablets (50 mg and 200 mg) should be taken at least one hour before, or one hour following, a meal. VFEND/V-FEND I.V. for Infusion requires reconstitution and dilution prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours. VFEND/V-FEND I.V. for infusion is supplied in a single use vial as a sterile lyophilized powder equivalent to 200 mg voriconazole. See chart below for dosing information.

	INTRAVENOUS	ORAL	
		Patients 40 kg and above	Patients less than 40 kg
Loading Dose Regimen (1st 24 hrs)	Two doses of 6 mg/kg 12 hrs apart	Two doses of 400mg 12 hrs apart	Two doses of 200 mg 12 hrs apart
Maintenance Dose (after 1st 24 hrs)	3 mg/kg every 12 hrs	200 mg every 12 hrs	100 mg every 12 hrs

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which sound-alike or look-alike to “VFEND/V-FEND” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name “VFEND/V-FEND”. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- DDMAC did not have any concerns with the name in regard to promotional claims.
- Six product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with VFEND/V-FEND. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

TABLE 1

Depen	Penicillamine 250 mg Tablet (Rx)	Dose various according to disease state.	S/A, L/A per OPDRA
Vivelle	Estradiol Transdermal Patches 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg (Rx)	Apply patch twice weekly	S/A, L/A per OPDRA
Ocufen	Flurbiprofen 0.3 % ophthalmic solution (Rx)	Instill 1 drop approximately 30 minutes, beginning 2 hours before surgery	
Finevin ***	Azalaic Acid 20% cream (Rx)	Apply to affected areas twice daily	

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

Z-gen	Multivitamins with Minerals	1 tablet once daily	S/A, L/A per OPDRA
Phenergan	Promethazine 12.5 mg, 25 mg, 50 mg tab; 6.25 mg/5 mL, 25 mg/5 mL syrup; 12.5 mg, 25 mg, 50 mg suppository; 25 mg/ mL, 50 mg/ mL injection. (Rx)	Varies according to indication	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive	**L/A (look-alike), S/A (sound-alike)

NOTE: This review is proprietary and contains confidential information that should not be released to the public.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of VFEND/V-FEND with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 87 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. OPDRA staff members wrote two separate outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for VFEND/V-FEND (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

WRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><i>Outpatient:</i></p> <p>V-fend 200 mg Sig: 1 po BID Disp #60</p>	<p>VFEND 200 mg</p> <p>Take 1 tablet twice daily Dispense #60</p>
<p><i>Inpatient:</i></p> <p>VFend 200 mg po BID</p>	

2. Results

Results of these exercises are summarized below:

	VFEND/V-FEND Participants	Correct Responses (%)	VFEND/V-FEND Incorrect Responses	Other Responses
Written Inpatient	29	19 (66%)	2 (11%)	17 (89%)
Written Outpatient	30	18 (60%)	3 (17%)	12 (83%)
Verbal	28	15 (54%)	0 (0%)	15 (100%)
Total	87	52 (60%)	5 (10%)	44 (80%)



Correct
 Incorrect

Among the participants in the written prescription studies, 29 of 37 respondents (78%) interpreted the name incorrectly. The interpretations were misspelled/phonetic variations of "VFEND/V-FEND", such as *V-find*, *Vifend*, *Vifind*, and *Vifund*. Other interpretations included *Vitead*, *Vfesd*, *Vfesol*, *Vfead*, *Vtard*, and *Vferol*. One participant provided *Feosol*, an approved drug product, as an interpretation.

Among the verbal prescription study participants, 100% of the participants interpreted the name incorrectly. Some of the incorrect name interpretations were phonetic variations of "VFEND/V-FEND" such as *Z-pen*, *Z-fen*, *ZeePhens*, *Z-phen*, *Zeesen*, *Zefen*, *Veesend*, *Vecin*, *Zesend*, *Zesan*, *Youssend* and *Zefin*. One participant provided *Depen* as an interpretation, which is a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "VFEND/V-FEND", the primary concerns raised were related to a sound-alike name that already exist in the U.S. marketplace. The drug product, *Depen*, is believed to be the most problematic in terms of medication error prevention.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that VFEND/V-FEND could be confused with *Depen*. *One participant (7%) from the verbal prescription study analysis provided Depen as an interpretation.* Another participant from the written inpatient prescription study interpreted VFEND/V-FEND as *Feosol*. Both *Depen* and *Feosol* are currently marketed drug products. Although there are limitations to the predictive value of these studies, primarily due to sample size, *we have acquired safety concerns due to the positive interpretation with this drug product.* A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The majority of the outpatient written prescriptions were phonetic variations of the drug name VFEND/V-FEND.

Depen is the proprietary name for penicillamine which is a disease modifying antirheumatic drug. Depen is indicated in the treatment of Wilson's disease (removes excess copper), cystinuria (reduces excess cystine), and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. Depen is available as 250 mg Titratable Tablets. Dosage for the treatment of Wilson's disease can range from 250 mg to 2 grams per day; 250 mg to 4 grams per day for cystinuria; and 125 mg to 750 mg per day for rheumatoid arthritis. Although VFEND/V-FEND and Depen do not look similar when scripted, the names do sound similar as the first letter of each tradename "V" and "D" is phonetically similar. Furthermore, vocal emphasis is not placed with the pronunciation of the last letter "D" in VFEND/V-FEND. In fact, one study participant from the verbal study analysis interpreted VFEND/V-FEND as Depen. While VFEND/V-FEND and Depen do not share an overlapping strength, the dosage of VFEND/V-FEND may be titrated by increments of 50 mg for a dose of 250 mg, which is similar to the dose of Depen. Additionally, VFEND/V-FEND and Depen share overlapping dosage forms. Serious and life threatening consequences may result from the inadvertent confusion of these two drugs, especially, if Depen is dispensed in place of VFEND/V-FEND. The use of Depen has been associated with fatalities due to certain diseases, such as aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome, and myasthenia gravis. The drug interaction profile of VFEND/V-FEND involves common drugs such as carbamazepine, phenytoin, benzodiazepines, and warfarin.

Although one participant provided Feosol, an over-the-counter iron supplement, as an interpretation to the written inpatient study analysis, the potential for confusion with VFEND/V-FEND is low.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft container label and draft package insert for VFEND/V-FEND, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified one area of possible improvement, in the interest of minimizing potential user error.

A. CARTON LABELING

1. We recommend relocating the statement "Rx only" to the primary display panel. Also, increase the prominence of this statement on the container labeling of the 200 mg sample size.
2. We recommend revising the statement "Two 200 mg TABLETS" on the individual sample packets to read "2 x 200 mg TABLETS". We also recommend revising the statement on the sample carton labeling to read "6 cartons of 2 x 200 mg TABLETS. Spelling out the number may be confused as directions.
3. We recommend revising the statement "For in-institution use only" to "For institutional use only."
4. The dosage form should be associated with the established name to appear as:

(Voriconazole) Tablets

5. The abbreviation or acronym "TBD" is unclear as to what it means or what it stands for. We note that the IV is manufactured by Catalytica Pharmaceuticals.
6. The statement "200 mg* of voriconazole" on the IV container label and carton labeling is not necessary since the 200 mg strength is prominently displayed. This avoids duplication.

B. BLISTER FOIL

We recommend relocating the strength to appear in conjunction with the tradename and not in conjunction with the quantity (back panel).

IV. RECOMMENDATIONS

OPDRA does not recommend the use of the proposed proprietary names "VFEND" or "V-FEND".

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3161.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

/s/

Alina Mahmud
2/16/01 08:33:09 AM
PHARMACIST

Jerry Phillips
2/20/01 08:25:21 AM
DIRECTOR

Martin Himmel
2/20/01 12:17:04 PM
MEDICAL OFFICER

February 14, 2001

**To: Dr. Wiley Chambers
Director, Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products**

**From: Dr. Rosemary Tiernan
Medical Officer, Division of Special Pathogens and Immunologic Drug Products**

**Re: Ophthalmology Consult
Voriconazole NDA 21-266 and 21-267**

We are currently in the process of reviewing the Voriconazole NDA. At present, I am evaluating the safety in Study 305 (indication for treatment of Candida esophagitis). Dr. John Powers is reviewing Study 603 (indication for empiric therapy of the febrile neutropenic patient). As we weigh the risks and benefits of this new drug and prepare to make specific recommendations regarding its use, we would appreciate your expertise in evaluating the visual adverse event profile.

The following questions represent some of our major concerns :

- 1) Do you believe that the Applicant adequately monitored visual function throughout the conduct of the studies included in this NDA submission?
- 2) Do you agree with the reported frequency and severity of visual adverse events that are reported in these studies?
- 3) After reviewing the safety data pertaining to vision in this NDA submission, do you believe that the visual adverse events experienced by these patients are reversible? If not, what additional measures should be taken, at this time, to ensure the safe use of this new drug.

Thank you in advance and please let us know if we can provide assistance in areas such as accessing the electronic submission, in requesting additional safety information from the Applicant or in providing further statistical analysis regarding any safety concerns.

/s/

Diana Willard
2/16/01 09:17:25 AM

Pfizer Limited, Sandwich, Kent CT13 9NJ
Telephone: Sandwich (01304) 616161 Telex: 966515
Facsimile: CCITT Groups II & III (01304) 616231



15 February 1996

Central Research

Direct Line: (01304)616377

TO WHOM IT MAY CONCERN

This is to confirm that the Process Research and Development Department, Pfizer Central Research, Sandwich, Kent, England have engaged _____ of _____, USA to prepare an intermediate for Pfizer's antifungal drug candidate Voriconazole (UK-109,496). An IND for voriconazole, reference number _____ was submitted to the FDA on August 28th 1995.

One starting material for the preparation of the aforesaid intermediate is _____

_____ understanding that the _____
the manufacture of the voriconazole intermediate on behalf of Pfizer Central Research
and no part is re-distributed or re-sold.

Furthermore, it is my
_____ is used entirely for

Yours faithfully

DR. M.N. EDINBERRY
DIRECTOR
PROCESS RESEARCH & DEVELOPMENT DEPARTMENT

MNE:atv



Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ

Medical Team Leader's Memorandum #1

TO: NDAs 21-266 and 21-267

FROM: Marc Cavaillé-Coll, M.D., Ph.D.

RE: VFEND™ (tablets) NDA 21-266 and VFEND™I.V. (for intravenous infusion) NDA 21-267

DATE: December 17, 2001

GENERAL

The original NDAs for VFEND™ (tablets), NDA 21-266 and VFEND™I.V. (for intravenous infusion), NDA 21-267, were submitted November 17, 2001. The applicant, Pfizer Global Research and Development, has requested approval for the following indications:

- Treatment of invasive aspergillosis
- Empiric antifungal therapy of febrile neutropenic patients
- Treatment of *Candida* esophagitis
- Treatment of serious *Candida* infections
- Treatment of serious fungal infections caused by *Fusarium* and *Scedosporium* spp.
- Treatment of serious fungal infections in patients refractory or intolerant to other therapy.

The review of these indications was divided among several reviewers. Dr. Rosemary Tiernan, the Lead Medical Reviewer for this application, performed the review of esophageal candidiasis, invasive aspergillosis, and the Integrated Review of Safety and coordinated the clinical reviews with the assistance of the Project Manager for this product, Ms. Jouhayna Saliba. Dr. John Powers reviewed the empiric antifungal therapy of febrile neutropenic patients. Dr. Regina Alivisatos reviewed the serious fungal infections, and Dr. Rosemary Johan-Liang reviewed serious *Candida* infections and the safety of voriconazole in pediatric patients. Dr. Edward Cox reviewed the hepatic safety of the product and Dr. Wiley Chambers reviewed the ophthalmologic safety data.

Review of this very bulky submission was facilitated by the electronic submission of data files, case report forms and study reports. The applicant submitted data files in SAS-transport format which could be used with the JMP program recommended by Center's existing Guidance on Electronic Submissions (www.fda.gov/cder/guidances/index.htm). Case report forms and patient profiles for all patients enrolled in the trials were submitted in PDF format. Study reports for the trials were submitted as MS-Word documents.

After submission of the initial NDA, the randomized open-label Global Comparative Study (307/602) was completed and a study report was submitted a MAJOR CLINICAL AMENDMENT on June 19, 2001. This submission extended the primary review goal date to November 17, 2001. A subsequent MAJOR AMENDMENT concerning proposed measures to address manufacturing and compliance issues was submitted to the NDAs in November 2001, and extended the primary and secondary review goal date to December 17, 2001.

Part of the application was presented to a meeting of the Antiviral Drug Product Advisory Committee, on October 4, 2001. At that meeting the committee recommended unanimously that VFEND™ should be approved for the treatment of invasive aspergillosis. A majority of the committee (8 No versus 2 Yes) voted that the information presented did not support that voriconazole is safe and effective for the empiric antifungal therapy of febrile neutropenic patients.

At the moment of this regulatory action, no acceptable commercial intravenous formulation is available, due to compliance issues at a contract site where the final product is manufactured. FDA is working with the firm to resolve these issues expeditiously. VFEND™ is intended to be marketed as an intravenous and oral product with a common package insert. The lack of an acceptable intravenous formulation precludes the full approval of indications that would require such a formulation.

The remainder of this memo will address particular aspects of the approvable indications, the non-approvable indications, risk management considerations, waiver of requirement for pediatric studies, and the phase 4 commitments.

APPROVABLE INDICATIONS

The applicant has requested several indications for which other antifungal therapies, including other triazoles, amphotericin-B deoxycholate, liposomal formulations of amphotericin-B, and caspofungin, exist. As a class, the triazole antifungal agents possess a different mechanism of action than the amphotericin-B products and the echinocandins, and are expected not to share overlapping mechanisms of resistance with them. Voriconazole demonstrates good oral bioavailability, which opens up the possibility for initiation of therapy with intravenous drug followed by switch to oral therapy.

These considerations, in addition to the evidence of effectiveness, summarized in this memorandum, favor the approvability of voriconazole for the indications below:

Approvability of voriconazole for these indications is also based on a favorable risk benefit assessment, which should be enhanced by proposed wording in the WARNINGS and PRECAUTIONS sections of the revised label (See SAFETY CONSIDERATIONS and RISK MANAGEMENT below).

Treatment of invasive aspergillosis due to *Aspergillus fumigatus*.

The clinical data for this indication were derived from three clinical studies, including a randomized, open-label, controlled study comparing voriconazole IV/oral to intravenous amphotericin B followed by other licensed antifungal therapy (The Global Comparative Aspergillosis Study 307/602), the Non-comparative Aspergillosis Study 304, and the contemporaneous Historical Controlled Study 1003. The Global Comparative Aspergillosis Study 307/602 was made of the combined umbrella analysis of outcome of Study 307 and Study 602 that had a similar protocol design. A total of 392 subjects with documented aspergillosis were enrolled at sites in the United States, Europe, Israel, Canada, Australia, Brazil, Argentina, Columbia, Mexico, and India.

The use of a Data Review Committee (DRC), which was blinded to treatment assignment, to assess the outcome of treatment was one of the strengths of this study. At week 12 a satisfactory global response (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was observed in 53% of voriconazole treated patients compared to 32% of amphotericin B treated patients. The stratified difference and corresponding 95% confidence interval were 21.6% and 9.6%-33.6%. At week 12 the survival rate on voriconazole was 71% compared to 58% on amphotericin B.

The results of the comparative trial are supported by the results of an earlier trial in the primary treatment of patients with acute invasive aspergillosis (Study 304). In this study an overall success rate of 60% [95% CI (46.8%, 73.8%)] was observed at 12 weeks.

Overall, voriconazole demonstrated clinical benefit including improved survival in the treatment of this serious and life-threatening condition, for which there are limited treatment options.

From a microbiologic point of view voriconazole demonstrated activity against *Aspergillus fumigatus*, and a few non-fumigatus species. While the clinical response rate were excellent in patients infected with *Aspergillus fumigatus*, there were too few numbers of patients infected with non-fumigatus species to reliably assess the clinical efficacy of voriconazole in the treatment of invasive aspergillosis due to these organisms.

I concur with the medical reviewer's recommendation that voriconazole is approvable for the treatment of invasive aspergillosis due to *Aspergillus fumigatus*, pending availability of an acceptable commercial intravenous formulation. Voriconazole, represents an important addition to the antifungal armamentarium for the treatment of invasive aspergillosis infection and sets a new standard for active controls in non-inferiority trials for this indication. Its development program, based on the multicenter, randomized, controlled, comparative clinical trial, represents an example that should be followed in future development of antifungals for the treatment of invasive aspergillosis.

Treatment of serious fungal infections caused by *Fusarium* and *Scedosporium* spp.

The clinical data for this indication were derived from pooled analyses of patients enrolled across the development program. Successful response to voriconazole therapy

was observed in 15 of 25 (60%) patients with documented infection with *Scedosporium apiospermum*. Three of these subjects suffered a relapse within 4 weeks of cessation of therapy. Ten subjects had evidence of cerebral disease and 6 of these had successful outcome. In addition, a successful response was observed in only one or three patients with mixed organism infections.

I concur with the primary medical reviewer's recommendation that voriconazole is approvable for the treatment of serious fungal infections caused by *Scedosporium apiospermum*, pending availability of an acceptable commercial intravenous formulation.

In contrast, a successful response to voriconazole therapy was seen in only 2 of 7 patients (29%) with documented infection with *S. prolificans*. This number is too small to recommend approval for this indication.

Successful response to voriconazole therapy was observed in 9 of 21 (43%) patients with documented serious infections with *Fusarium spp.* Of these nine patients, three had eye infections, one had an eye and blood infection, one had a skin infection, one had a blood infection alone, two had sinus infections, and one had disseminated infection (pulmonary, skin, hepatosplenic). Three of these subjects (one with disseminated disease, one with an eye infection and one with blood infection) had *Fusarium solani* and were complete successes. Two of these patients relapsed, one with a sinus infection and profound neutropenia and one postsurgical patient with blood and eye infection.

I concur with the primary medical reviewer's recommendation that voriconazole is approvable for the treatment of serious fungal infections caused by *Fusarium spp.* including *Fusarium solani*.

In vivo studies in dogs have demonstrated prolongation of QT intervals, PVC's and arrhythmia at high doses of voriconazole. There was one sudden-death in a patient who had just received an intravenous infusion of voriconazole in another phase III study. Although there is data on the relationship between voriconazole plasma concentrations and QTc, which do not show QTc prolongation with increased concentrations, there is insufficient information on QTc at concentrations representing the higher end of the range expected at the proposed clinical dosages.

or tolerate oral drug.

NONAPPROVABLE INDICATIONS

Empiric antifungal therapy of febrile neutropenic patients

In support of this indication, the applicant has submitted data from a larger, randomized, open-label, concurrently controlled study in patients with neutropenia secondary to cancer chemotherapy, comparing voriconazole to liposomal amphotericin B (Ambisome™, L-AMB). The study was designed as a non-inferiority study. The stratified analysis of the primary endpoint, failed to meet the prospective statistical definition of non-inferiority.

Prior to approval for empiric antifungal therapy in febrile neutropenic patients, a drug should have demonstrated efficacy against the most common pathogens in neutropenic hosts, namely *Aspergillus* and *Candida* species. The applicant has demonstrated efficacy in invasive aspergillosis. While the applicant has demonstrated efficacy in esophageal candidiasis (a mucosal disease) in advanced HIV-infection there is insufficient information to support efficacy in invasive candidiasis. Esophageal candidiasis in largely non-neutropenic AIDS patients may not be representative of invasive candidiasis in neutropenic patients.

Overall, I concur with the medical reviewers recommendation that voriconazole should not be approved for empiric antifungal therapy of febrile neutropenic patients.

Treatment of other rare serious fungal infections

The applicant has provided a pooled analysis of efficacy in rare and serious fungal infections due to emerging fungal pathogens across the voriconazole development program. Except for *S. prolificans* and *Fusarium ssp.* including *Fusarium solani*, there were too few documented cases of individual pathogens to fully evaluate the efficacy of voriconazole in the treatment of other rare serious infections. The ongoing compassionate use clinical program may be able to generate additional well-documented cases that could support future applications for these indications.

The applicant has also provided some data from Study 608 designed to evaluate the efficacy and safety of voriconazole in the treatment of invasive candidiasis and candidemia. These data represent an interim analysis of 10% of the total targeted enrollment. The numbers are too small to draw a definitive conclusion. Although pooled analyses of serious candida infections show promising results, including activity against *Candida albicans* and *Candida kruseii*, it would be premature to grant such an indication without confirmation of the efficacy of voriconazole in the treatment of invasive candidiasis from study 608.

SAFETY CONSIDERATIONS

The pooled safety database included experience with voriconazole exposure in approximately 2000 human subjects.

Visual Abnormalities

The administration of voriconazole is associated with visual disturbances, including but not limited to, photophobia, distorted color perception, and hallucinations, in up to one out of three patients. In a 28-day visual safety study in healthy adult volunteers that included systematic evaluation of visual acuity, color perception, electroretinograms and fundoscopy, abnormalities were found to occur after the first dose and persisted throughout the dosing period. The observed abnormalities were reversible by 28 days after cessation of dosing. The reversibility of visual abnormalities after greater than 28 days of voriconazole therapy has not been fully evaluated.

Hepatic Abnormalities

The liver is a potential target organ of voriconazole toxicity. At dose that mimic the recommended human dose, voriconazole produced hepatic findings in animals. In clinical studies, administration of voriconazole was associated with elevations in transaminases and to a lesser extent alkaline phosphatase. In the comparative esophageal candidiasis study, these effects were more common with voriconazole than with

fluconazole. Overall, I agree with the medical reviewer's assessment that voriconazole is associated with hepatic adverse events and possibly with infrequent serious adverse events. Liver function tests should be monitored during treatment with voriconazole.

Rash

Skin rash was observed in approximately 18% of patients treated with voriconazole. A variety of terms were used to describe such events in the clinical studies, and there were no specific characteristics that could be used to distinguish a rash due to voriconazole. Although, the majority of the events were mild to moderate and reversible after cessation of dosing, a few cases of Stevens Johnson Syndrome were reported. Overall, I agree with the medical reviewer's assessment that voriconazole is associated with dermatologic adverse events and possibly with infrequent serious rash.

Drug Interactions

Voriconazole is an inducer and substrate of the cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4, which creates a potential for multiple drug interactions. The Applicant has evaluated the pharmacokinetic interactions between voriconazole and important concomitant medications. The evaluation of additional potential interactions is not needed for the approval of voriconazole, but should be considered in phase 4.

RISK MANAGEMENT CONSIDERATIONS

Drug Interactions

Overall, voriconazole's metabolism and potential for drug interactions, may pose a greater safety challenge than some of its individual adverse effects. Information on interactions, recommended dose adjustments and contraindications are included in the revised draft package insert attached to the regulatory action letter, dated December 17, 2001. At the time of approval and when VFEND™ becomes commercially available reciprocal labeling should be added to the package insert of products known to have serious interactions with voriconazole, that lead to contraindications or the need for dose adjustments.

WAIVER/DEFERENTIAL OF PEDIATRIC STUDIES

Persuant to 21CFR§314.55(c)(3), a request for deferral for submission of certain requirements under the Pediatric Final Rule was submitted by the applicant on September 29, 2000. The Division granted a deferral for pediatric studies under 21CFR§314.55(b) on March 8, 2001.

Marc Cavallé-Coll, M.D., Ph.D.
Medical Team Leader, HFD-590

Concurrence:

HFD-590/Acting ODE4 Dir/GoldbergerM

cc:

NDA 21-266

NDA 21-267

HFD-590/Acting ODE4 Dir/GoldbergerM

HFD-590/Acting Div Dir/AlbrechtR

HFD-590/MOTL/Cavaillé-CollM

HFD-590/MO/PowersJohn

HFD-590/MO/TiernanR

HFD-590/MO/AlvisatiosR

HFD-590/MO/Johan-LiangR

HFD-590/MO/CoxE

HFD-590/PM/SalibaJ

HFD-590/Biopharm/MeyerJ

HFD-590/Biopharm/ColangeloP

HFD-590/Biostat/HigginsK

HFD-590/Biostat/DixonC

HFD-590/Pharmtox/MacMasterO

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/s/

Marc Cavaille Coll
6/11/02 02:18:04 PM
MEDICAL OFFICER

Medical Team Leader's Memorandum #2

TO: NDAs 21-266 and 21-267

FROM: Marc Cavallé-Coll, M.D., Ph.D.

RE: VFEND™ (tablets) NDA 21-266 and VFEND™ I.V. (for intravenous infusion) NDA 21-267

DATE: May 20, 2002

The applicant has submitted, on March 26, 2003, materials, that address the requirements for approvability of VFEND™ (viroconazole) for the treatment of invasive aspergillosis and of serious fungal infections caused by *Fusarium* and *Scedosporium* spp. This submission of March 26, 2002 constituted a complete response to our December 17, 2001 action letter. In particular, the manufacturing and compliance deficiencies of the intravenous formulation have been adequately addressed.

Revised labeling has also been submitted and reviewed. Additional recommendations concerning the Indication, Mechanism of Action, Microbiology, Clinical Studies, Precautions, Warnings and Adverse Event sections of the label were communicated to the applicant. These recommendations lead to additional revisions and discussions with the applicant. In particular, there is insufficient information to date to support that voriconazole has cidal activity *in vitro* or *in vivo* against *Aspergillus* species. There is no consensus yet as to what standards should be used to reliably demonstrate such activity. Information on the ophthalmologic abnormalities associated with voriconazole administration was made more prominent. The drug interactions section has also been strengthened.

VFEND™ should be approved with the revised labeling submitted May 20, 2002.

RISK MANAGEMENT CONSIDERATIONS

At the time when VFEND™ becomes commercially available reciprocal labeling should be added to the package insert of products known to have serious interactions with voriconazole, that lead to contraindications or the need for dose adjustments.

WAIVER/DEFERENTIAL OF PEDIATRIC STUDIES

Persuant to 21CFR§314.55(c)(3), a request for deferral for submission of certain requirements under the Pediatric Final Rule was submitted by the applicant on September 29, 2000. The Division granted a deferral for pediatric studies under 21CFR§314.55(b) on March 8, 2001. The applicant intended to develop a pediatric oral suspension by March 31, 2002.

On January 31, 2002 the applicant requested an extension of the deferral date for submission of the pediatric oral formulation of VFEND (voriconazole). Upon review, the Division agreed that an extension of the deferral date is justified for submission of the pediatric oral formulation of VFEND (voriconazole) because of stability problems with the current formulation have been encountered. Accordingly, submission of the pediatric oral formulation of VFEND (voriconazole) is deferred under 21 CFR§314.55 until December 31, 2003.

Marc Cavallé-Coll, M.D., Ph.D.
Medical Team Leader, HFD-590

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/s/

Marc Cavaille Coll
6/11/02 02:25:51 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION IV

DATE: May 21, 2002

TO: NDA 21-266 and 21-267
VFEND™ (voriconazole)
Sponsor: Pfizer Pharmaceuticals

FROM: Shukal Bala, Ph.D.
Microbiology Team Leader,
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

SUBJECT: NDA resubmission dated March 26, 2002

In clinical trials (reviewed in the original submission), the majority of the isolates recovered were *Aspergillus fumigatus* (for details see microbiology review dated 11-02-01). There were a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus*. In addition, limited information was available on the *in vitro* susceptibility of voriconazole against *A. terreus*, *A. nidulans* and *Fusarium* species (other than *F. solani*). In the resubmission the sponsor has included additional information from studies 150-309 and 150-604 and several published articles supporting the activity of voriconazole against species of *Aspergillus* other than *A. fumigatus* and *Fusarium* species other than *F. solani*. The submission also includes revisions of the draft label, which includes a claim for cidal activity in the mechanism of action section.

Review of the additional information submitted by the sponsor supports the following:

- Inclusion of *Aspergillus terreus* (in addition to *A. fumigatus*, *A. niger* and *A. flavus*) and *Fusarium* species (in addition to *F. solani*) in the microbiology section of the label.

However, the information reviewed does not support the following:

- Inclusion of *A. nidulans* in the microbiology section of the label. The *in vitro* susceptibility against a very small number of isolates/strains of *A. nidulans* was determined and none of the clinical isolates were included in such testing.
- The claim that voriconazole is cidal against *Aspergillus* species in the mechanism of action section of the label. The information available is ambiguous and in the absence of standardized methods and established criteria it would be premature to state that voriconazole is cidal against *Aspergillus* species.

The sponsor has agreed to assess cross-resistance and has stated that a worldwide surveillance study will be conducted to detect/monitor trends in voriconazole susceptibility over time and any changes in fungal species from epidemiological standpoint.

This NDA should be approved with respect to Microbiology.

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/s/

Shukal Bala
5/23/02 04:53:48 PM
MICROBIOLOGIST

DATE: May 10, 2002

TO: Maureen Garvey, Ph.D.
Regulatory Affairs

ADDRESS: Pfizer Inc.
Eastern Point Road
Groton, CT 06340

FROM: Jouhayna Saliba, Pharm.D.
Regulatory Project Manager

NDA: 21-266 (Voriconazole Tablets)
21-267 (Voriconazole I.V.)

SUBJECT: Pharmacokinetic data obtained from adolescents (aged 12-17 years) in the compassionate use program for voriconazole

We have reviewed the pharmacokinetic data that supports the adolescent age group (12-17 years) that was submitted May 2, 2002 and included in the label submitted March 26, 2002.

At this time we can not accept the final paragraph under the Pediatric subsection of the **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** section. The other steady-state plasma concentration values in the label were calculated by a population pharmacokinetic analysis. The new values from the resubmission are medians of geometric means from each patient.

We would be willing to reconsider the data on 12-17 year olds at a later date, if a population pharmacokinetic approach was used, similar to what was used for the adult healthy volunteers and pediatric (2 to < 12 year olds) patients.

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

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/s/

Jouhayna Saliba
5/10/02 08:40:15 AM
CSO

DATE: June 15, 2001

TO: Maureen Garvey, Ph.D.
Regulatory Affairs

ADDRESS: Pfizer
Eastern Point Road
Groton, CT 06340

FROM: Jouhayna Saliba, R.Ph.
Regulatory Project Manager

NDA: 21-266 (Voriconazole Tablets)

SUBJECT: In Vitro Dissolution Testing of voriconazole tablets

The Division would like to request the following:

- Please submit the data you have previously collected on _____
- Please perform full dissolution testing for _____
There is no need to repeat the dissolution testing for _____ since it is outdated.

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

DATE: June 12, 2001

TO: Maureen Garvey, Ph.D.
Regulatory Affairs

ADDRESS: Pfizer
Eastern Point Road
Groton, CT 06340

FROM: Jouhayna Saliba, R.Ph.
Regulatory Project Manager

NDA: 21-266 (Voriconazole Tablets)

SUBJECT: In Vitro Dissolution Testing of voriconazole tablets

We would like to request the following regarding NDA 21-266 for voriconazole tablets:

As you are aware, the initial proposed biobatch of voriconazole — was not shown to be bioequivalent, in terms of C_{max} , to the final proposed commercial formulation — . The dissolution profiles of these two batches were shown to be similar (—) . In order to help the Agency understand the utility of the Biopharmaceutics Classification System (BCS) in the assessment of *in vivo* bioequivalence, we would like you to provide full dissolution profiles for voriconazole in two additional types of media. In the Guidance for Industry "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" dissolution testing in three types of preferred media is discussed. Since you have already studied — HCl, please perform the testing of voriconazole in a pH — buffer and a pH — buffer.

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID NUMBER: _____

DATE: May 2, 2001

FROM: Judy A. Staffa, Ph.D., R.Ph., Epidemiologist
Division of Drug Risk Evaluation II (DDRE II)
HFD-440

THROUGH: Kathleen Uhl, M.D., Acting Director
DDRE II, HFD-440

TO: Mark Goldberger, M.D., Director
Division of Special Pathogens, HFD-590

SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW
Consult – Use of historical controls as comparator group in submission of
NDA-21-266 for Vfend (voriconazole)

Executive Summary

Voriconazole (Vfend™) is a broad-spectrum antifungal agent that is being evaluated for its safety and efficacy in treating acute invasive *Aspergillus* infections. Protocol 150-304 is an open, uncontrolled, multi-centre study of voriconazole. Protocol A1501003 was designed to create a group of historical controls, with which to compare the experience of patients in P150-304. OPDRA was asked by the reviewing statisticians in HFD-590 to review protocols 150-304 and A1501003 to provide some epidemiological insight into the appropriateness of the sponsor's use of non-randomized, non-concurrent historical controls.

A brief review of the medical literature identified three major biases – information bias, bias from secular trends in diagnosis and treatment, and selection bias – that frequently affect comparisons using historical controls. A review of the study protocols 150-304 and A1501003 suggests that, despite substantial efforts by the sponsor, the potential for information bias and selection bias to affect the results were not adequately controlled. As a result, these two study populations do not appear comparable, which is actually a common situation in studies using historical controls. The persistence of these biases, and the resulting differences between study populations, could act to predispose the historical control group to have a lower success rate and the voriconazole-treated group to have a higher success rate, independent of treatment with voriconazole.

I. Introduction

Vfend™ (voriconazole) is a new azole antifungal agent which is being tested for efficacy and safety in treating invasive *Aspergillus* infections. The data submitted to the Agency (NDA-21-266/267) under Protocol 150-304 represents an open, uncontrolled, multicentre study of voriconazole use as primary or salvage therapy. Protocol A1501003 was designed to create a group of historical controls, with which to compare the experience of patients in P150-304.

OPDRA was asked by the reviewing statistician in HFD-590 to review protocols 150-304 and A1501003 to provide some epidemiological insight into the appropriateness of the sponsor's use of historical controls. Two questions were detailed as key for OPDRA's focus.

II. Background

Historical controls are defined as non-randomized, non-concurrent comparators to the current study treatment of interest. Historical controls are sometimes used as comparators when the use of a randomized trial is considered to be either infeasible or unethical. Studies using historical controls, however, are more likely to find a treatment effect than those using randomized controls. A review of the medical literature found six therapies for which 50 randomized controlled trials and 56 historical controlled trials were published.¹ Although 79% of the historical controlled trials found the study treatment better than the control, only 20% of the randomized trials confirmed this finding. This systematic skewing of results toward a positive treatment effect is predictable, due to a number of biases that are introduced through the process of identifying a historical control group and comparing it with the treatment group.

The major biases that have been identified to be associated with the use of historical controls² are as follows:

a. Information bias

This bias can occur if the data collected for the current, treated group is not comparable to that collected for the historical controls with regard to either quality or completeness. For example, if information for the current, treated group is collected prospectively, using research instruments, but the information for the historical controls is collected from abstracting medical records that were not designed for study data collection, bias could result. Most often, information is more accurate and complete for the current, treated group than for the historical controls. This better information could lead to an apparent treatment effect that in actuality is due to differences in the quality of information available.

b. Bias from secular trends in diagnosis and treatment

The difference in calendar time between the experience of the current, treated group and that of the historical controls can also make observed differences difficult to interpret. Changes in other factors, unrelated to the treatment of interest, that occur over time could produce effects that are falsely attributed to the studied treatment. Such factors include:

- Improvements in supportive patient care over time, leading to differences in characteristics of the patient population and their management;
- Temporal trends in mortality in the affected patient population. A valid comparison with the current, treated group would be the baseline mortality of the current patient population, rather than that of a past patient population. This is particularly true if there have been major changes in mortality from the disease over time;
- Different methods of evaluation or assessment of diagnosis or outcome for the same disease over time. These can lead to differences in the severity of disease between the current, treated group and historical controls and/or changes in the ability to assess outcome. Changes in diagnostic technology or standard medical practice are often the reasons for these differences.

c. Selection bias

Selection bias occurs when certain types of patients are selected into the treatment group but not into the control group, or vice versa. For example, if patients who are less severely ill are more likely to be in the current, treated group than in the historical controls group then better survival in this group could be falsely attributed to the treatment. Randomization is designed to minimize this type of bias, by increasing the probability that the treated and control groups are similar with regard to factors known to affect outcome, as well as unknown or unmeasured factors.

The major implication of these types of biases, as stated earlier, is to produce an apparent treatment effect when in actuality there is none. There are numerous examples in the medical literature, particularly from the field of oncology, in which treatments believed to be effective based upon comparisons with historical controls were later proven false when evaluated through randomized trials^{iii,iv}. The effect size must be large enough to overcome the effects of random error and bias introduced by the design – but since it is hard to quantify the effects of all the biases, it is hard to know how large an effect size is “large enough” to overcome them.

III. Questions raised by HFD-590 statisticians

1. *Have the usual biases associated with historical controls been adequately addressed in the design and conduct of Protocol A1501003?*

A review of the protocol with regard to the biases of concern produced the following observations:

a. Information bias

- Less clear information is available to assess outcome from record abstraction for the historical controls than from observation of the voriconazole-treated group. In addition, response to treatment was ascertained by three independent experts in P150-304, but by only one investigator in PA1501003. These differences could bias the success rates down in the historical control group, as evidenced by a global response rate of 25% in this group. Background information from the medical literature suggests that amphotericin B may have a success rate between 40 and 55%.^{v,vi}

- Less clear information is available on potential confounders from the historical controls as well. This limits the ability of post-hoc statistical analyses to adequately control for confounding.

b. Bias from secular trends in diagnosis and treatment

- P150-304 was conducted from January 1994 through July 1996. In P-A1501003, data were collected retrospectively from January 1993 through December 1995. There is unlikely to be bias from secular trends in diagnosis and treatment between two studies that overlap to such a great extent.

c. Selection bias

- There were differences in the distribution of domestic and foreign patients between treated and control groups, which could impact on the success rate of treatment if standards of patient care and support differ across countries. P150-304 was conducted exclusively in Europe, whereas P-A1501003 included U.S. patients. When the U.S. patients were removed, the differences in global assessment remained, but the differences in survival between the two groups became smaller and lost statistical significance.
- There were substantial differences in total days of treatment, with the treated group having a much longer duration of antifungal therapy. Was it treatment with voriconazole per se, or just longer treatment with any antifungal that produced the improved outcome?
- Differences in inclusion and exclusion criteria resulted in the historical control group being older, having more concomitant drugs on board and possibly including patients with abnormal laboratory values. These characteristics could certainly indicate that the historical control group was sicker than the voriconazole-treated group, and may underlie their poorer response and survival. It is not clear why, but the historical control group also included more non-whites. If these were non-whites in the U.S., it is possible that these patients may reflect a lower socioeconomic status and thus poorer prognosis in general.

These observations suggest that two of the potential biases associated with historical control studies, information bias and selection bias, could have affected the comparison of the voriconazole-treated group with the historical controls.

2. *Are the two study populations, Protocol 150-304 and Protocol A1501003, comparable? If so, what conclusions can be drawn?*

- No, these two study populations are not comparable, which is actually a common situation in studies using historical controls. In general, studies with historical controls are considered to generate hypotheses for subsequent confirmation using more rigorous, randomized studies^{vii}.
- The differences between the treated group and the historical control group provide alternative explanations for the effects seen, rather than being due to the tested treatment. These alternative explanations need to be ruled out before the effects can be reasonably attributed to

the drug, which the sponsor attempted to do using statistical techniques such as stratified analyses and multivariate analyses. These efforts can only control potential confounding to a limited extent, however, due to the small number of patients in the study overall. These techniques also cannot control for the effects of confounders that are unknown and unmeasured, which is one of the main benefits of randomization. Finally, such efforts cannot examine clinically important interactions between key variables.

- The primary differences between these two populations are due to differential sources of information for each (retrospective medical record abstraction versus prospective patient observation) and selection of different types of patients into each group. The overlapping timeframes of the studies make bias from secular trends in diagnosis and treatment of underlying disease rather unlikely.

IV. Conclusions

A review of the study protocols 150-304 and A1501003 suggests that, despite substantial efforts by the sponsor, the potential for information bias and selection bias to affect the results were not adequately controlled. As a result, these two study populations do not appear comparable, which is actually a common situation in studies using historical controls. The persistence of these biases, and the resulting differences between study populations, could act to predispose the historical control group to have a lower success rate and the voriconazole-treated group to have a higher success rate, independent of treatment with voriconazole.

Signed
Judy A. Staffa, Ph.D., R.Ph.
Epidemiologist

References

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Cc:

NDA 21-266, 21-267

HFD-590 Division file

HFD-590 Goldberger/Cavaille-Coll/Tiernan/Higgins/Dixon/Willard

HFD-440 Uhl/Piazza-Hepp/Staffa/Singer/Dempsey

**This is a representation of an electronic record that was signed electronically and
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/s/

Judy Staffa
5/2/01 03:08:57 PM
MEDICAL OFFICER

Kathleen Uhl
5/2/01 05:12:34 PM
MEDICAL OFFICER

(b4)

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MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Date: April 4, 2001

Time: 1:00 p.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.
Rockville, MD 20850

Application: NDAs 21-266 and 21-267

FDA Attendees, titles, and Office/Division:

Mark Goldberger, M.D., M.P.H., Division Director
Renata Albrecht, M.D., Deputy Director
Marc Cavallé-Coll, M.D., Ph.D., Medical Officer Team Leader
Rosemary Tiernan, M.D., Medical Officer
John Powers, M.D., Medical Officer
Linda Gosey, Microbiology reviewer
Owen McMaster, Ph.D., Pharmacology/Toxicology Reviewer
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Jouhayna Saliba, R.Ph., Regulatory Project Manager

External Constituent Attendees and titles:

Maureen Garvey Ph.D., Regulatory Affairs (NY)
Reinhard Baildon M.D., Clinical Leader (UK)
Helen Boucher M.D., Clinical
Bradley Marchant M.D., Clinical
Lynn Purkins Ph.D., Clinical Pharmacology
Keith Tan Ph.D., Clinical Pharmacology
Konrad Tomaszewski Ph.D., Clinical Safety
Suresh Chahwala, Clinical
Rob Wallis Ph.D., Clinical
Elina Srulevipch-Chin, Regulatory Affairs

Background: Pfizer had stopped enrollment into the QTc study due to anaphylactoid reactions in two subjects. Pfizer has requested a teleconference to discuss the voriconazole cardiac safety data, and to get the Division's opinion regarding the importance of the QTc study on the overall assessment of the safety of voriconazole.

Meeting Objective: To discuss with Pfizer the time at which the QTc data will be submitted and the significance of this data to the application.

Discussion Points:

The Division informed Pfizer that since the QTc study will not be completed until November 2001, this may pose a problem in regard to the action the Division will be taking.

Pfizer consulted with experts with regard to the QTc data. Pfizer suggested that the Division meet with these consultants to discuss the QTc study.

The Division will grant a meeting in order to discuss issues relating to the QTc study. The Division asked Pfizer about their plans while awaiting this meeting.

Pfizer will continue with the QTc protocol and will prepare a comprehensive package to help facilitate this meeting.

Pfizer informed the Division that the database for the aspergillosis study has been closed, and that they are now analyzing the mortality data. Draft data will be completed in a week and will be sent to the Division to look at. The final data sets will be submitted in by June 2001.

The Division asked that Pfizer would submit any summary tables including a description of the data, which will be submitted by June 17, 2001.

Minutes Preparer: _____
Jouhayna Saliba, R.Ph. ✓

/S/

5/12/01

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

/S/

Concurrence:

Marc Cavallé-Coll, M.D., Ph.D., Medical Officer Team Leader 6/12/01

Rosemary Tiernan, M.D., Medical Officer 4/30/01

John Powers, M.D., Medical Officer 5/16/01

Linda Gosey, Microbiology reviewer 5/17/01

Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer 5/2/01

Minutes of a Teleconference

Meeting Date: February 5, 2001

Applications: IND — (voriconazole – oral)
IND — (voriconazole – I.V.)

NDA 21-266 (VFEND {voriconazole} Tablets)
NDA 21-267 (VFEND {voriconazole} IV)

Sponsor: Pfizer Global Research and Development

Subject: Pediatric Issue
Infusion Related Reactions in Study A1501021

Attendees:

Pfizer:

Reinhard Baildon, M.D.	Clinical Team Leader (UK)
Maureen Garvey, Ph.D.	Director, Regulatory Affairs Department
Irja Lutsar, M.D.	Clinical (UK)
Bradley Marchant, M.D.	Clinical Development
Lynn Purkins, Ph.D.	Clinical Pharmacology
Keith Tan, Ph.D.	Clinical Pharmacology
Konrad Tomaszewski, Ph.D.	Clinical Safety

FDA:

Mark Goldberger, M.D., M.P.H.	Division Director, HFD-590
Renata Albrecht, M.D.	Deputy Director, HFD-590
Marc Cavaillé-Coll, M.D., Ph.D.	Team Leader/Medical Officer, HFD-590
Rosemary Tiernan, M.D.	Medical Officer, HFD-590
John Powers, M.D.	Medical Officer, HFD-590
Rosemary Johann-Liang, M.D.	Medical Officer, HFD-590
Funmilayo Ajayi, Ph.D.	Team Leader/Clinical Pharmacology & Biopharmaceutics, HFD-880
Joette Meyer, Pharm.D.	Clinical Pharmacology and Biopharmaceutics, HFD-880
Fonda Chen, Ph.D.	Visiting Clinical Pharmacology & Biopharmaceutics Fellow
Karen Higgins, Sc.D.	Team Leader/Mathematical Statistician, HFD-725
Cheryl Dixon, Ph.D.	Statistician, HFD-725
Ellen Frank, R.Ph.	Chief, Project Management Staff, HFD-590
Diana Willard	Regulatory Health Project Manager, HFD-590

IND _____
IND _____
February 5, 2001
Page 2

NDA 21-266
NDA 21-267

Background

Pediatric Issue

A September 29, 2000 submission to INDs _____ from Pfizer Global Research and Development (Pfizer) requested "a deferral for submission of certain requirements under the Pediatric Final Rule." One of the requests was for a "time-limited" deferral for submission of data in pediatric subjects 0-2 years of age. This submission further stated that "As suggested by the Division, we plan to convert this request for a deferral to a request for a waiver by December 1, 2000." A January 18, 2001 facsimile transmission (FAX) from Pfizer stated that "We now wish to convert the request for a time-limited deferral to a request for waiver for children <2 years."

Infusion Related Reactions in Study A1501021

A February 2, 2001 FAX from Pfizer outlined two occurrences of infusion related reactions in Study A1501021 entitled "A multi-centre, double-blind, placebo-controlled, 5-way crossover, dose escalation study with random insertion of an active comparator (oral ketoconazole 800 mg) and placebo (intravenous SBECD) to investigate the effect of 3 intravenous doses of voriconazole (4 mg/kg, 8 mg/kg and 12 mg/kg) on QTc interval in healthy subjects aged 18-65 years."

Discussion

Pediatric Issue

Pfizer began by stating that during internal discussions held to draft a Proposed Pediatric Study Request (PPSR), a decision was made to request a change from a time-limited deferral for children under 2 years of age to a request for a waiver in this age group.

The Pediatric Rule states that applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration for which an applicant seeks approval must have a pediatric assessment. Dr. Albrecht stated that the Division prefers to defer studies in the pediatric population rather than grant a waiver for any specific age group in order to make the best assessment as to the appropriate pediatric studies to conduct. A deferral provides maximum flexibility for the Division to assess over time, as data become available from completed and on-going trials, what voriconazole studies to conduct in the pediatric population.

IND _____
IND _____
February 5, 2001
Page 3

NDA 21-266
NDA 21-267

NDA 21-061 and 21-062 were submitted seeking approval in adult patients for invasive aspergillosis, serious *Candida* infections, infections caused by *Scedosporium spp.* and *Fusarium spp.*, and rare and refractory infections and empirical treatment. Dr. Albrecht stated that under the Pediatric Rule, if any indications in the VFEND applications currently under review are approved for the adult population, the Division would then request that Pfizer address each approved indication in the pediatric population in all cases where there is an identifiable pediatric population for that indication. To obtain Pediatric Exclusivity, Pfizer should submit a PPSR and then the Division would interact with Pfizer to determine which indications to pursue in the pediatric population and which age groups to enroll for those indications.

Dr. Baildon stated that "significant data" from both single and multiple dose studies in adults were submitted in the VFEND NDAs. To date, Pfizer has received only seven requests for compassionate use of voriconazole in children under 2 years of age.

For treatment of Candidiasis, Dr. Baildon stated that the neonate population is currently well served with fluconazole and amphotericin B with fluconazole being the treatment of choice. To date, Pfizer has received only two requests for compassionate use in neonates for *Candida* infections where fluconazole and amphotericin B have failed.

Dr. Baildon stated that during internal discussions regarding the feasibility of conducting efficacy or safety studies in the under 2 years of age pediatric population, agreement on an acceptable endpoint was elusive. Pfizer's external experts recommended that pharmacokinetic endpoints be utilized in this population. Pfizer believes that a clear population to study the efficacy of voriconazole using the defined best treatment versus voriconazole in the under 2 years of age pediatric population can not be defined.

Dr. Goldberger stated that the Division almost invariably requests submission of clinical pharmacology data from a broad range of ages, including the under 2 years of age pediatric population. For 2 years old and above, the Division usually expects clinical data. Although the pediatric population for studying the efficacy of voriconazole may not be large, it is difficult to believe that a population does not exist given some of the benefits being claimed in the NDAs. The Division is not sufficiently familiar with the data in the NDAs at this point in time to determine what beyond clinical pharmacology data should be in a Written Request for voriconazole.

The Division currently believes that a deferral is the appropriate decision regarding conduction of pediatric studies. The Division acknowledged that it may be difficult to define endpoints and conduct clinical trials in the under 2 years of age pediatric population. To obtain Pediatric Exclusivity, it may be sufficient to provide available clinical pharmacology data in this population if the safety profile is acceptable.

Pfizer proposed to submit a report containing epidemiological data in the under 2 years of age pediatric population and then revisit the issue with the Division.