

\$250.00

**RBS**

1

MININNO LAW OFFICE  
John R. Mininno, Esq. (JRM 7223)  
475 White Horse Pike  
Collingswood, New Jersey 08107  
Tel. No. (856)833-0600  
Attorney for Plaintiffs

IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA *ex rel.*  
Catherine A. Brown and  
Bernard G. Vezeau,

Civil Action No. 05 6795

BRINGING THIS ACTION ON BEHALF  
OF THE UNITED STATES OF AMERICA

Filed Under Seal  
Pursuant to  
31 U.S.C. § 3720(b)(2)  
and Local Rule 5.1.5(a)(1)

Plaintiffs and Relators,

vs.

**FILED**

PFIZER, INC.,

DEC 29 2005

Defendant.

MICHAEL E. KUNZ, Clerk  
By: [Signature] Dep. Clerk

**COMPLAINT FOR VIOLATIONS OF THE FALSE CLAIMS ACT**

Relators Catherine A. Brown and Bernard G. Vezeau, acting on behalf of the  
United States of America and themselves, allege as follows:

**INTRODUCTION**

1. Catherine A. Brown and Bernard G. Vezeau ("Relators") bring this action on behalf of the UNITED STATES OF AMERICA against Pfizer, Inc. ("Pfizer"), for treble damages and civil penalties arising from Pfizer's conduct in violation of the Civil False Claims Act, 31 U.S.C. § 3729, et seq. ("FCA"). The violations arise out of requests for payment by Medicaid, Medicare, TRICARE, and other federally-funded government healthcare programs (hereinafter collectively referred to as "Government Healthcare

Programs").

2. This complaint details several related areas of false statements and records in connection with Pfizer's New Drug Applications (NDAs) for and marketing of the patented antifungal drug voriconazole, known as "Vfend." These false statements and records were made by Pfizer to the United States Food and Drug Administration ("FDA"), and subsequent false statements and claims have been included in subsequent Pfizer marketing materials, all causing submission of millions of dollars worth of claims to Government Healthcare Programs in violation of the False Claims Act.

#### **JURISDICTION AND VENUE**

3. This court has jurisdiction of the subject matter of this action pursuant to 31 U.S.C. § 3732(a) and 28 U.S.C. § 1331, and has personal jurisdiction over defendant Pfizer because defendant Pfizer does business in and with the Eastern District of Pennsylvania.

4. Venue is proper in this District pursuant to 28 U.S.C. § 1391 and 31 U.S.C. § 3732(d), because Pfizer transacts business in this District.

5. The facts and circumstances alleged in this complaint have not been publicly disclosed in a criminal, civil or administrative hearing, nor in any congressional, administrative, or government accounting office report, hearing, audit investigation, or in the news media.

6. Relators are "original sources" of the information upon which this complaint is based, as that term is used in the False Claims Act.

7. Relators provided disclosure of the allegations of this complaint to the

United States prior to filing.

**PARTIES**

8. The real party in interest to the claims in this action is the United States of America.

9. Relator Catherine Brown was until November 4, 2005, Senior Marketing Manager for defendant Pfizer, and employed at its headquarters location in New York City. Ms. Brown, who is a native of South Africa, holds Bachelor of Science degrees in genetics, zoology, and pharmacology and a post-graduate diploma in business administration, all conferred by the University of Witwatersrand in Johannesburg. She became employed by Pfizer as a Sales Representative in Johannesburg in January 1995, where she was Representative of the Year in 1996. She was promoted to South African Product Manager for the antifungal Diflucan in March of 1997. In January of 2000, she accepted a position as Marketing Manager with Pfizer Global Pharmaceuticals in New York, and was promoted to Senior Marketing Manager in January 2002, the position she held until her resignation in November 2005.

10. Relator Bernard Vezeau was until December 21, 2005, a Senior Product Manager on defendant Pfizer's Worldwide Vfend Marketing Team. Mr. Vezeau is a Distinguished Graduate of the United States Military Academy at West Point, and received a Master's degree in Business Administration from the University of Chicago Graduate School of Business in 1993. He was a highly-rated commissioned officer in the United States Army from 1984 through 1989, at which time he held the rank of Captain. He now serves as a Major in the United States Army Reserve. Mr. Vezeau was first employed by Pfizer from 1989 through 1992, during which period he was

recognized as an "All Star" sales representative and had one of the highest-producing sales territories in the nation. Mr. Vezeau rejoined Pfizer in November 2003.

11. Defendant Pfizer, Inc., a Delaware corporation, is a developer and marketer of pharmaceutical products. As relevant here, Pfizer developed the drug voriconazole, which it markets under the trade name "Vfend." Pfizer has sought and obtained approval from the United States Food and Drug Administration ("FDA") to market voriconazole as a first-line treatment for invasive aspergillosis, and for candidemia in non-neutropenic (non-immunosuppressed) patients. Pfizer sought, but was denied, FDA approval to market Vfend as "Empiric Therapy" for patients with suspected, but unconfirmed, fungal infections.

#### **New Drug Approval and Off-label Use**

12. The Federal Food Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 321 *et seq.*, provides a systematic scheme for the approval of new drugs and new drug formulations intended to be marketed for use in interstate commerce. Under the FDCA, a new drug product cannot be marketed unless the FDA approves the product and determines that it is safe and effective for its intended use. See 21 U.S.C. § 355(a). When the FDA approves a drug, it approves the drug only for the particular use for which it was tested, but after the drug is approved for a particular use, the FDCA does not regulate how the drug may be prescribed. Thus, a drug that has been tested and approved for one use only can also be prescribed by a physician for another use, known as "off-label."

13. Generally, once Vfend was approved by the FDA initially in 2002,

physicians could, using their independent and untainted medical judgment, prescribe the drug for any medical condition for which the doctor believed the drug was beneficial for the patient without violating the FDCA. This is so even if the FDA had not determined that it was safe and effective for treating that condition. This practice, known as "off-label" use, includes treating a condition not indicated on the label, or treating the indicated condition but with a different dosing regimen or in a different patient population.

14. Although a physician may prescribe most, but not all, drugs for an off-label use without violating the FDCA, a manufacturer may not market or promote it for such unapproved uses. If a manufacturer wishes to market or promote a drug for a new use, it must demonstrate, with adequate studies, to the FDA's satisfaction that the drug is safe and effective for that new use. 21 C.F.R. §314.54. It must also receive FDA approval for the revised labeling that includes the new use. 21 C.F.R. §314.70(b)(3).

15. The United States Civil False Claims Act provides, in pertinent part, that:

(a) Any person who (1) knowingly presents, or causes to be presented, to an officer or employee of the United States Government or a member of the Armed Forces of the United States a false or fraudulent claim for payment or approval; (2) knowingly makes, uses, or causes to be made or used, a false record or statement to get a false or fraudulent claim paid or approved by the Government; (3) conspires to defraud the Government by getting a false or fraudulent claim paid or approved by the Government;

\* \* \*

is liable to the United States Government for a civil penalty of not less than \$5,000 and not more than \$10,000, plus 3 times the amount of damages which the Government sustains because of the act of that person.

31 U.S.C. § 3729.

16. The federal government enacted the Medicaid program in 1965 as a cooperative undertaking between the federal and state governments to help the states provide health care to low-income individuals. The Medicaid program pays for services pursuant to plans developed by the states and approved by the U.S. Department of Health and Human Services (“HHS”) Secretary through CMS. See 42 U.S.C. §§1396a(a)-(b). States pay doctors, hospitals, pharmacies, and other providers and suppliers of medical items and services according to established rates. See 42 U.S.C. §§1396b(a)(1), 1903(a)(1). The federal government then pays each state a statutorily established share of “the total amount expended ... as medical assistance under the State plan[.]” See 42 U.S.C. §1396b(a)(1). This federal-to-state payment is known as Federal Financial Participation (“FFP”).

17. Medicare Part A is funded primarily by a federal payroll tax, premiums paid by Medicare beneficiaries and appropriations from Congress. Medicare Part A generally pays for inpatient services for eligible beneficiaries in hospital, hospice and skilled nursing facilities, as well as some home healthcare services. 42 U.S.C. §§1395e - 42 U.S.C. §§1395i-5. Prescription drugs are covered under Medicare Part A only if they are administered on an inpatient basis in a hospital or similar setting.

18. Medicare Part B is optional to beneficiaries and covers some healthcare benefits not provided by Medicare Part A. Medicare Part B is funded by appropriations from Congress and premiums paid by Medicare beneficiaries who choose to participate in the program. 42 U.S.C. §§1395j - 42 U.S.C. §§1395w-4. Medicare Part B pays for some types of prescription drugs that are not administered in a hospital setting. 42

U.S.C. §1395k(a); 42 U.S.C. §1395x(s)(2); 42 C.F.R. §405.517. These typically include drugs administered by a physician or other provider in an outpatient setting, some orally administered anti-cancer drugs and antiemetics (drugs which control the side effects caused by chemotherapy), and drugs administered through durable medical equipment such as a nebulizer. 42 U.S.C. §1395k(a); 42 U.S.C. §1395x(s)(2); 42 C.F.R. §405.517.

19. TRICARE is the component agency of the U.S. Department of Defense that administers and supervises the health care program for certain military personnel and their dependents. TRICARE contracts with a fiscal intermediary that receives, adjudicates, processes and pays health care claims submitted to it by TRICARE beneficiaries or providers. The funds used to pay the TRICARE claims are government funds.

20. In the TRICARE program, drugs may be cost-shared for off-label uses when the contractor has determined that reliable evidence demonstrates such usage is safe and effective. As presented in order of relative weight in 32 C.F.R. §199.2, reliable evidence means:

- a. Well controlled studies of clinical meaningful endpoints, published in referenced medical literature.
- b. Published formal technology assessments.
- c. Published reports of national professional medical associations.
- d. Published national medical policy organizations.
- e. Published reports of national expert opinion organizations.

#### **The Voriconazole New Drug Applications**

21. Pfizer developed voriconazole because its industry-leading antifungal medication, Diflucan (fluconazole) was to lose patent protection in 2004 and Pfizer would be susceptible to competition from generic-drug manufacturers. During the final years of patent protection, Pfizer annual revenue from Diflucan sales was approximately \$1.1 billion, with about half that amount in domestic sales.

22. Voriconazole, like Diflucan, is a triazole. Voriconazole was developed from the Diflucan molecule with the intention of exhibiting efficacy against aspergillosis, which Diflucan did not, and to enhance efficacy against non-*albicans* species of *Candida*.

23. Vfend therapy for invasive candidemia is significantly more expensive than fluconazole therapy, as well as therapy with many other antifungal agents. For example, a 15-day course of Vfend IV costs up to \$3,775, while a similar course of fluconazole costs up to \$1,671. A 15-day course of Vfend oral tablets costs up to \$2,930, while the similar course of fluconazole by oral tablet costs up to \$462. As more manufacturers begin to produce generic fluconazole, this price gap will increase.

24. Vfend is one of a class of drugs called "azoles." Azoles, and other families of drugs (most relevant are polyenes, to include Amphotericin B, and candins)<sup>1</sup>, are used to treat seriously-ill patients who develop fungal mould or yeast infections.

---

<sup>1</sup> Polyenes and azoles combat fungal infections through different mechanisms. Polyenes primarily are cidal compounds which kill fungi by binding to cell membranes and causing the fungal cells to leak electrolytes. Azoles are not fungicidal; rather, they primarily are fungistatic, meaning that they block the replication of fungal cells by inhibiting the synthesis of ergosterol, a compound necessary for these cells to function. Voriconazole appears to be fungicidal against *Aspergillus*, but is fungistatic against *Candida*.

Such patients are almost always hospitalized for underlying conditions when these dangerous infections manifest themselves. The most seriously ill patients are those who are "neutropenic" (immunosuppressed), to include those with AIDS, transplant recipients, and chemotherapy patients. Vfend is approved to treat immunosuppressed patients suffering from some mould infections (such as aspergillosis) but it is not approved for treatment of Candidemia in such patients. Rather, its *Candida* approvals are limited to non-neutropenic patients, most commonly surgical patients whose infections developed post-operatively. On the order of one-third of patients who require antifungal treatment are receiving ventilatory assistance, many have central venous catheters in place, and all are very sick. Mortality rates range from 45% to 95% depending on the pathogen and the site of fungal infection.

**A. Pfizer's Unsuccessful Campaign to Secure Broad-Spectrum Approvals for Vfend To Serve As A Replacement for Diflucan**

25. The categories of fungal infection which are the focus of this complaint are aspergillosis, which results from fungi of the genus *aspergillus*, and invasive candidiasis, which results from the *Candida* genus of yeast. In this context, "invasive" refers to invasion of the fungal infection past the skin, to include wound sites, burn sites, insertion sites for intravenous and catheter lines, organs, and other locations.

26. Aspergillosis is relatively uncommon, accounting for only about 5% of documented fungal infections. Candidiasis is more common, and is an umbrella term for pathogens which vary significantly in ways which are described below in considerable detail.

27. In or about 1998, Pfizer submitted two New Drug Applications ("NDAs") for

what was then known only as voriconazole, one (NDA 21-266) for intravenous delivery and one (NDA 21-267) for oral delivery in tablets and suspension.

28. Pfizer's campaign to obtain approvals for voriconazole was keyed to the treatment continuum employed by physicians with respect to fungal-infection patients. This continuum begins with prophylaxis—the prescribing of antifungal medications to patients at risk for fungal infections, but without any symptoms. The next step is “empiric” therapy, which refers to patients who have generalized symptoms of fungal infection but have not yet been diagnosed. The third step is “documented” therapy, which refers to cases in which laboratory results have documented the specific pathogen which is causing the infection.

29. Pfizer sought label indications for voriconazole for six groupings of fungal infection:

- a. Treatment of invasive aspergillosis;
- b. empiric antifungal therapy of febrile neutropenic patients;
- c. treatment of *Candida* esophagitis;
- d. treatment of serious *Candida* infections;
- e. treatment of serious fungal infections caused by *Fusarium* and *Scedosporium spp.*; and
- f. treatment of serious fungal infections in patients refractory or intolerant to other therapy.

30. Of these, the most important indication for Pfizer was that for empiric therapy. This is so because approximately half of all prescriptions written for antifungal drugs fall into this category.

31. The second most important indication was that for the treatment of serious *Candida* infections. This category of infection accounts for approximately 80% of prescriptions written for treatment of documented fungal infections.

32. The third most important indication was that for *Aspergillus*. Pfizer's goal was to secure first-line indications for both *Aspergillus* and *Candida*, with fall-back positions of refractory/salvage for both. Once Pfizer had the *Aspergillus* data they were confident they would get a first line indication but knew they may have to accept the fall-back position of a second line indication.

33. The remaining indications were for forms of candidiasis and other fungal infections which infect very small numbers of patients, but Pfizer believed that receiving indications for those conditions would enhance its ability to assert that Vfend was a "broad spectrum" product.

34. Pfizer sponsored Phase III clinical trials for the *Candida* and Empiric therapy indications. The Empiric Therapy study was called Study 603, and the *Candida* study was called Study 608.

#### **Early Rejection: Efficacy Deficiencies Noted**

35. Pfizer was granted FDA approval in 2002 to label Vfend for treatment of invasive aspergillosis and as salvage therapy for fungal infections caused by the pathogens *Scedosporium apiospermum* and *Fusarium* species.<sup>2</sup> Vfend also has been

---

<sup>2</sup> The approved indications for Vfend, together with the dates of approval by the FDA, are as follow:

May 24, 2002            Invasive aspergillosis  
                                 Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and

approved for esophageal candidiasis, a form of the disease which infects primarily patients with full-blown AIDS. The incidence of esophageal candidiasis in HIV patients has diminished considerably with widespread availability of anti-retroviral therapy for HIV patients, and fluconazole (now available in generic forms) is highly effective against the disease. Thus, the market for Vfend in connection with esophageal candidiasis is minuscule.

36. Although Pfizer obtained two first-line indications for Vfend in 2002 (for *Aspergillus* and for "serious fungal infections caused by *Scedosporium apiospermum*) and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy," these conditions constitute a tiny fraction of the antifungal market which Pfizer expected Vfend to capture.

37. The FDA considered and rejected the request for an indication for "treatment of other serious fungal infections in patients refractory or intolerant to other therapy." "Refractory" in this context means resistant to treatment; refractory patients are those for whom first-line treatment was ineffective. The non-approval was due to the non-comparative nature of the studies, and small sample sizes, not only of the total population but of each specific pathogen.

38. FDA did not approve the "serious *Candida* infection" indication based on

---

*Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

2/24/04 Esophageal candidiasis

12/21/04 Candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.

the 10% 608-Study interim data analysis, because that interim analyses showed no efficacy difference between the two study arms and did show that Vfend had more adverse events than the comparator arm. There were eight adverse-effect discontinuations in the voriconazole arm due to adverse effects and none in the amphotericin B→fluconazole arm.

39. The FDA review of the interim study report states:

the safety concerns [in the voriconazole arm] outweigh the comparable efficacy results when compared to amphotericin B-to-fluconazole exposure. Continued monitoring is needed for safety issues (especially with regards to liver, vision, and skin) as the protocol proceeds forward. The interim results reviewed do not favorably add to the safety profile of completed Vfend trials seeking candida treatment indications.

40. The review also notes that at the 10% point, there were very few *glabrata* patients. "The sponsor's view that Vfend is superior in efficacy over fluconazole for resistant candidal isolates cannot be tested when the isolates are not available for comparison. We hope that as this study progresses more sizable numbers of subjects with different candidal isolates will be studied." The FDA subsequently observed that "all four patients with the isolate of *C. glabrata* failed with Vfend treatment in comparison to three out of five patients in the amph-fluconazole arm."

41. After the serious Candida infection indication, which is a primary/ first line indication, was declined by the FDA based on the interim analyses, Pfizer immediately requested approval for Vfend in patients with refractory candidiasis, a second-line or "salvage" indication.

42. In a lengthy review, an FDA Medical Officer evaluated this request on a pathogen-by-pathogen basis. The FDA's pathogen-specific evaluation demonstrates

the significant variants in species of *Candida*.

43. For *C. glabrata* (17 isolates from 12 patients) the Medical Officer concluded that Vfend "appears marginally effective in treatment of refractory infections due to *Candida glabrata* with a large number of failures from the blood, one of the most common foci of infection with this isolate. The Medical Officer does not recommend approval for the use of Vfend in the treatment of infections due to *Candida glabrata*."<sup>3</sup>

44. For *C. tropicalis* (7 isolates from 6 patients) and *C. parapsilosis* (2 isolates from 2 patients), the Medical Officer concluded the numbers were too small and recommended against approval.

45. Despite Pfizer's repeated efforts to obtain an early *Candida* indication, the FDA declined to approve an invasive Candidiasis claim for either first line or salvage therapy.

46. Finally, with respect to Pfizer's specific NDA request for an indication for "treatment of serious fungal infections in patients refractory or intolerant to other therapy," the Medical Officer recommended against the request because it was over-broad and not specific. "The issuance of such a generalized approval is not feasible given the vastly different clinical responses (depending upon underlying disease and presence or absence of risk factors) that can be seen as well as the varying efficacy rates between the different species of *Candida*."

---

<sup>3</sup> *C. glabrata* is sufficiently distinct from other species of *Candida* that it was for many years, and as recently as the late 1990s, called *Torulopsis glabrata*. Advanced analysis has led to its classification as a strain of *Candida*, but the medical literature clearly establishes that it is a distinct pathogen with unique responses to treatment.

### **Empiric Therapy Rejection**

47. The FDA next dealt with the requested indication for Empiric Therapy. "Empiric therapy" is a phrase used to describe the use of antifungal agents when a physician suspects that a fungal infection may be present but has not yet obtained diagnostic verification. While there is debate in the medical community, empiric therapy is thought by many to be an appropriate treatment modality when a patient remains febrile (has a fever) after receiving three to four days of antibiotic therapy (because antibiotics are not effective against fungal infections).

48. In the domestic market, empiric therapy accounts for more than a third of the sales of antifungal drugs. "Empiric Antifungal Therapy of Febrile Neutropenic Patients," or "ETFN," denominates the FDA indication which allows an antifungal to be so used.

49. Most ETFN patients have iatrogenically-induced neutropenia (that is, they are patients in which treatment of an underlying medical condition has caused immunosuppression, most commonly chemotherapy patients, bone-marrow transplant recipients, and solid organ transplant recipients). Iatrogenically-induced neutropenia is the single most important risk factor for invasive fungal infections.

50. The FDA rejected Pfizer's request for a label indication for empiric treatment of presumed fungal infections for two reasons: First, because Pfizer's ETFN Phase III clinical study, denominated "Study 603," yielded data which failed to satisfy the test for clinical non-inferiority as tested at the primary endpoint of the study; and second, Pfizer failed to demonstrate efficacy of voriconazole in invasive *Candida* infections.

51. The FDA's principal work on the ETFN NDA's was performed by FDA Medical Officer John H. Powers, M.D. Dr. Powers advised Pfizer that an ETFN indication hinged on both a successful ETFN clinical trial, and demonstrated efficacy against *Aspergillus* and *Candida* species. He recognized that the ongoing 608 Study was the vehicle by which Pfizer hoped to demonstrate efficacy against *Candida* species.

52. The FDA has approved caspofungin (Merck product Cancidas, approved in 2004) and itraconazole (Johnson & Johnson product Sporanox , approved in 1997) as empiric therapy for presumed fungal infection in febrile neutropenic patients. AmBisome, a lipid form of amphotericin B, is also FDA-approved for ETFN. It was the first antifungal to receive that approval and Pfizer viewed it as Vfend's strongest competitor for empiric therapy.

53. Despite the denial by the FDA of the requested indication for Vfend to treat ETFN, Pfizer has marketed Vfend as though it had received that indication, resulting in submission of millions of dollars worth of false claims to Government Healthcare Programs.

54. Examples of such marketing activities include references to Vfend as having an "extended spectrum" and marketing to physicians on the basis that "[i]nitia-ting treatment at the earliest clinical suspicion [of a fungal infection] may improve outcomes." Pfizer promotional materials exhort physicians to "Choose Vfend First."

**B. The False 608 Study**

55. In rejecting the Serious Candida indication for Vfend, the FDA noted that Pfizer believed that voriconazole was not merely non-inferior, but actually superior to

the comparator arm, Amphotericin B→fluconazole, in “resistant candidal isolates.” The FDA further noted that as of 2002, the 608 Study did not have enough subjects with *C. glabrata* to test the hypothesis. Specifically, Pfizer predicted its study would demonstrate “efficacy in non-albicans pathogens” with respect to which fluconazole is either ineffective or exhibits reduced sensitivity. By that time, Pfizer had presented to the FDA, in attempting to support its request for a Serious Candida indication, a 10% interim data analysis from the 608 Study.

56. The FDA reviewers further noted that of the four subjects to that point with *C. glabrata* in the voriconazole arm of the 608 Study, treatment failed in 100%; while of the five subjects to that point with *C. glabrata* in the Amphotericin B→fluconazole arm of the Study, 2/5, or 40%, had been “cured.”

57. The Medical Officers also expressed concern that, at the 10% interim analysis, voriconazole was causing a greater number of Adverse Events in patients than Amphotericin B→fluconazole:

The evaluation of the safety profile at this 10% interim analysis is concerning. The amphotericin B-to-fluconazole group had more renal adverse events (increase in creatinine) than the voriconazole group which is not unexpected. Other than that, the voriconazole group had comparable or higher AE over the comparator.

58. The Medical Officer also commented on the apparent lack of efficacy with respect to *C. glabrata*:

The numbers for different candidal isolates were quite small, but the breakdown from this study suggests equivalent results between the two arms for *C. albicans* and *C. tropicalis*, better results against *C. parapsilosis* for voriconazole, and poorer response against *C. glabrata* for voriconazole.

59. At this point, the voriconazole New Drug Applications were in serious trouble. Pfizer had lost the most coveted indication (that for ETFN/empiric therapy) and its Worldwide Candida study was not going well at all. It is at this juncture that the issue of the switched endpoints comes into play.

#### **False Endpoints**

60. The original 608 Study protocol included primary and secondary “endpoints.” Endpoints are outcome variables used to judge the effectiveness of a treatment. An “endpoint” does not signify the end of a study, but rather a point at which data are compared. The “primary endpoint” of a study is the outcome variable on which the study focuses. “Secondary endpoints” are outcome variables which are known or believed to be related to the primary endpoint or are otherwise of interest to the researchers.

61. The original 608 protocol states the study’s primary endpoint as being to “compare the efficacy and safety of voriconazole (Vfend) and conventional amphotericin B with optional fluconazole follow-on therapy, in the treatment of candidemia in non-neutropenic patients.”

62. Original secondary endpoints were stated as being “[t]o examine health care resource utilization in subjects treated with voriconazole and conventional amphotericin B” and “[t]o evaluate the population pharmacokinetics of voriconazole.”

63. The original 608 protocol defines the phrase “end of therapy” as the termination of protocol, which can occur at least 2 weeks after the complete resolution of all clinical findings of an active infection or at least two weeks after the last positive blood culture, whichever is later. The original protocol also provides that “clinical and

culture data will be collected out to 12 weeks follow up.”

64. Ms. Brown and Mr. Vezeau have been informed by Pfizer personnel, to include Dr. Haran Schlamm, Global Clinical Development Leader for Voriconazole and Senior Associate Medical Director, and Dr. Colin Edwards, Vfend Marketing Team Leader, that the original endpoints in the 608 Study were inadvertently “swapped” so that the intended primary endpoint became the secondary endpoint, and *vice versa*.

65. As a result of this endpoint swap, the protocol which was submitted to the FDA was not that intended by the Pfizer personnel who designed the study. Rather, the “primary” endpoint became a date three months after the end of treatment, by which time countless intercurrent events could occur and the result of the study as related to the efficacy of voriconazole would be so obfuscated as to be uninterpretable.

66. As noted above, Pfizer performed an interim analysis when 10% of the data to be collected for the 608 Study had been amassed. The 10% interim data analysis showed that there was no efficacy difference between the two study arms, and showed that Vfend caused more adverse effects in patients than did the Amphotericin B→Fluconazole regimen.

67. As a result of this 10% interim analysis, Pfizer personnel realized that the 608 Study had been submitted to FDA with the endpoints reversed. The improper 12-week endpoint, Pfizer feared, would allow what Pfizer hoped would be the superiority of Vfend to disappear in a mass of intercurrent events, while the extended data collection meant that Pfizer was unwittingly testing the safety of Vfend against that of Fluconazole, which has a superior safety profile, rather than of Amphotericin B, which is known to have more serious side effects.

68. Based upon representations made to Relators by Dr. Schlamm and Dr. Edwards, Pfizer contacted the FDA and asked for permission to change the endpoints back to what was originally intended. However, because the study was ongoing and Pfizer already had seen early study results, the FDA refused to permit the requested change.

69. These events are discussed in slides contained in an internal Powerpoint presentation believed to be the work of Dr. Schlamm and Dr. Mike Hodges, Pfizer Global Development Team Leader. The slides, which bear the title "History of 608 Primary Efficacy Endpoint," assert that the original "protocol definition for the primary endpoint" was "based on response to antifungal treatment at the final assessment (12 week follow-up)." Dr. Schlamm refers to this as "ambiguous," and states that "[i]n the Statistics Analysis Plan this was interpreted as a fixed 12-week follow-up timepoint."

70. Dr. Schlamm's slides confirm "[p]ost 10% interim analysis recognition that this interpretation was at variance with [a prior study] which used the single DRC response at a variable timepoint." The next slide states:

Further discussions indicated DRC [Data Review Committee] and internal preference to change the secondary endpoint to primary endpoint and vice versa.

- ***This was the original intention of the protocol.***
- Existing primary endpoint would inevitably demonstrate poorer outcomes compared to previous candidemia studies (label implications)
- Statistical assumptions were based on original *Candidemia 1* design

(Emphasis supplied.)

71. Finally, Dr. Schlamm reports a "[t]elecon with FDA July 2002 to present

the case for changing the primary endpoint,” but “FDA did not agree to change primary endpoint since the 10% interim had been done *but said that both endpoints would be taken into consideration during review.*” [Emphasis supplied.]

72. Dr. John Powers of the FDA has asserted that secondary endpoints should be examined closely and reported fully to the FDA when the data observed at the secondary endpoints may have a significant impact on the outcome of the study, because secondary endpoints do not imply that the data are of secondary importance.”

73. Pfizer elected to continue the study with the unintended primary endpoint and the swapped secondary endpoint.

74. Subsequent presentation to senior Pfizer management represented that “[t]he WWT [World Wide Team] in conjunction with PGRD [Pfizer Global Research & Development] has thoroughly examined the statistical analyses plan to ensure that we prospectively audit all analyses to ensure we present the data in the most favorable light.”

75. When the full universe of data was collected and analyzed, Pfizer found that the unintended 12-week fixed endpoint yielded data which supported its position better than the intended endpoint of two weeks after the end of therapy. Vfend met the new “primary” endpoint by showing non-inferiority to the Amphotericin B→fluconazole arm.

76. However, when the data were evaluated at the *intended* primary endpoint, a different story emerged. 26.2% of Vfend-treated patients “fail[ed] at end of treatment” under study criteria, while only 21.3% of the comparator-arm patients “failed.” Relapse rates were higher in the Vfend arm (4.4% to 2.5%); “non-successful responses” were

higher in the Vfend arm (34.7% to 28.7%); and “other non-successful outcomes” were higher in the Vfend arm (8.5% to 7.4%).

77. Most importantly, when measured at the *intended* primary endpoint, the study failed to show that Vfend was non-inferior to the comparator arm.

Rather, at the new “secondary” endpoint, Pfizer reported in the Study Report which it submitted to the FDA the following:

In the MITT and PP populations, the stratified difference in success rates was -5.80% (95% CI; -15.77% to 4.16%) and -5.74% (95% CI; -16.56% to 5.08%).

Study Report, § 7.5.1.2. These statements are important because the study protocol requires that in order to be statistically significant, data must achieve a 95% Confidence Interval of 15%; here, the 95% CI on the Vfend arm for the MITT population was -15.77%, which is outside the 15% study-design requirement; similarly, on the PP population, the 95% CI on the Vfend arm was -16.56%, which is outside the 15% study-design requirement. Thus, the study findings at the intended primary endpoint did not constitute statistically-significant data supporting Vfend non-inferiority.

78. These differences disappeared at the unintended 12-week “primary” endpoint: “The stratified difference in success rates 12 weeks after EOT was 0.26% (95% CI: -11.08% to 11.60%). The stratified success rate was 39.71% and 39.58 in the voriconazole and amphotericin B→fluconazole groups[.]” Thus, the endpoint switch salvaged the study by causing the disappearance of the inferiority of Vfend.

79. This failure at the “secondary” endpoint is tacitly acknowledged in a Powerpoint presentation presented to the Pfizer Data Review Committee, or “DRC,”

regarding the study on December 12, 2003. That presentation includes a slide heading "Failure: reasons for imbalance at secondary endpoint?" The body of the slide identifies a variety of intercurrent events which caused the "secondary" endpoint failure.

80. The same presentation details the reasons why the data failed at the intended primary endpoint to support Vfend non-inferiority, but succeeded at the *unintended* (12-week) primary endpoint. In particular, it noted that 73% of the amphotericin B→fluconazole patients who were successes at the end-of-therapy endpoint died between the end of therapy and the 12-week endpoint, while only 59% of the Vfend patients who were success at the end-of-therapy endpoint died between the end of therapy and the 12-week endpoint.

81. Once Pfizer understood that Vfend's supposed noninferiority to Amphotericin B followed by fluconazole was shown by the unintended and switched endpoint, but not by the by the original, intended endpoint, Pfizer personnel referred to the FDA's unwillingness to allow the endpoints to be reconfigured after the endpoint switch was found as "the bread landing jelly-side up."

82. Pfizer's claim that the 12-week endpoint on the 608 Study was appropriate has been vigorously criticized in the medical community. Pfizer's manuscript reporting the results of the 608 Study was rejected for publication by the New England Journal of Medicine. The comments of the New England Journal editorial reviewers were provided to Pfizer, and include the observation that the 12-week endpoint "significantly obfuscate[s] the presentation of results." One reviewer found the manuscript "a bit deceptive" in its claim that voriconazole caused "fewer adverse events," and requested presentation of the pathogen-specific results for the various

*Candida* isolates.

83. The manuscript subsequently (and after substantial revision) was accepted for publication in The Lancet,<sup>4</sup> but the same volume of The Lancet included an editorial *Comment* entitled "Voriconazole for candidosis: an important addition?" In his *Comment*, Dr. John Graybill, Chief of Infectious Diseases for the University of Texas Health Center and a world-renowned expert in clinical trials of anti-fungal drugs, asserted that the 12-week primary endpoint was "[m]ost perplexing" and "seems seriously flawed" with "no bearing on the reality of treatment responses." Dr. Graybill further observed that the "secondary endpoint success rates at end of therapy . . . are more realistic."

84. Pfizer's article describing the results of the 608 study withheld the information that the primary endpoint was intended to be precisely the "success rates at end of therapy" which Dr. Graybill found "more realistic." Rather, the article claims that the 12-week primary endpoint was deliberately "chose[n]" by the researchers "to capture any late occurrences of persistence, relapse, adverse effects, or excess mortality" among study subjects. This statement is false, as nobody "chose" the 12-week endpoint.

---

<sup>4</sup> Kullberg, B.J., J.D. Sobel, M. Ruhnke, P.G. Pappas, C. Viscoli, J.H. Rex, J.D. Cleary, E. Rubinstein, L.W.P. Church, J.M. Brown, H.T. Schlamm, I.T. Oborska, F. Hilton, & M. R. Hodges, "Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial." *The Lancet* Vol. 366, p. 1435 (October 22, 2005). Of the authors, Schlamm, Oborska, Hilton and Hodges are employees of defendant Pfizer; Kullberg, Sobel, Ruhnke, Pappas, Viscolu, and Rex are "Key Opinion Leaders" who have received speaker fees, accommodations, business-class international air fare, and the like from Pfizer.

85. The effect of the 12-week-after-treatment primary endpoint is to disguise the true findings of the study, which is that when the results were analyzed according to the design of the study intended by the researchers, Vfend failed. This effect occurred because of what are called “intercurrent events”—in the intervening months between the end of treatment and the improper 12-week-after-treatment end point, test subjects died from unrelated illnesses, failed to report back for evaluation, etc. As the comment in *The Lancet* stated, “[r]esponse rates of 40% clearly reflected many other intercurrent events, mostly unrelated to candidaemia, and with no bearing on the reality of treatment responses.” The data clearly validate this observation: voriconazole success rate at the end-of-treatment endpoint success rate was 65%, and the Amphotericin B→Fluconazole end-of-treatment endpoint success rate was 71%; by the 12-week “primary” endpoint, these rates dropped to 41% and 40%, respectively.

86. In December 2004, based on the 608 Study, the FDA granted Pfizer label indications for Vfend for “Candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.”

87. In sum, by switching the 608 Study primary and secondary endpoints, Pfizer (1) salvaged a failed study; (2) hid from view the lower efficacy and higher mortality rates among the patients in the 608 Study who had *C. glabrata* infections; and (3) and obtained approval from the FDA when it could not have done so had it provided the analysis which the study was designed to achieve.

### **C. The Hidden *C. glabrata* Data**

88. Beginning in 2000, Relator Brown was assigned responsibility to develop Vfend sales materials for use by the World Wide Vfend Marketing Teams. Pfizer had secured European approval to label Vfend for use as a second-line or salvage therapy for patients with fluconazole-resistant *Candida* infections. This indication was denied Pfizer by the FDA because it could not demonstrate efficacy against *C. glabrata*. Ms. Brown began working to develop promotional materials which leveraged the European indication by asserting that the additional expense of Vfend therapy was appropriate because Vfend was available in both intravenous and oral forms and had "broad-spectrum efficacy" against *Candida*.

89. While working on the marketing materials, Ms. Brown experienced a confrontation with a senior Pfizer researcher, Dr. Alice Baruch, who at the time was the Vfend Medical Director.

90. Dr. Baruch had been, prior to becoming Vfend Medical Director, a member of the Vfend Global Development Team responsible for submitting the 608 Study to the FDA with the swapped endpoints.

91. Dr. Baruch told Ms. Brown that her marketing materials were too aggressive in claiming "broad spectrum efficacy" for Vfend, and for claiming efficacy for Vfend against *Candida glabrata*. Dr. Baruch stated, paraphrasing, that research to date had not shown Vfend efficacy against *C. glabrata*, and she expressed doubt that such efficacy would ever be shown.

92. At this time, Ms. Brown had no knowledge of the interim results under Study 608, but Dr. Baruch obviously did. Indeed, she had attended many meetings with FDA personnel where the interim data were discussed, and undoubtedly had full

knowledge of the FDA's evaluation of the *C. glabrata* efficacy in connection with denial of the salvage-treatment indication.

93. Dr. Baruch did not advise Ms. Brown that in the 10% interim data analysis of the early 608 Study results, "all four patients with the isolate of *C. glabrata* failed with Vfend treatment in comparison to 3 out of 5 patients in the amphi-fluconazole arm." Additionally, Ms. Brown was not advised that in refractory analysis for *C. glabrata*, "Vfend appeared marginally effective in treatment of refractory infections due to *Candida glabrata* with a large number of failures from the blood, one of the most common foci of infection with this isolate."

94. Sometime after Ms. Brown's conversation with Dr. Baruch, Dr. Baruch was replaced as the Pfizer physician in charge of the Vfend study by Dr. Haran Schlamm.

95. Ms. Brown continued working on the Vfend world-wide marketing strategy. On December 11, 2003, she was provided with an abstract of the results of the 608 Study, and learned that the 608 Study demonstrated non-inferiority of Vfend to the comparator arm and that FDA therefore approved the indication for candidemia in non-neutropenic patients.

96. In particular, the abstract she was sent for Study 608 stated as its conclusion that "VOR is at least as effective as AMB/FLU for the treatment of candidemia, including non-*albicans* species, in non-neutropenic pts."

97. Ms. Brown was particularly pleased to learn that, according to Pfizer's representations regarding the results of the 608 Study, Vfend appeared as effective as

amphotericin B→fluconazole in cases of *C. glabrata*. Ms. Brown was aware that *C. glabrata*, because it is far more deadly than the more common *C. albicans* pathogen, was a primary consideration for practitioners considering prescribing antifungal therapy for patients with suspected *Candida* infections. As “Key Opinion Leader” Dr. Jack Sobel, Professor and Chief of the Division of Infectious Diseases at Wayne State University School of Medicine, has stated, “it is the fear of *C. glabrata* that drives a physician’s choice of antifungal.”

98. A majority of all *Candida* infections are of the strain *C. albicans*. However, because of the success of fluconazole in combating *C. albicans*, the group of other *Candida*, often called “non-*albicans Candida*,” has become the most feared; and of this group, *C. glabrata* is the pathogen associated with the highest levels of mortality. Because fluconazole is known to exhibit reduced efficacy against non-*albicans*, it was of unparalleled importance to Pfizer that Vfend be accepted as a credible treatment.

99. The emerging significance of non-*albicans Candida* is well-known. For example, the Infectious Disease Society of America has stated that “[a]lthough *Candida albicans* remains the most common pathogen in oropharyngeal and cutaneous candidiasis, non-*albicans* species of *Candida* are increasingly associated with invasive candidiasis.”<sup>5</sup>

100. In 2003, a group of authors, including several Pfizer employees, published the results of a study showing that Vfend was only 25% effective for patients with *C.*

---

<sup>5</sup> Pappas, P.J., *et al.*, “Guidelines for Treatment of Candidiasis,” Clinical Infectious Diseases 2004:38 (2004).

*glabrata* which was refractory to fluconazole.<sup>6</sup>

101. Vfend was more effective in these refractory patients with other *non-albicans* strains of *Candida*, showing a response rate of 100% against *C. parapsilosis*. This observed differential led a subsequent research team to refer to the *C. glabrata* result as "quite disturbing."<sup>7</sup>

102. Because of the emergence of *C. glabrata* as a primary driver in physician decision-making regarding *Candida* infections, and because Vfend did not perform well against *C. glabrata* in the refractory-patient study, it was critically important to Pfizer that the 608 Study validate the efficacy, or at least the non-inferiority, of Vfend in the treatment of *C. glabrata*.

103. Once the 608 Study was complete, a document was provided to the FDA in support of the requested Vfend *Candida* indication called "Study Report". The Study Report spans 72 pages, and is preceded by a six-page "Study Report Synopsis." The document included no information regarding the results of the 608 Study with respect to those study subjects infected with *C. glabrata* at the unintended secondary endpoint except to indicate that they are included in sources external to the Study Report.

104. When Ms. Brown reviewed the 608 Study Report, she recalled Dr. Alice Baruch's statements that Vfend likely would not be found efficacious against *C.*

---

<sup>6</sup> Perfect, J.R., et al., "Voriconazole Treatment for Less-Common, Emerging, or Refractory Fungal Infections," Clin. Infect. Dis. 36:1122-31 (2003).

<sup>7</sup> Barkiest, F., et al., "In Vitro Activities of Voriconazole in Combination with Three Other Antifungal Agents against *Candida glabrata*," Antimicrobial Agents and Chemotherapy 48:9 (September 2004).

*glabrata*.

105. The marketing campaign on which Ms. Brown and her colleagues was working touted Vfend as a physician's "one chance to get it right" in cases of suspected fungal infections. To ensure that this was consistent with the study results, Ms. Brown orally asked Dr. Schlamm, whose office was near her own, for the breakout of the 608 Study results by strain of *Candida*. Ms. Brown's first such request was in late 2004.

106. Dr. Schlamm promised to provide Ms. Brown the *glabrata* data, but failed to do so.

107. Over the ensuing months, Ms. Brown made two more oral requests, then advised her boss, Nick Gurreri, that she had been unable to obtain the information she had requested from Dr. Schlamm. This was the only time during Ms. Brown's career at Pfizer that repeated requests for important medical data were ignored.

108. Mr. Gurreri directed Ms. Brown to request the *glabrata* data from Dr. Schlamm in writing. On April 18, 2005, Ms. Brown sent Dr. Schlamm this e-mail message:

Haran,

At ECCMID a few KOL mentioned that underlying pathogen will drive choice of antifungal for *Candida*. Can you please send me the data from the Candidemia study at EOT not 12 weeks after end of therapy by pathogen?<sup>8</sup>

109. Late that evening, Dr. Schlamm responded:

Catherine,

---

<sup>8</sup> ECCMID is the European Congress of Clinical Microbiology and Infectious Diseases. It was held in Copenhagen, Denmark, on April 2—5, 2005. "KOL" are "Key Opinion Leaders."

Here they are!

Note: For *C. Glabrata*, although the response rates at EOT were higher (not significantly) on the ampho arm, a greater proportion of these patients failed during the follow-up period.

110. Attached to Dr. Schlamm's e-mail were three Powerpoint slides which showed that, at the End of Treatment endpoint which was mandated by the study design but mistakenly converted by Pfizer to a "Secondary Endpoint," Vfend was substantially less effective against *C. glabrata* than Amphotericin B→fluconazole. In particular, the slides showed that at the end of treatment, Voriconazole was 53% successful against *C. glabrata*, while Amphotericin B→fluconazole was 76% successful; that at the "Most Appropriate Timepoint," Voriconazole was 53% successful, while Amphotericin B→fluconazole was 73% successful; but that at 12 weeks after end of treatment, both treatment arms were 33% successful.

111. Ms. Brown was quite disturbed to learn that Vfend had been nearly 50% less effective against *C. glabrata*, which she knew to be the most common and serious form of non-*albicans Candida*.

112. When Ms. Brown initially discussed with Dr. Schlamm the *glabrata* data, he stated to her that because the *glabrata* failure was part of the "secondary" endpoint, and the numbers evened out at the "primary" endpoint, it was not necessary to highlight the data to FDA or acknowledge it at all in marketing materials.

113. Ms. Brown forwarded the *glabrata* data to Jeff Duffour, a Pfizer Marketing Director for Spiriva who previously had been on the Vfend Canada marketing team. Mr. Duffour was unaware of the data and expressed shock.

114. She also forwarded it to Dr. Colin Edwards, her prior supervisor, who had been the Vfend Marketing Team Leader and had closely read the 608 Study Synopsis before it was submitted to the FDA. Dr. Edwards advised her that he had no knowledge of the *glabrata* results.

115. Ms. Brown then confronted Dr. Schlamm and inquired if he had withheld the data purposely. Shortly afterward, she was summoned to a meeting with Dr. Schlamm and Ms. Brown's second-tier supervisor, Alison Ayres, whose responsibilities include all HIV, anti-fungal, and antibiotic products. In the meeting, Ms. Ayres gave Dr. Schlamm ample time to describe his position but did not do the same for Ms. Brown.

116. Dr. Schlamm stated, among other things, that he had reviewed the clinical data, and the *glabrata* patients in the Vfend arm of the 608 Study were "sicker" than the patients in the Amphotericin B→fluconazole arm. However, the 608 Study was randomized, and the Acute Physiologic And Chronic Health Evaluation (APACHE II) illness-severity scores in both arms of the study were actually slightly higher on the Amphotericin B→fluconazole arm of the Study.

117. There are no reported data which support the assertion that the *glabrata* data were unreliable because the randomization failed.

118. Dr. Schlamm also asserted that the lack of success against *glabrata* on the Vfend arm was statistically insignificant. When questioned, he stated that he based this conclusion on a Chi-square test for statistical significance to which he subjected the data. However, Chi-square testing is not properly used on relatively small data samples such as the *glabrata* samples, because the Chi-square test relies on a large sample approximation.

119. Moreover, this point, while of some consequence to statisticians, in no way justifies suppressing the *C. glabrata* data, particularly given the importance to the prescribing community of efficacy versus *C. glabrata*—a fact obviously well-known to Pfizer.

120. Dr. Schlamm also said that the information had been given to the Vfend Advisory Board, a panel of Pfizer employees and “outside” physicians paid by Pfizer to monitor the study. The data were, according to Dr. Schlamm, presented at a meeting in Miami, Florida, in December 2003. However, Ms. Brown has since spoken with Ms. Gail Triggs, Pfizer Director of Professional Communications and a senior organizer of the Vfend Advisory Board, and Ms. Triggs has indicated that she had no knowledge of the *C. glabrata* data nor any recollection of its having been presented at the Miami meeting.

121. The Miami Advisory Board presentation was contained in two Powerpoint presentations which were forwarded by Dr. Schlamm to Ms. Brown in an e-mail with the message “full disclosure!” This transmittal occurred on May 3, 2005, more than two weeks after the initial transmittal of *C. glabrata* results by Dr. Schlamm to Ms. Brown.

122. The e-mail sent by Dr. Schlamm includes an e-mail message sent to him by Pfizer employee Dr. Iwonka Oborska, Global Research & Development. Dr. Oborska wrote: “Note slide 49 has the responses by both primary and secondary endpoint, by bug. Also there's a KP survival curve by bug showing glabrata did worse on voriconazole a few slides later.” After identifying the *glabrata* slides in the Powerpoint presentations, Dr. Oborska wrote that her transmittal “[m]ight be reassuring” to Dr. Schlamm.

123. Ms. Brown was shocked, rather than “reassured,” by Dr. Schlamm’s “full disclosure,” because the data did not support the claim that Vfend was effective against non-*albicans Candida*. The data are as follows:

Pathogen	Treatment	“Secondary” Endpoint	“Primary” Endpoint
<i>C. albicans</i>	Vfend (n=107)	62.60%	43.00%
	AMB/Flu (n=63)	77.80%	47.60%
<i>C. glabrata</i>	Vfend (n=36)	52.80%	33.30%
	AMB/Flu (n=21)	71.40%	33.30%
<i>C. krusei</i>	Vfend (n=4)	25.00%	25.00%
	AMB/Flu (n=1)	100.00%	
<i>C. parapsilosis</i>	Vfend (n=45)	73.30%	53.30%
	AMB/Flu (n=19)	78.90%	52.50%
<i>C. tropicalis</i>	Vfend (n=53)	66.00%	32.10%
	AMB/Flu (n=16)	43.80%	6.30%

124. The table shows that with respect to *C. glabrata*, only 52.8% of Vfend patients satisfied the study’s criteria for a successful result at the *original* primary endpoint of two weeks after the end of treatment, while 71.4% of Amphotericin B→Fluconazole patients qualified as successes. In more human terms, this means that 15 of the 21 Amphotericin B→Fluconazole patients were successes, while only 19 of 36 Vfend patients were successes.

125. Remarkably—and entirely coincidentally—at the 12-week “primary” endpoint, the *C. glabrata* results precisely equalized, with 33.30% in each study arm

counting as successes.

126. One of the Powerpoint presentations forwarded to Ms. Brown was a 175-page underlying-data set regarding the 608 Study. Therein, she found a document she considered particularly disturbing: a Kaplan-Meier Curve documenting the mortality associated with each arm of the 608 Study. The Kaplan-Meier curve is a widely-accepted analytical tool used to plot the probability that a patient will be alive at a given point in or after a study.

127. The same data deck, which consists of 182 pages of charts and tables, includes a large bar graph representing that Vfend was more effective against *Non-albicans* at the primary endpoint, with no mention at all of the fact that Vfend was dramatically less effective against *glabrata*, both at the end of treatment and, from a mortality perspective, 14 weeks *after* treatment.

128. With respect to *C. glabrata*, the Kaplan Meier Curve, which is reproduced below, showed with respect to whether patients were alive or dead at certain points during the 608 Study, the following:

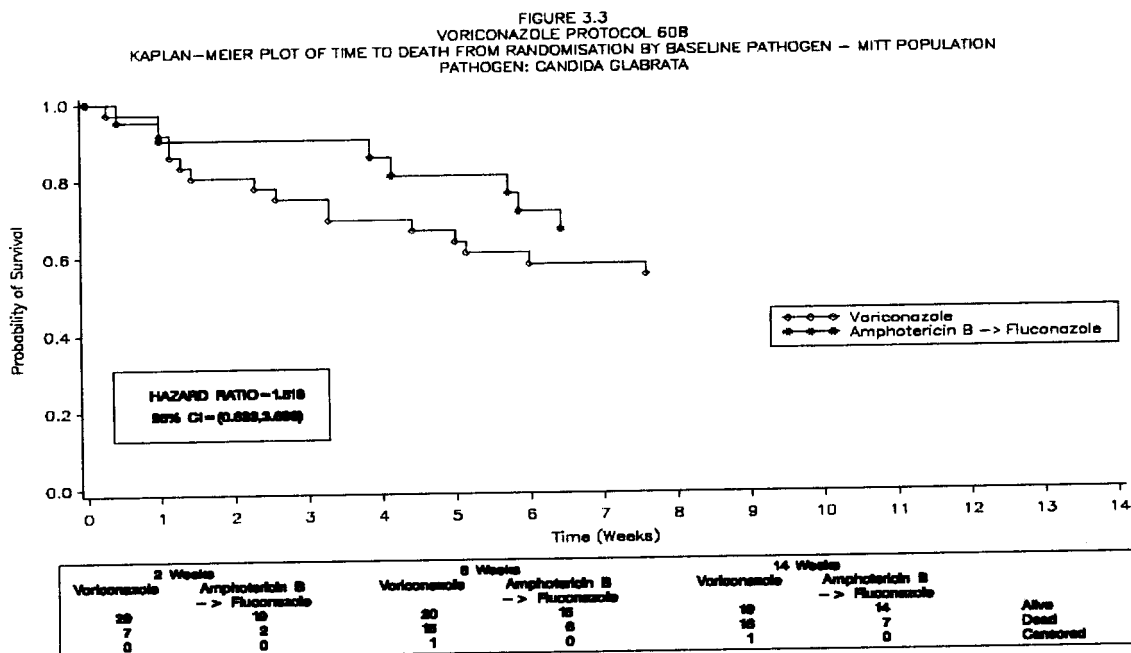
Vfend, 2 weeks	AmB/Flu, 2 weeks	Vfend, 8 weeks	AmB/Flu, 8 weeks	Vfend, 14 weeks	AmB/Flu, 14 weeks
29 alive	19 alive	20 alive	15 alive	19 alive	14 alive
7 dead	2 dead	15 dead	6 dead	16 dead	7 dead
0 censored	0 censored	1 censored	0 censored	1 censored	0 censored

129. Twice as many patients in the 608 Study were randomized into the voriconazole arm than into the comparator arm, but at the time of the randomization, the researchers did not know what specific pathogen infected a given patient. Reduced

to percentages, these data show that at the two-week interval, 19.4% of the *glabrata* patients receiving voriconazole were dead, while 9.5% of the patients receiving amphotericin B→fluconazole were dead. At 14 weeks, the respective percentages were 45.7% and 33.3%.

130. The Kaplan-Meier curve also computes a Hazard Ratio, which is identified as being 1.518 at a 95% confidence interval. This Hazard Ratio demonstrates that a *C. glabrata* patient administered Vfend was 49% more likely to die than a patient administered Amphotericin B→Fluconazole. This information is not contained in the Study Report, and the Lancet article reports only that *across all strains of Candida*, “[t]he hazard ratio for dying in the voriconazole group was 0.82.”

131. The Kaplan-Meier curve is reproduced here:



D: 21SEP2003 – 22SEP2003  
T: 03DEC03(14:13)  
Source: Section 11 Item 11 Table 6.10.1  
NOTE: The hazard ratio is Stratified by Region

132. Ms. Brown felt that she had been deceived by Pfizer and by Dr. Schlamm, because the 608 Study results did not support the assertion that Vfend was safe and effective against *C. glabrata*. She also believed that she had learned why Dr. Baruch had been adamant that Vfend might never be shown to have efficacy against *C. glabrata*.

133. In the ensuing weeks, Ms. Brown repeatedly discussed with Dr. Schlamm and others within Pfizer regarding the *glabrata* data. She confirmed that no one else on the Vfend marketing team was aware of the data.

134. Ms. Brown ultimately was instructed by her second-tier supervisor, Alison Ayres, not to discuss the *glabrata* data, or her concerns regarding those data, with anyone. Ms. Ayres did advise Ms. Brown that the issue would be presented to the Vfend Global Steering Committee. That presentation occurred several weeks later; Ms. Brown was then advised by Mr. Gurreri that Jacob Plotsker, U.S. Team Marketing Lead, also was unaware of the *glabrata* data.

135. Ms. Brown was advised by Mr. Gurreri that the Global Steering Committee decided that physicians should be provided with disclosure of the data regarding the performance of Vfend by pathogen. She was relieved by this news, because she believed that once physicians became aware of the actual study results, they would not elect to prescribe Vfend for *Candida*—and so would not elect to use Vfend for empiric therapy.

136. The task of writing the physician letter was delegated to Relator Bernard

Vezeau.

137. Mr. Gurreri subsequently directed Mr. Vezeau to write a *C. glabrata* "white paper" to be sent only to Pfizer employees who were involved in promoting Vfend to physicians. The objective of the white paper was to communicate the Vfend *C. glabrata* data to these individuals and to advise them to "tone down" their Vfend promotional efforts for *C. glabrata*. Mr. Vezeau was never directed to write a *C. glabrata* white paper that would be sent directly to physicians in the medical community.

138. Mr. Gurreri instructed Mr. Vezeau to work with Dr. Schlamm in writing the *C. glabrata* white paper but Dr. Schlamm did not cooperate in this effort. On two occasions, Dr. Schlamm stated to Mr. Vezeau, closely paraphrasing, that "if we want to ruin the Vfend business we just need to send this white paper out."

139. Mr. Vezeau reported back to Mr. Gurreri that Dr. Schlamm was not fully cooperating to write the *C. glabrata* white paper. Mr. Gurreri stated that he would seek further guidance from the Vfend Global Steering Committee on how to resolve this problem with Dr. Schlamm.

140. Several weeks later Mr. Gurreri informed Mr. Vezeau that the GSC requested two versions of the *C. glabrata* white paper. The first version of the white paper would be sent only to Pfizer affiliates marketing Vfend and the second version would be a letter retained on file at Pfizer HQ and only sent to those physicians who contacted Pfizer to specifically request information on Vfend's efficacy against *C. glabrata*.

141. On November 14, 2005, Ms. Ayers (Mr. Gurreri's supervisor) approached

Mr. Vezeau to discuss the *C. glabrata* white paper he was tasked to write. Ms. Ayers told Mr. Vezeau that she needed to speak with him because Dr. Schlamm complained to her that Mr. Vezeau was asking too many questions about the 608 Study, which Dr. Schlamm did not feel was relevant to the task of writing the *C. glabrata* white paper.

142. During Ms. Ayer's discussion with Mr. Vezeau she called the 608 Study switched endpoints "Pfizer's dirty laundry that we don't want to air out." She also stated that she was willing to accept Vfend's weak performance against *C. glabrata* because she did not believe many *C. glabrata* patients were receiving Vfend therapy.

143. During this discussion, Mr. Vezeau informed Ms. Ayers that he felt Pfizer was not conducting itself in an ethical or proper way by concealing the errors associated with the 608 Study. Ms. Ayers responded by removing Mr. Vezeau from the *C. glabrata* white paper project.

144. On November 15, 2005, Mr. Vezeau was informed by Mr. Gurreri that Ms. Ayers felt Mr. Vezeau was exercising "poor judgment by questioning the 608 Study protocol in emails" and that "people who exhibit poor judgment do not get promoted."

145. As of December 9, 2005, Mr. Vezeau's last day at Pfizer, neither version of the *C. glabrata* white paper was completed.

146. Ms. Ayres's observations regarding the lack of usage of Vfend in cases of *C. glabrata* are false. According to a graphic provided to Mr. Vezeau by Pfizer employee Mark Shapiro as an e-mail attachment on November 9, 2005, while only 5% of the market consists of patients with *C. glabrata*, 11% of Vfend Oral sales and 10% of Vfend IV sales were for patients where the known or suspected pathogen was *C.*

*glabrata*.

147. The title of this graphic is "Vfend utilization is skewed in favor of Aspergillus and *C. glabrata* relative to the market overall."

148. Pfizer's reasons for failing to issue the *glabrata* white paper are obvious: Its marketing efforts representing Vfend as being effective against *C. glabrata* have worked.

149. The same graphic shows that although the FDA denied Pfizer's NDA for an indication for ETFN (Empiric therapy) for Vfend, Empiric therapy represents 35% of the market, but 42% of sales of Vfend IV. Because physicians focus on the risk of *C. glabrata*, this sales figure reflects the medical community's acceptance of Pfizer's false claims of efficacy against that pathogen.

150. Pfizer is now heavily marketing Vfend as being effective against *C. glabrata*. Pfizer knows that this is not true. It also markets Vfend as having few significant side effects. It knows that this claim is not supported by the 608 Study. The obvious implication of Pfizer's marketing efforts is that Vfend is on balance a superior choice, which Pfizer knows not to be true.

151. Based on the excess mortality data which resulted from the 608 Study, Ms. Brown and Mr. Vezeau believe that patients who have *C. glabrata* infections and are treated with Vfend are unnecessarily at increased risk of dying.

152. Pfizer has proceeded to fully embrace and tout the claim that Vfend is equally efficacious against all species of *Candida*, despite having irrefutable evidence that it is not. Pfizer has leveraged the "all species" efficacy claim to promote use of

Vfend for empiric therapy, even though the FDA refused the EFTN indication.

153. At the December 16–20 2005 Interscience Conference on Antimicrobial Agents and Chemotherapy (“ICAAC”), conducted in Washington, D.C. and attended by approximately 12,000 medical personnel with interests in infectious diseases, Pfizer’s marketing booth aggressively promoted its claim that Vfend exhibited efficacy against *C. glabrata*.

154. Pfizer’s current marketing materials include many misleading or false statements regarding the 608 Study. The *Lancet* article, written by a team including Pfizer employees and Pfizer-sponsored physicians and published in October 2005—months after this issue surfaced internally—squarely represents that “[f]or *C. albicans*, *C. glabrata*, and *C. parapsilosis*, **successful response rates were similar between the voriconazole and amphotericin b/fluconazole groups[.]**” The Lancet, Vol. 366 at 1441 (emphasis supplied). This statement is flatly false, because it is based on the obviously-spurious 12-week “primary” endpoint. The same article represents that “casprofungin or voriconazole are currently the most useful options for primary treatment of candidemia in non-neutropenic patients.” *Id.* This claim is false; there is no credible evidence that voriconazole is more “useful” than Amphotericin B→fluconazole against *C. glabrata*. The conclusion of the article states:

In summary, the results of this large, multicentre study show that voriconazole is as effective as the commonly used strategy of amphotericin B followed by fluconazole in non-neutropenic patients for the treatment of candidaemia, *including C. albicans and non-albicans candida species*. The broader spectrum of voriconazole, its better safety than amphotericin B, and the availability of intravenous and oral formulations, provide an important new treatment option for candidemia.

*Id.* This statement, too, is false: The data do not demonstrate that voriconazole is as effective against *C. glabrata* as amphotericin→fluconazole. Moreover, the stated objective of the 608 Study was not to demonstrate that Vfend was “as effective,” but rather to demonstrate that it was “non-inferior.” Even if the endpoints had not been manipulated, the study does not support the “as effective” claim.

155. In a December 28, 2004 Pfizer press release discussing the FDA’s granting Pfizer the candidemia indication, Pfizer Vice President and U.S. Medical Director, Dr. Ann Kolokathis, is quoted as stating:

This new approval is important because there is now clinical proof of Vfend’s first-line systemic efficiency against a broad range of serious fungal infections . . . Vfend is effective against clinically relevant *Candida* species including hard-to-treat pathogens, such as *C. glabrata* and *C. krusei*, which cause these life threatening infections.

At present, this press release is still available on Pfizer’s website,

[http://www.pfizer.com/pfizer/are/news\\_releases/2004pr/mn\\_2004\\_1228.jsp](http://www.pfizer.com/pfizer/are/news_releases/2004pr/mn_2004_1228.jsp).

156. Pfizer-approved slides used at medical conferences include such statements as “Voriconazole is as effective as the regimen Amphotericin B→fluconazole in the treatment of non-neutropenic patients with candidemia” and “Response rates are similar for *C. albicans* and non-*C. albicans* infections (both arms).”

157. The marketing literature includes other false or misleading claims. For example, current Vfend literature asserts that Vfend “eradicated *Candida* as quickly as Amphotericin B.” This assertion is based on the fact that in both arms of the 608 Study, patients achieved negative blood cultures within four days. Pfizer asserts that “Vfend sterilized the blood within 4 days in almost 80% of patients with positive blood cultures

at baseline.” In fact, however, the removal of catheters alone is a highly important factor in resolving *Candida* in the bloodstream of non-neutropenic patients, with studies showing the clearance of *Candida* in up to 70% of patients treated by catheter removal without any drug therapy.

158. Pfizer’s broad *Candida* label, and these false statements and documents, were made possible because the Study Report and the attached Synopsis for the 608 Study, which Pfizer submitted to the FDA in support of its request for an indication for broad treatment of *Candida*, were false documents.

159. The documents are “false records or statements” for multiple reasons, including but not limited to the following:

160. On p. 3 of the Synopsis, Pfizer wrote: “The primary endpoint provided a robust assessment of response as post-treatment deaths and other events, were taken into account whereas in the secondary analysis (DRC success rate at the latest appropriate timepoint) subjects could be assessed as a success, even if they subsequently died prior to 12 weeks after EOT.” This statement is false as Pfizer knew that the primary endpoint results could not scientifically be “a robust assessment of response” because the primary endpoint not only was a mistake but also that it did not and could not validly measure non-inferiority of voriconazole to Amphotericin B→fluconazole.

161. In Section 7.5.4.1 of the Study Report, entitled “Response Rates by *Candida* Species,” Pfizer writes that “Table 5.9.2 shows the DRC assessment of response . . . by baseline pathogen type . . . .” However, Table 5.9.2 is not included within the lengthy Study Report, which nowhere acknowledges that voriconazole was

far less effective against *C. glabrata* than the control arm of the study.

162. The Study Report also strongly leverages the manipulated endpoints, by addressing the pathogen-specific data only at the unintended 12-week "primary" endpoint. Section 7.6 of the Study Report states:

The results of the primary analysis, DRC success rate at the fixed time-point 12 weeks after EOT, showed that voriconazole was non-inferior to amphotericin B→fluconazole. The stratified success rate was 40.72% and 40.70% (the difference after adjustment for region was 0.04% with 95% confidence interval of -10.6 to 10.6) in the voriconazole and amphotericin B →fluconazole groups, respectively. The results in the PP population were consistent with these results in the MITT population.

163. From this assertion, Pfizer falsely concludes, also in Section 7.6 of the Study Report, that "voriconazole was as effective as the regimen of amphotericin B →fluconazole, in both *C. albicans* and non-*albicans* candidemia." The truth, however, is that voriconazole is not "as effective as the regimen of amphotericin B→fluconazole in both *C. albicans* and non-*albicans* candidemia," and it is false for Pfizer to so assert, because voriconazole is inferior when treating *C. glabrata*. At the secondary endpoint, which Pfizer itself acknowledges to have been the most clinically relevant, Voriconazole had far less efficacy than the comparator arm.

164. Open disclosure of the *C. glabrata* data would have been pivotal to FDA approval/disapproval of the Vfend NDA based on the 608 Study. Pfizer was on notice that improved (from the 10% interim analysis) *C. glabrata* results would be important to FDA's decision to approve its Vfend Candidemia indication, but chose to conceal adverse results. In 2002, the FDA refused to grant Vfend a broad indication for candidemia because of this very concern:"The issuance of such a generalized approval

is not feasible given the vastly different clinical responses (depending upon underlying disease and presence or absence of risk factors) that can be seen as well as the varying efficacy rates between the different species of *Candida*. (emphasis supplied.)

165. To the same point, in a September 2001 FDA Medical Officer's Review, the Medical Reviewer wrote on p. 27:

In conclusion, voriconazole appeared marginally effective in the treatment of refractory infections due to *Candida glabrata* with a large number of failures from the blood, one of the most common foci of infection with this isolate. The MO does not recommend approval for the use of voriconazole in the treatment of infections due to *Candida glabrata*.

166. Section 7.6 of the 608 Study Report contains the following language concerning the (EOT) secondary endpoint:

In the secondary analysis (DRC success rate at the latest most appropriate timepoint) the unstratified success rate was 65.5% and 71.3% in the voriconazole and amphotericin B→fluconazole groups, respectively. A contributing factor to the observed treatment difference was the higher rate of study drug discontinuations due to adverse events reported in the voriconazole group. However, the frequency and severity of adverse events and laboratory test result abnormalities in the voriconazole and amphotericin B→fluconazole group was similar.

167. From this language, Pfizer falsely states, in Section 7.6, that "voriconazole was as effective as the regimen of amphotericin B→fluconazole, in both *C. albicans* and non-*albicans* candidemia."

168. The statement that overall "the unstratified success rate was 65.5% and 71.3% respectively" is false because the result failed to meet the required 15% confidence interval. By omitting information that the data on the secondary endpoint did not meet the required confidence interval, Pfizer falsified the comparability of the efficacy of Vfend at the secondary endpoint.

**COUNT I  
FALSE CLAIMS ACT VIOLATIONS  
31 U.S.C. §§ 3729(a)(2)**

169. The allegations of ¶¶ 1-168 are realleged as if fully set forth below.

170. Defendant Pfizer has used a variety of false documents, including false submissions to the United States FDA and false marketing materials, to cause the United States to pay claims for reimbursement under the Medicare, Medicaid, and military healthcare systems which would not have been reimbursed had the United States known that false representations were made to both the FDA and to practitioners about the true state of affairs regarding the efficacy of Vfend against non-*albicans* candidemia.

171. Defendant Pfizer has vigorously marketed Vfend off-label for empiric therapy, despite having been specifically denied an indication therefor.

172. From on or about 1998 to present, Defendant's conduct violated the False Claims Act, 31 U.S.C. §§ 3729(a)(2).

**PRAYER FOR RELIEF**

WHEREFORE, Relators, on behalf of the United States and on their own behalf, demands judgment against Defendants, as follows:

A. That this Court enter judgment against the Defendant in an amount equal to three times the amount of damages the United States Government has sustained because of Defendant's actions, plus a civil penalty of \$11,000 for each false claim, together with the costs of this action, with interest, including the cost to the United States Government for its expenses related to this action.

- B. That Relators be awarded all costs incurred, including their attorneys' fees.
- C. That in the event the United States Government intervenes in this action, Relators be awarded 25% of any proceeds of the claim, and that in the event the United States Government does not intervene in this action, Relators be awarded 30% of any proceeds.
- D. That the United States and Relators receive all relief, both in law and in equity, to which they are entitled.

Of Counsel:

Kenneth J. Nolan  
Marcella C. Auerbach  
Nolan Law Firm  
435 North Andrews Avenue  
Suite 401  
Fort Lauderdale, Florida 33301  
Telephone: (954) 779-3943  
Fax: (954) 779-3937

Frederick M. Morgan, Jr.  
Jeffrey L. Maloon  
Volkema, Thomas  
700 Walnut Street, Suite 400  
Cincinnati, Ohio 45202  
Telephone: (513) 651-4400  
Fax: (513) 651-4405

Respectfully submitted,

John R. Mininno (JRM-7223)  
Mininno Law Office  
475 White Horse Pike.  
Collingswood, NJ 08107  
Telephone: (856) 833-8600  
Fax: (856) 833-9649



---

John R. Mininno (JRM-7223)

Counsel for Plaintiffs/Relators