

**Case Name – Aventis Pharmaceuticals, Inc. - Ketek**

**Agency Case # - 2006-TFM-709-0263**

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**Subject Information**

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**Case Narrative**

In 2/00, Aventis submitted to the FDA a New Drug Application (NDA) for Ketek. Ketek is the brand name for telithromycin, an anti-biotic used to treat respiratory tract infections. In 6/01, the FDA requested that Aventis conduct a safety study of Ketek. There were concerns with liver toxicity as a side-effect of Ketek use. In 7/02, Aventis submitted an amendment to the NDA, which included the data from this safety study (Study 3014). Study 3014 was conducted during the fall and winter of 2001-2002 with 12,000 patients receiving the drug at 1,872 sites.

Inspections of Study 3014 high enrollers were conducted by FDA Division of Scientific Investigations (DSI), and identified significant problems at some Study 3014 sites. In 3/04, DSI issued a memorandum to the FDA review team recommending that four trial sites be excluded from consideration in the NDA stating, "The integrity of data from all sites involved in Study 3014 cannot be assured with any degree of confidence."

In 4/04, FDA approved Ketek. The data from Study 3014 was excluded from consideration. Safety data was instead evaluated based on two years of foreign post-marketing data where Ketek was already being sold.

Based on a referral from FDA DSI, FDA OCI SA Bob West conducted an investigation of Dr. Anne Marie Kirkman-Campbell, Gadsden, AL, Study 3014's highest enroller with 407 subjects. This resulted in Dr. Kirkman-Campbell being indicted for in the Northern District of Alabama on 8/29/03 for charges relating to clinical trial fraud. She subsequently pled guilty to one count of 18 USC 1341 and was sentenced to 56 months incarceration. (Attachments 1-3)

Since Ketek's approval, the FDA is aware of twelve cases of liver failure including one death attributed to Ketek use. In 6/06, Aventis, after negotiations with the FDA, added a warning to the Ketek label. The new warning informs patients to discontinue use if signs or symptoms of hepatitis appear, which include fatigue, anorexia, nausea, jaundice or liver tenderness. Patients with a previous history of hepatitis, which affects the liver, are advised not to take the antibiotic.

In 3/06, SA West reported to FDA OCI Special Prosecution Staff that Kirkman-Campbell had recently alleged that Aventis was aware of the problems at her site. Information since obtained by the investigation has provided evidence that Aventis was aware of fraud at the Kirkman-Campbell site, yet provided this data to the FDA.

The investigation has found that PPD, Inc., the Contract Research Organization hired by Aventis to monitor Study 3014, had advised Aventis at problems at the Kirkman-Campbell site, including forged informed consent forms, altered patient records, possible blood-splitting, randomization of large numbers of patients in bulk during hours the office was closed to patients, and a lack of hepatic (liver) adverse events.

Despite these warnings, Aventis included the Kirkman-Campbell data in the NDA Amendment submitted in 7/02. In a 12/19/02 meeting with the FDA review committee, Aventis was asked about possible data integrity problems with Study 3014 and Kirkman-Campbell's site specifically. Aventis stated they were aware of problems at the Kirkman-Campbell site, but did not state why this data was not excluded. Aventis further stated that enrollment was stopped at the Kirkman-Campbell site when problems were discovered (Attachment 4). However, Robert McCormick, VP for Quality Assurance, PPD, advised the reporting SA that enrollment was stopped at two sites, but enrollment was not stopped at Kirkman-Campbell's site.

Problems were identified by PPD personnel who personally inspected the Kirkman-Campbell site, and by Dr. John Reynolds of PPD, who conducted lab reviews of Study 3014 data. The reporting Special Agent has obtained a number of e-mails that document the Kirkman-Campbell site was a concern to PPD and Aventis.

Dr. Reynolds lab reviews identified possible blood-splitting, randomization of large numbers of patients in bulk during hours the office was closed to patients, and a lack of hepatic (liver) adverse events. In 2/02, Reynolds identified the suspicious randomization of patients and reported it to PPD and Aventis (Attachment 5). The Interactive Voice Response System (IVRS) was used to randomize patients. IVRS was a telephone touch-tone system, into which the clinical investigator inputs patient data, and is then given a number to assign the patient and instructed which drug (Ketek or Augmentin) to give the patient.

Nadine Grethe was the Aventis project manager for Study 3014. On 2/25/02, 9:13 a.m., she e-mailed William Stager of Aventis. "We have a big concern with our highest enrolling site. They have research experience but there are questionable things (one of those sites where something smells funny but nobody can find anything definite). QA was there and felt the same way... if there is anything you can run on this list of enrollment that would be helpful that would be great...I just want to be sure as possible that there is no fraud here." Stager responds at that same day at 4:22 p.m., "Nothing strikes me other than the proficiency in using IVRS and the proportion of females..." (Attachment 6)

On 2/25/02, 5:36 p.m., Reynolds e-mailed Grethe regarding his analysis of lab work and stated, "I identified many pairs/trios of lab results which were so uniform to be potentially the same sample." (Attachment 7)

On 2/27/02, 10:05 a.m., Cathy Tropman, PPD, e-mailed Teresa Dunlap, PPD, "I asked Susan if she had someone in the stat group who could look at Kirkman Campbell's lab data... If they want to bill, we'll just convert a few CRA hours or something. I'm afraid Bill Stager may not look at it." (Attachment 7)

On 2/27/02, 3:15 p.m., Jessica Lasley of PPD e-mailed Grethe and Aventis employee Ranjan Khosla, and identified the following items of concern identified by their monitoring (Attachment 9):

- proper medical diagnosis to enter a patient in the study was lacking
- medical charts were very limited
- IVRS randomization (large number of patients randomized in a short time increment with most occurring when the office is closed for lunch and not seeing patients)
- Consent form anomalies including date modifications and signature inconsistencies
- Analysis of lab values for multiple patients suspiciously similar.

Grethe e-mailed a response on 2/27/02, 7:02 p.m., stating, "I agree we should we talk but could we please be very careful how we disseminate information on this site until we do. By then we will also have Bill's final analysis on the lab value. For randomization however there were no statistical issues. I just do not want people panicking before there is a need to." (Attachment 10)

A teleconference was subsequently held, and it was resolved that Aventis would audit the site and conduct further analysis. At this point, the reporting Special Agent has found no records or testimony from PPD that Aventis shared this analysis with PPD.

Additionally, the reporting Special Agent has interviewed PPD employees that visited the Kirkman-Campbell site. They reported that they identified questionable signatures and entries on medical charts, and pointed these out to Grethe. Additionally, they observed Grethe provide leading questions to

Kirkman-Campbell to address protocol deviations identified at her site, for example, "Did the patient tell you, but you forgot to write it down?" and "Did you randomize these patients in bulk, because you were out of study drugs?" They also allege that Grethe stated, "They (the patients) did not have to take the drug for the indication but they had to take the drug."

In 3/02, PPD employee Anne Marie Cisneros e-mailed Robert McCormick, PPD VP for QA, "Aventis wants to keep the 'forged' consent issue out of the f/u letter, however, I do have it noted on my trip report." McCormick responds, "I do not agree again with Aventis regarding the potential of inappropriate subject signature. At this point make sure that we retain the documentation and clearly document that Aventis required the removal from the follow-up letter." (Attachment 11)

The reporting Special Agent believes that testimonial and documentary evidence indicates that Aventis was aware of serious data integrity problems at the Kirkman-Campbell site, yet submitted this data to the FDA. When questioned by the FDA review committee, Aventis stated they had knowledge of problems, but did not explain why this data wasn't excluded from their submission nor did they explain why they didn't notify the FDA. Additionally, Aventis falsely claimed to have stopped enrollment at the Kirkman-Campbell site.

### **Applicable Statutes**

21 USC 331 (FD&C Prohibited Acts)  
18 USC 371, 1001, 1341, and 1343

### **Attachments**

- 1) Indictment
- 2) Plea Agreement
- 3) Judgment
- 4) Meeting Minute Notes, FDA – Aventis 12/19/02 meeting
- 5) Reynolds e-mail 2/20/02
- 6) E-mail chain – Reynolds, Master TREAT file, Grethe Stager, 2/20 – 2/25/02
- 7) Reynolds e-mail 2/25/02
- 8) Tropman e-mail 2/27/02
- 9) Lasley e-mail 2/27/02
- 10) Grethe e-mail 2/27/02
- 11) E-mail chain – Cisneros, McCormick 3/19/02