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OFFICE OF CRIMINAL INVESTIGATIONS
REPORT OF INVESTIGATION

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CASE NUMBER: 2006-TFM-709-0263
RELATED CASE NUMBER:
TYPE OF CASE: 709.100, APPLICATION FRAUD - CDER
CASE TITLE: AVENTIS PHARMACEUTICALS, INC. - KETEK
CASE AGENT: DOUGLAS LOVELAND
INVESTIGATION MADE AT: Multiple; See Text
INVESTIGATION MADE BY: Douglas M. Loveland
REPORTING PERIOD: FROM: 04/04/2007 TO: 06/28/2007
STATUS OF CASE: Closed

SYNOPSIS: Subject and Witness Interviews Completed, Prosecution Declined.

RESTRICTED INFORMATION

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REPORT SUBMITTED BY Douglas M. Loveland DATE: 07/17/2007
Douglas M. Loveland, Special Agent

REPORT APPROVED BY: Kim A. Rice DATE: 7/30/07
Kim A. Rice, SAIC

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1. INTRODUCTION:

This investigation was opened on 03/09/06 after AVENTIS PHARMACEUTICALS, INC. (hereinafter, "AVENTIS") submitted falsified data in a new drug application (NDA). This is the sixth ROI in this investigation.

On 02/28/00, AVENTIS filed NDA # 21-144 seeking approval of Ketek (telithromycin), the first antibiotic of the ketolide class, for various respiratory infections. Concerned about hepatotoxicity signals in reported Phase I and Phase III trials, and after seeking guidance from an advisory committee, FDA suggested AVENTIS conduct a phase III study to further assess adverse events associated with telithromycin.

AVENTIS conducted Study # 3014 from 10/19/01 to 05/14/02, enrolling, treating and analyzing the results from 24,137 patients at 1824 sites. In its final study report submitted to FDA 71 days later, AVENTIS represented that the trial had been conducted to good clinical practice (GCP) standards. Subsequent inspections by FDA's Division of Scientific Investigation (DSI) demonstrated that much of the data produced by the highest enrolling, most intensely monitored and audited sites were unreliable. DSI concluded that the integrity of the entire trial data could not be assured. An OCI investigation of the highest enrolling clinical investigator revealed that data from approximately 91% of her patients were falsified. Despite warnings by its own contract research organization (CRO), AVENTIS included all of the site's data in its study submission to the FDA in July 2002 and in a subsequent presentation before a second advisory committee meeting in January 2003.

FDA asked AVENTIS to provide support for the study data were reliable and submit foreign post-marketing data from Europe and South America, where the drug had been approved since 2001. AVENTIS did both, but FDA remained uncertain of the data's integrity. Eventually relying entirely upon foreign post-marketing data and clinical trials other than Study #3014,

2. DETAILS OF INVESTIGATION:

During this reporting period, OCI file number 2003-NEL-707-0040-J, regarding Dr. Anne Kirkman-Campbell, was reviewed. Several interviews were documented in that case file which are pertinent to the instant investigation. They are:

1. Anne Marie Cisneros, a Clinical Research Associate employed by PPD, was interviewed by SA Robert West on 02/17/03. Cisneros said she knew other PPD employees found indicators of fraud while monitoring Kirkman-Campbell's site during Study #3014, including rapid randomization of patients, randomizing patients when the office was closed and splitting blood samples. Cisneros herself participated in one monitoring visit at Kirkman-Campbell's site and found inadequate source documentation, problems with virtually every informed consent form and a possibly forged consent form. She said she discussed her findings with PPD and AVENTIS personnel. SA West's interview is memorialized in a Memorandum of Interview (MOI) which is copied into this case file by inclusion in this report (Attachment 1).
2. Nadine Grethe, AVENTIS' Study Manager for Study # 3014, was interviewed by SA West on 2/25/02. Grethe explained how she contacted Kirkman-Campbell to get her to respond to PPD monitors and what Kirkman-Campbell told her in response to questions and concerns raised by PPD. She said Kirkman-Campbell had plausible explanations for everything, and AVENTIS' statistician convinced her that Kirkman-Campbell was not splitting lab samples. She said that even though there were problems with Kirkman-Campbell's site, it was collectively decided to submit her data with the rest of the study. SA West's interview is memorialized in an MOI which is copied into this case file by inclusion in this report (Attachment 2).

3. Ranjan Khosla, MD, AVENTIS' Senior QA Specialist who audited clinical investigators throughout Study #3014, was interviewed by SA West on 02/25/02. Khosla said he audited Kirkman-Campbell's site and found the study coordinator was dating the informed consent forms and the office staff was enrolled into the study. Khosla said he made her report these and other irregularities to the Institutional Review Board (IRB), but AVENTIS did not communicate these issues to the IRB. He also noted that Kirkman-Campbell used the case report forms (CRFs) as source documents, which was not proper, and missed adverse events of specific interest to AVENTIS. He said he constantly provided training to Kirkman-Campbell during his two-day audit. SA West's interview is memorialized in an MOI which is copied into this case file by inclusion in this report (Attachment 3)..

4. Michael Shoemaker, AVENTIS' Head of Good Clinical Practices, was interviewed by SA West on 02/24/03. Shoemaker said that after Khosla's audit unveiled informed consent dating issues, he ordered the monitoring of Kirkman-Campbell's site increased. He said Khosla found and asked Kirkman-Campbell about randomizing patients in clusters, and she gave him a plausible explanation that had to do with study drug availability. He said AVENTIS prepared the FDA's Form 483 based upon what Kirkman-Campbell told them in a teleconference. SA West's interview is memorialized in an MOI which is copied into this case file by inclusion in this report (Attachment 4).

5. Michael Aschenbrenner, PhD., an AVENTIS Global Expert for Good Clinical Practices, was interviewed by SA West on 2/24/03. Aschenbrenner said before he participated in the pre-inspection visit to Kirkman-Campbell's site to help her prepare for the FDA inspection, he learned that PPD had some suspicions about her conduct in the study. He said AVENTIS thought the PPD analysis which suggested lab sample splitting was a statistical fallacy and he did not confront Kirkman-Campbell about any of the remaining concerns. He audited ten medical records and found symptoms which could be identified with acute sinusitis or chronic bronchitis. SA West's interview is memorialized in an MOI which is copied into this case file by inclusion in this report (Attachment 5).

6. Gerard Marini, PharmD, AVENTIS' North American Head of QA, was interviewed by SA West on 02/25/02. Marini said he asked Khosla to schedule an on-site audit of Kirkman-Campbell's site at the beginning of the trial. When Khosla returned, he underwent a peer review which resulted in several findings. With respect to the informed consent dating issue, they determined it should be handled with a memo to file and increased training at the site. They also determined she should be monitored more frequently because they thought she was sloppy and disorganized. SA West's interview is memorialized in an MOI which is copied into this case file by inclusion in this report (Attachment 6).

On 05/02/07 and subsequently, Christian Mahler, Esq., Chief Counsel for the DHHS Office of Research Integrity (301-443-2212) was telephonically contacted regarding what the Government's position is regarding when data lose their integrity. In a series of phone messages, Mahler said that data lose their integrity when there has been a significant deviation from accepted practices or protocol as determined by the sponsor of the research. He said there is normally a formal review process by the organization conducting the research that determines whether significant deviation from accepted practices or protocol occurred and whether such deviation(s) rendered the data unreliable.

On 5/3/07, _____ who requested confidentiality,

... identified specific allegations of fraud and scientific misconduct committed by Kirkman-
reported to AVENTIS during a teleconference on March 4, 2002.
identified a specific document _____ that PPD used to convey these concerns to AVENTIS

With respect to Nadine Grethe, the AVENTIS study manager, stated that when she gave the PPD monitors training at the start of the trial, she spoke derisively about the FDA and its request that AVENTIS conduct this study. For additional information provided by see SA Loveland's MOI relating to this interview.

A copy of the videotaped presentation Grethe gave to PPD at the outset of Study #3014, obtained by the previous case agent, was viewed. While introducing the protocol, Grethe emphasized that this study was to be conducted in the "usual care setting" in order to determine what safety issues arise in patients exposed to the drug the way it would occur after approval. At various times throughout the training session, Grethe made the following inaccurate statements: that the FDA required the trial be accomplished before it would approve the drug; that the FDA told AVENTIS that even one case of drug-induced hepatitis would result in the drug being denied approval to market, and that the only reason AVENTIS was going through "this turmoil" was because one patient in a Phase III trial experienced hepatitis which AVENTIS did not believe was drug related, but the FDA wasn't sure. However, each statement was made in the context of emphasizing why it was imperative that all adverse events be collected and promptly reported. No negative tone was noted and no derogatory comments concerning the Agency were made.

On 5/07/07, SA Loveland re-interviewed Nadine Grethe, now known as Nadine Knowles, regarding what AVENTIS knew about fraud allegations throughout the course of Study #3014. Knowles explained the decision-making process the AVENTIS study team used to determine whether data from Kirkman-Campbell's site should be used in the final study report. They decided that because safety data is non-evaluative, and is therefore less subject to misinterpretation or manipulation, it was more reliable than efficacy data. The team further decided that because the protocol required all adverse events experienced by anyone exposed to even one dose of the drug be reported, it was required. Finally, AVENTIS was afraid that if they didn't include the data on the grounds that it may have been produced by fraud, and it was later determined Kirkman-Campbell did not commit fraud, she could sue the company. Hence, they included the data because they suspected, but could not prove, that Kirkman-Campbell committed fraud. For additional information provided by Knowles, see SA Loveland's MOI relating to this interview.

On 5/9/07, Dr. Mathew Thomas, Division of Scientific Investigations (DSI), CDER (240-276-8825) was telephonically interviewed regarding whether monitors or sponsors' auditors routinely contacted patients during trials. Thomas said that across industry, it was not common practice for either group to contact patients because of various privacy concerns. He also said that IRBs rarely contacted patients, though there was no specific prohibition against it.

On 5/10/07, Sharon Hill-Price, President and CEO of The Copernicus Group Inc., (Copernicus), 118 MacKenan Dr, Suite 400, Cary, NC 27511 (919-465-4310), was interviewed. Copernicus was the IRB which oversaw the research conducted in Study #3014. Hill-Price denied receiving any notification from anyone, including Cisneros or the sponsor, about any misconduct or fraud during the course of Study #3014. She noted that the memos-to-file which PPD prepared for clinical investigators who committed protocol and informed consent violations arrived in "batches" after enrollment in the trial had ended, so nothing was done with them. She said Copernicus never contacts clinical research subjects, though some subjects call the IRB. She said monitors are best positioned to contact patients but don't have time to do so during their monitoring visits. For additional information provided by Hill-Price, see SA Loveland's MOI relating to this interview.

On 5/10/07, Dawn Pope, Copernicus' Director of IRB Services, was interviewed. Pope said her only concern about Study #3014 was that the safety reports arrived at the IRB in batches, causing the staff to

get backed up. She said no sites were terminated after the study began enrolling, but affirmed that some clinical investigators were denied entry into the study prior to the start of patient enrollment. Pope said her points of contact at PPD were Teresa Dunlap and Phaedra Logan. The only contact between Copernicus and AVENTIS was between herself and Nadine Grethe, and these contacts had to do with protocol approval before enrollment started. Once the trial got underway, no contact occurred between AVENTIS and Copernicus.

On 5/14/07, this matter was coordinated with Dr. Gary Della'Zanna, Director, DSI (240-276-8819). Della'Zanna stated that he had considered conducting an inspection at AVENTIS to support seeking an Application Integrity Program (AIP) finding against AVENTIS, but was advised that this case would not be strong enough to warrant an AIP. He said he is contemplating seeking a warning letter against the firm for its submission of Kirkman-Campbell's data to the FDA. With respect to information provided by Knowles and Cisneros about how safety data are by nature more reliable than efficacy data and may be submitted on some occasions when efficacy data wouldn't be, Della'Zanna agreed, stating "They have a point there."

On 5/16/07, a representative of the Division of Corporations, Office of the Secretary of State, State of Delaware provided the corporate status of AVENTIS PHARMACEUTICAL, INC., and SANOFI-AVENTIS. According to Delaware's records, both corporations are active and in good standing.

On 05/17/07, Ann Begley, an attorney with Kirkpatrick & Lockhart Preston Gates Ellis LLP (202-778-9365) advised via letter that her law firm represented Copernicus and asked that any further contact between the Government and Copernicus be made through her office. A written request for the IRB's documents regarding Kirkman-Campbell was sent to Begley on 05/22/07 and the documentation arrived on a CD-ROM shortly thereafter. The documents did not contribute to this investigation and the CD-ROM was returned to Begley on 06/25/07.

On 05/22/07, Dr. Marjorie Spears, Executive Director of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) 915 15th Street NW, Suite 400, Washington, DC 20005 (202-783-1112) was telephonically interviewed regarding whose responsibility it was to establish whether patients truly exist in a study. AAHRPP, a closely held corporation, is the only body which accredits IRBs and other organizations involved in human subject research. Spears said the role of an IRB is to review the protocol and determine if everything is in place to protect research subjects. It can approve, disapprove, suspend or terminate research. She said an IRB does not monitor a study nor look at data to determine if the protocol was followed or the data are valid. She added that an IRB has the authority to monitor the conduct of research, but that is actually a function of the study monitor. Spears said if anyone should be checking the bona fides of a patient, it should be the monitor.

Spears said that AAHRPP accreditation standards call for the accredited organization (the IRB) to have a written agreement with the sponsors of human research which requires a "sponsor promptly reports to the [IRB] findings that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study." She said sponsors across the industry won't do it, and it has been a source of deep concern at AAHRPP. She said this standard is written on AAHRPP's website (see Standard IV-2, Element IV.2.A of Attachment 7).

Asked if she was aware of any monitoring organization or CRO which actually checks the existence and bona fides of a patient or a percent of patients in a trial, Spears said she did not know of anyone who did that. She said it would have to be something negotiated at the beginning of the trial and the patient would have to be informed that a study monitor may be contacting them.

Spears was informed of the specific circumstances found in the Kirkman-Campbell case. She said that if the IRB was notified of protocol violations after the trial had closed, there was nothing it could have done about them. She also noted that this occurred in early 2002, before such events were considered reportable to IRBs as an unanticipated problem. Informed that the only way the fraud was proven at Kirkman-Campbell's site was to physically and personally contact the patient population, Spears interjected, "You're talking about changing the entire industry." She said AAHRPP is coming up against a lot of opposition to changing the status quo.

On 05/22/07, Charles Cooper, MD, Office of Biostatistics, CDER (301-796-0698) was telephonically interviewed regarding the post-marketing data upon which FDA relied to approve Ketek. Cooper was the safety officer who reviewed the second NDA cycle for Ketek. He said that when AVENTIS provided the first batch of foreign post-marketing data, most prescriptions were written in Germany and Italy. Shortly thereafter a second, larger batch of data was received in which Germany and France had the highest number of prescriptions written. Although some adverse events were reported in Germany and France, there was a problem with data from Italy, which Cooper thought may have involved the way data were coded. He recalled that little data seemed to be produced in that country, but he didn't know why. Conversely, he said Germany and Brazil seemed to produce the most data.

Cooper described the way foreign data are collected. He said that the sponsor collects the data in the language spoken in the country from which the data are produced. The sponsor then translates the report into English and provides a summary, narrative or translation of the report to FDA. He said he wouldn't know how to go about trying to verify the accuracy of the data because, among other things, even the translations of the foreign language reports could be subject to interpretation. However, he said he had no reason or evidence to doubt the veracity of the foreign post-market data.

Cooper also said that when AVENTIS submitted Study #3014 to FDA, they should have notified the agency that it had suspicions about the integrity of data produced at Kirkman-Campbell's site and allowed the agency to determine whether or not the data should be included. He said other sponsors do this routinely and he didn't understand why AVENTIS did not. Cooper dismissed AVENTIS' fear of being sued by Kirkman-Campbell. By not so advising FDA, Cooper said AVENTIS was "trying to slip one past us." He said the company seemed to be more cooperative after the second advisory committee.

On 05/29/07, AVENTIS legal counsel Glenn Forrester and Heidi Allen (908-981-6900) were contacted to arrange for interviews of current AVENTIS employees William Stager, Ranjan Khosla, Gerard Marini, Michael Aschenbrenner, Michael Shoemaker and Roomi Nusrat. Forrester and Allen advised that AVENTIS wanted to cooperate with the instant investigation and is represented by outside counsel with respect to the Ketek issue. They made arrangements for outside counsel to contact OCI.

On 05/29/07, Attorney Dan Kracov, a partner in the law firm of Arnold and Porter and head of its regulatory affairs section (202-942-5120), telephonically advised that because of domestic and international travel as well as a maternity leave, only one interviewee was immediately available. He promised to facilitate interviews later in June. Kracov was also asked to provide a copy of AVENTIS' standard operating procedure (SOP) GREGU-QAC-PR-01-01, "Scientific Misconduct and Fraud."

On 05/29/07, Dr. Gary Della'Zanna and Assistant Division Director Joseph Salewski, DSI, were contacted regarding whether the FDA had ever communicated to industry a desire that sponsors formally or informally notify the Agency when they suspect, but cannot prove, that a clinical investigator engaged in fraud as was related by Cooper (above). They said that the only obligation to notify FDA of clinical investigator fraud exists in ICH E6 "Good Clinical Practices" guidelines, which have been adopted by FDA as guidance to industry. ICH E6 states that a sponsor should notify the regulatory agency when an

investigator's or institution's participation is terminated because of non-compliance (See: ROI #5, Attachment 9). Moreover, a federal regulation requiring sponsors notify FDA when they determine fraud was committed during the course of clinical research was proposed five years ago and is still pending final approval.

On 05/30/07, Kracov provided AVENTIS' SOP relating to Scientific Misconduct and Fraud in PDF form (Attachment 8). A review of the seven-page SOP revealed that a specific procedure was to be followed when fraud was suspected in any clinical trial in which AVENTIS was involved. The initiator was to verbally notify supervisors and QA, followed by a "strictly confidential" (emphasis in the original) report to the same recipients. Within four days, a meeting was to occur between the initiator, the Medical Director and QA upper management at which a decision should be made whether to conduct an investigation. If this group decided that an investigation was not necessary, a confidential memo to the file was to be prepared and maintained in QA files. If the group decided that an investigation was necessary, it was to be expeditiously accomplished and a written confidential report prepared. The threshold for action was whether it was "determined that there is a reasonable possibility that scientific misconduct [had] occurred." A report would then be generated to several department heads, decisions taken regarding termination of the investigator and re-evaluation of the data. Alternatively, "if the involved parties agree, based upon the investigation report, that suspected Fraud/Scientific Misconduct is not confirmed," a written final confidential report which "describes the situation, the investigation plan and results including an explanation of why fraud is not confirmed" is required. At the SOP's Appendix 2, a visual flow chart details the process and decision-making point.

On 6/12/07, Kracov supplemented the AVENTIS Fraud and Scientific Misconduct SOP with a one-page document labeled GREGU-QAC-SD-01-01, "Methods for Detection of Fraud or Scientific Misconduct" (Attachment 9). The list suggests 13 fraud indicators that "may be utilized" to detect fraud. Kracov was re-contacted and asked for copies of whatever reports were created with respect to Kirkman-Campbell under the provisions of this SOP. Kracov agreed to make them available on 6/18/07 prior to any subject interviews.

On 06/18/07, Kracov, accompanied by Arnold and Porter attorneys Brandi A. Kupchulla and Arthur N. Levine, as well as AVENTIS in-house counsel Heidi Allen, gave a presentation regarding AVENTIS' oversight of Kirkman-Campbell's participation in Study #3014. With respect to how the firm complied with its SOP following PPD's February 27, 2002, request for a teleconference to voice its monitors' concerns about Kirkman-Campbell, Kracov provided a number of documents which he contended showed that AVENTIS followed its SOP. First, AVENTIS QA held a meeting on March 4, 2002, and minutes were taken (Attachment 10). Kracov said that the minutes reflect AVENTIS received all of the allegations and identified three essentially separate tasks to be undertaken which would either confirm Kirkman-Campbell engaged in scientific misconduct or show that she did not. The first task was for William Stager, the project biostatistician, to do a statistical analysis to see if PPD's allegation that Kirkman-Campbell engaged in splitting blood samples was accurate. The second task was to ask Kirkman-Campbell for explanations for a number of protocol and informed consent violations the monitors found, as well as how she rapidly randomized patients. The third task was to increase the monitoring at Kirkman-Campbell's site. QA decided that once all of these actions had been taken, they could then decide whether to confront Kirkman-Campbell with the allegation that study subject #249's signature was forged.

Kracov said that with respect to Stager's statistical analysis, on March 14 and June 3, 2002, Stager produced two versions of his report (collectively appended at Attachment 11) that compared lab values from Kirkman-Campbell's site with those of two other high-enrolling sites. The analyses showed there was little variation and the team thought those analyses resolved the allegation of sample splitting.

Kracov said that through PPD, AVENTIS then queried Kirkman-Campbell on March 18, 2002, about the protocol and informed consent violations which monitors found during their February monitoring visit to Kirkman-Campbell's site (Attachment 12). Although Kirkman-Campbell did not respond directly to this letter, PPD created a series of memos-to-file which individually address these issues and Kirkman-Campbell provided answers on the memos during the April monitoring visit. The memos addressing low adverse event reporting, overwrites on original records, informed consent irregularities and rapid randomization, all bearing Kirkman-Campbell's explanations, are appended at Attachment 13.

Kracov said that in April, PPD and AVENTIS' Study Manager Nadine Grethe co-monitored Kirkman-Campbell's site, during which time the memos (above) were answered and signed. Newly discovered protocol violations were addressed in subsequent memos-to-file. According to Kracov, this completed the third task set forth in the action plan agreed upon in March, and QA then asked PPD on June 5, 2002, to address the matter of study subject #249's signature with Kirkman-Campbell (Attachment 14). PPD did so later that day by creating a memo-to-file documenting the finding and asking Kirkman-Campbell to put in an explanation (Attachment 15). On June 17, 2002, Kirkman-Campbell submitted the memo back to PPD with the notation, "Question regarding the signature of pt n 248. Message left at work and multiple attempts to call pt at home - no answer. Will continue to try and reach pt" (Attachment 16). Kracov said that in October 2002, AVENTIS QA personnel Ranjan Khosla and Mike Aschenbrenner conducted an inspection preparation visit to Kirkman-Campbell's site and determined during that visit that the signature really was patient #249's.

Kracov said that as the results of the above taskings came back in, the Ketek study team made a collective decision that fraud was not confirmed and the data were left in the clinical study report. AVENTIS Counsel Heidi Allen said, "It did not look like fraud to our people."

Kracov was asked for a copy of the final investigative report required by section 4.3.1 of the AVENTIS SOP was (refer back to page 4 of Attachment 8). He said no such final report was ever written. Because that report is the basis for deciding that fraud or scientific misconduct either did or did not occur, Kracov was then asked how AVENTIS made the decision that fraud was not committed. He said the documents (above) were collectively used to base an opinion upon. Since the decision was made that fraud had not been found to be a reasonable possibility, Kracov was asked for a copy of the written final report describing the situation and having an explanation as to why fraud was not confirmed, as was required by section 4.3.4 of the SOP. He said that report was also never written.

Kracov provided a copy of AVENTIS' QA organizational chart in effect at the time (Attachment 17). They show that Khosla, a QA auditor, worked for Gerard Marini, who was the manager of the Audits branch. Marini reported to Mike Shoemaker, who was the head of Global GCP QA for AVENTIS at the time. Michael Aschenbrenner was the Global GCP expert who also answered directly to Shoemaker.

On 06/18/07, William Joseph Stager, AVENTIS' study biostatistician assigned to Study #3014, was interviewed at AVENTIS' Bridgewater, NJ offices. Stager was represented by attorneys Kracov, Levine, Allen and Kupchella. After acknowledging that his participation in the interview process was voluntary, Stager said that he originally intended to see if lab values for supposedly unique patients were similar from Kirkman-Campbell's site, but he could not find a definition for "similar." He then decided to compare the inter-day and intra-day lab values between Kirkman-Campbell's site and two other high enrolling sites. He did not find a great deal of variance and so notified the team. He did not expect them to take his findings as the definitive answer to the issue. As to Kirkman-Campbell's practice of rapid randomization, Stager said he looked at the IVRS data using a digit preference analysis in the dates of birth. Not finding one, he was unable to opine that she was doing anything amiss. He assumed

monitoring would actually uncover any scientific misconduct and his analyses would only be used to support the monitors' findings. For additional information provided by Stager, see SA Loveland's MOI documenting this interview.

On 06/19/07, Keith Michael Shoemaker, then AVENTIS' Head of Global Clinical QA and Compliance, was interviewed at AVENTIS' Bridgewater, NJ offices. Shoemaker was represented by attorneys Kracov, Levine, Allen and Kupchella. After acknowledging that his participation in the interview process was voluntary, Shoemaker explained how the Study #3014 team had monitoring and auditing plans, executed the plans as written and reported the results properly. He said their investigation of PPD's concerns about Kirkman-Campbell did not uncover any indications or signals of fraud. Shoemaker said that at the time, AVENTIS did not have access to fraud investigators to handle clinical trial fraud complaints and SANOFI-AVENTIS still doesn't. Nonetheless, he believes monitoring and QA auditing processes at SANOFI-AVENTIS are "solid." For additional information provided by Shoemaker, see SA Loveland's MOI documenting this interview.

On 06/19/07, Gerard Marini, PharmD, then AVENTIS' Head of Good Clinical Practices North America, was interviewed at AVENTIS' Bridgewater, NJ offices. Marini was represented by attorneys Kracov, Levine, Allen and Kupchella. After acknowledging that his participation in the interview process was voluntary, Marini said AVENTIS saw no difference between GCP and usual care setting trials because GCP was flexible enough to incorporate less structured trials. He described the process of collecting additional data from Kirkman-Campbell's site and engaging in statistical analyses in an effort to determine whether misconduct had occurred, but each indicator was individually interpreted as being unable to confirm fraud existed. Because there was only one allegation of a forged signature, Marini did not believe it was forged because no one would forge only one signature when there were 407 patients in a trial. For additional information provided by Marini, see SA Loveland's MOI documenting this interview.

On 06/19/07, Karl Michael Aschenbrenner, PhD, then AVENTIS' Global GCP Expert, was interviewed at AVENTIS' Bridgewater, NJ offices. Aschenbrenner was represented by attorneys Kracov, Levine, Allen and Kupchella. After acknowledging that his participation in the interview process was voluntary, Aschenbrenner said he thought each of the four topic areas identified in the action plan attached to the teleconference meeting minutes (refer back to page four of Attachment 10) were individually resolved. He thought Stager's variance analyses addressed the allegations about lab sample splitting; that Kirkman-Campbell's explanation for the rapid randomization was sufficient; and that the protocol and informed consent deviations were adequately addressed in the memos-to-file prepared by PPD and signed by Kirkman-Campbell. He said he personally looked at the suspected forged signature and determined that, because it appeared to be so dissimilar to the patient's known signature in medical files, that it could not possibly be an attempted forgery. For additional information provided by Aschenbrenner, see SA Loveland's MOI documenting this interview.

On 06/20/07, Ranjan Khosla, BCCS, MD, AVENTIS' Audit Specialist assigned to Study #3014, was interviewed at AVENTIS' Bridgewater, NJ offices. Khosla was represented by attorneys Kracov, Levine, Allen and Kupchella. After acknowledging that his participation in the interview process was voluntary, Khosla detailed his education, stating that he had no fraud detection training and neither did anyone else at AVENTIS. He described how he first audited Kirkman-Campbell's site and recommended increased monitoring and training. When PPD's concerns about her trial activity surfaced, he described AVENTIS' efforts to get more information. When told that approximately 91% of Kirkman-Campbell's patients were thought not to have existed as legitimate study subjects, he noted that with trust comes the opportunity for betrayal. Khosla said that out of 1824 sites, only 18 were found to have significant GCP issues, or

only 1% of the study total. He said the study was powered highly enough to account for that level of deviation. For additional information provided by Khosla, see SA Loveland's MOI documenting this interview.

On 06/20/07, Roomi Nusrat, MD, PhD, AVENTIS' Study Director assigned to Study #3014, was interviewed at AVENTIS' Bridgewater, NJ offices. Nusrat was represented by attorneys Kracov, Levine, Allen and Kupchella. After acknowledging that his participation in the interview process was voluntary, Nusrat said he joined AVENTIS after Study #3014 was already underway and was appointed its new study director. He tried to keep up with team meetings but quickly began focusing on the adverse events of significant interest (AESIs). He knew generally about allegations surrounding Kirkman-Campbell, but thought they had been resolved by the study team. He did not participate in discussions about including or excluding data from Kirkman-Campbell's site in the clinical study report, but thought that the data were reliable when he signed it. He reiterated that his primary concern as study director was to ensure each AESI was thoroughly documented, reviewed and reported to FDA. He said it cost AVENTIS slightly more than \$50 million to conduct the study. For additional information provided by Nusrat, see SA Loveland's MOI documenting this interview.

On 06/20/07, Kracov telephonically confirmed that AVENTIS spent approximately \$50 million in external costs conducting Study #3014, and even more both in internal costs and in its subsequent defense of the study.

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On 06/22/07, DSI Director Gary Della'Zanna was telephonically briefed as to the outcome of the AVENTIS interviews. Specifically, Della'Zanna was told that individually and collectively, the AVENTIS' clinical study personnel and QA officials (1) lacked the training and ability to identify basic fraud indicators either in clinical trials or when presented with them during an interview; (2) did not have access to a fraud-trained resource to assist them when an allegation of fraud arose in a clinical trial; (3) did not have a basic armamentarium of fraud investigation methodologies; and (4) failed to properly document their collective findings concerning Kirkman-Campbell, which resulted in their further misinterpreting the signs and signals arising from Kirkman-Campbell's site and those of other high enrollers. Of particular note, AVENTIS has not instituted any fraud training or awareness in its monitoring or QA processes since study 3014 was concluded in 2002, suggesting the firm's ability to detect fraud is no better than it was in 2002.

On 06/28/07, Janice Soreth, MD, Director, Division of Anti-Infective Drug Products (DAIDP), CDER, and members of her staff were briefed as to the outcome of this investigation. In addition to what was provided to DSI (above), DAIDP management and personnel were further provided with the pattern of how the data were falsified, how the monitoring and auditing failed to interpret the fraud indicators, and how AVENTIS' clinical study personnel and QA officials relied upon an ineffective monitoring and audit plan. DAIDP was further advised that SANOFI-AVENTIS has not instituted any fraud training or awareness in its monitoring or QA processes.

3. JUDICIAL ACTION:

None this reporting period.

4. DISPOSITION OF EVIDENCE, CONTRABAND, AND PERSONAL PROPERTY:

None this reporting period; no evidence was taken during the course of this investigation.

5. STATUS OF INVESTIGATION:

Closed.

6. SUSPECTS/DEFENDANTS/OTHER:

Aventis Pharmaceuticals, Inc. (SHF previously submitted)

7. ATTACHMENTS:

1. Cy of SA West's MOI re: Cisneros, 02/17/03
2. Cy of SA West's MOI re: Grethe, 02/25/03
3. Cy of SA West's MOI re: Khosla, 02/25/03
4. Cy of SA West's MOI re: Shoemaker, 02/24/03
5. Cy of SA West's MOI re: Aschenbrenner, 02/24/03
6. Cy of SA West's MOI re: Marini, 02/24/03
7. Cy of AAHRPP Accreditation Standards, downloaded 05/22/07
8. Cy of AVENTIS SOP GREGU-QAC-PR-01-01, 10/20/00
9. Cy of AVENTIS' Fraud Detection Sheet, 10/20/00
10. Cy of Teleconference Meeting Minutes, 03/04/02
11. Cy of Stager's Lab Data Variance Analyses, 03/14/02 and 06/03/02
12. Cy of PPD letter to Kirkman-Campbell, 03/18/02
13. Cy of Memos-to-File, Kirkman-Campbell, 04/19/02
14. Cy of Khosla e-mail re: Forged Signature, 06/05/02
15. Cy of PPD fax re: Forged Signature, 06/05/02
16. Cy of Kirkman-Campbell's response to Forged Signature Question, 06/17/02
17. Cy of AVENTIS QA & Compliance Org Chart, 01/13/03
18. _____



Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
MEMORANDUM OF INTERVIEW

CASE NUMBER: 2003-NEL-707-0040
CASE TITLE: DR. ANNE K. CAMPBELL
DOCUMENT NUMBER: 71378
PERSON INTERVIEWED: Anne Marie Cisneros
PLACE OF INTERVIEW: Morrisville, NC
DATE OF INTERVIEW: 02/17/2003
TIME OF INTERVIEW: 2:24 PM to 4:25 PM
INTERVIEWED BY: SA Robert J. West

OTHER PERSONS PRESENT: None

Ann Marie Cisneros, BS, MT, CRA was advised that she was being interviewed since she was one of the monitors for PPD, Inc., who had a contractual agreement with Aventis Pharmaceuticals to monitor the Ketek clinical trial.

Cisneros stated that she worked for PPD, Inc., from 1999 until 2002. She related that she was the Senior Clinical Research Associate (SCRA) for PPD, Inc. at the time of the monitoring visits conducted at Dr. Anne Kirkman-Campbell's clinic. She related that when she visited Campbell's site in February 2002, she was accompanied by Beth Hedging, CRA and Stephanie Love, CRA. She related that her observations were documented based on documentation she retrieved from the site, trip reports, follow up letters, and general correspondence located in the files at PPD. Prior to the visit, Cisneros knew that Dr. Campbell enrolled over 400 patients and that she had just been audited by Ranjan Khosla, QA at Aventis. According to Cisneros and based on the sponsor's audit, she was informed that several Informed Consent issues were noted as well as a significant under-reporting of Adverse Events and no reported Serious Adverse Events.

Cisneros was also told that Dr. Campbell enrolled primarily Acute Sinusitis (AS) patients until randomization of those subjects was no longer allowed. Once Campbell exhausted the enrollment of AS patients, she subsequently enrolled a large number of Acute Exacerbation of Chronic Bronchitis (AECB) patients. Cisneros stated that prior to her visit, she was instructed by Ranjan Khosla to scrutinize the Case Report Forms (CRF's) and consents for those AECB patients.

Cisneros further stated that prior to her site visit, she met with Abby Wear, site management CRA for Dr. Campbell and John Reynolds, MD in charge of reviewing lab values for all sites in the study. She related that during her discussions with Wear, she was told by her (Wear) that she was concerned with how Campbell randomized patients within minutes of each other and upwards of 10 patients per day. In addition, Wear told Cisneros that Campbell's office is closed 2 hours a day and closed on Wednesdays. According to the Interactive Voice Response System (IVRS), Dr. Campbell enrolled patients within this time period as well as on Wednesdays. John Reynolds provided Cisneros with a spreadsheet that he prepared which listed all lab values that had similar results for different patients. According to Cisneros, Reynolds suspected that Campbell had been splitting blood samples.

Cisneros continued by saying that according to PPD/Aventis contract, it was a requirement that PPD monitor 25% of all randomized patients which amounted to 100 patients. As requested by Aventis, PPD personnel were only to review the informed consents that were not reviewed at the recent QA audit. She related that

ATTACHMENT

they (PPD) reviewed approximately 100 informed consents and from what she can remember, there was an issue with each of the consents reviewed. She related that several consents looked as if the consent pages were initiated by someone other than the patient.

Cisneros said that this was the case for subject 361, subject 388/ subject 335/ and subject 333/ She felt that the subjects were signing the back page of the consent form and someone else was initialing the other pages. She also felt that the signature on the Informed Consent Forms for subject 249/VGS appeared to be forged. She said that this subject's signature and date matched the study coordinators handwriting in the chart. Cisneros also provided her observations regarding the below listed study subjects enrolled in the study:

Subject 077/ The Subject was an and from the subject's medical record; it appears the subject resides in a nursing home. This subject signed, but did not date her own consent. The subject was diagnosed with AECB; however, the subject did not have a history of bronchitis. The subject was also allergic to penicillin which was exclusion for the study.

Subject 361. The Subject's medical chart consisted of 3 pages. The pages consisted of the subject's name, date subject was randomized, and date drug dispensed.

Subject 333/ - The Subject's medical chart consisted of 2 pages. The day of visit 1 was changed from 1/17/02 to 01/18/02. The subject was being seen for a follow up for hypertension; however, in different ink someone wrote sinus congestion x 2 days.

Subject 272/ ' The Subject was randomized in the IVRS and the day of visit 1 on the CRF occurred on 1/16/02, however the consent was signed and blood sent on 01/09/02. The source document does not indicate a visit on 01/09/02, however the subject had labs drawn (not study related) on 01/08/02. In the medical chart there is documentation of a visit occurring on 01/08/02, however that date was changed via overwrite to 01/16/02. The lab results from 01/08/02 are similar to those sent to Covance Laboratories on 01/09/02. Not all the dates were changed via overwrite, so it was hard to establish when this patient was actually seen. It was Cisneros' opinion that this patient was seen on the 8th which was probably their visit 1 date and when the patient signed the consent.

Subject 077. - Subject was seen on 11/30/01 for feet and ankle swelling. In a different pen, chest congestion x 3days was marked on the form and Acute Exacerbation of Chronic Bronchitis indicated. The subject's physical exam was normal in the respiratory section and the medical records reflect that the respirations were even and unlabored, clear/equal sounds bilaterally, lung fields no flatness, dullness or hyper resonance. The subject did not have a history of bronchitis.

Subject 405/ - The day of visit 1 for the study was the first time this patient had been seen in the office. The subject's chief complaint was back pain; however, in different ink in the middle of the medical history page, chest congestion 2-3 days was written. The subject was diagnosed with AECB, however, did not have a history of bronchitis.

Cisneros continued by saying that subjects 312, 361, 344, 355, 300, 263, 223, 196, 359, 407, 405, 393, 188, 161, 135, 077 and 063 were diagnosed with AECB, however they had no history of bronchitis or at least a limited history that did not meet the "chronic" definition. She related that while at the site she called Ranjan Khosla at Aventis, Melinda Edwards, Project Manager at PPD and Jessica Lasley, Associate Director at PPD to inquire about the eligibility of all the patients that were diagnosed with AECB that did not have any history of bronchitis. She was told by all three that Aventis was not concerned about medical history in terms of the diagnosis. She related that she does not know if this concern or the lack thereof is documented anywhere in the PPD files. Cisneros stated that she expressed her concerns over whether these patients actually met the criteria to be in the study.

Cisneros stated that she observed other interesting trends in which patients enrolled and/or monitored were 100% compliant with taking study medication. She further stated that according to documentation, there were no out of window visits and no subjects that were lost to follow up or early termination. She further noticed that there were no reported serious adverse events.

Cisneros stated that after 2 days at Campbell's site, she called and spoke with the President of Copernicus IRB to inform them of the number of informed consent violations that occurred at the site. She stated that during her conversation with the IRB, she discussed her concerns about Dr. Campbell. She inquired with the IRB as to what action they might want her to take while at the site. She said the President of the IRB seemed concerned about her findings, but stated that she wanted to wait to see what Aventis was going to do about the situation. Cisneros stated that she never spoke with the IRB again since she left the company shortly after this monitoring visit. She further related that the IRB should have received written documentation of all the protocol violations that occurred at Campbell's site.

Cisneros stated that during her site visit, she was extremely nice and cooperative with Campbell in an attempt to get her to feel comfortable around her and maybe reveal how she randomized such a large number of patients. Campbell told her that at the beginning of the study she inquired as to the maximum number of patients she could enroll which was approximately 400. Cisneros stated that there was an e-mail that circulated about the number of patients that could be enrolled at each site as calculated by statisticians at Aventis. Campbell told Cisneros that if she had known she was going to be the target of so many audits she wouldn't of enrolled so many patients. Campbell asked Cisneros questions about the FDA and what potentially could happen to her if she was audited. She further stated in repeated conversations with Campbell if she could get her into other studies at PPD. She called Melinda Edwards, her Project Manager at PPD and asked her the same question proposed by Campbell. Cisneros stated that she does not know if Edward attempted to assign Campbell another study.

Cisneros further related that at one point, Campbell was not going to allow her stay another day to monitor. Campbell told Nadine Guenthe, Project Manager, Aventis, that the only way she would let Cisneros stay additional days to monitor was if Nadine Guenthe could get her in a diet study that was being conducted by Aventis. According to Cisneros, Nadine Guenthe agreed to assign her another study; however, she does not know whether Nadine Guenthe followed through with that promise. Cisneros also stated that Campbell continuously inquired on what the average amount of money most studies paid per patient. She stated that Campbell repeatedly called her at PPD after returning from her site inquiring about getting her into other studies.

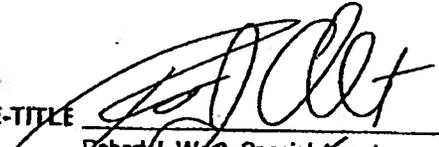
Cisneros stated that before leaving Campbell's site, she was encouraged by PPD to bring back documentation which would confirm her suspicions. She was further asked not to speak with Dr. Campbell about the findings due to fear that she would alter the documents. Cisneros stated that after she returned to her office, she e-mailed a summary of her findings to Robert McCormick, head of QA at PPD. She further stated that she sent the same e-mail to Aventis personnel. She further stated that subsequent to her site inspection, she participated in a teleconference between PPD and Aventis to discuss findings at Campbell's site.

Cisneros stated that she left PPD to pursue another position shortly after the teleconference with Aventis. She said that there was rumors around the office that Robert McCormick, PPD QA had received an e-mail indicating that Aventis would be taking over in dealing with the problems at Campbell's site. She further stated that she was told by Beth Heding that Nadine Guenthe said "I don't care if the patients take the drug as long as they receive the drug." She further stated that when Nadine Guenthe was at Campbell's site, Nadine Guenthe was filing out adverse event forms and other documentation required by the study. She also stated that if she asked Campbell a question, which she (Campbell) could not answer, Nadine Guenthe would propose the same question but in a leading question format. She felt that Nadine Guenthe did this so Campbell would know how to answer the question.

Cisneros stated that the following PPD and Aventis personnel were involved with Campbell's site:

Beth Heding, CRA
Stephanie Love, CRA
Christianne Hammond, Sr. CRA
Abby Wear, CRA
Kim Reed, CRA
John Reynolds, MD
Cathy Tropman, Associate Director

Robert McCormick, Head of QA
Melinda Edwards, Project Manager
Roxanne Evans, Project Manager
Jean Noone, Project Manager
Ranjan Khosla, Aventis QA
Nadine Guenthe, Project Manager, Aventis

NAME-TITLE 
Robert J. West, Special Agent

NAME-TITLE _____

DATE 2/28/03

DATE _____

APPROVED: 
Michael S. Niemiec, Resident Agent in Charge

DATE: 03/06/2003

DISTRIBUTION: NEL: Original and 1 cc
MIF: 1 cc
IOD: 1 cc

ATTACHMENTS: None



Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
MEMORANDUM OF INTERVIEW

CASE NUMBER: 2003-NEL-707-0040
CASE TITLE: DR. ANNE K. CAMPBELL
DOCUMENT NUMBER: 72012
PERSON INTERVIEWED: Nadine Grethe
PLACE OF INTERVIEW: Aventis Pharmaceuticals, Bridgewater, NJ
DATE OF INTERVIEW: 02/25/2003
TIME OF INTERVIEW: 10:45 AM to 11:50 A
INTERVIEWED BY: SA Robert West

OTHER PERSONS PRESENT: See Below

Grethe was advised that she was being interviewed because of her direct involvement in the clinical trial conducted by Dr. Anne Campbell.

Grethe was interviewed at the headquarters for Aventis Pharmaceuticals, Bridgewater, NJ and in the presence of Colleen Hickey, Thomas Valen and Lawrence Lustberg, Attorneys for Aventis. She stated that she has been working for Aventis for about 5 years. She stated that for protocol 3014, she was the Study Manager. She had the responsibility for working with the Clinical Research Associates (CRA) and making sure the study was on track. She also assisted in analyzing the budget before the study started.

Grethe related that there was 1824 Principle Investigators (PI) along with 24,562 study subjects. She related that Dr. Campbell was one of the PIs involved in conducting the clinical trial. Grethe stated that she was not involved with any of the previous studies of Ketek, which was the new drug being evaluated during the study being conducted by Campbell and the other PIs.

Grethe stated that she did not have any contact with Campbell until the 1st audit. She stated that she was notified by monitors employed by PPD Development that they were having difficulty with Campbell in that she was not answering queries prepared by them. She said that she contacted Campbell and during this conversation, Campbell inquired about additional studies even though the paperwork for the on-going study had not been completed to their satisfaction.

Grethe continued by saying that she does remember that one of the monitors explained that Campbell would not allow them to stay longer to monitor unless Campbell obtained additional studies. She related that she told Campbell that if she did a good job with the on-going study, her name would be considered for additional studies. She denies ever telling the monitors that she promised Campbell additional studies if she would allow the monitors additional days for monitoring.

Grethe related that she went to Campbell's site in April 2002 for the sole purpose of making sure the required paperwork was being completed correctly and in accordance with the protocol. Grethe said that while she was there, she questioned Campbell on how she randomized the patients and the lack of Adverse Events reported by Campbell.

Grethe was questioned on whether or not she made the following comments "I don't care if the patients take the drug as long as they take the drug." or "I don't care if the patients take the drug for the indications as long

as they take the drug." She denied making the first comment but admitted to making the comment relating to taking the drug for the indications. She said that she made this comment but it was taken out of context. She related that after making this comment she explained that it was very important for the patient to take the drug because this study was evaluating the safety of the new drug. She said that she explained that the safety data was the only data being evaluated. She explained to the monitor, who she made the comment to, that taking the drug for the indications was important; however, the efficacy of that data was not. She said that this data was not being evaluated so the efficacy portion of the study was not their primary concern. She said that the comment was made to one of the monitors while they were conversing within Campbell's clinic.

Grethe was further questioned on whether or not a study subject had to have a documented history of chronic bronchitis. She said that a history of bronchitis could be satisfied by having the patient verbally acknowledge the fact he/she had suffered from bronchitis in the past. She said that even though there was no history documented, it was satisfactory for the inclusion criteria if the patient verbally acknowledges bronchitis in the past.

Grethe denied removing any documents from any of the files within Campbell's office. She further stated that she has no knowledge of anyone else including Campbell of removing documents from the records associated with the clinical trial. Grethe further denied filling out any documents or assisting Campbell fill out documents associated with the clinical trial. She also denied asking Campbell leading questions in order for her to provide a proper answer to questions proposed by PPD personnel. Grethe further denied ever having a conversation with Campbell about how many patients she could enroll before her data becomes statistically significant.

Grethe did acknowledge that she knew of Dr. Reynolds laboratory evaluation but disregarded his findings based on the evaluation conducted by their in-house statistician. She further related that she never confronted Campbell on whether or not she was splitting blood samples because of the report prepared by their statistician.

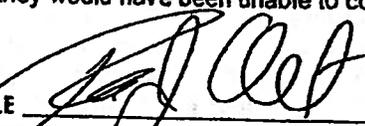
Grethe stated that as far as she can recall, no PIs and/or sites were terminated after they had enrolled patients. She related that all findings uncovered by PPD were explained by Campbell. She related that Campbell provided her and other members of Aventis plausible explanations for the findings uncovered by PPD. Grethe stated that Campbell did explain how she randomized patients in cluster. She told Grethe that once the patient signed the consent form, the patient would be asked to return at a later date for the purpose of obtaining the study medication. According to Grethe, Campbell told her that once the patient returned for the medication, they were randomized.

Grethe was questioned on how Campbell was recruited as one of the PIs for the clinical trial. Grethe related that she believes Campbell was recruited based on a recommendation by one of their sales associates that work within the Gadsden, AL area. She was further questioned on how the Case Report Forms were received by Aventis and the data extracted and provided to the FDA. She said that the CRFs were sent to PPD, who provided them to Quintiles so that they could perform data entry on the information contained within the document.

Grethe further related that once the documents were in the hands of Quintiles, they were scanned and archived. She said that the information was placed in a database and ultimately submitted to Aventis, who provided the data to FDA with the New Drug Application. She stated that even though there were problems uncovered with Campbell's site, it was collectively decided to submit Campbell's data along with the rest of the PIs. She said that Quality Assurance handled the actual submission. Grethe continued by saying that the submission was based on the explanations provided by Campbell which resolved many of the issues uncovered by the monitors for PPD, Inc.

Grethe related that she never told Robert McCormick or anyone else to "lay off" Campbell. She denied ever telling McCormick that Quality Assurance for Aventis would handle Campbell's protocol discrepancies. Grethe stated that based on her recollection, the Institutional Review Board (IRB) received all information regarding the findings uncovered by the monitors for PPD. Grethe said that according to their audits, the study medication supplied to Campbell can be accounted for based on Campbell's drug accountability report.

Grethe admitted that no one from Aventis ever check with any of the patients enrolled in the study to determine if they actually participated in the study. She said that the sponsor did not have the names of the patients so they would have been unable to contact any of the patients to make that determination.

NAME-TITLE 
Robert J. West, Special Agent

NAME-TITLE _____

DATE 4/8/03

DATE _____

APPROVED: 
Michael S. Niemiec, Resident Agent in Charge

DATE: 4/8/2003

DISTRIBUTION: NEL: Original and 1 cc
MIF: 1 cc
IOD: 1 cc

ATTACHMENTS: None



Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
MEMORANDUM OF INTERVIEW

CASE NUMBER: 2003-NEL-707-0040
CASE TITLE: DR. ANNE K. CAMPBELL
DOCUMENT NUMBER: 72013
PERSON INTERVIEWED: Ranjan Khosla
PLACE OF INTERVIEW: Aventis Pharmaceuticals, Bridgewater, NJ
DATE OF INTERVIEW: 02/25/2003
TIME OF INTERVIEW: 9:00 AM to 10:30 AM
INTERVIEWED BY: SA Robert J. West

OTHER PERSONS PRESENT: See Below

Khosla was advised that he was being interviewed because of his direct involvement in the review process of Dr. Campbell's clinical trial.

Khosla was interviewed at the headquarters for Aventis Pharmaceuticals, Bridgewater, NJ and in the presence of Colleen Hickey, Thomas Valen and Lawrence Lustberg, Attorneys for Aventis. He stated that he is a medical doctor, however, he is not licensed in any state to practice medicine. He stated that he graduated from medical school in India. He stated that he started working for Aventis Pharmaceuticals on 11/12/01, as Senior GCP (Good Clinical Practice) specialist as well as Quality Assurance specialist. He stated there are 3 groups within the company. They are GLP, GMP, and GCP. He stated that he was one of the auditors that reported to Gerard Marini. He stated that each auditor was assigned a few studies that were sponsored by Aventis. He related that he is the only medical doctor assigned to the section.

Khosla stated that as the only physician within the section, he is assigned the more complex clinical trials. He said that prior to working for Aventis, he worked for PPD Development. He said that he worked for PPD, Inc., from August 1999 through November 2001. He said that when he started working at Aventis, he was assigned the treat study for "Ketek". He said that prior to being assigned the treat study or even working for Aventis, he attending a meeting in New York City regarding Ketek. He said that this was the take off meeting for Ketek. During this meeting, the protocol was presented along with the labeling aspect of the treat medication.

Khosla stated that in the beginning, this clinical trial was going to be multi-national; however, the trial ended up taking place only in the United States. He stated that when he was assigned the treat study, it was decided that he would audit 10 Principle Investigators (PI) which included Dr. Campbell. He said that this treat study was in relationship with protocol 3014.

Khosla related that he in fact conducted 9 audits. He related that one of the 9 sites was Campbell. He stated that he audited the sites that had the highest enrollees of study subjects. He recalls auditing the top 5 sites which included a site in Kansas City and Mobile, AL. He said that Dr. Susan Blanchard, Mobile, AL enrolled 100 plus study subjects. Khosla related that he audited her site before he went to Campbell's site.

Khosla related that between 1/17/02 and 1/18/02, he conducted an audit of Campbell's site. He stated that when he arrived at Campbell's clinic, she had already enrolled 327 study subjects. He related that to the best of his recollection, 170 study subjects had already completed the clinical trial.

Khosla related that when he first was assigned the task to audit Campbell, she had already begun enrolling patients into the clinical study. He said that at the end of November, Campbell enrolled 65 patients. He related that towards the end of December, she had enrolled 130 plus patients. He related that when he arrived in January, she had enrolled 327. He said that he would have scheduled additional days for his audit if he would have known she had enrolled that many patients.

Khosla continued by saying that all audits were conducted in accordance with standard operating procedures (SOP). He related while at Campbell's clinic, he reviewed her regulatory binders, the FDA Form 1572, and all Informed Consent Forms (ICF). He stated that during his review of the ICFs, he made the determination that patients were not dating their own form. He stated that this was later confirmed by the Campbell and her study coordinator. They both admitted that they were dating the form for the patients.

Khosla stated that Campbell and the study coordinator prepared a memo explaining their reasoning for dating the ICFs. He stated that he spent approximately 7-8 hours reviewing the ICFs. He further confirmed from the study coordinator that she was dating the ICFs for the PI Dr. Campbell. According to Khosla, Campbell and/or the Study Coordinator (SC) prepared a memo outlining the fact the SC was dating the form for the PI.

Khosla further stated that during his review, he did notice a few over-writes on dates. He stated that after reviewing the ICFs, he reviewed only 10 medical records. He stated that during these reviews, it was apparent that Campbell missed documenting Adverse Adverts. He also noticed that several of the records he reviewed, the 2nd and 3rd visits were outside of the window for treatment or follow-up for treatment. He also determined that Campbell enrolled the study coordinator along with the other staff members of her office.

Khosla stated that it was department policy to discourage enrollment of staff members of those PIs that were conducting the clinical trials. He related that he thought this was a significant finding and required Campbell to report the finding to the Institutional Review Board (IRB) by memo. He further determined that Campbell had not annotated in the source document (medical records) the administration of the clinical trial. He said that it was later determined that Campbell had placed a sheet within the individual medical records which reflected the progress of the trial.

Khosla was questioned on what was considered to be a completion in regards to study subjects completing the trial. He stated that he was not aware of any definition that defined when a study subject completed the trial.

Khosla stated that before Dr. Campbell started the clinical trial, she was given a training session. He further stated that during his audit, he continuously trained her especially if he saw something that needed to be rectified or emphasized. He related that based upon his audit of Campbell, he concluded that she was very sloppy.

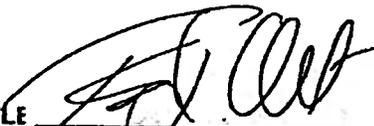
Khosla stated that prior to the FDA inspection; Campbell asked him if she would be able to use the Case Report Forms as documentation for the source document (Medical Records). He related that he told Campbell no but he discovered later that she went ahead and used the CRFs within the source records.

Khosla denied having a conversation with Campbell about statistical significant or hearing anyone making the following comments "I don't care if the patients take the drugs as long as they take the drug." or "I don't care if the patients take the drug for the indication as long as they take the drug."

Khosla related that no one from Aventis contacted the IRB with any of the findings uncover by PPD Development. He further stated that he and other members of his team had a teleconference with Campbell on 10/24/03, regarding the issuance of the 483. He said that her concerns were addressed and the response to the 483 was prepared.

Khosla could not provide any further information that would be helpful in this investigation.

NAME-TITLE


Robert J. West, Special Agent

NAME-TITLE

DATE

4/18/03

DATE

APPROVED:


Michael S. Niemiec, Resident Agent in Charge

DATE:

4/10/2003

DISTRIBUTION: NEL: Original and 1 cc
MIF: 1 cc
IOD: 1 cc

ATTACHMENTS: None



Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
MEMORANDUM OF INTERVIEW

CASE NUMBER: 2003-NEL-707-0040
CASE TITLE: DR. ANNE K. CAMPBELL
DOCUMENT NUMBER: 71980
PERSON INTERVIEWED: Michael Shoemaker
PLACE OF INTERVIEW: Aventis Pharmaceuticals, Bridgewater, NJ
DATE OF INTERVIEW: 02/24/2003
TIME OF INTERVIEW: 10:58 AM to 11:50 AM
INTERVIEWED BY: SA Robert J. West

OTHER PERSONS PRESENT: See Below

Michael Shoemaker was advised that he was being interviewed because of his direct involvement in the review process of Dr. Campbell's clinical trial.

Shoemaker was interviewed at the headquarters for Aventis Pharmaceuticals, Bridgewater, NJ and in the presence of Colleen Hickey, Thomas Valen and Lawrence Lustberg, Attorneys for Aventis. He stated that he has been working for Aventis for several years and is responsible for Quality Assurance. He further stated that he is Global Head of Good Clinical Practices (GCP) as well as internal quality assurance of clinical trials. He stated that he has been directly involved with protocol 3014 which was a clinical study conducted throughout the United States. He stated that it was an open label randomized study.

Shoemaker stated that Nadine Grethe was the study manager and PPD Development had the responsibility of monitoring the clinical sites. He stated that he personally did not visit any of the clinical sites conducting the clinical study. He stated that in January 2002, a member of his team by the name of Ranjan Khosla conducted an on-site audit of Campbell's site which resulted in several findings. He stated that Khosla determined from reviewing Informed Consent Forms (ICF) that there were problems primarily with dating of the form. He stated that the majority of the consent forms had dating issues which resulted in him recommending that the site be further monitored. He stated that when Khosla arrived at Campbell's site, the study was still on-going and Campbell was still enrolling patients.

Shoemaker stated that it was very important for each PI to follow-up with the patient after the patient was exposed to the drug. He stated that the protocol and instructions would dictate the course of action that each PI had to undertake during the clinical trial. He further stated that during Khosla's audit, it was determined that Campbell was randomizing patients/study subjects in clusters. He stated that Campbell was questioned about the way she randomized and she provided them with a plausible explanation. According to Shoemaker, Campbell provided the explanation in writing. He stated that her explanation dealt mainly with the availability of the study drug for dispensing.

Shoemaker further stated that he did have knowledge of Dr. Reynolds' report in which he prepared for PPD Development. He stated that Aventis had their own statistician evaluate the laboratory data which resulted in no significant findings. Shoemaker related that Aventis did have a teleconference with Dr. Campbell regarding the 483 response. He did state that Aventis did prepare the 483 response based on information provided by Campbell.

Shoemaker stated that during this clinical trial, he never heard anyone including Nadine Grethe make any comments similar to "I don't care if the patients take the drug for the indication as long as they take the drug." or "I don't care if the patients take the drug as long as they take the drug." He further stated that he does not know of anyone that removed documents from Campbell's file and that he does not have any information that anyone was covering for Campbell.

Shoemaker stated that each PI was required to identify a patient that met the criteria, randomize that particular patient, and then provide that patient with the study medication. He stated that a history of chronic bronchitis was required for a patient enrolled with AECB (Acute Exacerbation of Chronic Bronchitis).

Shoemaker further stated that he had no first hand knowledge of Campbell being involved with other studies. He did state that she was conducting a post marketing study which is being sponsored by Aventis. He stated that it is a diabetic study. Shoemaker was questioned on whether or not he or the company had any information that would have substantiated fraud on the part of Campbell. He related that he did not have anything to substantiate fraud including the fact that individuals suspected consent forms were being forged. He did not think, after reviewing the consent forms, that the signatures appeared to be similar.

Shoemaker related that PPD Development was made aware of their findings and/or explanations provided by Campbell along with the findings of their statistician. He could not provide any further information that was relevant to this investigation.

NAME-TITLE _____ NAME-TITLE _____
Robert J. West, Special Agent

DATE 04/06/2003 DATE

APPROVED: _____
Michael S. Niemiec, Resident Agent in Charge

DATE: 04/08/2003

DISTRIBUTION: NEL: Original and 1 cc
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IOD: 1 cc

ATTACHMENTS: None



Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
MEMORANDUM OF INTERVIEW

CASE NUMBER: 2003-NEL-707-0040
CASE TITLE: DR. ANNE K. CAMPBELL
DOCUMENT NUMBER: 71727
PERSON INTERVIEWED: Dr. Michael Aschenbrenner
PLACE OF INTERVIEW: Aventis Pharmaceuticals, Bridgewater, NJ
DATE OF INTERVIEW: 02/24/2003
TIME OF INTERVIEW: 9:07 AM to 10:45 AM
INTERVIEWED BY: SA Robert J. West

OTHER PERSONS PRESENT: See Below

Dr. (PhD) Michael Aschenbrenner was advised that he was being interviewed because of his direct involvement in the review process of Dr. Campbell's clinical trial.

Dr. Aschenbrenner was interviewed at the headquarters for Aventis Pharmaceuticals, Bridgewater, NJ and in the presence of Colleen Hickey, Thomas Valen and Lawrence Lustberg, Attorneys for Aventis. He stated that he has been employed by Aventis for the past 2 years and is responsible as the Global Expert for Good Clinical Practices. He stated that he provides advice and conducts audits of clinical trials being conducted within North America. He stated that during this project (Protocol 3014), he conducted an audit or follow-up audit on approximately 30 clinical sites. He stated that he went to Campbell's clinic for the purpose of conducting a pre-inspection review. He said that this pre-inspection review was to prepare the site for the upcoming FDA inspection.

He related that he spent 2 days at Campbell's site reviewing medical charts, case report forms (CRF), and regulatory binders. He stated that while at the site he reviewed 10 medical charts, and 10 case report forms which he selected at random. He stated that he sat in one of Campbell's examination rooms for the purpose of conducting his review. He stated that while he was reviewing the medical charts, he noticed that the records contained very limited historical notes pertaining to this clinical trial or historical diagnosis.

Aschenbrenner stated that the charts he reviewed were annotated with specific symptoms whether those symptoms were bronchitis or sinusitis. He did say that the medical records for those patients that were enrolled for Acute Exacerbation of Chronic Bronchitis did have some previous annotations which would have reflected a history of bronchitis. He did also notice that work sheets were edited after Campbell was monitored and told of the discrepancies. He stated that the work sheets were corrected and the corrections initialed.

Aschenbrenner did state that he might not have seen annotations within the medical charts he was reviewing of a 2nd visit. He was told by Nadine Grethe, Project Manager, that if a patient did not come back for visit 2 but was contacted later, this was considered to be a completion. He stated that the completion status was to be considered a completion of the protocol. He related that there are written instruction on the meaning of completion. He did state that if a patient did not come back for visit 2, it was to be reported.

Aschenbrenner further related that during the review of medical charts, he noticed that prescriptions

annotated in the chart were not listed within the case report form. He said that this was a requirement according to the provisions of the protocol. He further related that the required 3rd visit was not always crossed checked by Campbell's staff. He said that this was the explanation made by Campbell while he was speaking with Campbell during his pre-inspection.

Aschenbrenner stated that he was not involved with the Ketek Investigative New Drug (IND) submission; however, he has since learned that fraud was uncovered during the Initial NDA submission. He stated that 3 or 4 clinical sites were excluded from the submission because of suspected fraud. He said that he thought the data from these suspected sites were removed after the submission was made to the FDA.

Aschenbrenner stated that he had no idea how Campbell was recruited to participate as a Principle Investigator; however, several of his colleagues knew she was inexperienced and disorganized. He stated that prior to going to her site, he learned of the issues raised by PPD Development, who was responsible for monitoring Campbell's site along with the other sites conducting the clinical trials. He also acknowledged that prior to going to Campbell's site; he knew that a consent form was suspect in that it was believed to have been forged. He also knew which was considered suspicious by PPD, that the study coordinator for Campbell was dating the consent forms. He related that he did not confront Campbell on the issue of the suspected forgery or the dating of the consent forms.

Aschenbrenner further acknowledged that he was told about the suspicions that blood samples were split; however, that suspicion was disregarded after their statistician evaluated the data. He related that other team members thought it was a personal interpretation regarding the analysis conducted by Dr. Reynolds. He related that the company, after receiving the statisticians report, felt that it was a statistical fallacy in regards to how Reynolds determined blood samples were being split. He said that this was the reason why the company disregarded Reynolds report.

Aschenbrenner stated that members of his team also were aware that employees and family members were enrolled in the clinical study. He stated that at the time there was no policy against enrolling employees or family members.

Aschenbrenner stated that he never heard anyone make the comment, "I don't care if the patient takes the drug for the indications as long as they take the drug." He further stated that he also never heard anyone say, "I don't care if the patients take the drug as long as they take the drug." He related that during his review, he never removed documents or corrected any of the documents. Aschenbrenner did indicate that Campbell was allowed to participate as a Principle Investigator for a diabetic study. According to him, Campbell is still conducting the study.

Aschenbrenner stated that Campbell was recruited for the diabetic study or any other study before the many issues were raised by PPD Development. Aschenbrenner continued by saying that the primary objective of this study was safety. He related that the secondary objective and very secondary was efficacy. He further related that he did not get the impression that anyone was conspiring with Campbell to falsify records.

NAME-TITLE _____ NAME-TITLE _____
Robert J. West, Special Agent

DATE 03/27/2003 DATE

APPROVED: _____
Michael S. Niemiec, Resident Agent in Charge

DATE: 03/31/2003

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ATTACHMENTS: None



Food and Drug Administration
OFFICE OF CRIMINAL INVESTIGATIONS
MEMORANDUM OF INTERVIEW

CASE NUMBER: 2003-NEL-707-0040
CASE TITLE: DR. ANNE K. CAMPBELL
DOCUMENT NUMBER: 71981
PERSON INTERVIEWED: Gerard Marini
PLACE OF INTERVIEW: Aventis Pharmaceuticals, Bridgewater, NJ
DATE OF INTERVIEW: 02/24/2003
TIME OF INTERVIEW: 2:00 PM to 3:15 PM
INTERVIEWED BY: SA Robert J. West

OTHER PERSONS PRESENT: See Below

Marini was advised that he was being interviewed because of his direct involvement in the review process of Dr. Campbell's clinical trial.

Marini was interviewed at the headquarters for Aventis Pharmaceuticals, Bridgewater, NJ and in the presence of Colleen Hickey, Thomas Valen and Lawrence Lustberg, Attorneys for Aventis. He stated that he has a doctorate in Pharmacy along with a MBA. He related that he works strictly the North America Operational Center as it relates to Aventis and their pharmaceutical products. He related that during this entire clinical trial, protocol 3014, he never went to Dr. Campbell's site. He said that he believes Campbell was selected as a Principle Investigator (PI) from a database of physicians maintained by PPD Development. He stated that during the beginning of this clinical trial, he asked Ranjan Khosla, one of the auditors, to schedule an on-site audit of Campbell.

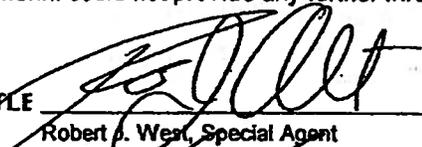
Marini stated that the company's relationship with the PI is of particular importance. He stated that even though the PI must comply with the protocol, they must also feel that they have a partnership with the sponsor of the clinical trial. Marini stated that he never had a personal contact with Campbell. He related that in January 2002, Khosla conducted the first audit of Campbell. He stated that when Khosla returned, he underwent a peer review which resulted in the several findings.

According to the audit conducted by Khosla, there were some major issues with the Informed Consent Forms (ICF). He related that Khosla determined that the ICFs were not initialed by the patient but rather by the staff. He said that based on this, they determined that Campbell should undergo additional training. He said that this was documented within a memo and that additional monitoring was recommended.

Marini stated that Khosla prepared an audit report which was forwarded to the study manager, who provided the report to Campbell. According to Marini, he did not have personal suspicions except that he thought Campbell was disorganized and sloppy.

Marini further stated that he never heard anyone make the following comments: "I don't care if the patient takes the drug as long as they take the drug." or "I don't care if the patient takes the drug for the indications as long as they take the drug." He said that he would be shocked if anyone made those comments/statements. He said that each PI including Campbell had to make sure the patient existed, the patient met the inclusion criteria, the protocol was adhered to, visits and assessments took place, and the safety of the drug was reported.

Marini did state that they did have a meeting in March 2002 in which blood splitting was discussed. He said that an internal statistician conducted an evaluation of the laboratory data; however, there were no significant findings. Marini could not provide any further information that would be helpful in this investigation.

NAME-TITLE 
Robert A. West, Special Agent

NAME-TITLE _____

DATE 4/6/03

DATE _____

APPROVED: 
Michael S. Niemiec, Resident Agent in Charge

DATE: 4/8/2003

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