DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

VIA EMAIL AND
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Gregory Irace
Chief Executive Officer
Sanofi-Aventis U.S. LLC.
55 Corporate Drive
Bridgewater, NJ 08807

Ref: 07-HFD-45-1002

Dear Mr. Irace:

This Warning Letter is to inform you of objectionable conditions found during the U.S. Food and Drug Administration's (FDA) investigation into Aventis Pharmaceuticals' (hereafter referred to as Aventis) role as sponsor of study HMR3647A/3014 (study 3014) entitled "Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin [Ketek®] and Amoxicillin-Clavulanic Acid [Augmentin] in Outpatients with Respiratory Tract Infections in Usual Care Settings" of the investigational drug, Ketek (telithromycin). We note that the issues addressed in this letter pertain to the time period prior to the merger of Sanofi-Synthelabo and Aventis Pharmaceuticals in August 2004. FDA notes that the legal name of the current firm is Sanofi-Aventis and that Sanofi-Aventis is the current sponsor of the Ketek New Drug Application (NDA).

This investigation is a part of FDA's Bioresearch Monitoring Program which is designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. Another objective of the program is to ensure that data submitted in support of New Drug Applications are scientifically valid and accurate.

In July 2002, Aventis submitted to FDA the clinical study results obtained from study 3014 in support of NDA 21,144. Subsequent FDA data validation inspections of several clinical investigators participating in study 3014 revealed multiple and significant violations of FDA regulations codified at 21 CFR 312 that affected the integrity of data submitted to NDA 21,144. As a result of these findngs, FDA requested in its January 24, 2003 Approvable Letter that Aventis provide information on its sponsor monitoring and auditing of clinical investigator sites for study 3014. Aventis submitted this information to the FDA in July 2003 (preliminary response) and October 2003 (final response). FDA obtained additional information related to Aventis's oversight of study 3014 in a subsequent investigation.

From our review of these records, we conclude that Aventis did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. **Failure to secure investigator compliance with the investigational plan and applicable FDA regulations [21 CFR 312.56(b)].**

   Under FDA regulations, a sponsor who discovers that an investigator is not complying with the signed investigator agreement [Form FDA 1572], the general investigational plan, or the requirements of applicable FDA regulations shall promptly either secure compliance or discontinue shipment of the drug to the investigator, terminate the investigator's participation, and notify FDA. Our investigation found that despite several clinical monitoring visits from Aventis's designated monitors, PPD Development (hereafter referred to as PPD), and Aventis's own audits documenting serious protocol violations and regulatory noncompliance by multiple clinical investigators, these violations persisted. We were unable to find evidence that Aventis promptly secured compliance or terminated participation of these clinical investigators and notified FDA. For example:

   a. Review of PPD monitoring records, Aventis Quality Assurance (QA) audit records, and email communications between PPD and Aventis disclosed that Aventis knew of pervasive problems at the clinical investigator site of Dr. Maria Anne Campbell aka Anne Kirkman Campbell (hereafter referred to as Dr. Kirkman Campbell), a solo practitioner in rural Alabama who had never previously conducted an FDA-regulated study, but randomized 407 subjects into Study 3014 over a 3 month time period (i.e., November 2001-January 2002.)

      FDA's October 2002 routine data validation inspection of this investigator raised numerous concerns with her conduct of study 3014, including potential fabrication of study subjects, fabrication of study data, and enrollment of ineligible subjects. FDA investigated Dr. Kirkman Campbell and found that she falsified Case Report Forms (CRFs) that were submitted to the sponsor and falsified documentation to support the existence of a fictitious subject. Dr. Kirkman Campbell subsequently pled guilty to one count of mail fraud in connection with this fictitious subject and was sentenced to 57 months in federal prison.

      While study 3014 was ongoing, PPD conducted monitoring visits of Dr. Kirkman Campbell on November 29, 2001, after 65 subjects were enrolled; on February 18-21, 2002, after all 407 subjects were enrolled; on April 1-5, 2002, after all the subjects completed the study, and on October 8-10, 2002, to prepare the site for the upcoming FDA inspection. In addition, Aventis conducted a quality assurance (QA) audit at this site on January 17-18, 2002.

      Our review found that PPD identified significant problems at Dr. Kirkman Campbell's site and subsequently informed Aventis of its findings and concerns. We note that Aventis failed to promptly secure compliance from Dr. Kirkman

Campbell and did not adequately investigate allegations of fraud at this site. Specifically, our investigation found the following:

i. Numerous emails, faxes and letters were sent to Dr. Kirkman Campbell's site requesting follow-up to items identified during the PPD and Aventis monitoring and auditing visits, but most went unanswered. For example, in an email dated March 15, 2002, PPD informed Aventis that "Numerous attempts have been made to resolve the findings noted during [Aventis QA auditor's] visit to Dr. Kirkman Campbell's site (site #1129) to no avail. Dr. Kirkman Campbell refuses to address any issues via phone or she states she doesn't have the time to spend with us on the phone. Not only have we called the site, we have sent several faxes and FedEx's in an effort to bring resolution to these matters. Upon the site management CRA's most recent conversation with the PI, she stated that she will only review the findings with the next monitor who is scheduled to visit her site." We note that the Aventis QA auditor's visit to Dr. Kirkman Campbell's site occurred in January 2002. Despite this visit, Aventis did not adequately ensure compliance.

   In addition, our investigation found that in July 2002 after the study had been completed, PPD ceased their attempts to resolve remaining issues identified during their monitoring visit at Dr. Kirkman Campbell's site because the site missed several extended deadlines for requests for information.

ii. FDA regulations at 21 CFR 50.27(a) require that informed consent shall be documented by the use of a written consent form approved by the IRB and **signed and dated by the subject or the subject's legally authorized representative at the time of consent** [emphasis added]. Under FDA regulations at 21 CFR 312.62(b), the clinical investigator is required to prepare and maintain the case history for each individual that shall document that informed consent was obtained prior to participation in the study. Our investigation found that Dr. Kirkman Campbell was in violation of both FDA regulations.

   Specifically, study documents and communications reveal that informed consent documentation problems identified during the monitoring visits when subjects were actively being randomized into the study continued through the randomization of all 407 subjects. For example, during the first monitoring visit in November 2001, when 65 subjects had been randomized, the monitors noted that the study coordinator dated the informed consent document for several subjects and dated all informed consent documents for Dr. Kirkman Campbell. Moreover, the study coordinator continued to date the informed consent documents for subjects and for Dr. Kirkman Campbell through the randomization of all 407 subjects at the site.

   Additional informed consent documentation problems were identified at the January 2002 Aventis QA audit after 327 subjects had been randomized into the study. These problems included but were not limited to the following:

a) There were no dated entries in the source documents to show that a copy of the informed consent document was given to subjects at the time of consent as required under 21 CFR 312.62(b) and 21 CFR 50.27(a). Instead, the site inserted into the medical records a photocopy of a document containing no subject identifiers or date which stated that the subject signed the informed consent document and was given a signed and dated copy;

b) For several subjects either the initials on each page of the informed consent document did not match, or the initials had not been placed on all pages of the informed consent document; and

c) There were overwrites on several subjects' signature dates; thus, the actual date the subject signed the consent document was not clear.

Our investigation found that Aventis failed to take any action to secure compliance while the study was ongoing except to generate numerous memos to the file after all subjects had completed the study.

According to an FDA interview with an Aventis manager involved with study 3014, these memos to file served as a mechanism to train the investigator. However, this same Aventis manager conceded that because the majority of these memos to file were generated after all subjects had completed the study, there wasn't much value in training the clinical investigator. We note that generation of numerous memos to file after all subjects have completed the study does not adequately secure compliance of an investigator.

iii. Subsequent to the February 2002 monitoring visit, PPD requested a teleconference with Aventis to discuss concerns they had identified during the on-site monitoring visit to Dr. Kirkman Campbell's site. These concerns included the lack of source documentation to verify the diagnosis of an appropriate medical condition to warrant study entry; medical records that provided insufficient information; large numbers of patients randomized in short increments of time, with most occurring when the office was closed for lunch and not seeing patients; consent form discrepancies including date modifications and signature inconsistencies; and lab values for multiple subjects being suspiciously similar.

A teleconference between PPD and Aventis was held on March 4, 2002 to discuss these concerns and to develop a plan of action. The plans were inadequate as follows:

a) PPD informed Aventis in February 2002 that the lab results from Dr. Kirkman Campbell's site looked "...so uniform as to potentially be the same sample...all her results are strangely low and uniform. A potential explanation for this might be dilution of samples." The plan of action developed to address this concern consisted of having an Aventis statistician "...perform a statistical analysis of the lab data from [ ]

to determine the likelihood of obtaining the observed numbers of matching lab samples by chance."

In an email dated March 14, 2002, the Aventis statistician reported his findings on the analysis of the lab values for Dr. Kirkman Campbell's site in comparison to the two other highest enrolling sites (i.e., sites 1057 and 096). The report noted that there was a "...greater consistency in laboratory values within days than expected for site 1129 [i.e., Dr. Kirkman Campbell's site]. However a similar outcome was obtained in data from site 096." Based on this finding the Aventis statistician concluded that a "systematic pattern" at Dr. Kirkman Campbell's site was unlikely.

We note that the original analysis plan to determine the likelihood of obtaining the observed lab values by chance was dropped by the Aventis statistician because he was unable to ascertain the proper criteria for "similar" lab values to conduct the statistical analysis. The analysis was changed to "comparison of the variation in laboratory values collected on the same day with the overall variation in the full data set" for Dr. Kirkman Campbell's site in comparison to the next two highest enrolling sites (sites 1057 and 096). Aventis failed to acknowledge that the same issue (i.e., suspiciously similar lab samples) may have occurred at site 096 as well. According to an internal PPD email, PPD conducted an analysis of site 1129 in relation to nine other high enrolling sites and found that site 096 also had laboratory values that appeared similar, indicating that "whatever potential lab anomalies exist at site 1129 [Dr. Kirkman Campbell] may also exist at site 0096." We could find no evidence that Aventis investigated this issue further.

b) Regarding the lack of source documentation for clinical diagnosis required for study entry, the plan of action was to have Dr. Kirkman Campbell explain the source documentation practices used at her site. In addition, Dr. Kirkman Campbell was to address the findings from the February 2002 monitoring visit which included numerous overwrites and date changes noted in study subjects' charts and case report forms, late entries in the medical charts, lack of source documentation for the conditions under study, and date discrepancies.

Our investigation found that Dr. Kirkman Campbell's site did not adequately address these issues and that Aventis and PPD did not adequately follow up to explain the data discrepancies. For example, during the February 2002 monitoring visit, PPD monitors identified that several subjects were diagnosed with acute exacerbation of chronic bronchitis even though source documents showed no history of bronchitis. The March 4, 2002 meeting minutes summarized this problem as follows: "It is understood that the nature and extent of the disease state is not critical to this clinical trial mimicking normal practice but the PI [principal investigator] should explain the source documentation practices followed

by the site and clarify the issues observed in the monitoring visit." This comment appears to contradict the objective of the protocol, which was to investigate the safety and effectiveness of Ketek in a defined population of subjects..

c) In February 2002, PPD informed Aventis that they prepared a log of the exact randomization times for each of Dr. Kirkman Campbell's subjects and that there "...were many many days in which she randomized 10-15+ subjects only seconds to one minute apart from one another." The plan of action was to request in a follow up letter that Dr. Kirkman Campbell explain the randomization process used by the site.

In a memo to file dated April 19, 2002, Dr. Kirkman Campbell noted that the site was given inaccurate information on the date of drug delivery. Therefore if the site had no drug, patients were given the option of returning next morning for a brief re-chart and drug, and at that time patients were randomized in blocks.

Email communications within Aventis indicate that the Aventis statistician who examined the randomization process found no problems except for possible proficiency problems using the IVRS [interactive voice response system] and the proportion of females enrolled in the study. Specifically, the Aventis statistician found "[o]ccasional repeats in years of birth, but no obvious second-digit preference in dates of birth which is what tends to happen if someone forges dates (usually 0 and 5)." This explanation does not consider the possibility that the information could have been obtained from actual individuals who did not participate in the study. In addition, the protocol stipulated that subjects were to be dispensed the drug on the same day that they were screened and randomized for the study (i.e., visit 1). Thus, randomization of subjects into the study should have occurred only on days in which the site had sufficient study drugs.

d) The primary objective of study 3014 was to obtain safety data. Aventis failed to ensure that safety data was collected according to the investigational plan.

At the January 2002 Aventis QA visit, the Aventis auditor noted that the site did not know the definition and reporting requirement of adverse events of significant interest (AESI) and serious adverse events and recommended that the site be retrained. At this time 327 subjects had been randomized into the study. During the February 2002 monitoring visit, PPD noted that there were very few adverse events reported for the 407 subjects randomized to the study. During the February 2002 monitoring visit, PPD monitors retrained the site on this issue.

The site signed a memo to file dated March 1, 2002 noting that they had received this training. In an email dated March 6, 2002, PPD personnel stated that in their review of case report forms for Dr. Kirkman

Campbell's site, adverse events were not reported for subjects 1-360. PPD noted that the adverse events reported for subsequent subjects were of four types (nausea, diarrhea, yeast infection, and abdominal pain,) and most were filled out in a different colored ink at visit 2.

In evaluating these issues with adverse event reporting, our investigation found that Aventis did not adequately pursue follow up to ensure accurate reporting.

e) Because of the numerous problems observed, the plan of action recommended additional monitoring of Dr. Kirkman Campbell's site. The March 6, 2002 minutes of a March 4, 2002 teleconference noted that "the monitoring plan requires a monitoring of 25% patients." As of the March 4, 2002 teleconference, however, only 49 of the 407 (~12%) subjects had source data verification completed by PPD and Aventis.

The next monitoring visit held after the March 2002 teleconference occurred in April 2002, after all subjects had completed the study. At the April 2002 monitoring visit, the findings identified at Dr. Kirkman Campbell's site included inclusion of ineligible subjects into the study, lack of documentation to show that subjects had the disease under study, visits not within the protocol required time periods, and continued problems with informed consent documentation. At least 89 memos to file were generated during the April 2002 monitoring visit to address these violations. As noted above, generation of memos to file after all subjects have completed the study does not adequately secure compliance of an investigator.

f) To explain the large number of subjects enrolled at the site, the plan of action requested that Dr. Kirkman Campbell provide data on the total number of patients seen by her during the months of October, November, and December 2001.

Our investigation found no documentation that Dr. Kirkman Campbell responded to this question until October 2002 when Aventis and PPD visited the site in preparation for the FDA inspection. Dr. Kirkman Campbell stated that she saw 50 to 60 patients per day at her clinic. We are unable to determine, however, whether Aventis auditors verified this information by reviewing patient logs to determine whether her patient population would adequately support the high enrollment at her site.

iv. Aventis failed to properly investigate the possibility that an informed consent document was forged, an issue identified by PPD during the February 2002 monitoring visit. Specifically, PPD noted that the signature of subject 249 on the consent document did not match the signature in the medical chart. According to PPD's monitoring report, the signature on informed consent document appeared to match the study coordinator's handwriting. We note

that Aventis failed to follow up on this issue until the October 2002 site visit, just prior to FDA's inspection.

The methods employed by Aventis to resolve this issue were inadequate. Specifically, at the October 2002 visit, Aventis QA auditors compared this subject's signature on the informed consent document with a signature in the subject's medical record and concluded that there was no forgery because: (1) while the signatures looked very different, there appeared to be no attempt to get them to look like each other; and (2) the subject's initials on the informed consent document appeared similar to the subject's initials on a document in the medical record. We were unable to verify that Aventis QA auditors were qualified to make definitive findings on whether the informed consent document was forged.

In summary, our investigation found that Aventis did not adequately secure compliance of Dr. Kirkman Campbell. In addition, Aventis's method for securing compliance, (i.e., the generation of more than 125 memos to file for protocol and informed consent deviations noted at the site) was not adequate.

b. Aventis failed to promptly secure compliance of Dr. Jeffrey McLeod, another clinical investigator conducting study 3014, or end his participation in the clinical investigation and notify FDA. During the course of study 3014, Aventis was informed that Dr. McLeod (site #2557) did not adequately document informed consent as required by 21 CFR 50.27. Specifically, PPD found that Dr. McLeod did not have written informed consent documentation for 30 subjects. Dr. McLeod explained to PPD that verbal consent was obtained from these subjects.

On March 6, 2002 Aventis QA requested that PPD conduct an interim monitoring visit, requesting that the site have the subjects sign the consent document in the current date and write a statement that they had consented orally on a previous date. During the monitoring visit PPD noted the following: (1) 4 subjects were missing documentation to show that they were verbally consented; (2) several informed consent documents had been backdated; and (3) several subjects had not returned to the site to sign any consent documents. The monitoring report noted that all violations were documented in memos to file.

On October 31, 2005 Dr. McLeod was disqualified from receiving investigational drugs, and is no longer entitled to conduct any further studies, intended or required for submission to FDA. Dr. McLeod was disqualified for (1) failure to obtain the legally effective informed consents from human subjects enrolled in study 3014, which included signing of informed consent documents by subjects after they had completed the study and backdating of informed consent documents; (2) submitting false information to the sponsor or FDA in a required report; and (3) failure to conduct the study in accordance with the investigational plan.

As noted previously, memos to file are inadequate to address the falsification (backdating) of study documents.

c. We note that similar findings of noncompliance were observed during inspections of other clinical investigators conducting study 3014. Specifically, of the 8 clinical investigator sites inspected under Study 3014 for data validation, data from 4 sites were considered unreliable due to numerous regulatory violations affecting data integrity.

2. **Failure to ensure proper monitoring of the clinical investigation [21 CFR 312.50].**

Our investigation found that Aventis failed to properly ensure monitoring of the study. Aventis submitted a draft monitoring plan for study 3014 to the FDA on August 28, 2001, and the final monitoring plan was submitted when the final study was submitted to the FDA later that year. Under the original study protocol only 5 to 50 subjects were to be enrolled per center. However, in December 2001 Aventis permitted the number of subjects per site to be increased to a maximum of 500 per site, without amending their monitoring to adequately adjust for the increased enrollment during the time that subjects were actively enrolled into the study.

Although Aventis had contracted with PPD to conduct monitoring visits, Aventis conducted its own QA audits and conducted co-monitoring visits with PPD of Dr. Kirkman Campbell's site. As the sponsor of the NDA, Aventis retains responsibility for ensuring proper monitoring.

3. **Failure to select qualified investigators and provide investigators with the information needed to conduct the study properly [21 CFR 312.50].**

Aventis failed to select qualified investigators to conduct the study. For example, our investigation found that at the time Dr. Egisto Salerno was selected to participate as a clinical investigator in study 3014 and then randomized subjects into the study, his medical licensure was on probation by the Medical Board of California for gross negligence and failure to maintain adequate and accurate records. Subsequent to his participation in the study, his medical license was suspended. We note that Dr. Salerno was one of the highest enrolling investigators.

4. **Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND [21 CFR 312.50].**

Our investigation found that Aventis failed to ensure that study 3014 was conducted according to the investigational plan. For example,

a. According to the study 3014 protocol, the investigation planned to recruit 24,000 subjects, which would require approximately 2000 to 5000 centers with a recommended 4 to 50 subjects per center. In addition the protocol stated that neither the investigator nor the sponsor was to alter the clinical study protocol without obtaining the written agreement of the other. Once the study had started, amendments were to be made only in exceptional cases.

In an email dated December 3, 2001, Aventis informed PPD that sites could continue to enroll up to 500 subjects. We note that several clinical investigator sites enrolled greater than 50 subjects; however, the clinical study protocol was not amended to reflect this change. In addition, we note that several clinical investigators including Dr. Kirkman Campbell, Dr. Richard Harker, and Dr. Terpestra enrolled more than 50 subjects without obtaining prior Institutional Review Board approval.

b. The protocol required that subjects be excluded if they had a hypersensitivity to telithromycin, beta-lactams, or macrolide class of antibiotics. Any waiver of these inclusion and exclusion criteria was to be approved by the investigator and the sponsor on a case-by-case basis prior to enrolling the subject. Further, this was to be documented by both the sponsor and the investigator.

   We note that during the April 2002 monitoring visit at Dr. Kirkman Campbell's site the monitors identified several subjects, including but not limited to 59, 66, 76, 85, 110, 111, 230, 370, who had been enrolled into the study although they had conditions that should have excluded them from participation because of the above-referenced exclusion criteria. Our investigation found no prior approval by the sponsor for enrollment of these subjects. Documentation for study inclusion via memos to file was created only after these subjects had completed the study.

c. To be included in study, the protocol required that subjects be diagnosed with community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), or acute sinusitis (AS).

   Specifically, Section 13.1 of study 3014, "Study Monitoring and Source Data Verification" states "[m]onitoring will be done according to the monitoring plan by representative of the sponsor (study monitor) who will check the case report forms for completeness and clarity, and crosscheck them with source documents..."

   We note that during the January, February and April 2002 PPD monitoring visits to Dr. Kirkman Campbell's site, the disease diagnosed (e.g., AECB) and reported on the case report forms could not be verified with information contained in source documentation. PPD discussed this finding with Aventis in the March 4, 2002 teleconference. According to the minutes of this teleconference, Aventis required minimal verification of diagnosis: "[i]t is understood that the nature and extent of the disease state is not critical to this clinical trial mimicking normal practice but the PI [principal investigator] should explain the source documentation practices followed by the site and clarify the issues observed in the monitoring visit."

   Our investigation found that the Aventis study manager asserted that merely asking a subject if they had bronchitis was sufficient to fulfill the inclusion criteria for study 3014. We note that under this interpretation, no source documentation would be required, contradicting the protocol requirements for

verification of source data. As a result, we are unable to ascertain that subjects enrolled in study 3014 had the condition under study and were appropriately treated.

This letter is not intended to be an all-inclusive list of deficiencies regarding Aventis's sponsor responsibilities It is the sponsor's responsibility to ensure adherence to each requirement of the law and relevant FDA regulations.

Within fifteen (15) working days of your receipt of this letter, the FDA requests that you address these deficiencies in writing and inform us of corrective actions and procedures that you have or will take to prevent and ensure that similar violations will not occur in any on-going or future studies. FDA also plans to meet with your company. In your response, please name the appropriate individuals and a point of contact for this meeting. Please note that at the appropriate time FDA will conduct additional inspections to ensure that adequate corrective actions have implemented.

If you have any questions, please contact Joseph Salewski at (240) 276-8817; FAX (240)-276-8844. Your written response and any pertinent documentation should be addressed to Dr. Leslie Ball at the address below.

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Division Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

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/s/

Leslie Ball
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