United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

December 13, 2006

Via Electronic Transmission

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner von Eschenbach:

The United States Senate Committee on Finance (Committee) has exclusive jurisdiction over the Medicare and Medicaid programs. Accordingly, the Committee has a responsibility to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to oversee the proper administration of these programs, including the payment for prescription drugs regulated by the Food and Drug Administration (FDA), Department of Health and Human Services (HHS).

Last Spring, the Committee on Finance began investigating extremely troubling allegations related to, among other issues, the approval and post-market surveillance of telithromycin (Ketek) by the Food and Drug Administration. Two of the allegations brought to the attention of the Committee relate to an FDA advisory committee meeting,[1] specifically the Anti-Infective Drugs Advisory Committee (AIDAC or Advisory Committee) meeting held on January 8, 2003. On April 27, 2006, I brought to your attention allegations related to FDA management instructing FDA officials to present fraudulent data to the Advisory Committee because discussing issues regarding data integrity and the conduct of a safety study would not be "productive." The second allegation related to the FDA actually presenting fraudulent study data to the Advisory Committee. The purpose of this letter is to report the Committee's preliminary findings solely with respect to these two allegations. The Committee continues to investigate several other allegations relating to the approval and post-market surveillance of Ketek by the FDA.

[1] The FDA convenes expert advisory panels pursuant to the Federal Advisory Committee Act. *See* http://www.access.gpo.gov/uscode/title5a/5a_1_.html. According to the FDA, the value of an advisory committee is to provide independent expert advice, to lend credibility to the FDA's review process, and to allow for public discussion of controversial issues, among others. *See* http://www.fda.gov/oc/advisory/Presentations/NMT05/NMT05TalkShermanLinda.pps#260,20,The Value of an Advisory Committee.

This letter report presents findings and information obtained by the Committee based on the Committee's ongoing investigation to date. It is limited to those allegations related to the AIDAC meeting the FDA convened on January 8, 2003. It is based on interviews conducted by the investigative staff of the Committee (Committee Staff), letter requests to Advisory Committee members, and the Committee's review of documents and information obtained by and provided to the Committee to date. The Committee will continue to investigate all allegations related to Ketek.

The findings presented in this letter may be preliminary for several reasons. First and foremost, the FDA has yet to respond to multiple questions asked by the Committee on June 7, 2006. More than half a year later, the Committee does not have answers from the FDA related to the allegations regarding the AIDAC meeting. In addition, last May the Committee subpoenaed documents and information related to Ketek. To date, HHS and FDA have failed to comply fully with the two congressional subpoenas issued seven months ago. For months, HHS and FDA have failed to take good faith steps toward complying with the Committee's subpoenas.

I also am fully aware that relevant documents and information have been "overlooked" or purposefully withheld from the Committee. Throughout this investigation the Committee has sought and received assurance from FDA that all relevant FDA officials who worked on Ketek matters were notified to produce documents responsive to the Committee's subpoenas. However, the Committee confirmed that at least three FDA officials, who played integral roles in the FDA's review of Ketek, were never asked to review their files and turn over relevant documents in their possession. Therefore, the findings and conclusions in this report to you may be limited in some respects.

To summarize, the Committee Staff reviewed documents and information obtained and received from the FDA and sanofi-aventis,[2] the manufacturer of Ketek, and found the following:

- FDA management knew or should have known that a multitude of questions and concerns regarding serious data integrity problems with a large safety study, Study 3014, were unresolved. Nevertheless, FDA management instructed FDA officials to present that data to the Anti-Infective Drugs Advisory Committee and the public. About two months prior to the Advisory Committee meeting, the study site with the largest number of enrolled subjects was under investigation by FDA's Office of Criminal Investigations. The FDA also inspected the second and third highest enrolling sites and found them to have similarly violated the protocol for Study 3014. In addition, 72 other sites raised red flags for FDA officials and investigators, including nonadherence to the study protocol, which recommended between 4 and 50 study subjects per site. 72 sites enrolled more than 50 subjects and 30 sites enrolled more than 80 subjects. FDA officials also questioned how quickly more than 24,000 patients were enrolled in the study.

- The FDA presented data from Study 3014 to the Advisory Committee, including study data from one study investigator whom the FDA's Office of Criminal

[2] Sanofi-Synthélabo merged with Aventis Pharmaceuticals in 2004, forming sanofi-aventis.

Investigations, Division of Scientific Investigations, and the local United States Attorney's Office all believed had falsified and fraudulently submitted clinical trial data. Based in part on data from Study 3014, a majority of the Advisory Committee voted in favor of approving Ketek for the indications of community-acquired pneumonia, acute bacterial sinusitis, and acute exacerbation of chronic bronchitis. Many of the Advisory Committee members were not aware until this past spring of the serious data integrity problems with Study 3014 and that the FDA did not use Study 3014 in approving Ketek.

- The FDA did not ensure that the Advisory Committee had all of the accurate, science-based information it needed to provide the FDA with informed recommendations and advice regarding Ketek. Despite reaching the conclusion that data from the site under criminal investigation should be censored, the FDA did not censor the suspect data before the Advisory Committee meeting. Some of the Advisory Committee members stated that the FDA should have informed them of significant issues or problems related to Study 3014, in a confidential manner if necessary, and that knowledge of the data integrity problems might have affected their actions at the Advisory Committee meeting.

I. Background

On December 13, 2002, the FDA published in the Federal Register a notice for a meeting of the AIDAC. The agenda for the meeting read: "On January 8, 2003, the committee will discuss new drug application (NDA) 21-144, KETEK (telithromycin), Aventis Pharmaceuticals, Inc., proposed for treatment of community-acquired pneumonia [CAP], acute exacerbation of chronic bronchitis [AECB], and acute maxillary sinusitis."[3]

Aventis Pharmaceuticals, Inc., (Aventis) originally submitted its Ketek NDA to the FDA on February 28, 2000. The Ketek NDA was assigned for review to the FDA's Division of Anti-Infective Drug Products (Review Division), Office of Drug Evaluation IV (ODE 4, now Office of Antimicrobial Products), Center for Drug Evaluation and Research (CDER). Accordingly, supervisory authority of the Ketek NDA review was held by the Director of the Review Division, and the Director of ODE 4, who supervised the Division Director.

The AIDAC meeting convened by the FDA on January 8, 2003, was the second meeting of the Advisory Committee to consider the Ketek NDA. Previously, the FDA convened the AIDAC in April 2001. At the first meeting of the AIDAC, the Advisory Committee members recommended that Aventis obtain additional safety data from a large sample of patients before Ketek could be approved for acute bacterial sinusitis (ABS) and AECB.

After consideration of the Ketek NDA by the Review Division, as well as the recommendations made by the AIDAC, the FDA issued an "approvable letter" to Aventis on June 1, 2001, for the indications of CAP, ABS, and AECB.[4] The FDA's approvable

[3] http://www.fda.gov/ohrms/dockets/98fr/02-31443.htm.

[4] According to a Medical Officer Review on hepatic adverse events of special interest, dated July 24, 2002, "During the review of that [Ketek] application and in subsequent discussion by the Anti-Infective Drugs Advisory Committee on April 26, 2001, safety concerns, including potential for hepatotoxicity, were

letter requested that Aventis perform a large safety study of patients in a usual care setting to examine the potential toxicities of Ketek with regard to cardiac, hepatic (liver), visual, and vascular safety. The FDA's approvable letter stated:

> It would be helpful to conduct a Phase III study of CAP/AECB/ABS to assess further adverse events associated with telithromycin, particularly in patients at increased risk for potential drug-related toxicity. Such a study should be randomized, with at least 35% of the recruited study population consisting of patients 50 years of age and older. Exclusion criteria regarding concomitant medications should be minimized. Recruitment of patients with renal and/or hepatic impairment is encouraged. This study should include the monitoring and analysis of all adverse events, with particular attention to hepatic, visual, cardiovascular, and vasculitic adverse events.

In response to the FDA's June 2001 approvable letter, Aventis submitted an amendment to the Ketek NDA on July 24, 2002, containing the large safety study requested by the FDA to evaluate adverse events in the usual care setting (Study 3014).[5] Aventis conducted Study 3014 primarily to address the request for a large safety study to examine adverse events of special interest (cardiac, hepatic, visual, and vasculitic) and to better characterize the hepatic risk profile of Ketek in a usual care setting.[6]

Pursuant to the FDA's Bioresearch Monitoring (BIMO) Program,[7] the FDA inspected the highest enrolling investigation center for Study 3014—Dr. Marie "Anne" Kirkman-Campbell, who enrolled 407 subjects—in mid-October 2002. Shortly thereafter, the FDA field investigator reported to the FDA's Office of Criminal Investigations (OCI), within the Office of Regulatory Affairs (ORA)[8] that the regulatory inspection of Dr. Kirkman-

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raised…there were two serious hepatic adverse events plausibly associated with telithromycin administration…These cases factored into the recommendation by the AIDAC and the Division's decision to require a larger safety study prior to drug approval. Study 3014 was designed to examine adverse events of special interest, including hepatic events, in a large population of patients with acute community-acquired respiratory infections…The study was powered to detect with 95% confidence adverse events occurring at rates of at least 1 in 4,000."

[5] 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, HMR3647A/3014, Telithromycin.

[6] At the request of the Committee, Aventis prepared and submitted a "Ketek® Study 3014 Timeline" in October 2006. Aventis completed design of the protocol for Study 3014 on September 27, 2001, and officially submitted it to the FDA on October 17, 2001. According to the clinical study protocol, the duration of the study was expected to be five to eight months. Aventis enrolled the first subject on October 19, 2001, and the last on January 29, 2002. Over 24,000 patients were enrolled at 1824 investigation centers in less than four months.

[7] According to the FDA, the BIMO Program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research. The BIMO Program was established to assure the quality and integrity of data submitted to the agency in support of new product approvals, as well as, to provide for protection of the rights and welfare of the thousands of human subjects involved in FDA-regulated research. It has become a cornerstone of the FDA pre-approval process for new medicines, medical devices, food and color additives, and veterinary products introduced to the U.S. consumer. See http://www.fda.gov/ora/compliance_ref/bimo/background.html.

[8] According to the FDA website, the Office of Criminal Investigations "has the primary responsibility for all criminal investigations conducted by the FDA, including suspected tampering incidents and suspected counterfeit products." OCI investigates criminal activities that violate the Federal Food, Drug, and

Campbell "identified numerous regulatory deficiencies along with possible criminal violations."[9] At the end of October, OCI reported the preliminary results of its investigation to the United States Attorney: "it is believed Dr. Campbell falsified clinical trial results … ."[10] By mid-November 2002, OCI notified the Review Division that a criminal investigation of Dr. Kirkman-Campbell had been initiated.[11] By then the Review Division had also requested additional BIMO inspections of the second and third highest enrolling sites.[12]

While the DSI inspections and OCI investigation related to Study 3014 were ongoing, the Review Division continued its preparations for the second AIDAC meeting to be held on January 8, 2003. Data from Study 3014, as well as foreign post-marketing data, were prepared for presentation to the AIDAC. On January 8, 2003, the FDA asked the Advisory Committee members to address four questions[13]:

1. Do the safety and effectiveness data presented support the use of Ketek for CAP, ABS and/or AECB? If yes, are there any special caveats that should be included in the label? If no, what other information would be required?
2. Do the safety and effectiveness data presented support the use of Ketek for the treatment of penicillin-resistant *S. pneumoniae* for CAP and/or ABS? If yes, are there any special caveats that should be included in the label? If no, what other information would be required?
3. Do the safety and effectiveness data presented support the use of Ketek for the treatment of macrolide-resistant *S. pneumoniae* for CAP and ABS? Please consider in your discussion the public health impact of macrolide-resistant *S. pneumoniae*. If yes, are there any special caveats that should be included in the label? If no, what other information would be required?
4. Are there any additional studies of Ketek you would recommend?

For question 1, 11 members voted yes and 1 member voted no for the indications of CAP and ABS; 8 voted yes and 4 voted no for AECB. For question 2, 7 members voted yes and 5 members voted no for both indications. Similarly, for question 3, 7 members voted yes and 5 members voted no for both indications.

Two weeks after the Advisory Committee meeting, DSI provided the Review Division with its findings and recommendations to date regarding data from the three highest enrolling investigation sites. In its memorandum dated January 21, 2003, DSI recommended that the Review Division consider excluding specific data from one site and not use any data from another in support of the Ketek NDA until outstanding issues

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Cosmetic Act, including schemes to defraud the Medicare and Medicaid programs that involve FDA-regulated products. OCI often collaborates with other federal and state law enforcement agencies.

[9] FDA, OCI, Report of Investigation submitted by Special Agent Robert West on November 29, 2002.

[10] Letter to United States Attorney Alice Waters from Mr. R. Bradenbaugh, Acting Special Agent in Charge, FDA Office of Criminal Investigations, dated October 30, 2002.

[11] Email from OCI to Review Division and DSI, dated November 14, 2002.

[12] "DSI Consult: Request for Clinical Inspections," dated November 13, 2002.

[13] http://www.fda.gov/ohrms/dockets/ac/03/questions/3919Q1.htm.

were investigated and resolved. Several days later, on January 24, 2003, the FDA issued an approvable letter to Aventis.[14]

II. FDA Management Instructed FDA Officials to Present Highly Suspect Study Data to an Advisory Committee; FDA Presented Study Data to an Advisory Committee Despite Numerous "Red Flags" About the Integrity of the Study Data

Prior to the Advisory Committee meeting on January 8, 2003, FDA management, the Office Director and Division Director, should have been fully aware that a multitude of questions, concerns, and red flags regarding serious data integrity problems with Study 3014 were unresolved. In fact, nearly two months before the Advisory Committee meeting, OCI notified the Review Division and DSI that a criminal investigation was underway involving Study 3014. In November 2002, OCI communicated to the Review Division that the site under investigation might affect "the overall 'approvability' of this [Ketek] NDA." Communications between DSI and the Review Division in early December also suggest that "the [Ketek] NDA should be placed on hold until the matters are resolved."

Six days before the AIDAC meeting, the team leader for the Ketek NDA emailed the Office Director and copied the Division Director seeking to talk about "the extent to which we should communicate to or discuss with the committee issues regarding data integrity and study conduct for Study 3014":

> DSI has sent us the 483 for the second highest enrolling site (Dr. Lang) for the large Ketek safety study (Study 3014); they identified some (although not all) of the same GCP problems seen in the highest enrolling site (Dr. Kirkman-Campbell), including:
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> - Patient enrollment far in excess of limits recommended by the IRB
> - Enrollment of clinic staff in the study
> - Enrollment of patients who should have been excluded (patients with drug allergy or who were nursing)
> - Failure to obtain baseline LFTs in >two dozen patients (~10% of total) or on-therapy LFTs in a dozen patients.
> - Significant discrepancies between source documentation and clinical investigator memos.
>
> Dr. Kirkman-Campbell had similar GCP issues; in addition, she enrolled a substantial number of patients who presented to her clinic for weight control, and were not seeking medical attention for a respiratory tract infection. DSI has recommended exclusion of data from her site, has referred her case to the Office of Criminal Investigations, and is considering an official action such as disqualification.

[14] A timeline of major events related to the approval and post-market surveillance of Ketek is attached to this letter (Attachment 1). An approvable letter means the NDA substantially meets the requirements of the Food and Drug Administration's regulations on the approval of new drugs (Part 314 of Title 21 of the Code of Federal Regulations), and the agency believes that it can approve the application if specific additional information or material is submitted or the applicant agrees to specific conditions.

> The third largest enroller, Dr. Salerno, did not have signficant [sic] GCP violations, but had been placed on probation by the state of California for poor record-keeping at the [time] that he was involved in the study; three months after the last patient was enrolled at his site, he was arrested on weapons and drug use charges.
>
> We do not know how pervasive these problems are at this point. Since we will be asking the AC to make recommendations on the basis of the data presented to them, Janice and I would like to talk with you about the extent to which we should communicate to or discuss with the committee issues regarding data integrity and study conduct for Study 3014. Is there any time this afternoon that would work for you?

The Office Director replied: "In general I don't believe spending time on these issues in front of the AC [Advisory Committee] wil [sic] be productive. I do feel that having the company make the best possible presentation of their PM [foreign post-marketing] data focusing on information from countries where we have confidence in reporting will be useful."

However, at least as early as November 19, 2002, the Review Division reached the conclusion that data from the highest enrolling site, which was under criminal investigation, would have to be censored from Study 3014. Despite reaching this conclusion nearly two months before, several Review Division officials informed Committee staff that data from this site was not censored after all. Data from all sites submitted by Aventis was included in the FDA's and Aventis' presentations to the Advisory Committee on January 8, 2003. FDA officials stated that there was not enough time to remove the data and re-analyze Study 3014 before the meeting. Other FDA staff stated that removing the data from the site under criminal investigation, or data from any other site under for-cause inspection related to data integrity problems, would raise questions from Advisory Committee members and potentially jeopardize ongoing investigations.

A. Criminal Investigation of Highest Enrolling Study Site—Dr. Kirkman Campbell

Two months before the AIDAC meeting, the FDA's Office of Criminal Investigations initiated an investigation of the highest enrolling site in Study 3014. The principal investigator at this site, Dr. Kirkman-Campbell, enrolled 407 patients in the study, eight times more than the recommended maximum enrollment specified in the study protocol and approved by the institutional review board.

According to Committee interviews with FDA officials, the number of enrolled patients, as well as how rapidly Dr. Kirkman-Campbell reached those numbers, raised red flags within the Review Division. The Division of Scientific Investigations conducted its inspection of Dr. Kirkman-Campbell's site in September 2002,[15] and referred its

[15] A "DSI Consult: Request for Clinical Inspections," dated September 11, 2002, shows the Review Division Director requested that inspections be performed and Inspection Summary Results be provided for Dr. Kirkman-Campbell by December 17, 2002.

inspection findings to OCI for criminal investigation in October 2002[16] On November 1, 2002, DSI notified the Review Division about "major documentation problems" found at Dr. Kirkman-Campbell's site.[17]

OCI began investigating Dr. Kirkman-Campbell in October 2002. On November 14, 2002, OCI notified the Review Division and DSI about its investigation:

> As I have stated, OCI has initiated a criminal investigation of Dr. Kirkman-Campbell. There is good reason to believe that Dr. Kirkman-Campbell falsified a lot of the patient data on this study . . . It is my understanding that the advisory committee will convene on 01/08/2003 to review this NDA for approval. I would encourage a careful consideration of the impact Dr. Kirkman-Campbell's data might have on the overall 'approvability' of this NDA.

According to an email written by the Regulatory Project Manager responsible for the Ketek NDA, dated November 19, 2002, the Review Division reached the conclusion that Dr. Kirkman-Campbell's data would have to be censored from Study 3014:

> We have an advisory committee meeting on January 8, 2003, and the action date is January 24, 2003. But do not despair yet!!! The Division already decided to take Dr. Kirkman-Campbell's data out of the database.

The conclusion that Dr. Kirkman-Campbell's data would be censored from Study 3014 is also supported by an email exchange within OCI, dated November 25, 2002: "My contact at CDER advised that Campbell's data has been removed from the NDA database."

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[16] According to a summary of a Regulatory Briefing held on February 19, 2003, DSI referred Dr. Kirkman-Campbell to OCI based on the following findings as well as communications with PPD, the contract research organization (CRO) hired by Aventis to monitor the study: "Enrollment of patients who were being seen for weight loss therapy, rather than the conditions specified in the protocol," "Documentation of patients as having completed courses of therapy despite statements from patients that they had not received medication," "Enrollment of patients in numbers far in excess of those approved by the local IRB, without IRB review," and "Enrollment of patients documented as being ineligible for the study on the basis of drug allergies." Other findings of concern were enrollment of the investigator's family and staff and the absence of any reported adverse events for the first 100 patients enrolled at the site. According to the Regulatory Briefing Summary, the investigator did not begin reporting adverse events until confronted by PPD.

[17] Email sent from DSI to Review Division on November 1, 2002: "This is an update to you all in regards to our inspection of Dr. Kirkman-Campbell at Gadsden, AL site. DSI has not received the EIR yet. But, the field has issued a 483 to Dr. Campbell. It appears that the site has major documentation problems. One of the items on 483 stated 'subjects were routinely enrolled in the study that were seen by the PI for reasons other than the conditions under study (AS, AECB, CAP) i.e., as part of a weight loss program. Many subjects were not seeking treatment for the study conditions nor were reporting the study conditions as a reason for the visit to the clinic. Several subjects were enrolled with questionable diagnoses or lack of documentation of history of chronic bronchitis.' The field investigator also noticed that the site enrollment did not seem to include subjects with pneumonia. Dr. Campbell told her that that would require chest X-ray. The other items cited that the IRB approved protocol was to enroll 4 to 50 subjects per site and this site enrolled over 400 subjects including her study coordinator and two staff members in the study. I will inform you all with more information upon our review of the EIR and exhibits when received. Thanks."

By early December, officials within the Review Division were greatly concerned about Study 3014. An email exchange within the Review Division on December 10, 2002, highlighted the level of concern:

> Official 1: "read these [DSI] messages. The validity of 3014 is growing more suspect by the day."
>
> Official 2: "I think [the Division Director] agrees with us. While it might not go in the briefing document, it will eventually come back to haunt all parties involved—us if we do nothing, the public if the data is not trustworthy, and the sponsor for not having disclosed these findings to us."

On December 19, 2002, the Review Division discussed its concerns during a meeting with Aventis to prepare for and discuss the agenda for the upcoming AIDAC meeting. According to the minutes of that meeting:

> Aventis indicated that they had reviewed the Division's briefing package for the upcoming AC and having identified some areas of disagreement, they would like to discuss them. These areas are related to the conduct of study #3014 . . . The Division is concerned about the integrity of the data for this study based on recent Division of Scientific Invetigations [sic] (DSI) inspection. At the Division's request, Aventis described the monitoring process they used during the conduct of the study. They pointed to difficulties with follow-up on reported irregularities, considering the fast enrollment achieved during this trial. The following investigators were mentioned specifically: [FDA REDACTION] Anne Kirkman-Campbell, M.D. (largest enroller)- DSI issued a 483 form to this investigator. Aventis indicated that when they became aware of irregularities at this site, her participation was discontinued. The sponsor indicated that they did not identify other investigators with the same degree of irregularities as Dr. Kirkman-Campbell. [FDA REDACTION] Egisto Salerno, M.D. (third largest enroller). Aventis indicated that a 483 form was issued to Dr. Salerno the same day of this meeting and that they were unaware that Dr. Salerno was on probation [FDA REDACTION] at the time the study was conducted.

An email exchange between officials in the Review Division on December 23, 2002, highlighted the frustration of one official coming out of this meeting:

> Famous quote for future reference "There are no other Kirkman-Campbells in this NDA." - said by Aventis at Thursday's meeting. I suppose technically speaking they are correct, since there is only one Kirkman-Campbell. I just wish we could find even a single credible large-enrolling site in 3014.

B. Inspections of Second and Third Highest Enrolling Sites in Study 3014—Drs. Lang and Salerno

According to DSI officials interviewed by the Committee staff, it is relatively routine for DSI to inspect several of the highest enrolling sites as part of FDA's review of an NDA. A number of Review Division officials also stated that it was common for there to be isolated data integrity problems in clinical studies, especially in a large study, conducted in a usual-care setting. The Office Director described Study 3014 as an "experiment."

After the data integrity concerns identified at Dr. Kirkman-Campbell's high-enrolling site, the Review Division submitted requests to DSI on November 13, 2002, for inspections of the second and third highest enrolling sites prior to the AIDAC meeting. The Division Director requested that inspections be performed and Inspection Summary Results be provided for Dr. Carl Lang, who enrolled 251 subjects, and Dr. Egisto Salerno, who enrolled 214. Based on the Committee Staff's review of emails, there appeared to be a sense of urgency among DSI staff to get these additional inspections completed before the AIDAC meeting. The day after the Review Division submitted the request, DSI sent it to the regional field investigators, setting a deadline of December 20, 2002, for completion of the inspections.

The FDA's inspection of the second highest enrolling site was completed prior to the AIDAC meeting, and the investigators found some of the same GCP problems that were seen at Dr. Kirkman-Campbell's site. On December 23, 2002, a DSI official notified two Review Division officials regarding its inspection of the second highest enrolling site:

> The 483 for Dr. Lang is being drafted and will be issued 12/30. The inspector is seeing some similar problems found at Kirkman Campbell. The issues were 251 subjects enrolled over the the [sic] max 50 recommended, enrolling study coordinator and his family, inadequate documentation that subjects were not hypersensitive to beta-lactam and macrolide antibiotics, some records lacked documentation of negative pregnancy test results for wocbp, and drug accountability log entries were not concurrent. Also the site shipped laboratory samples incorrectly, and numerous laboratory samples were beyond stability. When we receive the 483, [DSI will] fax it to you . . . .

Shortly thereafter, the email was circulated within the Review Division, including to the Division Director and the Office Director, with the message:

> As you may recall, Dr. Lang is the second largest enroller in study # 3014, with 251 patients. The first enroller was Dr. Kirkman-Campbell with 407 patients, and a 483 was issued to her too. The third enroller (214 patients) was Dr. Salerno, who had his license suspended at the time of the study, as per the California Medical Licensing Board. This brings the total of 872 patients (3.5%) with questionable data."

The FDA ran into some difficulties with the inspection of the third highest enrolling site. An email exchange between a DSI official and Review Division officials, dated December 4, 2002, identified problems encountered in attempting to inspect the third highest enrolling site:

> FDA Investigator [] is trying to arrange the inspection with Dr. Salerno . . . he is out on medical leave, for brain tumor, until January. Due to the pending advisory meeting and PDUFA due date, we have asked . . . to see if the study coordinator could provide access to the records earlier. Meanwhile, [the field investigator] emailed me the following "interesting reading" on Dr. Salerno. It appears that there may be problems with his study site too, even before starting the inspection.

According to the "interesting reading," in June 2001, Dr. Salerno had been disciplined by his state Medical Board for gross negligence and failing to maintain adequate and

accurate medical records. He was placed on 2 years probation. In May 2002, a state judge also ordered the temporary suspension of his medical license.

An email from a DSI official to an FDA field investigator, dated December 10, 2002, stated, "….With the new findings (see below) and your 'interesting reading' on Dr. Salerno, the review division feels it is very important to look at the quality of his data and have a report before the Advisory Committee meeting on January 8, 2003."

Aside from communicating this information regarding Dr. Salerno, DSI did not provide a report to the Review Division prior to the AIDAC meeting. However, according to a DSI memorandum to the Review Division dated January 21, 2003, DSI received the observational findings from the field investigation of Dr. Salerno on December 19, 2002 three weeks before the Advisory Committee meeting.

C. FDA Officials Aware of Red Flags Regarding Study 3014 prior to Advisory Committee Meeting

In addition to the criminal investigation of Dr. Kirkman-Campbell, the FDA had several additional red flags regarding Study 3014. Even before Aventis submitted Study 3014, FDA received at least one complaint from a study subject in Study 3014. As early as January 2002, FDA investigators interviewed a study subject enrolled in Study 3014, who "reported that following her completion of the study she complained of abdominal pain, headaches, and dry mouth. Four days later she had chills, fever (108º) and cough . . . the subject alleges that the investigator may not have reported adverse event(s)." In May 2002, DSI requested that an FDA field investigator initiate a directed inspection of this site to determine if adverse event reports were adequately documented and if the Clinical Investigator's overall conduct of the study was in compliance with federal regulations and good clinical practices.[18]

Also, in June 2002, Aventis notified FDA that data from two low-enrolling study sites, the fourth and fifth questionable sites, "cannot be confirmed or corrected, and therefore will not be included in the study."[19] Pursuant to notification from Aventis, DSI issued a request for a "for cause" inspection of one of these study sites in October 2002.

Review Division officials interviewed by the Committee Staff stated that "red flags" were apparent as soon as Aventis submitted Study 3014 in July 2002. One official stated that he recognized potential data integrity issues with Study 3014 and recalled that more than 100 centers did not adhere to the study protocol, which recommended enrollment between 4 and 50 subjects per site. Another red flag for this official was how quickly Aventis enrolled more than 24,000 patients. This official wanted to look at the study data closely because the study was conducted in a "usual care setting" where one would

[18] By letter dated May 8, 2003, the FDA notified this study site's clinical investigator that: "You did not maintain adequate and accurate records [21 CFR 312.629(b)] in that you did not document a past medical history of chronic bronchitis for subjects [4 out of 30 subjects] to support the diagnosis of acute exacerbation of chronic bronchitis; and you did not document that a visit 1 pregnancy test was performed for [a] subject."

[19] *See* footnote 4.

expect to see less rigor. On August 4, 2002, this Review Division official sent an email under the subject "Ketek – Statistical Issues" to colleagues in the Review Division, and wrote:

> When I began to look at the report it appears we have a significant under reporting of AE in the big study 3014 approx 23% while in the phase III studies about 50%. The number [Aventis] gave at our pre-NDA meeting of 50% is not true for the big study. I think more care should be given to what we want to achieve.

Several FDA officials told Committee Staff that the sponsor's past behavior on the Ketek NDA was also a red flag. As a result, these FDA reviewers and investigators stated that they were raising questions and concerns about the completeness and timeliness of the information submitted by the sponsor after FDA received the sponsor's resubmission of the Ketek NDA in July 2002. As summarized in his email dated February 19, 2006, an FDA official in the Review Division stated, "[Aventis'] 'cultural' problem is something that has been a consistent recurrent theme throughout the history of the NDA and its something that we've just had to work around."

A series of emails between FDA officials also highlight the scrutiny being given to high-enrolling sites in Study 3014. These emails between officials in OCI, DSI, ORA, and the Review Division show that a fourth high-enrolling study site in Study 3014 had problems. In fact, ORA raised to the Review Division placing a hold on the Ketek NDA. By email dated December 9, 2002, the FDA field investigator who inspected Dr. Kirkman-Campbell's site reported similar problems at a fourth study site:

> We just learned (from a source) of another [site] that should be inspected on the Ketek study . . . The town is smaller than Gadsden, AL & [the site] enrolled 99 patients . . . [including] staff and [] family members. There were scant study records & numerous informed consent violations. It looks like there were many other sites with numerous [informed consent form] violations, small towns w/large enrollment, & sites that enrolled their won [sic] staff, etc. . . . It looks like the NDA should be placed on hold until the matters are resolved.

DSI forwarded this email to the Review Division and stated:

> [The FDA investigator for Dr. Kirkman-Campbell] has unearthed more troubling news on the Ketek study. It is too late to issue an assignment now though we could certainly inspect the site post-PDUFA. I will let you know as soon as I hear any findings on Lang and Salerno.

An email dated December 23, 2002, stated:

> One thing that all three of these investigators have in common is that they enrolled a total number of patients that was in excess of the allowable amount (which was 50, I believe). I looked through the rest of the sites and there are a total of 72 sites that enrolled over 50 patients. The total number of patients at sites in which an excess of 50 patients were enrolled comes to 6,459. I'm not sure what this means. Is it common for companies to allow centers to enroll beyond the allowable amount? Is this viewed as acceptable? Obviously, the

> company is sending the investigators additional ketek to cover the additional patients, so they must be aware of this.

An email exchange on December 14, 20002, between Review Division officials, which copied the Division Director, related to the subject "High Enrollers in 3014 – food for thought":

> Official 1: "I looked at enrollment patterns for all sites in 3014 that randomized 80 patients or more; there were 30 such sites. Of these, 9/30 (30%) enrolled 1% or more of the adult population of the city or town in which they are located (based on 2000 census figures). This is equivalent to a site in Montgomery County enrolling over 6500 patients in a 3 month period. While for some sites high enrollment can be explained by the size of the catchment area, this is not true for all such sites. . . . Another point to keep in mind is that the incidences of the respiratory tract infections studied in 3014 probably don't exceed 1% in this country; thus, for those sites where high enrollment figures cannot be explained by the size of the surrounding catchment, virtually *every* patient seeking medical attention for a community-acquired RTI would have had to be enrolled for the figures to be real.
>
> Official 2: "that's very interesting and very concerning. It certainly adds further doubt as to the veracity of the study results. It seems a little unusual for a study to have so many questionable sites and it certainly raises alarms as to the way in which the study was conducted."
>
> A third official responded in early January: "I agree with your thinking on this--I would like to look at how census and CDC reporting data may help us locate fraudulent sites in NDA databases. I am not sure why so many are classified as 'Unknown Race' not Caucasian, Asian/oriental or black---could be Hispanic?? but that should have been a known category. When race and age are missing data fields it often suggests the subjects are made up. I guess without DSI's help it is very difficult to know."

Contemporaneously with the scrutiny of the high-enrolling sites, including Drs. Campbell, Lang, and Salerno, in November and December 2002, the FDA conducted an investigation of a seventh site in Study 3014 and also found objectionable observations.[20]

In his memorandum dated November 6, 2003, the Medical Team Leader summarized other red flags regarding the conduct of Study 3014. Specifically, he stated:

> The settings in which high enrollment occurred also raised concern over data integrity. Of the top 30 enrollers, 8 enrolled 1% or more of the adult population of the cities in which they were located. Although in a few sites high enrollment may be explained by proximity to large urban areas, for others the actual

[20] By letter dated February 11, 2003, FDA concluded this site "did not adhere to applicable statutory requirements and FDA regulations governing the conduct of clinical investigations . . . includ[ing] your failure to maintain completed informed consents and case report forms for study subjects, and your failure to sign the return shipment form for investigational product [21 C.F.R. 312.62 (a) and (b)]."

> enrollment is inconsistent with the enrollment predicted on the basis of the catchment population. Given the incidences of the respiratory tract infections under study and the investigational nature of this drug, this finding raises further concerns over data integrity in this study. . . . None of these issues regarding data integrity were presented at the January 2003 AIDAC meeting.

During his interview with Committee Staff, the Review Division official charged with presenting Study 3014 at the AIDAC meeting stated that he was not satisfied with what he knew about the integrity of Study 3014 and he was against presenting it at all. When asked why he presented a study he knew to have data integrity problems, the official replied that he was asked directly by the Division Director to present Study 3014 during a team meeting. He said he viewed this as a verbal instruction. He said he proposed a closed session to discuss the agency's "significant concerns" with Study 3014 with the Advisory Committee members, but was told by his Division Director that FDA could not disclose information related to an ongoing FDA investigation. The official who presented Study 3014 stated to the Committee, "[the FDA] should never have a role in deceiving the public," and added, "[a]ll of us will have a consequence for this."

Many FDA officials interviewed acknowledged that, at a minimum, Dr. Kirkman-Campbell's data should have been censored. Several officials acknowledged that, with hindsight, the AIDAC meeting should have been postponed or canceled.

II. Anti-Infective Drugs Advisory Committee Member's Comments

In October, the Committee sought comments from 11 voting members[21] of the Advisory Committee present at the January 8, 2003, meeting.[22] The Committee provided copies of two letters the Committee sent to the FDA in April and June of 2006, which outlined the allegations and concerns brought to the attention of the Committee regarding the FDA's approval and post-market surveillance of Ketek. Since October, seven Advisory Committee members have provided comments to the Committee.

The October letter to the AIDAC members requested their response to a series of questions regarding their knowledge of the data integrity problems of Study 3014 and their participation in the January 8, 2003, meeting. A table of the AIDAC members' responses is attached to this letter (Attachment 3). Information that could identify the respondents directly or indirectly has been redacted. Also redacted are references to products other than Ketek.

The data integrity problems with Study 3014 were intentionally withheld from the AIDAC members during the January 8, 2003, meeting. However, the Review Division Director stated to Committee staff that she advised members of the advisory committee of the data integrity problems with Study 3014 during a closed session of the AIDAC on March 6, 2003. Given that participation of advisory committee members may vary from meeting to meeting, the Committee asked the members who attended the January 8, 2003, meeting, "Did you attend a closed meeting of the AIDAC on March 6, 2003? If yes, do

[21] The Committee was not able to obtain contact information for one of the voting members of the January 8, 2003 Anti-Infective Drugs Advisory Committee.
[22] *See* Attachment 2

you recall whether or not the FDA discussed data integrity problems with Study 3014?" Five of the seven members who responded to the Committee's letter did not attend that meeting, and one of the two respondents who may have attended stated that Study 3014 data integrity problems were not discussed at that meeting. Therefore, even if the AIDAC did receive a status report on Study 3014 in March 2003, it appears that the FDA was not updating all of the appropriate members of the advisory committee—the members who actually voted on Ketek and recommended approval in a public forum.

Since the AIDAC voted on Ketek based, in part, on Study 3014 data, which FDA ultimately did not consider in its decision to approve Ketek, the Committee asked the AIDAC members, "If you did not attend the AIDAC meeting on March 6, 2003, when do you first recall learning about data integrity problems with Study 3014?" Five out of the 7 respondents were not aware of the data integrity problems until this year. One did not provide a response and another was not sure when he/she first became aware of the problems. Two members stated that they were not aware of the data integrity problems associated with Study 3014 until they read a report in the media regarding Ketek. Two other members first learned of the data integrity problems associated with Study 3014 when they received the Committee's letter.

A copy of DSI's March 2004 memorandum, which outlined DSI's findings and recommendations regarding the data integrity of Study 3014, was provided to the AIDAC members as an attachment to the Committee's October letter. The AIDAC members were asked about their awareness of the extent of data integrity problems associated with the conduct of Study 3014 prior to reviewing the DSI memorandum, and none of the respondents stated that they had been aware of the extent of the problems. For example, one AIDAC member stated, "I was not aware of the extent of data integrity problems until I received a letter dated July 7, 2006, from the FDA that included Senator Grassley's letter dated June 7, 2006, and subsequent materials from Senator Grassley's office dated October 27, 2006." Another stated, "I was certainly not aware that FDA had decided to withdraw any consideration of Study 3014 in their decision but there was discussion, limited, at the 2nd Advisory Committee meeting concerning the availability and validity of the EU data."

Several AIDAC members also responded that knowledge of the data integrity problems might have affected their vote. The Committee asked each member "Do you believe your vote and recommendations regarding the risk-benefit profile of Ketek would have changed if the FDA had disclosed that Study 3014 had some data integrity problems and that the FDA was still reviewing the extent of the problems?" Two members stated their votes would have changed, and one of those individuals added that had the information been revealed to the advisory committee, "the meeting might well have gone a different way." Another AIDAC member said that he/she would have recommended postponing the decision on Ketek "until the extent and significance of the data integrity problems were better defined," while another said he/she would have sought more information about the nature and extent of the problems.

Furthermore, several AIDAC members did not share the Office Director's opinion that it would not have been "productive" to spend time on issues regarding data integrity and the conduct of Study 3014. While some of them responded that there are conditions

under which known data integrity problems could be withheld from an advisory committee, such as information associated with an ongoing investigation or minimal or trivial data integrity issues, others felt that the advisory committee should have been informed of the problems with Study 3014. For example, one respondent stated, "I believe that all information of note or with significant ramifications should be made available to the committee." One of the respondents who commented that it would be appropriate to withhold trivial information from the advisory committee noted that "study 3014 appears to be riddled with problems and these should have been disclosed to the subcommittee (in a confidential manner if necessary)." Five of the respondents also answered that FDA should have disclosed data integrity problems to the AIDAC, especially when the problems are "as extensive and potentially significant as the problems evident with Study 3014" or "problems that may have affected the validity of the data."

In addition to specific questions related to Study 3014 and the Janaury 8, 2003 AIDAC meeting, the Committee's October letter asked the AIDAC members to provide any additional comments or concerns regarding Ketek or any other matter. One respondent's comments raised further questions about FDA's decision to present Study 3014 to the advisory committee on January 8, 2003. During his interview with Committee staff, the Office Director stated that he decided to proceed with the AIDAC meeting because he wanted the advisory committee's input on all of the data to be assessed (animal and human trials, Study 3014, and foreign post-marketing data). He added that based on the data that he saw, there was a reasonable chance that the advisory committee would raise concerns about Study 3014.

However, it appears that the Review Division Director spoke so positively at the AIDAC meeting about the data in support of Ketek's approval that it is not surprising that the advisory committee did not raise concerns about Study 3014. One AIDAC member wrote specifically, "…the Ketek case represents an error of commission, allowing the hearings to go forth under false circumstances. [The Review Division Director's] initial introduction to the 2nd Advisory Committee meeting is glowingly positive, which may indicate that she was not aware of any glitches in the data; if she was aware of these issues, she gave no indication that this drug should be anything but fast track approved that day."

III. Further Findings and Conclusions

When Aventis submitted Study 3014 to the FDA in July 2002, its title page included a "GCP Statement: This study was conducted in accordance with good clinical practice and Aventis standard operating procedures for clinical investigation and documentation." Aventis also provided verbal assurances to the FDA regarding the integrity of Study 3014 during a meeting held in late December 2002 to discuss the AIDAC meeting agenda, including the assurance, according to several FDA officials, that there were "no more Kirkman Campbells in Study 3014." Aside from these written and verbal assurances to the FDA regarding the integrity of Study 3014, the vast majority of documents and information available to the Committee suggest that the FDA had sufficient information to determine that Study 3014 had serious data integrity issues, which were not isolated to Dr. Kirkman-Campbell. In fact, serious questions had been raised with respect to at least

7 study sites, both high-enrolling and low-enrolling, in Study 3014. The Review Division Director and the ODE 4 Director knew, or should have known, about the extent of the concerns, questions, and problems with the data integrity of Study 3014.

Several Review Division officials indicated to the Committee that the timing of events and decisions regarding the Ketek NDA generally, and presenting Study 3014 at the AIDAC meeting specifically, were driven by concern for meeting the deadlines imposed under the Prescription Drug User Fee Act. The FDA began planning for the AIDAC meeting to review the Ketek NDA and Study 3014 within weeks after Aventis resubmitted the Ketek NDA in July 2002. The Office Director stated that ultimately it was his decision to hold the AIDAC meeting and present Study 3014 in January 2003. Further, he stated he did not consult anyone else in reaching his decision. The Division Director stated that she consulted with the FDA's Associate Director, Office of Regulatory Affairs, and the Executive Secretary of the Advisory Committee prior to deciding the Review Division should present Study 3014 at the AIDAC meeting. Both the Division Director and Office Director said that the conclusions drawn from the ongoing criminal investigation and inspections of high-enrolling study sites in Study 3014 were preliminary. The Division Director stated she did not receive a draft consultation memorandum from DSI regarding the three highest enrolling sites until after the AIDAC meeting. Therefore, she believed that issues of fraud and serious data integrity problems with Study 3014 were isolated to Dr. Kirkman Campbell's site.

Last June, the former Division Director for DSI, who is no longer at the FDA, wrote to the FDA's Director of Medical Policy to share several thoughts regarding the FDA's approval of Ketek and the Committee's investigation of these matters. With regard to the AIDAC meeting, the DSI Division Director wrote:

> It is quite unfair to say that the FDA failed to disclose the ongoing investigations to the Advisory committee. As you know, OSI and OCI never publicly reveal conclusions from an investigation until the evidence from an investigation until the evidence has been fully evaluated at headquarters, the case closed and appropriate action taken. Since most of the FDA Ketek investigations were quite complex, and often involved multiple simultaneous investigations by different authorities, I do not believe any information could have been released from OCI or DSI at the time of the Advisory committee meeting. The release of raw and unverified investigation outcomes to the Advisory committee, in the absence of a determination that a regulatory violation had occurred, would not only have been unprecedented and a violation of due process, but also would not have provided any meaningful context for Committee consideration.

Both the Division Director and Office Director confirmed to the Committee that it was their belief that they could not disclose what they knew about data integrity issues with Study 3014 at the AIDAC meeting because of an ongoing criminal investigation. Several FDA officials stated to the Committee that disclosing what the FDA knew about data integrity problems with Study 3014 during a closed session of the AIDAC meeting was not an option under FDA regulations, which limit when and how a closed session of an advisory committee may be held. The Office Director stated that it was reasonable to present Study 3014 because its findings were "consistent with other data in the Ketek NDA." He reasoned that it would be valuable for the FDA to have the AIDAC consider

the Ketek NDA despite the concerns with Study 3014. The Office Director expected that Advisory Committee members would raise more concerns regarding the Ketek NDA and that the AIDAC would come down more negatively on the drug than it did. Both the Division Director and Office Director concluded that proceeding with the AIDAC meeting was the right thing to do. Both appeared to believe that postponing or canceling the AIDAC meeting, rather than present Study 3014, was out of the question.

Consequently, the Division Director instructed a Review Division official to present Study 3014 at the AIDAC meeting despite not having a reasonable assurance of the data integrity of Study 3014. The documentary record and interviews conducted by the Committee, suggest that officials within OCI, DSI, and the Review Division raised and communicated sufficient data integrity issues regarding Study 3014 in the months preceding the AIDAC meeting to call into question the decision and judgment of the Division Director and Office Director to convene the AIDAC meeting for FDA to present Study 3014 findings publicly.

Furthermore, the aforementioned statement made by the Director of DSI with the benefit of hindsight underscores the rationale that appeared to hold sway at FDA. Despite "doubt as to the veracity of the study results," "alarms as to the way the in which the study was conducted," and concerns that "the validity of 3014 is growing more suspect by the day," "it will come back to haunt all parties involved—us if we do nothing, the public if the data is not trustworthy, and the sponsor for not having disclosed these findings to us," and, finally, "just wish we could find even a single credible large-enrolling site in 3014,"—all concerns expressed by staff within the Review Division—supervisory officials at the FDA continued to believe it was neither an option to disclose data integrity problems nor would it be "productive."

In sum, the FDA did not ensure that the public received accurate, science-based information regarding the Ketek NDA. Advisory Committee members and the public who relied on the FDA's presentation of Study 3014 were misled because not all of the relevant findings and conclusions regarding the Ketek NDA were presented. If the FDA could not find a way to present only accurate, science-based information, the FDA should not have presented Study 3014 publicly or, alternatively, should have postponed or canceled the AIDAC meeting.

Many of the FDA officials involved with the Ketek NDA are highly accomplished professionals with graduate degrees—either an M.D. or Ph.D. or both—and with numerous published works to their name. During interviews conducted by the Committee, the question was posed to a number of them: "Would you submit your work product for peer review and publishing, if you had any reason to believe your data was suspect or potentially had data integrity problems?" No official answered affirmatively.

Commissioner von Eschenbach, I appreciated the comments you made by email to all FDA staff following your confirmation. Specifically, you avowed:

> We will be a science-led regulatory agency. We will look closely at how we do business and make improvements where appropriate, and we will do this in an atmosphere of openness and with mutual respect for others' opinions. I will be

> expecting much of you, but I expect even more of myself and of FDA's leadership.

In light of your recent avowal to FDA staff and the findings presented in this letter to you today, I respectfully request answers to the allegations and questions I brought to your attention more than 6 months ago:

1. What regulations and/or policies govern withholding relevant information and/or data from an FDA advisory committee?

2. What categories of information may be withheld from an advisory committee that otherwise would be considered relevant information necessary to fulfill its advisory function?

3. Describe in detail the basis and rationale for withholding potentially detrimental information related to a safety study while presenting beneficial information from that same safety study. For example, if a matter regarding data integrity has been identified in a study and is under investigation by the Office of Criminal Investigations and/or under review by the Division of Scientific Investigations, why would it be appropriate to present study data when there are unresolved concerns about the integrity of the study data?

4. How many times since January 1, 2000, has the FDA presented study information and/or data to an advisory committee when unresolved integrity concerns existed? For instance, the data integrity concerns were the subject of an internal FDA investigation and/or review, by the Office of Criminal Investigations, the Division of Scientific Investigations, and/or an Application Integrity Policy Committee at the time of presentation?

In addition, I request answers to the following questions:

5. What is your opinion of the comments the Advisory Committee members provided to the Committee? Do you share their concerns?

6. What steps, if any, has FDA taken since the allegations regarding the January 8, 2003, AIDAC meeting were brought to your attention?

7. Given the explanation provided by the Division Director and Office Director as to why data integrity issues with Study 3014 were not shared with the Advisory Committee members, *i.e.*, ongoing criminal investigation and a closed session of the AIDAC meeting was not an option under FDA regulations, will you reconsider how FDA will handle such matters in the future? Under what conditions, if any, do you believe known serious data integrity problems and/or other information that would be relevant to an advisory committee discussion should be withheld from an advisory committee by the FDA?

I look forward to hearing from you regarding the allegations, concerns, and questions set forth in this letter by no later than January 17, 2007. If you anticipate any difficulty in complying with the deadline, please immediately contact my Committee Staff. Any questions or concerns should be directed to . All formal correspondence should be sent via electronic transmission in PDF format or via facsimile to and original by U.S. mail.

Sincerely,

Charles E. Grassley
Chairman

Attachments

ATTACHMENT 1

Timeline of Major Events Related to FDA's Approval and Post-market Surveillance of Ketek

Date	Event
February 28, 2000	Aventis submits New Drug Application (NDA) for Ketek to FDA
April 26, 2001	First Anti-Infective Drugs Advisory Committee (AIDAC) meeting on Ketek – committee recommends that Aventis obtain additional safety information from a large sample of patients
June 1, 2001	FDA sends Aventis an approvable letter for the indications of community-acquired pneumonia, acute bacterial sinusitis, and acute exacerbation of chronic bronchitis and requests a large safety study to evaluate hepatic, cardiac, visual and vasculitic effects FDA sends non-approval letter for Ketek for the indication of tonsillopharyngitis
July 2001	Ketek is approved for marketing in Europe
September 27, 2001	Aventis completes design of the protocol for Study 3014, a large usual care study
October 19, 2001	Aventis enrolls the first subject in Study 3014
January 29, 2002	Aventis enrolls the last subject in Study 3014; more than 24,000 patients are enrolled at 1824 sites
October 2001-June 2002	PPD, the contract research organization selected by Aventis to monitor Study 3014, conducts on-site and phone monitoring of the study sites
June 25, 2002	Aventis notifies FDA that data from two low-enrolling study sites could not be confirmed or corrected and thus would not be included in the study
July 24, 2002	Aventis resubmits NDA to FDA with data from Study 3014 and foreign post-marketing safety data from first million prescriptions
September 27, 2002	FDA's Division of Scientific Investigations (DSI) issues inspection assignment on the highest enrolling site of Study 3014, the site of Dr. Marie "Anne" Kirkman-Campbell
October 15-24, 2002	FDA investigators inspect Dr. Kirkman-Campbell's site and find study protocol violations and concerns regarding the conduct of the study, including enrollment of patients who should have been excluded, e.g., for drug allergies, documentation of patients having completed the course of therapy even though those patients stated that they did not receive the medication, and absence of any reported adverse events for the first 100 patients enrolled
October 31, 2002	FDA's Office of Criminal Investigations formally initiates investigation of Dr. Kirkman-Campbell
November 14, 2002	DSI issues inspection assignments on the second and third highest

ATTACHMENT 1

Date	Event
	enrolling sites of Study 3014, the sites of Dr. Carl Lang and Dr. Egisto Salerno
December 19, 2002	DSI receives observational findings from the inspection of Dr. Salerno's site; Dr. Salerno was disciplined by his state Medical Board for gross negligence and failing to maintain adequate and accurate medical records, and was on probation at the time of his participation in Study 3014
December 30, 2002	DSI receives observational findings of inspection of Dr. Lang's site; field investigators identified Good Clinical Practices violations, including enrollment of patients who should have been excluded and significant documentation discrepancies
January 8, 2003	Second AIDAC meeting on Ketek; data from Study 3014 and foreign post-marketing data are presented to the advisory committee; majority of AIDAC members votes for approval of Ketek for CAP, ABS, and AECB
January 21, 2003	DSI provides its Clinical Inspection Summary of the site inspections of Drs. Kirkman-Campbell, Lang, and Salerno to the Division of Anti-Infective Drug Products, the division responsible for review of the Ketek NDA
January 24, 2003	FDA sends approvable letter to Aventis requesting further information on Study 3014 and additional foreign post-marketing safety data
April 2, 2003	FDA inspects Aventis to assess sponsor's oversight of Study 3014
October 17, 2003	Aventis resubmits NDA to FDA
October 23, 2003	Dr. Kirkman-Campbell pleads guilty to fraud
March 25, 2004	DSI concludes that data from Study 3014 is unreliable
April 1, 2004	FDA approves Ketek for the treatment of community-acquired pneumonia, acute sinusitis, and acute exacerbation of chronic bronchitis
January 20, 2006	FDA issues public health advisory on Ketek
January 26, 2006	*Annals of Internal Medicine* releases article on three cases of liver damage in North Carolina patients who took Ketek
May 1, 2006	*Wall Street Journal* article on fraud associated with Study 3014
June 8, 2006	Sanofi-aventis voluntarily pauses enrollment in pediatric trials of Ketek
June 29, 2006	Sanofi-aventis revises Ketek labeling to include additional warnings about the risk of liver toxicity as well as strengthening warnings for patients with myasthenia gravis

ATTACHMENT 2

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

October 27, 2006

Dear Dr.

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage, including prescription drugs, under those programs.

As Chairman of the Committee, I initiated an investigation in April of this year into the approval and post-market surveillance of telithromycin (Ketek) by the Food and Drug Administration (FDA). A primary concern is that the FDA and Aventis Pharmaceuticals (Aventis) publicly presented a large drug safety study to the Anti-Infective Drugs Advisory Committee (AIDAC) without disclosing known data integrity problems with the study or censoring suspected fraudulent data.

As a member of the AIDAC, you may recall that the FDA convened the AIDAC twice, on April 26, 2001, and January 8, 2003, to consider the safety and efficacy of Ketek. At the first meeting, the AIDAC voted for approval of Ketek for the indication of community-acquired pneumonia and recommended that Aventis obtain additional safety data from a large sample of patients before it could recommend approving Ketek for acute sinusitis and acute exacerbation of chronic bronchitis. The FDA acted on this recommendation by requesting that Aventis conduct a large safety study to evaluate the risks of toxicity with Ketek, including hepatic, visual, cardiovascular, and vasculitic adverse events. Aventis enrolled the first patient in its large usual-care safety study, identified as "Study 3014," in October 2001 and closed enrollment at over 1,800 physician practice sites by January 2002. Aventis enrolled over 24,000 patients in a little over three months, submitted Study 3014 to the FDA in July 2002, and presented its findings at the second AIDAC meeting in January 2003. The FDA also presented data from Study 3014 at the second meeting, but elected not to disclose to AIDAC members the fact that the FDA's Division of Scientific Investigations (DSI) and Office of Criminal Investigations were actively reviewing and investigating serious data integrity problems at numerous sites, including suspicions of fraud. The AIDAC voted to recommend approval of Ketek at this second meeting.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

MEMORANDUM

DATE: March 25, 2004

TO: [redacted] Regulatory Health Project Manager
[redacted] Medical Officer
[redacted] Team Leader
Division of Anti-Infective Drug Products, HFD-520

FROM: [redacted]
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

THROUGH: [redacted] Branch Chief, GCP-II
[redacted] Director
Division of Scientific Investigations, HFD-47

SUBJECT: DSI Recommendations on Data Integrity

Re: NDA 21-144, Ketek (Telithromycin), protocol HMR3647A/3014 entitled: "A 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"

ASSESSMENT:

The sponsor's monitoring program for study 3014 uniformly failed to detect data integrity problems when they clearly existed. FDA inspected eight sites that reflected the highest enrollers in study 3014. Each of these sites received the sponsor's highest level of scrutiny: on-site monitoring by the contract research organization during the trial, with two of these sites also receiving quality assurance audits by the sponsor. These eight sites thus represented the sponsor's best effort to detect data integrity problems.

Comparison of findings from FDA inspections with the sponsor's monitoring/audit findings revealed that the sponsor/CRO failed to detect the systematic problems detected during the FDA inspections. FDA inspection revealed serious data integrity problems at four of the eight sites (sites 1129, [redacted], [redacted], and [redacted], and the data from these sites should not be considered acceptable for evaluation. The clinical investigator at another site (site 1057) was not qualified to conduct the clinical trial (investigator was on probation from the state Medical Board for gross negligence and failure to maintain adequate and accurate medical records). Shortly after the study ended, the investigator was arrested for being under the influence of and possession of cocaine; he has since surrendered his medical license. Although the FDA inspection of his site did not identify serious non-compliance, data integrity from this site is highly suspect.

FDA did not inspect the sites that were monitored remotely by the sponsor (remote monitoring consisted of weekly phone calls by the sponsor to the site). Although there is no objective data to evaluate the sensitivity of this monitoring, we expect that the remote monitoring would be far less effective in detecting data integrity problems than on-site monitoring.

RECOMMENDATION:

Based on observations of non-compliance with FDA regulations and multiple instances of fraud detected at four of eight high-enrolling sites that FDA inspected, DSI recommends that data from sites 1129, [redacted], [redacted], and [redacted] should be excluded from consideration in the NDA. In addition, the data from site 1057 is highly suspect since we consider that this clinical investigator was not qualified to perform clinical trials. Monitoring of study sites by the sponsor/CRO failed to detect the significant problems found during the FDA inspections, calling into question the utility of the sponsor monitoring to detect data integrity problems. If the on-site monitoring of these eight sites did not detect the significant problems, there is no reason to expect that the on- or off-site monitoring of all other sites would have fared better at detecting significant problems. For these reasons, the integrity of data from all sites involved in study 3014 cannot be assured with any degree of confidence.

BACKGROUND:

After review of the initial submission and resubmission for telithromycin (NDA 21-144), questions remained regarding the overall data integrity of study 3014 and what role it could have in support of the marketing application. Inspections conducted by FDA of three sites (Drs. Anne Kirkman Campbell, Carl R. Lang, and Egisto Salerno) revealed numerous irregularities and/or violation of good clinical practices during the conduct of the study (see specific findings below). In response to Question 1.A.1 of the January 24, 2003 Approvable letter, Aventis Pharmaceuticals, Inc. (sponsor) submitted an amendment on October 17, 2003 with: (a) a list of the sites at which the sponsor and/or CRO conducted quality assurance audits or monitoring visits, the dates of these audits/visits, and the requested monitoring and audit documents for 89 sites, selected by FDA, out of 1824 sites; (b) records of communications between the sponsor and CRO regarding irregularities; and (c) information on specific steps taken post-monitoring to address irregularities. The Review Division requested a consultation from DSI to determine the adequacy of the monitoring program of the sponsor/CRO by reviewing and comparing the submitted information with the FDA inspectional observations for eight high-enrolling sites (#1129-Campbell, #96-Lang, #1057-Salerno, [redacted], [redacted], [redacted], [redacted], and [redacted]).

Study 3014 was conducted in 2001/2002 at 1824 United States clinical sites with 24,562 subjects enrolled. The monitoring plan called for on-site monitoring of all high-enrolling (more than 15 subjects) sites, research naïve sites, and sites where good clinical practice findings raised concerns about study conduct; at least 25 % of enrolled subjects were to have source data verification. The monitoring plan also called for central monitoring via weekly telephone calls. The applicant provided the following information on the monitoring and investigator site audits:

- 952 of 1824 (52%) enrolling sites were monitored on site.

- 26,646 scripted telephone contacts were completed.
- 9376 out of 24,562 (38%) enrolled subjects had 100% source data verification.
- 10 audits of high-enrolling sites were performed between December 2001 and April 2002.

SPECIFIC FINDINGS:

FDA inspection of eight sites revealed numerous instances of non-compliance at each site. Although findings varied by site, the non-compliance included informed consent issues, protocol violations (i.e., enrolling ineligible subjects, safety laboratory results not obtained at all or not within the required time frames), inadequate and inaccurate record-keeping, non-reporting or late reporting of adverse effects to the sponsor, or not obtaining IRB approval for a research change (enroll more than 50 subjects). Specifically, the FDA inspection of site [redacted] revealed that many subjects had visit 2 safety laboratory tests performed well outside of the required interval; the FDA inspections of sites #1129 (Campbell), [redacted] and [redacted] raised serious concerns as to whether subjects existed, were eligible for the study, received study medication, and completed the study. The latter three cases were referred to the Office of Criminal Investigations (OCI). The OCI investigation of site #1129 (Campbell) resulted in Dr. Campbell pleading guilty to one count of a federal indictment on the charge of mail fraud. OCI has not to date investigated the other two sites.

1. Site #1129 (Campbell)

   a. The FDA inspection revealed that the site enrolled 407 subjects; no subjects were reportedly discontinued. There were major documentation problems to ensure that subjects fulfilled the eligibility criteria, failure to obtain IRB approval for enrollment of 357 subjects in excess of 50 subjects; drug accountability and data discrepancies.

   b. The monitoring revealed concerns about subject enrollment/randomization, the informed consent process, and source documentation practices. The analysis of laboratory values for multiple patients was suspiciously similar; there were very few adverse events (AEs) reported to the sponsor.

   c. The OCI investigation revealed that one subject (subject 26) was fictitious; many other subjects never participated in and/or completed the study. Some subjects never had blood drawn; blood from other persons was substituted and sent for laboratory analysis.

2. Site [redacted]

   a. The FDA inspection revealed that the site enrolled 116 subjects; no subjects were reportedly discontinued. For three subjects, progress notes for the study visits appear to be backdated as the form bears "Printed April 2003" and the data was recorded approximately 1-1/2 years before the form was printed. Multiple source documents were maintained for four subjects, with conflicting information. There were also many discrepancies between data on the source documents and case report forms (CRFs).

b. The monitoring revealed that source documents generally did not denote if subjects met the inclusion/exclusion criteria or were women of child bearing potential (WOCBP).

3. Site [redacted]

a. The FDA inspection revealed that the site enrolled 99 subjects; two subjects were discontinued due to adverse events. There was a questionable pattern of enrolling 12 community acquired pneumonia (CAP) subjects. During the inspection, Dr. [redacted] refused to provide a subject roster list, with identifying information such as address and social security number, citing subject confidentiality. Without this information, we cannot confirm the existence of these subjects.

b. The monitoring revealed that source documents were inadequate to support the qualifying diagnosis for 15 subjects; for 17 subjects, their initials on the informed consent document appeared different than their signature on the informed consent document; and there was low AE reporting.

4. Site [redacted]

a. The FDA inspection revealed that 121 of 168 subjects enrolled had visit 2 safety laboratory tests performed outside the requisite time frame (study days 17 to 22) in that 25 subjects had visit 2 later than study day 30, seven had visit 2 later than study day 50, six had visit 2 later than study day 100, and one had visit 2 on study day 153.

b. The monitoring revealed that there were discrepancies in drug accountability, safety laboratory results were not obtained for three subjects at visit 2, and the site had lower than average ($\leq$ 10%) AE reporting.

5. Site #0096 (Lang)

a. The FDA inspection revealed that the site enrolled 251 subjects. There was inadequate record keeping to ensure subject eligibility; the laboratory test results required at visit 1 and 2 were not obtained for 27 subjects and 12 subjects, respectively.

b. The monitoring revealed that 43 laboratory specimens, some from visit 1 and some from visit 2, were beyond stability; Dr. Lang and his study coordinator were not aware of the complete definition and reporting requirements of serious adverse events (SAEs) and adverse events of special interest (AESIs).

6. Site #1057 (Salerno)

a. The FDA inspection revealed that the site enrolled 171 subjects. For six subjects, the required safety laboratory tests were not obtained at visit 2; records were inconsistent whether seven subjects completed the study.

b. The monitoring revealed that source documentation for most subjects was missing the outcome of visit 3; for WOCBP, there was generally no documentation of the performance and/ or results of a pregnancy test.

c. At the time the sponsor hired Dr. Salerno as an investigator, he was on probation from the Medical Board of [redacted] (gross negligence and failure to maintain adequate and accurate medical records). As such, the sponsor did not fulfill its obligation to select a qualified investigator to perform a clinical trial. Shortly after the study ended, Dr. Salerno was arrested for being under the influence of cocaine; chasing non-existent people with a loaded weapon and threatening to kill his wife. When arrested, he possessed cocaine, numerous unregistered weapons and 300 rounds of ammunition at his home. Dr. Salerno has since surrendered his medical license. This information appears on the Medical Board of [redacted] website ([redacted])

7. Site [redacted]

a. The FDA inspection revealed that the site enrolled 168 subjects. Dr. [redacted] did not promptly report an AESI for one subject to the sponsor; there was no documentation that a pregnancy test was performed for six subjects.

b. The monitoring revealed informed consent violations; subject enrollment was temporarily suspended until a revised informed consent document was obtained from the IRB. Many adverse effects (1 AESI, 3 SAEs, and 52 AEs) were not reported to the sponsor.

8. Site [redacted]

a. The FDA inspection revealed that the site enrolled 81 subjects. Dr. [redacted] did not report all AEs experienced by eight subjects to the sponsor.

b. The monitoring revealed that two subjects missed visit 2 safety lab draws and two subjects had unscheduled hepatic labs drawn at visit 3.

cc:
NDA 21-144
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s/[redacted]
HFD-45/RF

[redacted]

Attached are two letters, dated April 27 and June 7, 2006, that outline a number of the allegations and concerns that were brought to the attention of the Committee regarding the FDA's approval and post-market surveillance of Ketek. Please note that I requested that the FDA provide each AIDAC member a copy of the June 7 letter, which states, in pertinent part:

> The [AIDAC] never knew, and its members may still not know, that it based its conclusions partly on fraudulent clinical trial data. The agenda for the second meeting of the advisory committee indicates that the large safety study at issue here was a key item under consideration because the committee had requested that the drug company conduct the study at its first meeting. The attached email demonstrates that FDA management took a calculated gamble when it decided to present the large safety study without disclosing its data integrity problems. In this email, an FDA office director stated that it would not be "productive" to spend time on issues regarding data integrity and study conduct in front of the advisory committee. So, FDA presenters withheld this information from the advisory committee. Not surprisingly, the drug company did not mention any problems with the study either. . . . Not only was the advisory committee not playing with a full deck, the FDA intentionally stacked the deck against the committee.
>
> Withholding select information and presenting fraudulent information to an FDA advisory committee has tremendous consequences for the integrity of the advisory committee system. If the value of an advisory committee is to provide independent expert advice, to lend credibility to the FDA's review process, and to allow for public discussion of controversial issues, then it is essential for the advisory committee to have the relevant and truthful information it needs to fulfill its advisory function. If fraudulent information is presented or relevant information is withheld, as a matter of policy, expediency, or whim, then the value of the advisory committee system itself has been subverted.

Please also find attached a copy of the aforementioned email, as well as a copy of the DSI memorandum, dated March 25, 2004, which states that Study 3014 involved "multiple instances of fraud" and that "the integrity of data from all sites involved in [the] study . . . cannot be assured with any degree of confidence."

Pursuant to the Committee's ongoing investigation, I ask that you assist the Committee by responding to the following questions and requests for information related to your participation at the January 8, 2003 AIDAC meeting:

1. Did you receive a copy of my June 7 letter?

2. Have any FDA officials contacted or communicated with you since publication of the article, "Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review," by the *Annals of Internal Medicine*, in January 2006? If yes, please describe each communication.

3. Did you attend a closed meeting of the AIDAC on March 6, 2003? If yes, do you recall whether or not the FDA discussed data integrity problems with Study 3014?

4. If you did not attend the AIDAC meeting on March 6, 2003, when do you recall first learning about data integrity problems with Study 3014?

5. Prior to reviewing the DSI memorandum regarding Study 3014, were you aware of the extent of the data integrity problems and fraud associated with the conduct of Study 3014? For example, were you aware that FDA decided that Study 3014 could not be relied upon for regulatory purposes and reportedly did not rely upon it to approve Ketek? Were you aware that in the absence of the safety data from Study 3014, the FDA relied upon foreign post-marketing data to assess the risk-benefit profile of Ketek? If yes, please describe how much you knew about the problems with Study 3014.

6. To what extent did you base your vote and recommendations regarding the risk-benefit profile of Ketek on data from Study 3014? For example, of the three principal sources of clinical data to assess the safety of Ketek (Study 3014, foreign post-marketing data, and Phase III studies) how much weight did you give to each?

7. Do you believe your vote and recommendations regarding the risk-benefit profile of Ketek would have changed if the FDA had disclosed that Study 3014 had some data integrity problems and that the FDA was still reviewing the extent of the problems?

8. After reviewing the attached email, do you share the FDA official's opinion that it would not have been "productive" to spend time on issues regarding data integrity and the conduct of Study 3014?

9. Do you believe the FDA and/or Aventis were ethically obligated to disclose known data integrity problems to AIDAC members?

10. Under what conditions, if any, do you believe known data integrity problems should be withheld from an advisory committee meeting by the FDA or a sponsor? For example, the FDA has asserted that it could not jeopardize an ongoing investigation(s) related to 3014 by disclosing that it was under review and investigation. Is this rationale acceptable to you?

11. Provide any additional comments or concerns you may have regarding Ketek or any other matter. For example, are you aware of any situation where the FDA or any company may have withheld information that you believe to be relevant or presented information that you believe to be suspect.

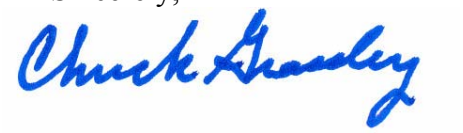
Attached is a copy of these questions, which you may use to fax your responses to the Committee at .

In closing, please hold this letter and attachments confidential and please do not consult your AIDAC colleagues, or anyone at the FDA, in preparing your responses. I have asked my staff to follow-up with you personally upon receipt of your responses. In

the meantime, should you have any concerns, please do not hesitate to contact

Thank you in advance for your assistance with these important matters.

Sincerely,



Charles E. Grassley
Chairman

Attachments

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

April 27, 2006

Via Electronic Transmission

Andrew C. von Eschenbach, M.D.
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

The Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs, and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage, including prescription drugs, under those programs.

As Chairman of the Committee, I am writing to inform you that the Committee has been investigating extremely troubling allegations related to, among other things, the approval and post-market surveillance of telithromycin (Ketek) by the Food and Drug Administration (FDA). The FDA approved Ketek, an antibiotic manufactured by Aventis Pharmaceuticals (Aventis), on April 1, 2004, for the treatment of community-acquired pneumonia, sinusitis, and acute exacerbation of chronic bronchitis. Several serious allegations related to Ketek have been brought to the attention of the Committee. Among the most troubling are allegations that the FDA approved Ketek despite unresolved questions about the drug's safety and efficacy and with full knowledge that some of the clinical safety data supporting its approval was beset by systemic data integrity problems.

Documents and information available to the Committee reveal that at least one of the "three principal sources of clinical data to assess the safety of telithromycin: Study 3014" was fraudulent, in whole or in part. In particular, a memorandum, dated March 25, 2004, prepared by the FDA's Division of Scientific Investigations (DSI) and entitled, "DSI Recommendations on Data Integrity," states unequivocally that Study 3014 involved "multiple instances of fraud" and that "the integrity of data from all sites involved in [the] study . . . cannot be assured with any degree of confidence." Additional allegations brought to the attention of the Committee assert that FDA management:

1. accepted from Aventis the resubmission of a new drug application for Ketek, which included fraudulent data in support of approval of Ketek;
2. instructed FDA scientists preparing to appear before an advisory committee that they should present fraudulent data because discussing

issues regarding data integrity and the conduct of the safety study would not be "productive";

3. presented fraudulent study data to an advisory committee tasked with recommending Ketek's approval or disapproval;
4. approved a pediatric clinical trial of Ketek, involving infants as young as six-months old, despite concerns related to known toxicities, including hepatic, visual, cardiovascular, and vasculitic adverse events; and
5. continued to knowingly cite fraudulent study data in publicly released safety information on Ketek.

Given that an advisory committee had recommended conducting Study 3014 in the first place, theses allegations are all the more outrageous. Specifically, in April 2001, Ketek was first brought before an advisory committee (the Anti-Effective Drugs Advisory Committee (AIDAC)) to consider the question: "*Given the risks of cardiac and hepatic toxicity of [Ketek], does efficacy for [Ketek] in respiratory infections support its use for … community acquired pneumonia; acute exacerbation of chronic bronchitis; and acute sinusitis?*" Based on continued concerns related to the toxicity of Ketek, AIDAC recommended that Aventis conduct a large clinical safety study. Accordingly, by letter dated June 1, 2001, the FDA asked Aventis to conduct just such a safety study:

> It would be helpful . . . to assess further adverse events associated with [Ketek], particularly in patients at increased risk for potential drug related toxicity. . . . This study should include the monitoring and analysis of all adverse events, with particular attention to hepatic, visual, cardiovascular, and vasculitic adverse events. Investigations of any mortality outcomes by investigators should be conducted to evaluate optimally possible cardiac or liver toxicities or evidence of systemic vasculitis.

Aventis agreed to conduct a large safety study -- designated Study 3014 -- and subsequently submitted the results of Study 3014 to the FDA, despite allegedly knowing and not fully disclosing that the study was fraught with data integrity problems. When AIDAC reconvened to consider Ketek's risks and Study 3014, the safety study it had requested, the FDA presented data from Study 3014 without disclosing, in closed or open session, the fact that DSI and the FDA's Office of Criminal Investigation (OCI) were actively investigating both the integrity and conduct of the study. Without the benefit of this relevant information, AIDAC members voted to recommend approval of Ketek. The AIDAC board members would undoubtedly have been interested to know that the highest enrolling sites in Study 3014 were being investigated for major problems and that there appeared to be "significant under reporting of [adverse events]." For example, the principal investigator at the highest enrolling site was found to be enrolling patients when the clinic was closed and patient consent forms at the site were found to have date modifications and signature inconsistencies. In August 2003, eight months after the AIDAC meeting, this particular investigator was indicted for falsifying study data, pleaded guilty in October 2003, and in March 2004 was sentenced to 57 months in jail.[1]

[1] http://www.fda.gov/fdac/departs/2004/404_upd.html#fraud

It is even more shocking that the FDA continued to cite Study 3014 in publicly released safety information for Ketek. Just a few months ago, on January 20, 2006, the FDA issued a Public Health Announcement (PHA),[2] following the publication of an article in the *Annals of Internal Medicine*, which reported that three patients experienced serious liver toxicity, one case required liver transplantation and one resulted in a patient death, following administration of Ketek.[3] Coincident with the PHA, the FDA also publicly released a document entitled, "Questions and Answers on Telithromycin (marketed as Ketek)" (Ketek Q&A), which stated, in pertinent part:[4]

> **What information was known about liver problems related to telithromycin prior to approval?**
>
> Based on the pre-marketing clinical data it appeared that the risk of liver injury with telithromycin was similar to that of other marketed antibiotics.
>
> *Prior to approval, FDA looked extensively at the potential for hepatic toxicity in patients treated with Ketek. The data examined included a 25,000 patient controlled study, as well as information in nearly 4 million postmarketing prescriptions outside the United States*. Ketek was the subject of two advisory committee meetings with input from a national expert on drug-induced liver disease. The committee concluded that the risk for hepatotoxicity from Ketek was similar to Augmentin and erythromycin which are other approved antibiotics. (emphasis added).

In this Ketek Q&A, the FDA cited the very study that DSI determined in March 2004 had "multiple instances of fraud" and that "the integrity of data from all sites involved in [the] study . . . cannot be assured with any degree of confidence." It defies explanation why the FDA would continue to cite Study 3014 in safety information for Ketek provided to the American public and do so without also disclosing that the advisory committee's recommendation came without knowledge that Study 3014 was fraudulent, in whole or in part. Please explain in detail why the FDA has continued to cite Study 3014 in its safety information for Ketek. Further, why would disclosing this information to AIDAC not be "productive"?

The Committee has also received equally serious allegations related to the post-market surveillance of Ketek. For example, there is presently an ongoing, FDA-approved pediatric clinical trial of Ketek, known as "TELI COM – Telithromycin in Children With Otitis Media."[5] Despite the known toxicities of Ketek, including evidence of hepatic, visual, cardiovascular, and vasculitic adverse events, the FDA is allowing Aventis to experiment with Ketek on children as young as six-months old. For example, my Committee Staff is aware of a report submitted to the FDA's Adverse Event Reporting System that details a suspected visual adverse event in a 15-month old girl participating in the pediatric trial. According to the report, on three occasions the mother observed her baby girl have staring spells one day after taking Ketek. One time the staring spell lasted

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[2] http://www.fda.gov/cder/drug/advisory/telithromycin.htm
[3] http://www.annals.org/cgi/reprint/144/6/415.pdf
[4] http://www.fda.gov/cder/drug/infopage/telithromycin/qa.htm
[5] http://www.clinicaltrials.gov/ct/show/NCT00315003?order=2

for 60 seconds. The investigator initially reported that the event was related to Ketek and "serious." According to subsequent addendums to the report, dated months later, the investigator downgraded this event -- it was later assessed to be "non-serious," not interpreted as a "visual event," and that a "staring spell is considered unexpected." Given that the Ketek label warns of severe cases of visual problems,[6] please advise the Committee what action has been taken to fully inform the parents of infants and children enrolled in this study about the risks and benefits of Ketek, including its known liver and visual toxicities.

Furthermore, as Chairman of the Committee, I respectfully request that your staff make immediate arrangements for my Committee staff to review documents and information related to Ketek and Study 3014 at the FDA, including, but not limited to, the administrative files within DSI, OCI, and the Office of Compliance. Given the gravity of the Ketek allegations, I respectfully request that your staff contact by no later than Friday, April 28, 2006, so that my Committee staff may travel to your offices as soon as possible to review the requested administrative files. If you anticipate any difficulty in complying with this deadline, please immediately contact .

As Chairman of the Committee, I also respectfully request that senior FDA management officials be prepared to brief my Committee staff within three weeks of the date of this letter. To expedite this request, my staff will be available to travel to the FDA for the briefing. I respectfully request the attendance and participation of the following individuals at that briefing:

1. Director, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)

2. Deputy Director, OND, CDER

3. Office of Drug Evaluation IV (ODE IV), OND, CDER

4. Deputy Director, ODE IV, OND, CDER

5. Director, Division of Anti-Infective Drug Products, ODE IV, OND, CDER

Please advise that they have the right to speak directly and independently to Congress, or to a Committee of Congress, without interference from the FDA if they wish, in accordance with 5 U.S.C. § 7211. Retaliation against these individuals, or any other FDA employees, who communicate with the Committee in reference to Ketek will not be tolerated. Such conduct is further punishable by 18 U.S.C. § 1505 and false statements and perjury are likewise punishable pursuant to 18 U.S.C. § 1001. Further, under 5 U.S.C. § 2302(b)(8), a federal employee authorized to take, direct others to take, recommend or approve any personnel action may not take, fail to take, or threaten to take any personnel action against an employee

[6] http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Prntlbl.pdf

because of protected whistleblowing. Protected whistleblowing is defined as disclosing information which the discloser reasonably believes evidences: a violation of law, rule, or regulation; gross mismanagement; gross waste of funds; an abuse of authority; or a substantial and specific danger to public health or safety.

Please also note that P.L. 109-115 enunciates a government-wide prohibition on the use of appropriated funds to pay the salary of any federal official who prohibits or prevents or threatens to prevent or prohibit a federal officer or employee from contacting Congress, and "any punishment or threat of punishment because of any contact or communication by an officer or employee with a Member, committee or subcommittee."

Finally, I respectfully request that all FDA employees involved directly or indirectly with Ketek be immediately provided with a copy of this letter to inform them of their right to speak and to cooperate with Congress. All FDA employees should be informed that that no documents, records, data or information related, directly or indirectly, to Ketek shall be destroyed, modified, removed or otherwise made inaccessible to the Committee. Further, if any FDA employee believes that they have been subject to retaliation for meeting with Committee staff and/or for anything associated with the Committee's ongoing investigation of Ketek, the employee should contact the Committee immediately. Please also provide the Committee with a list of all FDA employees who were forwarded a copy of this letter.

Thank you in advance for your assistance. If you have any questions, please do not hesitate to contact

Sincerely,

Charles E. Grassley
Chairman

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

June 7, 2006

Via Electronic Transmission

Andrew C. von Eschenbach, M.D.
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage, including prescription drugs, under those programs.

On May 16, 2006, I wrote to ask you why fraudulent clinical trial data was referenced in safety information posted on the Food and Drug Administration's (FDA) website.[1] First of all, thank you for removing one of these references. As recently as May 17, 2006, the "Questions and Answers on Telithromycin (marketed as Ketek)" (Ketek Q&A), stated, in pertinent part:[2]

> Prior to approval, FDA looked extensively at the potential for hepatic toxicity in patients treated with Ketek. The data examined included a 25,000 patient controlled study, as well as information in nearly 4 million postmarketing prescriptions outside the United States. Ketek was the subject of two advisory committee meetings with input from a national expert on drug-induced liver disease. The committee concluded that the risk for hepatotoxicity from Ketek was similar to Augmentin and erythromycin which are other approved antibiotics. (underline added)

The revised Ketek Q&A, updated on May 18, 2006, now reads:

> ~~Prior to approval,~~ FDA looked extensively at the potential for hepatic toxicity in patients treated with Ketek. ~~The data examined included a 25,000 patient controlled study~~ **Data was examined from clinical studies**, as well as information in nearly 4 million postmarketing prescriptions outside the United States. Ketek was the subject of two advisory committee meetings with input from a national expert on drug-

[1] http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm accessed May 31, 2006.
[2] http://www.fda.gov/cder/drug/infopage/telithromycin/qa.htm accessed April 25, 2006.

> induced liver disease. The committee concluded that the risk for hepatotoxicity from Ketek was similar to Augmentin and erythromycin which are other approved antibiotics. (strikethrough and bold added)

Unfortunately, the FDA failed to remove all references posted on its website to the fraudulent Ketek safety information. Indeed, if FDA had thoroughly reviewed the Ketek safety information, it would have identified other references to the same fraudulent clinical trial data, as well as to other misleading information. For example, as of June 6, 2006, the Ketek Q&A states, in pertinent part:

> FDA has also received other reports of liver-related adverse events in patients taking telithromycin. Some of these reports were difficult to interpret because they involved patients already taking other medicines or patients with other medical conditions that might cause liver problems. In pre-marketing clinical studies, <u>including a large safety trial</u>, the occurrence of liver problems was infrequent and usually reversible. (underline added)

Another example is the FDA Public Health Advisory for Ketek, created on January 20, 2006, and posted on the FDA's website, which reads, in pertinent part:[3]

> In pre-marketing clinical studies, <u>including a large safety trial</u> and data from other countries, the occurrence of liver problems was infrequent and usually reversible. Based on the pre-marketing clinical data, it appeared that the risk of liver injury with telithromycin was similar to that of other marketed antibiotics. Nonetheless, the product label advises doctors about the potential for liver-related adverse events associated with the use of telithromycin. (underline added)

If removing one reference to fraudulent clinical trial data in the Ketek Q&A was the right thing to do, why is it appropriate for it to remain here or in other sections of the Q&A?

Second, it is disingenuous, if not outright misleading, for the FDA to remove one fraudulent reference from the Ketek Q&A while continuing to emphasize the conclusion drawn by the advisory committee that "the risk for hepatotoxicity from Ketek was similar to . . . other approved antibiotics." The advisory committee never knew, and its members may still not know, that it based its conclusions partly on fraudulent clinical trial data. The agenda for the second meeting of the advisory committee indicates that the large safety study at issue here was a key item under consideration because the committee had requested that the drug company conduct the study at its first meeting.[4] The attached email demonstrates that FDA management took a calculated gamble when it decided to present the large safety study without disclosing its data integrity problems. In this email, an FDA office director stated that it would not be "productive" to spend time on issues regarding data integrity and study conduct in front of the advisory committee. So, FDA presenters withheld this information from the advisory committee. Not surprisingly, the drug company did not mention any problems with the study either. Thus, the conclusion

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[3] http://www.fda.gov/cder/drug/advisory/telithromycin.htm accessed on May 31, 2006.
[4] http://www.fda.gov/ohrms/dockets/ac/03/agenda/3919A1_Final.pdf

the FDA has chosen to emphasize in the Ketek Q&A is called into question by the fact that the advisory committee wasn't playing with a full deck of cards. Not only was the advisory committee not playing with a full deck, the FDA intentionally stacked the deck against the committee.

Withholding select information and presenting fraudulent information to an FDA advisory committee has tremendous consequences for the integrity of the advisory committee system. If the value of an advisory committee is to provide independent expert advice, to lend credibility to the FDA's review process, and to allow for public discussion of controversial issues, then it is essential for the advisory committee to have the relevant and truthful information it needs to fulfill its advisory function. If fraudulent information is presented or relevant information is withheld, as a matter of policy, expediency, or whim, then the value of the advisory committee system itself has been subverted. Accordingly, as Chairman of the Committee, I request answers to the following questions:

1) What regulations and/or policies govern withholding relevant information and/or data from an FDA advisory committee?
2) What categories of information may be withheld from an advisory committee that otherwise would be considered necessary for the committee to fulfill its advisory function?
3) Describe in detail the basis and rationale for withholding potentially detrimental information related to a safety study while presenting beneficial information from that same safety study. For example, if a matter regarding data integrity has been identified in a study and is under investigation by the Office of Criminal Investigations and/or under review by the Division of Scientific Investigations, why would it be appropriate to present study data when there are unresolved concerns about the integrity of that data?
4) How many times since January 1, 2000, has the FDA presented study information and/or data to an advisory committee when unresolved integrity concerns existed? For instance, the data integrity concerns were the subject of an internal FDA investigation and/or review by the Office of Criminal Investigations, the Division of Scientific Investigations, and/or an Application Integrity Policy Committee at the time of presentation.

Finally, as Chairman of the Committee, I respectfully request that your staff make immediate arrangements for my Committee staff to individually interview the following FDA officials and special government employees, who were involved with the Anti-Infective Drugs Advisory Committee meeting on January 8, 2003: M.D., M.P.H.; M.D.; M.D.; , M.D.; Ph.D.; M.D; M.D.; and M.D. Please make sure that each of these individuals as well as all members of the January 8, 2003 Anti-Infective Drugs Advisory Committee are provided with a copy of this letter.

Please have your staff contact my staff by no later than June 9, 2006, to begin making arrangements for these interviews to be conducted by the end of the month. Please also provide a written response to this letter by June 21, 2006, unless it is available

sooner. If you anticipate any difficulty in complying with these deadlines, please immediately contact my Committee staff. Any questions or concerns should be directed to .All formal correspondence should be sent via electronic transmission in PDF format or via facsimile to and original by U.S. mail.

Thank you for your prompt assistance with these critical matters.

Sincerely,

Charles E. Grassley
Chairman

Attachment

From: [Medical Officer/Team Leader, Division of Anti-Infective Drug Products]
Sent: Thursday, January 02, 2003 12:31 PM
To: [Office Director, Office of Drug Evaluation 4]
Cc: [Division Director, Office of Drug Evaluation 4];
[Medical Officer/Team Leader, Division of Anti-Infective Drug Products]

Follow Up Flag: Follow up
Flag Status: Red

[Office Director, Office of Drug Evaluation 4],

DSI has sent us the 483 for the second highest enrolling site [REDACTED] for the large Ketek safety study (Study 3014); they identified some (although not all) of the same GCP problems seen in the highest enrolling site (Dr. Kirkman-Campbell), including:

* Patient enrollment far in excess of limits recommended by the IRB
* Enrollment of clinic staff in the study
* Enrollment of patients who should have been excluded (patients with drug allergy or who were nursing)
* Failure to obtain baseline LFTs in >two dozen patients (~10% of total) or on-therapy LFTs in a dozen patients.
* Significant discrepancies between source documentation and clinical investigator memos.

Dr. Kirkman-Campbell had similar GCP issues; in addition, she enrolled a substantial number of patients who presented to her clinic for weight control, and were not seeking medical attention for a respiratory tract infection. DSI has recommended exclusion of data from her site, has referred her case to the Office of Criminal Investigations, and is considering an official action such as disqualification.

The third largest enroller, Dr.[REDACTED], did not have signficant GCP violations, but had been placed on probation by the state of [REDACTED] for poor record-keeping at the that he was involved in the study; three months after the last patient was enrolled at his site, he was arrested on weapons and drug use charges.

We do not know how pervasive these problems are at this point. Since we will be asking the AC to make recommendations on the basis of the data presented to them,[REDACTED]and I would like to talk with you about the extent to which we should communicate to or discuss with the committee issues regarding data integrity and study conduct for Study 3014. Is there any time this afternoon that would work for you?

Thanks,

[Medical Officer/Team Leader, Division of Anti-Infective Drug Products]

[Redacted]
Medical Officer/Team Leader
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Voice: [redacted]
Fax: [redacted]
E-mail: [redacted]

From: [Office Director, Office of Drug Evaluation 4]
Sent: Thursday, January 02, 2003 7:09 PM
To: [Medical Officer/Team Leader, Division of Anti-Infective Drug Products]
Cc: [Division Director, Office of Drug Evaluation 4]
Subject: Re:

Follow Up Flag: Follow up
Flag Status: Red

I won't be back in the office till Monday and won't be at a place where I can talk re this this afternoon. I will be available at home tomorrow (Friday) from noon till about 2:30 and possibly in the am if that time won't work . In general I don't believe spending time on these issues in front of the AC wil be productive. I do feel that having the company make the best possible presentation of their PM data focusing on information from countries where we have confidence in reporting will be useful.

Thanks.

[Office Director, Office of Drug Evaluation 4]

Sent from my BlackBerry Wireless Handheld.

1. Did you receive a copy of my June 7 letter?

2. Have any FDA officials contacted or communicated with you since publication of the article, "Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review," by the *Annals of Internal Medicine*, in January 2006? If yes, please describe each communication.

3. Did you attend a closed meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) on March 6, 2003? If yes, do you recall whether or not the FDA discussed data integrity problems with Study 3014?

4. If you did not attend the AIDAC meeting on March 6, 2003, when do you recall first learning about data integrity problems with Study 3014?

5. Prior to reviewing the Division of Scientific Investigations (DSI) memorandum regarding Study 3014, were you aware of the extent of the data integrity problems and fraud associated with the conduct of Study 3014? For example, were you aware that FDA decided that Study 3014 could not be relied upon for regulatory purposes and reportedly did not rely upon it to approve Ketek? Were you aware that in the absence of the safety data from Study 3014, the FDA relied upon foreign post-marketing data to assess the risk-benefit profile of Ketek? If yes, please describe how much you knew about the problems with Study 3014.

6. To what extent did you base your vote and recommendations regarding the risk-benefit profile of Ketek on data from Study 3014? For example, of the three principal sources of clinical data to assess the safety of Ketek (Study 3014, foreign post-marketing data, and Phase III studies) how much weight did you give to each?

7. Do you believe your vote and recommendations regarding the risk-benefit profile of Ketek would have changed if the FDA had disclosed that Study 3014 had some data integrity problems and that the FDA was still reviewing the extent of the problems?

8. After reviewing the attached email, do you share the FDA official's opinion that it would not have been "productive" to spend time on issues regarding data integrity and the conduct of Study 3014?

9. Do you believe the FDA and/or Aventis were ethically obligated to disclose known data integrity problems to AIDAC members?

10. Under what conditions, if any, do you believe known data integrity problems should be withheld from an advisory committee meeting by the FDA or a sponsor? For example, the FDA has asserted that it could not jeopardize an ongoing investigation(s) related to 3014 by disclosing that it was under review and investigation. Is this rationale acceptable to you?

11. Provide any additional comments or concerns you may have regarding Ketek or any other matter. For example, are you aware of any situation where the FDA or any company may have withheld information that you believe to be relevant or presented information that you believe to be suspect.

ATTACHMENT 3

In an effort to prevent disclosing the identity of each respondent, Committee Staff redacted information that could identify a member of the January 8, 2003 Anti-Infective Drugs Advisory Committee directly or indirectly, including redactions of references to FDA-regulated products other than Ketek. In addition, responses to each corresponding question are presented in a random order to eliminate any identifiable pattern. For example, the respondent in the first row of one table may or may not be the same respondent in the first row of another table.

Have any FDA officials contacted or communicated with you since the publication of the article "Severe Hepatotoxicity of Telithromycin" in *Annals of Internal Medicine* in January of 2006?
Yes, I have been contacted a number of times regarding further analysis of the accumulated Ketek cases . . . .
No FDA official have contacted me regarding telithromycin
To the best of my recollection I have not been contacted by anyone in the FDA relative [sic] this matter
No
No one from the FDA has contacted me or communicated with me regarding the article.
No
No

Did you attend a closed meeting of the AIDAC on March 6, 2003? If yes, do you recall whether or not the FDA discussed data integrity problems with Study 3014?
No . . . .
I did not attend that meeting. I do not recall any data integrity problem discussion at any meeting at which I was in attendance.
No
No
Yes, integrity problems were not discussed on 3/6/03
No, I did not attend the FDA meeting on March 6, 2003. . . .
I do not remember the date of the meeting I attended, and did not keep any information but I do recall an AIDAC meeting where the drug was discussed

ATTACHMENT 3

If you did not attend the AIDAC meeting on March 6, 2003, when do you first recall learning about data integrity problems with Study 3014?
I have no specific date in mind but had probably read about it in the . . . and I believe in the same time frame heard on . . . that there were further integrity issues with the study that had been put forth at the second Advisory Committee.
No response
I first learned of data integrity problems with Study 3014 when I received the copy of Senator Grassley's June 7 letter.
I recall first learning of these issues in an article that appeared in the Wall Street Journal (May 1, 2006) by Anna Mathews, "Fraud, errors taint key study of widely used Sanofi drug."
Upon receipt of the June 7, 2006 letter.
I was first made aware of data integrity problems with Study 3014 when a reporter from the . . . contacted me to ask my opinion. . . .
I don't recall discussions about serious integrity problems

Prior to reviewing the DSI memorandum regarding Study 3014, were you aware of the extent of the data integrity problems and fraud associated with the conduct of study 3014?
I don't think I have to this day reviewed a specific DSI memo unless it was contained in substance in the June 7 letter or the documents sent recently. I was certainly not aware that FDA had decided to withdraw any consideration of Study 3014 in their decision but there was discussion, limited, at the 2nd Advisory Committee meeting concerning the availability and validity of the EU data.
I did not know anything about integrity issues Re: Study 3014
I don't recall discussions about serious integrity problems
No
I was not aware of the extent of data integrity problems until I received a letter dated July 7, 2006 from the FDA that included Senator Grassley's letter dated June 7, 2006, and subsequent materials from Senator Grassley's office dated October 27, 2006.
I was not aware of the extent of the data integrity problems and fraud associated with the conduct of Study 3014, nor was I aware if the FDA's reliance upon foreign post-marketing data to asses the risk benefit profile of telithromycin.
I was not aware of any data integrity problems with Study 3014 until I received Senator Grassley's June 7 letter.

ATTACHMENT 3

To what extent did you base your vote and recommendations regarding the risk benefit profile of Ketek on data from Study 3014?
Study 3014 was the cornerstone of the final approval. Weighing the three data sources, I would have given 50% to 3014 and 25% each to EU and Phase III data. The reason is the sample size and the allegedly superb follow- up of all study subjects that the study demonstrated (and the total absence of a signal of serious drug toxicity in that patient cohort).
I cannot respond to questions # 6, 7 or 8 I do not recall
As regarding the risk-benefit profile of Ketek, I based perhaps 50% of my opinion on study 3014, 15% on post-marketing surveillance, and 35% on the Phase III study.
I only had access to the data presented by the company and the FDA, available publicly at the FDA's docket. I do not remember giving more or less weight to the data of any of the studies presented. I do not believe that I or any other member of the committee had reason to doubt the validity of any of the data. I would like to emphasize, however, that the AIDAC'S concern regarding the adequacy of data presented by pharmaceutical companies (in the sense that not enough patient data is ever available) has been documented in essentially every committee meeting that I have attended.
I relied on all 3 sources and voted accordingly
. . . . I do not recall my assessments of the safety data and have found no relevant comments of mine on safety in the transcript.
I gave the greatest weight to phase III studies. However, these data were derived from limited numbers of subjects and thus may not detect infrequent, but potentially significant, adverse events (I believe this is the reason the subcommittee recommended the larger safety study to be performed). I relied heavily on the 3014 study for safety data. I gave little weight to post-marketing data from non-US sites.

ATTACHMENT 3

Do you believe your vote and recommendations regarding the risk- benefit profile of Ketek would have changed if the FDA had disclosed the Study 3014 had some data integrity problems and that the FDA was still reviewing the extent of the problems?
It is impossible to play Monday-morning quarterback, in that there is never enough data to make an unequivocal decision in Advisory Committee hearings. The FDA does not need an Advisory Committee meeting for slam dunk, up and down, submissions. We are convened when the submission is in a grey zone. In other words, we are asked to help the FDA when studies entail a small number of patients enrolled. The committee debates the real efficacy, as well as the rare side effects, not yet captured due to the relatively small enrollment in the studies presented to us. In this regard, even a study of 20,000 or more patients still may not capture serious adverse effects that occur with a frequency of only 1 in 100,000 to 1 in 100,000,000. Furthermore, any Advisory Committee decision may be second-guessed afterwards. The "second- guessing" starts with the FDA itself, which is free to accept or deny the Advisory Committee's decision.
I cannot say based on the information provided in this letter whether my vote would have changed. I would have sought more information about the nature of the problems, in addition to their extent. Some problems might not affect the validity of the information, even widespread.
Absolutely yes
I believe I would have recommended postponing the decision on the compound until the extent and significance of the data integrity problems were better defined.
I think this should have been revealed at the meeting and that the meeting might well have gone a different way; however, this becomes speculation at this point. I would be pretty certain that my own vote would have changed.
I cannot respond to questions # 6, 7 or 8 I do not recall
No, see answer to #6 [previous table]. . . .

ATTACHMENT 3

After reviewing the attached email, do you share the FDA official's opinion that it would not have been productive to spend time on issues regarding data integrity and the conduct of Study 3014?
All data is assumed to be valid unless otherwise reported. The only vaguely possible justification for not disclosing something like this is that the day is very short and there is a lot of ground to cover. There is a sense at these meetings that more could have been said or more discussion taken place but that time is of the essence and there is a lot of ground to cover. If the FDA believed that these were only allegations and that there was a reasonable possibility that the study might have been fully exonerated, then making the judgment call might have seemed valid but even these hypothetical circumstances do not justify in any way withholding this information. It might have diverted the committee but approval is not a freight train that has any specific time to get to the station. Although this is speculation on my part, the writer's implication was that this drug was on track for approval that day.
See answer to # 10 [From news reports, it seems common that investigative bodies withhold details from the public during their investigations so as not to jeopardize the investigation. Whether this consideration is relevant in this case I do not know.]
No
I cannot respond to questions # 6, 7 or 8 I do not recall
I believe that it would have been productive to spend time on these data integrity issues at the committee meeting.
No
In the AIDAC meetings that I have attended, data integrity has never been addressed. The committee addresses only issues of safety and efficacy, presented to us by both the pharmaceutical company and the FDA. I cannot therefore speculate about the FDA's opinion regarding the productivity of spending AIDAC's time regarding the conduct of Study 3014.

ATTACHMENT 3

Do you believe the FDA and/or Aventis were ethically obligated to disclose known data integrity problems to AIDAC members?
The FDA and pharmaceutical manufacturers provide all the data necessary to make decisions about which the Advisory Committee is asked to address. In all of my work with the AIDAC, the committee has never been asked to pass judgment on ethics. The purpose of the committee, as I have understood it, has been to ensure statutory responsibility. The AIDAC, in my experience, never has sufficient (if any) information to determine whether or not ethical obligations have been fulfilled.
I am not an ethicist and so would prefer not to give an opinion about ethics. . . . I believe that evaluation of data requires a full understanding of the validity of the data, so I think that data integrity problems that may have affected the validity of the data should be disclosed to the committee
Yes
Yes
I believe that all information of note or with significant ramifications should be made available to the committee
See answer to # 10 [From news reports, it seems common that investigative bodies withhold details from the public during their investigations so as not to jeopardize the investigation. Whether this consideration is relevant in this case I do not know.]
Data integrity problems, when as extensive and potentially significant as the problems evident with Study 3014, should have been presented to the AIDAC.

Under what conditions, if any, do you believe known data integrity problems should be withheld from an advisory committee meeting by the FDA or a sponsor? For example, the FDA has asserted that it could not jeopardize an ongoing investigation(s) related to 3014 by disclosing that it was under review and investigation. Is this rationale acceptable to you?
The FDA has certain legal obligations in terms of proprietary rights to the pharmaceutical manufacturer whose drug is under consideration. I can, therefore, easily understand why the FDA cannot disclose all available information to the AIDAC, which is within the public domain. The AIDAC, in this sense, is never informed of all the information available to the FDA. It has been my experience that the FDA asks us only specific questions to which they want answers. These questions are only a few of those that the FDA asks of itself, and these questions address grey areas about which the FDA wants outside expertise. It seems reasonable to me that if there is an ongoing investigation within a federal agency, that an outside public entity, such as the AIDAC, should not be told about an ongoing, as yet unresolved, investigation. If the FDA had already fully determined that fraudulent data had compromised the data we reviewed, I would have thought that they would have canceled the committee meeting.
I believe that all information of note or with significant ramifications should be made available to the committee.
In the interest of time, data integrity problems that are trivial or could not possibly affect the validity of results may be withheld from the committee. I have not seen the FDA statement referred to in this question and would therefore prefer not to comment on it.
Data integrity problems should always be disclosed to an advisory committee so an informed recommendation can be made
It should be kept in mind that almost all large clinical trials, including very carefully performed phase III studies, have some small degree of data integrity issues (minor deviations from protocol, less than 100% source document verification, etc). Very minimal or trivial issues could be withheld from the subcommittee without jeopardizing the process. However, study 3014 appears to be riddled with problems and these should have been disclosed to the subcommittee (in a confidential manner if necessary).
From news reports, it seems common that investigative bodies withhold details from the public during their investigations so as not to jeopardize the investigation. Whether this consideration is relevant in this case I do not know.
Not sure what the issues would be here. Why could the investigation not proceed? It would be unusual to do a closed committee session but that would be one solution I can imagine.

Provide any additional comments or concerns you may have regarding Ketek or any other matter. For example, are you aware of any situation where the FDA or any company may have withheld information that you believe to be relevant or presented information that you believe to be suspect.
I am very supportive in general of the FDA. These are, by and large, very hard working public servants who could be making much more in industry but who do these jobs, I can only imagine, out of altruistic concerns and feelings of satisfaction in protecting the nation's health. There is detective work involved, scientific process, a lot of interesting aspects in their jobs as well. I have had serious concerns regarding the overall agenda of FDA regarding . . . and also regarding . . ., far more than Ketek ever will. . . . I believe that both these failings of FDA are the result of political pressure placed on FDA. . . . NOTHING has been done in the succeeding four years to address this . . .! These two issues aside, I am still uncertain how to analyze the Ketek scenario as it has played out. The company is certainly to blame for a faulty study and one should consider that any flawed data in a study throws out all that data. If the FDA had taken that position then and thrown out the flawed data, the 2nd Advisory Committee meeting could have been postponed. While the . . . situation represents incredible slowness of action (perhaps an error of omission), the Ketek case represents an error of commission, allowing the hearings to go forth under false circumstances. [The Review Division Director's] initial introduction to the 2nd Advisory Committee meeting is glowingly positive, which may indicate that she was not aware of any glitches in the data; if she was aware of these issues, she gave no indication that this drug should be anything but fast track approved that day.
No response
I do not have any other comments or concerns. I am not aware of any situation where the FDA or any company may have withheld relevant information or presented suspect information.
No response
No additional comments
I have no additional comments or concerns regarding telithromycin or any other matter. I am not aware of any situation where the FDA or any company may have withheld information that I believe to be relevant or presented information that I believe to be suspect.
I do not know of any other information. It was wrong that neither the FDA or the pharmaceutical company did not make all information available to committee members. This needs review.