Appendix A

Additional Questions Regarding Ketek's Safety

1. On January 20, 2006 the FDA also posted a document with questions and answers about Ketek on the FDA website that stated,
   "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."[1]
   a. Is study 3014 the "large safety trial" cited in these FDA statements?
   b. Is the committee that "concluded that the risk for hepatotoxicity from Ketek was similar to Augmentin and erythromycin" the same Advisory Committee that was evidently not informed of the serious data integrity issues involved in study 3014?
   c. If the answer to a) and/or b) is yes, why has the FDA chosen to use this trial to assure the public of the safety of this product when its own Office/Division Memorandum states that the study could not be relied upon to support a regulatory decision?
   d. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision to cite this study.

2. The Anti-Infective Drugs Advisory Committee that was supposed to resolve any outstanding concerns about liver toxicity, cardiac and visual adverse events, and wanted to see a more complete risk/benefit profile of Ketek based on the results of study 3014. According to FDA documentation,[2] the Committee does not appear to have been informed of the serious data integrity concerns associated with Study 3014.
   a. Is this true? If in fact the Advisory Committee was informed prior to its January 2003 meeting, please provide copies of all documentation, including emails, memos, meeting notes or transcripts or other correspondence.
   b. If not, why not? Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision to provide or not provide this information to the Advisory Committee.

3. According to FDA documentation, Aventis did not alert the FDA to any problems with the 3014 study, but later admitted that it had been aware of at least some of the problems. Aventis reportedly did not explain why it had chosen to retain the investigator who was

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[1] http://www.fda.gov/cder/drug/infopage/telithromycin/qa.htm accessed April 28, 2006.
[2] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf, p 23, 43 accessed April 26, 2006.

subsequently incarcerated for her role in study 3014 even after it found out about the related data integrity issues, nor did Aventis explain why it did not immediately inform the FDA about the problems' existence.[3]

a. Did the FDA ever investigate whether Aventis was
    i. complicit in providing the FDA with fraudulent data or
    ii. complicit in undermining or ignoring Good Clinical Practice guidelines?
b. If not, why not? If so, what did the FDA investigation conclude, and what actions were taken as a result?
c. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in reaching FDA's conclusions and in determining its actions.

4. Did the FDA ever raise concerns regarding study 3014 with Aventis and/or ask the company to provide more information regarding how this study could be used to support an approval? Please provide copies of all such correspondence, requests for information, memos, meeting notes, emails and other documents sent by FDA personnel to Aventis as well as Aventis' responses thereto. Please also provide copies of all internal FDA correspondence, memos, meeting notes or transcripts, emails and other documents relating to study 3014.

5. Is the FDA confident that study 3014 can be used to support the safety of Ketek?
    a. If so, why, in light of the serious issues raised regarding more than one investigator responsible for collecting the data?
    b. If not, why did FDA use study 3014 after approval as partial evidence of its safety in light of reports of adverse events?
    c. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision to use or not to use some or all of this data.

6. According to FDA documents,

> *"Since description of the risk profile of telithromycin and assessment of its risk-benefit ratio (particularly with regard to hepatic and visual toxicities rested heavily on this large safety study, the Agency issued a second approvable letter in order to better understand how study 3014 was conducted. The October 2003 submission addressed issues of study 3014 conduct, and included as well post-marketing reports for spontaneous adverse events for approximately—prescriptions for patients in foreign countries. The conduct of study 3014, including systematic problems with its monitoring, led to questions regarding what role this study could play in determining regulatory action. However, the Agency was able to rely on the post-marketing*

[3] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf page 42 accessed April 26, 2006.

experience to conclude there was substantial evidence of safety." [4]

However, FDA's February 2004, Medical Team Leader Memorandum states, *"...post-marketing data provided to the FDA have been incomplete or reported in a dilatory fashion. It is not clear from the data provided by the Applicant that either quantitative or qualitative descriptions of post-marketing adverse events represent all data in the possession of the company."*[5]

a. Did the FDA rely on foreign post-marketing data to assess the safety of Ketek?
b. If so, please explain specifically which adverse event reports were used and how these reports were sufficient to resolve the cardiac, liver, and visual safety issues raised in the FDA's June 2001 letter.
c. What evidence does the FDA have to support the accuracy, completeness, and reliability of post-marketing adverse event reports from each of the other countries for Ketek submitted by Aventis.
d. What did FDA do to address concerns that the post-marketing data was "incomplete or reported in a dilatory fashion"?
e. Did FDA receive any additional post-marketing study information from the sponsor after February 2004? If so, what information was received?
f. If foreign post-marketing data were not used, what other information provided the basis for the approval?
g. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision regarding reliance on foreign post-marketing data.

7. According to the FDA website as of January 20, 2006, "the FDA is continuing to evaluate the issue of liver problems in association with use of telithromycin in order to determine if labeling changes or other actions are warranted. As a part of this, FDA is continuing to work to understand better the frequency of liver-related adverse events reported for approved antibiotics, including telithromycin."[6] What information is the FDA using as the basis of this ongoing evaluation?

8. Have other medications been approved using foreign post-marketing adverse event reports as the sole or primary basis for resolving serious safety questions about a drug? If so, please list each medication, and the circumstances surrounding its approval.

9. Has the FDA received any other case reports of Ketek related liver toxicity? In light of the liver toxicity examples already reported, did the FDA require Aventis, as a condition of approval, to take any special measures, such as requesting submission of all serious

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[4] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf, p 23 accessed April 26, 2006.
[5] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf, p 43 accessed April 26, 2006.
[6] See http://www.fda.gov/cder/drug/advisory/telithromycin.htm accessed April 18, 2006.

hepatic events as expedited post-marketing reports? If so, has Aventis done so? Please provide all documentation. If not, why not? Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were or should have been taken into consideration in determining whether or not to make this a condition of approval.

10. The transcript of the January 8, 2003 Advisory Committee shows that Dr. Paul Lagarenne of Aventis stated,

> *"Study 3014, our large usual care study enrolled more than 24,000 patients, including more than 12,000 subjects treated with telithromycin... Follow-up was actively pursued in all subjects enrolled in this study. Only 2 telithromycin-treated subjects and 1 AMC subject were treated but had no post-baseline assessment... 99.5 percent of telithromycin subjects and 99.2 percent of AMC subjects had detailed adverse event information available on day 28 or later, that is detailed AE (adverse event) status information... overall 99.8 percent out of these 24,000 subjects with follow-up information obtained at day 28 or later."*[7]

    a. Are these statements accurate given questions about the integrity of the data?
    b. Did this presentation indicate whether any of the fraudulent data that was collected by Kirkman-Campbell- was excluded from the results cited above?
    c. Did this presentation indicate whether any of the data collected by any of the other investigators that were investigated by the FDA was excluded from the results cited above?
    d. If the data was excluded, was the Committee informed why, and if so, please provide all documentation.
    e. If the Committee was not informed about the exclusion of data, why not?
    f. If the data was not excluded from Aventis' presentation of the results from the study, why not? Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision to inform or not inform the Committee and/or to include/exclude information from the study.

11. How many patients were enrolled in the 3014 study? For each site at which data integrity issues were identified, please provide a) the numbers of patients enrolled at the site b) whether, as a result of the data integrity issue identified, the data was eliminated from the final study, and c) if the data was not eliminated, why not? Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision whether or not to eliminate data from the final study.

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[7] See http://www.fda.gov/ohnns/dockets/ac/03/transcripts/39 19T1 .doc

12. During their monitoring of study sites, did the sponsor and/or the Contract Research Organization detect any of the significant problems found during the FDA inspections?
    a. If not, is there any reason to believe that their on- or off-site monitoring of all other sites would have fared better at detecting significant problems? Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making this assessment.
13. Was the Ketek NDA referred to the FDA's Application Integrity Policy committee, which is charged with handling cases in which data integrity questions are raised?[8]
    a. If so, what were their conclusions/recommendations? If not, why not?
    b. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in regarding a decision of whether or not to refer the Ketek NDA to the Application Integrity Policy committee.
14. Did FDA visit Aventis to review documents related to study 3014?
    a. If so, what did they find? If not, why not?
    b. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making the decision to visit Aventis and/or review documents related to study 3014.
15. Did the FDA Office of Criminal Investigations or the Division of Scientific Investigations ever provide the Division of Anti-Infective Drug Products with recommendations or other information regarding study 3014 prior to Ketek's approval on April 1,2004?
    a. If so, please provide copies of all materials, including emails, memos, meeting notes or transcripts or other correspondence and explain how the investigation into study 3014 affected the approval process of Ketek.

16. Other than the Kirkman-Campbell case which resulted in her conviction, please describe all other data integrity concerns that were discovered at any of the other trial sites.
    a. Please provide a list the sites and describe the concerns, including whether these sites were investigated and visited, and any resolution of the resultant investigation.
    b. If a decision was made not to proceed with a particular site investigation or if an investigation was dropped without charges being filed, please explain the basis for that decision.
    c. Please provide all correspondence, requests for information, memos, meeting notes, emails and other documents which were taken into consideration in making this decision.

Questions on Ketek's Effectiveness – Non-Inferiority Trials

[8]See http://www.fda.gov/ora/compliance_ref/aip_page.html accessed April 26, 2006.

1. It is our understanding based on the advisory committee presentations that Ketek was approved on the basis of non-inferiority trials rather than placebo trials.
    a. Did the sponsor explain to FDA, as required by FDA regulations, in the analysis of the study *"why the drugs should be considered effective in the study"?*
    b. If so, please provide a copy of that explanation. If not, why was this explanation not provided?
2. Does the FDA believe that Ketek is more effective than placebo? If so, on what basis?
3. In the past 6 years, has the FDA Office of Antimicrobial Products approved other medications on the basis of non-inferiority studies? If so, please provide:
    a. a list of all such medications, the medical conditions for which each was approved, the sponsors of all of the NDAs, and the date on which each was approved;
    b. whether the control medication used to establish non-inferiority for each medication was itself approved on the basis of a placebo study, or if it too was approved on the basis of non-inferiority;
    c. for each medication, the required explanation contained in the analysis of the study for why the results of the non-inferiority trials could be believed to assure the effectiveness of the drug and;
    d. if the required explanation was not included in the analysis of the study, why not.

4. Please list all other antibiotics that are available to treat bacterial lung and sinus infections in persons older than 18 years of age.
    a. For each such antibiotic, please indicate whether the antibiotic was approved on the basis of a non-inferiority study or a placebo study.
    b. Are there antibiotics available whose effectiveness has been shown via the use of a more reliable placebo trial and for which serious safety concerns do not exist?
    c. If so, then why did FDA consider approving Ketek for these purposes?

Questions Regarding Testing Ketek in Children

It is our understanding that there are at least two ongoing clinical trials in which Ketek is being provided to children as young as 6 months old with acute ear infections and tonsillitis[9].

1. What is the FDA doing to ensure the safety of these children in light of the hepatotoxicity and visual adverse events that have been noted in the approval letter and reported in the Med Watch?
2. How many children have been enrolled in these studies?
3. Have any adverse health effects been reported for children taking Ketek? If so, please describe each of them.

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[9] See www.clinicaltriais.gov references numbers NCTO03 15042 and NCTO03 15003

4. Are these studies designed to show Ketek's efficacy, safety or both? Are the pediatric studies designed as non-inferiority studies? If so, how does this ensure that Ketek is effective in these diseases?
5. Since very young children may not be able to tell an investigator about visual disturbances and these visual disturbances may not be otherwise evident, how can the FDA ensure that these potential adverse events are being recorded and evaluated?
6. Please provide a copy of the informed consent form required for participation in these trials.