U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
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For Immediate Release
Monday, May 1, 2006

Grassley slams FDA for citing fraudulent safety study

WASHINGTON — Sen. Chuck Grassley today released information about his ongoing investigation of the Food and Drug Administration regarding the drug-safety agency's initial approval and post-market surveillance of the antibiotic Ketek.

Grassley, who chairs the Senate Committee on Finance, said he is concerned about the FDA's complicity with the drug maker and subsequent failure to ensure the integrity of a pivotal study about the benefits and risks of this drug. He said he is also alarmed at the FDA's continued reliance on the study as evidence of Ketek being safe, despite the FDA's own determination that the study is riddled with fraudulent information. Finally, Grassley said the stakes continue to grow when it comes to overseeing this antibiotic, since it is being studied in children as young as six months old.

"The allegations of misconduct in this case are as bad as I've heard yet," Grassley said. "It looks like the FDA caught the drug company red handed and let them get away with it. On top of that, the FDA failed to set the record straight and, in fact, continues to cite a discredited safety study as a principal reason to feel okay about using this drug."

The text of a letter Grassley sent last week to the Acting FDA Commissioner follows here.

April 27, 2006

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]

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.
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> 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 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 my Committee staff 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.

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. Director, 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 these officials 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 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 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.

Sincerely,
Charles E. Grassley
Chairman

[1] http://www.fda.gov/fdac/departs/2004/404_upd.html#fraud
[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
[6] http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Prntlbl.pdf