U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
http://finance.senate.gov

For Immediate Release
Thursday, June 8, 2006

Grassley questions FDA about risks to children, infants in antibiotic drug trials

WASHINGTON — Sen. Chuck Grassley today asked the Food and Drug Administration to explain what it is doing to inform parents about the safety concerns surrounding pediatric trials of the Ketek antibiotic.

Grassley said he posed the same question of the nation's drug safety agency six weeks ago but hasn't gotten an answer yet. He said he was repeating his inquiry based on a *New York Times* story today that revealed experts' concerns about these trials involving children and infants. "The adverse events identified with Ketek are serious ones and the possibility that any six-month old child is being exposed to these kinds of risks unnecessarily is unconscionable," Grassley wrote in a letter to Acting Commissioner Andrew C. von Eschenbach.

Grassley's oversight of the Food and Drug Administration began in 2004 over the agency's reluctance to allow information to become public about the risks of pediatric use of certain anti-depressants. He has put pressure on the Food and Drug Administration to make administrative changes to improve its transparency and post-market surveillance of drugs, in addition to introducing legislation to make these kinds of reforms.

The text of Grassley's June 8 and April 27 letters to von Eschenbach follow here.

June 8, 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 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.

I read with great interest and concern today's New York Times article entitled, "Halt Is Urged for Trials of Antibiotic in Children," regarding the recommendations of officials in the

Office of Drug Safety ("ODS") at the Food and Drug Administration ("FDA" or "the agency") and a consult conducted by Dr. Danny Benjamin, an infectious disease specialist at Duke University. I understand that Dr. Benjamin was asked by the FDA to examine the pediatric trials.

According to the article, a recent internal review of safety reports by ODS officials found 110 cases of liver problems (liver failure and serious liver injury) associated with telithromycin ("Ketek"), since the antibiotic was approved in April 2004. It is alarming that most of these serious events occurred in otherwise healthy people. Based on their review, these officials recommended that the FDA "consider forcing Sanofi-Aventis [the manufacturer of Ketek] to withdraw Ketek from the market, severely restrict its uses, even in adults, or add a prominent warning to its label about potentially fatal side effects."

The New York Times further reports that in light of the risk of fatal liver failure, blurred vision and loss of consciousness, Dr. Rosemary Johann-Liang, an FDA official in ODS, questioned the agency's decision to allow pediatric trials of Ketek to proceed. She also questioned whether or not it was possible to assess blurred vision and loss of consciousness in very young children. In his separate consult, the article reports that Dr. Benjamin also "concluded that the pediatric trials with Ketek were a cause for concern and 'hard to support.'"

My concern about the safety risks to infants and children was first expressed to you in my letter of April 27, 2006. Now my concerns are even further heightened by the New York Times article on ODS's assessment of adverse events associated with Ketek and Dr. Johann-Liang's and Dr. Benjamin's conclusions regarding the pediatric trials.

Let me reiterate that 6 weeks ago I asked you to advise the Committee of "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." Unfortunately, I have not received a response to this important question, and I presume that parents who have enrolled their children in the trials have not been advised of anything either.

Accordingly, as Chairman of the Committee, I request that the FDA respond to the following immediately:

1. Describe the current efforts by the agency to provide parents and patients with updated safety information regarding Ketek and specify the timeframe for implementation of these efforts. If there are no plans to update consent forms and patient brochures at this time, please provide a rationale for the FDA's decision.

2. A search of the ClinicalTrials.gov website shows that Sanofi-Aventis has three ongoing trials in children as young as 6 months old, "TELI COM - Telithromycin in Children With Otitis Media," "TELI TON - Telithromycin in Tonsillitis," and "Comparative Study to Evaluate the Efficacy and Safety of Telithromycin Given Once Daily Versus Cefuroxime Axetil Given Twice Daily in Children With Middle Ear Infections," and a fourth trial involving adolescents 13 years of age and older, "TELI TAD - Telithromycin in Tonsillitis in Adolescents and Adults." Is the FDA considering temporary suspension of these trials until the serious concerns and issues related to Ketek are resolved?

3. Please make available Dr. Rosemary Johann-Liang for an interview with my Committee staff no later than June 28, 2006. Please ensure that Dr. Johann-Liang is provided with a copy of this letter and have your staff contact my staff by no later than June 12, 2006, to make arrangements for the interview.

Thank you for your attention to this very important matter. I look forward to hearing from you regarding my questions and concerns immediately. The adverse events identified with Ketek are serious ones and the possibility that any six-month old child is being exposed to these kinds of risks unnecessarily is unconscionable.

Sincerely,
Charles E. Grassley
Chairman

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.
>
> 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

The New York Times
June 8, 2006 Thursday
Late Edition - Final
SECTION: Section A; Column 5; National Desk; Pg. 16
LENGTH: 1091 words
HEADLINE: Halt Is Urged for Trials Of Antibiotic in Children

BYLINE: By GARDINER HARRIS
BODY:

A Food and Drug Administration official called in May for a drug company to halt clinical trials of an antibiotic in children because the drug could be deadly, according to internal memorandums sent to other F.D.A. officials.

The drug, Ketek, made by Sanofi-Aventis, is being tested as a treatment for ear infections and tonsillitis in nearly 4,000 infants and children in more than a dozen countries, including the United States, according to postings on a government Web site. But Ketek, which is currently approved for use only in adults, has been reported to cause liver failure, blurred vision and loss of consciousness in adults.

"How does one justify balancing the risk of fatal liver failure against one day less of ear pain?" Dr. Rosemary Johann-Liang, an official in the Office of Drug Safety at the agency, wrote in one of the memorandums, a copy of which was obtained by The New York Times.

Sanofi-Aventis is sponsoring four clinical trials in children ages 6 months to 13 years, according the Web site posting. The drug agency approved plans for the trials.

There is growing evidence that Ketek is unusually toxic, according to a recent review by F.D.A. safety officials. Twelve adult patients in the United States have suffered liver failure, including four who died; 23 others suffered serious liver injury.

The safety officials wrote in their review that the agency should consider forcing Sanofi-Aventis to withdraw Ketek from the market, severely restrict its uses, even in adults, or add a prominent warning to its label about potentially fatal side effects.

More than five million prescriptions for Ketek have been written in the United States since its approval two years ago.

Asked about the memorandum written by Dr. Johann-Liang, an F.D.A. spokeswoman, Susan Bro, said that it was "a preliminary, raw assessment" and that "the final decision will be made by experts who have the full benefit of a large section of opinion and scientific fact."

Melissa Feltmann, a spokeswoman for Sanofi-Aventis, said in an e-mail message, "We are engaged in ongoing discussions with the F.D.A. regarding Ketek."

Other antibiotics cause liver failure, but Ketek seems to do so almost four times as often, the safety officials concluded in the review.

Ketek can also cause blurred vision and loss of consciousness, problems that are unique to it. In her memorandum, Dr. Johann-Liang asked how Sanofi-Aventis's investigators were going to assess whether infants were suffering blurred vision.

"If we cannot monitor for this event in infants/young children appropriately in the clinical trial setting, what can we conclude from the safety results of the trial?" she asked.

Dr. Danny Benjamin, an infectious-disease specialist at Duke University who was consulted separately by the drug agency, concluded that the pediatric trials with Ketek were a cause for concern and "hard to support," according to the memorandums obtained by The New York Times.

Dr. Benjamin did not respond to voice-mail or e-mail messages left for him yesterday.

In his memorandum, Dr. Benjamin said that in up to 87 percent of cases, pediatric ear infections resolved within a few days without treatment. Tests of an unusually risky antibiotic in infants with ear infections might be justified if the infants had already been treated unsuccessfully with safer antibiotics first, he wrote.

Sanofi-Aventis planned to give Ketek as a first-line therapy, according to the company's trial descriptions.

The drug agency's actions in regard to Ketek are being investigated by Senator Charles E. Grassley, the Iowa Republican who is chairman of the Senate Finance Committee, as well as by Representatives Edward J. Markey of Massachusetts and Henry A. Waxman of California, both Democrats.

Sanofi-Aventis first asked the agency to approve the drug in February 2000. But officials demurred, citing reports of side effects. So the company undertook a study of Ketek in 24,000 patients to prove its safety. The trial was marred by fraud. One of the investigators on the study is now in federal prison; another lost his medical license.

The F.D.A. said it dismissed the study's results and instead asked the company to report its experience with Ketek in Europe, where it was approved in 2001. Although it is unusual for the agency to approve a drug based upon its use elsewhere, in April 2004, it . did just that, approving Ketek to treat sinusitis, bronchitis and pneumonia.

Since then, problems with the drug have continued to mount. By April, the agency had reports of 110 cases of liver problems associated with Ketek, most of which occurred in otherwise healthy people, according to the safety review. In one, a 49-year-old woman took no more than two doses of the drug before becoming nauseous and vomiting. She was hospitalized five days later and died.

Since they are submitted voluntarily, these kinds of case reports usually represent only a small fraction -- estimates range from 1 percent to 10 percent -- of actual drug problems. The reports that the F.D.A. has received so far are unusual because of their "rapid tempo and severity," the agency's internal safety report said.

The agency officials estimated that Ketek caused acute liver failure in 23 people for every 10 million prescriptions, about four times the rate of such events seen in other antibiotics.

In 1999, sales of the antibiotic Trovan were severely restricted after it was shown to cause liver failure in 58 people for every 10 million prescriptions.

In her memorandum, Dr. Johann-Liang suggested that Ketek's risks outweighed its benefits.

She noted that powerful antibiotics known as fluoroquinolones can also damage the liver. But she said that those drugs were available in intravenous forms and "are also used for more serious infectious diseases rather than solely for minor upper respiratory indications," as Ketek is.

Dr. Johann-Liang wrote in her memorandum that the parents of patients in Sanofi-Aventis's pediatric trials must be better informed about Ketek's risks "in order for any of these trials to continue to proceed."

She added that the parents "need to know that the 'close monitoring' for visual events is not possible in very young children, and the long-term consequences of such adverse reactions are unknown for the developing system."

Dr. Benjamin agreed that the brochure about the trials and informed-consent material given to parents "must address in plain language the risks, and severity of risks, of adverse events."