Congress of the United States
Washington, DC 20515

May 1, 2006

Andrew C. von Eschenbach, M.D.
Acting Commissioner
US Food and Drug Administration
U.S. Department of Health and Human Services
Parklawn Building
5600 Fishers Lane, Room 15-47
Rockville, MD 20857

Dear Dr. von Eschenbach:

We are writing regarding the FDA's actions surrounding its approval of the antibiotic telithromycin (Ketek). Ketek is an antibiotic that is approved for treatment of certain bacterial lung and sinus infections in people 18 years and older. Although the FDA has consistently assured the public of Ketek's safety and efficacy, public documents obtained and examined by our staff indicate that the approval process for this drug was seriously flawed. The public has a right to know how the FDA reached its decision to approve Ketek and whether they can rely on those conclusions.

The staff investigation raised many questions with regard to:

A. **The Safety of Ketek and the "3014" study:** Despite reports of serious health problems that were related to the use of Ketek, the FDA continues to vouch for the safety of the medication, citing a 'large safety trial.' However, an FDA investigation of serious data integrity problems in this "large safety trial" led to the conviction of the physician who recruited the most patients for the study for falsifying data for the study. Apparently, FDA has also investigated other investigators involved in Study 3014--the status of these investigations remains unclear. According to FDA documentation, the FDA apparently relied on foreign post-marketing adverse event reports to resolve the serious safety questions that study 3014 had been designed to address and ultimately approved Ketek.

B. **The Effectiveness of Ketek's and Non-inferiority trials:** Ketek's effectiveness was established on the basis of so-called "non-inferiority" studies, which many experts believe are inappropriate for studying the sorts of diseases for which Ketek was approved. Moreover, in approving Ketek, it is not clear that the FDA followed its own regulations that require the sponsor to explain how the non-inferiority trial proves the effectiveness of the drug before the study analysis to be used to support the drug's approval.

C. **Testing Ketek in Children:** Despite the safety and efficacy concerns regarding Ketek of which the FDA is aware, FDA made the decision to permit Aventis to conduct pediatric studies of its use for common conditions such as ear and throat infections, raising the possibility that an unsafe drug may be provided to children.

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We are concerned that the facts and circumstances surrounding Ketek's approval by the FDA may be indicative of broader systemic problems at the FDA which, if left unaddressed, could result in physicians unknowingly prescribing unsafe and/or ineffective medications to Americans. As Members of the House Energy and Commerce Committee, which has oversight and legislative responsibilities with respect to the FDA and the laws and regulations it is responsible for administering, we ask for your prompt assistance in responding to the following questions and requests for information which are contained in Appendix A.

A. The Safety of Ketek and the "3014" study:

Prior to the approval of Ketek on April 1, 2004, the FDA Anti-Infective Drugs Advisory Committee expressed concerns about the potential for Ketek-related liver toxicity, cardiac and visual problems due to findings in the early phase pre-clinical and clinical trials. When the Anti-Infective Drugs Advisory Committee reviewed Ketek's application for the first time in 2001, the Committee recommended that the FDA not approve Ketek until the company had established a more complete toxicity risk profile in a larger number of patients likely to receive telithromycin.[1] In a June 1, 2001 letter, FDA subsequently informed Aventis that it could not approve Ketek at that time because of outstanding safety concerns related to liver, heart and visual concerns. The FDA letter states,

> *"...the data are insufficient in your NDA to assess fully the potential risks posed by the concentration-related effect of telithromycin on cardiac repolarization, hepatotoxicity, and drug exposure in patients with renal and/or hepatic impairment... Before this application may be approved it will be necessary for you to address the following... You should conduct a large clinical study of CAP/ABS in order to capture further patients with S. pneumoniae isolates resistant to penicillin and/or erythromycin, and beta-lactamase producing strains of H. influenzae. Within this large database, monitoring and analysis of adverse event reports, including hepatic, cardiac (QT interval) and visual adverse events, are highly recommended in order to obtain a larger safety database upon which to assess the benefit/risk profile."* [2]

In response to the FDA's concerns and to better evaluate the occurrence of serious adverse effects, Aventis launched study 3014. Study 3014 was designed as a large usual care open-label, active-controlled safety study conducted at 1824 sites. In the study, approximately 12,000 patients received Ketek and approximately 12,000 received the control medication, Augmentin.

When the results of study 3014 were provided to the FDA in July 2002, serious data integrity concerns were noted and the Division of Scientific Investigations initiated an

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[1] See http://www.fda.gov/ohrms/dockets/ac/01/minutes/3746m1.htm accessed April 26, 2006.
[2] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Approv.pdf, p8 accessed April 26, 2006.

investigation.[3]

> *According to the February 2004 Medical Team Leader Memorandum for Ketek: "The inspection [of the top enrolling site in study 3014] revealed a number of serious GCP (good clinical practice) violations, particularly:*
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> - *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 the 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...*
>
> *Because of the results of this inspection, DSI was asked to inspect the next two highest enrolling sites. These inspections revealed significant irregularities at the second-highest enroller (enrollment of ineligible patients, incomplete laboratory testing, failure to use drug accountability logs.) The investigator at the third-highest enrolling site (Dr. [redacted] was found to have been on probation at the time of this study (for gross medical negligence and failure to keep adequate medical records). Seven weeks after seeing his last patient in this study, this investigator was arrested on drug, weapons, and assault charges; his medical license was suspended."*[4]

While the FDA's Division of Scientific Investigations' investigation was ongoing, the study data were presented at the January 8, 2003 meeting of the Anti-Infective Drugs Advisory Committee which was charged with providing the FDA with a recommendation as to whether Ketek should be approved. Remarkably, according to the FDA Office/Division Memorandum for NDA 21-144 Ketek (Telithromycin), the "presentation to the Advisory Committee, however, did not include a discussion of serious data integrity issues uncovered in this large usual care study by Agency inspections."[5] At that meeting, the Committee voted to recommend the approval of Ketek, evidently without ever being told that the primary safety trial had such grave problems associated with it.

Nine months after the Advisory Committee recommended Ketek for approval on Oct. 23, 2003, the top enroller in study 3014, Anne Kirkman-Campbell, entered a guilty plea to the charges of falsifying data for the study.

On April 1, 2004, the FDA approved Ketek. An FDA Office/Division Memorandum for NDA 21-144 Ketek (Telithromycin) explaining the approval decision states that "*Review of study 3014 was complicated by systemic failure of the trial monitoring program to detect data integrity problems when they clearly existed, making it difficult to rely upon this study to support a regulatory action.*"[6] Instead, according to the memo, FDA apparently relied on foreign post-marketing adverse event reports to resolve the serious safety questions that study 3014 had been

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[3] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf, p 42 accessed April 26, 2006.
[4] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf p 42 accessed April 28, 2006.
[5] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf, p 23 accessed April 26, 2006.
[6] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf page 22 accessed April 26, 2006.

designed to address.[7]

On January 20, 2006, The *Annals of Internal Medicine* published an article detailing three cases of drug-induced hepatotoxicity (liver toxicity) related to the use of the antibiotic telithromycin (Ketek).[8] One affected individual died of liver failure. Other reports of liver failure have also been reported elsewhere. In response to these reports, the FDA issued a Public Health Advisory[9] and Canada's Health Ministry issued a warning about Ketek[10]. In light of these serious adverse events, the public and medical community looked to the FDA for recommendations on how to respond to these cases. The FDA responded by releasing information to assure the public of the safety of this antibiotic. The public health advisory released on January 20, 2006 stated,

> *"In pre-marketing clinical studies, including a large safety trial 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.*[11]

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."*[12]

This "large safety trial" was again cited by an editorial published in *Annals of Internal Medicine* to suggest that the hepatotoxicity was not a major problem because "the rate of adverse events was similar to the comparator drug."[13]

Unfortunately, it appears that the North Carolina events are not the only serious Ketek related adverse events that have been reported to FDA. According to a review of the cases

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[7] See http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek_Admindocs_P1.pdf page 23 accessed April 28, 2006.
[8] Clay KD, Hanson JS, Pope SD et al. Brief communication; severe hepatotoxicity of telithromycin: three case reports and review of the literature. Ann Intern Med 2006 Mar 21:144(6):415-20,Epub 2006 Feb 15. PMID: 16481451 n
[9] See http://www.fda.gov/cder/drug/advisory/telithromycin.htm accessed April 28, 2006.
[10] See http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_07_e.html accessed April 28, 2006.
[11] http://www.fda.gov/cder/drug/advisory/telithromycin.htm accessed April 18, 2006.
[12] http://www.fda.gov/cder/drug/infopage/telithromycin/qa.htm accessed April 28, 2006.
[13] Turner M, Corey GR, AbrutynE. Telithromycin. Ann Intern Med 2006 Mar 21;144(6):447-8.PMID:16549859

reports submitted to the FDA through the Adverse Event Reporting System (AERS) between July 2005 to September 2005, (the most recent 3 month period for which data is publicly available) two deaths, 35 liver adverse events, 44 cardiac adverse events, and 80 visual adverse events were reported. (See Appendix B for a summary of the review) While it is important to recognize that for any given report, there is no certainty that a suspected drug caused the reaction, we believe that given the circumstances surrounding the approval of the drug, these reports warrant further examination.

It appears that the FDA reached the conclusion that Ketek was safe by relying on the foreign post-marketing experience. Yet this was not the evidence that the FDA presented to the Advisory Committee that had concerns about the safety of Ketek and requested additional data in the form of a study on the Ketek related liver, visual and cardiac adverse events, nor was it the primary evidence presented to the public when questioned about the cases of adverse events published in the Annals of Internal Medicine. We fail to understand why the FDA repeatedly points to this study—which their own investigation found to be so wrought with fraud and problems that the data can't be trusted—as evidence that Ketek is safe. We are hopeful the FDA's response to questions in Appendix A, will resolve some of these concerns.

B. Ketek's effectiveness/Non-inferiority trials:

Ketek's effectiveness was established on the basis of so-called "non-inferiority" studies, which many experts believe are inappropriate for studying the sorts of diseases for which Ketek was approved. When considering the effectiveness of a medication, the most straightforward manner of establishing it is to compare the patient outcome when taking the medication to the patient outcome when taking a placebo. However, in some cases, this is neither possible nor ethical. For example, if the likely patient outcome of taking a placebo would be death or other serious adverse health impact, then establishing the effectiveness of a new medication must be done via some other means. One of these means involves the use of a "non-inferiority" study, in which one group of patients are given a medication of known effectiveness and a second group is given the medication for which effectiveness is sought to be established. The new medication's effectiveness can be established if it performs in a similar manner (within some statistical range) to the known medication.

Over the years, however, concerns have been raised about the use and limitations of such trials. For example, in 1985, the FDA regulations (see 21 CFR 314. l26(b)(2)(iv)) were amended to state:

> *"If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results*

in previous placebo-controlled studies of the active control drug."[14]

In other words, since it is possible that a non-inferiority study could merely prove that a new proposed medication is only as *ineffective* as the medication to which it is being compared in a individual study, the sponsor must explain why this study design is capable of proving that the drug is effective in order for the sponsor to use the study to support a new drug application.

In 1998, the International Conference on Harmonization Guidance ICH-E9, *Statistical Principles in Clinical Trials* was published in the Federal Register and went into force in the United States as of September 1998. It stated:

> *"There are well known difficulties associated with the use of the active control equivalence (or non-inferiority) trials that do not incorporate a placebo or do not use multiple doses of the new drug. These relate to the implicit lack of any measure of internal validity (in contrast to superiority trials), thus making external validation necessary. The equivalence (or non-inferiority) trial is not conservative in nature, so that many flaws in the design or conduct of the trial will tend to bias the results towards a conclusion of equivalence."*[15]

In 2002, a note of clarification added to Paragraph 29 of Declaration of Helsinki which states that,

> *"a placebo-controlled trial may be ethically acceptable, even proven therapy is available, under the following circumstances: where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."*[16]

Since Ketek is indicated to treat only mild to moderate lung and respiratory infections it would seem that because of the inherent difficulties in non-inferiority studies, establishing its effectiveness using a placebo-controlled study would have been the preferred course of action.

C. 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. [17]

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[14] See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126
[15] The International Conference on Harmonization Guidance JCH-E9, *Statistical Principles in Clinical Trials* Federal Register (Vol. 63, No. 179, September 16, 1998, page 49583)
[16] See http://www.wma.net/e/policvTh3.htm
[17] See www.clinicaltriais.gov references numbers "NCTO03 15042" and "NCTO03 15003"

We are very concerned about allowing clinical trials to go forward in children when there may be serious concerns about the safety of Ketek. In particular, we are concerned about using this drug in very young child (as young as seven months old) in light of the fact that children at this age may not be able to communicate any visual adverse events that they experience while taking Ketek. We look forward to the FDA's response to questions in Appendix A regarding this issue.

Thank you for your attention to this important issue. We are very concerned about the process that FDA used and the data that FDA upon which relied to approve Ketek and look forward to FDA's response to our questions. We respectfully request a response by June 1, 2006. If you have any questions regarding this request, please do not hesitate to contact Ms. Katharine Reinhalter or Dr. Michal Freedhoff on Mr. Markey's staff at 202-225-2836 or Ms. Rachel Sher on Mr. Waxman's staff at 202-225-3976. We look forward to your prompt reply.

Sincerely,

Edward J. Markey
Member of Congress

Henry A. Waxman
Member of Congress