**Summary:**

**Statement of**
**Paul Herbert Chew, M.D.**
**President, Research and Development**
**sanofi-aventis U.S. Inc.**

**February 12, 2008**

- The safety and efficacy of Ketek® (telithromycin), an innovative antibiotic now indicated in the U.S. for treatment of community-acquired pneumonia, are well-supported by clinical data. In 2006, after a comprehensive review, FDA and two advisory committees concluded that Ketek® continues to have a favorable benefit-risk profile..

- Study 3014, conducted by Aventis in Winter 2001-2002, was the first large, pre-approval "usual care" study for an anti-infective drug. The study involved over 1,800 investigators treating over 24,000 patients in a brief time period. It is important to note that this "real world" study supplemented the typical pivotal clinical trials, and was never designed to find every possible adverse event that could occur in the future Ketek® patient population.

- Extensive records confirm that Aventis and the study monitor PPD sought to address investigator Good Clinical Practice (GCP) deviations. At the highest enrolling site, that of Dr. Kirkman-Campbell, numerous GCP deviations were identified and questions were raised regarding the legitimacy of certain practices and data. Those questions were actively investigated by Aventis and PPD under a documented investigation plan, which required the investigator to act upon their findings.

- Despite those efforts, criminal fraud was subsequently discovered by FDA at that site. Dr. Kirkman-Campbell, an independent physician investigator, pled guilty to falsifying clinical trial records. Aventis cooperated fully in the investigation of Dr. Kirkman-Campbell -- as sanofi-aventis has cooperated in all of the extensive investigations into Study 3014. It is important to note that FDA criminal investigators have tools at their disposal, such as interviewing patients and various investigative techniques, that are typically unavailable to study sponsors and monitors. We must separate out what we know now about Dr. Kirkman-Campbell and other sites from what Aventis was able to determine at the time as the study sponsor.

- We greatly regret that Dr. Kirkman-Campbell's fraud was not confirmed during the study, as well as the study compliance problems later identified at other sites based upon additional information obtained through extensive post-study reviews. We firmly believe, however, that Aventis submitted the study report in good faith, believing that the GCP issues at the various sites had been addressed within the context of the monitoring plan and did not affect the safety data that was the focus of the study. We fully respect FDA's decision not to rely upon Study 3014 to support the approval of Ketek®. FDA's review -- including its ultimate decision to approve Ketek -- was quite rigorous and appropriate.

- We have learned important lessons from Aventis' Study 3014 experience. In addition to changes in policies, practices and personnel since Sanofi acquired Aventis in 2004, we have undertaken a comprehensive review of the lessons learned from Study 3014 to ensure that sanofi-aventis' policies, procedures, and training reflect those lessons. The changes we have instituted have been presented to FDA, and are detailed in my testimony.

- We recognize that the problems identified in Study 3014 are a very serious matter. FDA, Congress and the American public have the unequivocal commitment of sanofi-aventis to rigorous and compliant clinical research.

**Statement**
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**Paul Herbert Chew, M.D.**
**President**
**Research and Development**
**sanofi-aventis U.S. Inc.**

**Subcommittee on Oversight and Investigations**
**Committee on Energy and Commerce**
**U.S. House of Representatives**

**February 12, 2008**

Chairman Stupak, Ranking Member Shimkus, and Members of the Subcommittee, I am Dr. Paul Chew, President, Research and Development, for sanofi-aventis U.S. Inc.

I am here today to provide you with my perspective on the issues that have been raised regarding the development and approval of our antibiotic Ketek® and, in particular, the conduct of the clinical trial Study 3014. I also hope to contribute to your consideration of the broader pharmaceutical research and safety issues on the Subcommittee's agenda.

I would first like to provide some background about sanofi-aventis. We are an innovative, research-based company dedicated to improving health by discovering and developing new medicines that address unmet medical needs and ease or eliminate the burdens of illness and disease. Our research and development budget is one of the highest in the

industry, and we have research facilities around the world, including four U.S. R&D centers that employ approximately 2,600 scientists, physicians and support staff.

Patient safety is our highest priority at sanofi-aventis, and we are committed to conducting rigorous clinical research designed to provide a comprehensive understanding of the safety and efficacy of our products. Through ongoing monitoring and analysis of reported adverse events and other data, we thoroughly evaluate new information relating to our medicines. We are committed to timely and transparent communication with regulatory agencies around the world to ensure that benefit and risk information is clearly and accurately reflected in labeling.

Three key questions that I would like to address today are:

- One, what is the value of Ketek® and should the drug be on the market today?
- Two, what are the basic facts relating to Study 3014, and what went wrong in the study?
- And three, what have we learned from this experience?

**The Value of Ketek® (telithromycin)**

First, what is the value of Ketek® and should it be on the market today?

From a public health perspective, the development of new antibiotics is imperative. Antibiotic resistance is considered one of the world's most pressing infectious disease

challenges. Many significant bacterial infections are becoming resistant to commonly prescribed treatments, and such treatment-resistant pathogens can often require intensive interventions, including extensive hospital stays. The total cost of antimicrobial resistance in the U.S. was estimated by the Institute of Medicine to be nearly $5 billion annually. For several reasons, few pharmaceutical companies have pursued development of this important class of products. These factors include the costs of product development, the inherent scientific difficulties of antibiotic research, evolving standards for evaluation of safety and efficacy, and resistance concerns.

Despite these challenges, Aventis pursued the development of Ketek® as the first in a new class of antibiotics called ketolides. Ketek® has a unique mechanism of action, targeting two binding sites on common respiratory pathogens, including multi-drug resistant versions of the important pathogen *S. pneumoniae*.

Ketek® or telithromycin, now indicated in the U.S. for treatment of a very serious condition called community-acquired pneumonia, is well-supported by clinical data. Aventis' new drug application included 14 controlled phase III clinical trials, two additional studies, and extensive data from experience in more than 4 million patients taking Ketek® in other countries.

We recognize that issues have been raised regarding the use of non-inferiority study designs in the development of antibiotic products, including Ketek®. Such studies involve demonstrating non-inferiority of the new drug to an existing, FDA-approved comparator antibiotic drug. There has been a legitimate scientific debate regarding the use of non-inferiority studies to support efficacy for certain antibiotic indications, and it is

important to understand that such questions have been considered by FDA only relatively recently. In fact, in late 2006 FDA formulated its current position that non-inferiority studies would not be accepted to support the approval of indications for acute bacterial sinusitis (ABS) or acute exacerbation of chronic bronchitis (AECB), a position the Agency reiterated at the Advisory Committee meeting held in December 2006 to consider the appropriate indications for Ketek.

The use of non-inferiority studies to support the approval of Ketek® was consistent with the standards for antibiotic development then in place. The protocols for the Ketek® pivotal studies were agreed upon with FDA, and were considered the most appropriate and ethical approach to demonstrating efficacy for the indications under study. Thus, the issues that have been raised regarding non-inferiority trials are not Ketek®-specific. Indeed, virtually all of the currently marketed antibiotic products for these indications were approved based upon such study designs. In fact, we believe the database supporting Ketek® is one of the largest bodies of information available for any antibiotic at the time of initial approval.

As you are well aware, a supplemental “usual care” study – Study 3014 – was also conducted. However, the FDA has indicated that it did not rely upon Study 3014 to approve Ketek.®

The data on Ketek® has undergone intensive review. Most recently, in December of 2006, the FDA and two of its expert advisory committees concluded that Ketek® continues to have a positive benefit-risk profile for community-acquired pneumonia. The recently updated labeling for the product reflects a careful balancing of benefits and risks.

This is not uncommon in this therapeutic area; a number of common antibiotics are associated with serious warnings and contraindications. So, to the extent there is a question whether Ketek®, an innovative antibiotic, should have been approved in the first place, and whether it should remain on the market, the answer is yes.

**Study 3014**

Next, let me address the basic facts of Study 3014, and what went wrong in that study. Although I was not directly involved in the design or conduct of Study 3014, I have had an opportunity to review the matter carefully.

The Ketek® new drug application (NDA) was submitted to the FDA on February 28, 2000, and the Agency convened a meeting of the Anti-Infective Drugs Advisory Committee on April 26, 2001 to discuss the data and seek expert input regarding the overall benefit-risk profile. After consideration of extensive data from 14 pivotal clinical trials and two additional safety studies, the Advisory Committee believed that certain potential safety signals seen in those trials – the controlled clinical trials typically done to support drug approval – should be further explored in a supplemental large safety study. As the Advisory Committee recommended, FDA asked for such a study to provide further evaluation of infrequent hepatic, visual, cardiac, and vasculitic "adverse events of special interest," or "AESIs."

This study, known as Study 3014, was conducted by Aventis in the Winter of 2001-2002, and it was the first large "usual care" study conducted pre-approval for an anti-infective drug. This type of study involves trying to study an unapproved drug in a large

population of patients at many study sites in order to evaluate safety in the typical physician's office or "real world" setting involving treatment of a more diverse range of patients.

It is important to note that the study was never designed to find every possible adverse event that could occur in the future Ketek® patient population. No single study can accomplish that goal. Rather, as agreed upon with FDA, Study 3014 was focused on further characterizing -- in the usual care setting -- the "adverse events of special interest" that had already been identified in the controlled clinical trials.

Study 3014 was unusually large and complex, involving the coordination of over 1,800 investigators treating over 24,000 patients in a brief time period. Aventis consulted with FDA about the study design, submitted the draft monitoring plan, and hired experienced contractors to implement training and provide monitoring in an effort to ensure investigator compliance.

At the time of the study, Aventis believed that the compliance monitoring efforts were appropriate to the task at hand. For example:

- Approximately 93,000 weekly and other monitoring calls were made to investigator sites.

- Over 99% of the sites that enrolled 16 or more patients, and 100% of sites where the physician had not previously served as a study investigator and which enrolled 5 or more patients, received an on-site monitoring visit.

- Approximately 38% of enrolled subjects had complete source verification of study data by PPD.

- As the focal point of the study, AESIs were tracked and rigorously assessed by outside experts.

During the study, Aventis and its contract research organization PPD identified numerous deviations from good clinical practices, or “GCPs”, at various investigator sites. GCP deviations occur in virtually every large clinical study. Such issues, which include protocol deviations, failure to initial or sign documents, or other incomplete documentation, are typically successfully addressed through corrective actions. Thus, FDA’s regulations call upon companies sponsoring studies to first secure compliance with applicable requirements and, if such compliance cannot be secured, to end the investigator’s participation in the study. Extensive records confirm that Aventis and PPD sought to correct or address GCP deviations, consistent with FDA regulations.

At the highest enrolling site, that of Dr. Kirkman-Campbell, numerous GCP deviations were identified and questions were raised regarding the legitimacy of certain practices and data. Contrary to the allegations that have been made, those questions were actively investigated by Aventis and PPD under a documented investigation plan, and Aventis and PPD required Dr. Kirkman-Campbell to act upon their findings.

But, as you know, criminal fraud was subsequently discovered by FDA at that site, and Dr. Kirkman-Campbell, an independent physician investigator, was criminally prosecuted for her actions and pled guilty to falsifying clinical trial records. Aventis cooperated fully in the investigation of Dr. Kirkman-Campbell -- as we have cooperated in all of the

extensive investigations into Aventis' conduct in Study 3014 -- providing access to employees and thousands of pages of documents. At FDA's request, the company also submitted independent reviews of certain study sites, and a reanalysis of the study without the Kirkman-Campbell data. Notably, the exclusion of the Kirkman-Campbell data in this reanalysis did not impact the safety profile observed in the trial.

Although the investigator fraud at the site is now in clear focus, based upon our review, we believe Aventis was unable to confirm at the time that fraud had occurred at the Kirkman-Campbell site, as opposed to good clinical practice deviations. In evaluating Aventis' conduct as sponsor of Study 3014, it is important to note that FDA criminal investigators have tools at their disposal, such as interviewing patients and various investigative techniques, that are typically unavailable to study sponsors and monitors. We must separate out what we know now about Dr. Kirkman-Campbell and other sites from what Aventis was able to determine at the time as the study sponsor.

I can tell you that we greatly regret that Dr. Kirkman-Campbell's fraud was not confirmed during the study, as well as the problems later identified at other sites. With the benefit of hindsight and additional information obtained through extensive post-study review and subsequent information made available from FDA's inspections, sanofi-aventis acknowledges that Aventis was unable to secure compliance with the investigational plan and applicable FDA regulations at a number of sites. However, we firmly believe that Aventis submitted the study report in good faith, believing that the GCP issues at the various sites had been addressed and did not affect the safety data which was the focus of the study.

In this regard, it is worth noting the conclusions stated by Dr. Joanne Rhoads, the Director of FDA's Division of Scientific Investigations at the time Study 3014 was investigated, at the comprehensive December 2006 Advisory Committee meeting on Ketek®. At that meeting, Dr. Rhoads stated:

> *These are difficult studies to do and to monitor and inspect….Monitoring is highly variable. In my experience, even when fraud exists, monitors often don't find it. Even when serious problems exist, monitors often don't find it….And there were problems definitely identified. But, considering the nature of the trial and the extent of the problem, we did not see direct evidence that this information was ignored by the company.*

Although we agree with Dr. Rhoads' observations, we are determined to learn from this experience.

Ultimately, FDA decided not to rely upon Study 3014 to support the approval of Ketek® in April 2004. We fully respect that decision. However, Ketek® was approved on the basis of a large body of controlled clinical trials involving over 4,300 Ketek®-treated subjects, post-marketing data from millions of patients outside the United States, and other data provided to the Agency. Specifically, Aventis submitted extensive post-marketing safety data from use in actual physician practice in other countries, including countries of the European Union, where approximately 4 million patients had been treated with the drug. Such extensive data were not available when Study 3014 was requested by FDA in 2001. Overall, we believe FDA's review was quite rigorous and appropriate.

**Lessons Learned**

Finally, in addition to changes in policies, practices and personnel since Sanofi acquired Aventis in 2004, we have also undertaken a comprehensive review of the lessons learned from Study 3014 to ensure that sanofi-aventis' procedures -- and associated training -- reflect those lessons. Let me share with you a few of the steps we have taken.

First, in addition to reliance upon the integrity of physician investigators, we in the industry must improve our ability to detect investigator fraud in clinical studies. At sanofi-aventis, we have enhanced our approach to investigating potential fraud, and mandated additional training in these areas for all personnel engaged in study management, monitoring and auditing activities. We have also focused on improving our procedures for addressing persistent investigator non-compliance.

We also recognize that we must be more transparent in our interactions with the FDA. In retrospect, Aventis could have been more proactive in bringing the issues encountered at high-enrolling sites, and particularly the highest enrolling site, to the attention of the Agency so it could have used its superior knowledge and investigative tools to evaluate the potential for fraud at an earlier point. We have revised our procedures to address this lesson. However, additional guidance on reporting situations in which the sponsor has serious investigator compliance concerns – but not confirmation of fraud - would benefit our industry as a whole.

We also think that industry would benefit from additional guidance on addressing the more general compliance challenges in these very large, usual care study designs, particularly as requests for such studies become more frequent. In retrospect, more real-

time on-site monitoring may have mitigated many of the issues in Study 3014. We have revised our site initiation and initial monitoring approach to ensure that clinical study sites are visited, on site, shortly after the first subject has been enrolled, in order to assure protocol adherence and detect potential problems.

Sanofi-aventis has also implemented systems and procedures to strengthen the evaluation, selection and training of investigators. A comprehensive plan to validate each investigator's qualifications and capabilities prior to enrollment is essential in every study. Although Aventis and its contractors undertook significant efforts to train the investigators in Study 3014, in retrospect more intensive training of investigators may have resulted in a better compliance outcome.

Finally, many of the problems in Study 3014 occurred at the high-enrolling sites. At the time, although the study protocol included a recommendation as to enrollment numbers, Aventis believed that higher levels of enrollment were feasible in the usual care setting. In retrospect, we recognize that strict limits on enrollment are essential in every study, and we have instituted procedures to further limit both the number of patients enrolled and the rate of enrollment.

These are just a few of the lessons we have learned from this difficult experience.

In closing, we recognize that the problems identified in Study 3014 are a very serious matter. As you know, FDA recently issued an extensive Warning Letter documenting the findings from its investigation of Aventis' handling of Study 3014. We have responded with detailed information on the comprehensive steps that sanofi-aventis has taken, and

will continue to take, to address the lessons we have learned. As a company that places the highest priority on patient safety, the FDA, Congress and the American public have the unequivocal commitment of sanofi-aventis to rigorous and compliant clinical research.

Mr. Chairman, Ranking Member Shimkus, and Members of the Subcommittee, on behalf of sanofi-aventis U.S., thank you for the opportunity to participate in today's hearing. We understand your interest in these important issues, and we look forward to answering your questions. I ask that my statement be included in the record of the today's hearing.