United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

December 19, 2007

**Via Electronic Transmission**

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner von Eschenbach:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. Accordingly, the Committee has a responsibility to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to oversee the proper administration of these programs, including payment for prescription drugs regulated by the Food and Drug Administration (FDA or Agency), Department of Health and Human Services (HHS or Department).

Nearly two years ago, the Committee began investigating extremely troubling allegations and concerns related to, among other issues, the approval and post-marketing surveillance of telithromycin (Ketek) by the Food and Drug Administration. Last December, I wrote to you regarding the Committee's findings on two of the allegations brought to the attention of the Committee. These allegations related to the FDA's Anti-Infective Drugs Advisory Committee meeting, held on January 8, 2003.

The purpose of this letter is to report the Committee's findings to date and request your comments and responses regarding these findings and some of the other allegations and concerns that have been brought to the Committee's attention. Specifically, this letter presents findings and information related to the FDA's assessment of Ketek's safety for marketing and some of the inspections and/or investigations conducted by FDA's Division of Scientific Investigations (DSI) and Office of Criminal Investigations (OCI).

Current and former FDA employees alleged that FDA relied solely on foreign post-marketing adverse event reports as evidence of Ketek's safety for marketing when the Agency could no longer rely on the large safety study, Study 3014. These employees questioned whether or not the use of such data as the primary basis for the Agency's safety assessment of Ketek met the standards for approval of the drug.

In addition, DSI reviewers, OCI agents, and field inspectors from the Office of Regulatory Affairs (ORA) had voiced concerns and/or made recommendations regarding Study 3014 and the manufacturer of Ketek. Yet, it was reported to the Republican investigative staff of the Committee (Committee Staff) that FDA officials in the Center for Drug Evaluation and Research (CDER) did not act on the concerns and/or

recommendations. Study 3014 was one of the largest studies involving antibiotics, enrolling more than 24,000 patients at over 1800 sites in less than four months.

The findings and conclusions in this letter are based largely on information obtained and received by the Committee. Over the course of 16 months, Committee Staff interviewed 26 current and former FDA representatives. The Committee Staff also reviewed thousands of documents and materials provided by HHS, FDA, FDA advisory committee members, and sanofi-aventis,[1] the manufacturer of Ketek. The findings and conclusions are limited by the information made available to the Committee by these sources. HHS and FDA, in particular, have provided incomplete and, in some cases, no responses to the Committee's questions and requests; therefore, questions still remain regarding FDA's handling of the review and approval of Ketek. Over a year ago, in May 2006, the Committee subpoenaed documents and information related to Ketek. However, HHS and FDA have failed to comply fully with the two congressional subpoenas. Despite assurances of cooperation and transparency from the Secretary of HHS, documents and information relevant to the Committee's inquiries were withheld from the Committee or provided in an untimely manner, and no privilege log has been provided as requested repeatedly. For example, the FDA has submitted hundreds of pages simply marked with the number of pages removed as well as documents with paragraphs or sentences redacted without any explanation for what has been withheld or redacted and why.

Two weeks ago, the Committee finally obtained access to a Special Agent within FDA's Office of Criminal Investigations. Over the last 18 months, HHS had refused to accommodate the Committee's outstanding request to interview the Special Agent, in spite of the Committee's legitimate oversight authority and the fact that HHS has made front line agents available to the Committee in the past. This Special Agent played an integral role in investigating Study 3014, which was submitted to the FDA by the manufacturer of Ketek. Instead, the Department and FDA had offered and provided the Committee a briefing by the Special Agent in Charge (SAIC) of OCI's Miami Field Office. The Department assured Committee Staff that the SAIC would be prepared to answer any and all questions posed by the Committee, including those regarding the Special Agent's feelings, thoughts, and "at the time" impressions of specific meetings, telephone conversations, and actions taken by the FDA.

Despite the FDA's assurances, the SAIC could not provide details of conversations and communications the Special Agent had with DSI and CDER staff. He was also incapable of providing specific dates for many of the events and conversations related to the Special Agent's investigation of Dr. Marie "Anne" Kirkman Campbell and Study 3014. The SAIC was poorly prepared and admitted to reviewing only a small portion of the materials that were provided to him in anticipation of the interview. Many of the events discussed during Committee Staff interviews occurred at least three years earlier, yet when the OCI Director met with Committee Staff, he also told them that he reviewed few documents in preparation for his interview—about 20 pages. Thus, questions regarding the Special Agent's role and activities related to the investigation as well as his communications and interactions with other FDA offices and third parties related to Study 3014 remained unanswered until late November.

[1] Sanofi-Synthélabo merged with Aventis Pharmaceuticals in 2004, forming sanofi-aventis.

To summarize, the Committee Staff reviewed documents and information obtained and received to date from HHS, FDA, FDA advisory committee members, and sanofi-aventis, and found the following:

- FDA appears to have relied primarily on foreign post-marketing safety data to assess the safety of Ketek as a new antibiotic for marketing. Based on interviews with current and former FDA staff, heavy reliance on foreign post-marketing safety data in this context is unprecedented. A week before Ketek was approved, FDA's Division of Scientific Investigations concluded that the data from a large clinical trial were unreliable. The study was conducted to evaluate specific adverse events associated with Ketek. In place of the large clinical trial, the FDA based its assessment of the safety of Ketek on foreign post-marketing adverse event reports, despite inherent limitations with that data, including underreporting and reporting bias. When asked by Committee Staff, FDA managers and reviewers could not identify any other case where FDA relied on foreign post-marketing data as the primary basis of its safety assessment for the approval of a new antibiotic.

- FDA regulations govern the use of foreign clinical trial data as the primary basis for approval of a drug. However, no comparable regulations govern the use of adverse event reports from foreign countries as the primary basis for determining the safety of a new drug for approval. FDA guidance categorizes adverse events data, both domestic and foreign, as secondary data sources for evaluating the safety of a new drug.

- Based on information reviewed by Committee Staff, the FDA lacks a system for tracking concerns and recommendations from the Office of Criminal Investigations. In addition, the FDA lacks a formal policy or guidance that specifies which branches of the Agency are responsible, if at all, for monitoring or following up on matters that are referred to CDER. For example, the primary OCI agent on Ketek recommended to his supervisors and to division and office directors in CDER that a task force be formed to explore the scope of fraud in the conduct of the sponsor's large safety study, Study 3014. However, FDA did not form a task force and CDER did not follow up on the OCI agent's recommendation. In addition, the agent's supervisors believed that this safety matter would be addressed after it was referred to FDA management, in particular the Associate Commissioner for Regulatory Affairs. Interestingly, FDA ultimately opened a criminal investigation in March 2006, around the same time that I initiated my inquiry. The case was closed in July 2007, and FDA issued a warning letter to the sponsor in October.

- During interviews with Committee Staff, FDA managers, reviewers, and inspectors identified and discussed several lessons learned from their experiences with Ketek, including allowing dissenting opinions within the FDA to be presented at advisory committee meetings, delaying advisory committee meetings until clinical trial data integrity questions are resolved, and improving

communication between the branches of the Agency that review drug applications and the branches that enforce FDA laws and regulations.

I am heartened to hear that some of the lessons learned have been or are being implemented. I hope that the FDA will continue to address problems identified during the course of its handling of the Ketek application.

## I. Background

On February 28, 2000, Aventis (sponsor) submitted to the FDA a New Drug Application (NDA) for Ketek for the indications of community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), acute bacterial sinusitis (ABS), and tonsillopharyngitis.

The first Anti-Infective Drugs Advisory Committee (AIDAC or Advisory Committee) meeting on Ketek was held on April 26, 2001. At that meeting, AIDAC expressed concern about adverse liver events (hepatic events) that could be associated with the use of Ketek. According to the FDA's timeline of Ketek's regulatory history, the Advisory Committee "indicated preference for further pre-marketing assessment rather than post-marketing surveillance alone." The Advisory Committee recommended approval of Ketek for CAP by a vote of seven to three. However, it unanimously recommended against approval for AECB and recommended against approval for ABS by a vote of eight to two.[2] AIDAC also concluded that the data were not sufficient for a claim of pneumonia caused by penicillin-resistant or erythromycin-resistant *Streptococcus pneumoniae*.

AIDAC further recommended that the sponsor obtain additional safety information from a large sample of patients to assess the adverse effects of Ketek. A few advisory committee members noted that approval was not warranted because other treatment options were available for AECB and ABS. One member added that the risk benefit analysis "weighs more towards the potential risk in acute sinusitis."[3] Two other members suggested obtaining more safety information from the use of Ketek to treat CAP before considering approval of the drug for other indications.[4]

After the AIDAC meeting, the FDA sent a non-approval letter for the indication of tonsillopharyngitis and an approvable letter for the indications of CAP, AECB, and ABS. In the approvable letter dated June 1, 2001, the FDA requested, among other things, a large safety study to further evaluate hepatic, cardiac, visual and vasculitic events associated with the use of Ketek. The Agency also requested efficacy studies examining the treatment of CAP and ABS due to resistant pathogens, in response to AIDAC recommendations.

[2] A transcript of the April 26, 2001 Anti-Infective Drugs Advisory Committee meeting is available at http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Anti-Infective.
[3] Transcript of April 26, 2001 Anti-Infective Drugs Advisory Committee meeting, page 291.
[4] Transcript of April 26, 2001 Anti-Infective Drugs Advisory Committee meeting, pages 290 and 303.

Aventis conducted a large safety study, Study 3014, and resubmitted the NDA to the FDA on July 24, 2002. At that time, the sponsor submitted data from Study 3014 along with foreign post-marketing adverse events data for the first million prescriptions for Ketek, data from several Phase 1 studies examining cardiac and visual issues, and efficacy data from Phase 3 studies of CAP due to resistant *Streptococcus pneumoniae*.

On January 8, 2003, FDA convened a second meeting of AIDAC to consider data from the sponsor's resubmission. Prior to the Advisory Committee meeting, FDA conducted inspections of three of the highest enrolling study sites and found study protocol violations at all three sites. The highest enrolling site was inspected in mid-October 2002 and then referred to the Office of Criminal Investigations for further investigation. The principal clinical investigator of that site, Dr. Kirkman Campbell, pleaded guilty to fraud in October 2003 and was sentenced in March 2004. She is currently serving a 57-month prison sentence.[5] The other two sites were inspected in December 2002. After conducting the three inspections, several DSI reviewers concluded that additional sites should be inspected.

At the second AIDAC meeting on Ketek, data from Study 3014 as well as post-marketing adverse events data from France, Germany, other European countries, and Latin America were presented to the Advisory Committee. A majority of the AIDAC members voted to approve Ketek for CAP, AECB, and ABS. The Advisory Committee's recommendations, however, were based largely on Study 3014.

At the last Advisory Committee meeting, held on December 14-15, 2006, the Director of the Division of Anti-Infective and Ophthalmology Products (Division Director) stated that, "The Advisory Committee then, in January of 2003, judged that safety and efficacy for the three requested indications had been demonstrated and that was, in large measure, on the safety data in Study 3014."[6] Three of the seven AIDAC members who responded to my letter regarding their participation in the January 2003 AIDAC meeting also said they relied heavily on Study 3014 in making recommendations to the FDA and gave little weight to the foreign post-marketing data.[7]

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[5] According to the lead Special Agent on Ketek, FDA has yet to debar Dr. Kirkman Campbell under Section 306 of the Federal Food, Drug, and Cosmetic Act (FD&CA) "from providing services in any capacity to a person that has an approved or pending drug product application" because she was convicted of a felony for conduct related to a drug product under FD&CA. FDA did not initiate action to debar Dr. Kirkman Campbell until February 28, 2007, almost three years after the doctor was sentenced. The last correspondence regarding this matter to be posted on the Agency's Web site is a letter dated August 16, 2007, from the FDA to Dr. Kirkman Campbell, reiterating the August 30, 2007 deadline for submission of information by the doctor to justify a hearing on the proposed debarment.

[6] Transcipt of December 14-15, 2006 Advisory Committee meeting, page 122; full transcript available at http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective.

[7] Attached to the December 13, 2006 letter was a table of comments from seven of the voting members of the January 8, 2003 Advisory Committee. In October 2006, the Committee sent a letter to the AIDAC members who participated in the January 8, 2003 meeting, requesting their responses to a series of questions regarding their knowledge of the data integrity problems of Study 3014 and their participation in the January 8, 2003 meeting. One of the questions posed to the Advisory Committee was: "To what extent did you base your vote and recommendations regarding the risk-benefit profile of Ketek on data from Study 3014?"

As I stated in my December 13, 2006 letter to you, the FDA presented Study 3014 data to the Advisory Committee despite red flags about the integrity of the data, including data from one study investigator whom OCI agents, DSI reviewers, the primary ORA field inspector of the site, and the local United States Attorney's Office all believed had falsified and fraudulently submitted clinical trial data.[8] However, the Advisory Committee was not informed of the data integrity problems associated with the conduct of Study 3014 at the time of the AIDAC meeting. In fact, several of the Advisory Committee members said that they became aware of the data integrity problems only after they received my letter in October 2006.[9]

The FDA did not follow the recommendations of AIDAC. Instead, the Agency issued another approvable letter to the sponsor on January 24, 2003. The approvable letter requested further information related to Study 3014, including findings of quality assurance audits or site monitoring visits conducted by the sponsor and/or the contract research organization (CRO). The FDA also found the sponsor's submission on foreign post-marketing data to be incomplete and requested that the sponsor provide accurate and complete adverse event reports as well as additional foreign post-marketing safety data, including analyses of the post-marketing adverse events.

The sponsor resubmitted its NDA to FDA on October 17, 2003. Between January 24, 2003, and the sponsor's resubmission in October 2003, DSI requested inspections of an additional five high-enrolling Study 3014 sites. According to a DSI memorandum dated March 25, 2004, FDA found a range of problems at the additional sites, although none as egregious as those found at Dr. Kirkman Campbell's site. FDA inspections revealed serious data integrity problems at four of the eight sites visited, including Dr. Kirkman Campbell's site. FDA found that the clinical investigator at a fifth site was unqualified to conduct a clinical trial. For the remaining three sites, FDA found adverse event reporting issues, among other things.

Based on its findings from the inspections of all eight study sites and a review of information provided by the sponsor and the CRO, DSI also concluded that data from Study 3014 were unreliable and stated, in pertinent part, the following:

> Monitoring of study sites by the sponsor/CRO failed to detect the significant problems found during the FDA inspections, calling into question the utility of the sponsor monitoring to detect data integrity problems. If the on-site

[8] The December 13, 2006 letter is available on the Committee Web site at http://finance.senate.gov/press/Gpress/2005/prg121306a.pdf.

[9] FDA's June 11, 2007 response to my letter stated that "data integrity is not a topic that is routinely discussed with advisory committees or in a public forum such as an advisory committee meeting. It is not generally the role of the advisory committee to adjudicate matters of data integrity." My concern is not that the advisory committee be involved in adjudicating data integrity matters, but rather that they be provided with complete and accurate information upon which to base their findings and recommendations. Based on interviews with FDA staff, FDA could have postponed or canceled the advisory committee meeting, especially since members of the Ketek Review Team had concerns about presenting the Study 3014 data, and in hindsight should have done so. Moreover, even if FDA had made the appropriate decision to proceed with the meeting at the time, the Agency should have informed the advisory committee members present at the January 8, 2003 meeting as well as the public what happened with Study 3014 at the earliest opportunity. More than two years after Ketek was approved, some of the January 2003 advisory committee members were unaware that FDA had determined that the Agency could not rely on Study 3014 to determine if Ketek should be approved for marketing.

> monitoring of these eight sites did not detect the significant problems, there is no reason to expect that the on- or off-site monitoring of all sites would have fared better at detecting significant problems. For these reasons, the integrity of data from all sites involved in study 3014 cannot be assured with any degree of confidence.

On April 1, 2004, the FDA approved Ketek for the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis. In light of DSI's findings, the FDA decided not to rely on Study 3014 for determining whether or not Ketek should be approved.

In January 2006, the *Annals of Internal Medicine* published an article on three cases of liver damage in North Carolina patients who took Ketek, and the FDA issued a public health advisory on the drug. About six months later, the sponsor voluntarily paused enrollment in its pediatric trials of Ketek and modified the drug labeling to include additional warnings about the risk of liver toxicity and to strengthen warnings for patients with myasthenia gravis.

Almost a year after the release of the *Annals of Internal Medicine* article, FDA held a joint meeting of the Anti-Infective Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 14-15, 2006. The purpose of the meeting was to discuss whether or not the benefits of Ketek outweighed the risks for each of the drug's approved indications, in light of the current safety information on hepatic, visual, and other adverse events associated with Ketek as well as the shift in standards for antibiotic approval. At the time that the sponsor conducted pre-market approval studies of Ketek, non-inferiority trials were used to assess the efficacy of the drug.[10] In recent years, however, that trial design has been called into question for conditions that are typically self-resolving, such as AECB and ABS. Specifically, concerns have been raised that non-inferiority trials cannot determine if the observed clinical outcome is the result of the test treatment or the natural course of the condition.

At the end of the two-day meeting, the two advisory committees concluded by a vote of 17 to 2 that the available data on Ketek did not support the continued marketing for the indications of AECB and ABS. For the indication of CAP, the advisory committees recommended, among other things, the addition of a black box warning.

On February 12, 2007, the FDA announced that "the balance of benefits and risks no longer support approval of the drug for these indications," AECB and ABS. The Agency removed those indications from the Ketek labeling as recommended by the joint advisory committees. The Agency also announced labeling changes, including the strengthening of warnings about specific adverse effects such as loss of consciousness and visual disturbances.

[10] In non-inferiority trials, one group of patients is given a medication of known effectiveness while a second group is given a medication for which the sponsor is seeking to establish effectiveness. The effectiveness of the second medication can be established if the clinical trial shows that the second medication is equivalent, or at least not substantially worse, than the first medication.

## II. FDA's Approval of Ketek Based on Foreign Post-marketing Data Is Unprecedented

### A. FDA Reliance on Foreign Post-marketing Adverse Events Data to Assess the Safety of Ketek for Approval

A week after FDA's Division of Scientific Investigations concluded in March 2004 that the data from Study 3014 were unreliable, FDA approved Ketek for all three indications—CAP, AECB, and ABS. Since the FDA could not use Study 3014 to support its decision, the Agency based its assessment of the safety of Ketek for marketing primarily on foreign post-marketing adverse events reports, despite inherent limitations with that data, including underreporting and reporting bias. The Division Director and then-Office of Drug Evaluation IV (ODE IV) Director, [11] who oversaw the review of the Ketek NDA, told Committee Staff during interviews that the FDA relied on post-marketing data as well as other data to evaluate Ketek's safety. However, based on extensive interviews with other FDA representatives as well as a review of thousands of documents, the Committee Staff found only evidence to support that the FDA relied primarily on foreign post-marketing adverse event reports in place of Study 3014 to support approval of Ketek.

At the April 26, 2001 Anti-Infective Drugs Advisory Committee meeting, the Advisory Committee called for additional safety information from a large sample of patients to assess the adverse effects of Ketek. At the second AIDAC meeting on Ketek in January 2003, data from Study 3014, as well as post-marketing adverse events data from France, Germany, other European countries, and Latin America, were presented to the Advisory Committee. After reviewing the data, a majority of the AIDAC members voted in favor of approval of Ketek for all three indications.

Ketek's approval was delayed three years because both AIDAC and the FDA had safety concerns. The sponsor conducted Study 3014 because AIDAC called for more data on the potential adverse events associated with the drug before it could recommend approval of Ketek for AECB and ABS. At the time that the second Advisory Committee requested a large safety study, most of the safety data from Phase 3 studies had already been made available to the FDA and to the Advisory Committee.

According to a March 7, 2003 memorandum documenting a teleconference between the FDA and the sponsor, one point made during the conversation was that "Aventis may need to rely on the analyses of foreign post-marketing experience to support the safety of telithromycin, if the results of study #3014 are not acceptable." An internal regulatory briefing at the FDA on February 19, 2003, discussed that point as well. According to the briefing minutes, "If the data provided by study #3014 cannot be used to support the safety of Ketek, the Division might be able to rely on the post-marketing data provided from those countries where Ketek has already been approved."

[11] The former Office of Drug Evaluation IV Director was appointed the Medical Director for Emerging and Pandemic Threat Preparedness in FDA's Center for Biologics Evaluation and Research in July 2006 and left the Agency earlier this year. The Office of Drug Evaluation IV is now known as the Office of Antimicrobial Products.

However, the Committee has not received written documentation containing the details of that discussion or any written explanation of why foreign post-marketing data can be used in place of clinical trial data as the primary basis for determining a drug's safety for marketing. Nor did the FDA explain how the post-marketing safety data addressed the safety questions left unanswered when the Agency determined that Study 3014 could not be used to support regulatory action. The medical reviews and meeting minutes only document the failure of Study 3014 and that the FDA primarily considered foreign post-marketing data in assessing Ketek's safety. In fact, one of the medical officers on the Ketek Review Team stated in his March 31, 2004 safety review that, "The majority of the review focuses on post-marketing safety. Additional review is included on the reanalysis of Phase 3 visual adverse events."

The Division Director and then-ODE IV Director stated that there were other data considered in the Agency's assessment of the safety of Ketek for marketing in addition to the foreign post-marketing adverse event reports. However, the issue that was raised to the Committee was FDA's reliance on foreign adverse event reports to assess the safety of Ketek in place of Study 3014 when the Agency concluded that it could not rely on Study 3014. No one other than the Division Director specifically identified additional studies, which raises questions about the significance of these studies in FDA's safety assessment of Ketek.

In FDA's letter to the Committee dated September 13, 2006, the Agency listed the studies that the Division Director mentioned during her interview with Committee Staff. According to the Division Director, the sponsor submitted to the FDA three studies, in addition to Study 3014, in response to the second approvable letter issued in January 2003. However, one of the three studies examined the effect of a different antibiotic, clarithromycin, on the cholesterol-lowering medication simvastatin (Zocor). A second study examined Ketek's effect on Zocor. The third study was a foreign post-marketing observational survey, which was ongoing at the time—physicians in Germany who were participating in the study were asked to report all of the adverse events they observed in their patients taking Ketek.

### B. FDA Reviewers Questioned Use of Post-Marketing Adverse Event Reports Because of Data Quality

My Committee Staff asked one of the FDA reviewers why he considered it inappropriate for the FDA to rely heavily on foreign post-marketing adverse events data as the primary basis for assessing Ketek's safety. That reviewer stated that "post-market data do not have the same level of rigor as clinical trial data" and added that such reports are often fraught with incompleteness and reporting bias. Several other FDA reviewers also expressed concern about the quality of post-marketing adverse event reports, both foreign and domestic. They explained that there are problems inherent to all passive reporting systems, including the U.S. reporting system. In particular, they noted the underreporting of adverse events, reporting or recall bias because physicians and/or patients do not adequately recall or report details of the event, incomplete submissions, which makes it difficult to assess causality, and the lack of an appropriate denominator, the total number of patients exposed to the risk, for calculating the rate of an adverse event.

Several FDA reviewers also stated that they were further concerned about the differences in reporting rates among countries. The Ketek Review Team Leader wrote in an email dated December 27, 2002, to the Division Director, then-ODE IV Director, and several members of the Review Team that:

> Health care infrastructures in these countries [countries where Ketek had been approved for marketing] can be scored on a 1-5 scale (1=best infrastructure, 5=worst) using a typology constructed by the Armed Forces Medical Intelligence Center (AFMIC); this classification takes into account surveillance and reporting systems, availability of health care and pharmaceuticals, and health care expenditures….
>
> For the 17 countries in which Ketek is listed as marketed, the median AFMIC category is 4; the AFMIC characterizes countries in this category as having "epidemiologic surveillance, response, and prevention concentrated in capital; minimally present in rest of country." (Countries such as Brazil fall into this category). Of these 17 countries, 10 fall into category 4. This analysis does not, of course, take into account the number, rate, or localization of prescriptions written in these countries, but does suggest that the majority of countries in which telithromycin is currently marketed have adverse event surveillance and reporting systems that are less than robust.

Another medical officer on the Review Team expressed concern about the significant difference in the number of events reported through the foreign post-marketing surveillance systems, in particular Germany compared to Italy. According to this medical officer's safety review, a majority of Ketek prescriptions were written in Germany and in Italy. Yet, based on adverse events data reported to the FDA from July 2001 through October 1, 2002, Italy reported few adverse events compared to Germany.

The medical officer also stated in his October 15, 2003 safety review, "Disparities in the rates of post-marketing adverse event reporting (lower for Italy than for Germany or Brazil) potentially indicate differences in post-marketing surveillance capabilities. Surveillance data from Italy may be less able to detect safety signals in post-marketing." In an email to two members of the Ketek Review Team dated February 10, 2003, he also noted a 380 percent difference in the reporting rate between Germany and Italy. Specifically, he stated that Germany reported 218 patients with post-marketing adverse events out of 455,464 prescriptions, which is about 47.9 patients with adverse events per 100,000, whereas Italy reported only 25 patients with adverse events out of 199,577 prescriptions, which is 12.5 patients with adverse events per 100,000.

Thus, the question remains whether or not FDA should be relying on post-marketing adverse events data as the primary basis for its assessment of a drug's safety for approval when there are concerns about the quality and completeness of adverse event reports in general and foreign post-marketing data in particular.

### C. FDA Officials Could Not Identify Any Other Antibiotic Approved Based Primarily on Safety Data from Foreign Post-marketing Adverse Event Reports

Between August 2006 and April 2007, the Committee Staff interviewed two dozen FDA staff involved in the review of Ketek, including medical reviewers, safety officers, statistical reviewers, site inspectors, and managers. In light of the concerns regarding the reliance primarily on foreign adverse event reports as the basis for FDA's assessment of Ketek's safety, the Committee Staff asked at least eight FDA individuals directly involved in Ketek's approval to identify examples of other antibiotics that were approved based on foreign post-marketing safety data. Not one could recall a case where FDA based its safety assessment of a new antibiotic primarily on foreign post-marketing safety data, and some of FDA individuals questioned have been working at the Agency for more than 10 years.

Then-ODE IV Director described one scenario where new indications were added to a drug labeling based primarily on post-marketing safety data. However, the indications were not added based on foreign data. They were based on U.S. post-marketing adverse event reports. Furthermore, the data were used for the approval of additional indications for a drug already on the market in the United States, not for a new drug.

In defense of FDA's use of post-marketing data for safety assessments, some FDA managers stated that sponsors are required to submit available U.S. and foreign post-marketing safety data as part of their application. The Committee is not questioning the appropriateness of including post-marketing safety data in a sponsor's drug application and using that data to assess a drug's safety. In fact, one requirement listed under 21 CFR § 314.50, which governs what must be included in a new drug application, is:

> A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.[12]

There is no question that adverse event reports, foreign and domestic, provide useful safety information, especially for detecting rare, serious adverse events. As the FDA pointed out, exacerbations in myasthenia gravis due to Ketek were detected through foreign post-marketing surveillance. However, the fact that no one could identify another antibiotic approved based solely or primarily on foreign post-marketing safety data raises questions about FDA's reliance on such data in the approval of Ketek.

FDA officials stated that by the time the Agency approved Ketek, FDA had received adverse events information from over 4 million prescriptions written in Europe and Latin America. In addition, both the Division Director and then-ODE IV Director stated during

[12] 21 CFR § 314.50(d)(5)(iv)

interviews with Committee Staff that they believed that the data were sufficient for approval of Ketek and that approval would encourage development of new drugs in light of the growing concerns regarding antibiotic resistance. Then-ODE IV Director told Committee Staff that pharmaceutical companies need to see that their products will be approved by the FDA to encourage them to pursue new antibiotics.

I recognize the need for alternative treatments for patients with resistant infections, but ABS and AECB generally are considered self-resolving conditions. According to many FDA medical officers, other antibiotics are available should patients with ABS or AECB require treatment. Furthermore, some questioned the effectiveness of the drug for ABS and AECB because the efficacy of the drug was based on non-inferiority trials.[13] If doctors are unaware that Ketek (or any other antibiotic for ABS and/or AECB) may be no more effective than placebo in treating ABS and/or AECB, then the use of the drug for those conditions could potentially lead to more antibiotic resistance. It is troubling if FDA is approving new drugs based primarily on questionable data in order to incentivize companies to develop new antibiotics, especially when the drugs are for conditions that may not even require antibiotic treatment.

## III. FDA Regulations Are Silent about Reliance on Foreign Post-marketing Adverse Events Data for Drug Approvals; Agency Guidance Shows that Post-marketing Data Are Considered Secondary Sources for Safety Assessments

The FDA relies on various data to determine the safety and effectiveness of a new drug, including human pharmacokinetic data, animal data, microbiology data, and clinical trial data. However, while FDA regulations specify the required elements of a new drug application, they provide limited insight on how much weight FDA places on each category of data as the basis for approving or not approving a new drug. One provision governs the use of foreign data as the sole basis for marketing approval—21 CFR § 314.106—but the provision relates specifically to foreign clinical trial data, not post-marketing adverse event reports. The regulation states:

> An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA

[13] During a February 2003 regulatory briefing, FDA managers and reviewers discussed the use of foreign post-marketing data if Study 3014 were to be considered unacceptable. At that briefing, one office director indicated "that based on the risk/benefit profile of this product, even without usable data from Study # 3014, an approval action for the CAP indication could be warranted. However, in his opinion, approval for AECB and AS is questionable." As mentioned earlier in this letter, the April 26, 2001 AIDAC also did not recommend approval of Ketek for AECB and AS. One of the Advisory Committee members raised the possibility of approval for CAP so that information regarding usage in that population could be tracked and used as part of decision on whether or not Ketek should be approved for ABS or AECB. My Committee Staff asked then-ODE IV Director whether or not FDA ever considered a proposal similar to the one made by this Advisory Committee member, and the director said FDA did not consider such a proposal. In retrospect, he said FDA could have considered issuing a not approvable letter for ABS and AECB even though the Agency had already issued an approvable for all three indications in 2001.

> considers such an inspection necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on foreign data alone.

FDA's "Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" (Guidance) provides some insight into what data and information FDA considers relevant in a safety reviewer's report.[14] That Guidance, however, also raises questions about the Agency's reliance on foreign adverse event reports as the primary basis for the assessment of Ketek's safety.

As stated, the purpose of the Guidance is to "assist reviewers conducting the clinical safety reviews as part of the NDA or BLA review process, provide standardization and consistency in the format and content of safety reviews, and ensure that critical presentations and analyses will not be inadvertently omitted." Specifically, the Guidance states that reviews should include a description of primary clinical data sources as well as secondary clinical data sources used to evaluate safety.

The primary source of data is described as:

> generally the database derived from the applicant's development program. Studies in this program will generally have full study reports related to safety, or studies that are grouped for analysis of safety in an Integrated Summary of Safety; case report forms will be available. These studies usually will have been closely monitored.

Secondary data sources are:

> (1) data derived from studies not conducted under the applicant's IND and for which CRFs and full study report are not available, or studies so poorly conducted…that they cannot be reasonably included in the primary source database, (2) postmarketing data, and (3) literature reports on studies not conducted under the IND.

While the Guidance states that secondary data sources "may be a critical source of information for review, despite the generally lower quality of these data, because they often provide the larger database needed to look for less common serious adverse events and may be reliable with respect to deaths and serious adverse events," they are nonetheless categorized as secondary sources of data for evaluating safety. In the case of Ketek, FDA replaced Study 3014, a primary source of data, with foreign post-marketing adverse event reports, a secondary data source, as the basis for assessing the safety of Ketek.

## IV. FDA Failed to Respond to a Recommendation from the primary OCI Investigator to Create a Task Force To Examine Fraud in Study 3014

[14] The Reviewer Guidance is available on FDA's Web site at http://www.fda.gov/cder/guidance/3580fnl.pdf.

In light of the inspection of Dr. Kirkman Campbell's site, the OCI Special Agent leading the Ketek investigation (Special Agent) recommended that FDA create a small task force to investigate all of the study sites that enrolled 100 or more patients to determine the extent of fraud in Study 3014. The Special Agent also questioned whether or not the sponsor, or one or more of its employees, was aware of but disregarded potential fraud and problems at some of the study sites. Although FDA conducted eight site inspections and the Agency ultimately did not rely on Study 3014 to support regulatory action, CDER failed to follow up or act on the recommendation and repeated concerns of the lead Special Agent. Within OCI, the Special Agent's supervisors also failed to follow up on the recommendation once it had been referred to the Associate Commissioner for Regulatory Affairs. FDA ultimately opened a criminal investigation in March 2006, around the same time that I initiated my inquiry. The case was closed in July 2007, and FDA issued a warning letter to the sponsor in October.

The Division of Scientific Investigations began to raise red flags regarding Study 3014 as early as October 2002 after inspection of the highest enrolling site, the site of Dr. Kirkman Campbell. DSI reviewers and managers informed my Committee Staff that FDA typically conducts an inspection of one or two of the highest enrolling sites when an NDA is submitted to the Agency, so it was not unusual that Dr. Kirkman Campbell's site was inspected in October 2002. However, the field inspector for Dr. Kirkman Campbell's site said that as soon as she walked into Dr. Kirkman Campbell's office, she knew there were serious problems with the site, and indeed, she found significant violations of Good Clinical Practices as well as potential fraudulent behavior during her inspection. Soon after, the site was referred to OCI for criminal investigation. In an email dated November 14, 2002, an OCI special agent informed DSI and the project manager of the Ketek Review Team that OCI had initiated a criminal investigation of Dr. Kirkman Campbell. In that email, he stated:

> There is good reason to believe that Dr. Kirkman-Campbell falsified a lot of patient data on this study, and that an individual at Aventis may have had some knowledge of the doctor's activities. It is my understanding that the advisory committee will convene on 01/08/03 to review this NDA for approval. I would encourage a careful consideration of the impact Dr. Kirkman-Campbell's data might have on the overall "approvability" of this NDA.

As a result of the findings at Dr. Kirkman Campbell's site, DSI requested ORA field inspectors to conduct inspections of the next two highest enrolling sites. FDA inspectors found Good Clinical Practices violations at these sites as well. Even before completing these inspections, the inspector of Dr. Kirkman Campbell's site wrote to DSI managers on December 9, 2002, that a fourth site should be inspected and that there could be more sites of concern, stating:

> We just learned (from a source) of another PI that should be inspected on the Ketek study….He enrolled his staff and his family members. There were scant study records & numerous informed consent violations. It looks like there were many other sites w/ numerous ICF violations, small towns w/ large enrollment, & sites that enrolled their won [*sic*] staff, etc. We are hearing that the sponsor/staff was well aware of these problems. It looks like the NDA should be placed on hold until the matters are resolved.

Several weeks later, the Project Manager informed the Ketek Review Team, including the Division Director and then-ODE IV Director, that with the three highest enrolling sites, they had a "total of 872 patients (3.5%) with questionable data." In addition, the Team Leader wrote to the Ketek Review Team that 30 sites enrolled 80 or more patients, with 30% of those sites enrolling 1% or more of the adult population of the city or town in which they were located even though incidences of the respiratory tract infections studied in Study 3014 do not typically exceed 1% in the United States. A medical officer on the Review Team wrote back on December 24, 2002, that "it seems a little unusual for a study to have so many questionable sites and it certainly raises alarms as to the way in which the study was conducted."

Between February 2003 and June 2003, there were email exchanges between the Office of New Drugs (OND) and ORA, which oversees OCI, regarding the status of OCI inquiries into the Ketek NDA. It appears that OND, ORA, OCI and DSI were all concerned about problems with Study 3014.

Within OCI, the Special Agent in Charge (SAIC) of the Ketek investigation, wrote to his OCI field agents in an email dated March 7, 2003, that:

> I cannot overemphasize the importance of our effort, nor the exposure and attention this investigation has at the highest levels of the FDA and the pharmaceutical industry….Moreover, [the OCI Special Agent] has identified systematic weaknesses in the FDA process for inspecting clinical investigators, which has grave implications for the entire new drug approval process.

Several months later, on June 19, 2003, the Special Agent wrote to the SAIC, that:

> In order to proceed with Aventis or at least Aventis personnel, I believe that other PIs need to be inspected to see if there was a pattern of falsification. If other PIs were falsifying their clinical studies, I think we would have a better chance proving Aventis personnel knew of the falsification and submitted the NDA even though they knew of the fraud. The Center needs to inspect those PIs that enrolled a large number of patients.

On that same date, the Division Director asked ORA for an update on the investigation of Dr. Kirkman Campbell. On July 28, 2003, the Special Agent wrote to his supervisors and the OCI Director that he had a phone conversation with then-ODE IV Director, then-ODE IV Deputy Director, and the Division Director. According to the Special Agent's email, he briefed the directors on the investigation of Dr. Kirkman Campbell and what the sponsor allegedly knew before it submitted its NDA to the FDA. The Special Agent wrote, in pertinent part:

> I suggested to them that it was absolutely necessary for this agency (FDA) to inspect other clinical sites that participated in the clinical trial. I proposed to them that we establish a criteria for inspection (PI that enrolled more than 100 patients) and immediately inspect those sites….I explained that it was my opinion that these sites could not be inspected normally. We have to go in to

> prove or disprove fraud not whether or not the PI was in compliance with the protocol….
>
> …I am willing to be involved in any action you deem appropriate.
>
> I feel that all suspect sites and those sites that have 100 patients or more be inspected. This could be done by BIMO personnel or by OCI agents. If regulatory inspects, they can issue a notice of inspection and move forward. If OCI agents examine documents, we would have to either get the PI to voluntarily release all documents or we would have to get a US Attorney's Office interested for the purpose of issuing subpoenas for those documents….This would probably involved establishing a mini-task force.

During that telephone briefing, the Special Agent also spoke about his concerns regarding the sponsor. He wrote to his supervisors that he told then-ODE IV Director, then-ODE IV Deputy Director, and the Division Director that it was his feeling that:

> …Aventis knew sites were suspect but they did nothing to prove or refute their suspicions…. I also told them that I know they have a shortage of personnel but I think we have to take the necessary steps in order to protect the consumer. I am not interested in whether or not this drug works or doesn't work. I am only interested in whether or not PIs and Aventis blatantly disregarded the obvious. This is the key to whether or not we have any action against Aventis or other PIs.

The Special Agent ended his email with the following statement: "I think the three individuals from CDER understood my feelings and opinions but I don't know whether or not the necessary steps will be accomplished." Steps were not taken to implement the agent's recommendation. According to the SAIC, the Special Agent told him that he expected more enthusiasm for his proposal. He told the SAIC that the directors did not express any support and did not even ask him questions, unlike the ORA field inspector and DSI reviewers who wanted to move forward with further inspections. The Special Agent also said he and the ORA field inspector on Ketek were ready to proceed, but they could not do so without the support of CDER. During his interview with Committee Staff, the Special Agent acknowledged that when he briefed the "three individuals from CDER" he was unaware of their roles and functions within CDER.

When Committee Staff interviewed the three FDA directors who spoke with the Special Agent, one of them said that they did not know what OCI expected CDER to do with the information. Then-ODE IV Director commented that if OCI wanted to initiate additional investigations, it was OCI's call, not CDER's. Furthermore, if the Special Agent believed additional inspections were warranted, the director said OCI should have pursued the matter with DSI. The Division Director added that CDER worked with DSI to identify several additional sites for inspections, just not all sites enrolling 100 or more patients. According to then-DSI Director and CDER management, FDA lacks the resources to inspect so many sites and that FDA typically conducts only one or two site inspections per trial prior to approval of an application.

When my Committee Staff interviewed then-director of DSI, the director told them she never heard that OCI believed the company did something wrong. To their surprise, she also said that FDA rarely investigates companies because it is a "losing game," the

chances of getting warning letters was zero. She added that in the case of Ketek, she believed that the sponsor would "take the hit" in losing the ability to cite Study 3014 in the Ketek labeling.

I sincerely hope that your position is not that FDA should refrain from investigating sponsors because it is difficult to uncover fraud at companies. FDA is responsible for oversight of clinical trials. A position like that would only enable bad behavior. [15]

When Committee Staff mentioned the Special Agent's recommendation for more site inspections and the formation of a task force, then-DSI Director asked, "Who would do the work?" The Special Agent, however, explained to Committee Staff that the small task force that he proposed did not require extensive resources or staff time from CDER. He said his proposal only required Center support and coordination, especially from DSI because DSI issues the inspection assignments to the ORA field inspectors when inspections involve the integrity of clinical trial data and the protection of human subjects. DSI also reviews inspections results from a scientific and regulatory perspective to determine if regulatory action is required. However, in this case the purpose of the task force was to determine if there were fraud at other study sites and if the sponsor had knowledge of the fraud.

According to both CDER and DSI management and staff, it is uncommon for OCI to keep them apprised of OCI activities. Yet, with Ketek, the Committee Staff have reviewed emails documenting regular communication between OCI and DSI staff and the Project Manager for the Ketek Review Team. Furthermore, the Special Agent also recalled briefing the Deputy Director of OND during the summer of 2003 regarding Dr. Kirkman Campbell and his concerns about Study 3014. He briefed the OND Deputy Director because she was identified as a potential grand jury witness for the Kirkman Campbell case. The fact that OCI agents maintained communication with CDER and DSI staff on OCI's inquiries and the Special Agent briefed CDER management regarding his concerns should have raised a red flag about the seriousness of the problems with Study 3014 and elicited further discussion regarding an FDA response.

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[15] According to press reports in July 2006, FDA Deputy Commissioner/Chief Medical Officer stated that, "We [FDA] need to make sure there's the proper oversight and authority over all the parties that are involved in clinical trials." The FDA also announced that the Agency was working on a proposed rule for sponsors to notify FDA if they believe a researcher has committed fraud during a clinical trial. In the case of Study 3014, it seems to me that the sponsor also had an ethical responsibility to the human subjects participating in its trial to ensure that irregularities and concerns at specific study sites are adequately investigated and addressed. When told by the FDA about the problems with Dr. Kirkman Campbell's site in December 2002, the sponsor acknowledged that it was aware of the problems and that Dr. Kirkman Campbell's participation was discontinued when the sponsor became aware of irregularities (December 19, 2002 meeting minutes). Yet, FDA was never notified of that nor did the company remove Dr. Kirkman Campbell's data from its Study 3014 submission to the FDA. Furthermore, the company's own monitoring efforts failed to raise questions about potential fraud and other serious problems, which seemed apparent to FDA investigators during their inspection of the site. In fact, after the sponsor's initial on-site inspection of the site, the company continued to supply Dr. Kirkman Campbell with Ketek. One FDA inspector told Committee Staff, however, that she knew as soon as she walked into the office that the site was problematic. Representatives of the sponsor informed Committee Staff in October that the sponsor has since modified its standard operating procedures for monitoring clinical trials and has conducted training of its employees to better identify fraud and misconduct.

About nine months after the Special Agent briefed CDER management, Ketek was approved. The Division Director said that while CDER did not request additional inspections beyond the eight that were conducted, CDER did take action regarding Study 3014—the Center decided not to use Study 3014 to support regulatory action on Ketek. More inspections may not have been necessary for the Center to determine the approvability of Ketek, but the inspections might have uncovered fraud at other sites. In light of the potential fraud concerns raised by the Special Agent, why did further discussion not occur within CDER or between CDER and OCI and/or ORA regarding the Special Agent's proposal? If it is FDA's position that no additional inspections are required once a study is no longer useful for regulatory action, then how can FDA protect research subjects from the harm that may be caused by clinical investigators?

Based on interviews with the OCI Director, the SAIC, and then-Associate Commissioner for Regulatory Affairs,[16] within OCI there also was limited follow-up on the Special Agent's concerns and recommendations, despite OCI management's glowing comments regarding the Special Agent and his work. For example, the OCI Director wrote to the SAIC and two other OCI agents in an email dated March 6, 2003, that "This guy [the Special Agent] is world class. My hats off to him." After forwarding the Special Agent's write-up of the Dr. Kirkman Campbell case to then-Associate Commissioner for Regulatory Affairs, the OCI Director wrote to then-Associate Commissioner that, "It gives me max pride to read things like this. I admire my people so much. This guy is a WORLD CLASS lawman. MY people ARE great!"

The OCI Director confirmed this positive assessment during his interview with Committee Staff. The SAIC also told Committee Staff that the Special Agent's colleagues consider him an energetic, dedicated investigator and that the OCI Director talked about the Special Agent as a "damn fine investigator." Then-Associate Commissioner for Regulatory Affairs told Committee Staff that he had a lot of respect for OCI and all the investigators, stating that the investigators care about the work they do and the work he saw was "universally excellent."

Nevertheless, while the emails show that the Special Agent's supervisors praised his efforts, they did not ensure that his concerns and recommendations were addressed either by OCI or by CDER. The OCI Director told my Committee Staff that he forwarded the Special Agent's emails about the Kirkman Campbell investigation to then-Associate Commissioner for Regulatory Affairs and "assumed" action would be taken by that office. Then-Associate Commissioner, however, said that he offered to provide any assistance in Washington if OCI needed it, but did not hear anything more from OCI. Specifically, he stated in his email to the Special Agent and the SAIC, "Nice job…! Keep the pressure on and you guys let me know what we can do in Washington to help you." After Dr. Kirkman Campbell was indicted, then-Associate Commissioner informed FDA's Deputy Commissioner/Chief Medical Officer on September 2, 2003, by email, stating, "I doubt that this will be the end of the matter."

Based on the information reviewed by the Committee, it appears to me that communication broke down not only between CDER and OCI but also within OCI.

[16] The Associate Commissioner left the Agency in April 2005.

There is also a lack of clarity regarding which office was and/or should have been responsible for acting on concerns and/or recommendations made by the Special Agent.

The Special Agent suspected fraud in Study 3014 and recommended to CDER officials as well as to his supervisors that a small task force be formed to explore the scope of potential fraud. However, no such task force was formed, and the Special Agent did not receive an explanation for FDA's failure to act. The Special Agent's supervisors also did not follow up on whether or not the Center had taken any action based on the information provided by OCI. According to the Special Agent, he was not told by CDER that his proposal was rejected and that the Center would not be pursuing inspections of all sites enrolling 100 or more patients as a result of limited resources. He said that he learned of the decision through the ORA field inspector.

The SAIC told Committee Staff that he thought the Special Agent's proposal was a good idea. However, when asked why OCI did not pursue it, he said he referred the proposal to the people who would be responsible for initiating the task force, to CDER. When Committee Staff asked the SAIC what OCI's responsibility is when the office suspects or is aware of questionable data that is being used to approve a drug, the SAIC said CDER was briefed, so the ball was in CDER's court. He told Committee Staff that he believed that OCI went above and beyond in the Ketek matter. In addition, as I mentioned in a previous letter to you, the OCI Director told my Committee Staff that he did not know whether or not OCI routinely monitors or otherwise follows up on matters referred to Centers within the FDA. He also stated that he did not follow up on the Special Agent's recommendation regarding Ketek because he believed that OCI fulfilled its responsibility by reporting the agent's concerns and recommendation to FDA management. Furthermore, the OCI Director said that if CDER does not act on a referral, then there is not much OCI can do. The lack of follow-up by OCI is especially troubling in light of the safety issues related to Ketek and Study 3014.

On March 29, 2007, I also wrote to you regarding the OCI Director's interview with my Committee Staff, which covered many of the aforementioned issues and concerns. In FDA's response dated July 10, 2007, the Agency confirmed that it has no formal policy regarding the exchange of information between OCI and the Centers. Specifically, the letter states, "Whether a particular matter warrants follow-up by OCI is generally and appropriately left to the discretion of each Senior Operations Manager[17] and depends on the nature of the matter that is referred." Furthermore, FDA's July 10 letter also states:

> OCI, like other enforcement entities, has an established chain of command. Line-agents report to, and discuss issues with, their immediate supervisors. Depending on the nature and seriousness of an issue, the Special Agent in Charge (SAIC) of the OCI Field Office may discuss that issue or concern with OCI Headquarters. If warranted, the Director of OCI may bring the issue to the attention of the Associate Commissioner for Regulatory Affairs. The Commissioner of Food and Drugs has the ultimate responsibility to ensure that the issue is addressed appropriately.

[17] According to the FDA, Special Agents who are assigned to a particular subject area or to a particular center are referred to as "Senior Operations Managers." These managers are responsible for interacting with the specific centers.

That is essentially what happened in the case of Ketek—the Special Agent discussed his concerns and recommendations with his supervisor and the OCI Director in turn brought the matter to the attention of then-Associate Commissioner for Regulatory Affairs. Then-Associate Commissioner thought OCI was doing a good job and told the agents to "keep the pressure on" but OCI did not pursue the matter further. In addition, the Special Agent's concerns were not elevated so that the former FDA Commissioner could ensure that the issue was addressed.

The FDA also states in its July 10 letter that the Agency believes it is appropriate for OCI to rely on other FDA offices to determine, "based on their expertise, limited resources, and competing priorities, what if any further action is appropriate." If the action to be taken would primarily involve or impact FDA offices other than OCI, then it makes sense that OCI rely on the expertise and/or input of these other offices regarding further actions. However, the Special Agent recommended a task force that would involve input and collaboration from DSI, OCI, ORA and OND. It appears to me that each of those offices should have been at the table when deciding whether or not to pursue the Special Agent's proposal. Furthermore, the Committee did not see written documentation or receive explanation of affirmative actions to address issues with serious safety implications.

Recently, the HHS Office of Inspector General (HHS OIG) also reported a lack of follow-up within the Office of Regulatory Affairs. The HHS OIG issued its report on FDA's oversight of clinical trials in September. The OIG found that the FDA does not keep an internal clinical trial registry, is unable to identify all ongoing clinical trials, and does not keep a registry of Institutional Review Boards. The Inspector General also found that FDA does not consistently track inspection information and CDER downgrades a majority of ORA's classification of clinical trial violations. In September, I sent a letter to you regarding HHS OIG's findings and recommendations and asked that you keep me apprised on a quarterly basis of the status of FDA's implementation of HHS OIG's recommendations. Last month, FDA briefed my Committee Staff on its current initiatives for improving clinical trial oversight. I look forward to further updates from the FDA.

My Committee Staff initially received conflicting information from FDA representatives regarding whether or not FDA ever investigated what and when the sponsor knew about potential fraud in Study 3014. In September, they were finally informed that OCI did not open any investigation of the sponsor prior to the approval of Ketek. OCI initiated its investigation in March 2006 to examine potential wrongdoing related to Study 3014 and closed the case earlier this summer. At that time, the FDA said it would not provide the Committee with its findings from the investigation because the Agency was considering regulatory action on the matter. Regulatory action was taken on October 23, 2007, when the FDA issued a warning letter to the sponsor for failing to "ensure proper monitoring of [Study 3014]" and failing to "promptly secure compliance from Dr. Kirkman Campbell [with the study plan and FDA regulations] and did not adequately investigate allegations of fraud at this site," among other things.[18]

[18] The warning letter is available on the FDA Web site at http://www.fda.gov/foi/warning_letters/s6551c.htm.

## V. Concluding Remarks and Recommendations

Concerns about the safety of Ketek more than two years after its approval and a shift in FDA's approval of new antibiotics led to the removal of two indications from the drug labeling—ABS and AECB—earlier this year. Outstanding questions remain regarding FDA's initial decision to approve Ketek for those two indications as well as FDA's other actions, or lack of action, related to its review of the Ketek NDA, in particular Study 3014. By this letter, I am requesting that the HHS OIG examine, as appropriate, the way that FDA handled the investigation of the sponsor and Study 3014.

In addition, during interviews with Committee Staff, FDA managers, reviewers, inspectors, and agents discussed the lessons they learned from their experiences with the review and approval of Ketek and ways FDA could improve. The following recommendations are based on those discussions and on the information the Committee has reviewed. I would appreciate your comments on these recommendations. If you consider any of the recommendations as unviable options, I would appreciate receiving alternate proposals for addressing the concerns and issues set forth in this letter.

**Establish Policies to Improve Communication and Coordination between FDA Offices Regarding Clinical Trial Oversight**—The FDA needs to establish clear, written policies that define the roles, processes, and responsibilities of OCI, ORA, DSI, and the Centers regarding clinical trial oversight as well as standard operating procedures for communication and interaction between the offices. The Agency should ensure that its employees are familiar with those policies and procedures. The policies would include clarification of roles with respect to actions to be taken in response to the findings of inspections and investigations and the responsibilities for follow-up within FDA as well as with sponsors. The HHS OIG also recently recommended that FDA improve feedback between the Centers and DSI investigators so that there is common understanding of regulations and guidelines governing the inspections.

**Improve Tracking of Inspections and Investigations**—The HHS OIG recently recommended that FDA create a cross-center database. It was suggested that this database allow for complete tracking of DSI's inspections to help FDA better coordinate and track inspections. That database should include information from OCI's ongoing criminal investigations that can be appropriately shared with DSI, the Centers, and other FDA offices, findings from completed OCI investigations, and any actions or follow-up recommended by OCI and/or DSI. In addition, the database should allow FDA to track any clinical investigators that may have committed multiple violations in different clinical trials.

**Ensure that Complete Information Is Provided to Advisory Committees**—In my letter to you dated December 13, 2006, I raised a number of questions regarding the disclosure of relevant information and/or data to advisory committees on inspections and investigations of clinical trials used to support a new drug application. Several FDA officials and medical officers agreed that the Agency should consider delaying advisory committee meetings or determining a way to confidentially advise the advisory committee chair to avoid jeopardizing any ongoing investigations. If the FDA confirms fraud and/or data integrity problems with studies already presented before a public

advisory committee meeting, the Agency should have a clear mechanism for ensuring that advisory committee members as well as the public are advised of these subsequent findings. In addition, FDA should ensure that FDA reviewers can voice their professional medical opinions at advisory committee meetings without obstruction. In the past, FDA presented one perspective before an advisory committee. During the recent advisory committee meetings on the safety of Ketek and the diabetes drug Avandia, FDA reviewers were allowed to express their professional opinions and recommendations regarding those drugs. It is important not only that advisory committees be provided with complete and accurate data but also any differing scientific opinions and/or assessments regarding that data from FDA reviewers. An advisory committee cannot perform its duties adequately if it is not working with all available information and perspectives.

I look forward to hearing from you regarding these recommendations as well as the allegations, findings, and concerns set forth in this letter by no later than January 22, 2008.

Sincerely,

Charles E. Grassley
Ranking Member

cc: The Honorable Michael O. Leavitt, Secretary, HHS
The Honorable Daniel R. Levinson, Inspector General, HHS