

Statement of U.S. Senator Chuck Grassley of Iowa
“Ketek Clinical Study Fraud: What Did Aventis Know?”
Subcommittee on Oversight and Investigations
House Committee on Energy and Commerce
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Chairmen Dingell and Stupak, Ranking Members Barton and Shimkus, and distinguished colleagues, thank you for inviting me to speak today about my investigation of FDA’s handling of the large safety study Ketek, Study 3014. It has been a long road and it’s still not at an end.

More than two years ago, in January 2006, the journal *Annals of Internal Medicine* reported three cases of liver damage in North Carolina patients who took Ketek. In response the FDA issued a public health advisory.

After all, suffering severe liver problems is quite a price to pay for taking an antibiotic that was being used for such conditions as sinus infections until that indication was removed from the Ketek label a year ago.

Soon after, I heard allegations and concerns regarding FDA’s review of Ketek and I started asking questions. One of the more serious allegations was that the maker of Ketek, Aventis at the time, submitted clinical trial data to the FDA in support of approval, knowing it was fraudulent.

So I asked FDA to make arrangements immediately for my staff to review documents related to Study 3014 at the FDA’s offices.

Initially, FDA gave my staff access and agreed to provide copies of documents my staff identified during their review.

But then I asked for Special Agent Robert West from FDA’s Office of Criminal Investigations and the FDA pulled a 180 on me.

I had good reasons for asking for Agent West. One of the other allegations I received was that despite Agent West's concerns and recommendations, FDA never expanded its investigation to determine if the company did "knowingly" submit fraudulent data.

Agent West played an integral role in the investigation of Study 3014 and I am delighted to see that he will be testifying on the next panel along with two other special agents from the agency. Agent West was the lead agent on the investigation of Dr. Anne Kirkman Campbell, one of the principal clinical investigators for Study 3014. And as a result of that investigation Dr. Kirkman Campbell is currently serving a 57-month prison sentence. Agent West also was in frequent communication with the FDA consumer safety officers and reviewers involved in the Study 3014 inspections.

But as I testified before this subcommittee a year ago, FDA and HHS wouldn't make Agent West available—even after I went over to the HHS offices to ask personally to speak with Agent West and subpoenas were issued.

After all, if FDA had nothing to hide about how it handled Study 3014, why stop me from talking to Agent West? I smelled a "cover-up."

Well, I now have a better understanding of why FDA did not want me to speak to Agent West regarding Ketek. The answer to the "WHY" question is equally interesting. It seems to me that there were definitely reasons why the FDA did not want me to meet with Agent West or any other agents for that matter. FDA, it appears, did not want anyone to know that it didn't further investigate whether or not Aventis submitted fraudulent data knowingly to the FDA. The FDA did that even though Agent West recommended, in the summer of 2003—almost 5 years ago—to high level officials at the FDA that it needed to create a mini-task force look into Aventis.

When HHS and FDA finally made Agent West available a short time ago—18 months after I first requested him—Agent West confirmed that no one acted on his recommendations. In fact, I learned from HHS more than a year after my visit to the Department, that the FDA didn't open an investigation into the company until March 2006. Interestingly, that was around the same time I started poking around Ketek.

Agent West told his supervisors, FDA investigators involved in the Study 3014 inspections, as well as FDA directors overseeing the review of Ketek what he thought needed to be done—inspect all the study sites that enrolled over 100 patients. The protocol for Study 3014 had recommended a maximum enrollment of 50 patients per site, so that would have meant inspections of about 70 sites.

Agent West's supervisors told my staff that they supported him. The site investigators also thought it was a good idea. But what happened?

The head of the Office of Criminal Investigations told my staff that Agent West's concerns and recommendations were referred up the food chain, and he assumed the matter would be taken care of.

The Associate Commissioner for Regulatory Affairs at that time said he was prepared to offer any assistance if needed but never heard anything more from the Office of Criminal Investigations.

One of Agent West's superiors said the CDER folks were briefed so the ball was in their court. He also said that Agent West's task force proposal had nothing to do with concerns about Aventis.

But I have since learned that that's not true.

Agent West sent an email in July 2003 to his superiors about his conversation with directors in FDA's Center for Drug Evaluation and Research. These directors oversaw the review of Ketek.

In that email, Agent West said, "I told them that it was my opinion that Aventis knew sites were suspect but did nothing to prove or refute their suspicions."

Agent West was not the only agent who believed that the company or at least someone within the company knew there were serious problems, particularly at Dr. Kirkman Campbell's site. You have the two agents here today who were assigned to the criminal investigation that was opened in March 2006—Special Agents Robert Ekey and Douglas Loveland.

Agent Ekey said during a joint interview with our Committees that he thought the company too easily dismissed the concerns that were raised by its own contract research organization, the organization hired to monitor Study 3014.

Agent Loveland wrote in an internal email dated April 17, 2007, that the company knew significant issues existed at many sites yet the company submitted the data to the FDA and claimed the study was conducted according to good clinical practices. He also told my staff during an interview yesterday that Aventis should have known that there were problems with the integrity of the study data.

The case was closed in July 2007. FDA issued a warning letter in October to the company for failing to ensure proper monitoring of Study 3014 and not adequately investigating allegations of fraud at Dr. Kirkman Campbell's site. The letter cited many of the same problems that FDA's staff raised back in 2003 and 2004. So why wasn't an investigation initiated then?

Agent West stated in his July 2003 email, "I think the three individuals in CDER understood my feelings and opinions but I don't know whether or not the necessary steps will be accomplished."

When my staff spoke with the three directors, one of them told my staff that if the Office of Criminal Investigations wanted additional investigations, it was their call, not CDER's. He also said that the Office of Criminal Investigations should have talked to the Division of Scientific Investigations since the division oversees clinical trial site inspections.

So who's responsible?

Everyone seemed to be pointing the finger at someone else, with the exception of the head of FDA's office of Division of Scientific Investigations. This FDA employee told my staff that as far as additional inspections went, they didn't have the resources to do more. And besides, she said (1) the FDA didn't rely on Study 3014 for approval, (2) FDA completed 8 site inspections for Study 3014, which is many more than the one or two it normally does, and (3) astonishingly, she also said that investigating drug companies is a "losing game" and the chances of getting a warning letter is zero.

I find that attitude extremely troubling, as I'm sure you do as well.

We rely on the FDA to ensure that the drugs in our medicine cabinets are safe and effective. That includes FDA making sure that the data supporting the safety and efficacy of a drug is sound. To do that adequately, FDA has to do its job of oversight over clinical trials. Data integrity isn't the only issue of concern here. FDA also has an obligation to protect human subjects.

In December, I raised this matter to Commissioner von Eschenbach in a lengthy letter regarding my Ketek investigation. That letter I've been told is included in

your exhibit books. I asked Commissioner von Eschenbach: 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?

Not relying on a study for approval does not absolve FDA of its responsibility to protect the individuals who courageously volunteer in clinical trials so that we can all benefit from lifesaving cures and medical innovation. I am still waiting for the Commissioner's comments on this important matter.

Of course, this responsibility does not lie only with the FDA. The drug companies also have a responsibility to the people who participate in their clinical trials.

They also need to ensure that problems are adequately investigated and addressed.

In the case of Study 3014, there were sirens, red flags and bull horns, but it looks like the company and the FDA kept ear plugs and blinders on.

I like to close by saying that it troubles me that the FDA failed to act on the serious concerns raised by Agent West until almost 2 years after Ketek was approved and almost 3-1/2 years after Study 3014 was submitted to the FDA. It troubles me that an FDA manager would say that investigating a company is a "losing game" because in the case of Ketek, after the FDA did do the investigation, a warning letter was issued. This same individual, however, has also said that more oversight of clinical trials was needed.

FDA officials have told me that some initiatives are underway, including making sure that there's proper oversight and authority over all the parties involved in clinical trials. I hope we see significant improvements in the near future.

There's also been a lot of talk over the last several months about FDA inspections, especially foreign inspections. FDA has limited resources to perform this important function. Just as more and more drugs are being manufactured overseas, more and more studies are being conducted outside of the United States.

I look forward to working with this Committee and in particular with you, Chairmen Dingell and Stupak and Ranking Members Barton and Shimkus, as well as my colleagues in the Senate to ensure that FDA has the resources and tools to do its job.

Thank you.