THE HONORABLE BART STUPAK
CHAIRMAN
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
FEBRUARY 12, 2008

Before we begin, I have a couple of housekeeping items to discuss.

On January 29th the Subcommittee held a business meeting to issue subpoenas for several outstanding requests the Committee has made of FDA. The subpoenas were approved unanimously on a 12 – 0 bipartisan vote.

While we are pleased that the FDA has produced the agents for today's hearing, we are far less than pleased with a response received by the Committee regarding our subpoena for documents requested in March of 2007.

Yesterday afternoon a letter arrived at the Committee signed by the Assistant Secretary for Legislation at the Department of Health and Human Services and signed by the Chief of Staff for the FDA stating that they want to reach "alternative solutions" rather than producing the documents we subpoenaed at our January 29th Business Meeting.

This letter is troubling on several fronts. First, the subpoena was served on the Secretary of HHS, and he did not provide the Committee the courtesy of a response under his signature. Second, there appears to be a continued effort to keep secret the documents we have requested. This only causes Members to further question what could be so damaging in the materials that the Administration wants to stonewall our bi-partisan subpoena?

There is precedent for obtaining briefing book documents from both Democratic and Republican Administrations without having to issue a subpoena. The Secretary was made aware of precedents where the Committee chaired by Republicans (Mr. Bliley and Mr. Barton) received briefing books of FDA Commissioners in a Democratic Administration (Kessler). They were also obtained when chaired by a Democrat (Mr. Dingell) receiving briefing books of a Commissioner in a Republican Administration (Frank Young).

I find the letter received yesterday to be very disconcerting and I will be discussing options with Chairman Dingell and Ranking Members Barton and Shimkus in the coming days.

STATEMENT OF
THE HONORABLE BART STUPAK
CHAIRMAN
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
"KETEK CLINICAL STUDY FRAUD: WHAT DID AVENTIS KNOW?"
FEBRUARY 12, 2008

Today we hold the third hearing by the Subcommittee on whether the Food and Drug Administration (FDA) can fulfill its mandate to protect the American people from unsafe drugs. Once again, we will be exploring this question in the context of the controversial antibiotic Ketek. The deeper Members of this Subcommittee dig into the Ketek approval process, the more disturbed we become about the entire drug approval process.

Today's hearing will shine a spotlight on the little understood and rapidly growing world of private drug research and clinical trials. Specifically, we will examine the data integrity lapses and fraud contained in the large Ketek clinical trial, Study 3014, which was initially commissioned to assure the safety of Ketek.

The Ketek clinical study illustrates the failure by **all** stakeholders—FDA, drug companies, third-party monitors, and Institutional Review Boards—to ensure the integrity of clinical trials used to support the safety and approval of new drug applications.

A year ago, this Committee heard testimony from Senator Charles Grassley about his repeated attempts to secure information from the FDA and the obstacles that FDA erected to impede his investigation of the Ketek approval process. Senator Grassley also expressed concern that FDA management discourages, even muzzles, scientific dissent. Sadly, this Committee's parallel investigation of Ketek over the past year has confirmed Senator Grassley's dismal assessment of FDA.

Senator Grassley returns today to share the findings contained in his recently issued report of the Finance Committee's ongoing investigation into the safety of Ketek, particularly what he's uncovered regarding the criminal investigations conducted by FDA's Office of Criminal Investigations (OCI) into allegations of fraud in connection with Ketek Clinical Study 3014.

We also welcome back Ann Marie Cisneros, formerly a senior clinical research associate with PPD, the contract research organization (CRO) hired by Aventis to monitor Study 3014. Ms. Cisneros will open the second panel by explaining why she was convinced that Aventis, PPD, and Copernicus, the Institutional Review Board—all charged with protecting the patients in Study 3014—were well aware of the faulty and possibly fraudulent, data submitted to the FDA by Aventis in connection with the approval of Ketek. We are particularly grateful to Ms. Cisneros for sharing her experience with this Committee despite attempts by her former employer to extort her silence.

Ms. Cisneros was dispatched in February 2002 to inspect the site of Dr. Kirkman-Campbell who had enrolled more patients – 407 to be exact - into Study 3014 than any other

Investigator. Prior to her visit, Ms. Cisneros was informed by Dr. Reynolds of extremely suspicious activity at the site by other PPD personnel and was asked to scrutinize Dr. Kirkman-Campbell's site and try to bring back evidence of fraud. After only two days at the site, Ms. Cisneros found the site so troubling that she was afraid that Dr. Kirkman-Campbell was endangering patient safety. Consequently, On February 21, 2002 Ms. Cisneros called Copernicus, the Institutional Review Board working for Aventis, to urge them to intervene to protect patients. Copernicus did nothing.

Dr. Kirkman-Campbell was ultimately convicted of fraud in connection with Study 3014 and sentenced to nearly 5 years of prison. The fraud at this site was detected only after a routine audit by the FDA **not** because Copernicus or Aventis had warned them. Well before the FDA audit, however, Aventis, PPD, and Copernicus were all aware of scientific misconduct indicative of fraud at the site.

Evidence before this Committee suggests that only a company intent upon ignoring the obvious could have failed to detect fraud in Study 3014. At Kirkman-Campbell's site alone, obvious indicators of fraud included the following:

- Errors on nearly every informed consent form—date modifications, initials differ from signature, study coordinator entering date for subjects and the Principal Investigator;
- Blatantly forged signature on informed consent form;
- Medical records very limited;
- Use of different colored ink on medical charts—overwrites/crossouts—inserts of diagnosis in different colored ink;
- Routine failure to give pregnancy tests to women of childbearing age;
- Study Investigator and Coordinator unaware of definitions of Serious Adverse Event or Adverse Event of Special Interest;
- No adverse events for the first 300 patients enrolled with drugs known to have adverse events;
- Lab results indicative of blood splitting;
- Lack of proper diagnosis for study eligibility;
- Husbands and wives enrolling together;
- Large numbers of patients randomized in the Interactive Voice Response System in a short increment of time when the office was closed for lunch and not seeing patients; and
- 100 percent compliance by patients taking study medication.

Aventis, PPD, and Copernicus were aware of this misconduct, well before Aventis submitted Dr. Kirkman-Campbell's data to the FDA to support the approval of Ketek. At a minimum, Aventis should have discontinued enrollment at the site and notified the FDA.

We will also hear today from the three FDA criminal investigators who investigated misconduct and/or fraud in connection with Ketek Study 3014. FDA has done its best to deny this Committee access to these agents and their investigatory documents. These agents testify today under subpoena. Be assured, however, that we did not lightly compel the appearance of these witnesses before this Committee to discuss criminal investigative matters—and would not have done so were their testimony not of the utmost importance. I would like to remind FDA managers that retaliation against these agents for their testimony will not be tolerated by this Committee.

OCI Special Agent (SA) **Robert West,** led the criminal investigation which resulted in the August 2003 indictment and October 2003 conviction of Dr. Kirkman-Campbell for fraud in connection with Study 3014. SA West will explain how he tried to convince FDA management in 2003 to expand the investigation of fraudulent submission of trial data to include other sites and ultimately Aventis.

However, FDA did not open an investigation into the possible misconduct of Aventis until 2006—over 4 years after the study ended. In early March 2006, SA **Robert Ekey** was assigned the criminal investigation of Aventis. Today he will confirm that his investigation revealed evidence indicating that Aventis was aware of serious data integrity problems at the Kirkman-Campbell site, but submitted the site data to FDA notwithstanding.

The investigation languished until shortly after this Committee's Ketek hearing last year when the case was reassigned to SA **Douglas Loveland.** SA Loveland conducted an exhaustive re-investigation and became convinced of Aventis's guilt. On June 21, 2007, he presented FDA's evidence against Aventis to the United States Attorney of the District of New Jersey and recommended prosecution.

The U.S. Attorney ultimately declined to prosecute Aventis—but **not** because of a lack of evidence against Aventis. The declination letter states instead;

> "Put simply, the FDA's lack of reliance on the faulty study, and its subsequent decision to approve Ketek despite an ongoing investigation into Dr. Kirkman-Campbell's conduct, make any conviction against Aventis for fraud in connection with submission of the study highly unlikely."

Our final panel consists of the following industry officers:

1. Dr. Paul Chew, President of U.S. Research and Development, Sanofi-Aventis Pharmaceuticals;

2. Fred Eshelman, CEO of PPD, the contract research organization hired by Aventis to monitor Study 3014; and

3. Sharon Hill Price, the CEO of the Copernicus Group Institutional Review Board, hired to protect the human subjects of Study 3014.

Evidence before this Committee suggests that each of these firms had direct knowledge of serious misconduct and possible fraud in Study 3014, yet **none** notified the FDA. We expect them to explain why they did not do so.

Clinical research has changed dramatically within the last two decades. No longer anchored in the public sector, clinical trial practice like PPD and Copernicus Group is currently big business and largely self-regulating. Today's hearing will demonstrate how some actors behave in a climate of self-regulation. It may be time to seriously rethink the regulatory framework for the clinical trial industry and Institutional Review Boards and Contract Research Organizations.