

**NDA 21-144 (Ketek)
data integrity issues**

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Good morning. My name is David Ross. I am a board-certified infectious disease physician and an active clinician. I served as the primary safety reviewer for Ketek during the first review cycle and as the safety team leader during the second cycle.

Road map

- **Substantial evidence of fraud in NDA**
- **Aventis aware – but submitted data anyway**
- **FDA aware – but used the data anyway**
- **FDA ignored warnings from criminal investigators and reviewers to look for systemic fraud**

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I will present data showing that there was substantial evidence of fraud in this application. Aventis knew that there were problems, but failed to tell FDA reviewers. FDA managers knew, but failed to tell this Committee. FDA managers used the same data to approve Ketek, despite warnings from criminal investigators and reviewers about suspected systemic fraud. Management was so bent on approval that I was pressured to "soften" my review by the review division director. Other reviewers were also pressured.

Study 3014

- **26 Apr 2001: AIDAC requests large Ketek safety study**
- **24 Jul 2002 – Study 3014 submitted**
- **24 Oct 2002 – FDA learns of fraud**
- **8 Jan 2003 – 3014 presented to AIDAC. Fraud issues not disclosed; AC votes for approval**

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In April 2001, this committee requested a large Ketek safety study. After Study 3014 was submitted, FDA reviewers discovered serious issues pointing at fraud. Despite their concerns, FDA managers ordered 3014 presented to this committee, omitting the problems. As a result, the Committee recommended approval.

Summary of 3014 integrity issues

Site	Location	Date identified	Outcome
Campbell	AL	Oct 02	Conviction
Lang	IL	Nov 02	483 issued
Salerno	CA	Nov 02	483 issued
Site 759	NC	Dec 02	OCI referral
Harker	PA	Dec 02	483 issued
Khan	OH	Dec 02	483 issued
Site 1892	OK	Dec 02	OCI referral
Site 83	MI	Dec 02	OCI referral
Terpstra	IN	Dec 02	483 issued
McLeod	VA	N/A	Disqualified

Every 3014 site inspected by FDA – before the investigation was dropped – had major problems. By December 2002, FDA managers knew of serious data integrity issues. They could have postponed the Advisory Committee or not allowed presentation of Study 3014. Instead, they ordered it presented publicly. Two months later they told AC members about data integrity issues in a closed session, according to FDA managers. I was there; pertinent data known to FDA managers was not presented to the AC. A Senate Finance Committee report confirms that most AC members were unaware of these issues.

Warnings to Aventis from CRO

“On Feb. 27 [2002, an Aventis project manager] got an email from PPD warning that there were potential problems at the Campbell site. . . . Emails . . . indicate that PPD employees raised red flags about other doctors as well.”

Wall Street Journal, 1 May 2006

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Was this just a matter of a few bad apples? During the course of 3014, Aventis received warning after warning from its CRO about serious data integrity concerns, including its lead enroller. It did nothing. Aventis failed to report these problems to FDA, which found out only through its own inspections. Aventis finally admitted to FDA 5 months after submission of 3014 that it had known of problems at its lead enroller, but denied there were any other problems with the study.

FDA view of data integrity

“In general I don't believe spending time on [data integrity] issues in front of the AC will be productive. I do feel that having the company make the best possible presentation of their PM data . . . will be useful.”

M. Goldberger, 2 Jan 2003

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Aventis did not tell FDA reviewers what it knew. Six days before the 2003 meeting, I e-mailed the FDA manager responsible for Ketek about extremely serious data integrity concerns known to the review division, DSI, and OCI, and copied the review division director. I asked about presenting these possible fraud issues to this Committee. His response? It wouldn't be **productive** to present the data integrity issues. What would be useful, he said, would be for Aventis to make their best presentation possible using post-marketing data.

Pressure on reviewers

“When asked why he presented a study he knew to have data integrity issues [the review division official charged with presenting study 3014 at the AIDAC meeting], he replied that he was asked directly by the Division Director . . . He viewed this as a verbal instruction.”

Letter from Senator Charles Grassley to A. von Eschenbach, 13 Dec 2006

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FDA managers instructed a reviewer to publicly present 3014. When the reviewer protested, he was ordered to disregard data integrity issues and present the study.

“We obtained vital status, that is, additional information or other information whether the subject was alive or dead, in an additional 0.5 percent of subjects, resulting in an overall 99.8 percent out of these 24,000 subjects with follow-up information.”

P. LaGarenne, 8 Jan 2003

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As a result, FDA managers listened as Aventis told this committee that they had obtained virtually complete follow-up safety information on 24,000 patients – many of whom never existed. So misinformed, the Committee voted to approve Ketek and Study 3014 is now being cited in the medical literature.

“I just wish we could find even a single credible large-enrolling site in 3014.”

C. Cooper, 23 Dec 2002

“The integrity of data from all sites involved in study 3014 cannot be assured with any degree of confidence.”

CDER Division of Scientific Investigations, 25 Mar 2004

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The reviewers knew the real story. Prior to the meeting, a FDA safety reviewer wrote, “I just wish we could find even a single credible large-enrolling site in 3014.” CDER’s Division of Scientific Investigations concluded that 3014 was useless. Thus, the questions asked by this Committee in 2001 have never been answered. But Ketek is on the market.

July 2003 OCI recommendations

- **Form multi-jurisdictional task force**
- **Inspect **all** sites enrolling >100 patients**
- **Inspect as if looking for fraud (e.g., be prepared to obtain patient lists and interview patients who supposedly participated in Study 3014.**
- **OCI conclusion: there is no way FDA would ever be able to determine if Aventis had committed fraud, or been complicit in fraud, without this approach.**

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The criminal investigators knew the real story too. In July 2003, FDA's Office of Criminal Investigations told FDA managers that they needed to expand the investigation to determine Aventis's possible role in the fraud. An e-mail documenting this briefing has been turned over to the Senate Finance Committee.

FDA reliance on Study 3014

“In speaking with the division about this, they did not completely ignore the data from the 3014 study, but assessed those AEs that were identified to qualitatively assess patterns of toxicity.”

S. Kweder, 21 Mar 2006

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Despite these warnings, FDA managers used Study 3014. A senior FDA manager wrote that the review division used the data, saying that they “assessed those AEs that were identified to qualitatively assess patterns of toxicity.” I have two questions. First, what does that mean? Second, why does the FDA briefing package state five times that FDA did not rely on Study 3014?

FDA citation of Study 3014

**20 Jan 2006 - FDA cites Study 3014 in
Public Health Advisory and in
Questions and Answers on Ketek**

**“As for the PHA, I find the reference to
3014 in it not very concerning”**

S. Kweder, 21 Mar 2006

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FDA managers even cited Study 3014 in January 2006 in a Public Health Advisory, brushing aside reviewer protests.

FDA (in)action

- **28 Jul 2003 – OCI warning – no action**
- **11 Feb 2005 – First Ketek-related ALF death reported to FDA – no action**
- **17 Feb 2006 - Reviewer warnings – no action**
- **5 Mar 2006 – New OCI warnings – no action**

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In July 2003, FDA managers were warned by OCI about fraud with Ketek. They did nothing. In February 2005, they received the first report of fatal Ketek-related liver failure. They did nothing. In February 2006, they received written warnings from reviewers about fraud with Ketek, and about pressure to change reviews. They did nothing. They received new OCI warnings two weeks later. They did nothing. Only after Congressional subpoenas and stories about 3014 fraud in major media, did FDA finally do anything – they reworded the label.

FDA action

“[If people disagree about Ketek outside the locker room], the first time they’ll be spoken to, the second time they’ll be benched, and the third time they’ll be traded.”

A. von Eschenbach, 22 Jun 2006

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In late June of this year, FDA reviewers were summoned to a meeting with Commissioner von Eschenbach, in which he compared the FDA to a football team, and told reviewers that if they publicly contradicted management about Ketek, they’d be “traded from the team.”

Summary

- **Serious fraud issues in NDA**
- **FDA managers**
 - **Knowingly presented highly suspect data to previous Ketek AC**
 - **Told current AC that FDA did not use 3014 data, although FDA did in fact use it.**
 - **Told reviewers not to reveal negative data to AC or public**
 - **Failed to determine scope of fraud**
- **Overall integrity of application unknown**

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In summary, serious fraud issues in this NDA remain unresolved; FDA has allowed fraudulent data to be presented publicly and has used it; the scope of the fraud remains undetermined; and the Ketek team has been pressured to remain silent. At the same time, a number of patients have died after ingesting Ketek. The study that was supposed to answer critical safety questions was fatally corrupted; the post-marketing reports submitted in its place are no substitute for rigorous safety evaluation. It is up to this Committee to demand that the Applicant and the FDA provide real evidence of safety.

Thank you. The views presented here are my own. I have no conflicts to disclose. Your packets contain the source documents for this presentation not otherwise referenced. I would be happy to answer any questions.

