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U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN



March 14, 2007

David B. Ross, M.D., Ph.D.
2302 Twin Valley Lane
Silver Spring, MD 20906

Dear Dr. Ross:

On February 13, 2007, you testified before the Subcommittee on Oversight and Investigations in a hearing entitled "The Adequacy of FDA Efforts to Assure the Safety of the Drug Supply." We now ask for your help on several additional questions (attached).

Because we wish to include the questions and responses in the printed record of this hearing, please respond no later than Thursday, March 28, 2007. Please fax and e-mail the response. The faxed response should be directed to Kyle Chapman, Committee on Energy and Commerce, Majority staff, at 202-225-5288, and Matt Johnson, Committee on Energy and Commerce, Minority staff, at 202-226-2447. The e-mail copy of the response should be directed to kyle.chapman@mail.house.gov and matt.johnson@mail.house.gov. Due to the uncertainties of postal deliveries on Capitol Hill, we ask that your response not be sent through the postal service.

If you have any questions, please have your staff contact David Nelson, of the Committee on Energy and Commerce, at 202-226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Bart Stupak, Chairman
Subcommittee on Oversight and Investigations

The Honorable Ed Whitfield, Ranking Member
Subcommittee on Oversight and Investigations

**Questions for David B. Ross, M.D., Ph.D.**
**from the Honorable Bart Stupak**
**Committee on Energy and Commerce**
**regarding the February 13, 2007, Hearing entitled**
**"The Adequacy of FDA Efforts to Assure the Safety of the Drug Supply"**

1. Why was liver damage in a single patient in the Ketek clinical trials so alarming?

   A. First, the damage in this patient appeared very similar to that caused by another antibiotic called Trovan that was linked to dozens of deaths due to liver failure in the 1990's (and which was essentially withdrawn from the market). Reviewers were very concerned that we might be looking at a reprise of the Trovan situation with Ketek, in a setting where Ketek did not appear to have dramatic life-saving effects.

   Second, there's a statistical rule of thumb that if a side effect occurs in 1 patient out of a thousand, you need 3000 patients to be sure of finding it. There were roughly 3000 patients in the original Ketek trials, and one developed severe liver damage. So, the true rate might be as high as 1 case out of every 1000 patients exposed. There are roughly 100 million antibiotic prescriptions written every year in this country for respiratory tract infections. If Ketek had 10% of the share for that market, that side effect would translate into 10,000 cases a year of severe liver damage, and potentially hundreds or thousands deaths a year.

2. What is the risk of liver failure with Ketek?

   A. It is difficult to say with great certainty because of the poor quality of the data available, but the FDA's Office of Drug Safety estimated in May 2006 that the reporting rate (the number of cases reported divided by the number of prescriptions) is 23 reports/10 million prescriptions. By comparison, Trovan was associated with 58 reports/10 million prescriptions, while the next most riskiest drug compared to Ketek in the ODS analysis, had a rate of 6.6 reports/10 million.

   If we use the rule of thumb that only one out of ten cases of severe liver injury is reported (an underreporting rate of 90%; the true underreporting rate is probably higher, based on a French population-based study by Sgro et al. published in 2002 in the journal Hepatology, as well as the FDA's own estimates of how often adverse events are reported), the incidence rate of acute liver failure with Ketek would be about 1 case out of every 43,000 prescriptions. According to Dr. Peter Honig, a former ODS director quoted in the May 2001 issue of FDA Consumer, a rate of about 1/50,000 is the usual cut-off for withdrawing a drug from the market or severely limiting its use.

3. Why the concern over liver failure with Ketek if other drugs such as acetaminophen are more common causes of liver failure?

   A. Acetaminophen causes about half of all cases of drug-induced liver failure in this country, but the vast majority of these cases happen because of overdoses of acetaminophen or taking it with alcohol. Avoiding this situation greatly lessens the risk of liver failure with acetaminophen. Ketek can cause severe liver injury just with a single dose even in patients with no previous liver problems. There is no way to lessen the risk with Ketek. Second, acetaminophen is used much more than is Ketek, leading to many more opportunities for acetaminophen poisoning. Thus, the risk of liver failure with Ketek (when used as directed) is much higher than the risk with acetaminophen (when used as directed)

4. What exactly was the misconduct found in the safety study?

   A. The largest enroller was convicted of fraud. The second and third largest enrollers had significant violations of procedure that called into question the reliability of data from those sights. Of note, the third largest enroller was arrested shortly after the study on cocaine and weapons possession charges – not the type of study physician FDA likes to see conducting trials.

5. What happened to the criminal investigations?

   A. One doctor was convicted of fraud. From what I've been told, a second doctor refused to turn over his records, and FDA dropped the case. A third doctor was still under investigation the last I was aware. A fourth doctor had very suspicious findings (the doctor supposedly enrolled 90 patients in a town of about 190 adults), but there was not enough evidence to prosecute.

6. At the December 2006 Advisory Committee meeting, Aventis said that the fraud by this doctor had been "sophisticated." Was that true?

   A. No. This was a blatant act of fraud that should have been evident to Aventis's clinical trial team.

7. What reason is there to think the company might have known of and been covering up fraud?

   A. PPD warned Aventis about its lead enroller, both in terms of suspicious behavior and a statistical analysis that showed splitting of clinical samples. Aventis took over the statistical analysis, and dismissed the problems; the project manager who did this was the overall project manager for the study. There was another study site in the same town as the lead enroller that followed all the rules – this site only enrolled 12 patients, compared to over 400 at the lead enroller. It would have been impossible for Aventis to miss the contrast between the two. Aventis failed to tell FDA about the problems at the site until five months after they resubmitted their NDA.

8. What kind of warnings did FDA managers get about possible fraud on the part of the company?

   A. In fall 2002, there were multiple warnings about fraud on the part of individual doctors in the study. In December 2002, the company admitted not telling the FDA about knowing of "problems" at the site of the physician who was convicted. In April 2003, FDA managers were told that when FDA investigators had demanded records from the company, the company had supplied them with much of the text blacked out. Finally, in July 2003, FDA managers received a briefing from FDA criminal investigators about their suspicions about the company, and recommending a task force to investigate the possibility of systematic fraud.

9. Did the FDA start that investigation?

   A. No. It did not start an investigation until Ketek hit the news in 2006, at which it assigned an investigation to a "task force" consisting of a single agent.

10. What is the current status of the FDA investigation into Ketek?

    A. Essentially dead. FDA had one agent, who was new to FDA and had no experience in clinical trial fraud, working on the case along with many others he was responsible for. He left the FDA recently and to the best of my knowledge, no one has been reassigned to it.

11. Do you know if the line agent whom Senator Grassley is seeking to interview is willing to talk to Congress?

    A. Yes, he is, but FDA won't let him.

12. Is it true that the FDA couldn't tell the advisory committee about the problems because there was an open investigation?

    A. No. First, by their own admission, FDA managers did tell the committee 8 weeks later in a closed session, when there was still an open investigation; if FDA told the committee then, FDA could have told them in January – before the committee voted. Second, all the members of the committee were Special Government Employees and were cleared to hear this information. Third, people in OCI have told me that the investigation would not have been compromised by telling members of the AC in closed session.

13. Did FDA officials mislead the advisory committee that just heard about Ketek in December?

    A. Yes. First, they told the committee that they had stumbled on the fraud as a result of routine inspections – only the first one could be seen as routine (and even then there were suspicions before the site was inspected). Second, they told the 2006 committee that they couldn't have told the 2003 committee about the misconduct issues. That was untrue.

14. Were other reviewers pressured?

A. Yes. According to Sen. Grassley's report, the statistical reviewer on the safety study was instructed to present the results publicly even though he protested and thought the committee needed to be told about the misconduct issues. The primary medical reviewer who ended up recommending approval told me that he had been instructed not to look at records from the company that it was required to submit as part of the fraud investigation, even though that was supposed to be part of his review.

15. Did anyone else on the review team review those records and prepare a written report?

A. To the best of my knowledge, no. I had the necessary authorization to look at them myself, and did, but I was not asked to be part of the review team and so couldn't prepare a review.

16. What has happened to the FDA managers who were involved with Ketek?

A. My division director is still in her position. Her supervisor, who decided to allow the safety study to be presented without mentioning concerns over fraud, and who approved Ketek, was promoted last year to be director of pandemic influenza planning for the FDA. His supervisors are still in their positions.

17. Why was the liver failure death important in February 2005 if only one patient had died?

A. First, studies have shown that most adverse events are never reported, so that a report of one fatal case probably means there are many others that haven't been reported. Second, the appearance of this case so soon after the drug launch is very concerning – it's completely consistent with a relatively high risk of liver damage from Ketek. Third, the fact that the case occurred in an otherwise healthy young man is not only tragic, but suggests that Ketek is dangerous to people with normal livers. Finally, appropriate follow-up would have revealed that there were multiple cases of Ketek-induced liver failure at the same medical center; the occurrence of a cluster like that would be a tip-off that there may be many unreported cases.

18. Why do you say that Ketek is much more dangerous than other antibiotics?

A. A consult from FDA's Office of Drug Safety in May 2006 found that Ketek had a reported rate of acute liver failure 4-11 times that of comparable antibiotics.

19. Aren't those from post-marketing reports that are unreliable?

A. The magnitude of these differences is so huge that it would be difficult to explain by differences in things other than the drugs' relative risks. A randomized controlled trial would be better – but that was supposed to be the point of doing the original safety study.

20. Would you prescribe Ketek?

A. No. I do not believe it offers any advantages over other antibiotics for the same infections, I don't believe that it has acceptable risks, and given the unresolved fraud issues with this application, I do not believe that its efficacy and safety have been established.

21. A recent opinion piece by a former FDA reviewer in the Wall Street Journal of February 12 claimed that physicians attempting to obtain access to investigational drugs for patients with life-threatening diseases such as cancer have to go through hurdles with regard to manufacturing, statistical, and clinical questions that are akin to an IRS audit. Is this true?

A. No. This claim is flatly incorrect. Physicians seeking approval of emergency or single-patient Investigational New Drug Applications (IND) for individual patients typically piggy-back their request onto an existing IND from a commercial drug sponsor. The FDA's Oncology Office alone approves hundreds of such requests every year; the typical request is granted in 24 hours. In fields such as infectious diseases where such requests are made in the setting of acute disease, the approval time typically takes an hour or less; I personally approved dozens of such requests, and <u>never</u> turned one down. Situations where such requests are turned down are unusual and generally involve situations where a physician is requesting an investigational therapy when standard therapies known to be safe and effective are available and have not been tried.

22. How would you fix the problems with the FDA that Ketek revealed?

A. (1) Mandate (and fully fund) the use of reliable post-marketing safety data sources, such as observational data bases by FDA, (2) Remove the line authority for post-marketing regulation from the Office of New Drugs and give it to an Office of Drug Safety, either formed as a new center, or based on the current Office of Surveillance and Epidemiology. Just as OND now regulates pre-marketing with consults from OSE, ODS should regulate post-marketing with a consult from OND., (3) Make FDA managers criminally liable for coercion of reviewers, and make senior managers liable for failure to appropriately investigate and discipline managers who commit coercion, and (4) Mandate (and fully fund) posting of <u>all</u> FDA reviews immediately after a regulatory action is taken. Reviews should not be redacted except for proprietary manufacturing information.