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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

John H. Powers, III, M.D., FACP, FIDSA
18511 Fiddleleaf Terrace
Olney, Maryland 20832

Dear Dr. Powers:

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 John H. Powers, III MD FACP FIDSAfrom 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. When did the issues with noninferiority trials first become apparent to FDA managers?

   A. These issues have been known for some time. At a recent advisory committee on September 12, 2006, a senior FDA official pointed out that drug sponsors knew about the issues with noninferiority trials and that, in his words, this was "not hot news". It was senior FDA officials who published some of the first articles in the medical literature in the early 1980's that address the problems with noninferiority trials. In 1985, wording was added to the section in FDA regulations that defines adequate and well-controlled trials to state, *"If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug."*

2. Did FDA managers ever enforce these regulations with antibiotics?

   A. Over the last 8 years I can only remember one sponsor who submitted a justification for doing a noninferiority trial, and that was for an antifungal drug, not drugs like Ketek. At the September 12 advisory committee another senior FDA official pointed out that the drug sponsor had not, in his words, "done the mental exercise" needed to scientifically justify this kind of trial. Recently, after a letter from several members of Congress raised issues about noninferiority trials, the statistical team members began to send letters to drug sponsors asking for a justification for noninferiority trials. One division director expressed displeasure at them doing this. The justifications sent in by many sponsors were not scientific ones, but their reasoning was that FDA had allowed many of these trials before, so that they should be allowed to continue this practice.

3. You said that FDA managers knew that the evidence of effectiveness for Ketek was lacking at the time it was approved in 2004. Had there been prior discussions within and outside of FDA about the issues with noninferiority trials?

   A. Yes, there had been numerous discussions. In 2000, the International Conference on Harmonization guidance E-10, titled Choice of Control Groups and Related Issues in Clinical Trials was first published. This guidance outlined many of the issues with noninferiority trials. In addition, FDA held an advisory committee in February of 2002 to specifically address the issues of noninferiority trials, held advisory

committees in July of 2002 on ear infections, two workshops in November of 2002, an advisory committee on sinusitis in October of 2003, and another workshop in April of 2004, and an internal regulatory briefing in July of 2005. These issues again came up at recent advisory committees in September and December of 2006.

4. What were the results of these meeting?

   A. At all these meetings there was scientific agreement that noninferiority trials were not justifiable in self-resolving diseases. FDA statisticians did lobby hard and got a change in the FDA guidance on antibiotic development referred to as the "Points to Consider" document. However, sponsors continued to submit applications based on noninferiority trials without an accompanying scientific justification as specified in the regulations. Regarding serious diseases, at the February 2002 advisory committee on developing drugs for diseases due to resistant pathogens, the Office director at the time implied that the only thing sponsors needed to obtain approval in serious diseases due to resistant pathogens was "a few well characterized cases". This seemed to contradict FDA's own regulations about the need for adequate and well-controlled trials. FDA regulations require some comparison with a control, even if it is a comparison with a group of patients in the past who did not receive treatment in what is called a 'historical" control.

5. Did ignoring the regulations occur commonly?

   A. I can only comment on the area in which I worked. It seemed that there were other priorities other than following the scientific principles spelled out in the regulations. It's important to realize that the regulations are based in good science, and they are not just rules for rules sake. But often it was implied that the regulations were just a guide and they FDA, in the managers words, "had to be flexible". Certainly one can be flexible within what good science and th the regulations allow, but there is also a point where one can go beyond what these principles allow as well. The major issue seemed to be approving drugs for less serious diseases, which are far more common, to provide an economic incentive for drug sponsors to develop drugs for more serious diseases. Some FDA managers also seemed to have the idea that FDA could not make it "too difficult" for sponsors to do studies. Of course, this depends on what you consider "difficult", which is subject to opinion, not science. Sometimes it is challenging to do an appropriate study that is meaningful, but this is far better than exposing people to harm in a study that cannot provide useful information.

6. Did you inform senior FDA officials of there problems?

   A. Yes. I informed several levels of senior managers over the span of 5 years that these issues were occurring.

7. Why did they not address the problem?

A. I was never certain as to why the issue was never resolved. At several internal meetings, senior managers pointed out that these noninferiority trials were not appropriate and yet antibiotics continued to be approved on this basis.

9. Even after these meetings, were drugs for self-resolving diseases still approved based on noninferiority trials?

A. Yes. There were several drugs approved since 2000 for these indications based upon noninferiority trials. At the September 2006 advisory committee, the drug sponsor pointed out that they felt ill used since other drugs were approved based on noninferiority and they felt they should be approved also. They specifically pointed to Ketek as an example of where a drug had been approved based on noninferiority trials. One of the issues is some FDA managers believe that once FDA has agreed on a trial design, it cannot be changed. Section 505(b)(5)(C) of the Food Drug and Cosmetic Act states that FDA can change the parameters of a study if "*a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.*

10. Do you think drug sponsors will do placebo controlled trials in these diseases?

A. Yes. At the November 2002 workshop we held on antimicrobial drug development, one drug company representative stated that companies would be unwilling to do these trials, but they would do them if FDA made it clear that they were a regulatory requirement. That hasn't happened. And that same person submitted an application a few years later for a drug for ear infections in children based on noninferiority trials, and few years after that submitted another application for a different drug for sinusitis and bronchitis. You almost can't blame companies if it's not made clear to them that noninferiority trials are no longer acceptable. On the other hand, however, companies clearly know these kind of trials are not substantial evidence of effectiveness, yet they continue to submit them.

11. Haven't some drug sponsors said that investigators will not enroll patients in placebo controlled trials?

A. There have been 8 published placebo controlled trials in sinusitis since the year 2000 and two published just last year in ear infections so clearly people are doing these trials. If an investigator does not wish to participate in these trials they are free not to participate, but that does not mean FDA should not insist on doing trials in a way that provides the necessary information to evaluate drug effectiveness and potential harms.

12. If investigators have been doing these trials, what was FDA manager's response as to why they did not insist on drug sponsors doing placebo controlled trials?

A. At meeting with drug sponsors, some sponsors insisted that their investigators would not enroll patients in placebo controlled trials. Of course, these investigators are free

not to participate in the trials if they wish, but the publication of placebo controlled trials in medical journals shows these trials can and are being done. The companies brought in experts who insisted these trials cannot be done or would be difficult to do. But allowing expert opinion to determine which trials are done and how they are done sets us back to a time when drugs were approved based on expert opinion alone. The hearings at the time of the passage of the 1962 amendments and subsequent court cases made it quite clear that clinician opinion was not the standard upon which drug approval should be based. FDA should taking a leadership role in advancing the science and requiring trials that will answer important medical questions, such as whether the drug is effective in the first place. FDA has done so in the past in other therapeutic areas.

13. Don't we need drugs like Ketek for disease due to resistant infections?

A. We do need new antibiotics, but we need them in serious and life threatening diseases where resistance in a test tube has the most impact on people. If it's not clear when and where we need to use antibiotics in less serious disease, or whether we need to use them at all, the impact of resistance is also unclear. We have taken for granted that a measurement in test tube must inherently mean something for patients, but that is why we do trials, to see if what we find in the lab translates into some meaningful benefit for patients. That is still unclear in these less serious diseases. In addition, the definition of resistance is not clear for many of these diseases and it may overestimate the number of resistant organisms, making drugs look ineffective when they are not.

14. How about people who are allergic to other drugs? Wouldn't Ketek be an option for them?

A. For Ketek to be an option for any patient, even those who are allergic to other drugs, it still have to be proven to be effective first. It would not be useful to give an ineffective drug to someone just because they have allergies. It is important to realize that noninferiority trials do not show two drugs are equal, and even in appropriately designed and analyzed noninferiority trials, you might be giving up some effectiveness for whatever other benefits the drug might have, for instance improved safety. In the case of Ketek we just don't know what those benefits are since we don't know if the drug is effective in sinus and bronchial infections, and we probably won't know if it is effective in ear infections if it is studied in a noninferiority trial.

15. Who defines what organisms are called "resistant?"

A. FDA defines resistance in the labeling for a drug when it is approved. Over time, however, this definition may change as the drug is used and more resistance may develop. There have been many discussions over the last few years about how FDA will interact with other non-governmental groups as to how resistance will be defined. What is clear is that defining and monitoring resistance is an important safety issue just like other adverse events for other drugs. FDA need to approach antibiotic resistance as a safety issue and change labeling when necessary to make sure the

definitions of resistance are accurate. The changes should be based on adequate evidence and not isolated case reports.

16. So when drugs organisms are called resistant when they are not, does it cause doctors to use other antibiotics instead?

A. Yes it does. And those antibiotics are usually newer, which means that we have less experience with them in terms of their safety, and they are usually more expensive. Taxpayers may foot the bill for more expensive drugs that are really no better than older drugs.

17. So for all these drugs approved without knowing that they are any better than placebo, the American taxpayer is still paying for these.

A. Yes, they are.

18. If noninferiority trials only rule out how much worse a new drug might be compared to an old drug, why are we doing these trials in situations where we are concerned the old drugs don't even work any more because of resistance?

A. That is an important point. It is illogical even in serious diseases to compare a new drug to an old drug when we have concerns the old drug is no longer effective.

19. Yesterday the label for Ketek was changed to remove the indications for sinusitis and bronchitis. What should be done about the other drugs that carry labels for these indications?

A. FDA needs to clearly inform clinicians and patients that the evidence of effectiveness for these drugs is insufficient. That would not mean taking all those drugs off the market, as most of those drugs are approved for other diseases like pneumonia. FDA's own labeling regulations state, *"If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition."* A statement such as this should be included in all drugs that carry indications of sinus, ear and bronchial infections as well as older drugs that include these indications under the older name of lower respiratory tract infections. This is not regulating the practice of medicine, as some have asserted as clinicians can continue to use these drugs where they see fit, but it does state a fact that there has not been substantial evidence of effectiveness for these drugs. It was concerning to hear a senior FDA official state at the December 16 advisory committee that FDA will not address these drugs unless there is a safety issue. Lack of substantial evidence of effectiveness is a requirement according to the FD&C Act, and these criteria are not meant to be applied prospectively only, as court precedent has shown. Lack of evidence of effectiveness *is* a safety issue, given the inevitable spread of resistance and deaths from adverse events without evidence of

benefits. Since self-resolving diseases are so common, a good proportion of the adverse events with antibiotics occur in people who take them for self-resolving diseases. Many of these people don't even have a bacterial infection.

20. Why do clinicians believe these drugs to be effective in treating human disease when so many placebo controlled trials fail to show their benefits?

    A. First, clinicians confuse mechanisms of action with outcome. Because a drug kills bacteria in a test tube or even in a person does not necessarily mean that the drug is helping the person if they get better anyway without the drug, or if the cure is worse than the disease in terms of adverse effects. Secondly, the placebo controlled trials are not designed very well, and people correctly point to those flaws, but incorrectly state the drugs are effective until proven otherwise. This goes against the basic medical premise of "first do no harm". Thirdly, some researchers have attempted to combine these studies together in what is called a meta-analysis. However, if you pool together flawed studies, you get a flawed answer. A study in the New England Journal of Medicine in 1997 shows that meta-analysis were contradicted by subsequent large randomized trials almost half the time.

21. How would we avoid another Ketek?

    A. FDA needs to operate with transparency and with accountability. Managers need to make the final decisions on drug approvals, but they need to make those decisions based upon appropriate science and following FDA regulations. The reviews for all approvals, including any non-approvals or approvable actions for already approved drugs should be posted on FDA's website and linked to clinicaltrials.gov where the trials are registered within 7 working days of FDA taking an action. FDA needs to take action on drug when there is a safety or effectiveness issue even if sponsors do not initiate the request. And there needs to be accountability for FDA staff who do not follow the regulations or who attempt to intimidate of bully other staff. Science is a process of discussion, and some of the most momentous discoveries were made by people who did not accept the status quo. FDA needs to have an environment where those scientific discussions can take place without an emotional overlay. It would help tremendously to have a separate group evaluate drugs post-approval than the group who evaluate drugs pre-approval. This would put checks and balances into the system, and allow a fresh set up eyes, and might stimulate more rigorous decision making if people knew their decisions would be reviewed by both the public with the posted reviews and by their peers. Finally, there needs to be no more noninferiority trials in these self-resolving diseases and FDA needs to take a leadership role in advancing the science of clinical trials in infectious diseases.