

# Questions to Dr. Graham

## JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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### Highlights

- **WAS ALL NECESSARY INFORMATION PRESENTED?**

Dr. Wood asked if Dr. Graham had presented all the information the committee needed to here. Dr. Graham said that he had “been able to present what I thought was important to present” and said that the controversy arose because he was initially asked to present the unpublished Ingenix study from Merck but was told not to present his own unpublished California Medicaid study. This was resolved when it was agreed that he would present both unpublished studies.

- **POPULATION IMPACT OF A SMALL INCREASE IN RELATIVE RISK FOR A COMMON EVENT VS. LARGE INCREASE IN RELATIVE RISK FOR A RARE EVENT:**

Dr. Wood asked Dr. Graham to put the “excess population risk” that he estimated in

the context of “other drugs that have been withdrawn from the market.” Dr. Graham said that the “leading cause of drug withdrawals” was “acute liver failure” which has a background rate in the general population of about 1 million a year – similar to the risk of being struck by lightning. Thus, if a drug increased this risk 5-fold or even 100-fold the actual number of people affected would be fairly small on a population basis and be “measured in the tens and the hundreds”. In contrast, a small increase in risk for a common event can result in much larger numbers of people affected – for example he estimates that the high dose of Vioxx would increase the 1 in 50 yearly chance of heart attack for a male aged 65 to 74 to a chance of 5 in 50.

### Discussion Text

DR. WOOD: Thanks very much. David, it will come as no surprise to you that every time practically I pick up a

newspaper, I read about what you are not going to tell us. So, my question to you is what have you not told us that you

think we should know, because I would like to make sure. Lots of other people have shown up here without slides that they forgot, so I just want to be sure that if there is anything else we need to hear, we hear it.

DR. GRAHAM: Well, as far as the science goes, I think I presented the evidence that I am happy to be able to share with the committee that I thought it was important for the committee to have an opportunity to hear. The source of controversy surrounding my presentation related to the unpublished studies that I was going to be permitted to present or asked, actually asked to present the Ingenix results, the unpublished study from Merck, but that I was being told not to present the unpublished data from the California Medicaid study, and personally, I had great difficult standing here before this committee as an investigator and as a scientist, as a physician, and telling you the information that I have, that I am allowed to talk about, and remaining silent on things that I know about that I am not allowed to talk to you about. Fortunately, Dr. Crawford exercised great leadership in making it possible for me to present that data, recognizing it's preliminary, but the methods that we used are identical to our Kaiser study for the California Medicaid, and for me, I think the big reservation is, is that it's an untested database, but I think that everything that could be done to develop the database and to do quality assurance and to work out the kinks has been done.

If you look at the findings in the California Medicaid study and you compare them to the clinical trials data, and the anomalies and the questions that you were discussing yesterday about the

clinical trials' data, you look back at the California Medicaid data, and you are going to see I think great consistency between the findings that might help explain and interpret some of the things that seemed questionable or uncertain yesterday. So, in any event, I have been able to present what I thought was important to present, and I am happy to have had that opportunity.

DR. WOOD: So, the answer is we have seen it all, is that right?

DR. GRAHAM: You have seen it all.

DR. WOOD: Okay, good. Let me ask you a question. If you go back to your slide that showed the excess population risk, put that in proportion for us in terms of, say, the other drugs that have been withdrawn from the market. I mean what sort of numbers would we be expected to see?

DR. GRAHAM: That is a great question. The typical drug that has come off the market in the United States, like the leading cause of drug withdrawals in the United States in the last 20 years has probably been acute liver failure. Rezulin came off the market because of it, troglitazone, bromfenac, a number of other drugs. Acute liver failure in the general population has a background rate of about 1 per million per year. We are talking about that is the rate of being struck by lightning, 1 per million per year, and these drugs were pulled off the market because it increased the risk of that.

It might increase the risk 5-fold, it might increase the risk 10-fold, it might increase the risk 100-fold. The fact is the background rate was 1 in a million and

what that means is that the actual number of people affected is sort of measured in the tens and the hundreds for the liver failure that could be life-threatening.

In this situation, and this is why the lower relative risk becomes so critical, we are talking about a serious event that has a very high background rate. Heart attack is not a rare event, and as I pointed out before, there is a 1 in 50 chance that the average American male age 65 to 74 is going to have a heart attack this year, 1 in 50. That is an extraordinarily high risk. You increase that risk 5-fold with a high dose.

That is what happened with VIGOR. If I have got millions of people taking the high doses, and that is what had in the United States, and I have increased the risk 5-fold, you are going to get numbers that balloon out like this. So, there is no comparison in terms of what the population impact is of the typical drug that has come off the market in the United States and what we are dealing with here, and that is because of the high background rate of the underlying event that we are talking about.

DR. WOOD: So, this would produce many more cases from what I understand.

DR. GRAHAM: Many more.