

Question 6: Labeling for Approved NSAIDs – Lack of Controlled Trials

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

February 16-18, 2005, Hilton Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland.

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Highlights

- **100% VOTE FOR ADDED LABELING:** All 28 members voting on Question 6 voted for added safety labeling for approved NSAIDs.
- **OBSERVATIONAL STUDIES: MORE DATA NEEDED:** Dr. Pratt said that in the absence of clinical trial data on the traditional NSAIDs, we need to get more observational data “pronto”.
- **LABELING OF NSAIDs WOULD BE USEFUL TO NON-RHEUMATOLOGISTS:** Dr. Domanski approved of having additional safety information (as a warning or a precaution) in the labeling, especially for non-rheumatologists.
- **NON-COXIB COX-1 SELECTIVE DRUGS SHOULD HAVE SEPARATE LABELING:** Dr. Nissen’s concern (“Houston, we have a problem”) is with the “so-called COX-2-selective NSAIDs that are not called coxibs” and thinks that these agents should be specifically identified and given their own set of warnings. Dr. Shafer suggested that the same black-box warning for the coxibs should be given to four other COX-2 selective drugs (etodolac, miloxicam, diclofenac and sulindac). Dr. Wood disagreed with Dr. Shafer’s suggestion because it would “undercut the strength of black-box warnings”.
- **OTC DRUG LABELING A PROBLEM:** Dr. Wood asked how to handle the OTC drugs (naproxen, ibuprofen and ketoprofen). Dr. Temple said that the “nominal labeling” says “short-term use – not that we believe that anybody limits it. So that has to be coped with.” Dr. Ilowite said that FDA had told him

that giving an OTC drug a black-box means it is no longer OTC.

- **BLACK-BOX PRESENCE MORE IMPORTANT THAN CONTENT:** Dr. Morris said that a black-box should be used for all NSAIDs and that the important thing was the symbolic value of a black-box, and not necessarily the information inside the black-box. Dr. Gross agreed with a black-box for all NSAIDs.
- **LABELING OF SAFETY: DISPLAY OPTIONS:** Dr. Temple gave a brief overview of where safety information can reside in the label – black-box, description and clinical trials, warnings, and precautions. In a draft proposal, the latter two are combined into a section called “Warnings and Precautions”. A black-box “absolutely bars reminder ads.”

- **WILL NAPROXEN BE EXCLUDED FROM WARNING LABELING?** Dr. Platt said “it would be a mistake” to have the same warning for all NSAIDs “absent naproxen which I think we have excluded from any warning”.
- **SHOULD QUESTION 6 BE FOR TWO SEPARATE GROUPS?** Dr. Wood suggested that they break Question 6 into two parts, one for COX-2 selective non-coxibs and one or the rest of the traditional NSAIDs. Dr. Jenkins (FDA) said that the concern with this is that there is not agreement as to which drugs should be designated as “COX-2 selective”. Dr. Temple said that FDA could later “refine” the decision as to which drugs should be considered “COX-2 selective”.

Voting on Question 6

DR. ABRAMSON: Yes.

DR. NISSEN: Yes.

DR. ELASHOFF: Yes.

DR. GARDNER: Yes.

DR. PLATT: Yes. “Please don't use a blanket approach to this class”.

DR. DAY: Day. Yes. “I echo Platt”.

DR. FURBERG: Yes. “to precaution”.

DR. FLEMING: Yes. “to the first question. I haven't commented on the

second so let me do so. I am uncomfortable having a blanket approach to the second because I do think there is considerably different evidence, for example, on diclofenac versus naproxen. So I would hope that the agency approaches this thoughtfully looking at the totality of the data with agents that are in the diclofenac category getting a much clearer indication, potentially a black-box warning, with agents in the naproxen category looked at in a very different magnitude and a very different context, certainly without a black box. “

DR. DOMANSKI: Yes. “to the first question and I agree with Dr. Fleming for the second”.

DR. BOULWARE: Yes.

DR. DWORKIN: Yes. “And I think, for the second question, it should be comparable or consistent with whatever is decided about celecoxib with respect to whether it is a warning or black-box warning”.

DR. MANZI: Yes. “to the first question”.

DR. FARRAR: Yes. “to the first question with the advice that it be linked to the consideration of G.I. versus cardiovascular toxicity. Yes to the second in terms of a warning for the agents that have more of a COX-2. I understand that it is hard to determine that but I think we have to do that and I would strongly recommend against making them all the same, in fact, a strong plea to leave the current generation of NSAIDs with a warning.”

DR. HOLMBOE: Yes. “Also, I would consider a black box for those that are found to have similar data to the coxibs”.

DR. GROSS: Yes. “to the first one and, to the second one, I would be in favor of a black-box warning where the language varies depending on the strength of the evidence or lack thereof referring to a possible class effect”.

DR. WOOD: Yes. “to the first question and with exactly the same comments as Tom Fleming made”.

DR. CRAWFORD: Yes. “to the first question. I would be against, at this

point--based on the available evidence, I would be against a black box but yes to a warning or a precaution”.

DR. CUSH: Yes. “There is a need for a warning label for all non-steroidals with regard to cardiovascular risk and that, to get that warning removed, there should be a trial, I guess, with naproxen showing superiority or non-superiority, I guess.”

DR. BATHON: Yes. “to the first question. I would approach them as a class with the exception of naproxen.

MS. MALONE: Malone. Yes. “to the first question. I do not think it should be a blanket black box. I think it should be a warning of an individualized nature. But I think what we have to be extremely, extremely, careful of is setting off some hysteria with the public because here we are going from concern about three coxib drugs and now we are warning against almost anything that these people are taking”.

MR. LEVIN: Yes. “to the first”.

DR. ILOWITE: Yes. “to the first. I would be against a black-box warning for either naproxen or ibuprofen”.

DR. D'AGOSTINO: Yes. “to the first with precautions”.

DR. MORRIS: Yes. “in the method that Peter has outlined for prescription drugs. For over-the-counter drugs, I would suggest that there be a warning about long-term use at higher doses and the potential for cardiovascular risk”.

DR. CANNON: Yes. “with a warning regarding long-term use”.

DR. FRIEDMAN: Yes. “to the first part and, obviously, as others have said, tailored to the individual drug. The implications, of course, of saying that we don't have adequate research is that we are going to try to get it done. So, when we put that in there, we have to follow through.”

DR. HENNEKENS: Yes. “to the first question with the caveats that the short-acting NSAIDs, specifically ibuprofen,

ketoprofen, diclofenac appear to be at least as hazardous as the coxibs and that naproxen is neutral to maybe slightly favorable on cardiovascular risk and, secondly, that the warning would be the same as for the coxibs”.

DR. SHAFER: Yes. “with a graded warning based on both the available data and the pharmacologically established COX-2 selectivity”.

Voting Results on Question 6

Yes 28, No 0, Abstentions 0.

Discussion Text: Question No. 6

Discussion of Question 6

DR. WOOD: There are more than 20 non-selective NSAIDs currently approved for marketing in the United States. Unlike the situation with COX-2-selective agents, large, long-term, placebo-controlled clinical trials have not been conducted to evaluate long-term risks including cardiovascular risks. Based on the data presented in the background packages and during the committee meeting, please address the following questions regarding the approved non-selective NSAIDs. The first one is No. 6: Do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical trial data to assess the potential cardiovascular effects of these drugs? If

so, please describe how you recommend that this information be conveyed; for example, warning, precaution, and so on.

Fine. Let's put it in. But what does that do for anybody? There are lots of things that haven't been evaluated for. I certainly think it should be evaluated, but they haven't been evaluated for carcinogenicity in long-term trials, or whatever. So I am not sure of what that would actually do. But let's go. Richard?

DR. PLATT: It seems to me, in the absence of clinical-trial data, it is worth making use of the observational data we have and it is worth collecting more and better observational data pronto. I think Bob O'Neill made some excellent

comments about the things you would want of observational trials to provide the guidance we would like to have. I think that, in a relatively short time, reasonably good information could guide the agency in the absence of clinical trials.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: You know, I actually think the effect that it has is it does provide immediate education for people, not necessarily working with these things all the time. We have been through three days of this now and we probably have heard what there is to hear about it. But folks are going to hear about the problems with these other drugs, but there are clearly issues with the other non-steroidals. I think it would actually be quite informative to physicians making these prescriptions who are not necessarily rheumatologists to have that in there counterbalancing it. I don't know whether it should be a warning or a precaution but I think that is actually a useful thing to have.

DR. WOOD: Dr. Nissen?

DR. NISSEN: Houston, we have a problem. Let me tell you what it is. It is really very clear what it is. If you read the financial literature, or media, they will tell you that the biggest beneficiary of this controversy has been the so-called COX-2-selective NSAIDs that are not called coxibs. An example would be miloxicam. Apparently, miloxicam has something like doubled its market share in the wake of all this controversy. Now, do we know that an agent like miloxicam that is approximately the same in terms of COX-2 selectivity as celecoxib isn't going to produce exactly

the same outcomes. The answer is, we don't know. So, if the arguments that I heard a little while ago that said, well, we don't have a big enough database on valdecoxib to keep it on the market, and I was very sensitive to that. I voted the other way, but I understood where people were coming from. Well, if that is true, isn't it true for other agents? So, at the very least, we have to tell prescribing physicians and the public that we don't know whether these agents that are in that cluster of partially COX-2-selective agents, that they don't have the same hazard ratio that we saw for celecoxib. So I think that we ought to demand the same level of evidence. Now, how do you do that, particularly if an agent is now generic? I haven't the faintest idea. But, at the very least, we need the same warnings and we need the same level of evidence. Otherwise, we could actually shift people from celecoxib, let's say, to miloxicam and they would have the false reassurance that there is not a problem. And we don't know that there is not a problem. We just don't know. So I am worried about this, what we have done today, and I think there has to be equality in labeling across this class until proven otherwise.

DR. PLATT: Do you include naproxen in that class?

DR. NISSEN: I guess I don't because I think we know more. Let me just tell you why I think we know that. I mean, naproxen has beat COX-2 inhibitors pretty handily in some pretty well-designed clinical trials. So I think we have got some evidence. We have got very good epi data on naproxen. So I don't put it in that class. But I am talking about the partially COX-2-selective class. You have mentioned several times

the groups that are in that. We know what these drugs are. I think we have got to look at them individually and see what the database that we have for safety--my guess is you don't have very much inside FDA to not document an excess in cardiovascular risk for those agents. So I think we could be just hiding the problem under a great big rug rather than solving it by the actions we take today unless we act more broadly.

DR. WOOD: Just a question to the FDA. Many of these non-steroidals are available over-the-counter. Labeling changes there have different kinds of implications; right? Charley Ganley is here. He is always putting me on the spot.

DR. TEMPLE: I think it is only two, though, Charley; right? Only two; right?

DR. WOOD: Aleve is available.

DR. TEMPLE: Naproxen is and ibuprofen is. What else? Ketoprofen. The nominal labeling, of course, for OTC all says short-term use--not that we believe that anybody limits it. So that has to be coped with.

DR. WOOD: Right. That is a different issue. Maybe that is too complicated in the next 30 minutes, 32 minutes. Any other comments? We have got Dr. Morris.

DR. MORRIS: I want to reinforce what Steve said because you have to look at the black box in two ways. One is what is in the black box as information that should try to inform the physician. But there is a huge symbolic value of a black box in and of itself. Once a drug has a black box, it is just viewed, by

physicians, as something totally different than a drug without a black box. If we could just inadvertently send this huge signal to people that certain drugs have black boxes, certain drugs don't, I think that is why I am favor of a black box for the whole broad category. But if there is no information, what is in the black box is, we don't know. But it still gives the same symbolic value that this problem exists--we think it exists across the whole class.

DR. WOOD: Dr. Crawford.

DR. CRAWFORD: Thank you. I just have a question for FDA. Would you please remind us of the difference between--not a black box but a regular warning versus a precaution?

DR. TEMPLE: I am not sure what you mean by the difference.

DR. CRAWFORD: No. I understand the black box. But there is also a level in the labeling of warning, a labeling of precaution. Those I am not clear on.

DR. TEMPLE: Okay. Warning information shows up in various places in the labeling. If there is a black box, it is going to be the first thing in labeling, so it is prominent. We try not to make it too lengthy, but it really targets the thing. Under current labeling guidance, which is under review, the next thing that comes is a lot of description and clinical trials and then you get to the indications. Then you get to warnings. If there is a warning, that is where it goes. It could be in dark print if you want to emphasize it and that is where the warning goes. If it is of less concern, you generally put it under precautions. Frankly, the distinction between

warnings and precautions is not always as clear as we would like it and, in a recent proposal, not yet final, we propose calling them “Warnings and Precautions” and not trying to make that distinction anymore.

DR. WOOD: But, Bob, isn't the major difference that, if you have a black-box warning, you have to deliver all of the information every time you deliver anything.

DR. TEMPLE: Well, you do. But I would say, in dark print--

DR. WOOD: For example, it means you can't--I used to say it meant that you couldn't give out pens with just the name of the drug on it.

DR. TEMPLE: That's reminder ads. A black-box warning absolutely bars reminder ads.

DR. WOOD: But then somebody showed me a pen in which the end unscrewed and the entire thing was stuffed in like stuffed into a bottle. So I am not so sure even that is true anymore. But that is the fundamental difference.

DR. TEMPLE: Well, no. It is the visual quality of it and the--

DR. WOOD: For companies, that is the difference.

DR. TEMPLE: It depends on how important reminder ads is.

DR. WOOD: No yellow stickers. No pens.

DR. TEMPLE: But an ad would have to give prominence to a dark-print warning, too.

DR. WOOD: Right. Dr. Gross?

DR. GROSS: I think if we walk out of here with just a black-box warning for the COX-2 inhibitors and not for all the NSAIDs, it is going to extremely limit the use of the COX-2 inhibitors and a lot of people who would benefit by their use over the NSAIDs will not get that benefit. I think we need to have a black-box warning for all of them. The nature of what is said in the black box can vary somewhat, but we are going to be giving the wrong message if we don't do it for all the NSAIDs.

DR. WOOD: Dr. Shafer?

DR. SHAFER: First, specifically, I am afraid--I think we do have a purpose in trying to channel people to safer drugs. I am afraid that if we put a black-box warning on everything, we are actually going to dilute the message that we are trying to give people. I think we specifically know four drugs that are COX-2-like; etodolac, miloxicam, diclofenac, sulindac. The observational data would suggest that three of those, in particular, showed up; miloxicam, diclofenac and sulindac. So I would propose that, logically, the same black-box warning and the same concerns expressed about valdecoxib, exactly echoing your concepts, should apply to those four drugs specifically

DR. WOOD: Just to respond to that, I would be dead against that. I think it is one thing to put a black-box warning on something that says we don't have data. I think it is a very different thing to put a

black-box warning on drugs for which we have no data that implies we have data. I think we will undercut the strength of black-box warnings if we do that.

DR. SHAFER: What do we do with valdecoxib, though?

DR. WOOD: We know, absolutely not. Valdecoxib has two trials that show absolutely clear signal. It is not the same at all. Richard?

DR. PLATT: Whether they are black box or not I think is not so much an issue as the fact that I think it would be a mistake to attach the same warning to all the other non-coxib non-steroidals, absent naproxen which I think we have excluded from any warning. It seems to me we ought to use the information we have to produce an appropriately graded warning while the agency is ensuring that better data is collected. It seems to me, for drugs like miloxicam, it would make good sense to require the same kind of RCT that we have been talking about for valdecoxib and for some of these other agents. It may be better observational data is all you will have. But the better observational data can come sooner than we ever have hope of getting the RCT data.

DR. WOOD: Last comment on this from Steve Nissen.

DR. NISSEN: I feel compelled to point out that, in the CLASS trial, diclofenac was indistinguishable from 800 milligrams of celecoxib. So, yes; it is not the same but, you know, we have labeling--we put a black box on celecoxib for all doses. It is perfectly plausible that it is exactly equivalent to

celecoxib. Diclofenac and celecoxib could be equivalent in cardiovascular risk. They were in a pretty big trial, one of the bigger trials we had to look at. And Tom Fleming makes the argument that if A equals B, B doesn't necessarily equal C. And I believe that. But I am worried. I am worried about this because we will, by our actions today, cause a shift in prescribing practices. That shift should, to the best of our ability, be a shift toward greater safety. That is why we were called together for three days. I don't have clarity here about whether we are going to induce a favorable or an unfavorable shift. The only way to have some clarity is to require the same thing of all the drugs.

DR. WOOD: Then let's take a vote on 6. I'm sorry; where is there someone else? All right.

DR. ABRAMSON: I just wanted to, very importantly, echo some of the comments, particularly Steve's, that we do have data. We have it in TARGET and in EDGE and in CLASS, that diclofenac and, in some cases, ibuprofen, looks very much like the drugs that we consider warranting a black-box label. So I think it is very important that we be broad in our thinking enough not to send the message that we don't think there is concern. Now, the black boxes don't have to be identical but there has to be some message sent that we have some data to suggest these drugs also carry a cardiovascular risk.

DR. WOOD: So we have to vote, apparently, on 6.

DR. HENNEKENS: May I make one statement, please.

DR. WOOD: Charlie? Yes.

DR. HENNEKENS: In direct, randomized comparisons against placebo, there is a 41 percent hazard of the coxibs. Against naproxen, there is a 56 percent hazard of the coxibs. Against diclofenac and ketoprofen, there is a 14 percent possible lower risk. I think we can't ignore this. And I think that just saying a black box for the entire class is ignoring some of these direct randomized comparisons.

DR. WOOD: We have to vote on that so your vote can reflect these differences. I am not sure how, exactly, we are going to vote. Bob?

DR. ? : Alastair, just one thing. The question, as written, doesn't make any distinction between one or another of the so-called nonselective ones. In other words, it doesn't recognize even the possibility that some of the ones not identified as coxibs are selective. So, somehow, I think you need to--and that is what Steve's whole comment was related to. So the question, itself, doesn't really break that out.

DR. WOOD: So we could break the question out to say whether we think other putatively selective non-steroidals may carry the same risk and should carry some warning. So that would be first question. Whether the putatively nonselective drugs should carry the same or a different warning and, I guess, the third question would be, if so, describe how you recommend that information be conveyed. Is that fair, Bob? John?

DR. JENKINS: The concern I have with that approach is I think we heard, throughout the meeting, that this issue of

which one is a selective and which one is not a selective is very dependent upon who did the assay and whose table you are using. So I don't know which table you would refer to to say, these are the selective ones, even though they are not coxibs, and these are the nonselective ones.

DR. WOOD: I agree with that. I am trying to respond to Bob's request.

DR. TEMPLE: It is okay to tell us what your doubts are. One of the things we might be able to do, or have to do, is try to refine the statement about which ones are selective or not.

DR. WOOD: My concern about responding too definitively to this is that we spend a lot of time reviewing the data on the specific drugs that were on the table. While I agree that the other drugs were there sort of as mirror images, if you will, at times, I am not sure that the committee has put that much effort into reviewing all these other drugs. I have a certain sense of caution before we rush into other labeling changes. Dr. Ilowite?

DR. ILOWITE: The FDA people have informed me that we should know the consequences of our actions. They say if we put a black-box warning on something that is over-the-counter, it would no longer be over-the-counter.

DR. WOOD: Right. I realize that. I was actually going to bring that up. It doesn't actually say that--I mean, this question does not imply that we put a black-box warning on it. But if people feel that, they would a black-box warning on it, then that will be the consequence. That is absolutely right. Bob and John, do you think you have got enough from the

discussion or do you really want to force this to a vote?

DR. CUSH: Mr. Chairman, I would like to suggest that we not divide this up as selective and nonselective for reasons that have been stated, that we just say the remainder of the nonsteroidal class, excluding COX-2-specific drugs for which we have already discussion and vote on, if we could say just the remainder non-steroidals and then comment individually on naproxen as there seems there is a sentiment that that may merit some special consideration.

DR. WOOD: So we take the position that, apart from the three drugs we have talked about, the other drugs as a group, and naproxen as a separate drug.

DR. CUSH: From Indocin all the way up to miloxicam.

DR. WOOD: All right. Do people want to go around? Is there any more discussion on that?

DR. CUSH: And the vote would be whether or not there should be a warning or a black box or need for research and no warning.

DR. WOOD: Lots of comments on that. Dr. Nissen?

DR. NISSEN: It is the nature of the warning that I want to be clear about. I think the warning can be worded in such a way that it says that some drugs in this class of agents have been shown to increase the risk of cardiovascular and cerebrovascular events. Long-term data on the cardiovascular safety of this agent has not been established. What you are

telling people is, we don't know. That is a warning that says, we can't demonstrate one way or the other, not a warning that says, we know that the drug is harmful but simply that we don't know. I think that is informative and I think it is helpful so that people know that there is at least some reason to be cautious. Now, what you do after that, in terms of what kinds of trials should be done, we have already talked about. But I think you have to tell people that we suspect there may be a problem here.

DR. WOOD: John?

DR. JENKINS: I might suggest that we come back and just vote on the question the way it is written because if you look at the question the way we wrote it, it would be useful to hear whether you think we should add, as it says, do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical-trial data to assess the potential cardiovascular effects on these drugs. Probably, you want to have a yes or no there and let your discussion stand to let us, then, go back and decide whether it is going to be a warning, a precaution or a box. But I think it would be useful to hear if you think these other drugs, where we don't have data or we have limited data, we should say something to the effect that the question asks you about lack of data.

DR. WOOD: And you would be comfortable with the second sentence being conveyed from the discussion.

DR. JENKINS: Yes.

Voting on Question 6

DR. WOOD: Okay. Good. Then let's start--I have lost touch with where we started last time. Steve Abramson. Let's start with you.

DR. ABRAMSON: Okay. I would answer yes to that first question.

DR. NISSEN: Nissen. Yes.

DR. ELASHOFF: Elashoff. Yes.

DR. GARDNER: Gardner. Yes.

DR. PLATT: Platt. Yes. Please don't use a blanket approach to this class.

DR. DAY: Day. Yes. I echo Platt.

DR. FURBERG: Furberg. Yes to precaution.

DR. FLEMING: Fleming. Yes to the first question. I haven't commented on the second so let me do so. I am uncomfortable having a blanket approach to the second because I do think there is considerably different evidence, for example, on diclofenac versus naproxen. So I would hope that the agency approaches this thoughtfully looking at the totality of the data with agents that are in the diclofenac category getting a much clearer indication, potentially a black-box warning, with agents in the naproxen category looked at in a very different magnitude and a very different context, certainly without a black box.

DR. DOMANSKI: Domanski. Yes to the first question and I agree with Dr. Fleming for the second.

DR. BOULWARE: Boulware. Yes.

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DR. HOLMBOE: Holmboe. Yes. Also, I would consider a black box for those that are found to have similar data to the coxibs.

DR. GROSS: Gross. Yes to the first one and, to the second one, I would be in favor of a black-box warning where the language varies depending on the strength of the evidence or lack thereof referring to a possible class effect.

DR. WOOD: Wood. Yes to the first question and with exactly the same comments as Tom Fleming made.

DR. CRAWFORD: Crawford. Yes to the first question. I would be against, at this point--based on the available evidence, I would be against a black box but yes to a warning or a precaution.

DR. CUSH: Yes. There is a need for a warning label for all non-steroidals with regard to cardiovascular risk and that, to get that warning removed, there should be a trial, I guess, with naproxen showing superiority or non-superiority, I guess.

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DR. LEVIN: Yes to the first.

DR. ILOWITE: Ilowite. Yes to the first. I would be against a black-box warning for either naproxen or ibuprofen.

DR. D'AGOSTINO: D'Agostino. Yes to the first with precautions.

DR. MORRIS: Morris. I would say yes in the method that Peter has outlined for prescription drugs. For over-the-counter drugs, I would suggest that there be a

warning about long-term use at higher doses and the potential for cardiovascular risk.

DR. WOOD: That was Dr. Morris.

DR. CANNON: Cannon. Yes with a warning regarding long-term use.

DR. FRIEDMAN: Friedman. Yes to the first part and, obviously, as others have said, tailored to the individual drug. The implications, of course, of saying that we don't have adequate research is that we are going to try to get it done. So, when we put that in there, we have to follow through.

DR. HENNEKENS: Yes to the first question with the caveats that the short-acting NSAIDs, specifically ibuprofen, ketoprofen, diclofenac appear to be at least as hazardous as the coxibs and that naproxen is neutral to maybe slightly favorable on cardiovascular risk and, secondly, that the warning would be the same as for the coxibs.

DR. SHAFER: Yes with a graded warning based on both the available data and the pharmacologically established COX-2 selectivity.

DR. WOOD: Okay.

DR. WOOD: Question No. 7; what additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential cardiovascular risk of the nonselective NSAIDs. Please be specific with regard to which nonselective NSAIDs--all, or only selected agents--trial design, et cetera, et cetera.

DR. JENKINS: Dr. Wood, if I can make a comment. In the interest of getting to what I think is probably our most important remaining question and making sure we address that before we lose too many of the committee

members because I am seeing we are losing some already, I think No. 8 is probably the next most important question which is what the databases need to be for new agents.

Voting Results on Question 6

DR. WOOD: Okay. Before we move on to that, I have got the vote on Question 6; 28 yes, no abstentions, no no's.

Slide with Text of Question 6

6. Do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical trial data to assess the potential cardiovascular effects of these drugs?

If so, please describe how you recommend that information be conveyed (e.g., warning, precaution).