DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

VOLUME III

Friday, February 18, 2005

8:07 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

P A R T I C I P A N T S

Alastair J. Wood, M.D., Chair

Arthritis Advisory Committee:

Allan Gibofsky, M.D., J.D.
Joan M. Bathon, M.D.
Dennis W. Boulware, M.D.
John J. Cush, M.D.
Gary Stuart Hoffman, M.D.
Norman T. Ilowite, M.D.
Susan M. Manzi, M.D., M.P.H.

Drug Safety and Risk Management Advisory Committee:

Peter A. Gross, M.D.
Stephanie Y. Crawford, Ph.D., M.P.H.
Ruth S. Day, Ph.D.
Curt D. Furberg, M.D., Ph.D.
Jacqueline S. Gardner, Ph.D., M.P.H.
Eric S. Holmboe, M.D.
Arthur A. Levin, M.P.H., Consumer Representative
Louis A. Morris, Ph.D.
Richard Platt, M.D., M.Sc.
Robyn S. Shapiro, J.D.
Annette Stemhagen, Dr.PH. Industry Representative

FDA Consultants:

Steven Abramson, M.D.
Ralph B. D'Agostino, Ph.D.
Robert H. Dworkin, Ph.D.
John T. Farrar, M.D.
Leona M. Malone, L.C.S.W., Patient Representative
Thomas Fleming, Ph.D.
Charles H. Hennekens, M.D.
Steven Nissen, M.D.
Emil Paganini, M.D., FACP, FRCP
Steven L. Shafer, M.D.

National Institutes of Health Participants
(Voting):

Richard O. Cannon, III, M.D.
Michael J. Domanski, M.D.
Lawrence Friedman, M.D.

P A R T I C I P A N T S (Continued)

Guest Speakers (Non-Voting):

Garret A. FitzGerald, M.D.
Ernest Hawk, M.D., M.P.H.
Bernard Levin, M.D.
FDA Participants:

Jonca Bull, M.D.
David Graham, M.D., M.P.H.
Brian Harvey, M.D.
John Jenkins, M.D., F.C.C.P.
Sandy Kweder, M.D.
Robert O'Neill, Ph.D.
Joel Schiffenbauer, M.D.
Paul Seligman, M.D.
Robert Temple, M.D.
Anne Trontell, M.D., M.P.H.
Lourdes Villalba, M.D.
James Witter, M.D., Ph.D.
Steve Galson, M.D.
Kimberly Littleton Topper, M.S., Executive Secretary

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P R O C E E D I N G S

Call to Order

DR. WOOD: Let's get started. This is our third day and thanks to everybody for coming back. We have obviously entertained you sufficiently.

Kimberly has a statement to read.

Conflict of Interest Statement

MS. TOPPER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such. Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industry sponsors in academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topics at hand.

To determine if an conflict of interest existed, the agency has reviewed the agenda and all relevant financial interests reported by the

meeting participants. The Food and Drug Administration has granted general-matter waivers to the special government employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30, of the Parklawn Building.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to each member, consultant and guest speaker. FDA acknowledges that there may be some potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to the FDA's invited industry representatives, we would like to disclose that Dr.

Annette Stemhagen is participating in this meeting as a non-voting industry representative on behalf of regulated industry. Dr. Stemhagen's role on this committee is to represent industry interests in general and not any one particular company. Dr. Stemhagen is Vice President of Strategic Develop Services for Covance Periapproval Services, Inc.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

There is one administrative announcement. Would you please make sure that you take your phone calls outside. It is messing up with our audio and we would really appreciate it. Thank you.

DR. WOOD: The other administrative thing

that the sound person has asked me to say is, to the committee, try and remember to switch off your microphones when you are not using them. Apparently, it messes it up.

MR. LEVIN: Mr. Chairman?

DR. WOOD: Yes, Arthur?

MR. LEVIN: I wanted to express a concern I have in terms of the agenda for today's meeting. For those of us who have been at advisory committee meetings before, we know that there is often a tendency to sort of squeeze the most important part of these advisory committee meetings which is the discussion and answers to the questions and giving directions to FDA.

My concern is that, given the lengthy discussions we have had over the past two days and, given the fact that this is last day, that we will not have enough time to fully explore all of the questions that have been raised over the last two days and to give some definite direction to the FDA as to how to pursue these issues.

So I would like to suggest to the group

that we might shorten the presentations, or eliminate them entirely, in order to have adequate time to fully discuss all of our concerns and different points of view around the table. I think it would be really unacceptable to leave here today unable, because of a time constraint, to give direction to the FDA on this issue.

DR. WOOD: Did you have any particular people you wanted to eliminate? Or do you want to pass me a note, privately?

MR. LEVIN: It may be something the committee as a whole should decide.

DR. WOOD: Let me make a suggestion. I think that is a reasonable approach. I am sure the committee will want to hear the data from the ADAPT study and we should hear that in its totality. Milt Packer has come a long way so we should hear from him, I think. Milt is always entertaining, anyway.

Do we really need to hear from the two Bobs?

DR. TEMPLE: I don't have any ego involved

in this. A fair amount of--some of what I am talking about is about the adverse consequences of blood-pressure elevation which I think I could skip. So I could shorten it considerably. But you guys decide. It is there for you to read if you want.

DR. WOOD: Why don't you do this. Why don't you distribute your talk to us.

DR. TEMPLE: I think it has been.

DR. WOOD: Right; I understand that. I will take that as a given. And both of you make whatever remarks you would like to make from your seats there at the times that you are allotted, but brief and pointed. And let's not revisit all the things we have visited before.

DR. TEMPLE: That's fine.

DR. WOOD: Does that sound fair? Dr. O'Neill?

DR. O'NEILL: Yes; that is fine.

DR. WOOD: That will save us some time. So that is a good thought. In addition, we have got Sharon Hertz's talk which, I notice, has

40-something slides here--45 slides--which is a lot to get through in a few minutes. So I think, while we are sort of working up to that, she may want to look at that and decide what she really needs to say. I mean, after all, it is very unusual for the FDA to summarize the meeting for the committee, which is partly what the committee is here to do, I guess.

So let's make sure that she can finish that taking the time she has been allotted for it which is 30 minutes. She would be better to remove some slides rather than rush through it, I think.

Having said all that, let's get to the first presentation. Does anyone else have any thoughts on that? Yes, Annette?

DR. STEMHAGEN: I would like to ask whether the manufacturers could have just one or two minutes to make some summary comments before we start our deliberations after lunch.

DR. WOOD: Do they want to do that now? Is that what you are asking?

DR. STEMHAGEN: No; I think after these

presentations.

DR. WOOD: Okay.

DR. STEMHAGEN: Thank you. I appreciate it.

DR. WOOD: Let's have some discussion amongst the committee.

DR. CUSH: What would be the purpose of their having--they have had lots of time already to present their data and had lots of mike time in the back already.

DR. STEMHAGEN: Just in terms of the deliberations that have gone on, there might be some clarifying comments.

DR. CUSH: I think, if we have questions, we can ask for clarifying comments. I think that is what we--I would suggest--and I agree with Arthur Levin in that we should get on to discussion as quickly as possible.

DR. STEMHAGEN: I realize this is sort of in contrast to try to shorten it. But I would like to ask that that time be awarded.

DR. WOOD: Any other thoughts on that?

Let me get a sense of the committee. What is the committee's pleasure about that? Yes?

DR. BOULWARE: I actually support that recommendation, too, and would suggest you give them a limited time, like you did with the public comment where you will cut them off at two minutes, so we know it will be limited. I would be interested in the direction they plan to take. We heard some startling news yesterday about the possible remarketing of a product that they have withdrawn.

DR. WOOD: Does anyone object to them getting two minutes apart from Dr. Cush? Then, I think, the answer on that is that that is fine. Remind them that, in contrast to most of their experiences in the past for senior managers, the microphone will be cut off.

DR. STEMHAGEN: Thank you very much. I think we saw evidence of that yesterday.

DR. WOOD: Right. So they got the message; right? Okay. Let's move along to the first speaker, Dr. Lyketsos.

Investigator Presentation

Alzheimer's Prevention Study: ADAPT

DR. LYKETSOS: Good morning, everyone. I

do not have slides. My name is Constantine Lyketsos. I am a professor at Hopkins and I am presenting here today on behalf of the ADAPT study, Alzheimer's Disease Anti-inflammatory Prevention Trial. I would like to thank the committee for inviting us to present. I am here today with my colleague, Steve Piantadosi, who is also on the steering committee and will be available to answer any questions that might come up later on as well.

I have a prepared statement that will be distributed to the committee later on today. I delivered it to the staff this morning as I was arriving.

Before I get into the statement, I just wanted to take a few moments to remind us of the public-health importance of Alzheimer's disease to somewhat set the context about how the ADAPT trial has started specifically. Alzheimer's, as we all know, is a major public-health problem. It is a

devastating disease, typically runs a ten-year course of neurodegeneration affecting probably close to 4 or 4-and-a-half million of our citizens at present and the number is expected to rise given the aging of the population of the next several decades to approach, perhaps, 12 to 15 million, based on current projections.

Because of the these public-health numbers, there has been a very significant effort in our field for the last several years to develop preventive strategies for Alzheimer's disease because, once neuronal degeneration has started, the evidence that treatments work, so far, is very weak.

These preventive strategies have centered on several possible treatments but the most supported by the observational literature have been nonsteroidals with over 24 studies right now including four prospective population studies suggesting substantial reductions of risk of Alzheimer's disease perhaps with risk ratios, in some cases, as much as 0.4 or 0.5. So it is within

that context that ADAPT was started with the support of the National Institute of Aging.

I will move now to reading the prepared statement.

The steering committee of the ADAPT study welcomes the opportunity to present the rationale for its decision, on December 17, 2004, to suspend the NSAID treatments in ADAPT. This presentation is important because there is much public misunderstanding about our decisions and their rationale.

The ADAPT Steering Committee is deeply committed to the safety of human subjects, even more so in the context of prevention trials where risks are typically not balanced by any promise of tangible near-term benefit. In this notable way, prevention trials differ from treatment trials whose participants may hope for relief of symptoms or improved outcomes in a condition already diagnosed.

The risk:benefit balance in prevention trials is even further removed from a comparison of

the benefits of a proven treatment with its acknowledged risks. Because ADAPT has not quite completed the process of auditing and tabulating the trial's cardiovascular safety on the date of suspension, we cannot, today, present the trial safety results at the time of the decision to suspend.

We defer that presentation to a peer-reviewed publication planned for the near future. For today, we note that, even with the risk:benefit calculus of a prevention trial, these data would not, in themselves, have led to our decision to suspend either treatment. In reality, those decisions were made in very unusual circumstances. They reflected events external to ADAPT that raised strong concerns about the practicalities of continuing the treatments.

As the advisory committee probably knows, ADAPT is a randomized, double-masked, multicenter trial of celecoxib, 200 milligrams twice daily, or naproxen sodium 220 milligrams twice daily versus placebo for the primary prevention of Alzheimer's

dementia and for the prevention of age-related cognitive decline which is, in many instances, a prodrome of Alzheimer's disease.

ADAPT also provides an opportunity to study the long-term safety of its treatments in a healthy elderly population. Eligibility criteria include an age of 70 years or older at enrollment and a health history that excludes many of the known risk factor for adverse events with NSAID treatments; for example, we exclude those with preexisting uncontrolled hypertension, anemia or a history of gastrointestinal bleeding, perforation or obstruction.

To provide independent recommendations regarding continuation of the trial, the ADAPT Treatment Effects Monitoring Committee, or TEMC, which, I suppose, is our term for a DSMB, meets twice a year. In response to emerging concerns about cardiovascular risks with NSAIDs, membership of the TEMC was recently expanded to include Dr. Bruce Psaty, a physician with expertise in evaluation of cardiovascular risks in clinical

trials.

As an additional safeguard for participant safety, the ADAPT study officers and consultants also conduct reviews of safety data at intervals between TEMC meetings. Amid the emerging controversy about the cardiovascular safety of selective COX-2 inhibitors, the ADAPT study officer had been relatively reassured by their periodic reviews of the celecoxib safety data. The study chair communicated this information in a telephone conversation on 15 October 2004 with Dr. Sharon Hertz at FDA.

As of December 17, 2004, the data of suspension of treatments and enrollment in ADAPT, we had enrolled 2,528 participants. Of these, 2,463 had been randomized before October 1 of '04 with some 20 months average duration of observation. These participants contributed a total of 3,888 person years of follow up to analyses that were presented to the TEMC on December 10, 2004.

Those analyses suggested a weak signal

suggesting increased risks of cardiovascular and cerebrovascular events with naproxen. Reviewing the data, however, we understood well the TEMC's evident conclusion that this signal was not sufficiently compelling or definitive to warrant a recommendation to suspend the treatment or to otherwise alter the protocol. This was on December 10, 2004.

Thus, the study officers were surprised on December 17 by announcements that two trials of celecoxib for the prevention of recurrent adenomatous colon polyps had been suspended citing increased cardiovascular risks with treatment in one of these studies, the Adenoma Prevention with Celecoxib trial, or APC. This news led to extensive discussion among the steering committee on that day centering on the following considerations.

Number one; one arm of the APC trial had used the same celecoxib dosing as ADAPT, 200 milligrams twice daily, but over a longer period of time. News reports cited a relative risk of 2.5

for cardiac events in this arm of APC. Although this risk was reported as only "marginally significant," a greater cardiac-risk signal was reported with the higher APC dosage of 400 milligrams twice daily.

Thus, we took seriously the possibility of harm over time to ADAPT participants receiving celecoxib. Especially in a prevention trial with no strong prospects of immediate benefit, we had strong misgivings about continuing celecoxib treatments.

Knowing almost nothing at the time about the particulars of the APC trial and, in light of the apparent lack of risk with celecoxib in the other prevention trial, we might have discounted the APC data and continued celecoxib. To do so, however, we would clearly have needed the concurrence of the seven IRBs that oversee ADAPT. These IRBs began almost immediately to question us about implications of the APC results and seemed likely to question a decision to continue.

Even if we had persuaded them to permit

continuation of celecoxib using a revised consent process, we would surely be involved in lengthy discussions with these IRBs. In the meantime, we would be unable to offer much explanation to our participants, thereby endangering the relationship of trust that is vital to the success of long-term trials.

Number three; as is common in long-term trials, ADAPT was experiencing some difficulty with adherence to treatments. This difficulty grew following the withdrawal of rofecoxib and we expected the announcement of the APC results to exaggerate the problem further with scores of participants stopping treatment, in effect, "voting with their feet." This would erode statistical power and increase the potential for bias in ADAPT.

Thus, even though the ADAPT safety data did not, themselves, warrant suspension of celecoxib treatments. There seemed little practical choice but to do so.

We next confronted the dilemma of what to do about naproxen and its placebo. As suggested

above, we regarded the accumulated naproxen safety data as being somewhat more concerning than the celecoxib safety data. Yet, they, also, were not compelling. Although some post hoc data composites barely reached statistical significance--these are post hoc data composites barely reached statistical significance for naproxen versus placebo, no singular vascular event was clearly more frequent with naproxen versus placebo.

Furthermore, vascular risks were not expected with naproxen treatment. In fact, a substantial body of prior data at the time had suggested that naproxen offers some cardiovascular protection. This lack of prior expectation cast further doubt on the meaning of the naproxen data in ADAPT which were vulnerable, in any case, to the problem of multiple comparisons.

We could, therefore, have attempted to have revised ADAPT to a two-armed trial of naproxen versus placebo, instructing our participant to stop taking their "white pills," as they are known in the study, which are celecoxib and its placebo, but

continue to take their "blue pills," which contain naproxen and its placebo.

However the dangers were several. Participants might end up getting confused and taking the wrong pills and many would stop taking their treatments altogether. We faced an ethical dilemma. The suspension of celecoxib and continuation of naproxen would have created the impression among participants and among the general public that celecoxib was risky but naproxen was "safe." At least based on the signals from the ADAPT data, this impression would have been misleading.

What would we then tell participants about the risks with naproxen as we led through the inevitable process of revised consent necessitated by the protocol revision. Would the multiplicity of IRBs even allow us to follow this course?

Finally, there was another risk to consider. We began ADAPT expecting to see some increase with naproxen in gastrointestinal bleeding and other events. Even though we attempted to

reduce these excess G.I. risks by excluding participants with prominent risk factors other than age, the ADAPT data showed a notable increase in G.I. bleeding with naproxen versus placebo.

Especially amid concerns that ADAPT was exposing its participants to potential risks that were immediate, while the trial's hoped-for benefits lay in the future, the totality of the above arguments lead the steering committee to suspend both treatments and to also suspend enrollment into ADAPT.

As noted above, we expect, within a few weeks, to submit a scientific paper for peer review and publication. The paper's focus will be on the process and rationale underlying the decision to suspend treatments and enrollment in ADAPT. Because these decisions did rely, in some measure, on the ADAPT safety data as of 10 December, the paper will, also, disclose some of these data.

We are also cooperating with ongoing efforts at the NIH to investigate the cardiovascular and cerebrovascular risks of NSAIDs.

In addition, the NIA and the ADAPT Steering Committee are committed to a further two years of additional safety monitoring of our participants.

In preparation for a later, more definitive discussion of the ADAPT safety data, we plan to revisit a number of the adverse events to collect additional information and then to submit all information available now or later to a process of expert adjudication. Depending on particulars, the latter process will take months. In the nearer term, we concur with the expert opinion that, having taken these widely publicized decisions, the steering committee must fulfill its obligation to disclose its reasons for doing so based upon the data available.

At the same time, we are intent that our public presentation even of the current "working" data must be at the highest attainable standards of accuracy.

Thank you.

DR. WOOD: Thank you very much. Are there questions directed to the speaker? Dr. Nissen?

DR. NISSEN: I fully understand your rationale and I understand that the trial was fundamentally stopped because of an issue of

futility. You didn't think that you could keep people in the celecoxib arm. That is all well and good. The problem that occurred here is that a warning was issued on naproxen which had the effect of being the medical equivalent of screaming "fire" in a crowded auditorium.

All over the country, many of us got calls from patients saying, "I want to stop my naproxen because it causes a cardiovascular risk." I think, just a comment here, that it would have been far better to have announced that the trial was suspended for futility rather than for hazard when there was a non-statistically significant hazard. So, one man's comment.

DR. WOOD: I agree with that. Any other comments? Yes?

DR. FARRAR: I wonder if you could comment on the G.I. bleed component since, obviously, one of the deliberations we have to undertake is the

relative problems with G.I. bleed versus cardiovascular risk. Certainly, that was known a priori before starting the study.

As you commented very carefully, that wasn't the only consideration. But, in a drug trial where the outcome is unknown and the risk is really fairly well known, I wondered how you thought about that in terms of putting patients at risk of something on the order of a few percentage over the course of a five-year trial who might have serious complications from the G.I. bleeding.

DR. LYKETSOS: I guess you are asking me a human-subjects question.

DR. FARRAR: I am asking how, in the design of the study, obviously the choice was made to accept that risk for the unknown potential benefit of reduction in Alzheimer's disease over the course of the same trial. I am wondering if you have any insights into how that decision was made because, clearly, there are issues there about the use of these drugs and their risks.

DR. LYKETSOS: Well, I am glad you are

asking the question. It certainly is an issue that we have spent a lot of time discussing and which we discussed with study sections, IRBs, at quite some length and continue to discuss.

I think the fundamental point that I would start with is where I started my presentation which is the devastation that Alzheimer's disease brings and the fact that all the study participants were individuals who had a first-degree relative with the disease and had, therefore, personal experience.

In that context, we were very careful and very clear with them about what we thought at the time the known G.I. risks were so that, in the process of consent, and that was revealed through careful discussions in the consent process as well as the consent form, the risk of G.I. bleed was stated very clearly and that that, in some cases, might lead to death.

So I think we felt that this was a decision that our participants could make, given that the risks were relatively small, and the risk

that they would develop Alzheimer's disease was higher and that we felt they could make the decision for themselves if they were willing to take the risk:benefit calculus as we saw it.

DR. WOOD: Dr. Gibofsky?

DR. GIBOFSKY: I share Dr. Nissen's concern about this effect of crying fire in a crowded theater. Many of our patients called and suggested that they were going to stop their celecoxib because of the concerns that were raised from ADAPT as well. But you raised a very interesting concern that I confess I hadn't given enough thought to and that is the difference between a prevention trial and an outcome trial.

Much of our discussion here later today, I suspect, is going to focus on what action should be taken, if any, to restrict drugs based on treatment from data on prevention trials. I would be very curious to hear you expound on that a bit more.

DR. LYKETSOS: That is an interesting question. Let me just, if I could, because there have been three comments now--I just would like to

refer you to the early part of my statement where I said the presentation is important because there is much public misunderstanding about our decisions and their rationale.

Several of you pointed out that there was a cry of fire. I don't believe that that came from the study.

DR. WOOD: We won't ask you to speculate where it came from. There is certainly a view on that.

DR. LYKETSOS: I am not sure where it came from. But, to address the other issue, I must say I have not given it much thought as to whether prevention-trial safety data would generalize in the way that you are thinking about it. So I will defer on that because I think it would need a fair bit more thought by people who are more expert in that.

DR. WOOD: Dr. Fleming.

DR. FLEMING: It is my understanding, from what you are saying, that the steering committee was particularly influenced by the APC prior data

not by the internal data from ADAPT; i.e., there were, from you were describing, some emerging trends that, in my words, were in the unfavorable direction but in the context of monitoring trials, we know that one has to be extremely cautious, when you are looking at data continually over time, not to overinterpret emerging trends that can easily ebb and flow.

So my understanding, from what you are saying, is it wasn't that there were, at this point, some emerging trends that happen to be in the unfavorable direction on naproxen. Rather, it was the external data on the APC trial for Celebrex that was the driving issue behind the recommendation.

DR. WOOD: Just to develop that question, what I understood you to say was you hadn't passed some stopping boundary; is that correct?

DR. LYKETSOS: I'm sorry? I didn't hear the first--

DR. WOOD: You hadn't violated your stopping rule, or whatever stopping rules, you had

for safety.

DR. LYKETSOS: I think that our TEMC, our DSMB, had opined the week before with the same data from within the trial that they felt that we should continue. So it was interesting how the two events were back-to-back.

DR. FLEMING: I would like to come to that second. I am leading to that. But first I wanted to make sure that I understood what was the nature of the concern. Is my interpretation correct?

DR. LYKETSOS: I think so. Back to how I put it, the issue really was one of practicalities more than our internal data, is that we felt we would have to talk to IRBs and participants and tell them something about--

DR. FLEMING: Could I first understand what your sense of the evidence was. I want to discuss that first, versus the practicality.

DR. LYKETSOS: The sense of the study evidence.

DR. FLEMING: The sense of the evidence that was the basis for the decision in terms of

adverse effects. I have heard two things. One is the naproxen, but that was not compelling evidence. That was within the framework of emerging results that could be by chance alone when you are monitoring data frequently. But external APC data was very influential to you. That is what I am hearing. Is that correct?

DR. LYKETSOS: Well, in fact, we didn't know all the details of the APC data, as I pointed out. I think it was that plus the climate that had been created by rofecoxib coming off the market, the influence that that had to some extent on our participants, then the widely publicized APC results and the sense that, even though the data we were seeing and that our TEMC the week before had seen, did not compel us to stop treatment based on our own data, that there was now a climate created where, practically speaking, we had to stop and take stock and get more information, et cetera.

So it was that sort of the decision. I was a complicated decision and that is why it takes a three-page statement to try and explain what went

through our minds.

DR. FLEMING: There may not have been, to the steering committee at this time, access to data on PRECEPT for celecoxib or to the etoricoxib, the lumiracoxib, data on naproxen that were very favorable, but you did have access to the VIGOR data which was very reassuring for naproxen and you had evidence from the CLASS trial and some other data from Celebrex.

I am perplexed that you would look at the totality of these data and say that the results were conclusive in terms of at least not being able to provide information to the IRBs and to the patients and caregivers in the trial representing the totality of the data when your data-monitoring committee had looked at the totality of the evidence for benefit to risk.

On a data-monitoring committee, I have always argued, don't just show me the safety data, even if we are just looking at early assessments for safety. It always has to be benefit to risk. Even though, as you are pointing out, this wasn't a

therapeutic setting, prevention trials also provide major opportunity for benefit. Preventing major diseases is also a very significant benefit.

My understanding is your data-monitoring committee, in looking at the data, looking at the benefit as well as the risk, indicated the study should continue. How did the steering committee judge, without access to ongoing data, that benefit to risk couldn't be sufficiently favorable and that a notification to the investigators, to the patients and to the IRBs, that the monitoring committee has carefully looked at benefit and risk and that the totality of the data is beyond the APC trial when you are looking at Celebrex and naproxen? Why wasn't that strategy pursued?

DR. LYKETSOS: First, as I pointed out in my statement, some members of the steering committee did have access to the data that the DSMB had seen. That is the first point. The second point is, as you point out and as I think this whole discussion points out, is these are very difficult judgment calls. They have to take into

account evidence but also practical aspects of continuing to conduct this sort of a prevention trial in this sort of a population.

I think it was the judgment call, and I can tell you, there was substantial discussion around this when we had the steering committee meeting, about these very issues. It was the collective judgement at the time that this was the right thing to do, given the various issues that I have articulated in my statement.

DR. FLEMING: I will just pursue one more. I am dismayed to hear the steering committee, some steering committee members, had access to the data. That is also a violation of the principles of monitoring trials. It should have been in the sole possession of the data-monitoring committee.

I am also distressed because I am not hearing that monitoring committee was front and center in terms of having these issues brought back to it for reassessment. So, to me, what I am hearing raises very significant concerns about putting at risk the integrity of studies with

prejudgments using only access to partial external information.

DR. WOOD: There was one other thing, though, at least the word on the street was, and you sort of mentioned that as well, I understood there was a very large number of dropouts from the trial after the Vioxx withdrawal and others and that one of the perceptions was it was no longer possible to continue the trial. Is that true?

DR. LYKETSOS: Let me clarify that. The adherence had been declining on an annual basis even before rofecoxib was withdrawn from the market. So adherence was perceived as an issue in that we felt that now there were data about one of the study drugs and that that would further erode adherence. We did not see a huge erosion in adherence with rofecoxib, specifically, but there had already been an erosion that was concerning and we anticipated a further erosion.

DR. WOOD: Right. But the question for this committee that Dr. Fleming is pursuing vigorously, and I agree with him, is that the

announcement that you all made--the announcement, as it was picked up--maybe I should put it like that--was that this trial was being stopped for a safety signal.

What I heard in your statement and what I hear from you now is that the trial was being stopped for operational problems in the trial and the safety signal was a convenient moment at which to do that. But you had operational difficulties. That is a very different interpretation and a very different interpretation for the public and patients.

Is that what you are hearing, Tom?

DR. FLEMING: It certainly appears to be. It is part of what is concerning to me.

DR. LYKETSOS: I think my statement should speak for itself. In terms of what the data were, as I have pointed out, they will be submitted very soon so that you can judge for yourselves.

DR. WOOD: Okay. Any other questions? Sorry; Dr. Farrar. I beg your pardon. Dr. Farrar, go ahead.

DR. FARRAR: I think, actually, that this study provide some vitally important information with regards to our consideration of the entire

class of drugs; namely, the NSAIDs. I would like to just read on sentence from the statement.

It said, "Although some post hoc data composites barely reached statistical significance for naproxen versus placebo." Now, clearly, this discussion would be much clearer after the presentation of the data, a careful review of the data. But Dr. Fleming noted that, in the VIGOR study, there was some reassurance about naproxen. I would like to just question that.

What is very clear in the VIGOR study is that naproxen was safer than rofecoxib. But it does not comment at all with regards to the potential risk compared to placebo. In fact, I was surprised when I heard the statement by Dr. Fleming because, in fact, I have assumed, based on all the data that we have, that every NSAID will not fare well against a placebo.

I think that this data, and probably will

be supported by the publication although I don't want to try and foresee the future, but my guess is that naproxen will not fare particularly well against placebo in terms of its cardiovascular safety. I think we need to be able to accept the fact that all of them have some risk with regards to cerebrovascular disease and this study is likely to provide the data to support that.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I don't want to belabor this because we have got a lot more to discuss today, but I think it is extremely important that, as a medical community, we learn from this episode. In the kind of media frenzy that was going on during that period of time, this announcement, this warning that was issued on a national basis about naproxen, was inappropriate, led to some panic amongst the public and we simply can't do business this way.

We can't operate in this kind of a fashion. I would urge any of the individuals who were involved in the decision to issue a warning to

go back and look at what happened and try to ensure that we don't do this sort of thing again, because once this gets picked up by the media, it passes through generations of people and becomes the topic of extensive discussion and may lead patients who don't have the ability that we have around this table to filter data--they don't understand data-safety and monitoring boards. They don't understand stopping rules. And it caused a panic that was unnecessary and it shouldn't have happened, and I hope it doesn't happen again.

DR. WOOD: Thanks very much. Let's move on to next speaker, Dr. Packer.

Additional Background Presentations

Interpretation of Observed Differences in the Frequency of Events When the Number of Events is Small

DR. PACKER: Thank you, Alastair, members of the advisory committee, FDA, ladies and gentlemen. Today I have been invited by FDA to address a specific question which is how should be interpret differences in the observed frequency of

events in a clinical trial when the number of events is small.

Let me just say arbitrarily that I will define, for purposes of today, what I mean by a small number of events and that would have provided less than 70 percent power to have detected a true treatment difference assuming an effect size similar to that generally encountered in clinical research.

This is just a thought. Just suppose you do a trial for a noncardiovascular indication and you note that there are 13 major adverse cardiovascular events in the placebo group and 33 such events in the drug-treatment group. How should this difference be interpreted?

Many would simply perform a statistical test, derive the p-value, and get excited if the p-value were less than some arbitrary value such as 0.05. In this example, the p-value of 0.002 would suggest, to some, that this difference between 13 and 33 in a trial of about 3,000 patients, would have been observed only two times out of 1,000, an

effect unlikely to have been due to the play of chance.

However, before getting excited, we should remember that p-values must be interpreted in some context. P-values are most easily interpreted when they refer to predefined primary endpoints in trials adequately powered, more than 80, 90 percent power, to detect differences between treatments. However, even under such circumstances, p-values are not necessarily reproducible.

Bob O'Neill and others have made the point that, if a p-value in the trial is 0.05, the likelihood of seeing 0.05 in a second identical trial is only about 50 percent. It is only when the p-value in the first study is 0.001 that the likelihood of seeing 0.05 or less in the second identical trial is at least 90 percent.

These calculations are the basis of the frequent FDA guidance that, to demonstrate persuasive evidence for efficacy, a sponsor needs to provide two trials with 0.05 or less or one trial with a very, very small p-value.

But what if the event was not the primary endpoint in the study? What, in fact, if the event was not even precisely defined before the start of

the trial? What if the trial was not adequately powered to detect a treatment difference for the endpoint? What does a p-value mean under these circumstances?

Unfortunately, this happens quite frequently in clinical trials under a variety of circumstances. But it is particularly true in the analysis of adverse events. So lets make a list of things to worry about when using p-values to compare the frequency of adverse events in a clinical trial.

First, there are literally hundreds of adverse events in a clinical trial and, therefore, there are hundreds of possible comparisons that can be made. Now, this is classically referred to as the multiple comparisons problem. For example, if a typical large-scale clinical trial yields as many of 500 individual terms describing adverse events and if a p-value were calculated for each pairwise

comparison, one would, of course, by chance alone, expect about 5 percent of the terms, or about 25 events, at a p-value of 0.05 or less and 1 percent of the terms are about 5 events to have a p-value of 0.01 or less.

The second issue in interpreting comparison of frequency of adverse events is the fact that adverse events are spontaneous nonadjudicated reports. Now, adverse events are reported at the discretion of the investigator and then translated into standardized terms. There is little uniformity on how an event is identified, defined or reported and this uncertainty increases when the event is in a field remote from the investigator's focus.

Now, some of you may believe that you can fix this problem by carrying out blinded adjudication of events after the fact. Unfortunately, the rules guiding post hoc adjudication are inevitably influenced by the knowledge that a treatment difference has been seen. In fact, any bar set by a post hoc process,

is capable of magnifying or diluting an effect.

For example, if you set very strict criteria, a committee could reduce the number of events and, therefore, reduce statistical power. By setting very loose criteria, the committee can include many questionable events and reduce the magnitude of a treatment difference.

To make things more complicated, adjudication committees do not generally examine individuals who did not report an event to make sure they didn't have an event.

The third issue in interpreting comparisons of frequencies is that some signals are apparently only if adverse events are grouped together. Now, that is not much of a problem if the difference is fairly straightforward and focuses on one single event. But things can become a little bit more complicated if the analysis requires a combining event and combining trends across two or more events in order to reach some magical level of statistical significance.

Now, the problem is that these groupings

are frequently constructed after the fact, making it possible to include only events that showed the trend the investigator is interested in. For example, if an investigator believed the drug increased the risk of a major cardiovascular event, he or she might first look at myocardial infarction and stroke, but, finding little difference here, he or she might be tempted to look at other related events; for example, not seeing a difference in myocardial infarction, an investigator might be tempted to broaden the definition of a myocardial ischemic event to include sudden death or unstable angina if the differences between the groups supported some predetermined judgment.

Similarly, not seeing a difference in stroke, an investigator might be tempted to broaden the definition to include a TIA. But the possibilities of grouping is very, very large and the possibilities of finding something, if you want to be creative, are also quite large, even though these differences may be related to the play of chance.

As a result, the definition of grouping may vary from study to study. Now, some investigators try to fix this problem by setting up

a uniform definition to be used across all studies. But when the definition is developed after a concern has been raised, those creating the definition have frequently already looked at the data or have communicated with those who have looked at the data, and know either consciously or subconsciously what kind of definition is required to capture the events of interest.

The fourth, and what I want to focus on the most in my presentation, is the issue of interpreting comparisons of frequency of adverse events because the number of adverse events is small and, because they are small, they result in extremely imprecise estimates.

Now, you may think that investigators generally understand the difficulties of analyzing small numbers of events. For example, most investigators know that, when the number of events is small, the lack of an observed difference does

not rule out the existence of a true difference. We have been taught that this should be apparent by looking at the confidence interval and, as you can see here, the confidence interval is very wide and includes the possibility of benefit and harm.

So investigators, basically, consider these kind of data to be inconclusive. But what is generally not appreciated is that, when the number of events is small, the confidence interval is necessarily so wide that it may not truly represent the range of values that would include the true effect of the drug. As a result, even the finding of an observed difference does not necessarily prove the existence of a true difference.

To illustrate this point, this slide shows the effect size and confidence intervals required to reach statistical significance in a hypothetical trial of 3,000 patients assuming a range from a very small to a very large number of events.

Now, assuming the trial shows a statistically significant effect--that means that we are only going to look at this if a p-value,

let's say, is less than 0.05--the smaller the number of events, the larger must be the treatment effect in order for this effect to be statistically significant and the wider the confidence intervals have to be.

Put it another way, if the number of events is small, the trial will show a significant difference only if the treatment effect is very large and the estimate of the effect is very imprecise.

Unfortunately, when you look at adverse events in a trial, the number of events will always be small. This is because the trial, as you know, was designed to provide enough data to examine the primary endpoint, the trial produces a very precise estimate of, but it is not powered to look at any other analyses and, therefore, at the end of the trial, you get generally a less precise estimate of the secondary endpoint and an extremely imprecise estimate of any specific adverse event.

Now, you may ask, what is wrong with an imprecise estimate? Well, imprecise estimates are

fine if the intent is to withhold judgement until more data are collected to make the estimates more precise. But imprecise estimates are problematic if the intent is to stop and reach a conclusion.

That is because, when calculated in the usual manner, p-values and 95 percent confidence intervals are most easily interpreted in the context of a completed experiment. Unfortunately, the adverse-event data generated in a typical trial is not the result of a completed experiment. In fact, viewed from the amount of data needed for a precise estimate, the adverse-event data in a single study only represents a snapshot of an ongoing experiment to characterize the safety of the drug.

As a result, performing an analysis of adverse-event data is akin to performing an interim analysis of primary endpoint data in an ongoing clinical trial. Now, this is important because we know a fair amount of how to interpret interim analyses in a clinical trial and here I really must apologize to Tom Fleming because what I am going to

review here very quickly is borrowed heavily from his extensive work in this area.

But it is really important to think about small numbers of adverse events as an interim look on a global effort to characterize the safety of a drug.

Now, as you know, when you look at interim analyses in a clinical trial, one plots the treatment difference represented by a z-score against the amount of information that we have, and that is generally represented by the fraction of expected events.

We start the trial at zero effect and zero information. At the end of each interim analysis, we add a point until we get to get to the end of the study. Now, if we have assigned an alpha of 0.05 to the endpoint, we want to make sure that we evaluate the treatment difference seen at the end of the trial against an alpha of about 0.05 which generally corresponds to a z-score of about 2.0.

Now, some might think, naively, that, during the course of a study, the observed

difference between treatments will be so predictable that we would observe a linear march between the start of the study and the end of the trial. But know that when the amount of data is small, things tend to bounce around a lot, so much so that early results can be very misleading.

It is sort of like the situation of trying to predict the results of an election when only 1 percent of the precincts have been reported and they are not even representative. So, as a result, if we got excited about any difference in z-score more 2.0 early in the trial, we would be getting excited about effects that were not likely to be seen or sustained if we had more data even though a z-score of 2.0 would normally correspond to a p-value of less than 0.05.

In fact, the smaller the amount of data, the more things can bounce around a lot, the more it is likely that what we will be seeing will be due to the play of chance. Therefore, to prevent investigators from reaching a conclusion when the estimates are imprecise, statisticians,

particularly Tom, have recommended that investigators refrain from getting excited about nominally significant z-scores when the amount of data is scarce.

Specifically, they have proposed that boundaries must be crossed before we can feel comfortable that an effect seen early is likely to be present at the end of an experiment.

Now, Tom, in particular, has proposed a curvilinear boundary like this. There are many other boundaries that have been performed by others. But this is very, very commonly used in the United States. This represents a boundary with an alpha of 0.05 for a primary endpoint. It sort of looks like this. Because it is curvilinear, to be significant at the 0.05 level, the treatment difference must be extreme when the amount of information is small as would be the case early in the study.

However, as the trial proceeds, treatment differences required to conclude that there is an effect at the 0.05 level decreases and become

closer and closer to a z-score of about 2.0 at the end of the study.

Now, this is a very different thought process and a very different approach than getting excited about a p-value less than 0.05 no matter when you observed it during the study. For example, a z-score of 2.5--that is right here--would be meaningful if seen at the end of the study but it wouldn't be considered significant if seen early in the study even though the nominal p-value at this time is less than 0.05.

Now, if the number of events is small, the difference would need to be far more extreme--say, a z-score up here--to be meaningful at the 0.05 level.

Here is a specific example. This is an old cardiovascular trial. This is the Coronary Drug Project. It was carried out more than 30 years ago. It included a comparison of clofibrate, a lipid-lowering drug, and placebo on coronary events. At four separate times during the study, the difference in favor of clofibrate was

statistically significant at a nominal p of 0.05 or less. But, at the end of the trial, there was no difference between placebo and clofibrate. The difference seen early in the trial was related to the imprecision inherent when analyzing small numbers of events.

In fact, if a boundary had been used in this study, at no time during the trial would the treatment effect have crossed the boundary and led to the conclusion that clofibrate was better than placebo.

Now, let me say this kind of fluctuation early in a study is very, very common. There are even examples that at treatment has been associated with a nominally significant adverse effect which later was reversed during the course of the trial and became statistically significant at the end of the study.

Now, I should mention that the boundary that I have shown you is a boundary with an alpha of 0.05. This means, when the boundary is crossed, the p-value for the treatment effect is less than

0.05 not less than the nominal p-value that corresponds to the disease score that allowed the boundary to be crossed.

Now, for each p-value or each alpha, there is a separate boundary. The requirement for strength of evidence as it becomes more stringent, the boundary is shifted upward and to the right.

You might ask why am I going through all this. Because analyzing data derived in an underpowered trial raises the same concerns as analyzing data derived from an underpowered interim analysis in an adequately powered study.

The cardiovascular field is replete with examples of how misleading small numbers of events can be. Let me give you a few examples. For example, in an early pilot trial, the ACE/NEP inhibitor, Omapatrilat, reduced the risk of a major cardiovascular event by 47 percent when compared with an ACE inhibitor. As you can see, the confidence intervals are extremely wide because the analysis here was based on only 39 events.

Later, a definitive trial was carried out

that recorded nearly 1900 events. There was no difference between Omapatrilat and the comparator ACE inhibitor on the same endpoint in the same population.

Here is another example. In an early pilot trial, amlodipine reduced the risk of a major cardiovascular event by 45 percent, small p-value but wide confidence intervals. Later, in a definitive trial which recorded four times as many events, there was no effect of amlodipine on the same endpoint in the same population using the same investigators.

There are even examples when the effect seen in a pilot trial was reversed when the definitive study was carried out. Two examples. In two pilot trials, both in heart failure, one with the drug Vesnarinone, one with the drug Losartan, both drugs significantly reduced the risk of death--not a minor endpoint; death--by 50 to 60 percent. But these benefits were seen in trials that were each recorded fewer than 50 events and thus produced treatment estimates with extremely

wide confidence intervals.

When both drugs were reevaluated in definitive trials that recorded ten times as many events, both drugs were associated with increased risks of death, in one case, significant at the less than 0.05 level.

Now, notice that the confidence intervals of the treatment effect in the definitive trials do not overlap with the confidence intervals of the treatment effect in the early pilot studies. So here we have an effect, two examples, of an underpowered trial that showed a significant benefit whereas the definitively powered study showed significant harm.

Here is another example. This is a meta-analysis of a small number of trials looking at the effect of magnesium in acute myocardial infarction. A meta-analysis of a number of studies showed intravenous magnesium associated with the striking reduction in mortality, a 55 percent reduction in risk of death, but wide confidence intervals, a very small p-value, in a fairly large

study.

This effect appeared to be reinforced smaller treatment effect but wide confidence intervals and then, subsequently, in a definitive trial that recorded 4,000 deaths, there was a nearly significant adverse event of magnesium on the same endpoint in the same population.

Now, again, please note that the confidence intervals of the treatment estimate in this definitive study do not overlap at all, with the confidence intervals of the estimates in the earlier moderately sized study, and not at all in the meta-analysis. Again, this is really a reflection of the imprecision inherent in looking at small numbers of events.

Let me give you one final example because it actually deals with an adverse effect. In an early pilot trial with extended-release metoprolol--this is a study that looked at a very small number of events, about 20 events, showed a three-fold increase in the risk of hospitalization of heart failure in the metoprolol group compared

with the placebo group. Look at the confidence intervals here. They go from about Washington to California, very, however, nominally significant treatment effect.

When this trial was replicated in a similar population with exactly the same drug, exactly the same formulation, exactly the same dose, there was now a reduction in the frequency of hospitalization for heart failure. Let me just emphasize, this was recorded as an adverse event in this earlier trial.

So what have we learned from all this? Well, a couple of thoughts. To achieve statistical significance in an underpowered analysis, the effect size must be extreme and the estimate must be imprecise. Yet the more extreme the effect, the more imprecise the estimate, the less likely it will be reproduced in a definitive trial. That is why I think, of all the things that we can worry about in looking at adverse events, the most worrisome is the imprecision inherent in the analysis of small numbers of events.

Let me just close with a few final thoughts. You might ask, based on all of this, what should we do. Well, I think the first step,

perhaps the most important first step, is to develop an approach to analyzing data in trials with small numbers of events which actually accurately reflects the true imprecision of the treatment effect estimate and its statistical significance.

Let me just emphasize one thing, and I just want to put this as a proposal. In no way, would I propose this as a definitive solution but, to get the discussion going, this might be an interesting first way of thinking about this.

The conventional way of comparing small numbers of events is to calculate 95 percent confidence intervals followed by the derivation of the p-value. However, the conventional calculation of the confidence intervals incorporates into it a z-score that the investigator designates as the target value for statistical significance. For example, most statisticians, in calculating a

confidence interval, would simply use a z-score of about 2.0.

And they would do that because that is the critical value for the z-score at the end of an adequately powered trial with an alpha of 0.05. So what they would do is they would take this z-score and they will use it to calculate the confidence interval. What a lot of people, I think, fail to realize is that this z-score is not the critical value for decision making if one looks early in the same experiment.

Early in that experiment, the critical value for a z-score should be determined by the interim monitoring boundary appropriate for the information content, not the z-score at end of the study.

Now, if one uses the boundary z-score in the calculation of the 95 percent confidence intervals, the confidence intervals here will be much, much wider resulting in a p-value that will no longer be statistically significant. Now this is important because everyone talks about p-values

at these meetings. I showed you these data before. Conventionally calculated, the p-value would be 0.002 meaning the likelihood of chance alone being 2 in 1000.

Well, if, in fact, if one recognized that the data here really result in a very imprecise estimate and one incorporates the thinking process of an O'Brien-Fleming boundary into this, as a reflection of this imprecision, then the confidence intervals now truly reflect the imprecision in the estimate and now the p-value is a lot interesting than it was before.

Now, the use of boundary-adjusted confidence intervals would, I think, appropriately describe the great uncertainty inherent in the analysis of small-numbers events, hopefully markedly reducing the false-positive error rate.

In spite of using a boundary-adjusted confidence interval, adverse effects that are known to be characteristic of specific drugs would generally remain statistically significant. However, this approach, and it is just a thought

experiment, would not provide a way to interpret trends observed in imprecise data.

So, lastly, let me just conclude with some thoughts about what we should do with worrisome trends in imprecise data. The first thing we could do is believe in those that are biologically plausible. However, we need to be very careful here. Everyone knows physicians can always be relied on to propose a biological mechanism to explain the validity of an unexpected and potentially preposterous finding simply because it happens to have an interested p-value. Anyone who doesn't believe this, you know, I would be happy to show you overwhelming evidence that this is the case.

Second, is we could look for confirmatory evidence in other studies reminding that we shouldn't be selective. But, even if every study showed the same trend, how would you know that you had enough evidence to reach a conclusion? Some have proposed doing a cumulative meta-analysis in which each trial is considered to represent an

interim analysis on the way to a final judgement.

Indeed, Salim Yusef has proposed that, as each trial is added to the meta-analysis, that one use interim monitoring boundaries to interpret this cumulative meta-analysis. This has, certainly, a considerable amount of appeal.

Let me just emphasize. Salim has, in fact, underscored the fact that the conditions here are not identical those that exist for a true interim analysis. In the case of a true interim analysis, we generally know that the types of patients in studies are similar at all observation points. Here it is different.

In the case of a cumulative meta-analysis, the types of patients in studies differ across the various trials. So, as a result, Salim has proposed that, when reaching a conclusion based on data that has been combined across trials, that a boundary more strict than 0.05 be used.

Now, he has specifically outlined the importance of this using the example of intravenous magnesium. I showed you the data on intravenous

magnesium in myocardial infarction. When the early trials with magnesium were carried out, the z-score of greater than 2.0 was crossed early. As the cumulative evidence occurred, the initial boundary of 0.05 was crossed.

But then a large study, when added to the other cumulative analyses, brought this treatment effect down to a 0 level. So Salim, and others, in fact, have emphasized that, when you are using a meta-analysis approach and using intra-monitoring boundaries, that maybe one should require a p-value of less than 0.05 or even, perhaps, a small p-value.

Let me say that most of the effects the committee has seen over the past two days would not come even close to meeting these criteria.

Now, some of you may say, why not avoid all of this uncertainty and simply carry out an adequately powered definitive trial with the adverse event as the primary endpoint. Is this crazy? No; it is not crazy at all. Sponsors pursue encouraging trends. Most are disappointed,

but they will pursue them. Sponsors, therefore, should have an obligation to pursue discouraging trends realizing that most of them probably won't be confirmed either.

On a definitive trial can address ascertainment and classification biases as well as concerns about multiplicity of comparisons and imprecision of the data. However, can we really expect sponsors to pursue every adverse trend? There are some obvious limitations to doing this. Furthermore, if you could decide which adverse trend you wanted to pursue, how easy would it be to carry out the trial intended to definitively evaluate an increased risk of an adverse effect?

Can you imagine the consent forms for the IRBs for such a study? Some may say that we are being too stringent here, the that criteria of raising a safety concern need not be as stringent as the criteria for establishing efficacy. But I am not so sure that the criteria for establishing efficacy and safety should be that different.

As a rule, we are very strict in reaching

conclusions about efficacy because saying that there is a benefit when there is none means that millions will be treated unnecessarily and subject to side effects and cost. Now, although some might advocate being less strict in reaching conclusions about safety, please remember; saying that there is an adverse effect when there is none means that millions will be deprived of an effective treatment.

In conclusion, the findings of controlled trials are most easily interpreted when they represent the principal intent of the study. A non-principle finding is subject to many interpretive difficulties many of which we have reviewed; ascertainment biases, inflated false-positive rates due to multiplicity of comparisons and, the one I have emphasized the most, the imprecision of estimates inherent in the analysis of small numbers.

I think FDA, industry and academia remain in a quandary as to how to respond in a responsible fashion to observe differences in the reported

frequency of adverse events. Let me just emphasize, my presentation shouldn't be construed as favoring one particular side in all the discussions that have occurred. In my view, regardless of one's position, it is critical to understand the limitations of what we know and to resist the temptation to reach conclusions before we are justified to do so.

I think only by recognizing our ignorance will we be able to take the first step towards developing a rational approach that is in the interest of all patients.

Thank you. I will be happy to answer any questions.

DR. WOOD: Dr. D'Agostino?

DR. D'AGOSTINO: Thank you very much, Milt. I have a couple of questions that I think, I hope, are relevant to our deliberations. In terms of your sense of large and the idea of chasing after a safety event and making more out of it than one should, we have a study approved where there was a serious up-front prestated deliberation to

make sure they had good ascertainment and adjudication of cardiovascular events, and they come up with 45 versus 25 events, carefully collected.

I am struck by that's being small, but I am also struck by the carefulness in which it was done, say, as opposed to the APD where they did an interim analysis that has those problems. Could you comment on, say, the approved study?

DR. PACKER: I think that, when you have incomplete data, as you would if you have small-numbers events, you need to be a lot more careful about the thinking process. That doesn't mean you can't make judgments. It doesn't mean you can't incorporate a set of principles that would guide decision making by looking at the totality of the evidence and bringing to the process what you inherently believe. I think that is what the committee needs to do today.

What I really wanted to address, however, is how hard this is and that the normal reliance--as you know, clinical investigators,

because they don't understand p-values, rely on them. What I am trying to do is to explain that, in fact, we are less certain about what we know here than we, perhaps, should be.

DR. D'AGOSTINO: But that is on the approved, studies, it was reasonable, too.

DR. PACKER: I think you need to take that in the totality of the carefulness in which it was done, the prospective nature of it. But, remember, in all the examples that I showed you, the trend seemed sometimes very striking trends in early pilot trials that were prespecified, adjudicated endpoints but, because they were small-number events with very imprecise estimates, the definitive trial was non-confirmatory.

So just because it is up-front and predefined--

DR. D'AGOSTINO: That is my question, yes. That is my question. You still end up with small numbers. Let me have just a couple of other questions. The second question is really bothering me very much in terms of how we would recommend

trials. If you decide--if the group decides and suggests to the FDA that there should be more trials, more randomized clinical trials, the sponsors are, then, going to have to go back and say, well, they are going to set up a trial saying the null hypothesis that the relative risk is 1.0 versus the relative risk is not 1.0.

Now, the best thing a sponsor can do is to run a very sloppy study and they will accept that null hypothesis because the confidence intervals will so wide and they will contain 1.0. The alternative is to sort of do a noninferiority type idea that you end up the study, you end up with the confidence interval, and that confidence interval has to be below something like 1.3.

Do you have advice for us if you did this sort of second approach? We are dealing with rates like 1 percent. Could we live with a 1.3 relative risk that you rule out, a 1.3 relative risk? People may be dying if you do that. So how do you respond to that?

DR. PACKER: I wish I knew the answer to

that. I think that it depends on the type of adverse reaction. It depends on the particular drug. It depends on the vulnerability of the patient population. All of these need to be factored together with the actual feasibility of doing the study.

The one thing I would say is that one learns very little by doing a lousy trial. So, doing a good trial is the only way to get a reasonable answer or reasonable estimate of the answer.

DR. D'AGOSTINO: Just one more. I will make it quick. In these trials, in many of these trials, people just won't stay in the trial. Can you give us some advice on how to deal with the drop-out--now, there are rules that you could say, the individual wants to leave, has decided to leave because the blood pressure is building up or because of G.I. problems building up.

To say, we are only going to look at that individual for 14 more days after they leave, to me, is a problem because if the blood pressure is

building up, they may be on their way and it may take two or three months before they get an M.I. and so forth. So you have got the sort of dropouts, terminations, that are part of the protocol but you also have the individuals who just stop coming. And they could be substantial. So, any advice to us?

DR. PACKER: Gee, as you know, when we do trials for superiority, the effort that we put into adherence is extreme. We really want people to stay on treatment and we organize the trials to do everything we can to ethically and reasonably maintain adherence.

I take your point that, if the trial were a noninferiority trial, it is possible that the investigators and sponsor might be less motivated recognizing that poor adherence works in their favor. I think that there needs to be a reasonable effort--I mean, you can maintain adherence in most trials if you really, really want to.

DR. D'AGOSTINO: Thank you.

DR. WOOD: I suspect we are not going to

solve that problem today. Dr. Shapiro?

MS. SHAPIRO: Just a comment on your comment. We all know, of course, that the Federal Regulations require that participants be allowed to withdraw and not be badgered into staying. But what I really wanted to talk about was your observations about how it is wrong to suggest that we should not chase safety quite as rigorously because we will, then, deprive ourselves and others of information and access to effective treatment.

I don't think it is as simplistic as that, in that, when we are looking at potential harm or safety problems, we have to look not only at likelihood that it exists but prevalence and severity.

So I think that your response to that approach has to take account of those factors as well.

DR. PACKER: Let me try to reframe my response. You can't isolate benefit from risk. The judgment as to whether a drug should be used on an individual basis or on a population basis has to

be the relative value of benefit to risk. You may decide that you don't even want to pursue a safety trend in a non-fatal event when you know the drug prolongs life. That would be a very reasonable judgment.

On the other hand, you might want to vigorously pursue a very serious safety is in a drug for a symptomatic or cosmetic condition. So the risk-to-benefit relationship is the one that has to be vigorously defined.

MS. SHAPIRO: Right. I am sure you will agree with this; you also have to factor in prevalence of the condition and likely use of that drug in the population.

DR. PACKER: That's right. But it is always--it is risk to benefit. The goal here is not to say that the risk-to-benefit relationship can be altered, simply because you want to emphasize one part or another, has to be in the context of the clinical problem and looked at from the patient point of view.

DR. WOOD: Dr. Cush?

DR. CUSH: I have two questions. One, I need some education. You were frequently referring to very wide confidence intervals where it didn't

seem so wide. It was only, like, 0.3 and 0.4 where, obviously, when it ranged from 1.0 to 8.0, that is very wide. But you used those terms in both situations. Could you explain the differences there?

DR. PACKER: Actually, I have used "wide" to refer to extremely wide, moderately wide and wide.

DR. CUSH: And narrow would be--

DR. PACKER: Narrow is less than wide.

DR. CUSH: Okay.

DR. PACKER: Let me try. All the examples that I showed you that I characterized as wide truly reflected estimates that had a high degree of uncertainty associated with it. On the benefit side, benefits that range from an 80 percent reduction in risk on the high side to a 20 percent reduction in risk--remember, and I guess I should emphasize this and I guess Tom would reinforce this

dramatically, the concept of how these curves looked like in terms of the width is not symmetrical on both sides of 1.0. The lowest you can go below 1.0 is 0. So wide confidence intervals below 1.0 can be 0.2 to 0.8. Those would be wide confidence intervals. There is no limit for estimates greater than 1.0, so you can have 1.0 to 24 on the adverse side of this. So you have to sort of think about what is wide differently when you are looking at estimates below 1.0 than when you are looking at estimates above 1.0. Maybe that would be helpful.

DR. CUSH: That does help. Secondly, you have told us that when we are dealing with low-numbers adverse events and that being very imprecise and hard to make conclusions from, is it even less valid or even greater error to, then, take that data derived in one situation, like in an Alzheimer's trial, and then try to generalize that to the general population?

DR. PACKER: But we do that all the time. There is a general sense that efficacy is not

extrapolatable across diseases but safety that is not disease-specific is extrapolatable.

Let me put it this way. If we didn't do that, the problem that I put forward would be really impossible, really impossible. So I actually feel comfortable extrapolating safety data across indications as long as the safety item is not disease-specific.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Thanks. That was actually a very informative presentation and I can confirm the distance from Washington to California.

There are really two questions here that I think we need to bifurcate. One of them involves the scientific question of getting at the truth, whatever that is. I appreciate everything you say and, prior to a drug being approved, at least ideally, there would be adequate time and resources to do exactly what you are proposing.

But there is a second question which is how to inform clinical and regulatory decision making based on imprecise information following

approval because, in that setting, a daily decision is being made by patients and their physicians as to whether or not they need to take the drug.

One question about how to approach these sorts of imprecise data when, in fact, a daily decision is occurring, is can you take the confidence bounds for both the risk and the benefit and integrate those over the public-health hazard and the public-health benefit to try to incorporate the entire--both the point estimates but also the uncertainty about them into the regulatory decision-making process?

DR. PACKER: Oh, wow. Just a couple of comments. One, the precision of the estimates on efficacy is almost always more precise, much more precise, than the estimates on safety. So you have this very precise estimate on efficacy. You have this very imprecise estimate, in general, on safety. And you try to sort of integrate them and you have to now weigh them because it could be that the efficacy thing you are looking at is really important and the safety is sort of not very

important. Or it could be other way around, the efficacy is sort of very small--the efficacy is small, but the safety is a big risk.

DR. SHAFER: That is exactly the question.

DR. PACKER: You might think that someone in the world might be clever to create a statistical model that would allow that to take place. I am actually much more comfortable with people doing that than statistical models doing that. Somehow, people have the ability to integrate all of this, especially a group of people have an ability to integrate this, much better than any mathematical model.

I would be very uncomfortable if someone were actually to propose a mathematical model that replaced the human, very important human, element here.

DR. WOOD: Dr. Farrar.

DR. FARRAR: Every example that I have seen to date in looking at the risks in overinterpreting data seem to go from being a positive study to a negative study. I wonder about

the other way around and whether there are any inherent differences in thinking about it the other way around, the bottom line being that if you have ten studies that show no safety issue with a well-measured process, whether you can then say, well, maybe the 11th study is going to show it somehow.

DR. PACKER: I think you need to find out how much information there is in each study, how easily or how appropriate it is to combine the data across the studies to determine how precise the estimates, after you have collected and integrated all of the data, and put that into a judgement as to how much data you actually need to be confident about the precision of the estimate.

So there isn't a uniform way of thinking about. It is not like you will know it when you see it. There is some guidance, some mathematical guidance, that needs to be incorporated into the thinking process.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: You know, I am not nearly

as sophisticated, really, Milton, as you are about this sort of thing nor about some of the people in the room, but I am a little bit concerned about some of the examples. I will give you one. I don't think ISIS 4 was a definitive trial of magnesium, because I know something about that. We did the MAGIC study which was a very large study.

Like ISIS 4, it was negative, but ISIS 4 was substantially different methodologically in terms of when that was given. I think that example actually, to be honest, is fairly misleading as a result. I think it is an example of a stopped clock is right twice a day. But, yeah; it came out right.

But I a worried if that is the basis for this--that kind of thing is the basis for this discussion across more of the landscape.

DR. PACKER: Let me emphasize, Mike, that I knew that if I picked one study and gave you an example of one st that I would be at great risk because everyone knows something about these studies more than what I know about these studies

although some of the studies I actually mentioned were studies I was personally involved with and think that I know a little more about them.

So I just wanted to--I would not overemphasize--and, in fact, one might appropriately underemphasize--the magnesium example. But the other examples, time and time and time and time again. It is just like reaching conclusions during a very early part of a study based on interim monitoring. When you have small numbers of events, the estimates are very imprecise and may not reflect what happens at the end of a complete experiment. That is just a general principle.

I take your point about ISIS 4 but the number of examples here is just overwhelming.

DR. WOOD: It is important, Milton, to remember, we have replication for two of these drugs and these safety signals here. So it is not just single studies.

Dr. Furberg.

DR. FURBERG: Milton, I think that was a

great presentation. I think, for balance, it would be nice if you can have examples showing the other side, how trends in smaller studies were confirmed in definitive trials. And I know plenty of those.

DR. PACKER: Oh, yes.

DR. FURBERG: That was never discussed. You are painting a dark picture saying you can't trust smaller studies. You are right. You never know where you are going to end up and you need to be careful. But don't say that you can't rely on those.

DR. WOOD: I was actually on the advisory committee that turned down Vesnarinone, that looked at that study. There were lots of issues that came up at that time that led us to do that. So it wasn't just that there was a study that was compelling and that people went with that.

Dr. Nissen?

DR. PACKER: Curt, let me just say that--I think your point is very, very important. What I have not done is shown many, many examples of interim monitoring in trials where the early

results were reflective of the endpoint. I have not shown a whole host, probably more than I could think of, of all of the pilot trials where the initial trends encouraged someone to pursue it and that the second study was, in fact, very confirmatory.

Let me just make my point clear. It is just not as reliable as we think it is. It is not that it is worthless. I do not want to say that. If I have implied that, then I do not want to imply that. I just want to say that the risk of error early when you have small-number events is much, much greater than when you have a much more precise estimate at the end of the trial.

My plea here is that when you don't know, the best thing you can do is say, "I don't know." And that is my only plea.

DR. WOOD: Milt, when you have two trials that replicate one another, with a p-value of less than 0.05, if that was an efficacy endpoint, we would approve on the basis of that; correct?

DR. PACKER: That's right.

DR. WOOD: But you are telling us that, when it is a safety endpoint, we should not act on that. I think it is counterintuitive.

DR. PACKER: No, no, no.

DR. WOOD: Hang on. That seems to me counterintuitive. We have, for two of these drugs, two randomized trials that replicate the outcome. In three of the four trials, the outcome was predefined, adjudicated and so on. That is about as good as any drug that has been approved on the U.S. market that I can think of.

DR. PACKER: Let me just add one dimension, Alastair, to the thinking process and that is that when you have a p less than 0.05 on two trials, on the primary endpoint because it is efficacy, you have two trials that were designed for the endpoint and have fairly narrow confidence intervals and precise estimates.

That is not the same concept as having a p less than 0.05 on two imprecise estimates which are combined together.

DR. WOOD: No; I understand that very

well. I think we all do. The issue here is both of the second trials--both of the second trials--were designed to test the safety issue that was in the first trial even though they were efficacy studies. So it is not like they were just two trials that fell on the ground from Mars that arrived with something. These were designed, at least according to the sponsors, to check for that outcome.

So I think you are overselling the point a bit.

Let's move on. Dr. Jenkins?

DR. JENKINS: I found the presentation very interesting and I wanted to probe a little bit further on the APPROVe study because that is the one that I think we were feeling very comfortable with the finding in APPROVe. Yet, I went back to Merck's presentation, and their prospective plan was actually to combine three studies that were going to be placebo versus rofecoxib in three different populations.

Their plan was to have 25,000 patients to

evaluate the cardiovascular signal. Now, in APPROVe, presumably, they had stopping rules that the Data Safety Monitoring Committee saw an extreme effect that met those criteria so they stopped the study. But I am just interested in hearing your thoughts about how should we interpret APPROVe where the stopping rule is met for an individual study when the prespecified plan was to have three studies combined for 25,000 patients.

DR. PACKER: Gee, I must say that I am delighted to have everyone ask me the hard questions for this afternoon. I sort of think that this is what this committee has to do. I only wanted to add a dimension to the thinking process here. I don't come with any answers on how to put all of the data together. All of the points on how to synthesize these data, I am very comfortable with the human process of doing so as long as the human process incorporates an understanding of how difficult and imprecise this is and the fact that, in the past, although it has led to predictions that came true, it also led to predictions that did

not come true.

DR. JENKINS: I think, more specifically, the point I was trying to get you to comment on is not the overall interpretation of the rofecoxib data but the fact that there was a plan for 25,000 patients in three studies. What I am trying to understand is how should we, then, interpret a finding from one of those three studies where an interim analysis crossed the stopping boundary and met the criteria for stopping the study. What weight should we give to that finding in that single study?

DR. PACKER: I don't think there is a precise answer to that. Any time you deviate from your preplanned attack on the conduct of analysis of a trial, you weaken, to varying degrees, the precision of the estimate and the confidence you have in the data that you are looking at.

DR. WOOD: Dr. Nissen?

DR. NISSEN: Milt, there is an additional subtlety here. Let me see if I can drill down with you on it. What we have here is a class of drugs

where we have multiple trials within the class. So what we are asked to do is not necessarily, in some respects, for each individual drug, say, well, do we have replication or not.

But if we take the position that this is a class effect, then we have got four, or perhaps, five trials. This came up once before. It was kind of controversial. I think you may have been on the committee at the time when we had the angiotensin-receptor blockers for renal protection. What the two companies did with two different drugs is they stipulated that the other could use the data from the other company's trials as supportive.

So the reason that this is really much harder is that we have a lot of trials here. We may not have reached all the evidence in an individual drug, but we have trials across the class of drugs. I wonder if you have any thoughts about this because it is obviously a difference between studying a single agent and studying a class of agents.

DR. PACKER: I think that, Steve--I mean,

that is why the process works best when there are human beings involved in the thinking process. There is no predetermined sense that one should bring to the process--that you confine the analysis only to one drug. What you should allow yourself to do is look at the data with one drug, look at the data with drugs that you think are related.

If there are data that you think are in a drug that really isn't related, you might want to analyze that separately or do it both ways to see if it is consistent. There is no statistical formula that can guide the very important human process here.

My major point is that the precision that most clinical investigators think exists here isn't as precise as we think it is. But that doesn't mean that you--and Curt would emphasize this--that doesn't mean that you can't put together your own picture of the totality of the data and bring to it a sense of whether it reaches some critical level of concern.

In the absence of precision, you have got

to do that. But don't forget inherently that the data are imprecise.

DR. WOOD: Curt, do you want to say something else? No. Then let's move on. The next speaker is Bob Temple who we are going to confine to his seat.

DR. TEMPLE: Alastair, I have a question. What am I supposed to do about my slides? Can someone show them for me? I will delete many of them.

DR. WOOD: Okay. You can come up here if you do it quickly.

DR. TEMPLE: I don't care where I'm from. I really don't.

DR. WOOD: Then Kimberly will work the slides for you.

DR. TEMPLE: Okay; if Kimberly will do that.

Issues in Projecting Increased Risk of Cardiovascular Events to the Exposed Population

DR. TEMPLE: I was not in any way trying to address the main issues the committee is

grappling which is about what to do about these drugs. But it seems to me you can't help noticing that there is some data we would all like to have that we don't have and that is what I was trying to address.

Obviously, the main thing we are worried about is the effect of the COX-2-selective NSAIDs on cardiovascular outcomes, notably death, stroke and heart attack. But are particularly interested in the single drug effects, whether they are all the same. We are interested in whether we are looking at true class effects of differences.

We also can't help noticing there is not a lot of long-term data on the nonselective NSAIDs and, of course, has been pointed repeatedly, some of them are sort of selective anyway.

There is major interest in possible differences in the subpopulations that might be a different risks. I think there are mechanistic considerations, how much of this is really likely to be platelets and could there be a blood-pressure effect. The importance of that, to me, is that it

is not quite clear what to do about platelet effects, but, conceivably, you could manage a blood-pressure effect if that was a problem.

There is a lot of importance and interest in the dose and dose interval. And it is important to think about how long studies have to be to detect these things. Obviously, some of trials seem to have shown things in a matter of seven or eight months. There is some suggestion that some of the effects need much longer to detect.

Skip the next one.

With respect to cardiovascular effects, the main question is whether everything is really answered. You know, there are lots of studies, as Alastair was pointing out. They are not perfectly consistent, maybe, but there are a number of studies with a number of drugs that seem to be showing the same thing.

I guess, to me, they don't seem entirely consistent. There are a number of possible reasons for that. One is that there really are differences between drugs, or at least between doses. Another

is that even the best controlled studies sometimes give different answers. Another is that small effects are difficult to evaluate in epidemiologic and even controlled studies. Then the last is that the effects may be population-dependent. That has been discussed.

So it does seem to me there is more to learn. Skip the next. We all know that. Platelet effects.

One of the things that seems important to pin down and I don't think it has been pinned down yet is the possibility that blood pressure is a significant part of all this, that there is some impression that Vioxx has bigger blood-pressure effects than the other drugs, but I don't think there is what we would call adequate data on the effects of all these.

By adequate data, I mean data that gives you information about the effect of drug over the entire dosing interval, that has pinned down dose response and that has pinned down the effect of different dosing intervals. There is an

impression, though, that these drugs can reverse the effect of other anti-hypertensives, perhaps, especially, ones that work through the renal and angiotensin system. They seem to have, at least some of them, an effect on blood pressure generally and then there are isolated reports of hypertension in trials reported as adverse reactions, clearly more common in the treated groups.

I have a bunch of slides showing that elevated blood pressure is bad for you. You can deduce that from epidemiologic effects, from a mountain of clinical studies. The most recent study that of interest, which I will not describe--keep going--in detail is a study that Steve Nissen knows about called CAMELOT which you can read as saying that a change in blood pressure of even 5 millimeters of mercury systolic and 3 diastolic might have a reduction of about 33 percent in the kinds of events we are talking about in people whose diastolic pressure is only about 100.

That is not definitive. This is a subset

of the data and you can look at my slide to see what I did.

As I said, we don't know as much about the blood pressure as we should.

So a crucial question is in the larger assessment of cardiovascular effects; what can we really study more. My own view is that, given VIGOR and fairly consistent epidemiologic findings, it would be difficult to study 50 milligrams of rofecoxib. I doubt you could write a proper informed consent.

I take Milton's concern to heart but I guess my own view is there is probably enough information about that. But what you could with respect to other things depends on what you believe.

Suppose you believe that the cardiovascular risk of 200, 400, of celecoxib is not entirely clear. One polyp study says yes and other studies are not so clear. And you believe, also, that a class effect is uncertain or, more particularly, that the effect might not apply to

certain doses and certain dose intervals even if you are inclined to believe that the class does have a problem.

If you also believe that more needs to be known about the long-term use of all NSAIDs, including those that are nominally COX-2-selective and those that are not, if you believe that new COX-2-selective agents conceivably could be developed with appropriate information, and if you believe the pharmacology gives hypotheses that need to be tested, not necessarily just believed--sorry Garret--then here is what you might be able to do.

Again, I am not, in any way, saying who should do this. This will be a massive undertaking. But it does seem to me that there is information we all collectively need as a community. So I am calling it an ALLHAT study for anti-inflammatory drugs.

This is just one of what people could dream up as what might be compared. The drugs, it seems to me, one might think about putting in it include ibuprofen, which we think probably ought to

be neutral, not bad. It may not have the platelet effects you want. Naproxen--I am embarrassed to say this but I am letting myself be affected by the epidemiology studies. Naproxen sort of looks good. You might even say it is at least a placebo, but I am not quite ready to say that.

Diclofenac seems a good model of a regular NSAID that is really COX-2-selective, at least to a degree. Celecoxib possibly at more than one dose, although, maybe for caution, one would want to think about the lower dose first. Then I have two other groups that I will be interested in people's comments on, and I am not totally sure you could bring these off.

But could one include an aspirin full-dose study. We know it is an effective agent in arthritis accompanied by a proton pump inhibitor. Now, you would have to first show that proton pump inhibitors really do block the ulcerogenic effects of aspirin. That is a short-term study and maybe one could do that. So I will be interested in whether people think you can bring that off.

The reason for doing it is we know the effects of aspirin are not unfavorable and we think they are probably favorable in at least many

populations, in populations at high risk and probably not unfavorable in people at low risk.

The last one that seems worth considering, and my understanding is that, in many parts of the world, at least osteoarthritis is treated this way, to use acetaminophen plus codeine added as needed and try to do something about the constipation.

That would be as close to a true placebo group as I think you can get in a setting like this. So it seems quite interesting.

It is worth saying if one had a new single agent, my suggestion, and one still thought that drugs like this should be developed, that the single agent might be compared to naproxen and I would still hope for one of the other last two comparisons as a true placebo.

Obviously, these are all people who need chronic pain medications. You would want O.A. and R.A. stratified. I don't believe you could use the

APAP group for rheumatoid arthritis but others may not agree with that. You probably want to study a range of cardiovascular risks but you probably would want to study the lower-risk people first.

The reason I say that is anyone with known coronary-artery disease really has to be given aspirin just because that is part of treatment and it isn't clear yet, to me, how aspirin interacts with the COX-2-selective drugs. You would think it would make them unselective but the data don't seem to necessarily say that.

A good question is how big the sample would have to be and that depends on what you want to find out. If you are really trying to compare the drugs with a true placebo, they wouldn't have to be that large to rule out, say, a two-fold risk or something like that. We have seen studies with about 1,000 per group that have distinguished between drugs. So that is not so huge.

But if you really wanted to get at whether one drug is a little bit different from another, you are talking about studies of massive kind. I

have asked various numerically qualified people and the general impression is that if you wanted to rule out a 20 or 30 percent difference, you are talking about 50,000 per group. That is beyond my hopes even for ALLHAT 2.

Obviously, the outcomes of major interest are cardiovascular death, stroke, AMI and bleeding. I have heard some thoughts that maybe heart failure should be looked at in addition but I wouldn't make that the primary endpoint. I think you can look at that separately.

A big problem is what to do about blood pressure. My first thought was that you would monitor it and treat anything over 120 over 80, but that really isn't standard practice. So a question I would raise is whether one could leave people to go to 130 over 90, would that be acceptable.

A question one could raise is why do this at all? Do you really need these drugs? We have heard fairly strong feelings that G.I. intolerance is not trivial. But my answer is more that we really don't know enough about the whole range of

these drugs. There is no question that people are going to get something for their arthritis. I am not entirely comfortable with looking at the data and saying we know what we need to.

You could sort of deduce that naproxen usually looks pretty good. It usually beats what is there except we just heard about a study where it was a little worse. But it is not clear where ibuprofen comes. It doesn't show the same thing. It seems to me there is a serious population need to find out about these things and to understand more whether all selectivity is the same.

We have been through diclofenac at length and it is not clear what one needs. So I think the idea of doing a large study has weight.

If you believe that it is really all settled, that cardiovascular risk is clearly increased with all of the COX-2-selective agents, ignoring for now which ones are actually selective, there still are things one might want to know.

It might be of interest to do a study that still would have the ibuprofen and naproxen groups

and might still have my aspirin or APAP groups. One might consider trying a celecoxib with the addition of aspirin. I know the results of that have not shown that any adverse effect seems to be mitigated, but that still doesn't make much sense and it might be something one could still want to test. It would seem that if you added aspirin to a selective agent, you ought to have a de facto unselective agent. Of course, that presumes mechanism and you shouldn't presume mechanism. You should test it.

Anyway, those are my thoughts. I think my main point is that there is really a very important need for better information on the whole array of these drugs and the kind of study needed to do that is mind-boggling large. However, people are already undertaking studies with 25,000 and 30,000 patients already. So it is not as outlandish as I would have said it was before we started this process.

Thank you.

DR. WOOD: Okay. I am just interested,

why didn't you suggest a PPI with naproxen? For your ALLHAT study, why didn't you suggest a PPI with naproxen?

DR. TEMPLE: That is a fair question. I think the answer on--what did I suggest it with?

DR. WOOD: With aspirin. It doesn't matter.

DR. TEMPLE: I will tell you the reason. Full-dose aspirin is just plainly impossible to use because of massive G.I. intolerance. I believe, historically based, it is worse than we expect with naproxen. So I thought you had to do it there urgently. You could do it with naproxen, too. That would be okay.

I have to point out that we do not have definitive labeling or evidence that those drugs really do prevent this but we have heard about some studies that suggest it. I do think that is an early thing to discover.

DR. WOOD: Okay. Understood. Let's move straight on to Bob O'Neill's presentation who also is going to do it from his seat.

Issues in Projecting Increased Risk of Cardiovascular Events to the Exposed Population

DR. O'NEILL: I won't go through the

slides. I might point your attention to a few of them. I will try and do this in five or ten minutes.

DR. WOOD: Do you want us to have the slides up, Bob?

DR. O'NEILL: What I was asked to do is essentially provide a framework. This is a very difficult problem of projecting risk to the population. Very little has been published about how to do this appropriate so I was intending to go through sort of the logic and the framework of how you might think about this.

It requires the integration of exposure data at the national population level and it needs information relative to how long people are on drugs and it uses information from the clinical trials as well as from the epidemiology studies to the extent that they are relevant to the question that is being asked.

This is a very difficult problem. It was not intended to give any estimate, any single number. It was intended to show how hard it is to get there and, at the end of the day, how variable and sensitive the estimate might be to all the assumptions you have to make.

So I used the Vioxx VIGOR and APPROVe studies as an example of the process that one might go through. I made the point that event definitions and many things matter. But I guess if there is anything that I would like people to take home is that time matters. The hazard rate matters. And the hazard ratio matters as a function of time when you do any of these projections.

I would just recall two slides. One would be the VIGOR study which is Slide 12 so that everybody could remind themselves and Slide 16. The VIGOR study shows a separation of curves. Behind that is what is called a hazard rate. I believe the data supports that the escalation of the risk increases with duration of exposure.

Merck and we have talked about this in the past and sort of have different views of this, but we seem to feel that that risk does escalate.

That does not mean that there is no risk in that picture early on. I think David Graham has made this point that it may be a power issue but, nonetheless, it is what it is and I am not convinced that the epidemiological studies at this stage add anything to our knowledge about early risk for the points I made yesterday because I think time zero matters in terms of looking at the risk, in terms of how long you are on.

The next slide is Slide 16 which is the APPROVe study. Similar pattern, only delayed a year. So instead of the curve separating at approximately six months, four months, they separate a little later on. The idea here is that the relative risks that are summary relative risks for both of these trials, for VIGOR, for thrombotic event, it is approximately 2.28 and, for APPROVe, it is approximately 1.92 for confirmed thrombic events is an average relative risk averaged over

all the time points so that the relative risk at different times is a function of time.

That is an important concept when, then, you go and you look at the national projection of how many people are exposed for how long a period of time. I won't go through that because they are in the slides. But we have no data in the United States to do this. So we did a projection based upon the IMS National Prescription data, another separate database that allowed us to look at how long exposure, success of exposures, might be to get an idea of how long individuals may stay on the drug.

Surprisingly enough, a very small percentage of the millions of people that are prescribed the drug are on the drug for more than a year. That is in one of the slides on the Caremark. So what this meant is you multiply all these estimates which, essentially, are time. We calculated a time-specific difference in absolute incidence rates for the different trials, made a projection and essentially used in that projection

a number of assumptions many of which are not verifiable, and then came up with some crude estimate of what might even be an upper bound on a confidence interval for any estimate.

We probably don't believe it because there is no real methodology to support that estimate but nonetheless to say that an estimate is very variable.

So the bottom line, and the conclusions here, given the time frame, is that purpose of the projection effort was essentially just to provide--this is the last slide; it is Slide 47--it is essentially to provide a framework for considering how you would think about developing an estimate and to provide a range of estimates and, also, essentially, to point out that there are many limitations to any estimate that you would provide.

We are not supporting any, or putting forward any, one estimate but I do believe that we need to understand this problem by moving away from summarizing nonproportional hazards in person years. It is not a good idea. It begs the

question as to whether the risk is constant or whether the risk is dependent on time.

If there is one problem with the epidemiological literature, it constantly reports person-year risk as opposed to every one of the clinical trials we have seen presents a Kaplan-Meier curve that looks at the time-dependent risk. Unless you understand that, you can't come to grips with comparing one drug to another.

You can't come to grips with comparing a drug to itself. If you look at the VIGOR study relative to the approved study, they are in different populations. One is in a population of R.A. The other is in a polyp prevention trial. One is at 50 milligrams. The other is at 25 milligrams.

There are many things that need to be sorted out. So the point here is that this is a very difficult exercise to project. This was just a framework to say, here is how you might think about it. Most of the estimates are fraught with a lot of danger and have to have many caveats placed

on them were you to bank on any one estimate alone.

That is pretty much my bottom line.

DR. WOOD: Bob, just to make sure everybody in the audience understands what you are talking about with estimates, what you are talking about are absolute numbers of people--

DR. O'NEILL: An estimate of the absolute numbers of individuals that might have been at risk and had these events if they were exposed--if they were exposed. This is a model projection.

DR. WOOD: Right. I just wanted to clarify that. So it is not the relative risk. It is not the same as what Milt was talking about.

DR. O'NEILL: Right. Exactly. This is a long discussion to get into the concept of attributable risk in its own right. Given the time, I wouldn't be able to do that.

DR. WOOD: So you are talking about the number of people, these sort of numbers that are out there.

DR. O'NEILL: Right; to go through that exercise. It is hard enough to interpret a single

study or a collection of studies. To go to an estimate of what the increased number of events might be at the exposed level is what this effort was about, all the different, five different separate interlinked but disparate databases that you would need to get there to make this kind of an estimate.

DR. WOOD: Okay. Good. Thanks.

DR. WOOD: We will take a few minutes, a very few minutes, for questions to the last two speakers and then we will take a break and be back. So the panel needs to remember that they are eating into their break.

Dr. Nissen?

DR. NISSEN: Quickly, Bob, Bob Temple. The difficulty, of course, in the ALLHAT study is that it is very--it seems unlikely that it will get done. So the question is, putting some constraints on this, and I thought about this last night in some detail into the wee hours of the morning, it seems to me that what we really need for this class of drugs is a reference standard. That reference

standard, unlike many studies, can't be placebo because you can't treat arthritis patients with placebo.

So I would submit to you that, if you are going to do comparisons, that the reference standard, the best reference standard we have, is naproxen because we know as much about it as anything else. We think it is, at worst, neutral and maybe a little better than neutral.

So I would argue that, if you want to do ALLHAT light, then what you do is you test every agent both that stay on the market and that are proposed to bring onto the market against naproxen with an adequately sized trial and you set an upper bound, which we have to talk about, about what the upper bound of hazard you are willing to accept is, and the test that you run is on efficacy and on cardiovascular hazard.

If your drug is beaten by naproxen, you don't make it. If you can show equivalence within a reasonable upper bound of naproxen, then we would be pretty comfortable--I think I would be pretty

comfortable that the drug is not going to create a hazard.

What do you think about that strategy?

DR. TEMPLE: That is actually--I went through it very fast, but that is actually what I said at the bottom of one slide. I still would like to know better whether the naproxen is less bad or is really good. Therefore, as I said on the slide, in my heart, I would like to see somebody try to give full-dose aspirin for a while because we are really pretty sure that won't be bad.

I think the community, in the long run, needs that. Who is going to do it? That is a perfectly good question. I do want to point out, though, that the way some of the trials were done, like TARGET, they could have given answers on some of this, or at least closer. But, because they did separate trials, instead of randomizing to each of the treatments, that was obscured.

You could have had a very substantial naproxen-ibuprofen comparison, but you didn't get it because of the structure of the trials. So I

think it is very important to randomize to each of the treatments, obviously, whatever it is. But that would be my best guess at the moment. But, in line with what Alastair asked before, when you do naproxen and you are looking at G.I. effects, do you add a proton pump inhibitor? I think you need a little more information before you do that, but you might say that, which then raises the fundamental question of how much help you get from being COX-2-selective.

DR. WOOD: Dr. Cryer?

DR. CRYER: I wanted to comment on several of the questions, Dr. Temple, that you raised as well to ask a question. I guess I will just ask the question first. When you say "full-dose aspirin," are you referring to full anti-inflammatory doses of aspirin, 3.9 grams a day or--okay.

DR. TEMPLE: Which I assume most people will not tolerate and there will be huge bleeding. So you have got to do something.

DR. CRYER: Right. See, I think that is a

non-practical experiment design and I think we have come a long way from 3.9 grams of aspirin per day, particularly because of the concerns of the adverse events, the silicysm, the G.I. events. Clearly, 100 percent of those people are going to have gastric ulcerations assessed endoscopically.

So I also would prefer one of the newer NSAIDs, traditional NSAIDs, in that comparison.

With regard to--

DR. TEMPLE: Actually, before you leave that, do you know what would happen if you added a proton pump inhibitor to aspirin?

DR. CRYER: Not at 3.9 grams a day. I don't think anybody thought that would be a feasible design.

DR. TEMPLE: Short term, then, just to look at endoscopic ulcers.

DR. CRYER: I don't know and I don't think that it will ever be known.

DR. TEMPLE: Then I won't get the answer.

DR. CRYER: What I do know is that, if you give 3.9 grams of aspirin per day in the

short-term, greater than 90 percent of your patients who take aspirin will have endoscopic ulceration. I don't know what the effect of the PPI would be.

I wanted to address your last kind of question that you threw out there of whether or not a short-term study would show that celecoxib plus 80 milligrams of aspirin would have a favorable effect, a G.I. effect, compared to a non-selective NSAID. Those experiments have been done.

With respect to endoscopic ulcer, COX-2 plus aspirin equals traditional NSAID. With regard to hospitalizations, having said that, there is a recent study not yet published, epidemiologic study from Canada, indicating that COX-2 plus aspirin, hospitalizations for that are less than hospitalizations for non-selective NSAIDs plus aspirin. Then we have outcome studies not yet fully published in the abstract form which indicate that events on COX-2 plus aspirin are similar to events on non-selective NSAID plus aspirin--G.I. events.

DR. TEMPLE: It is possible that if you add aspirin--I mean, it is sort what I would expect--is that you would get something that is a

lot closer to being--in a cardiovascular sense, a lot closer to being just a regular NSAID and maybe you would still have some residual advantage in a G.I. sense.

But, I must say, the data so far don't show that. But they didn't seem definitive to me.

It raises the question of--you know, the idea of COX-2 selectivity is, at least, in part, a conceptual and promotional idea. As Garret pointed out the first day, five or six of those old drugs that aren't coxibs are COX-2-selective. So there is a whole range. My feeling is we need to understand the consequences of what all that means and there is a somewhat artificial separation between the coxibs and the others because those old drug at least are partially selective and may have some of the same properties.

So one of my hopes that we could look at a range of these.

DR. CRYER: With respect to your last comment, I am entirely in agreement with that.

DR. WOOD: Let's move on. Dr. Cush?

DR. CUSH: ALLHAT, I like the intention of it. I would suggest, though, that if you are going to have a study long enough to pick up some of

these events, a year or two, it is going to be very, very hard to keep O.A. patients on one of those drugs.

So maybe actually stratifying according to pure COX-2-specific drugs to COX-2-selective drugs to the non-selective drugs that are more predominantly COX-1 and then having a totally nonsteroidal, non-nonsteroidal group, which would be the Tylenol group you talked to or other analgesic agents might work over the long term.

DR. TEMPLE: That would answer a lot of the questions. My real hope--you have a better idea whether it is possible than I do--is that you could actually find a population that could be given what we are pretty sure is a cardiovascular-neutral treatment. That is really

the only way to pin this down and it does seem worth pinning down.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: I think I gleaned from Dr. O'Neill that if we determine there is a class effect that it varies not just by drug and dose but by duration of therapy. From Dr. Temple, the comment that--I am very attracted to the concept of what I would call a large simple trial rather than an ALLHAT trial. I think there is merit in seeing aspirin studied in therapeutic doses and I think there is evidence that anti-inflammatory effects are seen a doses far lower than the 3.9 grams.

But the question I have for Bob is there are three currently marketed FDA-approved coxibs. So would you include valdecoxib and 25 milligrams of rofecoxib in your design?

DR. TEMPLE: Part of the reason I didn't address that is I figured that is what the committee is going to talk about. I was willing to say that the celecoxib data look funny enough so that you might consider it.

DR. WOOD: That is part of what we are going to discuss.

DR. TEMPLE: That is what you are going to

discuss so I didn't address it.

DR. WOOD: Let's move that to later. Dr. Domanski?

DR. DOMANSKI: I will pass.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: Thank you. I want to probably say something rather naive in support of the study, Bob, and that is that we are at a moment where we can do a paradigm shift, meaning that study that you propose is an important one but it is very large and it is going to be very hard to get any resources to do that.

I think we are at a moment where for the companies and the FDA and the government to think about a collaborative study where, if you have a drug that has some--this information is important, that we put together a collaboration among industry to do a multi-arm study of multiple drugs. It is something, you know, in the osteoarthritis field,

the companies have supported largely this osteoarthritis initiative through the NIH to look at outcomes in large numbers of patients.

I think what we need is a similar COX-2 initiative where either with the FDA or the NIH participating, with collaboration among industry, we are doing a multi-armed large study with biomarkers, with pharmacogenomics studies, with genetics and other blood pressure, but try and do it in a utopian way.

I think everyone here wants to get the right answer, whether it is in industry or here at the table. This could be a good opportunity to do something very differently than we have done before in a large trial.

DR. TEMPLE: I don't disagree at all. I mean, some of the drugs are generic. They don't have any company that is massively interested in them. So it is going to be a mixture of government, generosity and a wide variety of other things that are scarce. So I don't know how to--you noticed I didn't have a slide on how to do

this.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: Just a minor point. I understand the need for a cardiovascular-neutral anti-inflammatory drug in an ALLHAT study. But I was a little confused because I am aware of some literature directed at people who are interested in Kawasaki disease suggesting that high-dose anti-inflammatory aspirin is actually prothrombotic because of differential effects on prostacycline and thrombotics.

DR. TEMPLE: There are aspirin studies going back to at least moderate doses that show beneficial effects. It is not just 80 milligrams. It is certainly at least a gram a day. Some of the early ones were more than that. That is worth thinking about. I am encouraged by the thought that you might be able to get away with doses less than 3 grams. So I didn't know that it was considered prothrombotic. I thought aspirin always looked good. But that is not up to grams. I don't think any of the studies have done anything like

that.

DR. WOOD: We will give Dr. Fleming the last word.

DR. FLEMING: I am just debating whether to do it now or after the break.

DR. WOOD: Let me help you. Go ahead.

DR. FLEMING: Now?

DR. WOOD: After the break will be great.

DR. FLEMING: All right. I will wait.

DR. WOOD: We will take a break and then we will be back here in ten minutes.

(Break.)

DR. WOOD: Okay, folks. Let's get started. The next presentation will be given by Sharon Hertz who is Deputy Director of the Division.

DR. HERTZ: Thank you. I am just going to spend a very few minutes summarizing some of our--

DR. WOOD: Let me, in fact, just before Sharon begins--Sharon Hertz has passed out a handout that includes a lot of her slides. In the interest of time, she has graciously agreed to

delete some of these slides and just focus on a smaller subset of what is in the handout.

However, the committee does have the handout and the committee may find that handout useful for referring to some of the data.

DR. HENNEKENS: Alastair, a quick comment. I want to make a quick clarification on the earlier comment about pro-inflammatory effects of high doses of aspirin.

DR. WOOD: Sorry; I missed that. About what?

DR. HENNEKENS: In the randomized trials, 135 randomized trials with over 212,000 randomized subjects, whether the doses of aspirin are 75 milligrams or up to 2 grams a day, there are significant cardiovascular benefits to aspirin even at high doses. The issue, as Bob pointed out, at the high doses, is not that there is a reversal of the benefit but that the side effects are increased.

So I think that is an important point to make.

DR. ILOWITE: I just wanted to say that in pediatrics, we think of anti-inflammatory doses as 100 milligrams per kilogram. So those are the

doses I was speaking of.

DR. GIBOFSKY: Finally, the high-dose aspirin that would be necessary to treat patients with rheumatoid arthritis of 3.9 grams or greater would have significant problems on the stomach, as Dr. Cryer said, significant problems on the hearing of the patient and significant problems, perhaps, on other organ systems as well. It is not a study that could be easily undertaken.

DR. HENNEKENS: I won't debate the value of the study of 3.9 grams of aspirin but, from the perspective of anti-inflammatory effects, they have been observed at doses of 2 grams of aspirin a day and, in fact, there are randomized studies going on directly comparing that somewhat higher doses of maybe 1 to 1-and-a-half grams a day might have significant anti-inflammatory as well as anti-atherogenic effects as measured by endothelial function, nitric oxide formation and other

parameters.

So I don't think that the traditionally high doses are the ones that necessarily would need to be done. But I don't want to debate whether we should be studying doses of 4 grams of aspirin.

DR. WOOD: What you are telling us, Charlie, is that you are comfortable that there is an antithrombotic effect at the high doses of aspirin. Is that right? Okay. Good.

Dr. Cush wants to say something.

DR. CUSH: Again, you need not anti-inflammatory doses but analgesic doses which can be substantially lower. I do want to make a statement with regard to a study that wasn't presented here that I think is germane and we should know about it, and this is quick. There is a very large trial that is NIH supported that is called the GATE study, glucosamine in osteoarthritis of the knee.

This is a 1588 study that is completed and is currently being analyzed. That Data Safety Monitoring Board of the study has analyzed it for

cardiovascular risk because there is a Celebrex arm. There are five arms in this 1500-patient study; placebo, Celebrex 200 milligrams once a day, glucosamine only, chondroitin sulfate only, and glucosamine and chondroitin sulfate.

The outcome here, in a six-month trial, is pain reduction in osteoarthritis in the knee. Because of all this press and what not, they have looked at the safety outcomes and they have not shown any increase in cardiovascular events including M.I., any difference between the Celebrex group and the other four control groups.

DR. WOOD: Let's move on to the program. Dr. Hertz?

Summary of Meeting Presentations

DR. HERTZ: There are now several versions of my slides around and you are free to look at whichever interests you. There is one correction on the lumeracoxib slides from the original set where I substituted the word diclofenac for ibuprofen. So those of you looking at those slides just be aware of that, please.

What I am really just going to do now is just focus down again some of the reasons why we are here. This would not be the current slide set.

Any help here?

Looking at the most recent set that were handed out, and we will just work from there because there is not a lot of data anymore to present, but, basically, I want to just point out that we are here because we do recognize that pain drugs are critically important, that the COX-2-selective NSAIDs have been extensively studied and there are, over time, studies that revealed new potential uses as well as new risks.

We need to determine how we feel about these risks. Are they limited to individual products? Are they applicable across the group of COX-2 selectives and how far does this extend to the nonselective anti-inflammatories.

There is a slide that describes--

DR. WOOD: Sharon, apparently everybody has hard copies of your slides.

DR. HERTZ: Right.

DR. WOOD: So if you want to just go through them and refer to the slide number, that would probably be helpful to people.

DR. HERTZ: Okay. If we go to the third slide, you can get a sense of the sizes of the databases that were presented in the individual

reviewer descriptions of FDA reviews.

A couple of points. The numbers there reflect predominantly patients on the drug of interest as opposed to the entire database. The outcome studies are more reflective of the entire populations including comparators. These drugs were assessed and have been assessed over time in fairly large numbers of patients.

I think it is useful to note that we have not approved, in this country, all of the COX-2-selective NSAIDs that have come to us in applications for a variety of reasons. Some of these may be related to cardiovascular-risk assessment. Some may be related to non-cardiovascular-risk assessment which we really haven't gotten into in this setting.

In addition, you may also note that parecoxib has not yet been approved in this country although it has been approved elsewhere. So I think that we have a lot of issues to consider with these products.

When we reviewed the studies that have been presented, we see that there is some increased risk for cardiovascular events but one of the key issues here is that the results are not consistent

across studies and across situations. We also have seen that there is risk that is being associated with some of the nonselective products.

So we have a story of conflicting data. I am up the Slide 5. We have data that has been present across short- and long-term studies, the epidemiologic studies. The challenge is to compare across populations, across comparators. It is striking that sometimes very similar study designs have very different results.

It is possible there is more than one mechanism. Again, the data has been inconsistent with the NSAIDs. We also have conflicting

information coming back on what occurs in the context of concurrent aspirin use. It is really unclear if aspirin use has a truly meaningful effect on whether there is any G.I. benefit of the COX-2-selective products. That has not been clear either.

I have been asked to point out that, in addition, time to onset of risk is something that we need to consider very importantly, too, which, again, is something that is evident when we look at the study data and important in our deliberations for this.

So, in spite of this conflicting data and the many questions, we have to move forward. We have to determine what the role of approved products are on the market today, what additional studies are necessary, what studies would be most helpful.

I am going to summarize and combine some of the questions that we have posed. These are questions we dearly would like input from the committee. To start, if we think about the first

three questions, does the available data support a conclusion that celecoxib, rofecoxib and valdecoxib significantly increase the risk of cardiovascular events. Does the overall risk-versus-benefit profile for each of these support marketing in the U.S. If yes, in whom? And which of the potential benefits of celecoxib or the others outweigh the potential risks and what actions would you recommend that we consider implementing to ensure safe use?

I think it is also important to understand that some of these answers are going to depend on if we think that this is a fairly uniform class effect and, if not, we are going to have weigh the amount of information available for each of the products. It is not the same. We don't have the longer outcome studies, for instance, with valdecoxib at this point.

Question 4 asks if the available data support a conclusion that one or more of the COX-2-selective agents increase the risk of cardiovascular events and what is the role of

concomitant aspirin in attempting to mitigate that risk. What additional clinical trials or observational studies, if any, would you recommend as essential for us to further evaluate celecoxib, rofecoxib and valdecoxib?

What about to further evaluate the potential G.I. benefits for these same products? Would you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical-trial data assessing potential cardiovascular effects and if you have a recommendation for how that should be conveyed in terms of warnings, boxes and such.

What additional trials would be essential to evaluate the nonselective nonsteroidal anti-inflammatory drugs particularly with respect to cardiovascular risk? Similarly, what will now become essential for products under development prior to approval to help gain approval?

We have to determine what studies would be necessary to evaluate the cardiovascular risk of these products and how much information do we need

to know about the gastrointestinal risk? If preapproval studies recommended as essential do not demonstrate an increased risk for a cardiovascular event, how would you propose the FDA handle that information in the labeling? Would the absence of a cardiovascular-risk signal preclude the need for any warnings or precautions in the labeling of a new product or should we rely more on a class warning or precaution in the absence of a signal of increased risk in the preapproval databases?

If you think a class warning is appropriate, please advise with particular attention to whether you recommend it apply to all NSAIDs or only COX-2-selective NSAIDs.

So I want to thank everybody here for their time and their commitment to helping us through this extremely challenging program and we really look forward to hearing your deliberations and your recommendations.

Thank you.

DR. WOOD: Thank you very much.

The companies have also asked for two

minutes to respond. We all heard the rules yesterday so it is two minutes. Microphone gets turned off two minutes later and just keep moving.

Sponsor Responses

DR. HARRIGAN: Could I have Slide No. 1. This is Harrigan from Pfizer. What I would like to do is first to summarize what we know about celecoxib and what we think that tells us about the benefit:risk equation for that drug.

I make the point in this slide about Celebrex being extensively studies and to remind the committee of the contrast of the very widely used nonspecific NSAIDs. On the next point, we see that efficacy has been demonstrated in arthritis pain and familial adenomatous polyposis. Our prescription data and observational study data tell us that approximately three-quarters of patients who are taking celecoxib are receiving daily doses of 200 milligrams or less.

Celebrex does have a favorable G.I. safety profile, a point emphasized by the very relevant G.I. safety findings that we heard about this

morning from ADAPT compared to over-the-counter doses of naproxen.

Cardiovascular risk was not detected in the setting of treating arthritis patients understanding all the caveats about that data that we have heard over the past two days. In APC, an increase in cardiovascular risk was reported apparently in a dose-related pattern. In contrast, two additional long-term placebo-controlled trials did not find evidence of increased cardiovascular risk at daily doses of 400 milligrams.

The comment about the ADAPT findings is supported by the initial announcements from National Institute of Aging. We await that data with great interest, particularly given the size, the duration in the elderly population study which would lead us to believe, expect, that the number of events in that trial will exceed the number of events in either or both of the other two trials combined.

The final ADAPT data and the polyp efficacy data will make significant contributions

to our understanding of the benefit:risk. In addition, as (microphone turned off.)

DR. WOOD: Next speaker? It might be worthwhile introducing yourself just so we know which company you are representing.

DR. ERB: Dennis Erb, Regulatory Affairs at Merck. On behalf of Merck, I want to again thank the committee and the FDA for providing us the opportunity to present our data and the benefits and risks of etoricoxib and rofecoxib.

We recognize that the safety of this class of medicines is an important public-health issue and, as we have heard over the past two days, there are many patients in need of effective therapies for their pain. We hope that the data that we included in our background package and the presentations have helped the committee in its deliberations.

When Merck made the decision to voluntarily withdraw Vioxx from the market, we stated that we believe that it would have been possible to continue to market Vioxx with labeling

that would have incorporated the data from the APPROVe. We concluded, however, that, based on the science available at that time, a voluntary withdrawal of the medicine was the responsible course to take given that there were alternative therapies and the questions raised by the data.

Since that time, the science has continued to evolve and new data on some of those alternate therapies have become available including the data that we have seen in this past week. Given this new information, it appears that the cardiovascular risk observed and approved is not unique to Vioxx.

We believe that the data suggest a class effect but the size of the class is uncertain. We believe that MEDAL is an important study to address the important question on the relative risk of COX-2 inhibitors versus traditional NSAIDs. As Dr. Packer said, studies with a sufficient number of endpoints are needed. The planned C.V. analysis will provide data on greater than 600 events, 200 of which will be in the 18- to 36-month time interval.

The importance of the study is shared by the steering committee for MEDAL study who, in a letter sent to Merck this week, support the

continuation of this trial.

We look forward to the deliberations of the committee on the questions before then and, as Dr. Kim stated last night, if the committee and the FDA conclude that the benefits of this class of medicines outweigh the risks (microphone turned off.)

DR. WOOD: Next?

DR. ORLOFF: Thank you for the opportunity to comment. My name is Dr. John Orloff and I represent Novartis Pharmaceuticals. We would like to make some general comments on how we might move forward.

While it is reasonable to consider these drugs as a class, we believe there are substantial differences in their profiles that deviate from an attempt to ascribe all follow-on their benefits and risks to a single unifying mechanism.

For example, the apparent cardiovascular

risks, as noted by Dr. Fleming and others in the discussion yesterday, do not seem to correlate well with COX-2 selectivity in the clinic. More specifically, some of the agents at the highest cardiovascular risk may not be the most COX-2-selective.

In addition, there are significant differences in blood-pressure profiles and in cardiorenal profiles including edema and congestive heart failure as we have shown in TARGET, a trial that enrolled over 18,000 patients. In TARGET, significantly smaller changes in blood pressure were observed for lumiracoxib relative to either naproxen or ibuprofen.

Furthermore, the strength of the G.I. outcomes data varies considerably across agents, a benefit that is central to the assessment of benefit:risk profiles of COX-2 inhibitors. For lumiracoxib, an unequivocal reduction in G.I. ulcer complications of 79 percent was shown in TARGET and, in response to comments made yesterday, it should be noted that subgroup analyses of patients

at higher G.I. risk demonstrated that the magnitude of this effect, about 70 percent, was similar to that observed in the overall population.

Thus, the benefit:risk profiles vary by drug, by dose and by exposure. Accordingly, each agent should be judged individually on its own merits. So how do we go forward? We believe it is reasonable to consider, for any particular indication, restricting the duration of use to a time frame that is supported by the data and that this should be accompanied by a robust risk-management plan including firm postmarketing commitments.

Thank you.

DR. WOOD: Thank you. Oh; there is more.

DR. PEITLER: Erica Peitler, Senior Vice President, Bayer Healthcare, Global Head of R&D. Bayer was pleased to have had the opportunity to share safety information on naproxen. Important points have been made regarding naproxen in both large observational datasets as well as large randomized clinical controlled trials.

We welcome the scientific debate and dialogue on our products. We believe that it helps to build trust and confidence in both the products,

the industry and well as our company. We appreciate the presentations today specifically on the ADAPT trial as well as the clarifying questions and comments put forth by this committee regarding how this study may have caused significant physician and consumer confusion.

Lastly, and most importantly, Bayer is committed to its consumers and its Aleve brand which contains naproxen and believes that, when used according to label directions, Aleve is a safe and effective pain reliever that offers millions of consumers an important treatment option for over-the-counter pain relief.

Thank you.

DR. WOOD: Thanks very much.

Committee Discussion

DR. WOOD: Thanks very much. I thought it would be helpful if I just made a few comments about what I think we have seen over the last three

days and why this has difficult.

I think what I have seen, at least, is we have seen four, maybe five, randomized controlled trials that show a significant cardiovascular hazard which was replicated for two of the drugs, Vioxx showing VIGOR and APPROVe and Bextra the early CAB study and the later CAB study, and, for Celebrex, the APC study.

It is important to recognize, this is a far larger randomized safety signal than we have seen for any of the drugs that have been withdrawn for safety reasons. In all of these studies, as Tom Fleming pointed out a number of times, the other adverse events seem certainly to trend at least the coxibs in many of them.

So you might say, well, why are we discussing this and you might also say, why has it taken us three days. I think the reason for that is that this is probably one of the first times that we or the FDA have had to deal with a drug that caused a substantial increase in the frequency of a common problem, common disease like MI or

heart disease or whatever, in contrast to an increase in the frequency of a rare disease like acute liver failure, even things like torsade de pointes in which there were other issues that made it difficult.

So the difficulty of struggling with that, I think, is real and has been talked about by many people. The other question that has come up and has been raised by many people is what do we see in the observational studies. Well, from a personal level, I guess, what I saw was, which is kind of backwards, I suppose, is in some of them, at least, it seemed to show the same as the randomized trials and that is somewhat reassuring, I suppose.

With all the caveats that we heard, the observational studies, may allow us to rank drugs by toxicity, and toxicity by dose, with all the caveats that we just saw with, I guess, Vioxx currently being the most toxic.

In terms of G.I. safety, although it is frequently thrown up there, we saw no data that showed better G.I. safety at the PUBs and a hard

endpoint for Celebrex or Bextra except the discredited JAMA Celebrex paper that failed to disclose the full dataset and that was now the subject of critical and apologetic comments from the Editor of JAMA, herself.

We heard testimonials from patients which I thought were both moving and important although, in fairness, it is fair to say that no one has been able to demonstrate specifically better response amongst any of these drugs in individual patients in any randomized way and, as Bob said earlier, such studies--Bob Temple said earlier--such studies would be useful.

So that brings us to the $64 million, probably, question, what should we do? Well, first, this is a much bigger--I mean, as was said earlier, however one passes these numbers, this is a much bigger safety problem than we have seen with the 16 drugs that the FDA has withdrawn. The only reason that we have not acted, I think, or the only reason we have agonized so much is that this is a relatively common problem and it is, therefore,

much harder for us to be sure that we have seen a signal.

Clearly, though, the Committee needs to act in a way that limits this hazard to patients and the public has the right to expect us, I think, to do that and I think we need to focus on that as we go through this. Although, it is interesting to discuss these issues, we really need to make sure that, before we leave here, we have provided some sort of reassurance.

If there are patients who uniquely benefit from these drugs, then we need to consider any revised marketing strategy which could range from withdrawal to great limitations on the use of the drugs. We need to identify patients who can uniquely benefit from these drugs and work out what they need to be told and what risk they would be willing to accept for that small number of unique patients who would benefit from the drugs.

We also, I think, learned a very important thing this morning which was that, in contrast to some of the information that had been put out in

the press, the ADAPT study seems to have been stopped largely for operational reasons and many of the "safety signals" that we heard about in that were not backed by the usual approach that we would take. That, I think, is an important lesson that we did get today.

So I wanted to frame our discussion to these issues and also to make clear to everybody that, when we leave here tonight, we need to have made really clear recommendations to the FDA that will help them move forward. It is wonderful to sit and discuss the issues and pontificate here, but we really need to come down to some conclusions here that they will be able to take away and act on.

Now, a number of people have indicated they wanted to say something. Garret FitzGerald wanted to say something in relation to some of the comments that came up in the last session. Garret?

DR. FITZGERALD: Thanks, Alastair. I thought it might be worthwhile to reemphasize one of the points that you have made, actually, and

that is that the focus of our deliberations would most appropriately be on the randomized controlled trials particularly the placebo-controlled trials for two reasons.

One, I believe that the quality of the evidence is much greater than in the observational studies and I think everybody has said that and, two, that the biological plausibility for the issues addressed in the placebo-controlled trials of the coxibs is much greater than the biological plausibility of risk relating to the traditional nonsteriodals that were the subject of the observational studies.

As far as biological plausibility is concerned, there have been several comments yesterday and today that seem to cast out the symmetry of the evidence with the plausibility of the mechanism advanced. I am only going to make comments about two of those issues. One, the most recent one, which was the TARGET study.

In the TARGET study, we had a highly selective drug which did not reveal a

cardiovascular risk significantly. However, as we heard yesterday, the TARGET study was set up in a way by choosing patients at low G.I. risk to amplify the detection of a G.I. benefit and, by choosing patients at low C.V. risk to minimize the likelihood of detecting a C.V. risk.

Indeed, that study was grossly underpowered to detect a signal albeit that, in the non-aspirin users, the hazard ratio for cardiovascular events was 1.47.

As far as the blood-pressure aspects of TARGET are concerned, which are, indeed, asymmetric with the mechanism, I draw your attention to the fact that blood pressure was assessed retrospectively in TARGET and the reliability of a 1- to 2-millimeter change, on average, under those conditions, to me, is extremely questionable especially as we assume that traditional nonsteroidal comparators in TARGET were raising blood pressure through inhibition of COX-2 that it would, indeed, be amazing, if an even more selective drug was less effective on blood

pressure.

It certainly doesn't relate to the duration of action of lumiracoxib which is given at roughly 30-fold greater than the concentration necessary to completely inhibit COX-2 so that, although it has a short half-life, its pharmacodynamic half-life is extended and we were shown that it is an impact on prostacycline by a synthesis. It is sustained throughout the 24 hours and corresponds to the other drugs in the class, yesterday by Paola Patrigniani.

So I think I would not view the TARGET experience as inconsistent with the plausibility of the mechanism. Finally, the other point I would make is that Bob alluded to the platelet activation issue as being the manifestation of the mechanism. As I described, this mechanism has acute and unfolding chronic manifestations and, indeed, the data that we have seen in the controlled trials are entirely consistent with an acute and chronic time-dependent evolution of risk.

Thank you..

DR. WOOD: Thanks. Tom, I put you off from before the break, so feel free.

DR. FLEMING: It's fine. Basically, I

wanted to quickly comment on the essence of what I see from the Packer, Temple and O'Neill presentations. Clearly, when judging strength of evidence, it is important to take into account multiplicity, as Milt Packer was indicating. When you are looking within the context of a single trial, that multiplicity can arise as multiple testing over time as well as multiple endpoints.

Clearly, as he notes, with safety issues, there is a wide array of different measures and we have to take that into account when considering strength of evidence; monitoring boundaries, give us a guideline. Yet many of us have struggled with trying to formulate monitoring boundaries when you are looking at safety because of the multiplicity of safety issues and the fact that you have to take into account severity of those safety issues and you have to take into account benefit to risk.

Ultimately, while those statistical

procedures that Milt was talking about can provide some guidance, there has got to be informed judgment. Data monitoring committees are critical and I think we see, from the ADAPT trial, just another example of why it is also critical for the data monitoring committee to have sole access to emerging data on safety and efficacy during the course of the trial.

What does this tell us, though, about where we are today now that we are looking at a wide array of studies. The VIGOR trial was the first study out. That study, as Milt would say, needs to be viewed in the context of confirmatory and exploratory. There is much less confidence that you have in the reliability of a result that was suggested by the data as opposed to a prespecified hypothesis.

There is also regression to the mean. So, when you are seeing an estimate of the two-and-a-half-fold increase, there is a reason to expect that that single trial might be overestimating that overall strength of evidence.

But we now have considerable insight beyond that first trial. We have got, by my count, at least a dozen trials and at least half of those

trials show an indication of excess risk and the majority of those are placebo-controlled trials.

So, in my own sense, the issues that Milt is raising are very relevant but we are now in a context of having an extensive amount of information. In my own view, it is clearly sufficient for a measured response and yet, at the same time, I would agree with Bob Temple, that we need greater insight. What he has put forward is one strategy for that insight, to get at a better sense of the extent to which this excess is specific to indication, to the dose, to the duration, to whether or not there is ancillary care. Just to kind of get it drilled down on the numbers here, if you were trying to rule out a doubling, it would take about 2,500 people per arm, or 88 events in a pairwise comparison.

I would be more, in this case, because my own sense is I think VIGOR is overestimating the

true risk. I don't think it is a two-and-a-half-fold increase. My best sense is, in a general aggregate sense, it is more on the order of a 1.4 to 1.5 relative risk.

To rule out a 1.5 relative risk would take 10,000 people per arm or, in Bob's study, about 50,000 people, a big trial. But METAL has 23,000 people so this does seem conceivably doable. Bob O'Neill makes the key point that duration--that the events, the risks, can be different over time. So this trial, if it were to be done, should be done in a way to get at longer-term effects as well, which does, also, allow us to somewhat reduce the size of the study.

So, bottom line, is we know a lot, enough to certainly take measured responses, but it is also going to be important for us to get additional insights that are necessary.

DR. WOOD: Dr. Gibofsky?

DR. GIBOFSKY: Mr. Chairman, we very much enjoy the interactions with our colleagues in Drug Safety speaking for my colleagues on the Arthritis

Advisory Committee. But I think I speak for most of them in suggesting that, while safety for patients in the absolute is important, the important language for us is the standard language of the introduction to the questions; namely, the notion that the original approvals and subsequent supplemental approvals were based on a determination by FDA that the potential benefits of each product outweigh the potential risks when used for the approved indications according to the directions included in the product labeling.

I think that is important because, depending upon whether that clause is inserted into Questions 1 through 3, quite possibly, there could be different answers for both the absolute and the relative answers depending upon whether or not we consider that clause.

My colleague and friend Dr. Abramson has suggested that we may be at the dawn of a new paradigm here. If so, I agree with our Chairman that, when we leave here tonight, we provide some clarity. But I would earnestly implore my

colleagues to remember that the last temptation and the greatest treason is, perhaps, to do the right thing for the wrong reason.

Where drugs have been withdrawn, whether it has been because of their numbers or because of the increased incidence of risk, it is my understanding that it has usually been in the context of adverse events in the group for which the drug was approved and not based on adverse events in a prevention or proposed group.

So I think these comments need to be considered somewhat carefully and that we need to look at our questions both in terms of absolute safety, which is critical, as well as relative safety as we define the populations which are going to get these drugs, namely the patients with arthritis and pain.

Thank you.

DR. WOOD: Well, let me just provide some correction to that. I am not sure that last comment is correct, the one about drugs being withdrawn because of adverse events in the

indication for which they were approved.

DR. GIBOFSKY: Not all of them; that's correct.

DR. WOOD: Hang on. Rezulin produced acute liver failure in two studies in which it was being used to prevent onset of diabetes.

DR. GIBOFSKY: I think that is absolutely correct and it is not a uniform finding.

DR. WOOD: Now, these were not--

DR. GIBOFSKY: My concern is the extrapolation from trials of prevention to trials of treatment and I merely indicate that we cannot be universal about that.

DR. WOOD: All right. I think we are ready, probably, to start--sorry; go ahead.

DR. GROSS: I would like to make a comment for the Drug Safety and Risk Management Advisory Committee and it is a perspective for the future. The question is, is there something we can do to avoid the confusion that comes up every time adverse events arise after marketing the new drug, particularly when the signal for the adverse event

was not totally clear before the drug was approved.

I suggest we consider an approach that our committee had discussed in the past and that approach is the review the drugs that have been pulled from the market and look for commonalities and differences that could guide policy decisions in the future, questions such as what were the adverse events, when were they recognized, what were the signals before marketing and what decisions were made when other drugs that were available in the same class, such as the statins, were done and what were the decisions made when there were no other drugs in the class such as occurred with alosetron or Lotronex.

If this were done, lessons could be drawn. Advisory committees would be better informed to make benefit/risk decisions and the public would be better informed because they would be able to acquire a better perspective and the press, along with the public, would have a better sense of relativity of all of these activities.

DR. WOOD: Okay. You will be glad to hear

I am not going to make a statement on behalf of the NDAC Committee.

Let me read the first part. Three COX-2 selective nonsteroidals are currently available for marketing in the United States, Celebrex, Vioxx and Bextra. The original approvals and subsequent supplemental approvals were based on a determination by the FDA that the potential benefits of each product outweighed the potential risks when used for the approved indications according to the directions included in the product labeling.

Since approval, additional data regarding the safety and effectiveness of these products has accumulated, in particular, new information regarding the potential cardiovascular risks of these products. FDA must consider the impact of these new data on the benefit-versus-risk profile of each product in making decisions about appropriate regulatory actions.

Although--and this is important--although Merck voluntarily withdrew Vioxx from marketing

worldwide on September 30, 2004, questions relating to Vioxx are included below since it will be necessary for FDA to determine the appropriate regulatory action regarding the approval status of this product.

Based on the data presented in the background package during the committee meeting, please address the following questions.

Question 1: Celecoxib

So let's address the first question 1.a. Do the available data support a conclusion that celecoxib significantly increases the risk of cardiovascular events? Anyone want to comment on that? No comments? Dr. Abramson; yes.

DR. ABRAMSON: I will just start. I wanted to start by questioning the premise of the first sentence which is that there are three COX-2 selective drugs on the market and just remember to point out that the drugs like Celebrex, there are four or five of them, diclofenac, et cetera, that have comparable pharmacodynamic profiles in terms of their COX-2 preferential effects and that in

randomized controlled trials of these drugs, whether it is CLASS or the development program or TARGET have comparable cardiovascular adverse events in those comparator trials.

So I think, just as a premise, as we go forward for each of these drugs, I think we need to circle back at the end to what we mean by COX-2 selective agents.

That said--

DR. WOOD: I agree with that and let me just add to that. I think it would be helpful if we go through each drug individually and not get into a big discussion about what we mean about COX-2 selectivity right now.

DR. ABRAMSON: Right; exactly.

DR. WOOD: Then we can come back to that later when we talk about nonsteroidals in general. So we are just confining our discussion to celecoxib.

DR. ABRAMSON: I agree and I just wanted to frame my comments. My own view on celecoxib, just to lead off on my opinion, is that, if there

is a cardiovascular event, this, among the coxibs, is probably the weakest signal that we have seen, that it is in the approved study but not in several other placebo-controlled, randomized trials--although there may be some trends in the precept. We don't see it--and that there is a large database in the randomized clinical-trial development program that does not show a signal that is excessive comparators.

So, while I am tending to think that that is a cardiovascular signal that is COX-2-dependent, celecoxib does not--has the weakest amount of evidence that it, in itself, is significantly worse than the others.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I will support that. Let me say that I think it depends on the dose. The evidence from the APC trial at the 800-milligram dose is strong. There is no question about it. There is a marginally statistically significant evidence at the 400-milligram dose and there is no evidence in any trial at the 200-milligram dose.

We have a number of pieces of data that I consider supportive of that concept. In the epidemiological studies, while we recognize that

they are flawed, there is no signal. There is really no signal at all for celecoxib and yet it has probably been the most widely prescribed agent in the class.

Now, why would there not be a signal? Well, as we heard, the vast majority of use is at the 200-milligram dose. What happened here was in the colon polyp trial, in an effort to get efficacy, doses of 400 and 800 milligrams were the doses that were tested and we see a signal there.

Interestingly, we don't see evidence in CLASS at an 800-milligram dose. We don't see evidence in PRECEPT. So using, I think, Milton Packer's logic here, now you have to ask the question, does the evidence around rofecoxib and valdecoxib--to what extent does it support a conclusion around celecoxib.

My view is that I can say that the 800-milligram dose is very likely to produce excess

cardiovascular risk, that it is probable at the 400-milligram dose but I can't find any evidence at the 200-milligram dose. So I think the answer to this question has to be based upon dose and, if somebody can give me some evidence that the 200-milligram dose increases cardiovascular risk. You can change my mind but I just don't see it, weighing the evidence very carefully.

DR. WOOD: Dr. Furberg?

DR. FURBERG: I think the previous speakers are changing the question. You posed one question that had nothing to do with the strength of the evidence, nothing to do with dose. So the way the question is posed, the answer is clear. We have evidence of significant increase in risk of cardiovascular events. I admit, it is in a select population, in a select dose, but that is not what the question is about.

So I think that should be reflected eventually in the labeling.

DR. WOOD: That is a fair comment, actually. The question right now is just about the

drug. So we are talking right now about the chemical entity, itself, and then we will get to issues of dose and patient subsets, perhaps, later--in fact, for sure, later, just to reassure everybody.

Dr. Shafer?

DR. SHAFER: Alastair, actually I have a question for you. I am not sure how we are actually going to proceed at this point in time. Is this the point in time where we actually start casting votes on the individual questions as they are put forward or is that scheduled for a later point during the day because at the time when we actually get to individual questions about individual drugs, it seems to me--I would actually like to hear, in order, from each person on the panel rather than us all trying to flag you for attention.

So clarification; what are we doing at this point?

DR. WOOD: We are discussing the question. So if you have got discussion on the question, by

all means, say it. Eventually, we will reach a point where we vote on many of these questions. But the issue that we are trying to do is discuss the question right now to provide information to your colleagues that will help them inform their decision.

DR. SHAFER: When it comes to discussion, will we then go around individually or are you just going to look for hands up, hands down, and we need to speak now.

DR. WOOD: I am looking for hands up now. No, no; wait a minute. Are you talking about the vote?

DR. SHAFER: Yes.

DR. WOOD: The vote, we go around the table.

DR. SHAFER: Fine.

DR. WOOD: Other comments? Tom?

DR. FLEMING: Looking at the data, I am basing my sense predominantly on the CLASS trial, the Alzheimer's OO1 trial, the APC and the PRECEPT studies. The CLASS study is the largest and

generally gives a favorable result of a lack of excess although one has to remember that is against diclofenac and ibuprofen.

When one does look in the non-aspirin users and you are looking at atrial SAEs, anginal SAEs, MI and thrombophlebitis, we have got 30 events on celecoxib and 14 on the control. So I am willing to take this as a relatively neutral study but there are elements of this that are consistent with some concern and we are also looking at a comparator group that is diclofenac and ibuprofen.

The other three studies are placebo-controlled. The APC trial is probably an overestimate. In fact, I would--my sense in the totality of the data is that it is giving us an excess and it is giving a fairly persuasive sense that there is an excess and yet, when you look at this in the aggregate with the PRECEPT trial, one gets a more tempered measure, although the aggregation of those two is in excess of a relative risk of 1.8.

The Alzheimer's 001 trial is also

suggesting an excess, 11 against 3 events, in a 2:1 randomization. So, if we use the three placebo-controlled trials, the aggregation of the evidence is in excess of about 1.6. My sense is, for all of these together, the excess is on the order of 1.4 to 1.5.

If we fold the CLASS trial in and it is relevant to do so, but remembering that is not a placebo-controlled trial, one gets a sense of about 1.3. In that regard, I agree with some other comments, that this seems to be less than the other two approved agents. Yet, there certainly is a suggestion, more than a suggestion, I would say. There is definite evidence that there is an increase, although potentially more modest than the other two agents.

One, though, does need to factor in what you know about the totality of the data from the other agents in the class. In that sense, you live by the sword and die by the sword. If those other agents look favorable, it gives you less concern. If they look unfavorable, it is more concern. So,

looking at the totality of the data, I don't like using the word "significantly" here, but I would say the available data do support a conclusion that there is some level of increase in cardiovascular events using the totality of the data, particularly influenced by the placebo-controlled trials.

DR. WOOD: Okay. Dr. Domanski?

DR. DOMANSKI: I will pass again.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: Perhaps Dr. Fleming could elaborate on his response, his comments in regards to when one looks at the statistical analysis of each of the studies and there being possibly the risk of exaggerating the relative risk, we also spoke earlier of how, in most studies, we exclude people who have more serious illnesses that would, perhaps, subvert a clean trial, people who have serious cardiovascular disease that is obvious, serious congestive heart failure who, nonetheless, are people who wind up using these drugs once they are on the market.

I don't recall, for each of these trials,

the degree to which there was exclusion of those patients but we have agreed that, at least in some of those trials, those patients were excluded. If we acknowledge that, then the risk, in fact, for the general population, may be underestimated.

DR. WOOD: So, for many of these trials, people with heart disease were excluded, so you are right. The risk will probably be higher in patients with heart disease. Certainly, in the Bextra trial, that would suggest--that was certainly true.

Did you want to address that question to Dr. Fleming? Did you want--okay. He addressed the question to you, Tom.

DR. FLEMING: I don't have anything to add to what you have just said.

DR. WOOD: Okay. Dr. Farrar?

DR. FARRAR: One point and then a point of clarification in terms of our discussion so I know how to approach my second point. The first point is a plea for changing the word "significantly." Are we talking about statistical significance? I

don't think so. But I think we need to be absolutely clear that we are talking about substantial benefit or substantial risk or important.

Significantly continually gets confused and so I think that if we all agree what we are talking about is important, or substantial, risk, not significant risk in terms of a p-value.

The second question is, in terms of discussion of these topics, are we talking--I think it would be useful, in fact, to talk about all three of the subquestions here as part of the discussion as opposed to trying to discuss each of the subquestions individually because, at the end, we have to take all of them into consideration in terms of our recommendations.

So my question is whether, as a procedure, can we talk about benefit at this point or would you prefer to restrict it currently to--

DR. WOOD: I think it will be easier to manage with the size of the committee if we actually stick to each subquestion and then we can

vote on that. Obviously, if people think there are other issues--as you look at each subquestion, you should bring the totality of whatever issues relate to that to bear on it. If there are discussion points you want to bring to bear on that then, by all means, raise them.

DR. FARRAR: So I will hold my comment to the next one.

DR. WOOD: Any other comments? Charlie?

DR. HENNEKENS: As I view the totality of the randomized placebo-controlled evidence using vascular events as the outcome, it appears to me that there is about a 41 percent higher risk of vascular events among those assigned at random to the coxibs, that it doesn't differ significantly by the drug being studied but, as has been pointed out by other people here, because the numbers are tiny, strictly speaking, the individual drug comparisons do not, on their own, achieve statistical significance.

DR. WOOD: I passed myself by. I agree with what Tom said. I think there is clear

evidence of risk from celecoxib and we will come back to the subgroups later. I am not persuaded in the absence of data that we can't extrapolate that to other disease states. It seems highly improbable to me that the risk of cardiovascular events would be less in situations where we know that that population have a higher risk of cardiovascular events such as rheumatoid arthritis.

So just focussing on the risk right now, it seems improbable to me that we can't extend this information to these other settings. Bear in mind why we have only placebo-controlled trials from non-arthritis patients. The reason we only have placebo-controlled trials from non-arthritis patients is you can't give placebo to patients for 18 months who have got pain.

So, stepping back from that and sort of seeing a safety benefit in patients who have not been studied in placebo-controlled trials seems to me a very hazardous thing to do, particularly when we have non-placebo-controlled trials that seem to show the same thing.

Other comments on the question? Yes?

DR. FRIEDMAN: Do you include hypertension or edema as major cardiovascular events? If so, I

think it is clearly there as well.

DR. WOOD: I interpreted that to mean events, meaning hard endpoints such as Charlie's events or whatever. Is that, Bob, you meant by that? Bob Temple?

DR. TEMPLE: That is what we have been focusing on. I mean heart failure is of interest, certainly, but it is a different kind of thing. It is potentially manageable whereas a heart attack and a stroke are not manageable.

DR. WOOD: Right. In fairness, in the published VIGOR trial, there were other events that were not in that published trial that appeared in other analysis.

Yes, Steve? Dr. Nissen?

DR. NISSEN: I just wanted to comment for the statisticians here. It is important to understand how much of the evidence comes from the 800-milligram dose which is not a dose that is

approved. So, what we have to understand and we have to filter into our thinking here is the fact that the best signals come from a dose that is two times the upper limit of the approved dose and four times the most commonly used dose.

Now, that may or may not reassure individuals but it is, I believe, relevant to our considerations and I would like you all to think about that.

DR. WOOD: I think that comes under 1.c. That is where we should deal with that. Right now, we are just addressing whether the drug, itself, can cause events.

Any other comments? Dr. D'Agostino?

DR. D'AGOSTINO: Just a comment that is going to be picked up later on, but I think that the data--you can look at it as a full package of all the data we have seen but just focusing on the Celebrex, alone, and the placebo-controlled trials, I think, is more than a signal that there is something going on there. So I feel very comfortable saying yes to this.

Dr. Cush?

DR. CUSH: I would concur with the original statements of Dr. Nissen and Steve

Abramson in that there is a marginal signal at best. But, again, when one considers the use of celecoxib at prescribed doses and for the approved indications, there really is no signal.

DR. WOOD: In the absence of seeing further discussion, are we ready to vote on this question?

DR. TEMPLE: No. I just want to correct something I said before that is wrong and might make a difference. I was unaware that some proton-pump inhibitors had actually been shown to improve the G.I. tolerance of some drugs and are actually approved for that purpose. Lansoprazole is approved for healing and risk reduction of NSAID-induced ulcers and there is a combination pill with lansoprazole and naproxen. S-omeprazole has a similar claim.

So I don't know if that is going to affect anything but I wanted to correct what I had said

before.

DR. WOOD: I think that is relevant, actually, and that is why I think I was surprised about it missed out with the naproxen.

DR. GROSS: I think we might want to consider altering the question. That is certainly acceptable for an advisory committee to do and we might want to comment on whether there is a significant increase in C.V. events at the approved dose versus the unapproved higher doses because, remember, whatever we approve, it is going to have a big impact on the public's perception and how they read this may not be how we intend them to read it.

DR. WOOD: We could come back to that and see where we make recommendations about what doses, if we decide--well, it depends how we vote on this--and deal with that there. I would suggest we deal with it at that stage and keep the current question the same. Sorry. Tom?

DR. FLEMING: Just for clarification, as we look at dose and we look at the three randomized

trials, certainly in the APC trial, the signal was greater at 400 compared to the 200. The signal was a relative risk of 3.4 at the 400 although it was still a relative risk of 2.5 at the 200. The second piece of information was the Alzheimer's 001 trial which also was the 200 BID dose that showed basically almost a doubling.

So I am a little uncertain. Are we challenging that the 200 BID dose isn't a dose level at which there is some evidence for excess?

DR. WOOD: I'm not. I mean, are others? I guess the other thing, which we have not talked about at all, has been dose creep in the use of these drugs.

DR. D'AGOSTINO: But we are definitely not saying that we think there is no dose response and so forth. I think it is the dose response that is going on here.

DR. FLEMING: That's right. I would certainly stop short of saying dose isn't important. That is not my issue. My issue is I thought I heard some comments that, if I

interpreted it right, the 200 BID dose is one for which there isn't evidence of an excess and, it seems to me, there is.

DR. WOOD: Yes; I agree.

DR. CUSH: Not in approved indications in the Alzheimer's and the in the APC study.

DR. WOOD: Let's go back to that. The reason we don't have evidence in the approved indications is because the studies couldn't be done in the approved indications. So that shouldn't wrap us in warm, fuzzy feelings, I don't think. That is a reflection of the nature of art rather than the science.

Any other discussion? Great. Let's go, now--now, I have got strict instructions as to how to do this. So we have to go around the room and everybody has to say their name and then vote yes or no. So you precede your vote with your name. And we are dealing with Question 1.a.

Let's start with Dr. Abramson. For the record, Dr. Cryer doesn't get to vote, apparently, and neither does Dr. FitzGerald. Neither does Dr.

Stemhagen.

DR. ABRAMSON: So I would answer yes, consistent with the COX-2 inhibition.

DR. NISSEN: Steve Nissen. Yes.

DR. ELASHOFF: Janet Elashoff. Yes with respect to placebo. No with respect to the NSAID comparator.

DR. GARDNER: Jacqueline Gardner. Yes.

DR. PLATT: Richard Platt. Yes.

DR. DAY: Ruth Day. Yes, and I look forward to the discussion of dose effects.

DR. FURBERG: Curt Furberg. Yes.

DR. FLEMING: Fleming. Yes.

DR. DOMANSKI: Domanski. Yes.

DR. BOULWARE: Dennis Boulware. Yes.

DR. DWORKIN: Robert Dworkin. Yes.

DR. HOFFMAN: Gary Hoffman. Yes.

DR. MANZI: Susan Manzi. Yes.

DR. FARRAR: John Farrar. Yes.

DR. HOLMBOE: Eric Holmboe. Yes.

DR. GROSS: Peter Gross. Yes.

DR. WOOD: Alastair Wood. Yes.

DR. GIBOFSKY: Allan Gibofsky. Yes, "but."

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. CUSH: Jack Cush. Yes.

DR. BATHON: Joan Bathon.

MS. MALONE: Leona Malone. Yes.

MR. LEVIN: Arthur Levin. Yes.

DR. ILOWITE: Norm Ilowite. Yes.

DR. D'AGOSTINO: Ralph D'Agostino. Yes.

DR. MORRIS: Lou Morris. Yes.

DR. CANNON: Richard Cannon. Yes.

MS. SHAPIRO: Robyn Shapiro. Yes.

DR. PAGANINI: Emil Paganini. Yes.

DR. FRIEDMAN: Larry Friedman. Yes

DR. HENNEKENS: Charles Hennekens. Yes.

DR. SHAFER: Steve Shafer. Yes.

DR. WOOD: So the total vote is unanimously yes.

Let's move on to Question 1.b.; does the overall risk versus benefit profile for celecoxib support marketing in the U.S.? So this is the question for which everybody is waiting, I guess.

Discussion? Dr. Elashoff?

DR. ELASHOFF: I would just like to comment that, in some trials, like those of the statins, it is a potential benefit weighed against a potential risk. Here we are talking about immediate benefit in terms of pain versus potential risk. I just wanted to make that distinction.

DR. WOOD: Right, although it is worth remembering the rationale for these drugs is a safety benefit. There is no evidence that we have been shown that these drugs have a greater analgesic effect than the other drugs.

Other discussion? Dr. Shafer?

DR. SHAFER: I would submit for Question 1.b. that we really don't have the efficacy data. There are no data on G.I. risk with concurrent steroid use which is a common co-administered drug in patients with arthritis, particularly rheumatoid arthritis.

I asked the Pfizer representative if there were data about celecoxib versus NSAID plus PPI. He said he didn't know of any. In fact, there are

two such studies both published by Dr. Chen, one in New England Journal 2002, one in Gastroenterology, 2004, with an editorial by Dr. Cryer. Neither was sponsored by a drug company and both showed no net benefit.

So I don't know what, if anything, we can conclude about the efficacy of celecoxib given that--versus what is likely the alternative therapy which is PPIs plus NSAIDs.

DR. WOOD: The CLASS study also showed no benefit in the full analysis.

Dr. Domanski?

DR. DOMANSKI: I think that what I am about to say is true not only for Celebrex but for all of them, but certainly for Celebrex. I think that the data presented support the view that the COX-2 inhibitors are effective for their intended use, probably not uniquely so in any group that we can define right now but almost certainly in some individuals.

Secondly, these drugs, Celebrex and all of them, in fact, do place patients at increased risk

for a heart attack or death but the absolute increase in risk is not such that these drugs should be taken out of the hands of wise physicians and their well-informed patients in whom these drugs were a last resort for achieving an acceptable quality of life.

So I think that, with this drug as with the others, we need a black-box warning that is carefully crafted. But taking them out of the hands, as though they were a smoking gun, is probably too extreme.

DR. WOOD: But you are talking about more than just a black-box warning. You are talking about using them as a last resort; right?

DR. DOMANSKI: That is how I would suggest they be used.

DR. WOOD: That may come in c., I think. Any discussion on 1.b.? Yes? Dr. Shapiro?

MS. SHAPIRO: I'm confused by that last comment. I have not walked away from this conversation with the view that they are a last-resort option for most of the people who are

taking them. Could you explain.

DR. DOMANSKI: Are you asking me for an explanation? I think that is how they should be used. I think there is clearly a significantly increased risk. I think many people will derive benefit from other drugs that probably are less--place them at less risk. But I think there also exists a group of people who don't derive benefit. There clearly are differences among people in which drug they respond to. Somebody who is leading a very poor quality of life, who understands the risk they are taking and is willing to take it, I think is a reasonable candidate for that drug and I don't think it ought to be pulled out of the hands of the physicians to prescribe it.

MS. SHAPIRO: I just want to be clear that, in thinking about the answer to this question, we are considering taking into account, for most people, as opposed to the smaller subset, the availability of less risky alternatives in giving our guidance to the FDA. Am I right?

DR. WOOD: Right.

DR. DOMANSKI: And I would certainly second that.

MS. SHAPIRO: Okay. Dr. Farrar?

DR. FARRAR: I need to bring up a couple of points here that I think are vital to our discussion. First of all, again, for clarity perspective, the lack of G.I. side effects is not the benefit we are talking about. I agree with Dr. Shafer that some of the benefit that they may provide to our patients is in a reduction of the side effects that are seen in the G.I. tract.

But the benefit that we are talking about here is the benefit to patients who are not responsive to other drugs perhaps because of G.I., known G.I., toxicity but, perhaps, also for another reason which is that these agents work in a different manner.

Dr. FitzGerald laid out very carefully for us the complexity of the COX-1/COX-2 story and it is not clear to me, as a pain specialist, that we yet understand all of the complexities of that. What we have heard from and seen from patients that

we have all treated and heard some comments yesterday is that these drugs work very effectively in certainly some of those patients where other drugs did not work. I would take serious issue with the comment that we don't know that they work better.

For sure, if you look at trials and you look at the mean value of the benefit, these drugs cannot be shown to be of superior benefit in an overall population. However, certainly from the clinical experience, we know that there are patients who will respond to one and not to another. I would argue, in fact, that there is a very strong reason for allowing drugs, as long as the risk is not abhorrently high, that these drugs be allowed to be available so that patients and clinicians can make decisions understanding all the risks in moving forward.

The last thing is, with regards to it being a last resort, I think if you looked at the comparison of lumiracoxib with ibuprofen, what we see there is that there is a reduction in the

cardiovascular--or a lower cardiovascular risk in one group compared to what we would normally consider and is even over-the-counter as a therapy, so one that we would sort of consider more safe.

I don't think that we have data yet that tells us that these are a last-resort medication.

DR. WOOD: Do we have data, just for clarification for me, that show that there are patients--data-driven studies that show there are patients who respond to these drugs who did not respond to traditional nonsteroidals? Can we point to published studies where that has been done?

DR. FARRAR: There are no published studies that I know of.

DR. WOOD: Okay. That's good. Let's move on to Dr. Ilowite.

DR. ILOWITE: I just wanted to comment about the words "last resort" also. I think it may convey that you have to go through all 20 NSAIDs or wait until you have a serious gastropathic event before using them. I don't think that is what you meant to say.

DR. WOOD: All right. Dr. Hennekens?

DR. HENNEKENS: I find answering b. difficult without at least thinking about c.

because those patients who are allergic to naproxen, those with GERD or other G.I. toxicities for whom NSAIDs and PPIs are deemed contraindicated by their doctors, those who wish to take it despite knowing that there is a 40 percent higher risk of CVD, these are things which drastically alter the risk:benefit equation, in my view.

DR. WOOD: Okay. Dr. Domanski?

DR. DOMANSKI: Let me flesh out the term "last resort." I want to be careful that it doesn't imply some mechanical necessity to go through every drug known to man. I think it is a matter of judgment. I think that they would be my last choice in a given patient but not necessarily the last of 20.

DR. WOOD: Dr. Holmboe?

DR. HOLMBOE: I agree that I think with some restrictions that this should be made available. I am also troubled that the other

available agents, I am not convinced after this meeting, that they are necessarily any safer. I think the only thing we have seen, some reasonable data, has been around Naprosyn but almost everything else we have seen with the other alternatives don't exactly give me great comfort that making patients take those over COX-2s would be necessarily better.

DR. WOOD: Dr. Nissen?

DR. NISSEN: That is exactly the same problem that I am having. It would be very easy if we knew that ibuprofen and diclofenac were placebo. See; I answered yes to the question, does celecoxib increase risk over placebo. I am convinced by all the statistical arguments that it does.

What I don't know is if it increases risk over ibuprofen or diclofenac. So, you know, it is a moving target, everybody, and I think your point is an extremely important point here. So how you answer that question depends on whether you accept the premise that all the other NSAIDs are at 1.0 for hazard, and I am not convinced that they are.

I am worried that some of them may be at 1.3, 1.4, 1.5 where we think celecoxib is, in which case our decision could be irrational.

So it is a really big problem.

DR. WOOD: Dr. Temple?

DR. TEMPLE: I don't want to participate in this discussion but I did want to point out to people, however, that where you are very worried about a side effect of a drug, it is possible, in a very easy way, to show that it works when other drugs don't work. You take failures on whatever the standard therapy is, randomize people back to that therapy or to the new drug. That is how clozapine got into the marketplace. That is how bepridil got into the marketplace. So, if that was really an important question, that is not that hard a study to do.

DR. WOOD: Right. But it is not a study that has ever been done.

DR. TEMPLE: Not to my knowledge.

DR. WOOD: If the data is as compelling as people would have us believe, it should have been

very easy to do.

Any other discussion? Yes?

DR. BATHON: I am very strongly in agreement with the last few comments about safety. I wanted to throw out one other comment for consideration. If a pharmaceutical company brings a conventional NSAID to the market, they don't have to prove that it is better than the existing agents. When the COX-2 drugs were brought to study, their initial studies were 6 weeks, 12 weeks, long. They were shown to be effective in reducing pain and so they were approved on that basis.

It was later, in the following studies, that they used the biology to then work towards an indication of safety from the G.I. perspective. But, as we are deliberating, I don't think it is entirely fair to hold them to higher efficacy standards because we don't hold conventional NSAIDs to that basis.

Now, if we then add in the safety perspective--if they are not more efficacious, then

we have to prove that they are less safe. The last few comments are relevant because of the safety signals that we might be seeing with conventional NSAIDs. We are in a quandary, I think, saying that they are more safe at the point.

So I would just like to put that perspective.

DR. WOOD: Tom, could I ask you to go back over for us what you saw as the safety signals with conventional NSAIDs. You went through that with us once.

DR. FLEMING: You mean specifically what we know from these trials?

DR. WOOD: Right. Just the conventional NSAIDs. It didn't sound very convincing to me, but maybe I missed it.

DR. FLEMING: I think what I was saying was just referring to the evidence that we had from these 12 to 14 trials and we had evidence on naproxen and we had evidence on diclofenac.

DR. WOOD: But they were not evidence of harm; right?

DR. FLEMING: My sense was that the evidence for naproxen, in relative comparisons here, was, overall, quite favorable and that was

based on the positive result in the VIGOR trial and the positive results in the etoricoxib setting and the lumiracoxib setting. The ADVANTAGE trial was fairly neutral.

So it seemed from those data that the naproxen experience looked more favorable than the coxibs it was compared to. The diclofenac was compared in the CLASS trial and in the etoricoxib setting. In the etoricoxib setting, it was neutral to slightly worse. In the CLASS trial it was what I might call comparable to the Celebrex.

DR. WOOD: So we are not hearing from you a lot of evidence-based concern about the other nonsteroidals. That doesn't mean they are not there, obviously.

DR. FLEMING: Certainly the data are much more limited. My own sense about this is that the diclofenac seems to be in the range of--its experience seems to be in the range of what we were

seeing with the coxibs that it was compared to while my own sense, in looking at the tally of the data, is that the naproxen does look more favorable, in the aggregation of evidence, compared to the coxib comparators.

DR. WOOD: And the diclofenac would fit, I guess, with the biology, perhaps.

DR. CRYER: Mr. Chairman, if I may, I feel compelled to respond to that specific question about the safety concerns of traditional NSAIDs because the response only addressed potential cardiovascular concerns. From a gastroenterology perspective, I feel compelled to remind the group that this was the original problem that led to this entire discussion.

DR. WOOD: I don't think anyone doesn't doesn't recognize that.

DR. CRYER: Okay.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: On Tuesday of this week, Dr. Colin Baigent of Oxford presented to the European Medical Evaluation Agency his preliminary

analyses of 113 trials with 135,000 patients. Looking at the placebo-controlled trials, the relative risk was 1.41. In the naproxen comparator, it was 1.56. In the non-naproxen NSAIDs, it was 0.86. So we were fortunate to have Tom here with what he has done because, in effect, Tom has given us the same perspectives that were reported to the European authorities.

DR. WOOD: Any further discussion on 1.b.? Dr. Abramson.

DR. ABRAMSON: Just, Alastair, I wanted to address your point that there is no evidence in randomized trials to be suspicious of the nonspecific nonsteroidals. The nature of the evidence, I think, is that they were no different in many of these trials from the drugs that we were imputing some cardiovascular risk. I guess Dr. Fleming, yesterday, one of the members of the panel, was talking about if a coxib is worse than placebo.

We have multiple randomized controlled trials from TARGET to CLASS and EDGE, that the

comparator nonselective NSAID looked like the coxib than b. looks like c., and b. is different from a. I think that is the nature of the evidence in the randomized clinical trials that gives a lot of us some concern about giving those drugs a pass.

DR. WOOD: Arthur?

MR. LEVIN: Not to be wordsmithing but I am somewhat uncomfortable with the wording of b. and c. and how it may be interpreted, and I would say not only for 1., but 2. and 3. as well. I guess I would interpret b. as a question asking does it support the marketing as "at present" in the U.S. I mean, that is how I would interpret that.

When we start nuancing that and modifying and saying, yes, but with a black-box warning or yes, but with this risk management strategy, that is for later discussion.

DR. WOOD: I interpret it as--and the FDA can correct me here--I interpreted that under any circumstances. Is that fair?

DR. JENKINS: I can address that. The

intent of these questions were that the questions would be the same for the three approved products. So the first question, we wanted to hear your view on is are there data to suggest that there is an increased cardiovascular risk for the individual product. That is why we put that first.

If you were to answer no to that question, it might make the second question less important. We also wanted you to answer the question which is b., which is essentially, should the product be withdrawn from the market It is not stated that way because, in a desire to keep the answers all the same for the three questions, it made it odd for the Vioxx, which has already been voluntarily withdrawn.

So that is why we asked, do the data support marketing. The third part of the question really gives you the opportunity to say, yeah; I think it should be on the market but we think you should make the following changes to manage the risks that we saw in a.

DR. WOOD: I mean, given what we heard

yesterday about Vioxx not being on the market but maybe being back, do you want to change it? Should they be withdrawn?

DR. JENKINS: No. I think it is fine to leave the questions the way they are because, you know, Merck has stated their perspectives on this but, presumably, if you find that these products have a cardiovascular risk and should stay on the market, you are going to give us advice about what we should do to change the labeling, the marketing, et cetera, et cetera, for these products. So Vioxx could not just reappear back on the market on Tuesday like a question we got last night in the press briefing. There would need to be substantial agreements to move forward on how to revise the labeling which we would have to approve.

DR. WOOD: Right. Okay.

Does that help, Arthur? All right. Dr. Cush?

DR. CUSH: I'll pass.

DR. WOOD: Any other discussion? Dr. Nissen?

DR. NISSEN: I want to be reassured that ibuprofen and diclofenac are not worse.

DR. WOOD: We don't have that data. I

would like to be reassured, too. Bob Temple designed the study. We would all want reassurance. But we are sitting here at whatever time it is, 11:00, 12:00--

DR. NISSEN: I understand. I am being provocative for a reason and the reason is that there is a lot of uncertainty about those other two agents. I think that, as we think about changing the landscape of the use of NSAIDs, there are some risks we are taking. Some of the risks are that we shift use to agents that may actually turn out, in the final analysis, to be less safe. I think we have to understand that.

DR. WOOD: We understand that. But I think we are faced with the data we have right now and we need to act and decide on that which is the position the FDA was in as well and why they found it tough.

Okay. In the absence of any other

comments--oh; I'm sorry. Dr. Manzi.

DR. MANZI: This is prior to voting for Letter b. I want to make sure it is clear that we are voting on risk:benefit in the population that there is an indicated use for. Is that correct--not the prevention population.

DR. WOOD: Right. I mean, if someone comes in and demonstrates that this drug cures cancer 100 percent of the time, then, obviously, they will come back and have a very different risk:benefit ratio than we would be discussing here. So I think all we can discuss right now are the indications for which it is being used right now.

If someone comes back with colon polyp prevention or some other, a curing of Alzheimer's, the individual risk:benefit analysis that people would take into account then I think would be different. Then I think that would be reasonable.

DR. MANZI: I just think it is important because, although we are extrapolating risk from a population that it wasn't indicated as far as

usage, we can't extrapolate risk:benefit.

DR. WOOD: The population--I mean, one question is do you think, as you take this into account, you should consider is, do you think the outcome for risk would be fundamentally different based on some biologically plausible probability in different populations. If it does, you might take that into account, I guess.

DR. MANZI: I don't think we have the answer to that. I think it is unknown. But I think the benefit may be very different.

DR. WOOD: It is not entirely unknown. The studies that were done in arthritis patients which were not placebo-controlled, done against active controls, showed the same kind of signal.

Now, we impute in them a placebo which is always risky, of course. But we would have to come up with some very convoluted kind of argument, I think, to do. But I hear your point.

Any other comments? Are we totally satisfied, as the auctioneer would say? Then let's start the vote and we will start it on the other

side this time. I would remind you, again, to state your name.

DR. SHAFER: Steve Shafer. I, unexpectedly, cast my vote last night when my father, an 89-year-old man with no other risk factors for heart disease but a sensitive stomach, asked me if he should stay on his Celebrex. I said yes.

DR. HENNEKENS: Charles Hennekens. Yes.

DR. FRIEDMAN: Larry Friedman. Yes.

DR. PAGANINI: Emil Paganini. Yes.

MS. SHAPIRO: Robyn Shapiro. Yes.

DR. CANNON: Richard Cannon. Yes.

DR. MORRIS: Lou Morris. Yes.

DR. D'AGOSTINO: Ralph D'Agostino. Yes.

DR. ILOWITE: Norm Ilowite. Yes.

MR. LEVIN: Arthur Levin. No.

MS. MALONE: Leona Malone. Yes.

DR. BATHON: Joan Bathon. Yes.

DR. CUSH: Jack Cush. Yes. No "buts."

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. GIBOFSKY: Allan Gibofsky. Yes.

DR. WOOD: Alastair Wood. Yes.

DR. GROSS: Peter Gross. Yes.

DR. HOLMBOE: Eric Holmboe. Yes.

DR. FARRAR: John Farrar. Yes.

DR. MANZI: Susan Manzi. Yes.

DR. HOFFMAN: Gary Hoffman. Yes.

DR. DWORKIN: Robert Dworkin. Yes.

DR. BOULWARE: Dennis Boulware. Yes.

DR. DOMANSKI: Michael Domanski. Yes.

DR. FLEMING: Fleming. Yes.

DR. FURBERG: Furberg. Yes.

DR. DAY: Ruth Day. Yes.

DR. PLATT: Richard Platt. Yes.

DR. GARDNER: Gardner. Yes.

DR. ELASHOFF: Janet Elashoff. Yes.

DR. NISSEN: Steve Nissen. Yes.

DR. ABRAMSON: Steve Abramson. Yes.

DR. WOOD: Okay. To allow everybody to go off and file their stories now, we will break for lunch and be back to start again promptly at 1 o'clock. Thanks a lot.

(Lunch recess.)

A F T E R N O O N P R O C E E D I N G S

(1:02 p.m.)

DR. WOOD: Let's get into our seats and let's begin. I have taken the chair's prerogative to change the program. What I have asked is Dr. Anne Trontell from the FDA to give us a short presentation on what the FDA's regulatory armamentarium looks like in terms of the potential restrictions or other changes they could make to a drug that might be relevant to this discussion in order that, as we go through the next question, and subsequent questions, we can do that in the most informed, thoughtful way.

Anne has very kindly agreed to do this very quickly--I mean, to prepare it very quickly, not to go through it very quickly. When we finish, I will ask her to stay up there and we will have the opportunity to discuss the various options with her in some detail so that we have got a really good handle on what the various issues are.

Anne.

DR. TRONTELL: Thank you. This is a list

of some of the options that have been outlined or experienced by the agency. I am going to present them quickly sort of in a rough progression from those that are voluntary and least intrusive to those that are most intrusive.

One option that I will start off by listing is not, in fact, one that is under the agency's purview to require but, certainly, a number of the sponsors have come forth and made voluntary limitations on marketing of their products perhaps by offering not to market it directly to consumers or, in some instances, some companies have voluntarily limited the detailing of their product to certain specialty groups or advertising, perhaps, to only certain specialty journals.

But let me turn now into the arena where FDA starts to have some regulatory purview. The first area is in the area of labeling. There, in a black-box warning, FDA can make quite salient certain risk information, certain contraindications or other conditions that they feel are appropriate

to the safe use of a product.

One consequence of giving a product a black-box warning is that it limits the use of what we call reminder ads, those that simply have the product's name. In practice, it makes marketing of these products directly to consumers rather difficult, it is actually mentioning that drug product.

Other options available in labeling or relabeling a product might to be to change its indication to some form of second-line use or, perhaps, to actually go so far as to contraindicate its use in certain patient populations.

Another broad tier of interventions that might be taken would be in the form of some kind of targeted education or outreach. This can go to clinicians and/or to patients. This can come in the form of public announcements or "Dear Healthcare Practitioner" letters as has been done repeatedly in the past.

One form of education directed to patients are medication guides which are, in fact, forms of

patient-friendly labeling informing of risks or of the methods to avoid risks directed to proteins and, in point of fact, required to be dispensed with each prescription of that product.

There are other forms of academic detailing that have been shown in some settings to be quite successful in targeting prescribers to direct their prescribing of a product to appropriate conditions felt to support its safe use.

The next broad category that I would suggest would be what we have termed, in draft guidance, reminder systems. These have ways of reinforcing or prompting people to seek appropriate use of the product. One candidate in this area might be some form of a patient agreement or informed consent where the patient acknowledges the risks of the product and notes that they accept them.

There have been several systems in this category also put forth where the physician makes some form of attestation on paper or otherwise that

some appropriate-use condition is being met. This is the case for the drug product alosetron that has been mentioned here previously. This might be attestation in the case of these products that some form of second-line use is being followed that the patient is otherwise intolerant of other therapies.

Other reminder systems may also take the form of some limitation put on the amount of the product that is supplied in any one particular prescription or, perhaps, limitations placed on whether or not refills can be obtained.

DR. FARRAR: By physician attestation, do you mean they have to write on the prescription what it is for?

DR. TRONTELL: I can give you the details of the two systems--there may now be three--where there is usually some form the physician fills out to attest that the patient meets the appropriate conditions that might be kept on file or that might, in fact, be some condition of the product being dispensed. So, in the case of alosetron, a sticker is placed on the prescription. The

pharmacist is to look for that sticker to be in place before they actually dispense the product.

The last category, short of marketing suspension, is what we have termed performance-linked access systems which, really, might otherwise be termed some form of restricted distribution of the product. In this setting, one sets forth some defined population, either of providers or patients, and sets up a process or system that restricts access to the product to those individuals.

Pharmacists may be involved if this is a product that is available through outpatient departments. These basically imply that not every physician, pharmacist or patient is able to get the product without going through certain conditions. Those conditions are required for access and, hence, the term performance-linked access.

Examples that may be known to many in this room include the drug product clozapine, sometimes abbreviated no blood, no drug. People are required to present proof of inadequate white count before

obtaining the product. Thalidomide has an extensive system of registering patients, providers and pharmacists that require input from several parties to assure that the woman obtaining the product isn't pregnant at the time of dispensing.

There are some others.

In these, just to reinforce the point, which is that the product is not dispensed, not shipped or otherwise made available to the patient unless defined conditions of minimal risk have been met.

That is a very quick run-through. I will be happy to entertain further questions.

DR. WOOD: Thanks for preparing that so quickly. Anne, a number of people have asked to have a printed preparation of that made. I wonder if we could do that as soon as we have finished.

Are there points of discussion or questions from the Committee? Yes, Arthur?

MR. LEVIN: Anne, how many drugs do we have registries for now. It is more than one, isn't it?

DR. TRONTELL: I'm sorry. You said registries?

MR. LEVIN: Right. With Accutane, didn't

we get to a registry?

DR. TRONTELL: There is not one currently in place with Accutane or isotretinoin, but some of the discussions by the Drug Safety Advisory Committee had made recommendations that one be put in place. Traditionally, when you get into this last category of restricted distribution, it is very difficult to put one in place without some form of registration. You really need a list of who can and who may not, in fact, prescribe the product. So registration is almost a condition of putting up the restrictions.

MR. LEVIN: Just one other question. In the beginning, you labeled something as voluntary. How would you characterize all of these other risks. Is this a negotiated--in other words, you have voluntary limitations on marking, but voluntary doesn't appear anywhere else, such as with labeling or anything else. But isn't all this

really a negotiation? Or does the agency have the power to say, this is the way it is going to be or it comes off the market.

DR. TRONTELL: I think that is a difficult question to answer directly. The distinction of voluntary limitations were placed here because, to my knowledge, these agreements that have been put in place relative to marketing have been ones that have been offered by the drug companies opposed to FDA trying to make any restrictions upon marketing.

Generally, all of these matters of risk management or risk minimization, there is a back-and-forth process that is directed to the feasibility of actually putting some of these systems into place.

DR. WOOD: But, in fairness, if this committee makes strong recommendations that something should be done, it would be pretty tough not to follow them, I would have thought. Dr. Platt?

DR. PLATT: Anne, questions about black-box warnings and academic detailing; does the

agency have a sense overall about how well black-box warnings work? I am mindful of the fact that cisapride was withdrawn from the market after several revisions of the black box failed to reduce inappropriate prescribing below something like 25 percent of all cisapride recipients.

So that is Question No. 1. Why don't you answer that and then I will ask you about academic detailing.

DR. TRONTELL: You know, evaluations of the effectiveness of any of these programs are really limited and cisapride was certainly an instance where we saw persistence of the undesired behavior despite repeated labeling.

It is difficult to say. There are some products, I was telling Dr. Wood at the break--ketorolac has a black-box warning and indications that it should be used for a very circumscribed length of time. Our examinations of prescription-use data would suggest that there is actually very high conformance in that particular instance. So I am not sure we have enough

information to predict the effectiveness of these, in particular the black-box warning.

Again, looking at the black-box warning put in place for the drug product Seldane and the occurrence of torsade de pointes in its concomitant administration with other products, there were some evaluations of that labeling intervention suggesting that upwards to 90 percent or more of an appropriate co-prescribing had been eliminated but it had not eliminated entirely and that there were still unacceptable levels persisting.

So it is a mixed picture and I would like to emphasize to everyone that, perhaps, with the exception of the restricted systems, which are put in place on a relatively limited basis because they are really quite a large undertaking and do restrict access as well as minimize risks, that we have very poor information.

The systems that register individuals, by the nature of the fact that we now have a defined population of people receiving the product, we can better estimate the adverse events and other events

that are reported to us. In the case of clozapine, we can actually look at how many low white counts have been observed.

DR. WOOD: But there are other examples. The Rezulin example with multiple changes in the label to invoke different liver-function test frequencies, there is good data on the fact that that was not followed, I guess. And the cisapride example is also true. Wasn't it bromfenac that was supposed to be for ten days and most of the patients got it for longer. So there are a lot of examples that, at best, don't provide you with much reassurance that labeling changes work.

That is not to say we shouldn't do them, but, certainly, just labeling change on their own have not been extraordinarily effective.

DR. PLATT: Right. So can I ask you about what mandatory academic detailing means. Who is responsible for developing the content? Who is responsible for delivering it? Who is responsible for overseeing compliance with an effective academic-detailing regimen?

DR. TRONTELL: This is something that I put down for--to my knowledge, I don't believe we have any mandatory academic detailing positions in

place but, as one example of a form of education that, in some settings has been shown effective to alter prescribing behavior. But, to my knowledge, that is not in place.

If you go back to some of the voluntary programs, some products are largely, if not solely, limited to certain specialty groups. Some of the human-growth hormones are largely confined to pediatric endocrinologists. So that has--I don't know the particulars of how those products are detailed to those prescribers.

DR. PLATT: Right. So it is not an option for us to recommend that the agency require an academic detailing program.

DR. TRONTELL: In this component, again, these slides were assembled hastily--I think the question might be, it still fits into some realm where we might define some targeted prescribing group that we thought would be appropriate to

determine which patients should receive this product. So I believe it is not an easy option to identify. It really probably relates a little bit more to some of these issues which is if there is some form of limited promotion directed toward one specialty group or a specially trained group in being able to prescribe these products.

DR. WOOD: Dr. Manzi.

DR. MANZI: Actually, my questions were answered. Thanks.

DR. WOOD: Okay. Great. Dr. Day?

DR. DAY: I just wanted to mention that, in addition to the attestation option, having people sign a piece of paper, either the physician but especially the patient, that they have read and "understand," we don't know that they really understand until we give them a comprehension test.

So, this could take the form of a very brief survey. This has been tried in Accutane. To start out with, it was a voluntary survey. Under a voluntary survey, I believe that 20 percent of the patients actually filled out the survey. I don't

think that the new guidelines for what is going to happen on Accutane have been released yet, but there was some talk that that might become mandatory.

So it doesn't need to be onerous. It can be very brief. But there might be some patients who are in such pain on a given day, give them anything, they will sign it to get their relief. But if they are going to be taking these products over the long term, we really do want to be sure they understand what the consequences are going to be.

DR. WOOD: You might sign something when you were getting your wisdom teeth out that might not be applicable later; right? Dr. D'Agostino?

DR. D'AGOSTINO: Could you just reiterate what you mean by the black box makes direct-to-consumer very hard. I thought it eliminated it. So could you explain what it actually does?

DR. TRONTELL: I will actually defer to Dr. Temple to give you those details.

DR. TEMPLE: The black box makes reminder ads impossible. How big a deal that is depends on how much reminder advertising there is. I think

that is not a major thing.

But the ad to be considered appropriately balanced would have to convey the contents of the black box in all its full unpleasantness. I think that is what Anne meant. It is hard to write an ad that is appealing to people when you are telling them about all this bad news, and that would have to be right up front.

I don't know how much you pay attention to ads, but you can't just stick it over in the place where all the small print is. It would have to be part of the main ad, whether that is a written ad or a t.v. administration.

DR. PLATT: These ads you see on television, at the end telling you may die from this.

DR. TEMPLE: Things like that. It would have to say the bad news.

DR. MORRIS: But, Bob, that is why there

is no oral contraceptive ads on t.v.? That's the point. That is black-box drug.

DR. TEMPLE: I wouldn't allege for a minute that all black boxes make it unattractive to do them. But those ads have to tell you this bad news and, if that is so unattractive, the ad doesn't appeal anymore, that is what would make it difficult.

DR. MORRIS: But, even if there is no black box, it has to tell you the bad news.

DR. TEMPLE: The contents of a black box are scary and unpleasant and that is all Anne meant, that it might be hard to get an appealing ad.

DR. MORRIS: I don't want to get off the impression that, if there is a black box, we don't have to worry about DTC.

DR. TEMPLE: No; I wouldn't say that.

DR. WOOD: No; that is exactly right. There are certainly ways to do DTC in print ads, particularly, that would be permissible with the black-box warning. They might not be pictures of

young ladies skipping through pretty fields, but they would be unlikely to have just skull and crossbones on their either.

DR. TEMPLE: Right. The only thing I would allege is that we would ask that the contents of the box be featured prominently in the ad. So it still might be possible.

DR. WOOD: So one way to summarize what Anne is saying about this would be that restricting DTC should be a separate or additional issue to black-box warnings. Is that fair, Bob, even though I understand restricting DTC is not within your--

DR. TEMPLE: Right.

DR. WOOD: But it is within the rubric of the commission's recommendations.

DR. TEMPLE: It is. I think what Anne said is we can negotiate on those things. We don't think we can ban DTC. Not everybody thinks that is true, but we don't think we can.

DR. WOOD: But we did hear yesterday that voluntary agreements can be changed pretty fast.

DR. TEMPLE: Right. Can I mention one

other thing?

DR. WOOD: Sure.

DR. TEMPLE: We do have one actual rule that does allow us to impose restricted distribution under what is called Subpart H for drugs that are important and that you could only be satisfied that they were safe for use in that setting.

We have not, to my knowledge, imposed such as Subpart H restriction after approval. I could be wrong about that. I am sure it would involve what you have been calling negotiation. But I don't think it is impossible

DR. WOOD: But that was mainly applied to oncology drugs; right? No?

DR. TEMPLE: No. Subpart H has two parts. One is approval on the basis of a surrogate. That one part. The other part is approval with limits on distribution that also make you--you would have to believe that drug couldn't be distributed safely without it. It is only supposed to refer to drugs that you really need to.

DR. WOOD: Dr. Gross?

DR. GROSS: Since direct-to-consumer advertising has been so effective for the

pharmaceutical companies, have you considered doing direct-to-consumer education from the FDA's point of view, either pairing it with the ad from the pharmaceutical companies, doing it separately. I know it costs money. Maybe you could have a PDUFA extended to cover the cost for that. But I think, since it has been so effective for them, why not consider it for you?

DR. WOOD: Which one of the three of you wants to take that?

DR. TEMPLE: Actually, I am embarrassed to say I didn't hear the very beginning of the question.

DR. WOOD: The suggestion is that, in addition to direct-to-consumer advertising by drug companies, there could be direct-to-consumer advertising by the FDA to put the other ads in perspective, I guess.

DR. TEMPLE: Ah. That takes money beyond

what we usually feel we have.

DR. GROSS: That is why I suggested PDUFA funding.

DR. TEMPLE: That's okay with--never mind. I am not allowed to say that.

DR. TRONTELL: What FDA does have is the opportunity, through its own broadcast resources, through MedWatch, through public-health advisories, the opportunity to speak. But, certainly, any kind of commensurate advertising campaign has largely been restricted to broad messages; you know, generics are safe, et cetera, like that.

DR. WOOD: Dr. Dworkin.

DR. DWORKIN: Are there other levels of warning in addition to black-box warnings?

DR. TRONTELL: Well, a black-box warning, or a boxed warning, is really--attaches to some of the marketing restricts that Dr. Temple described, but there is, certainly, as part of the package insert or physician labeling, a warning section that information can be placed. The black box is often set off in heavy type to make it prominent or

salient to the physician, anyone looking at this product, that there is some special risk that deserves attention.

DR. WOOD: Dr. Morris? Oh; okay.

MR. LEVIN: A couple of things. One of the reasons for my no vote was this concern and that is the ability of FDA to insist on and enforce conditions which will limit the distribution and use of the drug to appropriate populations.

That said, some of the risk-management experiences we have had actually have been positive. For example, with lotrinex, we did manage to reduce the population being prescribed the drug considerably and, I think, into the range of what experts estimated was the appropriate population.

My problem here is the time it takes to work through this. I can't remember when we had that Accutane meeting but it was over a year ago. Accutane meetings have occurred regularly over the last several decades and it just take forever, in this negotiated process, to get the things in place

that are recommended and then accepted by the FDA. So I am very concerned about the time-lag issue here, that whatever we recommend today, in terms of--if we do, in terms of these kinds of options for limiting risk, that you are not going to see this in the next couple of months based on prior experience. It is going to be a long haul.

DR. WOOD: I think part of the committee's job should be to make a recommendation about how fast we should see it and light a fire under these guys. That will provide some ammunition to the FDA in their negotiations and will provide some focus to others. If they are not doing it fast enough, then we--the other option, I suppose, is to put a more restrictive position until whatever issues are resolved.

Sorry. John?

DR. JENKINS: I think, as Dr. Galson said on Wednesday morning in the Introduction, we are committed to making our decision our your recommendations on these applications and these products very quickly after this meeting. We will

do everything we can to implement whatever those changes are as quickly as possible recognizing there are, sometimes, some just logistical issues that have to worked through. But we are committed to doing the action and getting it implemented as quickly as possible in this case.

DR. WOOD: There is nothing beats setting a time line, so we will probably do that. Any other comments?

DR. NISSEN: Quick question. If we think the dose is a particularly important issue, could one restrict the--could we change this label or change the doses that are marketed; for example, celecoxib is available in 100 and 200-milligram capsules. Could we limit it to the 100-milligram capsules as a way to avoid the exposure to higher doses. Is there a way to do that for the FDA?

DR. TRONTELL: That would fall in the category of what would be a reminder system; in other words, to make it difficult for people to take the higher dose. By requiring them to take more pills, they would use it up more quickly. So

that would be an option that I think we would be eager to hear from the committee if that was what they thought would be the best to do.

DR. NISSEN: What I am getting is to get 800 milligrams, you would have to take 8 capsules which, obviously, would have an effect on patients not doing that.

DR. JENKINS: If I could just make a comment on that. We have to be careful that, when we make our changes, that we don't have unintended consequences of our changes. One of the things that catches people off guard sometimes is that drug prices are not reflected, or based on the number of milligrams that are in the capsule. So 100 and a 200-milligram capsule often are very close to being the same price.

So you can have an unintended consequence for patients who need that higher dose of substantially increasing their cost by limiting the dosage that is available.

DR. WOOD: I agree with that and that is an important point, but one way, I guess, to

implement that kind of change would be to have a different restriction for a different dose. You could have the 200-milligram dose with different restrictions on it than the 100-milligram dose. But we will get to that point.

DR. JENKINS: Right. Stephanie?

DR. CRAWFORD: Dr. Trontell, could the options for action from a regulatory perspective include the requirement for definitive, well-designed postmarketing surveillance studies or is that not an option?

DR. TRONTELL: I think that is something that can enter into some of the regulatory options that FDA would consider, but they are not what we have classically described as an intervention to minimize risk. So that might be a way to better characterize the risk but that is something I think I will let Dr. Jenkins reply to more definitively.

DR. JENKINS: We could clearly have the companies enter into an agreement to do a postmarketing commitment study based on your recommendations. So postmarketing commitments are

not only made at the time of approval, they can also be made after approval when a new issue comes up. We probably haven't used those as much in the past as we should have in the post-approval arena, but it is certainly something we could do based on your recommendation to what studies are essential.

DR. WOOD: And your success in getting these studies completed has not been terrific; right?

DR. JENKINS: I think that is a misstatement on a lot of levels. I think the record is much better than it is portrayed often in the media. Part of the problem in the past has been record keeping as well as the agency was not as diligent in the past as we should have been in setting time lines for when the studies should be done. We are much more strict now that we set rigorous time lines for every aspect of a study including protocol submission, enrollment, completion. That information is now publicly available on our website so you can see if companies are meeting their obligations or if they

are falling behind.

DR. WOOD: Okay. Well, I have got us back on time before lunch and now we have lost some of that. So, unless there are some really important questions--oh; Dr. Shafer. All right. Dr. Shafer, is this really important?

DR. SHAFER: Yes. I think so. But I just want to say that I don't support the idea of limiting the drug by placing the burden and the hassle on patients, things that require the patient--

DR. WOOD: We will get to that issue. Just questions for Dr. Trontell.

DR. SHAFER: I am coming to the very last point on the slide here. The efforts that place the burden on the patients, themselves, I think are misdirected.

DR. WOOD: All right. Thank you very much, and thanks very much for preparing that at such short notice over your lunchtime.

MS. MALONE: I just wanted to thank him for that comment.

DR. WOOD: I beg your pardon, Dr. Trontell. There is one more question.

MS. MALONE: I just wanted to thank the

last speaker for that comment.

DR. WOOD: Let's return to where we were before lunch. We were about to begin the discussion--oh; before we do that, I should announce the vote. Like in Iraq, it takes a long time for the votes to be counted. The results of Question 1.a. were 32 to 0, in case any of you missed that, and, for Question 1.b., 31 to 1.

Let's go on to Question 1.c. which is, if yes, and it was yes, please describe the patient populations in which the potential benefits of celecoxib outweigh the potential risks and what actions you would recommend.

The reason that we had the immediately preceding talk was it seemed to me, at least, as I looked at that question, that the potential actions obviously included a raft of the various options that we heard from the last speaker.

So, do we have discussion on this point?

Dr. Cush?

DR. CUSH: The populations where the potential benefits outweigh the risks were, I believe, those that are currently indicated; osteoarthritis, rheumatoid arthritis and a few pain indications. I do think that we should make a call for additional study. I do think that there should be additions to the warnings within the label under Precautions or Warnings, although not a black box for celecoxib.

I do think that there should be, in those warnings, or in the study designs that have come forward, a risk-reduction strategy so that patients who may be at risk, that risk is minimized as much as possible.

DR. WOOD: Other discussion? Arthur?

MR. LEVIN: Could I just ask why you oppose a black-box warning?

DR. CUSH: In this instance and this compound, I don't think there is a preponderance of evidence that argues in favor of that.

DR. WOOD: I didn't hear that last

comment.

DR. CUSH: I believe, for this compound, there is not a preponderance of evidence that would suggest the need for a black-box warning for this compound.

DR. WOOD: All right. Other comments? Dr. Shafer?

DR. SHAFER: I think for indications the drug should be indicated for individuals who cannot tolerate NSAIDs with a proton-pump inhibitor. I think the drug should be started at the lowest possible dose as part of the indications.

I oppose a standardized black-box warning for the class because I think that can result in a dilution of the message by implying that the risk across the class is identical. But I think each drug should be evaluated individually. In the case of celecoxib, I think the FDA should mandate a black-box warning clearly stating the increased likelihood of cardiovascular adverse events including death. But I also think there should be a black-box warning that contraindicates the drug

following cardiopulmonary bypass based upon the pareoxib, valdecoxib, data. I think that part--these drugs should all not be used following cardiopulmonary bypass.

Pfizer has voluntarily suspended marketing of celecoxib. I believe they should continue to do that, although it is not in our purview, until the FDA has implemented the recommendations.

DR. WOOD: Other comments? Dr. Domanski?

DR. DOMANSKI: You know, I wonder--this is a small point, probably. I think they all ought to get a black box. I think there is something to be said for--you know, if the message is substantially the same for having substantially the same message in that black box, though, because it underscores the fact that we think there is a class effect, admitting that there is probably some variation among the drugs.

DR. WOOD: I think we may have to circle back to the class effect at the end. So I think, right now, we should just focus on the risk-management strategy for celecoxib and not take

in the other ones.

I also think there should be a black-box warning. I think there should be severe restrictions on the prescribing of the drugs at both the dose and the patient population. Curt?

DR. FURBERG: I agree with that. I think if you are consistent. We unanimously said the drug carries risks. So we have an obligation to be more specific obligation to be more specific about that, and the way to do it is to have a black-box warning and warn against use in high-risk people and in the use of high doses.

DR. WOOD: I mean, we could have direct-to-consumer advertising that had people, well-known skaters skating around an ice rink and then dropping dead, or something rather than just--okay.

DR. PLATT: So yes to black-box warning. I am very impressed by the seeming consensus we have had that naproxen appears to be a relatively safe drug. So I would favor considering the label and the instruction to clinicians being that this

be a drug to be used as a drug of second choice; that is, for individuals who have either failed a comparator--and I am toying with the idea of suggesting the we actually name naproxen--or who are intolerant for some reason.

I favor the attestation requirement because I think there is an important piece of risk communication that we could do but I think we won't do without having that. I think there is a lot of information living in the datasets that were presented to us that hasn't been put in a form that is most useful to patients and that is I think that I would have the attestation actually specify the incremental risk that patients might expect based on the accumulated literature and that incremental risk would be patient-specific based on fairly standard risk factors.

So I would really hope that the committee would support a request to FDA to collaborate with NIH to use the accumulated data to develop much more informative information for patients and physicians to allow them to estimate their

incremental risk.

I think there is a huge difference between a patient agreeing to take an incremental risk that might be a half a percent per year versus an incremental risk that might be 10 percent per year. We have the information to allow patients to know what size risk they are taking on.

DR. WOOD: Dr. Nissen?

DR. NISSEN: The problem with that, of course, is we don't have robust enough data to actually know that in an individual patient's situation. But let me come back--the thing is what do we really want here? What we want is to make certain that therapy is available for those people in whom it is appropriate and to make certain that people in whom it is inappropriate don't get it.

Now, a black box is a good way to communicate things. The question is what does it say? I think what it has to say is that there is evidence of an increased risk of cardiovascular and cerebrovascular and, obviously, in language that is very clearly written.

I also think that it is important to discuss--we have seen some pretty good evidence of a dose-response relationship with cardiovascular

toxicity. So, to say to physicians, you should limit the dose and you should limit the duration whenever possible is also very important to communicate.

I don't think direct-to-consumer advertising is appropriate at this point, given the fact that direct-to-consumer advertising tends to stimulate the use of a drug, excessive use of the drug. I think a patient guide is very helpful here. I think that patients--you have to respect the ability of patients to also make decisions. I think a patient guide that explains in lay language what our conclusions are about the extent of risk that must be dispensed with the drug is a very helpful way to educate the public about what these risks look like.

I would also say that we ought to offer a strategy for the sponsor here for getting these warnings removed. In my view, an adequately sized

trial against a comparator that we are comfortable with--namely, naproxen, at the 200-milligram dose--would be--we can set what those upper bounds are, but I think if someone can demonstrate, if the sponsor can demonstrate, that the 200-milligram dose does not produce excess cardiovascular risk versus naproxen, that we ought to give that option.

That would be an incentive, a strong incentive, to do that very pivotal trial because what we don't have is we don't have good data on what the 200-milligram dose, what its risks look like, compared to a very good comparator. So those are some of the thoughts I had.

DR. WOOD: I agree with that. I would say that, from my personal perspective, that it should have a restricted black-box warning. It should be given to very restricted patient populations in limited dose and for limited duration. There should be absolutely no direct-to-consumer advertising.

I would add that if a patient guide or even if the package insert, itself, was to try to

specify risk, we should do that in a more helpful way than we do that right now. I don't know what 1 percent increase means to me, even. So we should put it in some contextual basis like it is the same increased risk as you would get from smoking so many cigarettes a day. Or it is the same increased risk as you get from whatever it is, having diabetes or something.

You could give multiple different examples. So patients have some kind of sense of what they are talking about here because I don't see how any of us, certainly not people who don't think about risk every day, can really put that into a meaningful contextual basis.

You know, people worry about flying and then get in their car and drive drunk. So people have a relatively poor ability, I think, to assess risk and we need to help them do that with meaningful statements rather than other risks.

Are there any other--I'm sorry. Yes?

DR. MORRIS: Let me argue against a ban on DTC. Firstly, I am against a ban for three

reasons. One is I am not sure it is enforceable. Secondly, philosophically, I am against the idea of banning information. Thirdly, it won't work.

There are too many other ways of getting to the patient and I think what you will have is a big influx of money into public-relations efforts in which we won't even see what is being communicated to patients.

On the other hand, I would argue very strongly for a totally different way of communicating the risks of these drugs to patients. Right now, what you have in all these commercials, is about a third of the ad having some kind of message that no one understands and nobody takes away. It clearly just isn't coming across to people.

What I would suggest is that what we do is we break out the risk information on this drug into a single commercial and that, for every three benefit commercials, we play this risk commercial so people can have a whole story in which we can put this into a better context, not put together by

people whose job it is to market and sell the drug but let these commercials be put together by an independent group reporting to the FDA that meets the standards of fair balance for both the company and the FDA but which provides a full message to people about how the risks and benefits of the drug have to be carefully understood and whatever other message it is.

But I think that we need to think of--I mean, I have been--of all this whole story, the public reaction to the withdrawal of Vioxx just astounded me. I have to believe that part of their reaction was due to the direct-to-consumer advertising that was done for this class of drugs.

I think, unless we have a fundamental change and do a better job of educating the public and communicating better risks in the same way we communicate benefits, I think this is going to happen again in another class of drugs.

DR. WOOD: People who look at consumer ads apparently interpret toxicity statements as implying the drug is more toxic. The surveys of

the effects of the erectile dysfunction ads and the ones that have, because of the way they chose to advertise them--the ones that say, beware of a four-hour erection, are assumed by patients to imply more potency. No pun intended.

DR. MORRIS: But if there is a very vivid risk, like, for Xenical, or, for some reason, I have learned people love their livers. If you say it causes liver disease, it really upsets people. But, for the most part, this--if you look at the research on consumer takeaways, what they remember from seeing an ad, risk information is way down on the list. It just doesn't get through to people with the same prominence as the benefit information.

If we really want a balanced ad, I think we have to have a dedicated ad that balances all the benefit information.

DR. WOOD: Dr. Day?

DR. DAY: I agree with Dr. Morris' intended outcome but I do not think we need to go to separated ads at this time. I apologize for

bringing in results that are not yet published but I feel morally obligated to at this time. We have produced our own t.v. ad for a fake drug and, after analysis of what is going on in all the t.v. ads--for example, the location of where they put the side effect and showing that that is the least optimal place for memory and comprehension based on separate laboratory studies on other kinds of materials--we then did experiments where you put the side effects in where they normally come and people don't remember or understand them.

You relocate them somewhere else where all the lab studies say people will remember and you at least double what they take away. In some of our experiments, it has been even higher than that. So if we look at what the nature of cognitive processing is for a 60-second, 45-second ad, amount of information and put the information in an appropriate location, as well as adjust the language--we have done an extensive analysis of the readability level of what is being said for the benefits versus the risks.

We found that you need to have three grade levels more education to understand the risks than the benefits. If we can have fair balance on these

two things I have mentioned as well as others that we have looked at, then we will have more of a chance to have all the information at the same point in time.

DR. MORRIS: Ruth, I am not saying you could not build an ad to do this. When we first did the initial experiments on DTC, we actually varied different ways of presenting risk information and, yeah; you can communicate risk information.

But if you look at the way ads are produced, it is clear that the people who create these ads, their primary goal is to market the drug. It is not to produce information that is equally balanced. I don't think you can set up a structure that people can't get around.

It would be fairly easy for them to figure out a way to get around it. Also, this was a t.v. ad you did, or print?

DR. DAY: This is a t.v. ad.

DR. MORRIS: So, okay; you can do it. It just won't work.

DR. WOOD: We are getting--I understand. Let's move on. Dr. Elashoff?

DR. ELASHOFF: No.

DR. WOOD: No? Let's look at my list here. Dr. Bathon?

DR. BATHON: If we do recommend the black box, I am pretty strongly opposed to the idea of putting a dose and duration warning in that. I would say that, if you consider the four indications right now for these drugs, some don't have all four indications, three of the four conditions are chronic; R.A., O.A., and FAP. The exclusion is acute pain.

So, to come in and say, use for the shortest duration possible, contradicts the indications. Secondly, if you put in an indication to use the lowest dose possible, you are negating the fact that efficacy is better for some of these drugs at the higher doses for people with

rheumatoid arthritis in particular, and they need those higher doses. That is one of the four indications.

I would suggest, if we decide on a black box, that we ought to have the underlying theme be avoidance in patients with high cardiovascular risk profiles. That would be the underlying unifying theme.

DR. WOOD: Although the risks also appear in people with low underlying risk profiles in the studies.

DR. BATHON: The studies do show, the ones that we reviewed over these past few days, pretty clearly, in a number of them, that those people who have higher cardiovascular risk profiles, and who are on aspirin, have higher event rates than those not.

DR. WOOD: Right. They have higher event rates, but the others had a significant effect as well.

DR. BATHON: We have to play probability somewhere. We can't cover all of our bases.

DR. WOOD: Okay. Let's go on. Dr. Gibofsky?

DR. GIBOFSKY: No.

DR. WOOD: Dr. Manzi?

DR. MANZI: First of all, I agree with Joan on most of the comments but I wanted to get back to the suggestion that we regulate the order in which we are recommending prescribing the medications where they have to fail the tradition or "nonselective, nonsteroidal" first. I would say I would be opposed to that because I think, for various reasons, there may be reasons to go to these agents first-line, whether it is G.I. issues or anticoagulation issues or whatever the situation may be.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: Yes. I just want to express an overall concern that we are making fairly draconian recommendations for the drug that we thought had the least robust evidence, although we all agreed it had evidence.

DR. WOOD: We might make more draconian

recommendations for the others.

DR. ABRAMSON: I understand that. But I think we are doing it out of context because the notion that you put a black box to say that you can't use this primarily without failing other drugs is not data-driven. We saw in, even ADAPT, that there was increased negative outcomes on the Naprosyn group. So, while I agree with the consensus that Naprosyn does seem to be protective, an unintended consequence of making Naprosyn the first choice without being very careful is more G.I. bleeding.

We all understand the PPIs might protect but this becomes a very complex risk:benefit decision. I also think that, to say that, therefore, diclofenac, meloxicam, et cetera, look very much like the celecoxib, should be used before celecoxib is not data-driven.

So I think we have to be careful not to make decisions that are driven by our sense that there is something terribly wrong with this class that supports the use of other drugs that is going

to give us unintended consequences.

So I think we are going to end up needing a very serious warning, maybe a black-box warning. I think it is hazardous to discuss each of these drugs right now without defining what the nature of the class is because I am going to suggest that whatever we say for celecoxib it is going to be hard not to say for diclofenac and a couple of other drugs.

DR. WOOD: Dr. Domanski?

DR. DOMANSKI: I think that saying that something is a second-line drug doesn't necessarily mean that you have got to try a different drug if it is clear to the physician that that drug is inappropriate. I mean, it forces you to consider it as a second-line drug only but not necessarily to give something else.

I do think these should be a second-line drug, though, and I would just reiterate that I think that the warning should be a strong one and I entirely agree that that should apply to the other drugs in this class.

DR. WOOD: Dr. Dworkin?

DR. DWORKIN: I completely agree with Dr. Abramson. I am really uncomfortable with the

notion of giving this drug a black-box warning or considering it second-line because we have seen no data in the last two-and-a-half days that would warrant the huge migration of patients away from this drug to traditional NSAIDs. We just don't know that the cardiovascular risks of traditional NSAIDs are less than celecoxib, but there will be a huge number of patients, both because of clinical and patient decisions, migrating away from this drug to other drugs where we don't have an evidence base in support of that.

Now, while we have seen some data suggesting that naproxen has less of a risk than these other drugs, I think none of us would feel comfortable enough with that data to give naproxen, for example, an indication of having less cardiovascular risk. So I think we have to be very aware of the kind of very meager evidence base that we have here and the risk that we are going to

bring about an enormous migration of patients from one drug to other drugs where we don't really know much.

DR. WOOD: Dr. Gross.

DR. GROSS: I sense a discomfort in the group about committing ourselves to celecoxib and whether there should be a black-box warning or not. Maybe the solution is to consider what we want to say about all the NSAIDs including the coxibs, do we want to have a warning for all of them or a black-box warning for all of them, and then it might be easier to deal with the individuals.

DR. WOOD: The problem with that is we have to vote, first of all, whether--what the actions we take for each of the drugs. I think we should do that first because we haven't done that yet with the others.

Dr. Nissen?

DR. NISSEN: The reason everybody is uncomfortable, of course, is that we know so much less about the comparator drugs. We don't have robust cardiovascular safety data, for example, for

diclofenac. One of the things that is really troubling me about this, and I think you made some very good points, Steve, is that if you look at a trial like CLASS, you see, basically, the same cardiovascular event rates with diclofenac as you see with 800 milligrams of celecoxib.

So if, in fact, we do precipitate a migration away from celecoxib to diclofenac, we may not actually be doing good. We may actually be doing potentially harm. I am concerned that we don't have the evidence.

So I think we have to keep our warnings to what we know. What we do know is, and we have agreed, that celecoxib, compared to placebo, has excess risk. But we don't know whether that risk is excess in comparison to ibuprofen of diclofenac. So any statement that would tend to suggest using those alternative agents first is probably not warranted by the data because we simply don't have the data to make such a conclusion.

So I think we have to limit our statements to what has been proven within a reasonable doubt

here and that is that celecoxib is probably riskier than placebo.

DR. WOOD: Dr. Gardner.

DR. GARDNER: I am having similar discomfort about the benefit side when we look at all of these drugs in a group like this. So my comments will apply to everything that we are doing here today.

I think that we are not, this afternoon, going to get a whole lot more information about benefit. We have been focused on risk. But I would echo Rich Platt's request to the FDA to dig into all of the information we have on the various products including the observational data which can be very helpful here in helping to specify.

For example, we are all, now, very sensitive to the fact that R.A. patients and elderly patients tend to be, thanks especially to Dr. Cryer's presentations--we know that they are at higher risk both of cardiovascular and of G.I. bleeds. We know that. But the observational studies, at least in some of the clinical trials,

were done on much younger folks.

We heard yesterday from the Military that they have got very fit people who need these drugs. So I would like to--before we start specifying who are the populations that have need and what we should do to help them restrict, I would like to ask that, at least the FDA if not we, this afternoon, pay attention to better specification of the risks and benefits for communication of risks to other people besides the elderly R.A. patients whom we know are at higher risk and then find ways to communicate them appropriately.

I am in favor of med guides. I just want to comment, as someone who fills prescriptions, that when you put a med guide in a packaging, the way to get it to the patients is to have it packaged in the containers that you are going to distribute to the patients. That affects bulk packaging.

Any time you design a med guide that is supposed to be handed out by a pharmacist in a chain pharmacy after you have taken bulk drug out

and repackaged it is not going to get there. So think, as well, when we are talking about med guides, that you want to individualize them to the dispensing.

DR. WOOD: I think we have exhausted the discussion. Do we want to move to the vote on this.

DR. CRYER: Dr. Wood, over here in the corner.

DR. WOOD: I have been told that, as you are not a voting member of the committee, you are not allowed to comment during the discussion at this stage. Thanks.

DR. CUSH: Should not the first vote, then, be whether this is no warning, warning or black box?

DR. WOOD: I think what we could do--let me ask the FDA. It seems to me that there are multiple issues here so I would suggest that we go around the panel and ask each panel member what they think should be done, what is their kind of list of things that they would like to see done.

Is that reasonable?

DR. JENKINS: The intent of Question c. was not to have a specific vote. It was more to give a sense, from the committee, about the goals for the risk-management program and any specific ideas you have about how that should be implemented but not to take a vote on the exact wording of a box or whatever.

DR. WOOD: Sure. But would it be helpful to go around and ask each person what they think or have you got a sense of that already, John?

DR. JENKINS: Wait a minute, one of my colleagues is telling me--I don't know that you have to go around to every individual member, but if that is what you choose, that would be fine. We are always interested in hearing everyone's ideas.

DR. WOOD: Okay. Let's do that. Was that acceptable to the committee? Let's start with Dr. Abramson.

DR. ABRAMSON: I guess my bias on this is that we have to, as I have said several times, define what we mean by the class and what we think

the pathophysiology is here. I think we all agree that there is a risk from sustained, high-level COX-2 inhibition.

I think the challenge before us, and I will ultimately believe in some sort of serious warning, perhaps a black-box warning, is that we agree that we are talking apples to apples. My bias will be, as I have said, to include drugs other than the coxibs, drugs that fall into COX-2 preferential categories similar to celecoxib.

Just as a final point, I would remind the panel that when meloxicam was first marketed, in the U.S., it was marketed as a COX-2 inhibitor. After VIGOR, the company was prescient enough to stop marketing that way. It is, I believe, still the only COX-2 selective drug available in Japan. So, had they continued to market that drug as a COX-2 inhibitor, that would be among our four drugs of discussion.

So my plea is that we decide first, before we get into too much detail on the individual warnings and labeling, what it is we mean as a

group as COX-2 and try and draw a line somewhere that extends, in my view, beyond the three coxibs that we are discussing.

DR. WOOD: Let's just go around. And let's try and just list the things and not discuss it all again. Otherwise, we will take forever. Just list your recommendations.

DR. NISSEN: I am in favor of a black-box warning which basically says that there is dose-dependent increase in cardiovascular risk with the drug. I am in favor of no DTC advertising and I am in favor of a patient guide, a patient handout, that would inform the patient about the risks of the drug.

DR. ELASHOFF: I have no additional comments.

DR. GARDNER: I am in favor of no DTC advertising, a patient guide, a med guide, to communicate to the patient as well as the physician, and warnings that are appropriate to the risk group.

DR. WOOD: Richard?

DR. PLATT: I favor a substantially upgraded postmarketing-surveillance program, black-box warning. I would favor recommending this

drug be treated as a second-line drug and I would favor mentioning the suggestive evidence about naproxen possibly being a preferred alternative. I personally would favor attestation that requires the patient to acknowledge the magnitude of the risk and I was persuaded by the argument about putting that risk in the context of other easily, relatively easily, understood risks.

DR. DAY: I am for a black-box warning and I think that they can be differential across the different products and whatever the minimum is, this one might get that. The upper limit may still be high but I don't think we need to decide on this one, given defining the class and so forth, at this time. I would be in favor of the medication guide. Also, I know a lot of people say the "Dear Healthcare Professional" letter isn't read, but sometimes it is, so I think that both physicians, healthcare providers and patients should get this

information.

I am not necessarily in favor of suspending DTC at this time as long as it is done in a way that provides fair balance between benefits and risks if that can be achieved. I am open to having the patient attestation part, perhaps with a small survey for comprehension.

DR. FURBERG: I am for the black box. I agree with the contraindication for high dose. I would like to be more specific about the population by contraindicating the drug for patients with known coronary heart disease and stroke and for patients at increased risk.

I am also in favor of some form of patient agreement or consent. If we had any way of barring direct-to-consumer advertising, I would be in favor of that because I think that action, in itself, would prevent more serious adverse events than anything else we can do other than taking that drug off the market.

DR. FLEMING: I favor a black-box warning regarding the increased cardiovascular and

cerebrovascular risks. I am inclined to also agree with noting the particular concerns with those patients that have high cardiovascular risk and toward encouraging minimizing dose and duration, appreciating the comment that that is more challenging in certain settings, and yet it still doesn't preclude use for a longer term but it just notes that there are potentially increased risks with that.

I am in agreement with barring direct-to-consumer advertising unless Dr. Morris strategy that could be more effective is achievable--I don't have a clear sense about that--and the concept of the patient guide as well.

DR. WOOD: Okay. Let's just keep going. Dr. Domanski.

DR. DOMANSKI: Black-box warning that puts for the increased cardiovascular risk of the drug, patient pamphlet, second-line drug.

DR. BOULWARE: I favor a black-box warning expressing the known cardiovascular risk when used in the doses that were excessive of the approved

levels of 400 milligrams but also stipulating it is not quite clear what the relative risk is to the other known nonsteroidals.

DR. WOOD: Next?

DR. DWORKIN: I am not in favor of a black-box warning unless it is given to all NSAIDs, traditional and selective. I am in favor of a detailed and comprehensive cardiovascular warning for celecoxib. I will pass on the other stuff.

DR. WOOD: Dr. Hoffman.

DR. HOFFMAN: I am in favor of a black-box warning to be in place until more definitive studies are done and that warning should--well, we are not supposed to address the direct wordage but it was mentioned that there should be a limitation on duration.

I think that is impractical because most of the patients using this drug have chronic diseases that don't go away. But there definitely should be, within the guidances, doses not to exceed 200 milligrams a day. I would be against direct-to-consumer advertising and I would advocate

a patient guide with this being second-line therapy.

DR. WOOD: Dr. Manzi.

DR. MANZI: I am not opposed to a black-box warning. I think it should clearly state the cardiovascular risk with higher doses for longer duration but not directly advocate low doses for short duration. I am vehemently opposed to it being a second-line agent and I think a patient guide is sufficient.

DR. WOOD: Dr. Farrar.

DR. FARRAR: I am in favor of a black-box warning specifying cardiac risk factors. I am vehemently against direct advertising on this and all of the COX drugs. I feel strongly that a patient guide should be designed so that it can be read and understood by patients. I will pass on the rest.

DR. WOOD: Dr. Holmboe.

DR. HOLMBOE: I am in favor of a black-box warning. Again, I had some discomfort with regard to the nonselective NSAIDs. There should be a

warning for those as well. I am in favor of a patient medication guide, particularly one that should try to address not only health literacy issues but also health numeracy issues. I hope that the FDA will undertake study of these guides as well as, say, the medication themselves. I am also in favor of also adding to this some academic detailing to make sure the word gets out to the physicians who are using these drugs. I will pass on the others.

DR. WOOD: Peter?

DR. GROSS: I am in favor of a warning related to the dose-dependent toxicity and that a similar warning should be on all coxibs and nonselective NSAIDs. I favor a medication guide for patients and a consent for patients when they will be taking higher doses. I would favor direct-to-consumer advertising only if combined with FDA-approved education on the putative risks and I am opposed to it being a second-line agent.

DR. WOOD: Thank you. I am in favor of the black-box warning. I am in favor of a very

restricted patient group to exclude people who are likely at risk for cardiovascular disease. It is not just those who have previously identified themselves by having cardiovascular disease. It would include the elderly patients with high-risk factors and probably some others. I am against direct-to-consumer advertising, strongly.

I think a patient guide has to be useful and should be done. I think however we articulate risk to patients, it needs to be done in a way that is immediately obvious what we are talking about. I think it is hard for me and for most people to understand what a 1 percent increase in risk means to me or to anyone else. So I think it needs to be put in some contextual way that relates to people's regular daily lives.

I think one other thing I am in favor of that has not been said is I am in favor of the company having the opportunity to have the black-box warning removed if they can demonstrate in well-designed, well-controlled, double-blind trials that the drug, at any particular dose or on

any particular group, does not, indeed, have these risks.

So I think I am favor of viewing this as a step that we are taking right now based on the evidence we have but we are prepared to consider changing that if they come up with evidence, good evidence, excellent evidence, that overwhelms what we have got right now.

DR. GIBOFSKY: There are four indications for celecoxib, two short-term and two long-term. I think the population should be the intended populations, the indicated populations, to be used at the lowest effective dose. I oppose a black-box warning. I am in favor of patient handout. I oppose the use of or designation as a second-line agent. I am not opposed to DTC advertising so long as it is informative and educational and consistent with the message above.

DR. WOOD: Dr. Crawford.

DR. CRAWFORD: Thank you. I am strongly in favor of a black-box warning about the cardiovascular risks. Also, I feel strongly the

need for postmarketing commitment studies. I share the Chairman's thoughts about the possibility of such studies removing the need for a black-box warning in the future. Also, I am very much against direct-to-consumer advertising, but it if is not possible to make that a regulatory action, to say that there needs to be appropriate communication of the risk in that direct-to-consumer advertising.

DR. WOOD: Dr. Cush.

DR. CUSH: Jack Cush. I am opposed to a black-box warning. I am in favor of a general warning that stipulates some strategy for risk reduction and risk minimization. I am strongly in favor of direct-to-consumer advertising as long as the major statement significantly outlines this cardiovascular risk and that D.V.MAC take particular attention and making sure that that is highlighted. I am also in favor of further study of cardiovascular risk in the target population.

DR. WOOD: Dr. Bathon.

DR. BATHON: I am opposed to a black-box

warning but I am in favor of a strong warning that advises the association of cardiovascular risk and in the target population. I am very opposed to DTC advertising and I think that, if there were not DTC advertising and a strong warning, we would be more likely to target these drugs to the appropriate populations.

DR. WOOD: Ms. Malone.

MS. MALONE: Yes. I am opposed to a black-box warning. I think there should be a serious warning about cardiovascular risk and dose-dependency. I think there should be a limit on direct-to-consumer advertising. I don't like the idea of calling this a second-line drug. I think what that is going to do is have insurance companies require--it is not going to leave the decision with the physician and the consumer. It is going to make insurance companies say, you have to try these other drugs first.

I think there should be a patient guide that is readable, understandable, easily accessible and I think there should be very good education for

the doctors so that this dialogue can take place. And I am not opposed at all to a patient consent or attestation and I actually think that that will lead to a better communication between the doctor and the patient.

DR. WOOD: Arthur?

MR. LEVIN: Black box with the cardiovascular risk; medication guide, of course; some sort of informed consent or assent or agreement. But I agree with the Chairman that we have to learn how to convey risk in ways that are meaningful to consumers.

I would also argue that we have to learn how to convey benefit. We are only talking convening risk. We need to figure out how to convey realistically what we know about the benefits so that the balance can be made. Academic detailing, I think, has been shown to be effective and it would be intriguing. I just think it is an intriguing idea to tie black-box removal as a stick and carrot to encourage further study.

Until we figure out how direct-to-consumer

advertising can tell the truthful story about drugs, I would at least suspend it for now.

DR. WOOD: Dr. Ilowite.

DR. ILOWITE: I favor a black-box warning advising of the increased cardiovascular risk which is duration and dose-dependent. I favor a statement saying that it is relatively contraindicated in patients with high cardiovascular risk. I am opposed to calling it a second-line drug. I am opposed to direct-to-consumer advertising. I am in favor of a medication guide. And I wouldn't mention Naprosyn as the preferred NSAID.

DR. WOOD: Ralph?

DR. D'AGOSTINO: I am in favor of a black-box warning. I don't think there should be direct-to-consumer advertising. I think the evaluation of the cardiovascular risk is important and, as a matter of fact, I don't think it would be very hard to do with the clinical-trial data plus some things like we have at Framingham. There are comparators compared to--sort of the optimal person

compared to your average population. It is equivalent to being diabetic. There are lots of ways of doing this and I think it should definitely be done.

DR. WOOD: Dr. Morris.

DR. MORRIS: I am in favor of a black-box warning. I would like to see it for the broadest definition of class and every drug get the black-box warning in this class. Information can vary, but within that, there should be statements about the class because I am real concerned about switching when there is nothing known and I would like to include some kind of statement in that black-box warning about what is not known as well as what is known.

Obviously, I am in favor of DTC but restructuring it in favor of a really strong postmarketing-surveillance program and probably studies like Dr. Temple suggested. I am actually not in favor of a medication guide but I am in favor of a unitive-use patient package insert. I think some of the information in that should also

be broad and classwide so people can understand that the concerns extend beyond just COX-2s as they think of COX-2s.

I am also in favor of an insert for over-the-counter drugs in this class that also talks about the use of this drug. I guess that is it.

DR. WOOD: Dr. Cannon?

DR. CANNON: I am in favor of a black-box warning, a warning of increasing cardiovascular risk that is dose and duration dependent. I am also in agreement no DTC. I think a medication guide for patients is fine. I don't think this drug, though, should be prohibited for use in patients who have cardiovascular risk factors. I don't think we have the data to say that they are at particularly higher risk than those without risk factors.

I would say something that hasn't been mentioned and, in my view, should be included and that is, for those patients who do have cardiovascular risk factors, that the concomitant

use of aspirin will likely not reduce the risk that may be imparted by the use of Celebrex and that, in fact, it may negate the G.I. benefit of the drug.

DR. WOOD: Dr. Shapiro?

MS. SHAPIRO: I, too, favor a black-box warning; no direct-to-consumer; a patient guide; and prescribing restrictions that would assure lowest possible dose; and, also, second-line not in the sense that something else would have had to have been tried but that the physician would had to have considered and then discounted a non-COX alternative.

DR. WOOD: Dr. Paganini?

DR. PAGANINI: I favor a black box. I believe that it should contain a cardiovascular warning in understandable terms. I believe that there should be a statement of probable dose and time relationship, that it should be a second-line for those with G.I. failure to other options; there should be no direct advertising and there should be developed a patient brochure.

DR. WOOD: Dr. Friedman.

DR. FRIEDMAN: I favor a bar to direct-to-consumer advertising. I favor enhanced education both for patients and, frankly, for the

medical community. I favor a black-box warning mentioning the high-group, the problem with cardiovascular disease, the concern with the high dose. I also favor mentioning the uncertainties with regard to all of the NSAIDs. I assume that, under Question 5, we will discuss additional research activity which I see as absolutely essential.

DR. WOOD: Charlie?

DR. HENNEKENS: I would want all healthcare providers and patients to be aware that coxibs increase cardiovascular risk by about 40 percent. I would want them also to know that, in the comparator trials, naproxen compares favorably to all the coxibs. I would also want them to know that the short-acting NSAIDs appear to be at least as hazardous as the coxibs. I would want basically that all arthritis patients and all other patients treated with coxibs or the short-acting NSAIDs,

especially, as well as naproxen, should have their global cardiovascular risk assessed as the NHLBI has recommended in general, and they should have aggressive management of all their cardiovascular risks.

I am not in favor of this being a second-line drug. I am not in favor of direct-to-consumer advertising. I am not actually in favor of a black box but I am in favor of a strong warning that should be applied equally to all coxibs and all short-acting NSAIDs.

DR. WOOD: Steve?

DR. SHAFER: I believe it should be indicated for second-line therapy. I favor a black-box warning on dose- and duration-dependent cardiovascular risk. I concur with potentially removing the black box for certain doses in comparator NSAIDs as is supported by clinical-trial data in the future. It should be contraindicated following cardiopulmonary bypass. I would actually permit DTC advertising as we have understood what that would mean with the black-box warning. I like

the idea of the patient guide and I would oppose to mandatory physician and patient attestation.

DR. WOOD: Okay. Just in case you thought you had finished, let's move on to Question No. 2.

Question No. 2: Valdecoxib

DR. WOOD: Question No. 2 addresses valdecoxib. The first question is, do the available data support a conclusion that valdecoxib significantly increases the risk of cardiovascular events.

I think we have probably had a lot of the discussion on this so let's see if there is any new discussion that we would like to have and then we can, perhaps, go around the table and get everybody's brief individual comments on this.

Is there discussion first? Then let's go around the table--I beg your pardon. Yes?

DR. SHAFER: One point of discussion. Can we also discuss parecoxib, or think about parecoxib concurrently. I know it is not an approved drug but at least some of my thinking about this relates to my thoughts about parecoxib as well. Or is that

not appropriate?

DR. WOOD: Sure. I mean parecoxib is converted to valdecoxib in the body. Do you think there is a difference?

DR. SHAFER: That answers my question.

DR. WOOD: Pardon?

DR. SHAFER: That answers my question when it comes time for the vote.

DR. WOOD: Okay. Go ahead. We will start with you this time, Steve.

DR. SHAFER: All right. The question before us is do the available data support a conclusion that it significantly increases the risk of cardiovascular events. Yes, after cardiopulmonary bypass. I point out that CABG is just one type of cardiopulmonary bypass but it is probably common to all forms of cardiopulmonary bypass because the common thread is the bypass machine, itself. I don't think the cardiovascular signal is clear otherwise so I would say yes in the setting of cardiopulmonary bypass.

DR. WOOD: Let me just ask you. Why did

you not see a signal anywhere else given that there wasn't any evidence anywhere else.

DR. SHAFER: That is what you just said. There was no signal anywhere else because there was no evidence anywhere else.

DR. WOOD: So it is not that you think that it is safe in other settings. It is just that you don't know.

DR. SHAFER: The other places where they have looked at it, the signal has been weaker than other studies of approximately the same size as I interpreted the data, although Study 047, there was some increase in C.V. events versus naproxen.

DR. WOOD: Charlie?

DR. HENNEKENS: Hennekens. Yes.

DR. FRIEDMAN: Friedman. Yes.

DR. PAGANINI: Paganini. Yes.

MS. SHAPIRO: Shapiro. Yes.

DR. CANNON: Cannon. Yes.

DR. MORRIS: Morris. Yes.

DR. D'AGOSTINO: D'Agostino. Yes.

DR. ILOWITE: Ilowite. Yes.

MR. LEVIN: Levin. Yes.

MS. MALONE: Malone. Yes.

DR. BATHON: Joan Bathon. Yes.

DR. CUSH: Cush. Yes.

DR. CRAWFORD: Crawford. No relation to Lester. Yes.

DR. GIBOFSKY: Gibofsky. Yes.

DR. WOOD: Wood. Yes.

DR. GROSS: Gross. Yes.

DR. HOLMBOE: Holmboe. Yes.

DR. FARRAR: John Farrar. Yes.

DR. MANZI: Sue Manzi. Yes.

DR. HOFFMAN: Gary Hoffman. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. BOULWARE: Boulware. Yes.

DR. DOMANSKI: Domanski. Yes.

DR. FLEMING: Fleming. Yes.

DR. FURBERG: Furberg. Yes.

DR. DAY: Day. Yes.

DR. PLATT: Platt. Yes.

DR. GARDNER: Gardner. Yes.

DR. ELASHOFF: Elashoff. Yes.

DR. NISSEN: Nissen. Yes.

DR. ABRAMSON: Abramson. Yes.

DR. WOOD: With our new computerized system, it is 32 to 0.

The second question is, does the overall risk versus benefit profile for valdecoxib support

marketing in the U.S.? I think we should do some discussion on that first. Comments on that? I guess I would comment. I am not sure that the current data we have does support continued marketing in the U.S. In fact, I think it probably does not.

We have got a very clear and replicated signal of cardiovascular lack of safety in two studies and we have got a lack of clear G.I. benefit in terms of complicated risks. And we have already approved one drug which appears to have a lower signal than the others. It would seem to me that, if this drug were to be continued to be marketed, we would need a lot better data to justify its continued availability

Dr. Nissen?

DR. NISSEN: This one is really tough because there is just not any data in the population to which this drug is being used. The only data we have is two studies, one of which was small, the other of which was, I think, pretty clear after cardiopulmonary bypass and that signal was very strong really only in the arm that got the I.V. product.

So what really have is an absence of

information. Now, the question I think you are asking, Alastair, is was there a mistake made in actually approving this drug with the limited data that was available because that is really what you are saying, that in the absence of proof that it is safe, that it should be deregistered. I think that is really tough.

So I have a lot of trouble with this one because I don't see evidence one way or the other for valdecoxib. Now, maybe somebody can help me. Tom, you can do some mathematical highjinks over there and maybe you can convince me to the contrary, or Ralph or Charlie, but I don't have

evidence.

DR. WOOD: Just to respond to that, I think we have heard the argument many times that people need choices. I agree with that. But it seems highly improbable to me that this drug is safer than celecoxib. It is almost inconceivable to me why somebody would prescribe this drug over celecoxib if you were going to use that.

I am not arguing whether you should use celecoxib or not. We have been through that discussion. But, given the size of the signal and somebody used the expression before, the CAB studies may be a canary in a coal mine. It is a high platelet-activated group and that may be just reflecting a model in which it is easier to see a signal than it is in other models and it was possible, remember, to see it with a relatively small number of patients, 500 patients, or something.

So this was a very strong signal in a very small number of patients, a fifth of the number of patients seen in the approved study, for example.

DR. HENNEKENS: Alastair, you are quite right that there is no evidence that it is safer than celecoxib, but there is also no evidence that

it is more harmful than celecoxib.

DR. NISSEN: Exactly.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: I would agree. I think there is a strong database in terms of the clinical trials. What we are lacking are large outcome trials that show a VIGOR-like or a TARGET-like effect. So, therefore, it would be not a good precedent, in my view, to remove a drug because there is an alternative without a more serious safety signal.

I think there is a caveat with these CABG trials that we have to talk about which is that these patients, as we stressed yesterday, or the other day, were given low-dos aspirin. So, in effect, they had both COX-1 and COX-2 inhibition. It may be that, in that acute event, the platelets are so intensely clotting that the aspirin may have been overridden. But, in effect, these patients

were given a COX-mixed inhibition.

So since there was no comparator arm in that valdecoxib/parecoxib study, I don't know that we can draw a lot of conclusions about the intrinsic safety of this drug in arthritis use over time. I think that was a flawed study to draw specific conclusions about isolated COX-2 inhibition.

DR. WOOD: But the company had so little faith in the safety of the drug that they gave it with aspirin in the general surgery study.

DR. ABRAMSON: Nevertheless, it was a mixed compound.

DR. WOOD: They didn't feel it was safe to give to patients who were undergoing general surgery without aspirin.

DR. ABRAMSON: Right. But if we are doing clinical pharmacology and using that to make projections on safety of drugs, those patients were given mixed inhibitor.

DR. WOOD: Sure. Dr. Furberg?

DR. FURBERG: I agree with Dr. Nissen that

we have an absence of good evidence but I come down on the other side, and that is not a reason for leaving it on the market, a lack of evidence. So I think we need to face up to the fact that we don't have good evidence and take it off the market and the manufacturer can come back when they have good data.

DR. WOOD: Yes; motivate them. Dr. Elashoff?

DR. ELASHOFF: Doesn't this drug already have a black-box warning that the others do not?

DR. WOOD: No; a black-box warning for skin, not for cardiovascular.

DR. ELASHOFF: Yes, but I mean isn't that something that should be taken into account in terms of the risk:benefit for this particular drug.

DR. WOOD: Right. So there are additional risks, you are saying. Yes; that's right. Any other comments? Dr. Farrar?

DR. FARRAR: I think that this drug, in particular, also points out another suggestion that should be made and would make me feel a lot better.

I think it is much harder to take a drug off the market without evidence than not to put it on without evidence. That makes it a quandary for me but it also suggests, in fact, that drugs ought to have a renewal date. Our grants have a renewal date, lord knows. and we have to show that we have made progress. I would actually strongly recommend consideration of that. Obviously, that discussion is later but it would make me feel a lot better about this.

DR. WOOD: Dr. Cush?

DR. CUSH: This question speaks to risk:benefit and there is, obviously, demonstrated benefit as these drugs are, again, equipotent to available drugs. I am not convinced that there is a signal that says that there is a potential risk, a significant risk, when the drug is used as indicated.

DR. WOOD: Any other comments? Then let's go around the room--oh; sorry. Dr. Fleming? Let Tom go first and then Dr. Manzi next.

DR. FLEMING: Go ahead.

DR. WOOD: Dr. Manzi, you have been deferred to.

DR. MANZI: I just wanted to respond to

the comment that we need to wait until they can prove safety. I would say that we put the same charge to Celebrex in removal of the black-box warning, that we saw a signal, we felt that there was clearly a risk and now we want long-term safety data. I think we should do the same with this drug.

DR. WOOD: Dr. Fleming?

DR. FLEMING: I appreciate the fact that we have much more limited data here, I think about 3,000 patients. It is predominantly in the CABG setting. The signal, though, here, really impresses me with the magnitude of the signal. We are looking at the 035 trial at a 15 to 2 on events and that is 1-1 on M.I. It doesn't reflect the fact that the investigators called 9 to 2 on those M.I.s.

When we are looking at the other data as well, we have got quite a strong signal. The 069

trial was in general surgery and that was more neutral at 5-5, although DVTs were 2 to 1 for placebo. I know these are really small numbers but when you are looking at the events that are of greater interest, the M.I.s, the arrests, the cardiac deaths and the strokes, it is 3 to 2 so, again, it is really small data. But I don't consider that favorable. It is in the wrong direction.

Essentially, we have the 035 trial and the Nussmeier trial. Steve Nissen pointed out that it is relevant to look at the fact that we had the three arms. The combination arm had a relative risk of 3.7. The valdecoxib had a relative risk of 2. So it was less striking although, when you looked at all of the events, it was a relative risk of 1.9 in both.

So, essentially, there is very strong evidence here in the setting where it has been studied. What we are struggling with is that there is very limited evidence, though, in being able to look beyond. So what do you say?

I mean essentially where there is evidence, it is of significant concern, but this is understudied relative to other agents. And so do

we give it the benefit of the doubt, or do we view that in the absence of reliable evidence here? Continued marketing is of serious concerns, and we should wait until we have more reliable evidence to restore marketing. To me that's the debate.

DR. WOOD: And the drug clearly gives bigger signals than you see anywhere else. The general surgery study was so underpowered you couldn't possibly have seen anything, given the agent and so on.

DR. FLEMING: And I guess my point there is it's not a reassuringly positive study.

DR. WOOD: Right, not reassuring, and they were on aspirin.

DR. FLEMING: The key events are 3 to 2 in the wrong direction, and it's in the context of aspirin.

DR. WOOD: Right. I mean, you know, come on. Okay.

DR. : You know, I think that given the extensiveness of the review that we've had, I think it's reasonable not to accept the precedent that it's already on the market and to make an independent recommendation about whether it

should be regardless of what that turns out to be. But I think we--you know, given again the extent of this review, it's appropriate to give it that kind of de novo review and decide whether it should be there.

DR. : Okay. Dr. Gibofsky?

DR. GIBOFSKY: I have a question for Dr. Fleming. Is it possible?

DR. : Sorry. Yes, go ahead.

DR. GIBOFSKY: Dr. Fleming, in light of what Dr. Packer taught us this morning, if you apply, again, having only one time point to look at, and you're applying a second level of discrimination at a .05 level, do we have enough of a power--or a signal here that it does become significant? I mean I'm impressed by some of the participants say that this is a much bigger signal

we are seeing in other situations, which admittedly is lower at 1.4, as many of you said, but I'm not impressed that it's such a large signal, one-time signal, that it merits the drug being dropped from the market.

DR. FLEMING: Let me respond to that in one minute.

DR. : Okay, all right. And other questions? Yes, Dr. (?).

DR. : Yes. I share Dr. Abramson's and Nissen's concerns. I also am mindful of the volumes of data that we have reviewed. However, at the end of the day, as we've heard from one speaker in particular, we're obliged to make our decisions based on the weight of the evidence, and we practice evidence-based medicine. We don't practice the absence of evidence-based medicine. So consequently I think we have to look at the data that we have, be cautious, be concerned, have that discomfort in our gut, but go with the evidence and the data that we have.

DR. WOOD: I agree with that and we have

no evidence of G.I. safety. We have evidence of cardiovascular toxicity and that, to me, is compelling. Dr. Shafer?

DR. SHAFER: I just want to respond to the canary in the coal mine and the cardiovascular safety concerns because it really was the two CABG studies. The level of physiologic trespass imposed by cardiopulmonary bypass should not be underestimated or the effects of that on the entire immune and thrombotic systems.

So, if the message to a company is don't ever study a drug in in cardiopulmonary bypass patients because, if you get a bad outcome, it will be assumed to be a representative of your class of drugs and there will be no more studies of analgesic possibilities in patients on cardiopulmonary bypass.

So I totally rejected the concept that the naproxen studies should be separated out as a different sort of funny class effect. But in the case of cardiopulmonary bypass, I really do think that is a very different kettle of fish. I don't

think it is a canary in a coal mine although I could be proven wrong by future data.

But do not underestimate the level of trespass that that represents and the limits that that puts on the extrapolalatability of those data to patients on arthritis, or with arthritis.

DR. WOOD: Any other comments? Dr. Abramson?

DR. ABRAMSON: The point I was making about the aspirin is that I am not sure that we can use this CABG study as a surrogate for the safety of these drugs in the long term because there was no nonselective comparator. Had we done the same study with Motrin at high doses, because the COX-2 effect seems to be driving it and aspirin did not prevent the adverse event, I am concerned that, alone, without a comparator, it doesn't help us say what this drug does in the non-acute coronary-syndrome setting because this was a dual-inhibiting setting.

So I think we have to be cautious in extrapolating that as a surrogate study.

DR. WOOD: Although it is interesting that the general-surgery patients also got aspirin.

DR. ABRAMSON: But they did not have the

same strength of signal.

DR. WOOD: Oh, no; but that there was a need to give them aspirin.

DR. ABRAMSON: We don't know, Alastair, if there was a need to give it or not. They gave it. That is all we can say. We don't know what would happen without aspirin.

Steve, your points are well-taken. I am very troubled by this one because, as a cardiologist, I know what happens when you open a chest and stop the heart and put people on bypass pumps and blood circulating extracorporeally. It is a really very big insult. So it is very hard for me to extrapolate results in that population to a general population.

I agree with everything that has been said. It is a very strong signal and I was the one that said, the other day, that this happened with 10 days of exposure in the face of aspirin. That

is a very compelling result. But I don't know how to apply that knowledge to patients that are going to get 10 or 20 milligrams of the drug with arthritis. What I do know is that giving 40 milligrams right after cardiopulmonary bypass is not a good idea. I know that for certain. But I don't know what that needs for taking 10 or 21 milligrams with arthritis.

So what it really comes down to is how much weight do you all give to this notion of the class effect? If you really, really believe that there is unequivocal evidence of a class effect, then if see it in any population for any drug in the class, then, you got to do that.

But I must point out to you that we don't have long-term safety data on ibuprofen or diclofenac. Does that mean we should deregister those drugs? I think it is a really interesting issue.

DR. WOOD: Let's go to the question, then. The question is, does the overall risk:benefit profile for valdecoxib support--remember, the

question asked does it support marketing in the U.S., not just is it neutral. Let's start with Dr. Abramson.

DR. CUSH: Wait. Dr. Fleming was going to give us an answer, maybe.

DR. WOOD: Oh, I'm sorry. You're right. Sorry, Tom.

DR. FLEMING: I just was looking at the evidence in the totality. Essentially, the totality of the evidence, the problem is it is very limited. We have got, in what has been presented to us, three trials; the Nussmeier 071 trial, 035 trial, the 069. By my crude summary here, the relative risk is slightly more than 2.5 and, in terms of strength of evidence, the standard error is more than 3.0.

So, to my way of thinking, that is quite strong evidence. I would surely like to have a lot more data and my biggest uncertainty is how does this extrapolate to other settings. But there is quite strong data here in the CABG setting, in the surgery setting.

DR. SHAFER: How much of that is driven by the CABG study?

DR. FLEMING: Well, there are two and

almost all the data are from those two. The general-surgery study, I counted as 5.5 although, really, the events we are interested in are 3 to 2. So this is a slightly--it is.

DR. WOOD: But the question we are being asked here is does the data support marketing the U.S. So it is not just a question--if we have no data at all, that surely wouldn't support marketing in the United States. So, absence of data is important here, I think, particularly in the presence of a safety signal, a strong safety signal.

DR. CUSH: Absence of data means you take a drug off the market?

DR. WOOD: That is what we will have to decide. Dr. Gibofsky.

DR. GIBOFSKY: I have made my comments..

DR. WOOD: Sorry. Dr. Hennekens?

DR. HENNEKENS: I believe there is a class

effect which is similar for all the coxibs and the short-acting NSAIDs. As such, I interpret the valdecoxib signal to be that these classes of agents should not be used in cardiac-surgery patients, but they don't bear directly on their utilization in arthritis patients, in my view.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: Dr. Wood, you are, I think, getting back to Dr. Temple's wording of the questions. The only reason it says "support marketing" is because he didn't want to change the format of the questions for the three drugs. So it might have easily said, "does it support withdrawal?" The reason that wasn't done was because--

DR. WOOD: But it doesn't. I mean, he didn't want to change--well, that is fine. I think people know what we are voting on so I don't think it makes much difference. Do we want to have a discussion on this point? Go ahead, Dr. Ilowite, again.

DR. ILOWITE: One is more of a passive

effect. The hurdle is lower if you say, does it support marketing than if you say, does it support withdrawal.

DR. WOOD: That's right. But if we think that is truly different, then what we are saying is that the hurdle to remove a drug that we see as being unsafe, we are going to make that hurdle substantially higher than the hurdle to get it on the market in the first place. That is an interesting concept and one that we should, perhaps, discuss, but I am not sure that is--do you think, Bob--Bob Temple--do you think--Dr. Jenkins do you think the hurdle to remove a drug from the market should be higher than the hurdle to get it on the market?

DR. JENKINS: That is a very interesting and difficult question because, obviously, the product is already on the market. You are fundamentally being asked, given that you voted in 2.a. that you think that the drug increases the risk of cardiovascular events, should that have any impact on whether it remains on the market.

DR. WOOD: Is your proposal, Dr. Ilowite, that we change the question to should--or do you just want us--

DR. ILOWITE: No; the question was fine.

DR. WOOD: Then let's call the question.

DR. TEMPLE: Alastair, just one thing.

DR. WOOD: Yes, Bob.

DR. TEMPLE: In legal terms, as opposed to practical terms, it is fairly clear that the standard for approval says, all tests reasonably applicable have been done to evaluate safety and it is safe, and it has got to be effective. It is very clear from the law and court decisions that one of the things you could do, if you got more information that make you doubt that the risk:benefit calculus you made at the time of approval was still true, you could seek to withdraw it from the market.

These rules and the law doesn't give quantitative differences there. Of course, to take something off the market against the company's will, you have to go through a legal set of

proceedings. Therefore, you queried about the evidence arguably more than you are when you first do the approval decision. So there is a fair amount of evidence that you need to take a drug off the market as a practical matter.

Now, you know, in a different world where, at five years, you reconsider it just as though you didn't know anything, starting from the beginning, maybe the standards would be different.

DR. WOOD: But, from a patient's perspective, it is probably the same thing.

DR. TEMPLE: You, certainly, intellectually want to think of it as roughly the same thing. There is, of course, the fact that after a drug is marketed, you have certain assurances from spontaneous reports that you didn't have before you marketed that is irrelevant to these considerations, I would say.

DR. WOOD: Okay. Let's start the vote from Dr. Abramson. So the question is, still as written, does the overall risk support marketing in the U.S. A yes would mean leaving it on the

market. A no would mean taking it off the market, just to make sure.

DR. ABRAMSON: Yes.

DR. NISSEN: Yes.

DR. ELASHOFF: I am concerned that we are adding a new risk to something that already has a black-box warning. So I am unclear here.

DR. GARDNER: Pass.

DR. PLATT: Yes.

DR. DAY: Abstain.

DR. FURBERG: Furberg. No.

DR. FLEMING: Fleming. Abstain.

DR. DOMANSKI: Domanski. Abstain.

DR. BOULWARE: Boulware. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. HOFFMAN: Abstain.

DR. MANZI: Manzi. Yes.

DR. FARRAR: Farrar. Yes.

DR. HOLMBOE: Holmboe. No, because of the sulfonamide issue and the other black box for cardiovascular.

DR. GROSS: Gross. No.

DR. WOOD: Wood. No.

DR. GIBOFSKY: Gibofsky. Yes.

DR. CRAWFORD: Crawford. No, based on the

paucity of evidence.

DR. CUSH: Cush. Yes.

DR. BATHON: Bathon. Yes.

MS. MALONE: Malone. Yes.

MR. LEVIN: Levin. No.

DR. ILOWITE: Ilowite. Abstain

DR. D'AGOSTINO: D'Agostino. Abstain.

DR. MORRIS: Morris. Yes.

DR. CANNON: Cannon. Yes.

MS. SHAPIRO: Shapiro. No.

DR. PAGANINI: Paganini. Abstain.

DR. FRIEDMAN: Friedman. Abstain.

DR. HENNEKENS: Hennekens. Yes.

DR. SHAFER: Shafer. Yes.

DR. WOOD: If yes, and all those who abstained and voted no can participate in this as well, describe the patient population in which the potential benefits of valdecoxib outweigh the potential risks and what actions you recommend that

FDA should consider implementing to ensure safe use of valdecoxib?

Let's see if there is discussion on this or whether we want to do the same as we did with the last one and go around again and each person give their recommendations as to what restrictions, if any, they would like to see on the prescribing. Is that acceptable to the committee?

DR. HENNEKENS: Could I ask a question about procedure, Alastair?

DR. WOOD: Of course. Go ahead.

DR. HENNEKENS: If a person feels that they don't have enough information the really make a judgment about whether the drug should be on the market or not and, therefore, abstain, are they necessarily in a position that they could then say which patient populations would benefit from it?

DR. WOOD: Yes; I think they are. I think they can provide us with guidance to what should be done if the drug were to stay on the market. They could still provide us with guidance, yes. So I think we should be encompassing. Everybody has the

chance to respond.

Yes, Dr. Nissen?

DR. NISSEN: I am disappointed in the abstentions. We all sat here and listened to the evidence.

DR. WOOD: Steve, I don't think we should badger people into voting

DR. NISSEN: I actually do want to ask people, as we move forward, to think about making a commitment one way or the other because what you have is a minority of us making a decision. I think it is appropriate that people weigh in. So, one man's opinion.

DR. WOOD: Assuming that there is no objection to that, let's go around the table again and ask for suggestions as to how you would manage this.

I guess what I would do here is, I am going to--if people are agreeable, I will assume that we would do at least what we would do with celecoxib unless someone sees an objection to that. Let's only produce incremental changes, if any,

that you would like to see to this.

Bob?

DR. TEMPLE: You are going to discuss this in a later question, No. 5, like what studies should people do. I just wonder whether you want to speculate on that a little bit so that people can think about that as they give this answer. For example, do you mean a comparison with naproxen? Or what?

DR. WOOD: The committee, you mean, or me?

DR. TEMPLE: Huh?

DR. WOOD: The committee or me?

DR. TEMPLE: Everybody. I am only asking now, even though it is there later, because maybe that is relevant to the discussion that goes on as it might have been the celecoxib discussion, too.

DR. WOOD: Okay. Boy, that might make it complicated, I mean, because we--

DR. TEMPLE: You can duck it if you really want to.

DR. WOOD: Let's go around and make the recommendations here and then--we are not going to

forget that--because I want to keep us moving. Otherwise, we will never get to these other things.

Let's start with Steve Shafer and go around. Steve, to save time, set the tone by adding to your previous comments rather than--if there are things you want to add, add them. Otherwise, we will just with what you said before.

DR. SHAFER: My comments are the same as my previous comments with the one addition that, in anesthesia, we do desperately need better options in the immediate post-operative period for which the intravenous form is an intriguing opportunity. I will just say that.

DR. HENNEKENS: Hennekens. I make the same recommendations as for celecoxib.

DR. FRIEDMAN: Friedman. Same recommendations.

DR. PAGANINI: Paganini. I would alter the black box to include only post-cardiac surgery. I don't see that there is any other data on there for anything else.

DR. WOOD: Dr. Shapiro?

MS. SHAPIRO: I would mimic what I had said before and exclude its use ever in

post-cardiac surgery.

DR. WOOD: Dr. Cannon?

DR. CANNON: Same as my comments for celecoxib.

DR. WOOD: Dr. Morris?

DR. MORRIS: I would make some changes. For this one, I would suggest a medication guide. I would also suggest a contraindication that would be both in the contraindications section and the black box in cardiac surgery. I would also try to develop some kind of special program that would be coordinated with patients undergoing cardiac surgery that would have some kind of extra warning.

DR. WOOD: Dr. D'Agostino.

DR. D'AGOSTINO: D'Agostino. Nothing to add.

DR. ILOWITE: Ilowite. Nothing to add except discussion of the CABG data.

DR. WOOD: Arthur?

MR. LEVIN: Levin. Nothing to add.

DR. WOOD: Ms. Malone.

MS. MALONE: Malone. Much the same as with Celebrex but to also emphasize the need for postmarketing surveillance.

DR. WOOD: Dr. Bathon.

DR. BATHON: I would be in favor of a black-box warning for this drug with the advisory about the CABG patients and against chronic use until further safety data are available in the target populations.

DR. WOOD: Dr. Cush.

DR. CUSH: The same but I would then change the warning to a black box regarding CABG and any other acute cardiac situation.

DR. WOOD: Dr. Crawford.

DR. CRAWFORD: Same as my comments with celecoxib.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: No change from previous comments.

DR. WOOD: I would say the same as before

but I would have a triple black-box warning and I would, again, offer the company the option to get back off probation if they can come up with clear and unequivocal safety data.

Dr. Gross?

DR. GROSS: Same as Celebrex but I would make valdecoxib a second-line selective COX-2 inhibitor.

DR. HOLMBOE: I would contraindicate this drug for use in post-CABG surgery. I would strongly recommend banning it to consumer advertising and I clearly would make this a second-line drug.

DR. WOOD: Dr. Farrar?

DR. FARRAR: As opposed to what I said about Celebrex, I think I would provide in the black box an absolute contraindication in cardiac surgery, a contraindication stating that the long-term-use risk is unknown in the black box and that it is second-line with a clear indication that, if the company produces data obviating those, then those could be removed.

DR. WOOD: Dr. Manzi?

DR. MANZI: In addition to the Celebrex information I provided before, I agree with the

contraindication in any revascularization procedure.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: I would repeat the concerns I had about Celebrex in a black-box warning for this agent but, whereas I was not in favor of a duration limitation for Celebrex, I am in favor of a duration limitation for this agent for which we only have six-month data.

DR. WOOD: Dr. Dworkin?

DR. DWORKIN: For this agent, I would be in favor of a black-box warning and also stipulating that it should only be used third-line, I think, and then with the contraindications that other people have mentioned.

DR. WOOD: Dr. Boulware.

DR. BOULWARE: The same warning I had listed for the black box for celecoxib. I would also add a contraindication for CABG surgery and

also an listing that we don't know the long-term use in cardiovascular risk.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: Number one, I am going to ask that I be allowed--I am given pangs of conscience by Dr. Nissen. I think he is right. I don't think the data are there and I would like to change my abstain to a no, if I am permitted to.

With regard to the box, same as Celebrex but would add that it is contraindicated in the setting of post-bypass.

DR. WOOD: Dr. Fleming?

DR. FLEMING: I would add that it should be contraindicated in cardiac surgery. As I was thinking through this further, I was thinking there ought to be some mandated requirement, and we are going to get to this in Question 5, for trials that would give us the broader insight that we are lacking. I am troubled by the fact that when we look at the other four coxibs, they have all had, on average, 20,000 patients. We have three here.

Dr. Nissen has persuaded me that we do

need to be more forthcoming. We can't probably be as persuasive in mandating that as we can in voting no. So, with that logic, I would like to also change my abstain to a no.

DR. WOOD: Dr. Furberg.

DR. FURBERG: Same recommendation but I would add a limitation in use to 1 to 2 weeks mentioning in the black box or somewhere in the labeling that there is a lack of evidence for sort- and long-term benefit and safety in low-risk patients.

DR. WOOD: Dr. Day?

DR. DAY: Same as before except the contraindications that others have mentioned and also no DTC.

DR. WOOD: Richard?

DR. PLATT: I would add a contraindication for patients undergoing cardiovascular surgery. Even though we will talk about additional trials later, I would make continued marketing of this drug conditional on an appropriately designed randomized trial being undertaken forthwith.

DR. WOOD: Dr. Gardner?

DR. GARDNER: I will join my colleagues in converting from an abstain to a no and, therefore,

not make recommendations for continued.

DR. WOOD: That was another change in the vote. Did you get that? You can see how hanging chads come; right? Dr. Gardner changed her vote from an abstain to a no.

Dr. Elashoff?

DR. ELASHOFF: Elashoff. I would add a limitation to second-line therapy if this stays on the market.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I would offer a stronger warning than we put on celecoxib which particularly emphasizes that longer-term safety has not been established and that the drug should not be used long-term until further data are forthcoming.

DR. GIBOFSKY: Excuse me. You said celecoxib; don't you mean--we are discussing valdecoxib.

DR. NISSEN: Similar to, similar warnings

to, is what I said. So I wanted similar warnings but stronger with the proviso that we don't have the long-term safety data established and, therefore, the drug should not be used long-term.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: I would keep mine the same.

DR. WOOD: Let's take a break We will return at five past 3:00. That is ten minutes from now. And we will get started on the next question.

(Break.)

DR. WOOD: Okay. Let's get started.

Question No. 3: Rofecoxib

DR. WOOD: We are going to move on to Question No. 3. I think we have got the system down pat now. We know what we are doing here, hopefully. The first question is, do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events.

We have been over this a lot, I think, so we probably don't need a lot of discussion. But I will entertain discussion if there is any. Seeing

no hands, we will--which side did we start on last time? Over here.

Yes, Dr. Ilowite.

DR. ILOWITE: Just to remind everybody that this is the only celecoxib that has been approved for JRA and was available as a liquid.

DR. WOOD: Can we just hold for a moment.

DR. GARDNER: Would you say that again. I didn't hear what you said.

DR. ILOWITE: We are talking about Question 3; right?

DR. WOOD: Right.

DR. ILOWITE: I was just going to remind everybody, this is the only COX-2 inhibitor that has been approved for treatment of juvenile rheumatoid arthritis and was available as a liquid.

DR. WOOD: Dr. Elashoff's vote was not properly recorded because it was unclear what she said, apparently. Would she like to vote?

DR. ELASHOFF: I was told I had to say something other than "unclear," so I said no.

DR. WOOD: So you said no. That being the

case, roll of the drum, the vote is 14 yes, 5 abstain and 12 no.

DR. HENNEKENS: Alastair, a point of information. I think we run the risk of giving a bad message here. If we are saying that valdecoxib is contraindicated in cardiac surgery patients when we haven't acknowledged that, if there really is a class effect, we wouldn't want doctors to get the mistaken impression that they should use another coxib or another NSAID instead of valdecoxib.

DR. WOOD: I am assuming that the FDA will take that into account and contraindicate all of them in cardiac surgery. Am I wrong about that, Dr. Temple? Dr. Jenkins?

DR. JENKINS: That would certainly seem to be the logical conclusion since valdecoxib is only in oral dosage form and the others are oral as well.

DR. WOOD: So does that reassure you, Charlie? I know that someone said consistency is the hobgoblin of small minds, but I guess I have got one.

DR. WOOD: Let's move on, then. Which side did we start on last time. I have forgotten. You started last time? All right. Let's start

with Dr. Abramson. Do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events.

DR. ABRAMSON: Yes.

DR. NISSEN: Nissen. Yes.

DR. WOOD: Hang on. I have been asked to ask each of you to give your name before you give the vote. Sorry. So, Dr. Abramson?

DR. ABRAMSON: Abramson. Yes.

DR. WOOD: Nissen?

DR. NISSEN: Nissen. Yes.

DR. ELASHOFF: Elashoff. Yes; both against placebo and against naproxen.

DR. GARDNER: Gardner. Yes.

DR. PLATT: Platt. Yes.

DR. DAY: Day. Yes.

DR. FURBERG: Furberg. Yes.

DR. FLEMING: Fleming. Yes.

DR. BOULWARE: Boulware. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. HOFFMAN: Hoffman. Yes.

DR. MANZI: Manzi. Yes.

DR. FARRAR: Farrar. Yes.

DR. HOLMBOE: Holmboe. Yes.

DR. WOOD: Wood. Yes.

DR. GIBOFSKY: Gibofsky. Yes.

DR. CRAWFORD: Crawford. Yes.

DR. CUSH: Cush. Yes.

DR. BATHON: Bathon. Yes.

MS. MALONE: Malone. Yes.

MR. LEVIN: Levin. Yes.

DR. ILOWITE: Ilowite. Yes.

DR. D'AGOSTINO: D'Agostino. Yes.

DR. MORRIS: Morris. Yes.

DR. CANNON: Cannon. Yes.

MS. SHAPIRO: Shapiro. Yes.

DR. PAGANINI: Paganini. Yes.

DR. FRIEDMAN: Friedman. Yes.

DR. HENNEKENS: Hennekens. Yes.

DR. SHAFER: Shafer. Yes.

DR. WOOD: Dr. Gross has returned.

DR. GROSS: Yes.

DR. WOOD: Dr. Domanski has returned. The question we are voting on is, does the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events.

DR. DOMANSKI: Yes.

DR. WOOD: Okay. The vote is 32 yes. Let's move on to the next question; does the

overall risk versus benefit profile for rofecoxib support marketing in the U.S. We will start with--do you want discussion on that first?

DR. HENNEKENS: Yes.

DR. WOOD: All right. Charlie.

DR. HENNEKENS: I think it is important to point out that, in the placebo-controlled trials, the point estimates for rofecoxib are practically identical to that for celecoxib. Where there appears to be a discrepancy is the rofecoxib trials use naproxen as a comparator which always compares favorably. Some of the celecoxib trials use the short-acting NSAIDs which I continue to believe has

been an issue that we, I know, will discuss. But I think the overall placebo-controlled comparisons are pretty much identical to one another.

DR. WOOD: Any other discussion? Dr. Nissen?

DR. NISSEN: There are some troubling things, however. If you look at all the evidence including the meta-analysis, the blood-pressure effects for the drug are clearly outside of other drugs in the class including celecoxib and so on. So one of the things that troubles me is I happen to think that the prostacycline factor is not the only one. I share Bob Temple's concern that a 5- or 6-millimeter average blood-pressure increase over a period of time is very undesirable since there are other drugs in the NSAID and coxib class that do not appear to have that very large signal on blood pressure.

There is another signal here as well that I think it is important that we understand and that is the heart-failure signal. Compare the heart-failure events in the APC and approved

trials. What you see is almost no heart-failure events. Now, you don't know if they are the same definitions, but you would like to believe they are. And you see this pulmonary edema, heart failure, very, very strong signal, as evidenced by the Kaplan Meier curve that was in the New England Journal of Medicine.

So I think there are differences within the class. I think the problem emerges much more clearly with rofecoxib, particularly on the blood-pressure, heart-failure, side. So my thinking is that there are safer alternatives and, therefore, it isn't the same. It isn't identical.

DR. HENNEKENS: A quick question on that. If you think there is more hypertension and heart failure, then in the APT collaboration events of non-fatal M.I., non-fatal stroke and vascular death, in the placebo-controlled trials, why doesn't that added hazard translate into a higher risk estimate?

DR. NISSEN: What you are saying is heart failure and edema don't immediately translate to

thrombotic events.

DR. HENNEKENS: No; but blood pressure does on stroke and on M.I.

DR. NISSEN: There is a latency, of course. It takes a while for hypertension to yield an excess of events. So there may be some latency issues here as well. But I do think the signal on blood pressure is different for this age. I think, you know, if you look at the data dispassionately, you come to that conclusion. So it makes me more concerned.

DR. WOOD: I also have a view on this. I think the data here are very compelling. There are two trials, as Steve just said. There is not only the cardiovascular risk in the approved trial, there is also the very large risk from heart failure which separates very early. So there is a clear signal this drug appears substantially worse than the others. I can't see any reason to keep it on the market.

Curt?

DR. FURBERG: I don't think that is

correct for heart failure. In the placebo-controlled trials of Celebrex had a risk ratio of 6. The risk ratio in the approved study was 4. So there is no indication that Vioxx is worse than Celebrex for causing heart failure.

DR. WOOD: Dr. Paganini.

DR. PAGANINI: I think this drug really has a much stronger dose relationship than the others have. I think if you take a look at the doses, at the higher doses, you get a much higher response. The studies showed clearly that 50 milligrams is probably not very good, 25 a little bit better, but 12-and-a-half came back to where the other NSAIDs seemed to be.

So I would sort of strongly look at dose response in this particular drug versus the others. I think it is much more apparent here than the others.

DR. WOOD: Dr. Shafer. No? Any other comments? Sorry, Dr. Manzi. It is hard to see over in this corner.

DR. MANZI: I just wanted to point out in

the interest of a risk:benefit way, number one, that, as Dr. Ilowite pointed out, this is the only drug approved for pediatrics, for JRA, too. It is the only one with a G.I. safety proven indication. Other than its efficacy, I would also point out that the once-day dosing, whether it be 25 milligrams or whatever, has been a very favorable component for patients as far as compliance issues.

DR. WOOD: Of course, it might be related to its toxicity, even, the once-day dosing.

Any other comments?

DR. BATHON: It is also the only drug available that can be used in people who are sulfa-allergic.

DR. WOOD: Was there somebody else? Dr. Fleming?

DR. FLEMING: In addition to the excesses that are strongly seen in the VIGOR and the APPROVe trial, the APPROVe trial, Charlie, is placebo-controlled so maybe I missed the essence of what you were saying. The APPROVe trial does show a substantial increase in a placebo-controlled

setting and also shows, in that context, that the excesses are cardiac events as well as cerebrovascular events.

The most favorable of these is the Alzheimer's study if you are just looking at cardiovascular events and yet, that is the study--if that is our positive study, that is the study that shows a statistically significant increase in mortality at 41 against 23. So we have got some significant concerns in each of the trials. Even with the trial that is favorable, or neutral is a better term, in terms of the cardiovascular events, is very unfavorable in mortality.

DR. WOOD: Are we ready to go around the room? I think so. We would like to start with Dr. Abramson. I'm sorry. Dr. Shafer.

DR. SHAFER: I would say overwhelmingly no, although if individual patients can petition the company under some mechanism, I would support that.

DR. WOOD: Dr. Hennekens.

DR. HENNEKENS: Hennekens. Yes.

DR. FRIEDMAN: Friedman. No.

DR. PAGANINI: Paganini. Yes.

MS. SHAPIRO: Shapiro. No.

DR. CANNON: Cannon. No.

DR. MORRIS: Morris. Yes, but.

DR. D'AGOSTINO: D'Agostino. No.

DR. ILOWITE: Ilowite. Yes.

MR. LEVIN: Levin. No.

MS. MALONE: Malone. Yes, with reservation.

DR. BATHON: Bathon. Yes, but at lower dose, 50 milligrams.

DR. CUSH: Cush. Yes.

DR. CRAWFORD: Crawford. Yes.

DR. GIBOFSKY: Gibofsky. Yes.

DR. WOOD: Wood. No.

DR. GROSS: Gross. No.

DR. HOLMBOE: Holmboe. Yes, but only for children.

DR. FARRAR: Farrar. Yes.

DR. MANZI: Manzi. Yes.

DR. HOFFMAN: Hoffman. No.

DR. DWORKIN: Dworkin. Yes, with restrictions.

DR. BOULWARE: Boulware. Yes.

DR. DOMANSKI: Domanski. No.

DR. FLEMING: Fleming. No.

DR. FURBERG: Furberg. No.

DR. DAY: Day. No.

DR. PLATT: Platt. Yes.

DR. GARDNER: Gardner. Yes, with restrictions.

DR. ELASHOFF: Elashoff. No.

DR. NISSEN: Nissen. No, but with a possible compassionate-use program.

DR. ABRAMSON: Abramson. Yes.

DR. WOOD: Okay. While we are doing our counting, let's go on and review the restrictions we would want to have on this if it were on the market.

This time, we will start with Dr. Abramson.

DR. ABRAMSON: I think the concern with

rofecoxib is the dose response and the hypertension. I think there should be some addressing of the maximum dose--

DR. WOOD: Dr. Abramson, sorry. Could I interrupt you. The hanging chads have raised their head. They want to go back. We can't agree on the vote, apparently, for 2.b. So the question for 2.b. was, does the overall risk versus benefit profile for valdecoxib support marketing in the U.S. Even though we announced the vote, and everybody rushed out to file the story, it was premature. We are going to have to retake the vote because we are not sure what the vote was, apparently.

So, I have forgotten which side we started on now. Who started? Steve? Let's go around again and let me remind everybody what we are voting here. We are voting for valdecoxib. Does the overall risk versus benefit profile for valdecoxib--we are going back to retake the vote for valdecoxib for Question 2.b. because there is some discrepancy, apparently, in the vote counting.

Remember Florida? You thought I was kidding.

DR. NISSEN: Where is Katherine Harris now that we need her.

DR. WOOD: So we are going to go back and retake--isn't that right? We are going back to 2.b. We are going back to Question 2.b. and we are taking the vote on 2.b. The question is, for valdecoxib, Bextra, does the overall risk versus benefit profile for valdecoxib support marketing in the U.S. A yes would keep it on the market. A no would take it off the market. Steve are you--which one was it?

COMMITTEE MEMBER: Is it not on the tape recorder?

DR. ABRAMSON: Abramson. Yes.

DR. NISSEN: Nissen. Yes.

DR. ELASHOFF: Elashoff. No.

DR. GARDNER: Gardner. No.

DR. PLATT: Platt. Yes.

DR. DAY: Day, the hanging chad. I have to abstain because the question is based on the available evidence. That is the basis for my

abstention.

DR. FURBERG: Furberg. No.

DR. FLEMING: Fleming. No.

DR. DOMANSKI: Domanski. No.

DR. BOULWARE: Boulware. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. HOFFMAN: Hoffman. Yes, with restrictions on dose and duration.

DR. MANZI: Manzi. Yes.

DR. FARRAR: Farrar. Yes, with limitations on dose and duration.

DR. HOLMBOE: Holmboe. No.

DR. GROSS: Gross. No.

DR. WOOD: Wood. No.

DR. GIBOFSKY: Gibofsky. Yes.

DR. CRAWFORD: Crawford. No.

DR. CUSH: Cush. Yes.

DR. BATHON: Bathon. Yes. I had restrictions, also.

MS. MALONE: Malone. Yes.

MR. LEVIN: Levin. No.

DR. ILOWITE: Ilowite. I am one of the

abstainers before. I will change it to yes.

DR. D'AGOSTINO: D'Agostino. I will balance that and change it to no.

DR. MORRIS: Morris. Yes.

DR. CANNON: Cannon. Yes.

MS. SHAPIRO: Shapiro. No.

DR. PAGANINI: Paganini continues abstaining.

DR. FRIEDMAN: Friedman. I will go to a no.

DR. HENNEKENS: Hennekens. Yes.

DR. SHAFER: Shafer. Yes.

DR. WOOD: Okay. While we are counting that, we will go back to No. 3. We were about to take the vote on 3.b. Oh; we can't vote yet.

While we are waiting, is there discussion on 3.c.? 3.c. is what we would done in terms of restrictions were rofecoxib to come back on the market. Is there someone else that could do the count if we could vote? I beg your pardon. Go ahead.

DR. HOLMBOE: I just wanted to make a

comment that it sounds like Vioxx is really the only thing that is available for pediatric JRA. Since our major concern is cardiovascular risk, I am persuaded by the arguments that you have made that I would hate to remove something that may be of benefit to a population likely to be at very low cardiovascular risk.

DR. WOOD: But we could keep it on the market just for GRA if we wanted. All other drugs could get approval for that, I guess. So that is your comment. Any other comments? Sorry; Dr. Farrar?

DR. FARRAR: A comment about thinking about these drugs in general which is that, although hypertension risk and the edema risk may be higher in terms of the studies that we have looked at, they clearly occur with the other drugs in this category. In fact, a part of the labeling of the drugs ought to be recommendations about monitoring for those issues.

I think, in this particular case, perhaps one of the restrictions would be added to some more

formal warning. But I think the point is that, even a low risk of increased hypertension which may go unnoticed in a young, healthy person, would be an important criteria for long-term use of any of these drugs and clearly for this one.

DR. WOOD: Any other comments? Dr. Morris?

DR. MORRIS: This is a case where, even though I am in favor of the marketing of the drug, I am not in favor of the marketing of the highest dose. I think that should be removed from marketing. I also would very heavily support some kind of really bold warning on duration of use for this drug as well.

DR. WOOD: Dr. Paganini.

DR. PAGANINI: I would second those sentiments.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: I am concerned about the pediatric issue for two reasons, one, that Norm Ilowite stated in regards to lack of a lot of other options, but also the concern about silent,

insidiously progressive, cardiovascular injury. I would be very interested in Dr. Nissen's comments even though they may be entire theoretical about what we might be buying into in approving this for chronic use in children.

DR. WOOD: Okay. Let's--

DR. PLATT: One more.

DR. WOOD: Okay. Dr. Platt first and then Dr. Nissen.

DR. NISSEN: It seems to me, to the extent that we believe there are differences between drugs in this class, that rofecoxib is the extreme, both in terms of its potential danger and its potential benefit. So I think that the onus on informed choice is greater for this drug than for the others.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I am concerned. Part of it comes from a long history of studies with blood pressure that show that it is a continuous risk factor. It extends really way down into the normal range and part of the reason why I was arguing

against bringing the drug back is that, while it may be true that it is the only drug approved for JRA, there is not any reason to believe that other agents could not, in fact, be developed for use in that population.

I am worried that, if you increase blood pressure 5 or 6 millimeters of mercury over a long period of time, you will have a very adverse effect on the health of individuals. So, because I believe the blood pressure is such an important surrogate endpoint in cardiovascular risk, it puts the rofecoxib data in a different perspective.

I guess the other thing I want to make sure everybody understands, is that there are some differences in what was seen. The dose that was used and approved was the 25-milligram dose, not the 50-milligram dose. There is a very, very strong signal there.

That kind of signal is only seen at 800 milligrams in the APC trial. So I think that there is a much greater effect here with this agent even at doses that are not supratherapeutic. So, if we

do bring the drug back, I think that the 12-and-a-half-milligram dose is the only dose that I would be comfortable with because we have seen a pretty strong signal at 25.

If you recall, we haven't seen signals at 200 for celecoxib. So it is quantitatively and qualitatively quite a different signal with rofecoxib than celecoxib. So I just hope everybody understands the implications of a decision to put this drug back on the market.

DR. MORRIS: What is the effect, if blood pressure is raised, like you say, for, let's say six months, what is the effect if someone is taken off the drug? Does that effect go on or does blood pressure return to normal? Do we know?

DR. NISSEN: I don't have any data to that effect. I would believe that it would be likely, at least in large part reversible, but I am not sure anyone has such data.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: So, if there were a way to make approval in children contingent upon further

study on effects on blood pressure and other mechanisms of atherogenesis that might have long-term use, I would certainly be in favor of that.

DR. NISSEN: It is pretty difficult to study because the latency--you know, if you are going to say, well, I am going to increase the life-long risk of cardiovascular disease in a young person, you are going to have to wait a long time and do an awful big study to see it. So it is just not a studyable phenomenon. You have to accept the importance of blood pressure as a surrogate measure and make the decision on that basis.

DR. ILOWITE: If I could just comment. Certainly, blood pressure, which would be easy to study. Secondly, there are trials in existence now looking at surrogate early markers of atherosclerosis in adolescents an older children, not preadolescents, that might be useful.

DR. WOOD: That was Dr. Ilowite again. Are we ready to take a vote?

DR. FARRAR: One more.

DR. WOOD: Sorry, Dr. Farrar.

DR. FARRAR: This is Dr. Farrar. It actually is a very opportune time to think about

this kind of long-term study. As many of you know, the NIH is in the process of putting together approximately a billion dollars worth of money to study pediatric diseases. Perhaps, the advice of this committee could be used to sway them in terms of looking at those issues.

DR. WOOD: Dr. Manzi?

DR. MANZI: I just had a question because we didn't have, really, access to the data in JRA as far as efficacy with Vioxx. Were there blood-pressure issues in those trials?

DR. ILOWITE: There were no blood-pressure issues to my knowledge. I think it was a study against naproxen and showing--

DR. WOOD: Do we know there were no blood-pressure issues, or do we just not know?

DR. ILOWITE: I would know if there were blood-pressure issues.

DR. WOOD: Bob, do you know?

DR. TEMPLE: No; I don't know. But what I wanted to ask Steve was whether he thought seeing whether you could manage the blood pressure and how you could manage the blood pressure would be of interest. Blood pressure is something we ordinarily think of as treatable.

DR. WOOD: It was managed and approved, though, wasn't it? And you still ended up with a higher blood pressure. I forget the data now. Steve, isn't that right?

DR. NISSEN: Yes. What was observed was there was a blood-pressure differential. But, in addition, there was a greater use of antihypertensive agents.

DR. WOOD: There was a greater dropout because of hypertension, too.

DR. NISSEN: One of the problems is that if you actually look at the data very, very carefully and maybe Ralph may be able to comment on this, that treated hypertension still confers a risk over no hypertension; that is to say, bringing the blood pressure down to the same level with a

drug does not neutralize the risk of hypertension in all the epidemiological--

DR. D'AGOSTINO: Certainly, the Framingham data says that. You have a 160 systolic on treatment, you are at higher risk than a 160 systolic natural.

DR. NISSEN: That's right.

DR. D'AGOSTINO: You are presumably coming down from a much higher level and pulling it down. But it definitely does not restore you. You have to bring it down to something like 120 where you don't see a difference.

DR. WOOD: Okay. Let's go around the room starting with Dr. Abramson.

DR. ABRAMSON: On 3.c.?

DR. WOOD: We are on 3.c. I guess, again, the issue is are there incremental changes you want to make over your previous votes here.

DR. ABRAMSON: I think this is a tougher one and Dr. Nissen articulated the concerns. So I would have a stronger label in terms of hypertension and potential cardiovascular outcomes.

I would have a restriction of upper dose to be determined. And I would leave open the possibility of some change of this with future studies. This is one drug, based on the evidence right now, that I might make a second choice if I had to--given the evidence that we have.

DR. NISSEN: Because we have evidence both at 25 and 50 milligrams that is really quite robust, if anything is done with the drug, it should be at a dose of 12-and-a-half. Again, I am concerned. I would also just want to make sure everybody understands that if you look at all the observational studies, this was the outlier. So, if you really want to make this evidence-based, you have got to look at all the evidence.

You have got two trials and observational data that are telling you the same thing, that this is not a safe alternative. So I don't want to go there. But, if we do go there, I would put the most difficult and most complex warning on there possible.

DR. ELASHOFF: Elashoff. Stronger than

either of the two previous cases.

DR. GARDNER: Gardner. Stronger as well. This may be the drug that we ask to register patients or otherwise bring attestation into the risk-management program as well as a good, strong postmarketing or continued marketing ongoing evaluation.

DR. PLATT: Platt. I started off at the extreme with the other drugs. So I stay there, though I would add the dose restriction for this drug.

DR. DAY: More restriction, except I must say, were they unlucky that they used higher doses to begin with? They were the first one that entered, as I recall, the marketing fray.

DR. WOOD: No, no.

DR. DAY: Oh; that's right. So, if they had come in at 12-and-a-half and 25, it might have been different. But, okay; more restrictions, if it were to come back.

DR. FURBERG: Furberg. Stronger black-box warnings.

DR. FLEMING: Fleming. I would add the same conditions and concerns that Steve Nissen indicated.

DR. DOMANSKI: Domanski. I would use the same recommendations I did for Celebrex. I would underscore second-line drug.

DR. BOULWARE: I have nothing further to add. Boulware.

DR. DWORKIN: I agree with what has been said. I would actually think about making this third-line, but a patient will have had to have failed two NSAIDs, whether selective or not, before they try this drug.

DR. HOFFMAN: Hoffman. I agree with the black-box warning should this be remarketed with restriction in dose to 12.5 milligrams.

DR. MANZI: I agree with the black-box label. I would restrict only the 50-milligram dose. If there were a choice, I would rather have patient consent versus not having the drug available.

DR. FARRAR: John Farrar. A strong

black-box warning including an indication of ongoing monitoring of blood pressure in all patients including children. I am conflicted about the idea of registration but feel that some sort of patient consent to indicate the knowledge of the potential risks be made but that the drug be made available. I also agree with the restriction in dose.

DR. HOLMBOE: Eric Holmboe. I agree with what has been said previously. I also feel that, if this drug is to be used in adults, there should be some sort of informed-consent process.

DR. GROSS: Peter Gross. A strong black-box warning, second-line drug and restricted to 12-and-a-half-milligram dose.

DR. WOOD: Alastair Wood. I would say the same thing, black-box warning. I would have a very restricted access program in which consent would be obtained and, if it were to come back on the market, there would have to be such limited access that there would be an attestation and some clear ability of patients to consent.

Similarly, in children, I think we should be careful not to just assume children are not at risk here. While I understand the sentiment to

promote the drug in children, I think we need to be careful that we don't, then, put them at even greater risk with their lifelong hypertension risk, their lifelong exposure to cardiovascular risk factor, and so on when there might be safer drugs available.

DR. GIBOFSKY: Gibofsky. I would agree for restricting the dose to not above 12.5 milligrams in patients who need it for chronic use, not for acute use. I would favor a very strong black-box warning to emphasize the hypertension, cardiovascular, at the higher dose. I would favor language making this a less preferable agent, whether it is second or third choice, to be determined.

I question whether this is something that might be handled, if it comes back, under a Subpart H where there would be very strong restrictions on who would have access to it based on need and

determination of physician and patient.

DR. CRAWFORD: Crawford. In addition to what I stated with the other two, I think there should be a stronger black-box warning, dose limits as appropriate, duration limits, second-line and informed consent.

DR. CUSH: Cush. I would be in favor of retention of all current indications. However, I would strongly recommend removal of the 50-milligram dose from the market and its omission from the package insert as a potential dose for use in acute pain. I would strongly encourage a black-box warning.

DR. BATHON: Bathon. I am strongly in favor of a strong black-box warning with elimination of the 50-milligram and this drug as a second choice.

MS. MALONE: Malone. I have no problem with the black-box warning. I think, if it does come back on a market, that there have to be ongoing studies. And I am in favor of a patient consent that they acknowledge the risks that are

involved.

MR. LEVIN: Black-box warnings strengthened and I am intrigued by the notion of a Subpart H approach to limit prescribing and distribution of the drug.

DR. WOOD: That was Mr. Levin.

DR. ILOWITE: Ilowite. A strong black-box warning, elimination of the 50-milligram dose. I would encourage reexamination of the dose in children in addition to the studies of blood pressure and atherogenesis that were talked about before.

DR. D'AGOSTINO: D'Agostino. Stronger black-box warning, dose restriction to 12-and-a-half and restricted access.

DR. MORRIS: Morris. Black box, withdrawal of the highest dose. I would like to see a consent, initially, but also, based on that consent, a reminder sent to the patient about either six months or a year, depending upon issues related to duration to remind them about the risks of long-term use.

DR. CANNON: Cannon. I favor a strong black-box warning, no direct-to-consumer advertising. I would limit its use to a short-term

use for pain in adults and for chronic use in children and young adults with JRA with careful monitoring of blood pressure.

MS. SHAPIRO: Shapiro. I agree with what Dr. Cannon just said with some dose limitations, appropriate dose limitations.

DR. PAGANINI: Paganini. Black box to include very strong and severe dose and time restrictions as well as cardiovascular, to spell out the cardiovascular clearly to include blood pressure and congestive heart failure, no direct advertising and move from a patient brochure as a patient consent.

DR. FRIEDMAN: I agree with what has just been said with the elimination of the high 50 dose.

DR. HENNEKENS: Hennekens. I share Steve's concern that blood pressure is a greater potential issue here but Richard's that it is likely that higher doses of this drug lead to

greater benefits. This may offer one plausible explanation for the higher risk seen in observational studies.

As I said, with regard to the coxib, I think global risk assessment and aggressive management of cardiovascular risk is important. I would expand that I would definitely think we ought to be thinking about Ralph D'Agostino Framingham Risk Score and the aggressive management based on federal an AHA guidelines which are mandated based on these assessments for both statins and aspirin.

DR. SHAFER: Steve Shafer. If it is to be marketed, I think it should only be indicated for children not adequately treated with conventional NSAIDs. The black-box warning should state that the cardiovascular effects in children are unknown and that the use in adults is not recommended.

The adult use should be limited to compassionate use only which, I believe, is the Subpart H restriction.

DR. WOOD: Okay. I am now in a position to read you the votes for Question 2.b. and 3.b.,

at least for now. The vote for 2.b., which was the vote on valdecoxib, for those of you who have forgotten already, was 17 yes, 2 abstain and 13 no. The vote on 3.b., which was the rofecoxib vote, was 15 no, 17 yes.

Question No. 4

So let's move on the Question No. 4; if the available data support a conclusion that one or more COX-2 selective agents increase the risk of cardiovascular events, and we have clearly made that decision already, then please comment on the role, if any, of concomitant use of low-dose aspirin in reducing cardiovascular events in patients treated with COX-2-selective NSAIDs.

I am not sure how we can do that, apart from the sort of biological basis. There are not any randomized trials in which we have got data from that, are there? Ones that are on the market here?

DR. HENNEKENS: If we accepted a global risk assessment and aggressive management of cardiovascular risk based on federal and AHA

guidelines, that embedded in both of those sets of guidelines are guidelines for the aggressive management with statins and aspirin rather than a recommendation that is for a specific drug in specific response to this class of drug.

DR. WOOD: No; but I think the question here, Charlie, is that if we accept that this drug, in itself, carries a risk of cardiovascular disease--let me rephrase the question. I think the question that is being asked here is do we think that the cardiovascular risk produced by these drugs, or any one of these drugs, can be reversed by the administration of aspirin. That is what we are trying to get at.

DR. HENNEKENS: I wanted to rephrase the answer and say that I think aggressive assessment and management of all cardiovascular risks of these patients is what is indicated. I think it would be a mistake to limit it based on a pharmacologic argument to this one particular agent. And, in addition, there are exiting federal and NIH guidelines--AHA guidelines; I'm sorry--for the

management of these patients for both statins and aspirin which would kick in. That, to me, makes much more rational sense.

DR. WOOD: No, no. I understand that. But let me just correct it. This could apply to a patient independently of their--a patient who was not eligible for aspirin under AHA or federal guidelines. So the question that is being put here is whether a patient who is taking these drugs who would not otherwise be eligible for aspirin under federal AHA guidelines should take aspirin to counteract the adverse effects of this drug. Am I right; John?

DR. JENKINS: Yes. That is exactly correct. That would be a logical place you might go if you think these drugs have a cardiovascular risk. Based on the mechanisms proposed, you might think you can take a low-dose aspirin and reverse it. But we want to know your thoughts about whether that has any value in reversing the cardiovascular risk and what the impact is on the G.I. benefit because this will come down to a

question we will have to address in the labeling for these products whether there should be any comment about use of low-dose aspirin.

DR. WOOD: So I guess the study that speaks to that most, I suppose, would be the CLASS study. It wasn't a randomized comparison, although it does give some evidence that the G.I. benefit was antagonized by aspirin and the cardiovascular benefit was reversed as well, I suppose.

Steve?

DR. NISSEN: I understand the spirit of what you are asking here and let me see if I can frame this. You are asking whether we have evidence that the mechanism-specific effect of these drugs can be reversed by concomitant administration of aspirin. I have looked at all the data. I looked at that APC data. I looked at everything else. Just there is no compelling evidence of it.

It goes both ways and this is actually one of the biggest disappointments for the whole class because, when this whole hypothesis was first

raised, there were people who said, don't worry about these drugs. Just give everybody a baby aspirin every day and you can reverse the cardiovascular toxicity of the COX-2 inhibitors.

It turns out that that hypothesis, and I have said a number of times, the road to hell is paved with biological plausibility, and this is another example of that the, in fact, it was plausible but it appears to be wrong. Having said that, the amount of data we have upon which to make that judgment is limited. It would be useful, at some point in the future, if this class of drugs is to survive in the long run, to study this in a more formal way with larger sample sizes that will let people like Ralph and Tom and others calculate with more precision whether, in fact, aspirin is an effective antagonist to the toxicity of this class of drugs.

DR. WOOD: Dr. Bathon.

DR. BATHON: I agree with Steve that, with the available data that we have so far, the addition of aspirin not only does not appear to

reduce the cardiotoxicity but it also seems to undo the G.I. benefit. But, more importantly, if somebody is on an aspirin with a COX-2, you no longer have COX-2 selectivity anyway, so it doesn't make rational sense to put the two together. If somebody needs aspirin, then there is no particular advantage to them being on a COX-2 drug unless one argues that aspirin plus a nonselective NSAID has higher G.I. toxicity, perhaps, than aspirin plus a COX-2 selective agent and I don't know that we have those data.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: I think it is important to paraphrase Dr. FitzGerald--he may still be here--but I have learned from him. It is clear that there is--at least it seems clear that there is a derangement caused by these drugs and no particular reason to believe that aspirin mitigates the derangement.

DR. WOOD: It is always dangerous to paraphrase Garret. I will tell you that. Dr. Platt?

DR. PLATT: It seems to me the arguments for aspirin, if we accept them, could clearly move these drugs into second-line status. Those who

didn't think so before, I think, lose the rationale there is for treating these drugs as just regular NSAIDs.

DR. WOOD: Dr. Gross?

DR. GROSS: I think there is just not enough good evidence to comment on this one way or the other and the question raised was not a primary endpoint on any of the studies we used.

DR. WOOD: Dr. Farrar.

DR. FARRAR: I think we need to be careful. Aspirin is not a panacea for cardiac vascular disease. I think the cardiologists would know better than I but, in my discussions with a couple of people last night and in the past with some of my colleagues at the University of Pennsylvania, it is clear that, in people with cardiac risk, serious cardiac risk, aspirin is probably useful in the general population. It is not at all clear and the benefit is actually

reasonably small.

So I am not sure why there is a sense of loss that it doesn't work. But it is clear to me that it doesn't work. The only evidence that seemed to suggest it at all was the approved study and it was the outlier.

DR. WOOD: Any other comments? Dr. Cush?

DR. CUSH: To, again, paraphrase and reinforce what Joan said in that, if you probably need aspirin for cardiovascular prophylaxis and its modest effects on that, then you certainly shouldn't be on a COX-2 inhibitor.

DR. NISSEN: There was one question I had for our G.I. colleagues that never got answered and maybe you can help with this. Is there a comparison of a conventional NSAID plus aspirin for cardiac protection versus a COX-2 inhibitor plus aspirin. Is there a quantitative difference in the risk of G.I. toxicity?

DR. CRYER: It depends on how you make the comparison. If you derive your comparison--and I am speaking about data that, to my knowledge, has

not yet hit the peer-review published world. If you make the determination, epidemiologically, based upon hospitalizations for upper G.I. bleeding, the data would suggest that a COX-2 specific inhibitor plus aspirin appears to be a regimen that is associated with a lower rate of hospitalizations than nonselective NSAID plus aspirin.

If you make the determination based upon the traditional characterization of G.I. events, the two arms appear equivalent.

DR. WOOD: At a personal level, I agree with Dr. Gross. I don't think there is any evidence base that we can answer that on, however attractive the underlying hypothesis might be.

I don't think we need to go around and vote on that. Does anyone else have anything they want to say on that that has not been said? Yes, Ralph?

DR. D'AGOSTINO: Maybe the FDA could remind us. There was--I can't find it quickly, but there was concern in one of the noninferiority

trials that, if the study had too many individuals that were taking aspirin, not randomized to aspirin but taking aspirin, it was going to pull the two groups together. Could somebody from the FDA just remind us where that concern--

DR. VILLALBA: In the lumiracoxib studies, the subgroup on aspirin showed that--in the non-aspirin group, there is a clear signal for lumiracoxib versus naproxen. There were, like, 10 to 2 myocardial infarctions, while in the subgroup using aspirin, there was no difference.

DR. CRYER: I had forgotten about the TARGET--this is Cryer, again, to answer Dr. Nissen's question. I had forgotten about the TARGET trial and I will just remind the group of yesterday's presentation. In the 18,000 patients, there were no differences with respect to low-dose aspirin and G.I. events, no statistically significant differences.

DR. WOOD: Any other comments on that? Yes?

DR. FLEMING: Fleming. The data are

pretty limited. If you look at all 18,000 patients, it was 24, 23 in those that are aspirin users but it was 35, 27 in those that were not. So it is rather fragile while, in other studies like APPROVe, there was no evidence of interaction.

DR. WOOD: I am going to jump to Question 6 because Question 6 we have to take a vote on. So I want to make sure we get that under our belt and then we will come back to Question 5.

Question 6 is, 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, warning, precaution.

I have a sense, John, that we have already covered that, to some extent, haven't we?

DR. JENKINS: Again, noting that this question is about the agent other than the three we just discussed. This is about the other twenty.

DR. WOOD: I'm sorry. Then we will keep

going on 5, then. I beg your pardon. So we have dealt with 4. Let's go on to 5.

Question No. 5

What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential cardiovascular risks of celecoxib, rofecoxib and valdecoxib. What additional clinical trials or observational studies, if any, to you recommend as essential to further evaluate the potential benefits--reduced G.I. risk--of celecoxib, rofecoxib and valdecoxib. Please be specific with regard to which COX-2 selective agent to study, trial design, patient population, control groups, endpoints, duration, sample size, et cetera. And it is five to 4:00.

There is a three-day task right there, it seems to me. Do you really want that before we leave? Bob?

DR. TEMPLE: I guess I was struck by the fact that several of you, but not everybody, said that celecoxib or valdecoxib has to do something to

get rid of a certain nasty thing in the labeling, get rid of the box. So it raises immediately the question what would they have to do to do that; comparison with some other drug, not be worse than naproxen? What do they have to do?

That is why this deserves some attention. Nobody expects you to design the whole trial perfectly or fully in five minutes.

DR. WOOD: Four-and-a-half, now. Comments on that? How are we going to design a trial? Can we break it out easily? What would we need to evaluate the potential cardiovascular risk if we think there is a cardiovascular risk of celecoxib, rofecoxib and valdecoxib.

Comments on that? Yes, Dr. Farrar.

DR. FARRAR: I think this actually begs an issue that we ought to address which is that we cannot possibly, in the half an hour or forty-five minutes that is left do all of the issues that are being requested here. But it does suggest--

DR. WOOD: Did you think you were going home at 5:00?

DR. FARRAR: My mother is down the road. It's fine.

DR. WOOD: She'll be glad to see you

tonight. We're all coming. (Laughter.)

DR. FARRAR: But it suggests, in fact, that there needs to be a process that, perhaps, even expands beyond this particular class of drugs to really examine the issue of how the safety of drugs needs to be considered with regards to the patient populations that in whom the drugs are likely to be used and with regards to the potential uses for a particular drug.

I actually would strongly recommend that, for those of us who--I was one of those who recommended that there should be some trials or some studies done to try and remove some of the black-box labeling that, at least, I was in favor of. Rather than trying to design all of that now, what, really, I would suggest is that a group of academic folks made up of some of the people here but, clearly, including people with pharmoepidemiology, statistical, epidemiological

skills as well as the particular specialty skills of arthritis, pain or whatever is necessary, be put together to formulate a really good design based on the type and the discussions here and that the recommendation of this group ought to be that, not just the folks at the FDA, but that there should be an ongoing process with a group of academic advisors to really formulate an appropriate study.

DR. WOOD: I guess I was the person that suggested the sort of "get of out jail free" card if they came out with the studies. It seems to me the studies break into two different broad groups. There are studies that would be potentially against placebo that would establish whether the drug had an absolute risk and there are studies against some other comparator that would establish whether the drugs were superior or inferior or the same as the other comparator.

It seems to me the choice of the comparator would depend, first, on the indication, clearly, and one would like at least to be able to get some information on what the comparator looks

like on its own. So I am sort of going back to the question that Tom Fleming raised yesterday, or whatever day it was, not it all merging.

But, with so many of these studies, we are in the position of trying to impute what we would expect to see with a placebo or what we would expect to see--yes; what we would expect to see with the placebo--in the absence of the placebo, or even we are trying to impute what this drug would do versus that drug based on another study.

So it would be important to know, for example, unequivocally, whether naproxen plus, I would think, a PPI inhibitor does something good or bad in terms of cardiovascular risk. If we knew that, we might be in better shape to make judgements about how to design the trials.

So I am not sure I would jump in immediately to all these comparisons. We are going to get to some of that, I guess, in the next series of questions that look at the other nonsteroidals. But I think it is a complicated issue that would need to be addressed for both the

placebo-controlled group and the active control group and would need, actually, a third comparison which is a research program that looks at the active comparator so that we establish what it is we are actually looking at there because a lot of that we have imputed.

Bob?

DR. TEMPLE: Suppose you knew--there are a bunch of nonsteroidal anti-inflammatory drugs out there. Everybody agrees somebody is going to--you are going to treat pain with something. Several of you said that staying on the market with this box places you under some--that, ideally, at least, there would be some further studies designed to show something.

So, just to pose a couple of questions, suppose an adequately sized study of adequate duration showed that this drug was no worse than ibuprofen, a standard treatment, would that be reassuring up to a point even though you have never had a placebo-controlled trial of ibuprofen and you probably never will.

Or would you have to use naproxen which people sort of have an inclination to think is a little better. Or do you have to try to dream up

another placebo-controlled trial which is not easy to think how you do these days unless sort of polyp reduction raised its head again, maybe at a lower dose.

It would helpful not to design the whole trial but to think a little bit about some of those things and what is possible. If you can't do anything until you have the definitive naproxen versus placebo study, we are talking almost never because we don't have any of that.

DR. WOOD: Of course, the other issue that is on the table is that some of us believe these drugs were risky. And so inherent in that assumption is that you would be cautious about recommending a trial to be done because the likelihood is it would revalidate or replicate what has already been shown. So there is some hazard in suggesting that, I think.

But I actually think there is a value in

trying to demonstrate an effect against naproxen. I don't see a problem with that. Naproxen may be beneficial. We ought to know that, though, and we ought to be able to find that out fairly quickly, I would have thought. And let's get that.

After all, it is not that we are trying to define the origin of life or something here. This is not some fundamental discovery we are trying to make. We are trying to divine what the optimal therapy is for something. If we can evaluate naproxen plus a PPI and work out how that stacks up against placebo, and then move on from there, we could get a lot of information fairly quickly, I think, that would be very valuable.

DR. TEMPLE: So at least the initial study, perhaps you would add other groups like one of the other selective ones that isn't so named, but the first study would be a study of reasonable duration. You also--I hope you will say something about just how long it needs to be, too. I mean, is it a one-year or a three-year study?

The initial comparison might be against

naproxen and some dose of celecoxib. They already have a study against ibuprofen so that wouldn't be too helpful to do again, I guess. Is that the sort of thing you are thinking of ?

DR. WOOD: Yes. I would be unimpressed with a study against another selective COX-2 inhibitor. I think that is likely to be negative.

DR. TEMPLE: And it has been done.

DR. WOOD: And it is being done right now. I am not sure of what that will teach me. At the end of that study, if you gave two doses of the same drug, you would expect to see the same effect in both groups. If you give two drugs that are very similar in their pharmaceutical effect, you are unlikely to see a difference between them and I am not sure what that would tell me.

DR. TEMPLE: So, so far, at least, your thinking naproxen, if I hear you.

DR. WOOD: Right. Dr. Cush?

DR. CUSH: I think, by going through this data in the last few days, that we have acknowledged that there are a number of signals

that exist--that are worrisome that exist for the nonselective nonsteroidals especially for ibuprofen and diclofenac which have been often comparators in these trials. I think we also have been impressed by the performance of the naproxen.

Hence, I would say that, really, the whole class, all nonsteroidals, should have a warning that would include some lesser version of what may be in the black-box warning about cardiovascular risk and that everyone should basically carry that forward, maybe with the only pass being provided to naproxen which becomes a comparator drug for future trials.

I think that, to get off the list, to get that warning removed, you basically have to, as a sponsor, do a trial against naproxen or, in some other manner, show that you do not show a significant cardiovascular hypertensive risk to your patients.

I would also favor the performance of an NIH and/or FDA-funded--ALLHAT trial has been proposed--and such a trial should be two years

duration.

DR. WOOD: Dr. Nissen?

DR. NISSEN: Let me see if I can get very specific here. For each of the marketed COX-2s which I assume, at least for the moment, will be--who knows? Actually, I am not sure what we decided. But let me say that, in arthritis, it is very clear you can't do a placebo-controlled trial. While it might seem appealing to do your acetaminophen codeine control group, I just don't think it is a practical approach.

I think we need to have some clarity and some consistency in comparators because, if we don't, if every sponsor compares to a different active comparator, we will have no clarity at all. So I happen to think that the evidence is pretty good that naproxen is no worse than neutral. So I would like to see a celecoxib 200 milligrams, a dose that has not, at this point, been shown to have excess cardiovascular risk, against naproxen, 500 BID, with adequate size, and Tom has mentioned some numbers--we are talking about around 100

events, at least, maybe a little bit more--to get the upper limit of the hazard ratio to be at a level that would provide some comfort.

If you are going to do that trial, then it makes a lot sense to add a third arm to the trial which includes a conventional and non-naproxen NSAID. I happen to like diclofenac because it is an agent that looked, in CLASS, an awful lot like celecoxib.

So now you have clarity in a single trial of acceptable size on how a low dose of celecoxib, the most commonly prescribed dose, compares to an agent that you believe is, at worst, neutral and to an agent that has some potential suspicion to be worse than neutral. When you are done with that trial, you will know a lot more.

Now, Merck has already set up a diclofenac comparator with their agent and that is helpful. The problem is--

DR. TEMPLE: Not naproxen.

DR. NISSEN: Not naproxen. You know, obviously, is it very costly to redesign that trial

but there is a problem for me. If Garret FitzGerald is right, that diclofenac is similar to celecoxib in selectivity and, therefore, in cardiovascular risk, then the comparator to etoricoxib could be a comparator that is not neutral. It is not a naproxen comparator.

So we may not have clarity, the clarity that we would need. So I think that, in the absence of being able to do placebo-controlled trials, you have got to pick an agent that you think is probably no worse than neutral and try to show whether new drugs that are proposed and existing drugs are not worse than that agent on cardiovascular risk.

So that is one guy's opinion. But I am not an epidemiologist. I am just a knuckle-dragging cardiologist.

DR. TEMPLE: That sounds good. Actually, that is getting close to the ALLHAT study that we are hoping for.

DR. WOOD: Dr. Dworkin.

DR. DWORKIN: I was going to say much of

what Dr. Nissen said except that what I would prefer is a third comparator, ibuprofen, because I think we have this large class of traditional NSAIDs and, if we had a series of studies with these COX-2-selective drugs, whether it is celecoxib, rofecoxib, valdecoxib, and each of those studies had a comparator of naproxen and ibuprofen, while we wouldn't have a placebo baseline at the end of the day, we would have a lot of information about naproxen, which we would all like to know a lot more about, and, with the ibuprofen arms across all these studies, we would have a lot of information about the traditional NSAIDs that we know very little about at this point. Of course, we would also then know a lot about our coxibs as the third arm.

DR. TEMPLE: Not to state the obvious, there is a difference between what you can reasonably ask a company to do and what you could ask a larger group to do. We all want to know about diclofenac but it is not clear that some company wants to know about diclofenac. So it

could be slightly different, but this is a very helpful discussion.

DR. DWORKIN: Could I say one thing, Bob, about that. Isn't it the case that, in Europe, the European regulatory authorities really require a comparator arm. So you would not be doing much more than is done in Europe by saying that we would like to see at least one trial with an ibuprofen arm and also a naproxen arm, in addition to your drug. I don't think that is unreasonable.

DR. TEMPLE: That is fair. But if they were to come back and tell us, if we are as good as naproxen, aren't we okay? It would be hard to say the answer to that is no.

DR. WOOD: Dr. Fleming.

DR. FLEMING: I will defer discussion about ibuprofen and diclofenac until we get to the later questions. My sense is there is a trial that I believe should be done with celecoxib although it is optional, although I would tie it to the black boxes, as you have previously.

I believe that there are, however, studies

that should be viewed as essential for valdecoxib and rofecoxib. Relative to the celecoxib, what I had written down parallels what Steve Nissen had said with a few extra specifics. The design that Bob Temple had put forward, to me, makes a lot of sense. It would seem logical as one approach here that for celecoxib could lead to the kind of evidence that would remove the black box, is to do a trial.

I would urge that the comparator be naproxen or aspirin plus PPI, agents for which there is a considerable sense that the effect on cardiovascular excess risk is minimal, and it be a noninferiority design, essentially ruling out the magnitude of effect sizes that we are seeing overall which is actually going an achievable task; that is, ruling out a 50 percent increase.

Basically, if truth is no increase, you can rule out a 50 percent increase with 90 percent power with only a 2-and-a-half percent false-positive error rate with 250 events which, essentially, is a trial that would have about

10,000 people per arm. That would be the basic target that I would put forward. That trial is positive if your observed excess risk is in the neighborhood of 17 percent.

So anything that is not worse than about a 17 percent increase in the trial of that size would rule out a 50 percent increase.

In may view, if that type of evidence were available, and I would be inclined to think it would be the OA or RA setting and I would like to see it for two, to two-to-three years follow up. You had staggered entry and then additional follow up so we are looking at at least a couple of years of follow up. We are looking at duration of outcome. That is the kind of evidence that, from my perspective, would provide a considerable reassurance. I don't consider it mandatory, but I would link it to the black-box issue.

On the other hand, for valdecoxib and rofecoxib, linked to the fact that I voted no, to my way of thinking, if these product are going to be on the market, it should be essential that we

get additional evidence. I am very troubled that, that, for valdecoxib, we have 3,000 patients. We have minimal evidence here upon which to base a clear sense of whether or not there is excess risk.

I believe the FDA should consider it essential, within an acceptable time frame, to perform a study that allows us to get a clear sense of whether there is an excess risk. The dose should be chosen according to what the sponsor believes would be an appropriate marketable dose that we would want to be able to establish safety.

For rofecoxib, my sense is that, what we are hearing is that Vioxx may have gone forward with an improper dose. I think, if we are, in fact, going to get it back onto the market, there should be studies done at a dose that is, in fact, going to be marketed that needs to be established to be safe.

Similarly, as for the celecoxib, if these studies are done, and I believe they should be considered essential, they should be done in a manner to allow us to rule out a 50 percent

increase using a proper control and that control would depend on the indication, but either a placebo control, and aspirin plus PPI or a naproxen control would seem acceptable.

DR. WOOD: Okay. Dr. Hennekens.

DR. HENNEKENS: The randomized comparisons of the short-acting NSAIDs suggest to me that they are at least as hazardous as the coxibs. These are over-the-counter drugs that have direct-to-consumer advertising. I think there is a signal here that we should not ignore, so I would not limit the comparisons to naproxen.

DR. WOOD: We are getting to that, though, in a second. Dr. D'Agostino?

DR. D'AGOSTINO: Many of the comments I was going to make have been already made, but I think that, if you shift the indication to something away from arthritis, you can get a placebo as a third arm. I think the naproxen is a good idea.

I am concerned. I agree 100 percent that it should be noninferiority. I am concerned about

the 1.5 because some of the drugs that we have condemned may have something like a 1.5 or even smaller. So that may be too generous. I think that takes a lot of discussion and I don't know the answer.

The other point that I visited a few times and don't want to leave is that I think the follow up is very important, that people can leave because their blood pressure is building up, they are getting hypertensive, or they could leave because of G.I. problems. But those individuals need to be followed. They can get off the drug but they need to be followed.

Should the analysis be intent-to-treat or should it be something else, one can argue that again. But I think it is very important that it is, as much as possible, a complete follow up. There is also--it goes without saying, but we need a long enough time because we don't seem to have a constant hazard over time. So we have to make sure the studies do go the two or three years and the ascertainment adjudication of these CBD events has

to be a prime item in the particular studies.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: I liked what I have heard from Steve and Tom about suggestions for a study, a long-term study, going 1.5 to three years for arthritis. But I think we fall into potential traps here when we talk generically about arthritis. I think rheumatoid arthritis, being a systemic disease, which has an increased risk of cardiovascular disease to start with, becomes a very difficult situation to deal with if one uses that cohort in a long-term study.

These people are constantly having their multiple therapies tweaked to find the sweet spot which sometimes we find, sometimes we don't. However, if the study is done with a mild to moderate OA, a degree of osteoarthritis that is significant enough for which someone would take medication, then you don't run into the problems of multiple other medications and systemic illness.

So I like the idea. I think with mild to moderate OA, you can have an analgesic arm. You

can start with acetaminophen. You could even increase from acetaminophen to acetaminophen with codeine, if necessary. There are no known cardiovascular risks with that. You can compare that to the NSAID group, naproxen, if you like, or ibuprofen with a PPI, and then look at your COX-2. I think that becomes a much cleaner study.

DR. WOOD: Dr. Cush?

DR. CUSH: I want to echo some of the same comments but then specifically speak to some of the impracticalities of what Dr. Temple and Dr. Fleming had suggested, very good ideas, good plans, but, again, as Gary stated, we need a team of drugs to manage these people over the long haul. They don't stay on any one drug. So, to expect someone to stay on aspirin, 4 grams a day for two or three years, is not going to happen on any drug, in fact. It is just not going to happen.

Moreover, aspirin, 4 grams a day, is not used at all ever anymore by anybody who knows what they are doing. The gastroenterologists would have a field day with this. Okay? So to try to provide

some modicum of protection by putting a PPI on top of that is not going to be practical and this would never work in a clinical-trial situation.

As Dr. Hoffman has suggested, an analgesic class makes sense, whether that be acetaminophen, tramadol or propoxyphene, and if you want to throw in the added benefit of 81 milligrams of aspirin a day as a control, that probably would work.

DR. WOOD: Dr. Fleming.

DR. FLEMING: Under their proposal, there are, certainly options that were put forward and an alternative to the aspirin PPI would be to use naproxen as the control arm. Just to get back to Ralph's point, he is right that it is difficult to know exactly what the margin is here. What is an unacceptable level of increased risk.

I had mentioned that I would want us to rule out at 50 percent increase and that would take 10,000 per arm. If we, in fact, asked to rule out a 33 percent increase, it would be 20,000 per arm and, to rule out a 20 percent increase would be 60,000 per arm.

A reassuring aspect, though, is that if we are ruling out a 50 percent increase, which is 10,000 per arm or, in essence, 250 events in the

pairwise comparison, what one is doing to be successful there is getting an estimate that is far less than a 50 percent increase. It is an estimate of about 15 to 17 percent. It would have to be better than that to be a success.

Thereby, what one would be getting is, for that study to be positive, a result that would indicate that the estimated excess risk is, at most, one third what we are estimating it to be in the aggregate here and, hopefully, even better.

So, keep in mind that, in that trial design, it is not success if you see 1.5. It is success if you rule out 1.5 and that is going to take something that is an estimate of only about a 15 percent increase.

DR. WOOD: I am going to move us along to next that as we have already started to lose people and I think we have given them advice on this.

Question No. 6

There are more than 20 nonselective 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 interesting background package and during the committee meeting, please address the following questions regarding the approved nonselective 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 nonsteroidals.

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 go 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 marketshare 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 in 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 nonsteroidals 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; etdolac, miloxicam, diclofenac, sulinac. The observational data would suggest that three of those, in particular, showed up; miloxicam, diclofenac and sulinac. 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 noncoxib nonsteroidals, 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. WOOD: 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 nonsteroidals 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 nonsteroidals 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.

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.

DR. DWORKIN: 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: 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 nonsteroidals with regard to cardiovascular risk and that, to get that warning removed, there should be a trial, I guess, with naproxen showing superiority or nonsuperiority, I guess.

DR. BATHON: 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.

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.

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

DR. FLEMING: If we are jumping to 8, just very quickly, in 10 seconds, I would certainly urge, from a public-health perspective, that if there was any way possible to include ibuprofen and diclofenac in the Temple trial, that would be an extremely important added insight.

DR. WOOD: In the Temple ALLHAT trial. Okay.

Question No. 8

DR. WOOD: Question 8; with regard to evaluation of cardiovascular risk, what studies do you recommend as essential to be completed and

reviewed prior to approval of new NSAIDs. With regard to the evaluation of the potential benefits--for example, reduced G.I. risk--what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? Please be specific with regard to trial design, patient placebo, control groups, endpoints, duration, sample size, safety monitoring and patient protections, et cetera?

Some of this, actually, John, we have already covered. I think, in the studies that we recommended for the "get out of jail free" cards, we have covered that. So we could go back over that, I think, and see if there are additional things we wanted to do. We have covered some of these already. Yes?

DR. HOLMBOE: I just want to reiterate one thing I would suggest that applies to the previous studies discussed and to new studies. Again, I want to emphasize that, if we are going to do a randomized controlled trial, our hypothesis is that these drugs are causing harm. Therefore, you are

being randomized to harm, not benefit.

I would just make a plea that, if you are going to do these studies, as has been discussed using the various comparators, that we maximize, as part of that trial, the cardiovascular-risk-factor reduction, getting to Dr. Hennekens' point. I think not to do that would be unethical.

DR. GROSS: Any other comments? Yes; Dr. Nissen?

DR. NISSEN: Again, this is really challenging. I know what I am going to say isn't going to be population with the Merck folks, but I just don't think that--I think you have got to have a comparator that is neutral or better than neutral. So I want the new drugs to show an upper confidence boundary in the range of what Tom Fleming talked about against naproxen.

That is a high enough standard to protect the public which is what we are all talking about here today. So I am willing to accept that naproxen is no worse than neutral. So, if you are not 50 percent worse than naproxen, then you meet a

standard that I would consider acceptable and then that is going to be a point estimate that is no more than about a 15 or 17 percent worse than naproxen. That is a safe and secure way to proceed.

Now, that means restarting some development programs. I know it is very painful, but I don't think that being as good as diclofenac when we don't know how good diclofenac is, is the right standard.

DR. HENNEKENS: I agree with you, completely, Steve. I think the same bar should hold for any of the new NSAIDs.

DR. GROSS: Dr. Gardner?

DR. GARDNER: I think all the studies should be powered adequately for subgroup analysis and to have duration of use taken into account so that we can make some of these distinctions that we have been struggling with.

DR. GROSS: Dr. Farrar.

DR. FARRAR: Two quick but different points. One is that we need to be very careful

that the drugs are tested in populations in whom they are likely to be used, namely patients who are older and have either hidden or, perhaps, some mild known cardiovascular risk, obviously limiting it to people with mild risk, but in the group in which it is likely to be used.

The second issue is, you ask about the G.I. benefit. I do think that, given all the talk that we have gone through these three days, that it would be appropriate for any new drug to have a comparison against naproxen or one of the other COX-1s in combination with a protective agent for stomach ulcers. That combination, obviously, would need to be discussed.

DR. WOOD: I would say that we should certainly insist on at least the studies that we recommended before and that we should consider comparisons to naproxen and, if there is an appropriate indication, and to placebo if we can do that. Once we have got a naproxen PPI and placebo study in our bag, we would be in a lot better shape to interpret what we are actually looking at, I

think.

Dr. Fleming?

DR. FLEMING: I would just echo what has been said previously that I would want to see, depending on the indication, it could be placebo control, it could be naproxen control, evidence that essentially allows us to rule out a 50 percent increase in the relative risk for cardiovascular events.

DR. WOOD: Dr. Cush?

DR. CUSH: I think it is important to be practical. So, for new drugs not yet on the market, they should be required to do these trials just like APPROVe and CABG II with valdecoxib except these must be done in the indications for which a drug is being sought, so in osteoarthritis, in rheumatoid arthritis, or whatever, and that those trials should be done in low-risk individuals, that they should not be done in high-risk individuals, because, otherwise, you really shouldn't be using these drugs in high-risk individuals.

So they should be done in low-risk populations and they should be done with an appropriate active control group over a long period

of time, which is at least a year, but I think it would be preferable to do two years. These will be difficult and expensive trials to do but they must be done for those who want to come into the market.

For those that are currently in the market, I think that the answer could probably be helped a great deal by Dr. Temple's ALLHAT design or a modification thereof.

DR. WOOD: Any other comment on that? Is that helpful, John?

DR. JENKINS: Yes.

DR. WOOD: What is your pleasure? We are losing people so what is your pleasure for the next question? 9?

DR. JENKINS: I think 9 is getting us into the area of--it is fairly speculative and, in many ways, linked to No. 6 where you have already recommended that there be something in the labeling about products that don't have data. So I don't

know that 9 is critical because, obviously, any future NSAID that we get is likely to come back to this committee for your recommendation before we make an approval decision. So then we would actually have the data in front of us to decide what the labeling should say.

DR. WOOD: So do you want to go back to 7, then?

DR. FLEMING: Before we do, can I make one comment?

DR. WOOD: Yes; Tom.

DR. FLEMING: Basically, on 9, you are putting forward a potential condition upon which, if satisfied, could lead to the absence of a label indicating a warning. The critical distinction here is this is worded as, if there is absence of establishing an increase, which is very different from evidence against an increase, and that is basically failure to achieve statistically significant establishing an increase is not ruling out an increase. So this first sentence here--if you do trials that fail to show significant

increases, that is not a reassurance against an increase.

What you want is evidence sufficiently powered and sufficiently neutral ruling out unacceptable increases. That is a critical distinction. So the essence here is--I think the first sentence is very misleading as to the basis for removing the need for a black box.

It is what we have been saying when we have been talking about Question No. 7. What we would want is evidence sufficiently favorable and adequately precise that you can rule out an unacceptable increase. And some of us have put forward a suggestion that that could be a relative risk of 1.5.

So if studies are done of sufficient quality and sufficient size and sufficient precision with sufficiently favorable results that you can rule out a 50 percent increase, then I think it logically follows to then suggest that that would justify a substantial weakening of the precautions that would have to be in the label.

DR. JENKINS: Thanks for that clarification. The idea was that whatever studies you recommended in Question 8 carried over to the

findings that would then impact on the labeling in Question 9. So maybe the wording is imprecise but, if you are recommending that rule out 50 percent increase in Question 8, then 9 is--if we get that rule-out 50 percent increase, would that, then, result in something less in labeling than the others have.

DR. FLEMING: The essence of my point is it is not persuasive simply to say that we did trials that failed to show an excess. Rather, we need trials that rule out unacceptable increases.

DR. WOOD: I think we were saying, also, John that the studies we recommended in Question 5 all that we learned from that would carry over to this as well. At least that is what I thought we were saying. I was sort of, I guess, piggy-backing onto Tom's and my comments at that stage.

Richard?

DR. PLATT: I would like to make a comment

about Question No. 7, if I may.

DR. WOOD: No. which?

DR. PLATT: Question No. 7.

DR. WOOD: Wait a minute. Before we do that, are we finished? We are not going to do 9. Is that what you are saying, John?

DR. JENKINS: I think you are having some discussion about 9 now. You have kind of clarified what you would like to see as far as the preapproval databases. Dr. Fleming just helped clarify his thoughts, at least, on if those preapproval databases meet the criteria that he established, it sounds like he wouldn't think that they would have to carry the same level of warning that the approved products are going to be getting.

DR. WOOD: I think the other point, which I think he made as well, but just in case it was missed, is there is also a duration period. We would expect to see sufficient sample size and sufficient duration of exposure in these trials before approval which is not the case with some of the drugs we have right now.

DR. JENKINS: Right.

DR. WOOD: Dr. Cush?

DR. CUSH: I just want to ask Dr. Jenkins

and Dr. Temple, you are now suggesting, by this question, as a condition of future approval for future agents that this cardiovascular safety study would have to be completed prior to granting and considering a new drug application.

DR. WOOD: Absolutely, I think.

DR. CUSH: Because that is, obviously, a departure from what we have done. These are usually--of course, this trials would have safety issues as the primary endpoint, not efficacy, so it may take a longer time to do. Again, that is a departure in process, is it not?

DR. JENKINS: I think what the committee, so far, seems to be recommending for new products in this class of NSAIDs, you are essentially saying there needs to be an outcome study prior to approval, outcome meaning that cardiovascular and probably also the G.I. outcome study so you can really assess benefit:risk before the approval

decision.

So that is a departure from what was required in the past for this class of drugs where we heard people did 3, 6 or 12-month efficacy trials and had databases of 4,000, 5,000 patients. But they didn't have an outcome study specifically powered to rule out some degree of cardiovascular risk or to specifically evaluate the complicated G.I. leading issues.

DR. WOOD: It is not just cardiovascular risk. It is heart failure. It is G.I. bleeds. It is complicated ulcers. It is the whole gestalt of risk that we are talking about, it seems to me.

DR. TEMPLE: You can see from some of the presentations that some companies marketing COX-2-selective drugs have already seen that particular handwriting on the wall and have done those very studies, not necessarily perfectly.

DR. CUSH: I agree. But my concern is it is setting a new paradigm for clinical trials in the United States, that we actually now have to do trials for severe and worrisome, albeit common,

side effects prior to the approval of a drug. I am not so concerned about nonsteroidals. I am concerned about future drug development in other areas where novel medicines may be delayed and curtailed as far as development because of this new paradigm.

DR. NISSEN: Let me answer that and say that this is different. The reason it is different is that the disease we are talking about is the leading cause of death in the United States. It is vascular disease. So it is very common. We have got a lot of evidence that several drugs in this class can substantially elevate the risk of that very common and lethal disease.

We are not saying this is the regulatory standard for every product and every class. The other reason why we can afford to do this is we have alternatives here. There are 20 drugs on the market. We are leaving on the market some coxibs with some warnings. So the patient and the physician have a lot of choices.

So it is okay to now set a pretty high bar

because that is what we really need to do, now that we know what we know. We learned it the hard way. We learned it via a very, very difficult process that took place last fall. Now that we know that, we know where to set the bar for this class of drugs and it has to be set pretty high.

DR. TEMPLE: There is a lot of public discussion going on about how safe things have to be. But what Steven said is absolutely right. You have got priors here. There are other examples of this. I will very briefly give you two.

If you want a drug for heart failure other than, perhaps, an ACE inhibitor or something like that that we think we understand, we will expect an outcome study, a survival study, because so many drugs for heart failure have had adverse outcomes while improving exercise tolerance.

Similarly, any new antiarrhythmic drug has to provide similar data before it can be approved. That is not a good situation--it is not a good thing for drug development of those drugs, but we have had a disastrous outcome, CAST. So where you

have priors, you modify your expectations.

DR. WOOD: These were the examples I was going to give. I think we are in exactly the same situation here, Bob. We have been through the process. We have gained the experience. And we are in the same way as we are with phosphodiesterase inhibitors. If another phosphodiesterase inhibitor came along, we would view it somewhat skeptically.

DR. TEMPLE: Right. I think that is the point Steve was making, too.

DR. WOOD: Exactly.

DR. TEMPLE: We know something here.

DR. WOOD: We are going to move, then, to Question No. 7 and start with that.

Question No. 7

DR. WOOD: Dr. Platt was first on deck.

DR. PLATT: It seems to me unlikely that it will be possible to do conventional randomized trials for many of the now generic nonsteroidals, particularly the ones for which you are unlikely to put a very strong warning.

Therefore, I suggest that you consider a variation of the large simple trial. Specifically, I think that there is an opportunity to something

that is essentially new which is to do large-scale cluster randomized trials in the kinds of environments that Dave Graham described as being good ones in which to do observational studies.

The basic logic would be that practices or larger groups would be randomized to prefer ibuprofen as the first drug among a class prefer indomethacin, or for some other others. Those are just examples. That provides good randomization. It provides the opportunity to use the kinds of observational strengths of completely representative populations using the drugs as they are used in regular practice and it is an extremely efficient way to collect the exposure and the outcome data.

It would be efficient and it would provide an opportunity to do--it is essentially a new way to study important questions and I think it would be ideally suited to this kind of question for

which I don't think you are going to have another good trial approach.

DR. WOOD: We could take approaches where we actually examine people who were going on therapy in the real world. There are other approaches, as you discussed before.

The one caution I would say about using--about just taking away everything that David said is David, himself, acknowledged the Medi-Cal database is not well validated yet and it is has been hard to track deaths in that; right, David? The validity and the mortality.

DR. GRAHAM: Actually, California Medicaid does have linkage to death certificates up through 2002 so, for the older NSAIDs, you could theoretically obtain that data. Kaiser Permanente has linkage to death-certificate data. Tennessee Medicaid, with Wayne Ray, whom you know very well, Alastair, he has linkage to death-certificate data.

Then, in Canada, several of the large databases there also have linkage to death-certificate data.

DR. WOOD: I was talking about the Medi-Cal one specifically because of its relevance to this question. That is why.

Steve?

DR. NISSEN: On these other agents, probably the key is to create incentives for companies to do this. That means that the way you word the warnings that we suggested will have some impact. I think that one of the ways you get rid of that warning is to do an adequate trial.

This creates an incentive for companies that have popular currently branded agents which are being used a lot to do some more studies, do appropriate studies, so that they can lose that cardiovascular warning.

Now, if the warnings are really weak, there won't be any incentive at all to do that. So I think--I am just arguing in favor or your being a little tough on this one because these are drugs taken by tens of millions of people and, if they really do increase by a factor of 1.5 or 1.6, the risk of myocardial infarction and stroke on a

population basis, that is a really big deal.

So we need clarity here. The only way you get clarity, I think, is with randomized controlled trials. So I think you have got to create an environment that incentivizes people to do those randomized controlled trials.

DR. WOOD: There's one point we've not discussed and I guess, as the Chairman of the NDAC Committee, I think it should come up. It does seem to me that new NSAIDs should not go OTC in the absence of clear safety data. So if somebody's patent expired on that COX-2 right now, I don't think we should let that go OTC without really good safety data that we could evaluate before it went OTC.

So that might encourage people to get some of these studies done if they want to switch.

Any other comments? I agree with Dr. Nissen. Just to be sure that there is some incentive because, if we make all of these rules more stringent, there has to be some reason for the pharmaceutical companies to continue to develop new

drugs. What we want is a win, a double win, a triple win. We want the patient to win.

DR. WOOD: Right. Although, just to respond to that, Ms. Malone, I agree with that. Actually, in some ways, we are opening up a whole new opportunity for pharmaceutical companies to develop new drugs in that you won't be the fourth COX-2 inhibitor on the market. You may be something that has a safety signal that would be better than someone else.

So there actually are huge incentives now to encourage the development of novel compounds that are safer and effective.

Yes? Dr. Bathon?

DR. BATHON: In follow up to your comment, I would like to say that one thing that hasn't been said, I think, in three days, is it is nice to know that, if we can keep these drugs on the market, that we will be able to continue to explore the importance of COX-2 in other pathological processes because there may, as yet, be undiscovered applications for these drugs.

We are in an era of really targeted treatment to have these kinds of specific inhibitors still available to continue to study new

applications is important as well.

DR. WOOD: Of course, people can study--would study--new applications under and IND and they wouldn't need to be available to do that. I mean, all the ones that we saw in the second day were not currently available.

DR. BATHON: Yes, but if you take a drug like thalidomide or something, if you remove it from the market, you give it a pretty bad press and then people aren't too crazy about being in clinical trials.

DR. WOOD: It is back on the market.

Any other comments? Then I think--have we anything else that we need to discuss pressingly? If not, and the most important piece of information I need to give you is one that Kimberly has which is--where is it? The travel agency that you can change your flights to has changed, apparently. That has vanished. So that means you are out of

luck.

I think we are through. Thanks very much for everybody who stayed to the end and it has been a tough three days. Thank you very much.

(Whereupon, at 5:14 p.m., the meeting was adjourned.)

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