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 II

Thursday, February 17, 2005

8:00 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

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

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Richard Platt, M.D., M.Sc.
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P A R T I C I P A N T S (Continued)

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Milton Packer, M.D. (Speaker only)

NIH PARTICIPANTS (VOTING)

Richard O. Cannon, III, M.D.
Michael J. Domanski, M.D.
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GUEST SPEAKERS (Non-Voting)

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Ernest Hawk, M.D., M.P.H.
Bernard Levin, M.D.
Constantine Lyketsos, M.S., M.H.S.
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. WOOD: Let's get started and welcome back to another day. We are going to begin as on the agenda seeing we worked late last night.

A couple of housekeeping things first. As they say in the movie theater, please turn off your cell phones. We don't have the one that sort of, you know, spars you into space if you do that, the ejector seat, but then please don't answer your calls in here, so we don't have to hear the beginning of your conversation.

Kimberly, are you going to read the conflict of interest? Okay. Go ahead.

Conflict of Interest Statement

MS. TOPPER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made as 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 involved many industrial sponsors and 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 any of the 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 of 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 potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Annette Stemhagen is participating in this meeting as a non-voting industry representative acting 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 Development Services for Covance Periapproval Services, Inc.

In the event that the discussions involve any other products of firm not already on the agenda for which FDA participants have a financial interest, the participants involved 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 first whose products they may wish to comment upon.

Thank you.

DR. WOOD: Thank you.

Let's go right to the first speaker, Dr. Platt, who is going to tell us about observational studies.

Interpretation of Observational Studies of Cardiovascular Risk of Nonsteroidal Drugs

Richard Platt, M.D., M.S.

DR. PLATT: Thanks. The framers of the meeting thought it would be useful at this point to have a discussion about observational studies to put us all on the same page.

There was a view by some that the expertise around the table might be uneven and it would be worthwhile to have some discussion about some of the basics. It is clear that that is not the case.

I realize that a number of the people here have written a book and several of my teachers are

here, so to that extent, I think we can either make this a quick discuss or use this as an opportunity for a real interactive discussion, because there are some hard questions here and no matter how we sort we out, we are going to be left with less than in the way of firm answers than we would like.

I also understand that there is a point of view that says that there are lies, damn lies, and observational studies, so part of what I think is worth doing is using this time maybe to take our temperature about whether and under what circumstances we can put weight on observational studies.

We saw a version of this slide last night actually in the last presentation about why perform observational studies at all, because I subscribe to the general view that all things being equal, a clinical trial, a randomized trial is more credible, provides more information than an observational study.

The problem is all things aren't always equal and so there are reasons to ask what we can

learn from observational studies.

I think the most important of them is no matter how well a clinical trial is designed, the individuals who are recruited and consented to a clinical trial are inherently going to be different from the actual population of users, and if we want to understand how an agent performs among real users in the way they actually use the drug, then, I think there is no escape but to look to observational studies.

Additionally, observational data is by definition there, so when a pressing question arises, sometimes observational data is the first way we can get insight into the relationship between the drugs we care about and the exposures.

I think in that regard, these studies can often be thought of as helping us identify the areas in which it would be most fruitful to invest in full-blown randomized trials. We will never live in a world where we are able to do all the randomized trials we care about.

I know that Charlie Hennekens' landmark

randomized trial of aspirin was preceded by, as I recollect Charlie, a large number of observational trials, it made you think that it was reasonable to do those randomized trials, so observational studies can be useful in that regard.

Finally, when we are talking about trying to understand effects that are relatively unusual, we stress even the largest clinical trials. We talked yesterday about the fact that the most recent drug approvals have used much larger populations in the NDA phase than had been studied in the old days, and yet they are still small compared to the numbers needed to parse out relatively small differences.

There are a lot of different kinds of observational trials. I have listed a few of the most common. The ones between the lines here are the ones that are really the subject for discussion here.

Tom Fleming made the absolutely correct and somewhat counterintuitive point that it is often more difficult to do good observational

studies of relatively common outcomes than rare ones, and because of that, the group of studies that I think at least are reasonable to consider for looking at relatively common outcomes are case-control studies, nested case-control studies and cohort studies.

We have examples of each in the materials that have been handed to us. The study by Kimmel is a pretty traditional case-control study. The studies by Ray are cohort studies, as is the Aramis study. The study by Dave Graham, the Solomon study are nested case-control studies.

Just as a quick reminder, the distinguishing feature of cohort studies is the fact that the study population is defined on the basis of whether people are exposed to the drug or not, and then we look forward to what happens to them. In that way, they are exactly comparable to clinical trials, with the big difference that the assignment to drug is not randomized.

The strengths of those compared to case-control studies are you have a reasonable shot

at the outset of selecting individuals who are representative of the group that you are trying to study, and if you organize the study properly, you have a reasonably good chance of getting unbiased exposure assessments.

The weaknesses, particularly of observational cohort studies is that just because individuals had the right drug exposure at the outset, they may change that. You can deal with that with an intention-to-treat design, but you pay for a price for that, and in observational studies, loss to followup is a big problems.

We are particularly plagued by that because the large majority of the observational studies we are working in are ones that use administrative data from one sort of health plan or another, and individuals move in and out of health plans, so that it becomes difficult to follow them over time.

Case-control studies, remember are ones that start with individuals who have the outcome we care about, myocardial infarction or myocardial

infarction and sudden death, and compares them to individuals who haven't had that experience, then, you look back and ask what their drug exposures are, the reasons for doing those studies are that they are, first of all, very efficient studies.

You don't have to study thousands and thousands. You can study as many cases as you find and a reasonable number of controls, and you can look back and classify exposure however is most useful, and that is a very convenient and versatile feature of case-control studies.

The big weaknesses are that it is very hard to assure oneself that the cases and the controls are really representative of the populations that you care about, and for conventional case-control studies, for instance, the study by Kimmel that we are going to look at, it takes a lot of work to be sure that people who know what they have already experienced an MI don't differentially report their exposure to the drugs that we care about.

That can be for all sorts of reasons and

it might not even be wrong, but the individual who has had an MI and might be just thinking harder about whether he or she had been exposed to a drug that we care about.

By the way, nested case-control studies, for instance, the study that David Graham did is a hybrid that really, in my view, draws many of the strengths from both designs, that is, because nested means the case-control study is nested in a defined population, so it has a lot of the strengths of cohort studies and some of the efficiencies of the case-control studies.

The differences between the observational studies and randomized studies are pretty clear. Randomized trials have the tremendous advantage that there is lots more reason to expect the treated and untreated groups to be comparable to one another.

There is a lot more opportunity to be sure that the outcome assessment and adherence to treatment are good or at least well known, and we have reviewed the difference for the observational

studies.

I think it is worth making the point that there are a substantial number of similarities between observational and randomized studies. Just because we randomize individuals in randomized studies, it doesn't mean that the treated and untreated groups are comparable.

We talked about a study yesterday that was a randomized trial where there was a substantial imbalance in important risk factors. So, it is incumbent no matter what kind of study you do, I think to look for comparability, and both studies have as potential weaknesses that there are risks of false positive results and doing subgroup analyses and multiple comparisons increases that risk.

We talked a fair amount about that yesterday, and both are at risk for false negative results. That can be partly because the studies may not be powered well enough either because there is insufficient sample size or individuals aren't studied for a long enough duration to see the

biological effects that we care about, or a vulnerable group just isn't included.

That is a problem with both kinds of studies and I think all studies have to be evaluated on their own merits, so let's just step through the various places where observational studies might be into trouble or at least the things that need careful assessment when we look at these studies.

The first is are we studying the right outcomes. It is essentially impossible in any of these observational studies to use the kind of rigorous adjudication that is a hallmark of the randomized study, so I think we are going to have to ask ourselves are these outcomes good enough.

The several kinds of outcomes in the studies that we have been asked to look at are hospitalized MIs. The case-control study by Kimmel uses survivors. It had to use survivors because they were collecting the exposure information by interview after the individuals had left the hospital, so if we care about all MIs, then, that

study isn't going to tell us what we want to know.

Some of the studies use MI and out-of-hospital sudden death by linking to vital statistics records. I think that is probably the closest we can get in observational studies to the intention-to-treat all outcome designs of the randomized trials, and some of the studies use composite designs.

You have to ask are these outcomes measured appropriately. Most of the studies that we are looking at use some form of automated medical record or claims data that have been, in my view, reasonably well validated. That is, there is a moderate literature showing that claims data are not so bad for studying acute myocardial infarction. They have sensitivities in the 90s and positive predictive values in the 90s.

So, they are not perfect and I think we will have to ask as we review the studied can the amount of uncertainty that we know exists in those account for the effects that we see, or could they obliterate effects that we would like to see and

which aren't there.

My sense is that that is probably not a sufficient explanation to dismiss the studies that we are looking at. The issue of bias is one that I think always has to live as a sub-text, but quite frankly, in the studies that do outcomes in the way we have been describing, I don't think that is a serious problem.

For cohort studies, we have to ask are we studying the right population, and here I think we really do have to stop and ask carefully. One is are these people selected from the population under study. I think in most of these examples, they are reasonably representative, that is, a study of the people of Ontario or members of a large health plan.

I think that the data systems that are used to identify the individuals in the cohort are good enough to give us reasonable belief that we are identifying either all the people or a representative sample of them.

I think there is a fair question of

whether they are representative of the larger population. We could ask are health plan members systematically different from the general population of individuals who are taking these medications.

The range of studies we have include health plan members. I think that there is reasonable information that they probably are representative, at least with respect to the drug myocardial infarction outcomes that are studied. Studies in Medicare and population-based studies, such as those in Canada, I think also give us reason to think that they are representative.

But there is an important consideration about whether there are issues about the way clinicians practice in those setting that might have a serious impact on selecting individuals. In particular, to the extent that formularies are restrictive of, say, newer or more expensive drugs like the COX-2 inhibitors, but I think we have to ask very carefully whether the factors that would influence the prescribing of one class of drugs

over another is likely to seriously impact the risk of these outcomes.

Additionally, if there are cost differentials for these drugs, it may be that there is some form of self-selection that causes individuals who are sicker to receive these drugs, and I think that it is incumbent on us to expect that to be a problem in every one of these observational studies and to ask how well do these studies do in adjusting for that. I will circle back to that in a moment.

I think we have to be concerned about whether we are studying people who have had prior NSAID exposure, in which case we would be worried about survivor biases, of finding the individuals who are relatively immune to these problems.

Finally, there are study design issues about whether there are restrictions of eligibility that might importantly color the data. For instance, at least one of the studies we are looking at requires individuals to have received at least two dispensings of a nonsteroidal agent in

order to be eligible.

That means that you have to live long enough to have two dispensings, so it certainly doesn't tell us anything about the early effects of these drugs, and it might in an important way color the results with regard to later exposure.

There is an important question which is not unique to the observational studies, which is who are the right comparators. We had a number of discussions about that yesterday. I think that all the issues that we discuss with regard to the clinical trials are applicable here. In particular, there is a lot of reason to want to compare to other nonsteroidal users because that gives the best chance of having a group that is similar with regard to underlying disease status and presumably risk of myocardial infarction.

Similarly, it is possible to say that if you really care about COX-2 selective agents, you should compared one COX-2 selective agent to another.

That leaves us in the uncomfortable

situation of not knowing what is the risk compared to no use at all, so we have some comparisons that do look at non-users or at least remote users, and that has its strengths. It has the big weakness, of course, of putting us at risk of making comparisons against groups that are unrelated.

So, we are really talking here of mostly about a study like the Kimmel study, not the nested case-control study. The other kinds of concerns that raise red flags are the real concern about losing cases who make the group who are studied unrepresentative.

I would point out to you, for instance, that in the Kimmel study, only half of the MI survivors who were identified were actually interviewed and therefore part of the formal analysis.

We already talked about the fact that since that study was limited to MI survivors, that restricts us to a less serious set of outcomes.

The other problem that really bedevils conventional case-control studies is knowing

whether the group of people who are selected as comparators are really comparable.

I think that is one of the reasons that there is so much interest in doing nested case control studies, because at the end of the day it is really extremely difficult to satisfy oneself that controls really are appropriate.

Much of what we need to be concerned about in these studies is understanding exposures. Part of the issue is understanding how to characterize exposure. This is both a strength and a weakness of these studied.

You will remember I made the point at the outset that if we want to understand how drugs work in actual practice, that we have to do observational studies. On the other hand, that means we have to find a reasonable way to characterize these drugs.

We talked yesterday I think about all the important issues of understanding whether we had to look at absolute dose or cumulative effects or whether the effects start early or whether they

start late.

I think that the best of the studies that we are looking at tackle a number of these issues. I will mention in a minute some of the ways that these studies have gone about that.

I think in terms of ascertaining exposure, it is probably reasonable to put the most reliance on the studies that use administrative databases of pharmacy dispensing, but I will just make the point that we have to be clear that these studies are done in situations where we have reason to expect that the administrative databases are correct.

I think all the studies we are reviewing are ones where the investigators were careful to know that the individuals really had a drug benefit that was operating at the moment, that would likely find the prescription drug exposures that we care about, but as a general proposition, you can't assume that that is the case.

Most health plans have some kind of restrictions on benefits that might lead individuals to change their benefit status, so

there would be periods of time when we might know that they had an MI, and we might not know that their drug exposure is at the moment.

I will return to a point that we touched on yesterday, which is that although almost all of the studies that we are talking about report their results as relative risks, a 2-fold increase in risk, a 70 percent decrease in risk. What we really care about is the absolute difference in risk.

So, that is not different between observational studies and randomized studies, but I think it is really a critical piece of our thinking about the problem that we are dealing with.

The second thing that is just worth recalling is that when we talk about a 95 percent confidence interval, that our expectation about where the true value lies is not uniformly distributed over that interval.

Our best guess about where the true value lies is around the point estimate, and if that point estimate is wrong, the large majority of the

uncertainly is pretty close to that point estimate, so that it is particularly not helpful, in my view, to pay enormous attention to p values.

The difference between a p value of 0.05, as shown here, and a p value of 0.01 and a p value of 0.13 is not all that enormous in terms of the biological impact.

I think one of the things that is a particular concern that we need to pay attention to in these studies is the fact that it is easy to look at a lot of different comparisons, and to the extent that we do that, we are going to have to just be careful to know that the strength of any one comparison is weaker than it appears to be.

For instance, this is a quote from one of the studies that we are looking at. We undertook an observational study examining the association between rofecoxib, celecoxib, other nonsteroidals and myocardial infarction.

Well, there is no primary hypothesis there, and the results for all of the nonsteroidals. They are all interesting to look

at, they are all associated with p values. Those p values are all relatively too extreme given the fact that there are so many comparisons.

It is a problem for randomized trials. We talked about subgroup analyses. It is important to do those studies, those subgroup analyses, but absent having specified a principal hypothesis at the outset, I think that we have difficulties in knowing how much weight to put on any particular one.

We talked a lot about confounding. That is one of the most important concerns in randomized trials. I know you all know what confounding is. It wasn't obvious to me when I was making these slides that everyone knew that, but the example, so that we have it in mind is if what we know is drug A versus drug B, and MI or no MI, and we don't take into account important confounders, we can get importantly incorrect results.

So, here is an example of an aggregate analysis with a relative risk of 1.5 among 2,000 people who are exposed to two drugs. If you break

it apart and see that in the high-risk group, drug A accounted for 80 percent of the exposure, and in the low-risk group, drug B accounted for 80 percent of the exposure, you see that in each of those two categories, the high-risk group and the low-risk group, that, in fact, there is no association between drug and outcome, but you have to take them apart to do that.

Well, the good news is if you know what the confounders are, and you have measured them accurately, it is possible to adjust for them, and all of the studies we are looking at do a pretty job of adjusting for the confounders that we know about, so I guess one of the questions is how well do they do at identifying the important confounders.

I would say not bad on a lot of that. That is, if you take, for example, the Graham study or the studies that Wayne Ray did in Tennessee Medicaid, there are a number of strengths. I will sort of stop and back up on the things that make these look like relatively more credible studies in

the scheme of the factors that we care about.

They are inception cohorts of nonsteroidal users, that is, they are individuals who had to have been members of the health plan for at least a year before they received their nonsteroidal.

There was a lot of information about their underlying medical status that was available to the investigators using both claims data and medical record data to ascertain cardiovascular disease along a number of dimensions, utilization of procedures like surgery or angioplasty or diagnostic procedures that are intended to find cardiovascular disease, hospitalizations, emergency room visits, and a substantial amount of information about the medications that these individuals took that was related to or plausibly related to cardiovascular risk factors.

Those large number of factors were used to create separate risk models using only the unexposed, and then to use those risk models to create risk indexes for the individuals to use as an adjuster for underlying cardiovascular risk.

Is it perfect? No. Is it pretty good? It seems to me that it meets the sniff test of saying that it has a reasonable chance of

identifying important confounding.

Unfortunately, there are a number of important confounders for which health care systems typically don't have good data, like smoking, OTC NSAID use, obesity, family history, and those are typically much more problematic.

Some of these studies have worked pretty hard to try to either deal with it or understand whether it could be an important problem. One of the handouts we had, for instance, was the study by Schneeweiss and colleagues who looked back at one of the studies by Solomon that was performed in the Medicare data set, and asked how important could these unmeasured confounders be.

They actually had access to information from the Medicare Beneficiary Survey that asked representative Medicare beneficiaries detailed questions about many of the things that we would are about. They weren't the people who were

involved in that case-control study, but if you assume that the beneficiary survey, members were representative and they gave plausible answers, it is possible to extrapolate back to the source population, and the take-home message from that work, the answer didn't change very much, which is really what we want to know, not sort of the absolute difference, but whether those unmeasured confounders are important enough that they could cause a difference.

I think we still have to be concerned at the end of the day, we still have to be concerned about residual confounding as a potentially important problem.

One way I think that we can draw relative assurance from that work of adjusting for confounding is to ask how much did the estimate of risk change between the unadjusted and the adjusted result.

I think there is a world of difference between an unadjusted result of 10 and an adjusted result of 1.5, and having an unadjusted result of

1.6 and an adjusted result of 1.5. The former, I think the reasonable assumption is we arguably haven't been able to deal with confounding in a way that would let us believe that 1.5 means something.

I think there is a much stronger case to be made when adjusting for important confounders that we know about doesn't change the risk estimate very much, that that is a relative more credible answer.

Having said that, I think that observational studies are best at finding relative risks that are more than 2. I think that I would pay some attention to relative risks of 1.5. I get very nervous about adjusted relative risks of 1.2.

That doesn't mean that they are not right and I don't ignore them, but if we ask is that for sure the answer, my response to that is I am just less certain about that.

I think we are always left at the end, while we spend a lot of time thinking about and adjusting for confounding, and I think we can do a pretty good job of that, it is much harder to

adjust for misclassification, and it is essentially impossible to adjust for bias.

So, I think one of the things we have to ask about is are there plausible sources of misclassification and bias, and if there are, in which direction do they work and would they seriously change our interpretation.

We talked about the fact that absolute differences are the important ones that we care about. We have already started to look at data that talks about person level risk and population level risk, so beyond saying that at the end of the day, I think these are the answers that we really need to talk about, not about relative risk.

Personally, I think that we need two kinds of answers. One is what is the information that patients and their physicians need to have to make decisions for them personally about whether to accept certain kinds of treatments in exchange for certain kinds of anticipated benefits.

I think there is a population level concern that we have to have that emerges from the

same set of analyses, but takes on a different form.

So, you will be pleased to know that I am wrapping it up now, and I would say that both the cohort and nested case-control designs, which are the bulk of the observational studies that we are looking at, are relatively strong ones and I think deserve the committee's real attention.

I am sorry that not every one of these studies prespecified a primary hypothesis that we can attend to, but we should whenever possible do that. Even though we don't find important effects in some of these studies, I think it is important to recognize that they don't exclude one.

As I have said, I am least certain about attaching great weight to relatively small excess risks even understanding that when they are extrapolated to a large population, they could account for very important public health problems.

Finally, I would say that the things that support the studies' conclusions are the fact that when we do subgroup analyses and look for

dose-response effects, that they strengthen the cause-effect relationship, and I think that there is reason to look for consistency across studies.

I take the point that was made yesterday that it is possible that a dozen studies of naproxen could all have the same underlying bias that shift the point estimate in the same direction, but it is not so clear to me what that bias is.

So, I think that we would have to have a reasonable idea of what might explain consistent differences across studies and ask if they are of sufficient magnitude to explain that. As I say, I am not clear that there are those kinds of biases.

I think we have to be cautious about the fact that residual confounding bias and misclassification are all issues with these studies. So, I think that while they add to our discussion, they have to be considered in light of the fact that they are imperfect vehicles.

Thanks.

(Applause.)

DR. WOOD: Thanks very much.

Let's just go straight on to the next speaker and then we will take questions for Dr.

Platt after David Graham's talk.

The next speaker is Dr. David Graham from the FDA.

Review of Epidemiologic Studies on Cardiovascular Risk with Selected NSAIDs

David Graham, M.D., M.P.H.

DR. GRAHAM: Good morning. Today, I will give a review of epidemiologic studies and cardiovascular risk with selected NSAIDs. I will be evaluating epidemiologic data from the published literature plus two currently unpublished studies that I have evaluated.

My focus will be on providing estimates of risk of acute myocardial infarction in the setting of the use of COX-2 selective NSAIDs or naproxen, although I will have some comments in light of yesterday's discussion about other NSAIDs on those, as well.

The methodology was to do a PubMed search

by specific NSAIDs and then cross-check the citations in those articles to see if there are other articles I had missed.

I would also like to take this moment to thank Dr. Crawford for his leadership in making it possible for me to present some of our preliminary data from a study in California Medicaid, which Dr. Gurkiepal Singh from Stanford and I recently completed.

Before I get into the substance of my talk, I just want to comment a little bit on excess cases and projecting to the national population what was the impact of rofecoxib use, and I am doing this for two reasons - one, because it has been a source of controversy and concern. We cite a number in a paper that I and others have published from Kaiser Permanente in which we made an estimate of the impact of rofecoxib use.

Tomorrow, FDA will present its estimation of the number harmed by rofecoxib, modeling randomized clinical trial survival curves. A couple of things I would like the Committee just to

be aware of when they see that data tomorrow. It assumes a grace period at the beginning of use that is based on the VIGOR study and the APPROVe, 6-week grace period in which there is no difference in MI or increased risk of MI, and the first six weeks of high-dose use with the first 18 months of low-dose use of rofecoxib.

As I will show later in my talk, I believe that this is unreliable due to low statistical power early on, because we are only talking about in each of these studies a handful of cases early on in the study. Two or three cases of MI and wide confidence intervals, you could have divergence of the curves very early.

The epi studies, however, that I will present will show that there is a 3- to 50-fold more events to work with, more statistical power, and it suggests a different outcome.

The second is, is that the patient enrolled in randomized clinical trials are generally healthier than patients in the real world. So, if you are going to model what is the

number of people who have been harmed in the population, you have got to assume what is the background rate that you are modeling off of.

If you use a background rate from healthy people to model what is happening in the population of people who really aren't so healthy, who have a higher background rate, you will underestimate the actual population impact.

So, in any event, now on to the substance of my talk.

The next three slides provide a very dense overview of the major features of each of the epidemiologic studies that I reviewed. I am looking at COX-2 usage in acute myocardial infarction.

You can see that they are grouped in several groups. The top three studies I consider from an epidemiologic perspective to be stronger studies to have been done better. In terms of the things that Dr. Platt just talked about, I thought that these studies were the stronger studies.

The next two studies from the published

literature I thought were less strong, and I will describe why. Finally, I have separated out these last two studies, one submitted by Merck to the FDA, performed by Ingenix, and the other, the Medi-Cal study that Dr. Gurkiepal Singh and I have recently completed of unpublished studies, so they are separated out from the group.

You can see we are talking about different source populations, and so if we can see consistency of results across different populations, different age groups, and different study designs, I think that that adds support to the notion that there is a real effect.

If we begin to see that there is a lack of consistency across the studies, then, many of the things that Dr. Platt talked about before need to be considered sort of the individual level of the studies, so what might explain why one study shows something and another one doesn't.

This next slide shows the case definitions and in a number of cases that we were working with to come up with the relative risk estimates that I

will show you.

All of the studies began with hospitalized acute myocardial infarction. Several of the studies were able to link members of their base cohorts to death certificate data to identify sudden cardiac deaths, as well. So, those are the ones that have the +Sudden Cardiac Death.

The asterisk next to the Kimmel study is to remind me and to remind you that the Kimmel study was based on nonfatal MIs only. By their design, they had to interview their cases in person, so the patient had to survive their myocardial infarction to be interviewed. So, there are those differences in study design.

In the end, what is very important in an epidemiologic study in dealing with this issue I think in particular, is what is the statistical power of the study, and that is driven primarily by the number of events in the exposed group that we have to deal with.

So, in this column here, you will see the total number of cases of myocardial infarction that

were identified in each of the studies. The asterisk next to the Ingenix study 628 is to remind me that in that study, they identified about 1,700 MIs in total, but they excluded 1,100 of the MIs because they occurred in people who weren't exposed to an NSAID at the time of the myocardial infarction. So, as a result, they left them out, because in the previous slide, when we look at the reference group, most of these studies used either non-use or remote use as the comparator. The Ingenix study used active treatment with either diclofenac or ibuprofen.

I would like to say one thing about reference groups. Dr. Platt brought it up before. In this issue, I don't believe that there is a single best or optimal reference group. What you really want to do is get as close as you can to a placebo group that has been randomized and has all the risk factors of the people who are getting the drug.

In the observational world we can't get there, and so at the end of the day, if you want to

do a study, you are in a sense forced to pick among the least evil of that you think, and then it has to do with how you define things.

So, non-users, for example, could be viewed as being close to the placebo group, they are not getting the drug. The problem is people who don't use drugs tend to be healthier than people who do use drugs, so that raises a host or problems.

Yes, we can try to adjust for confounding and the like, but you are still left with that concern that they may be, in some way that we can't measure, different from the people who get the drug.

In the study I did, and in several other studies that people have done, we opted to use people who had been treated with NSAIDs in the past, but weren't currently taking an NSAID at the time of the event or the study, the reasoning there that whatever the selection factors are that lead to a patient getting an NSAID, that some of those selection factors are there in people who

previously received NSAIDs.

That is still not a perfect group, though, because you could argue that patients who are no longer taking NSAIDs might be healthier than people who are currently taking NSAIDs.

Finally, the problem that is posed by using an active comparator. If you have an active comparator, and I am comparing another drug to an active comparator, and I see a difference, I don't know what it means. I need some place to anchor the result, and for that reason, although none of them are perfect, I believe that the non-use and the remote use analyses at least give us a way of pegging results, and if we want to compare one drug to another drug, if we had that common reference point, at least it allows us to accomplish that.

The one other thing I would like to point out about the number of cases is that for rofecoxib, especially at the high doses of rofecoxib, most of these studies had relatively few exposed cases. The exception is the California Medicaid study where we had 157 exposed cases to

the higher dose of rofecoxib.

Now, this is a very busy slide and I won't spend a lot of time going over it, but I will be happy to answer questions later.

Basically, before we heard there are unmeasured risk factors in automated databases that frequently can't be accounted for, aspirin use and smoking are among the most common. So, you can see here that most of these studies, that information isn't obtainable.

Kimmel was able to get both because they interviewed the patients, the cases and the controls. In the Medi-Cal study, it turns out that aspirin is reimbursed, and so we have a handle on it there.

In the Graham study, a survey of controls was done to see what these unmeasured factors might look like in the source population. The Solomon study did the same thing, relying on the Medicare Beneficiary Survey that Dr. Platt talked about before.

Important limitations I think that need to

be highlighted are that in the Mamdani study, they excluded patients who had less than 30 days of NSAID use, so the survivor bias Dr. Platt talked about before, in my view, is big concern with this study, and for that reason I ranked it in sort of that category of low quality studies.

In the Kimmel study, as Dr. Platt also mentioned, there was low participation rate. Basically, half of the cases and half of the controls who approached volunteered to be in the study. More importantly I think in that study, and it's unfortunate, is that there was what I would refer to as the potential for, in quote "reverse recall bias."

Normally, with recall bias, we think oh, I have had a heart attack, I am going to remember more efficiently what happened to me immediately before the heart attack compared to some control where I say to the control what were you doing four months ago on this particular day.

That is the classic recall bias. This situation I think had what I would describe as

reverse recall bias. They interviewed the people who had heart attacks within four months of getting out of the hospital - what happened to you the day and the week before you had your heart attack four months ago.

For the controls, they call them on the phone and they way what happened to you yesterday and the week before, so it is actually the reverse. The controls actually would have better recall of what they were actually doing than the cases potentially, and we will see how this is reflected in some of the results.

Finally, with the Medi-Cal study, I think the single greatest concern for the committee in considering these data (a) that it is preliminary data, and (b) that this is a new database for research purposes.

For that reason, I am just including a slide to orient people to that. The other databases are ones that have been used before. This is a database that only in the last two years has come online to be sort of a quality sufficient

to begin contemplating doing studies.

Its strengths are that it is very large, it captures aspirin use, it doesn't censor people by age. It combines Medicare coverage when you go over the age of 65 with the prescription benefits of Medicaid, so you get the drugs and the outcomes.

Matching has been done to multiple cause of death tape, so that we have death data in this database up through 2002. We didn't include it in the data I will show today because we really want the information up through 2004.

Once people get into Medicaid or Medicare, they don't tend to drop out. The limitations are that we can't get medical records, and that is something to understand, and that is a very complicated database. Dr. Singh from Stanford who is the principal investigator for our Medi-Cal work, and who has worked to bring this database online, spent two years putting things together and working out the kinks in it before contemplating doing research with it, so at least you understand the limitations of that.

There is always the concern about unmeasured risk factors and Dr. Platt talked about that. I want to review for you very briefly some

of the evidence from the published literature where efforts were made to look at what unmeasured confounding looked like and did it differ across NSAID type.

In our study using Kaiser Permanente data, we did a survey, a random survey of random sample of controls, and we looked at aspirin use, smoking, and over-the-counter NSAID use. You say see by NSAID that there really was not significant or substantial differences in the distribution of these risk factors.

So, if they don't vary in the control group, they can't really confound that observation that you see very much.

In the Solomon study, these are the data from the beneficiary survey. Dr. Platt already mentioned a further analyses of these data that showed that the actual impact of all these unmeasured confounders on the measure of the

relative risk at the end was measured in the hundredths of an odds ratio, so if the odds ratio was 1.34, adjusting for these things and projecting it out would change it to maybe 1.35 or 1.33. We are talking about minuscule differences, not qualitatively important differences.

Finally, in the Kimmel study, they also, through their interview, were able to see that for most of these factors, there was similarity across NSAID groups except for current smoking where the rofecoxib group had much lower current smoking than any of the other NSAID groups, but for past smoking, it was more than the other NSAID groups or the remote groups, and if you added these two together, the rofecoxib was very similar to these, but the celecoxib group had more smoking.

My own conclusion from this is that yes, it is possible that some of these unmeasured risk factors could be influencing the results. I don't think that there is strong evidence that there is a systemic bias that would sort of lead to interfering with trusting the results and thinking

that these factors are confounding the observations that we see.

So, first, I will talk about rofecoxib, then I will talk about celecoxib, then I will talk about valdecoxib in terms of epidemiologic data.

These studies on the left, with their reference groups, are the ones that looked at myocardial infarction with rofecoxib. What I have shown is for all doses and where it was present less than or equal to 25 milligrams and over 25 milligrams, what the fully adjusted odds ratio and 95 percent confidence intervals were.

These studies varied in the extent of adjustment that they did. The Ray and the Graham studies each adjusted for about 30 cardiovascular risk factors. The Solomon study was a somewhat smaller number, Mamdani was a somewhat smaller number. Kimmel, they adjusted for somewhere in the 20s, the Ingenix study somewhere in the 20s, the Medi-Cal study adjusted for about 40 cardiovascular risk factors.

What you can see is when you look across

the All Doses is that, in general, the point estimates were elevated and for many the 95 percent confidence intervals excluded 1.

More importantly, though, is looking at the low dose and the high dose data because we know from the clinical trials data, and we would suspect it on just pharmacologic grounds, that if there is an association that it might be worse with the higher dose than with the lower.

So, four studies provide us estimates at the low and the high doses, the Wayne Ray study and our study from California Medicaid, and then the two unpublished studies, one from Ingenix and the other from California Medicaid.

We see there that in three of the four studies, there is an elevation in the point estimate. In the Graham study, it included one. When we look over 25 mg, we see greater consistency although in the Ingenix study, there is this paradoxical finding of sort of basically a neutral relative risk. I don't have an explanation for why that happened, but it makes me concerned to some

extent about what was going on in that study, because it is a result that goes in a very unexpected direction.

What I would like to point out, because I will come back to it again, is that when we are dealing with drug safety, and the goal now is what risk can I exclude, if my job is--now I am not talking about efficacy anymore, what I am talking about is safety--if my job is to protect the public from harm, what risk can I exclude based on the data that I have, I believe that is much more relevant to look at the upper bound of the confidence interval than the lower bound.

What traditionally happens is we look at the lower bound of the confidence interval and we say if it includes one, there isn't a problem, but the biggest reason, as Dr. Platt showed in his previous slide, for a wide distribution and a wide confidence interval in your study, is that the study doesn't have enough statistical power to get you a narrow enough confidence interval to say that you have the 95 percent certainty that you want.

So, if your mission is above all else I want to do no harm, that I want to protect patients from harm, then, based on the data you have, I

would submit that the upper bound of the confidence interval provides greater assurance to patients, and then if you are going to compare a benefit to a drug, that you might want to consider that benefit against that upper bound of the confidence interval, because that is compatible with the data. In any event, that is my view, and not the FDA's.

This is a slide from California Medicaid. It is preliminary data and I wanted to present it to you, because what it shows is a dose-response to rofecoxib from 12.5 mg up to and through 50 mg.

You can see that we have very wide confidence intervals for some of them, and that is a reflection of the limited number of cases, but I want to point your attention to the very narrow confidence intervals in the 12 to 25 mg and in the 25 to 50 mg, just to point out that in the previous slide here, where we are talking about what are these point estimates, that now you can what we

have done is we have fleshed them out a little bit more.

Another comparison that I think is important to consider, certainly it was for us, when we did our study in Kaiser Permanente, was at the time there were two COX-2 selective inhibitors on the market, celecoxib and rofecoxib.

The bigger study raised a question about high-dose rofecoxib. Our question as researchers was, and public health scientists, was, well, let's suppose that rofecoxib increases the risk of myocardial infarction.

We don't know that it does, but let's suppose that it does, what about celecoxib, because it actually had a larger share of the market, and if it turned out that these drugs have a benefit, and that benefit is worthwhile, then, it would make more sense from a practical perspective to use the drug that had a better safety profile.

So, to us, it was very natural to want to compare rofecoxib to celecoxib, and so several of the epidemiologic studies felt similarly and in

their design they included that analysis, and some of them it was, as Dr. Platt said, part of a we are going to make comparisons of everything against everything.

The Solomon study, for example, did that. They did not state in that study what their prior hypothesis was. In our study, we did state it. I mean yes, in a sense we had multiple comparisons, but we were interested in two different things. We were interested in rofecoxib versus remote use, and we were interested in rofecoxib versus celecoxib, but we thought it beforehand and we planned that analysis.

But in any event, what we say is, when you look at the all dose analysis, in all of the published studies, rofecoxib increased the risk compared to celecoxib. When we looked at low dose rofecoxib, we see the increased risk. When we look at the high doses of rofecoxib to celecoxib, again, we see the same pattern.

Dr. Platt, in his talk before, talked about relative risks, risk differences, individual

risk, and population risk. The next two slides are intended to address this at the level of the individual and at the level of population.

What I have done on this slide--and these slides now, no one should interpret this as meaning this is what actually happened in the population--the next slide is going to have numbers on it that are for illustrative purposes only, to help the committee understand what does a relative risk of 1.3 translate into at the individual level and at the level of population.

Your typical COX-2 user is somebody in their 60s who has several other health problems, so I went to the National Center for Health Statistics and got the myocardial infarction rate for 65- to 74-year-old men in the United States. That rate turns out to be 1 per 50 per year.

What I did is I took that as the background rate and I said if I have an individual using this drug with that background rate and then I applied to that person the relative risks or odds ratios found in these studies that are shown in the

previous slides, what would the excess risk to the person be, sort of what would that risk difference translate to for the individual.

For example, in the Ray study, if you remember, for 25 mg or less, the odds ratio was 1.02. Basically, it doesn't change. If we based it on the point estimate, that 0.02 would translate to 1 out of 2,500 in a year increased risk of heart attack.

Another way to view that number is, is that is the number needed to harm. If I treated 2,500 65- to 74-year-old men for a year with rofecoxib, and the rate was 1.02 that Ray found, treating 2,500 patients would produce 1 extra heart attack.

Now, with the other studies that found higher estimates for the lower doses of rofecoxib, you can see that the number needed to harm ranges from about 90 to 200. That is saying for every 90 people to every 200 people I treat with low-dose rofecoxib, I would generate 1 other case.

For high doses, because the relative risks

were higher, the number needed to harm becomes lower.

I have also shown it based on the upper bound of 95 percent confidence interval to show you that based on the data we have at hand, these are the excess risks that are consistent with the data, and from a public policy perspective, from a public health perspective, that is what I react to, and when I want to see a benefit and say does benefit exceed the risks, well, I want to know what is a real benefit in the population in terms of reduced hospitalization, lives saved, and does that benefit exceed what I can say is possibly the risk of these products.

At the population level, now we have gone from an individual. Remember in the Wayne Ray study we said it is 1 out of 2,500. Well, that would translate to 400 additional cases of heart attack if we treated a million men who were 65 to 74 years old, and we treated them with rofecoxib low dose for a year.

With the others, you can see that those

relative risks that might not look so impressive, that 1.23, that 1.30, that 1.4, that it projects out to a substantial number when you multiply it by the large number of people who use these products.

For high doses it ends up being even greater, and then if we focus on the upper bound of the confidence interval, we again see that the numbers are larger still. This very high number in our study was the result of our having low statistical power in addressing the high dose rofecoxib.

One other question that I think is important to consider is when does the risk of myocardial infarction with rofecoxib kick in. Now, we have seen data yesterday presented by both FDA and by Merck of various survival curves.

We saw the bigger curve that showed the separation after about 6 weeks with an overall relative risk of about 5. We saw, for the APPROVe study, this close overlapping line at about 18 months, and then they diverge with an overall composite hazard ratio of about 2.

I would submit to the committee that the reason for the failure of these studies to show divergence of the line shortly after the drugs are

used are low statistical power, that they just don't have enough events to show it, and as a result, you can interpret because of the low statistical power you basically--how to describe it--you presume that there is nothing there, and you err on the side of the drug rather than erring on the side of what could the risk be to the population.

If you really want to know what is going on in the population, then, you want to reduce the uncertainty. The more uncertainty you have, if you act basically on the lower bound of that confidence interval, which is what you are doing when you are saying the risk doesn't begin until 18 months, you are basically saying that the absence of evidence is evidence of absence.

I would say that in safety, what it is, is you just don't have enough power.

Looking at the epidemiologic studies, I

think that we have evidence to suggest that the risk begins much earlier. I will point it out, and you guys and women can consider it for yourselves.

In the Graham study, when we looked at low dose and high doses of rofecoxib, 50 percent of our cases at the low dose and at the high dose had used at the time--remember these are inception cohorts, so these people, their total use, this was 1.8 months, this was 2.7 months--50 percent of our cases occurred within 2 to 3 months of starting the drug.

That is a lot of power and that really speaks against the notion that the risk is backloaded, you know, it is for the low dose, that the risk doesn't happen until after 18 months. Nobody in our study was on rofecoxib for more than about 15 months. I think that was the longest duration of use we had in our study.

Now, in the Solomon study, they looked at the low dose and the high dose, and they presented data in several ways. One is that they grouped things in 1 to 90 days, and what they showed was

that for both the low dose and the high dose, there was evidence or risk early on.

The Kimmel study, for all its deficiencies, most of it was low dose rofecoxib, and almost all the patients used it for less than 12 months. So, their finding on rofecoxib, if anything, would also speak to that the low dose effect kicks in long before 18 months.

Finally, the Solomon and the Ingenix study looked at the first 30 days of use of these products, and both of them found elevated odds ratios of 4 for cardiovascular risk in the first 30 days.

Now, in both of these studies, they didn't separate it out by low dose and high dose, so this is a composite, but in both studies, about 85 percent of the use to 90 percent of the use was low dose.

So, basically, what I am concluding from this slide is that risk of myocardial infarction with rofecoxib begins when rofecoxib use begins, and that the inability to separate out those curves

is based on the fact that if you were to count the actual number of events in the bigger study in the first 6 weeks, we are probably talking about 3 or 4 events, and if you look at the confidence intervals, you are going to see they are wide.

For the APPROVe study, the same thing holds, that you have too few events. The whole study had 45 events, and I don't recall how many of those were on rofecoxib and how much of those were on placebo, but when you think about it, compare that and then look at the epidemiologic studies, and look at the number of cases that were in the epidemiologic studies, and for all their problems, and we can talk about those, they suggest there is a big discordance, and I think the answer, the reason is absence of statistical power in the clinical trials.

In the epidemiologic literature, this has been recognized, and people have written papers saying that when you are trying to summarize the overall risk from a survival study, and you want to look at specific time periods, that you are better

off taking the overall risk estimate for the entire study than focusing on a small segment at a time because of this issue of low statistical power, so I didn't invent this.

Now, switch over to celecoxib. There are a number of studies that have been done to look at celecoxib risk. What I have tried to do here is plot out for you the relative risk or the odds ratio, the author of the study, and then the point estimates in the 95 percent confidence intervals.

What you will see basically is that for most of these studies, there is no evidence of a protective or an injurious effect except for the Kimmel study that found a substantial protective effect.

Remember the Kimmel study and what I believe is this reverse recall bias, as well as the low participation rate, and I personally discount that study. The committee can decide for themselves that they want to do.

What about celecoxib lower dose versus higher dose? Well, unfortunately, the only place

where this is adjusted, is looked at are in the two unpublished studies. We have the Ingenix study and we have the Medi-Cal study.

What I would focus your attention on are the low dose and high dose, the low dose and the high dose. What we see is in both studies, evidence of a dose response. Now, the 95 percent confidence interval in the Ingenix study includes 1, but the point estimate is pretty elevated. That is 1.18 or so at 400 mg.

In the Medi-Cal study, we go from 1.01 up to about 1.24. Here, you can see the 95 percent confidence intervals.

What I would conclude from this, although they are unpublished studies, that there is evidence of a dose response at the higher doses of celecoxib do confer an increased risk of myocardial infarction.

I should point out that in the Medi-Cal study, the methodology that we used in that study is the exact methodology that we used in our Kaiser Permanente study that Dr. Platt before was gracious

enough to say is one of the better done studies.

There are no published studies on valdecoxib, so what do we do? Well, preliminary data from Medi-Cal, we had 54 exposed cases and we found a point estimate of 0.99. Now, this was mostly 10 and 20 mg use. I think that out of all the patients that we had in the study, there were 2 or 3 who had 40 mg valdecoxib use.

In Medi-Cal, they only reimburse for the 10-mg tablet, and they do this in an effort to try to discourage people having larger dose tablets and then taking more of it.

So, this is all the epidemiologic information that I am aware of, that I have had an opportunity to review on valdecoxib.

I will now move to naproxen. The issue of naproxen is important for several reasons. One, with the VIGOR study, the medical community was confronted with the hypothesis that naproxen was the single greatest and most effective cardio-protectant in the history of mankind, that it was far better than aspirin.

We heard yesterday that aspirin reduces cardiovascular risk about 20 to 25 percent. Naproxen, if we were going to believe the VIGOR

results, would have to reduce the risk of cardiovascular events by about 80 to 85 percent.

So, this stimulated a lot of research. Here, I have summarized in the same fashion as I did for the rofecoxib studies, the various studies that have been done. Again, I have separated them out by the studies that I think are better done, the studies that have more significant limitations, and then the two unpublished studies.

I point out the Rahme study to say that the only reason the Rahme study is listed among this group of suboptimal studies is that its reference group was other NSAIDs, primarily ibuprofen, because ibuprofen was the predominant other NSAID used in Quebec during the study.

Again, we have the various outcomes that were done. What I would point is that you can see the number of cases that we had to work with in these various studies, and I would point out that

for the Solomon study, they had about 240 MI cases that they studied overall, but as you will see in a few minutes, that exposure could occur anytime in the past 6 months, so they don't see in the paper how many people were actually on naproxen at the time they had their event, so I can't put down a list of how many people were currently exposed.

The Watson study is the only study that used a composite outcome. It included myocardial infarction, stroke, subarachnoid hemorrhage, and subdural hematoma. Why subarachnoid hemorrhage and subdural hematomas are in there is beyond me. In any event, 26 cases of that composite outcome and a much smaller number of actual myocardial infarctions. So, that is why that asterisk is there.

With the Ingenix study, the asterisk next to the 179 is that this included both prevalent and incident cases, and the best studies, the best results come if you base it on incident cases only or incident use only as opposed to prevalent use, because prevalent use can have survivor bias. But

in any event, in the Ingenix study, they had a number of different analyses, and they didn't always use their full number of cases.

There are important limitations to note. I think the one to focus is to realize (a) there is no perfect study, we have talked about that before, and, two, that among all the limitations listed here, I think the most important one to note was in the Watson study, was this composite outcome which really just makes it very difficult from an epidemiologic perspective to study things.

Myocardial infarction is very well validated in claims data, and Dr. Platt has already gone over that with you. Stroke is notoriously difficult to work with in claims data, and subdural hematomas most commonly occur because as people get older, their brains shrink. They bump their heads and then they get a little bleeding on the surface of the brain. What that has to do with myocardial infarction risk, which is what we are really concerned about today, is beyond me.

I have got two slides on the results.

This slide shows the studies that found no protective effect. There is four studies that found a protective effect, and I am saving them for a separate slide, because I want to look at those individually.

What you can see from the majority of these studies, and I would point out that the studies that were the best done studies in the top tier, they are on this slide, that all of them sort of suggest that there is no cardio-protective effect of naproxen. Several of the studies point to the possibility of a small increased risk with naproxen.

But we have four studies of positive results, and we will probably all remember the Archives of Internal Medicine publishing three of the articles in the same issue with an accompanying editorial that stated the issue is solved, naproxen is cardio-protective.

I want to look at those studies and just describe to you my view of them. The top three studies were the ones that were--well, no, not the

Kimmel study--Rahme, Solomon, and Watson were the Archive studies.

In the Rahme study done in Quebec, they compared current naproxen use versus other NSAIDs. That other NSAID was, by and large, ibuprofen, and they found a protective effect. Well, if ibuprofen increases the risk of myocardial infarction, let's just say that it does, and naproxen doesn't, naproxen could look like it's protective compared to ibuprofen, but not be protective really.

The data presented in that paper, if we re-analyzed it versus non-use, we get an odds ratio of 1.28, statistically significant. Now, this is not adjusted. It is not possible from the data there for me to adjust this result, but based on what is in the paper, when you compared the unadjusted to the adjusted point estimates, they don't change very much, and what that suggests to me is that this effect, this 0.128 is probably not far off the mark.

That would then make it comparable to the analyses I showed on the previous slide, that all

of these slides use non-use or remote use, so then it would add a fourth study to an elevated point estimate for naproxen.

Now, the Kimmel study, we have already talked about low participation rate and this reverse recall bias, and a small number of NSAID cases. In fact, they don't even tell us in the paper how many cases they had.

We move on to the Solomon study. This was the result that was reported in the paper and was picked up by the press, a 16 percent reduction in heart attack risk with naproxen. The problem, in my view, was that their definition of exposure in the study was any use of naproxen in the past 6 months, which means that if I took naproxen 6 months ago and stopped it, I could be included in this study as being exposed to naproxen.

So, the question is then, you know, how do we interpret the study. Well, Solomon was good enough to present data by current use and in recent use, and recent use included people who stopped their naproxen. Their naproxen prescriptions day

supply ran out between 1 day and 60 days before the MI or the index date for their controls, and remote users, their NSAID use, their naproxen use ended from 61 days to 180 days prior to the event.

So, let's look at what those results are then, and what we see is they are identical. So, unless the committee is prepared to believe that naproxen confers lifetime immunity to cardiovascular disease, I think we have to conclude from these data that what we really have here is selection bias, and it is not the fault of the investigator. Dr. Platt talked about before that there are some things you can't adjust for. You can't adjust for bias. What you can try to do is identify bias, and if you identify it, then at least you know what you are dealing with.

Here, I think we have what is classic selection bias. It is not naproxen that protects you again myocardial infarction, it is some other factor that in this health plan, that they used to study this drug, the patients who were being treated with naproxen happened to have lower

cardiovascular risk.

I can't explain why that happened. Dr. Solomon probably can't explain why it happened, but it's not due to naproxen.

Finally, the Watson study. This study was sponsored by Merck, and it was authored by Merck investigators. The result that was published as being the basis for the conclusion was this top result, a 39 percent reduction in cardiovascular risk.

First, I just want to remind everybody, composite outcome here, subarachnoid hemorrhage, subdural hematoma, stroke, as well as heart attack, 26 events total, much smaller number of heart attacks.

For this event, you can see the checkmarks. These are the various variables that they adjusted for in the study. The way they handed cardiovascular risk, if you read the paper, I would have to say that it doesn't measure up to the standards that were set by Dr. Wayne Ray.

We modeled our study in Kaiser and in

Medi-Cal, and Dr. Wayne Ray, I think that he has set the standard for how one needs to go about adjusting for cardiovascular risk. It is not enough to rely on diagnoses. You have to use the medications, because medications are much more accurate predictors of disease than diagnoses in these administrative claims data.

In any event, they didn't adjust for cardiovascular risk, and they didn't adjust for smoking although they had that data. Then, they present later on another analysis that now includes cardiovascular risk and it is no longer, in quotes, "statistically significant," and then they include smoking, and again it is not statistically significant.

My conclusion on the Watson study was that (a) they have got a composite outcome that, in my view, isn't very informative towards the question of myocardial infarction; (2) that it is very small numbers; (3) that a variety of approaches were used in the analysis that inadequately account for the risk factors that could confound the result, so I

have discounted that, as well.

So, a conclusion when I look at these, in quotes, "4 positive studies," I conclude that none of them provide credible evidence of a protective effect.

In light of yesterday's discussion in the afternoon about other NSAIDs and what might explain the differences, let's say, celecoxib and rofecoxib studies, the rofecoxib studies used naproxen as a background, a comparator, the celecoxib studies using ibuprofen or diclofenac.

Dr. FitzGerald is talking and saying, well, you know, all of these drugs could increase the risk because what is happening, you know, biochemically, with the balance of prostacyclin, could be influenced by these different drugs in ways that aren't immediately obvious or detectable in a clinical trial.

I thought I would just share some of that information on other NSAIDs with the committee, recognizing a couple things that no single study is definitive and what you want to look for I think is

consistency across studies, but as far as randomized trials go, I would like just to mention that there are generally too small, too few events, and you are not going to get the answers that you need from them unless you make these clinical trials substantially larger than anything people have contemplated up to now.

So, from our California Medicaid study, it is all preliminary and it has not been published, for ibuprofen we found a small but statistically significant increased risk. For indomethacin we found a risk of 1.7. I would like to say on indomethacin that we found an increased risk with indomethacin in our Kaiser Permanente study. It was 1.3 and it was highly statistically significant.

In at least two other studies that I reviewed in preparation for this advisory meeting, indomethacin is noted to have an increased risk of myocardial infarction.

It is not commented on in the text because that wasn't a primary analysis, but what I am

talking to you about now is consistency, and I would submit to the committee that indomethacin is a lot of smoke, there is a lot of smoke for indomethacin.

In our study, in our Kaiser study, for example, we did not think in advance to look at indomethacin separately. I mean we knew we were going to look at it, but it wasn't a primary hypothesis. We didn't adjust for gout. I mean everyone knows that indomethacin gets used in gout. Gout increases the risk of cardiovascular disease.

Well, in the Medi-Cal study, we adjusted for gout. Yes, gout increases the risk of myocardial infarction. It didn't change the odds ratio here.

I think this next finding, Meloxicam, is important. Meloxicam is now the number one selling branded NSAID in the country. With the removal from the market of rofecoxib, the medical community, shying away from the coxibs, are moving to other drugs that they perceive would have the advantages of COX-2 selectivity without the bad rep

that coxibs appear to be acquiring.

So, you now have a shift in the marketplace to Meloxicam. There have been articles in the Wall Street Journal and the New York Times on this. The company recently raised the price on the tablets.

In any event, we are presenting these data just to say that we found an increased risk. It is one study, but I think it is the only study. We looked at this in Kaiser. Meloxicam is almost not used in Kaiser, so we couldn't study it.

In our California Medicaid study, we only looked at drugs that had more than 50 currently exposed cases. Nabumetone came out in this study as not showing a whiff of a problem. Sulindac, there was an increased risk.

Regarding ibuprofen, in our Kaiser study, we found an increased of 1.06, which sounds really trivial. It wasn't statistically significant, but the confidence intervals were pretty narrow. It was 0.96 to 1.17.

My concern is, as Dr. Platt talked about,

you know, above 2 you feel really comfortable, above 1.5, you can believe it, below that you begin to get really edgy. The problem is most of the risks that we are probably facing, if it turns out that the non-coxib NSAIDs increase the risk of cardiovascular disease, that is where the risk level is going to be, and that is what we are going to have to contend with, because it has tremendous effects on the population.

Finally, dose response. This slide shows for diclofenac. This is from California Medicaid. What we wanted to do was show evidence of dose response, consistency in the data. Remember we pointed out diclofenac before. Diclofenac in this study overall did not have an increased risk, but at the high doses there is a suggestion of a dose response.

I will skip that. This slide was to say that depending on your reference point, you can get different results, if I use an active comparator versus remote, and this is showing the three NSAIDs from California Medicaid compared to non-coxib

NSAIDs, and you can see the rofecoxib is different than them, and the other two aren't necessarily that different.

My conclusions, and I am sorry to have gone so long. Celecoxib, we believe that based on the evidence we have at hand, that there is no apparent effect of risk at doses of 200 mg or less. Above 200 mg, we think that there is evidence of increased risk.

For rofecoxib, we believe that there is evidence of increased risk at both the lower doses and the higher doses, and that risk begin early in therapy and is apparent during the first 30 days of use.

With valdecoxib, there is a paucity of information, but the information we have at this time suggests that the risk is not increased at doses of 20 mg or less.

As a class, non-coxib NSAIDs may increase the risk with differences between each of the NSAIDs. I don't think we are going to be able to talk so much about class effects. In the end, it is

going to have to be looking at individual drugs.

The COX-2 hypothesis may be true, but if it is, we are still going to have to look at these other drugs in terms of their individual properties and what they do.

Finally, naproxen is not cardio-protective.

Thank you.

(Applause.)

DR. WOOD: Thanks very much. David, it will come as no surprise to you that every time practically I pick up a newspaper, I read about what you are not going to tell us.

So, my question to you is what have you not told us that you think we should know, because I would like to make sure. Lots of other people have shown up here without slides that they forgot, so I just want to be sure that if there is anything else we need to hear, we hear it.

DR. GRAHAM: Well, as far as the science goes, I think I presented the evidence that I am happy to be able to share with the committee that I

thought it was important for the committee to have an opportunity to hear.

The source of controversy surrounding my presentation related to the unpublished studies that I was going to be permitted to present or asked, actually asked to present the Ingenix results, the unpublished study from Merck, but that I was being told not to present the unpublished data from the California Medicaid study, and personally, I had great difficult standing here before this committee as an investigator and as a scientist, as a physician, and telling you the information that I have, that I am allowed to talk about, and remaining silent on things that I know about that I am not allowed to talk to you about.

Fortunately, Dr. Crawford exercised great leadership in making it possible for me to present that data, recognizing it's preliminary, but the methods that we used are identical to our Kaiser study for the California Medicaid, and for me, I think the big reservation is, is that it's an untested database, but I think that everything that

could be done to develop the database and to do quality assurance and to work out the kinks has been done.

If you look at the findings in the California Medicaid study and you compare them to the clinical trials data, and the anomalies and the questions that you were discussing yesterday about the clinical trials' data, you look back at the California Medicaid data, and you are going to see I think great consistency between the findings that might help explain and interpret some of the things that seemed questionable or uncertain yesterday.

So, in any event, I have been able to present what I thought was important to present, and I am happy to have had that opportunity.

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

DR. GRAHAM: You have seen it all.

DR. WOOD: Okay, good. Let me ask you a question. If you go back to your slide that showed the excess population risk, put that in proportion for us in terms of, say, the other drugs that have

been withdrawn from the market. I mean what sort of numbers would we be expected to see?

DR. GRAHAM: That is a great question. The typical drug that has come off the market in the United States, like the leading cause of drug withdrawals in the United States in the last 20 years has probably been acute liver failure. Rezulin came off the market because of it, troglitazone, bromfenac, a number of other drugs.

Acute liver failure in the general population has a background rate of about 1 per million per year. We are talking about that is the rate of being struck by lightning, 1 per million per year, and these drugs were pulled off the market because it increased the risk of that. It might increase the risk 5-fold, it might increase the risk 10-fold, it might increase the risk 100-fold. The fact is the background rate was 1 in a million and what that means is that the actual number of people affected is sort of measured in the tens and the hundreds for the liver failure that could be life-threatening.

In this situation, and this is why the lower relative risk becomes so critical, we are talking about a serious event that has a very high

background rate. Heart attack is not a rare event, and as I pointed out before, there is a 1 in 50 chance that the average American male age 65 to 74 is going to have a heart attack this year, 1 in 50.

That is an extraordinarily high risk. You increase that risk 5-fold with a high dose. That is what happened with VIGOR. If I have got millions of people taking the high doses, and that is what had in the United States, and I have increased the risk 5-fold, you are going to get numbers that balloon out like this.

So, there is no comparison in terms of what the population impact is of the typical drug that has come off the market in the United States and what we are dealing with here, and that is because of the high background rate of the underlying event that we are talking about.

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

DR. GRAHAM: Many more.

Committee Questions to Speakers

DR. WOOD: From the committee, we have questions. Let's start with Dr. Shafer.

DR. SHAFER: Dr. Graham, tomorrow we are going to be asked, as a committee, to consider the

question about a class effect for the selective COX-2 antagonists and for the non-selective NSAIDs.

One of the things that I am finding, that I am having trouble putting together here, is we have a lot of conflicting data, and for the COX-2 antagonists we have a lot of data from randomized controlled trials.

Certainly for the NSAIDs, we are going to have to go with a lot of these observational studies because we don't have a lot of data on the topic at hand from randomized controlled trials.

As I look at this, if we come up with some sort of common warning as a class, and it applies to everything, we have, in fact, communicated no relevant information. On the other hand, if we are going to come up with individual drug-specific

recommendations, we are going to have to have very different evidentiary standards in some ways, because for some of these, we have very little information, as you pointed out, and yet your data, particularly the unpublished data from the Medi-Cal trial, and I appreciate that there is all the issues of not being previewed and stuff, but we are all familiar with that process and know how it works.

What can you tell us to guide us? Should we try to go drug by drug specific? How do we set our evidentiary standards when we talk about class effects where in some cases, we are just not going to have a lot of data here?

DR. GRAHAM: Right. What you are going to be getting now, of course, is my opinion, not FDA's opinion. Probably if you were to talk to Bob Temple or John Jenkins, or anybody else, everybody is going to have a slightly different answer.

What we talking about now I think to some extent is philosophy, so what that preamble, first, I believe based on the evidence that there is a

COX-2 effect and that that COX-2 effect is dose dependent, and that we see evidence of that with rofecoxib, with celecoxib, and with valdecoxib.

The difference between rofecoxib and the other two coxibs on the market is that a safe dose for rofecoxib wasn't identified, the dose wasn't low enough. That raises a question in my mind about what is an appropriate therapeutic index for a drug.

I am giving you my opinion now, but when I listened to Dr. Cryer's presentation yesterday, the bottom line conclusion I came to at the end of that was there really doesn't appear to be a need for COX-2 selective NSAIDs based on what I heard yesterday. There is probably other information out there why I am wrong, but that was the conclusion I came from.

So, in any event, that is answer one. I believe there is an effect and it's dose related, and with celecoxib and valdecoxib, I think we have evidence. You said before we have a good evidentiary base based on clinical trials for the

COX-2s. I would challenge that in the sense of the survival curves and the things that I talked about there, that we have a very weak evidentiary base for things like protective, you know, is there a grace period for use, and also on the dose issue, we really don't have a great evidentiary base. But that being said, you understand me.

Now, for the non-coxib NSAIDs, my own view is that as an epidemiologist first, I try to report the phenomenon I observe and leave it to brighter minds to figure out why what I observed happens.

You are asking me sort of what do I think is happening underneath it all. I am attracted to the COX-2 hypothesis personally. Dr. Gurkiepal Singh, my colleague and co-author in Medi-Cal, he has a different view on that, but I think that we can these in vitro tests that say, oh, this is the COX-2 selectivity of this NSAID, you know, in a test tube.

What happens in the human body could end up being surprisingly different. We saw yesterday that the dynamic response of these differences,

that the platelet effect is very quick, the thromboxane effect is a very quick effect, the prostacyclin effect seems to be a more gradual effect, that this creates very complex interactions that ibuprofen, that any of these drugs could, in the end, end up with a deficit, a prostacyclin deficit that results.

I think Dr. FitzGerald showed that slide yesterday with the normal distribution of the time area under the curve and then this little sliver where they are not protected, and that may be the reason why, for these different drugs, that we end up with these different relative risks and these different odds ratios.

In the end, for the non-selective NSAIDs, my own advice would be let's look to see are there somewhere in studies--it is going to be observational studies--in observational studies that we believe have been reasonably well done.

By "well done," here, they have to be large. The literature is full of really small studies. I mean I could have presented Meloxicam

studies, 5 patients, no risk. Well, da, you know, you have got a confidence interval that goes from zero to infinity. They need to be large. Look in a systematic way to identify what the body of evidence is.

Can we identify bad actors? I believe indomethacin, for example, is clearly a bad actor, and if people looking at the data concluded that, take appropriate action, weed the garden of the bad actors.

Try to identify drugs that based on the evidence we have, appear to be less risk in the totality of their evidence, looking for consistency study to study to study, and then, in a rational way, suggest these are the drugs we think that the public should use, and these other drugs, well, then you have to decide do you want them on the market or not.

I am not really going to comment on that, but I think that is the approach I would take. I would be trying to sort of identify right off the bat the bad actors and let's get rid of them.

Things that look like they may actually be safe, and when I say "safe" now, I mean that they don't appear to have cardiovascular risk, identify

them and shift the market towards that, and then deal with the others.

DR. WOOD: Dr. Friedman.

DR. FRIEDMAN: Thank you. Several comments. First, as both Dr. Graham and Dr. Platt have mentioned, observational studies are essential, but they have a number of limitations, and because of those limitations, it is easy after the fact to critique away those whose results you don't much care for as we have seen.

But a couple of other points. One, can these particular drugs, their primary use, we are dealing with chronic conditions, conditions that last years, sometimes many years, and so the drugs are intended for use over those many years potentially.

Yet, most of the clinical trials we heard reported yesterday are 12, 18 weeks, a few of them go longer. You mentioned that one of the reasons

we didn't see the problems early on may be numbers, and I agree that is potentially it, but the fact is we didn't see problems arise in the studies until 14, 18 months.

We often see analyses by patient years of exposure. In this particular setting, I don't know whether patient years are always equal to patient years, and therefore, I guess I would say why aren't we doing more bigger, longer randomized clinical trials for these chronic conditions?

DR. GRAHAM: I am not speaking for the agency now.

DR. WOOD: We got that. Don't say it each time.

DR. GRAHAM: Okay. I think they are incredibly expensive and companies don't want to do them. There is not an incentive for them to do them, and you would have to talk to the people from the new drug side of the house, but the fact is that they are not requiring them.

So, that is a very legitimate question. You know, working as an epidemiologist, we try to

make do with what is, and so we use the observational data. You are going to get better quality data if you are able to do this, but just to give you a sense of the size of the studies that I think you would need to do, I mean you talked about before that you have the APPROVe study and we see no effect until 18 months, but there was study 090 that was talked about briefly by Dr. Villalba yesterday. It was a 6-week study at 12.5 mg, and it showed a difference, the suggestion of a cardiovascular risk within the 6-week study at the lowest dose. Now, it's a small study, as well.

But I am just saying that to say that I think the epidemiologic data, in my mind at least, answers the question about when the effect begins. The question is if you want to have--this is the philosophy--how much certainty do you need to make a decision.

Right now, when it comes to efficacy, the effect, does the drug work, you are looking at the lower bound of the confidence interval, and you want to see is that different than 1, because if it

is, then, I will conclude with 95 percent certainty or greater that the drug actually has an effect.

When it comes to safety, you are doing the same thing. You are looking at that lower bound. You want this 95 percent certainty that the drug is harmful. You are presuming that the drug is safe rather than let's presume we want to do no harm to patients.

Let's start off at the beginning assuming that the drug isn't safe, and we want to have a certain level of confidence about how bad this drug could be, and that is still tolerable to us. We want to cap the risk. It will be a completely different way of looking at studies for a safety perspective, one that actually gives a priority to safety and it maximally protective of patient safety, just as that high standard for efficacy is maximally protective of patient safety, because by keeping drugs off the market that don't work, I am protecting patients from unsafe drugs, and if I have pneumonia and I am given a drug that doesn't work, well, I get a harm from that.

But that's philosophy, and I think it's an outcropping, it's a development, a natural extension of the development of clinical trials in

the United States where the focus has always been on efficacy.

DR. WOOD: Let's try and keep both the questions and the answers reasonably short, otherwise, we will be here until after midnight.

DR. GRAHAM: I apologize.

DR. WOOD: That's okay. Let's go on to Dr. Elashoff.

DR. ELASHOFF: First, I have one comment and then one question. In terms of confounding, just because you put a lot of variables in some model doesn't necessarily mean that you have adequately removed the confounding effects even of those variables.

The second has to do with Dr. Graham's slide 13, the excess population risk. I note that the Ingenix data has been left out of the bottom category.

DR. GRAHAM: That's right, because for the

high dose.

DR. ELASHOFF: Yes, but the negative sign needs to be on the slide, otherwise, it's a biased presentation.

DR. GRAHAM: Well enough. I take that correction. Okay, fair enough.

DR. WOOD: Dr. Bathon.

DR. BATHON: Yes. As we weigh the risk-benefit ratio of these drugs, one consideration is that there are subgroups of patients in which the benefit might outweigh the risk possibly.

With that in mind, it would be helpful for us who are not cardiologists or epidemiologists to be able to put the relative risks that we have been seeing over the past day or two in context with all the cardiovascular risk factors that exist.

So, for example, if you were take the presumed relative risk of rofecoxib of 1.5 to 2.0, at least at the higher dose, and put it into some context for us of the 20 to 40 cardiovascular risk factors that exist in a sort of rank order, where

would you put the COX-2 drugs?

DR. GRAHAM: For the high dose it would be probably more significant than smoking or diabetes or hypertension, maybe more important than the combination of several of those factors in a patient. For the lower dose, it is probably more than hypertension, a little less than diabetes, and a little less than smoking.

I know, David, you know the cardiovascular risk factors much better than I do, and so does Dr. Hennekens, but that would be my ballpark on that.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: Yes. I want to go back to the question Dr. Shafer asked about if these classes of drugs or this group of drugs could be if there was a hierarchy of risk, and you first answered that you thought the coxibs were more risky, but I would challenge you a bit simply on your own presentation.

I would like you to discuss your data, because you then went on to talk about how indomethacin has a risk, Meloxicam has a risk.

Based on your data, the message that came through is that there was a dose response risk for cardiovascular outcomes, that we saw it within the coxibs, but we also saw it where the data were available in the non-selective NSAIDs.

There are data that we have seen that ibuprofen might increase risk. We didn't talk about the McDonald and Way paper that in cardiovascular discharge patients, people given ibuprofen had a higher mortality 2-fold.

So, as the smoke clears, I am not sure that the simple answer that the coxibs were different was actually supported by your data, nor your ultimate explanation. Can you defend that?

DR. GRAHAM: I think you are accurate. What I was saying was I was referring, I think, to the underlying COX-2 hypothesis and that it is clearer, I believe, and, well, maybe it's an overgeneralization, because we have the n that we are viewing is so small, that looking at rofecoxib as sort of the example where we can see very clearly the dose response at all the levels and its

progression, and understanding its mechanism of action, and then seeing similar things with celecoxib and valdecoxib.

I think what you are saying is fair. Maybe a better thing to say is, in the end, that you do need to look at it drug by drug.

What I was saying, though, in that answer that I gave to Dr. Shafer, I was really talking more about sort of the COX-2 mechanism and the coxibs as being, in quotes, "COX-2 selective," but I think your observation is correct.

DR. ABRAMSON: Add to that, that although there is a hazard that we don't accomplish a lot by simply saying the class of NSAIDs may have risk, I think we have under-appreciated that over the last 10 years.

It is not that different from the mid-nineties recognizing that there was a class GI effect of these drugs, and that compared to placebo, whether it's hypertension or long-term potential adverse outcomes, this is something that doctors have to be aware of, even the simple thing

of checking blood pressures when you put people on any nonsteroidal drug.

So, I don't know that it is necessarily a bad outcome to call attention to this class effect until we get better information on each of these individual drugs.

DR. WOOD: Dr. Day.

DR. DAY: I have a comment about recall bias and reverse recall bias. There is a huge research literature on how memory works both in the laboratory and in the every-day world, and there are two phenomena that have been very heavily studied that I think might be relevant here.

One is called flashbulb memory, and the idea is when an emotional spectacular event happens, such as when you first learn that JFK had been shot, or the Challenger blew up, or the World Trade Center had been hit, it is as if the old-time flashbulb from an old-time flash camera went off and captured all the details, and you remember all of those details forever afterwards associated with the event that you might otherwise have just not

even noticed or forgotten.

So, there is a lot of research on flashbulb memory that shows many of those details are indeed correct, but some are notoriously false. For example, there are accounts of people who remember a certain even with great emotional aspects to it, and they remember listening the world series when so-and-so is pitching and it was the bottom of the 9th, da-da-da, all these details, and when you go back and check the evidence of what was going on, on that day and time, that particular game was not on.

So, that phenomenon number one, flashbulb memory, and the second is eyewitness testimony. How you ask a person a question will affect what answers you get. So, if you have in the courtroom, someone who has witnessed a car accident, if the lawyer asks this witness, "Did you see the broken glass," then, the witness is more likely to say yes than if you ask, "Did you see any broken glass," because the broken glass presumes that there was some, and so forth.

So, I take your points seriously about potential recall bias and reverse recall bias, but we would have to look at both, whether there is an

emotional component or not. Those who have had an MI, for example, would have that most likely, but also how the questions are asked in these surveys, and it is not trivial how you ask people questions about were you taking any medications or were you taking medication X, and for how long, and what was the dosage, and so on.

So, I don't think that these details are always published with the studies, and I would like to encourage people who ask people about their experiences with drugs, take a look at the memory literature for some of these points.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: Dr. Graham, I am wondering if you separated out your populations based on the indication for which they were taking the drug. I ask that because we heard yesterday, and it's well known, that rheumatoid arthritis is itself a risk factor for cardiovascular disease, and higher doses

of coxibs, in particular celecoxib, are usually given to patients with rheumatoid arthritis as opposed to osteoarthritis.

So, I am wondering if you look at that in your breakdown.

DR. GRAHAM: Several of the studies that I reviewed have looked at the indication, but in automated claims data, it is very difficult to be sort of be sure does the patient have rheumatoid arthritis, and there are different algorithms one could use, but in general, what has been found in the studies where they have looked at that, that the prevalence of rheumatoid arthritis in the study populations has been low, very low, and that its impact on the results when they adjusted for it didn't materially affect things.

Now, in the California Medicaid study, one difference in that study was that our base population was limited to patients who had diagnoses of osteoarthritis or rheumatoid arthritis. Now, these are diagnoses, and so does that mean that they really had osteoarthritis or

rheumatoid arthritis, I don't know, but when we did try to eliminate in that study at least were the people who might be using an NSAIDs for a muscle injury, a short-term complaint as opposed to a chronic illness.

In none of those does the presence of rheumatoid arthritis seem to affect things, but again I think the prevalence is pretty low in all of these studies.

DR. GIBOFSKY: One quick question for Dr. Platt, if I might. I need to understand the concept of survivor bias somewhat in that I think there is a difference between a patient who is drug-naive, then put on a drug, and then an event happens versus a patient who may have seen a drug, perhaps seen another drug after that, 3 or 4 agents of the class, and is then switched to another agent and something happens.

I think we have talked about remote versus current, but there is also this issue of sequential effect, and I am wondering how you deal with that as a survivor, particularly because of the paper we

saw a few weeks ago in the Archives suggesting that discontinuation of an NSAID may itself be a risk factor for a thrombotic event.

DR. PLATT: Your point is exactly right. I think that the concern about survivor bias is that if we think that some people are particularly susceptible, which is almost certainly the case, then, if we start the clock after a person has already been exposed to a drug or to one that has the same effect, then, it is very much less likely that those individuals will have a problem.

That may be the explanation, for instance, for the reason that the literature was so badly wrong about postmenopausal estrogens and heart disease, that most of the epi studies started with prevalent users.

I think the majority of the studies that we were reviewing here, these were individuals who are known to have had at least a year of prior experience without exposure to the nonsteroidals.

Your study in Kaiser I know was an exception cohort at least with regard to a year of

prior history, but I am not aware that any studies have a longer drug-free prior interval than that.

DR. WOOD: Dr. O'Neil, do you want to comment particularly on this?

DR. O'NEIL: Yes, this is an important point and a lot of things have been covered in Richard's and David's presentation, but one thing I think that is relevant that Richard did not cover, that is, the value of a randomized trial, is the ascertainment and follow-up, and knowing the status of individuals in the sense of who goes off therapy and how long they stay on therapy.

That is very critical relative to the time dependency of the risk. It was mentioned, for example, the use in the observational sense of recent and remote and current use. Those are all terms that are nice, but they don't get at the issue that we are trying to get at with regard to the clinical trials, and that is essentially when does time zero start for you.

So, I think the appropriate question to ask is what is the duration of exposure since your

initial exposure to the drug, because I think that is very relevant to the interpretation of the three clinical trials that we have, two of which are in placebo-control populations.

There is a rofecoxib-naproxen control trial for one years, there is a placebo-control trial in polyp prevention for three years, and there is a placebo-control trial in Alzheimer's disease for four years, and the time dependency from time zero matters as you have seen in the plots.

It is relevant to the excess risk calculation. So, I would ask the committee, as well as I would ask David, of the observational studies that you have reported, how many of them are cohort studies, and how many of them are able to identify new initial use, and then track continued use for that individual, so that one could look at the relationship between the hazard rates and the hazard ratios that we are identifying in the randomized trials and match that to the odds ratios that are being reported in the observational

studies.

DR. GRAHAM: On one of my initial slides, you can see what the cohort studies were, and in some of the nested case control studies, you are also able to get the time on drug. Actually, in Wayne Ray's cohort study, most of these cohort studies include prevalent and incident users, so they will do what is called a "new user" subanalysis, which is to try to get to this issue of when does time zero begin.

We addressed that problem in our study here by the inception cohort design in our base population, so that we can identify what time zero was for the cases.

Now, none of those studies presented data in the form of a survival analysis, which I think in the end, that is what Dr. O'Neil would like to see.

DR. O'NEIL: No, my question is not so much in survival. I don't believe, and again that is why I am asking you, I don't think any of those studies were designed or able to capture the

question I am asking.

In fact, if I am not mistaken, in the Wayne Ray study, he defined new use, but he did not define any time from new use, which is essentially critical to when those risks start.

DR. GRAHAM: That study isn't cited as one of the studies where we are able to derive that information. This slide was a slide that I presented to show that from the epidemiologic literature, those studies where the investigators had identified when time zero began for rofecoxib use, and they didn't present the data as a survival analysis, but they identified when time zero began and then, in various ways, showed you either what the distribution of the cases were, so that you can see that it was impossible for the risk to have been delayed for 18 months, because nobody in the study used the drug for 18 months, or they parsed time out and looked at the first 30 days of use from time zero, and found the risks that they found down here.

But you are right, those studies aren't

designed that way, and we haven't had time in our Medicaid study to do these analyses yet, but we have the data to now do the cohort study and time to event, so we will have an opportunity actually within the data to actually compare and look to see exactly the question you are driving at.

But I would say that from the published data, in each of these studies, time zero for rofecoxib was identified and in some way or another, information that I think could be useful to the committee in establishing when does risk begin was contained in those studies.

DR. O'NEIL: Well, the other point here, which is the value of clinical trials, and it was the question that was discussed yesterday with regard to the intent-to-treat analysis, and that is to say to analyze all outcomes once randomized to the trial regardless of whether you want to track the individual to 14 days post-exposure.

You can't really maybe get access to this information in the observational studies. That is a conjecture, but it's one or the other biases, and

it was interesting to the comment, whether one would believe this or not, that discontinuation, discontinuation from an NSAID alone raises risk.

If that were to be the case, that is a different analysis altogether.

DR. GRAHAM: In that actual paper, it could be that people were discontinuing the NSAIDs because they were having chest pain and it was being interpreted as dyspepsia or something, and then they go to have their infarct.

I mean you are right about that, but this is the nature of how epidemiology is done, and I can't change it. I didn't make the rules, I am only following them. Nobody is arguing that clinical trials, if they could be large enough, that they would give all of us answers that we would have greater comfort trusting what they are saying.

What I am proposing is that we don't have that kind of data in the clinical trials. As large as the clinical trials are, for the questions that this committee is facing, you don't have the data

you need, and what I presented is the epidemiologic data, and it is imperfect and it has its warts, and that is why I would emphasize looking at consistency and trying to sort of derive from that a general sense.

I mean does it make pharmacologic sense that you would have an 18-month delay? I mean I guess I suppose it depends on what you think the mechanism of action is for the underlying disease, but even in the clinical trials, study 090 was 6 weeks long, 12.5 mg, and it had a cardiovascular effect.

DR. WOOD: I am happy to facilitate a discussion among the FDA, but I think we would rather hear from the committee right now. Dr. Farrar, you are next.

DR. FARRAR: I think that the recommendations of the committee tomorrow are going to depend on the assessment of the overall risk and the overall benefit of this class of drugs.

As a researcher and after all the data that has been presented, I am more than happy to

accept the fact that there are serious risks even of death from taking NSAIDs. In fact, though, there are serious risks in taking any medication at all.

For some of the NSAIDs, it is cardiovascular risks, for some of them it is clearly GI bleeding. As a doctor, though, who takes care of patients, I know that treating pain or not treating pain and not treating the disability of arthritis also has very serious risks even of death.

Given the extensive work that you have done, on the risk of both the cardiovascular and the GI bleed, I wonder what level of risk is acceptable you, and remembering that the only other drugs that are really available is analgesics or narcotics, and the only other drugs that are really available in terms of limiting inflammation are biologics or immunosuppressants, I wonder what drug is safe enough that you would recommend that I actually would be able to use it in patients to prevent some of their suffering.

DR. GRAHAM: Well, I am not going to give a product endorsement. A couple of things, though.

DR. WOOD: Try and make it brief.

DR. GRAHAM: One, the benefits of the treatment for the traditional NSAIDs compared to the COX-2 selective NSAIDs with GI bleed, we have clinical trial evidence that suggest that there may be a difference, but here, to me, is an anomaly.

Rofecoxib got the indication for being GI-protective, celecoxib didn't based on the clinical trials data you guys looked at yesterday.

There are two published studies in the literature looking at what I would say is actual benefit. There, they were looking at hospitalization for GI bleed--they didn't look at death from GI bleed, but I wish they had--but hospitalization for GI bleed, and what they found was, in both of these studies, that celecoxib was actually more beneficial, you know, lower rate of hospitalization for GI than rofecoxib. So, that is the population, two large studies.

You have got your clinical trials that

would have said it should be the reverse. So, I throw that out as one sort of conundrum.

The second is that I don't think that the actual benefits of these drugs are understood well enough to sort of try to weigh these very well. The case fatality rate for myocardial infarction in the United States approaches 40 percent. The case fatality rate for hospitalized GI bleeding is probably somewhere around 5 or 10, it is a much lower case fatality rate.

Nobody that I have seen anywhere has sort of worked this out very well, so I would submit to you and to the committee that you actually know very little about the actual population benefit of any of these products.

DR. WOOD: I don't think we are going to get an answer to that question, so let's move on.

Dr. Nissen.

DR. NISSEN: Let me briefly answer the earlier question about what does the hazard ratio of 1.5 to 2 mean. Before I came to the meeting, I made a point to look this up, because I thought it

would be very relevant.

It is equivalent to raising a cholesterol from 200 to 260, or taking up smoking. Another way for the committee, I mean as a cardiologist I have to deal with this all the time, the most effective drugs we have for prevention of morbidity and mortality are statins, and they reduce risk about 35 percent.

So, a hazard ratio of 1.5 to 2 is really a very, very big effect when you are talking about the most common cause of mortality, and that is why this discussion is so important.

Now, my question is this. We are going to be asked to balance risk and benefit, and so the magnitude of the hazard ratio is very important to all of us, and I am trying to reconcile what we see in the randomized control trials with, let's take rofecoxib for a moment, where it looks like the hazard ratio in the randomized trials is in the range of 2, 3, 4, maybe even higher, and in the observational data it is significantly lower.

I would like to propose a hypothesis to

you and just ask you if you think this is right. In your observational data, you are looking at mostly short-term exposure, so you are looking at less than 12 months typically of exposure.

It may well be that the hazard increases over time, so that by the time you get to 18 months, you can actually see it in a much smaller randomized trial, and so it doesn't rule out the possibility that, in fact, both observations are right, that, in fact, there is an early hazard, but that early hazard has a smaller hazard ratio than the hazard at 18 months or 24 months or even 36 months, and if we ever were to look out 5 years, it might still be increasing.

Do you think that is a reasonable hypothesis?

DR. GRAHAM: I think more likely it is, that in your clinical trials, early on you don't have enough power to distinguish the risk. The hazard is the same, but the lines are closer together, because we are closer to the origin.

I think one other explanation for the

lower risk ratios in observational studies, I would think is more likely due to misclassification of exposure and misclassification of outcome. It is likely to be nondifferential, so it would tend to reduce the odds ratios and relative risks towards 1.

Exposure, because people are going to take it, a lot of these people are taking it on a prn kind of basis. In a clinical trial, you have a greater certitude that they are actually taking it every day. That introduces a lot of misclassification, so the a priori hypothesis going into an observational study, with misclassification going on, you are fighting an uphill battle to see an effect.

DR. WOOD: We have got lots of people who want to ask questions. I want to make sure that the people who are asking questions have questions they want to ask for clarification of the speakers who have spoken rather than just general points.

Dr. D'Agostino.

DR. D'AGOSTINO: I have a couple of

questions along the way here. I have spent a good part of my career in the Framingham Heart Study, and it's an epidemiological study and a cohort study, and we take joy when somebody runs a controlled trial on hypotheses and then later on confirms it.

The first question is I am concerned that even though you have gone through this careful analysis, your conclusions are no apparent effect, probably increased effect, probable increased risk. They really don't help us in the sense of pinning things down. We have a couple of very strong I think good studies, the APPROVe study and the APC study as placebo-controlled trials.

Tell us quickly where is the weight of how we should look at these two pieces, the controlled trials we have versus what you have produced.

DR. WOOD: Really quickly.

DR. D'AGOSTINO: Really quickly, it can be done quickly.

DR. GRAHAM: My belief is that for the controlled clinical trials, for the levels of risk

that we are concerned about, that they do not have the statistical power early on to show risk differences.

DR. D'AGOSTINO: I think Bob O'Neil's comment is very important here.

The other two points, and again I will make them quick, I am very concerned about the high dose effect you have, and I am really concerned about the MI and the number of cases. I mean blood pressure, cholesterol, diabetes, smoking, this is what drives people to have heart attacks and what have you, and that is completely missing on your assessment of how many new cases, so I guess it is more of a comment that I am really concerned that that sheet needs sobering interpretation.

DR. GRAHAM: But it was based on the odds ratios and relative risks where those factors were adjusted for, so as well as they are adjusted for, that is what the projection represents, the excess after adjustment.

DR. D'AGOSTINO: Yes, but I mean the comment was made by you, throwing in the analysis

doesn't necessarily adjust for them.

The last one, you made a very nice point about the cardio-protective effect, and you tried to show that these uses, and what have you, somehow or other all have the same risk, and your interpretation that there must be some confounding going on, why doesn't that hold for all the studies you gave, why don't that hold for the Solomon study, which you thought was a great study, yet, this one result you don't like?

DR. GRAHAM: For what, the Kimmel study?

DR. D'AGOSTINO: Wasn't it the Solomon study that had the naproxen as the cardio-protective?

DR. GRAHAM: That is because the cardio protection was present when they were on the drug and when they weren't on the drug.

DR. D'AGOSTINO: I understand what you are saying, but if that's a problem, then, it means there is some confounding going on.

DR. GRAHAM: No, it's selection bias.

DR. D'AGOSTINO: Well, it's selection

bias, but why isn't it for the whole study? Why do you throw out a result you don't like and keep all the results you like?

DR. GRAHAM: No, that is not what I did. I pointed out a result where they showed the presence of the selection bias. In other studies, the Ingenix study is the only other study that looked at this. I don't have a slide of it.

DR. D'AGOSTINO: I don't know if it's a selection bias or misinterpretation of the data.

DR. GRAHAM: Well, to me it looks like selection bias.

DR. WOOD: Let's continue that conversation later.

Dr. Morris.

DR. MORRIS: David, would you go to slide 14. That is the risk, the duration of use. I think one of your points was that if you look at your study, tell me if I understand this right, that with the lower dose, that the median time to an AMI is sooner than with a higher dose, did I understand that right?

DR. GRAHAM: Yes.

DR. MORRIS: A month?

DR. GRAHAM: Had more cases, a greater

proportion of our cases, but the other thing is remember, down here, we are talking about 18 cases or so. The N here is small, the N here is like 58, and the N here is 10. So, I wouldn't read too much into the difference.

The more important point is that at the low dose, nobody was out there beyond 18 months, so all the action happened before 18 months, and the same for the others. I see what you are saying. I can only say that is what our data were.

DR. MORRIS: One interpretation is what you said earlier, that for this particular drug, we are talking about, as you said, no safe level. I was wondering if that is the way you interpreted it, that because we are talking about Vioxx here, and there is no safe level, that something is going to happen sooner, or is it something with the populations are different.

DR. GRAHAM: The populations could be

different, but I think, you know, you would expect the higher dose to have a shorter latency to onset than the higher dose, but the numbers are so small.

DR. MORRIS: Okay, it's a small number problem.

DR. WOOD: So, the answer is too small numbers at high dose.

Dr. Boulware.

DR. BOULWARE: I just want to make sure I understand something that you had proposed in your excess population risk slide, if you would put that back up.

As a rheumatologist, I use these drugs in a population much greater than what you have here with a 65 to 74 where the risk of an MI is fairly high in that group.

Did you want us to believe that this excess risk that you are proposing would be extrapolated to other population groups, too?

DR. GRAHAM: Well, no.

DR. BOULWARE: Do you have any numbers that may demonstrate that?

DR. GRAHAM: Well, the answer to the second is no. This was an example in conversation with people planning the talk, to try to help

people connect with what it means.

Cardiovascular risks go up. I mean in the next age group higher, the risks are higher. In the age groups lower, they are lower, but cardiovascular risk begins to increase in the 40s.

DR. BOULWARE: I understand, but it wouldn't be a linear type of thing.

DR. GRAHAM: No, the background risk isn't linear, the relative risks, though, are adjusted out.

DR. BOULWARE: Because one of the questions we will be faced with is are there subpopulations or groups that these may be safe in, and I just want to make sure I understand the relative risk in different age groups.

DR. GRAHAM: Nobody in any of the studies where they have looked at it have reported effect modification, which would be that the level of risk differs at different ages.

DR. BOULWARE: One more question here. I want to make sure I understand. I think I heard a comment that says when the risk approaches 2.0--maybe I just assumed that you said this--that it was an unacceptable level of risk.

Is there ever a case where a drug may have

a clinical benefit in which that risk is acceptable, because for the patients I see, not giving them any of these drugs will confer a great deal of risk on them, and physical impairment, and we have studies that show that the functional classification of rheumatoid arthritis patients carries with it a significant mortality as that class goes up?

DR. WOOD: I think that is a question for the committee to answer rather than Dr. Graham.

Let's move on to Dr. Cryer. Do you have a question?

DR. CRYER: I do. The comment and question I have of Dr. Graham addresses an issue that I think is an important difference between the observational studies and the prospective studies,

and this difference relates to assessment of drug compliance and missed doses, and I think it is critical as it relates to assessing drugs which potentially affect platelet function.

A huge difference, as you know, between aspirin's effect and every other NSAID including the COX-2 inhibitors, is that with the non-aspirin NSAIDs, as soon as you remove the drugs, whatever potential effect they would have had on the platelet are immediately reversed.

So, with naproxen specifically, my preconceived bias, which may be wrong, but my preconceived bias based upon everything I know about the pharmacology and the things that Dr. FitzGerald has reviewed for us, is that it should have some mild anti-platelet effects which would only be present when the drug is on board in the system.

So, the specific question is, in the observational studies, recognizing that in clinical practice people miss doses of their NSAIDs, they are not taking their NSAIDs consistently, how do

you account for the missed doses in the observational studies recognizing that this could potentially lead to a mitigation of whatever negative effect or positive effect that they may have?

DR. GRAHAM: It ends up being misclassification. Generally, what that means is it will force the observed level of risk, the relative risk of the odds ratio closer to 1. So, if we had an increased risk, it would make it lower, if we had a protective effect, it would sort of make it higher, closer to 1.

DR. CRYER: Right, we agree on that. The specific question is, is there a way to actually recognize or to account for when people do not take their doses in the observational databases?

DR. GRAHAM: No, there isn't, so when you are studying, say, an increased risk, that is why I said if you find something, you have to realize you found it despite the misclassification.

DR. WOOD: Okay. Dr. Domanski.

DR. DOMANSKI: I will save it for

tomorrow.

DR. WOOD: Okay, great. Dr. Furberg.

DR. FURBERG: No.

DR. WOOD: Okay, great.

Dr. Temple, who does speak for the FDA.

DR. TEMPLE: I am just asking questions. A couple. Actually, one point is it seems to me that since we expect that people are going to be getting one drug or another, comparisons with other NSAIDs seems like as good a comparison as we should make. You might want to leave out indomethacin if you are worried about it. That's one thing.

I guess my main question, though, is everybody has paid appropriate lip service to the idea that very small differences are hard to interpret in epidemiology.

People have said 1.5, 2. Actually, I notice in one of his editorials, Dr. Furberg cited a paper of mine where I said anything less than 2 really needs a lot of questions. Jerry Cornfield, who sort of invented all this stuff, used to say 3.

Well, we are talking about differences

here that are 0.1 differences, not that they wouldn't be hugely important if they were true, that is absolutely true. So, I guess I want to know what Richard and you make of all this, because the numbers are very small, and yet, just as an example, there is a very great consistency that you cite that celecoxib looks sort of okay, but you found one study where there is a little hint that maybe the higher dose is a problem, and since probably we all think dose response is likely, that looks good to you.

DR. GRAHAM: Two studies, there were 2.

DR. TEMPLE: Okay, 2. The valdecoxib data, which shows nothing, doesn't look so good because we probably all believe that there is likely to be a class effect.

What I am asking is, with numbers like this, how do you know what to do with them? That seems very fundamental for the epidemiology.

DR. WOOD: But, Bob, there are 4 randomized clinical trials here, and your comments don't apply to them, I assume.

DR. TEMPLE: No, they don't, although they are not perfectly consistent either. But, no, I am asking, what do we make of differences of this

magnitude with everybody having given lip service to the idea that small differences are hard to interpret, and yet we seem to be enthusiastically endorsing them, so I just want to know what Richard and David think about that.

DR. GRAHAM: Rich, do you want to go first?

DR. PLATT: I think we have to be cautious about how we interpret it, so I would say the finding of a relative risk of 3 in an epidemiologic study, as David found, is meaningful--

DR. TEMPLE: For high dose rofecoxib.

DR. PLATT: For high dose rofecoxib.

DR. TEMPLE: I would not dispute that at all.

DR. PLATT: It seems to me that in that context, that a dose response effect, that the information about lower doses gains weight by borrowing from that. I think that is also worth

keeping in mind when, in other studies that are working in that range that make us all nervous, there appears to be a dose response effect.

It is the kind of consistency that makes the study, in my mind, be worth more attention. I think there is something to be said for giving more weight to relatively small excess risks if they are seen in a number of different environments when we can't have good reason to think that there is a similar kind of biases that might be contributing to it.

After that, I agree with you. We are in relatively difficult terrain. I think that it is not the same as no data, though. I think we ought to distinguish between the situation in which we have no evidence from ones in which we have relatively weak evidence.

We didn't talk at all, for instance, about the enormous number of spontaneous reports of myocardial infarction following exposure to nonsteroidals. There are thousands and thousands of them. In my mind, they don't contribute at all

to the discussion, whereas, I think these need to be weighed in the mix when we don't have clinical trial information to depend on.

DR. GRAHAM: My answer is similar to his, but I think that what you are identifying is, is that we are hitting or at least right now the frontier is the limits of what the available tools we have to define the levels of risk that we are talking about.

We are talking about small levels of risk that turn out for this particular event to be enormously important in a population level. If you are talking liver failure, we wouldn't be having this conversation. For that reason, it becomes important and what I would say is sort of emphasizing what Rich said, is I would be looking for consistency across different studies, and if I found a number of studies, say, as with Indocin, for example, to me, that is more persuasive.

If I found a number of studies that pointed to a particular set of NSAIDs that seems to have low risks, I would take comfort in that in the

absence of perfect information. I mean some light in a storm is probably better than no light In a storm.

DR. TEMPLE: I take it if the differences were at the level of 10 percent, 1.1 versus 1.2--

DR. GRAHAM: I am thinking more in a very qualitative sense of things that they seem to cluster around 1. I mean 1.1 for ibuprofen, it could be that, for example, may naproxen increases the risk 3 percent in the real world, we are never going to figure that out, maybe ibuprofen increases it 10 percent or 15 percent, maybe we could figure that out, I don't know, but there is going to be a place where qualitatively, if we see enough studies kind of sort of pointing to the same place, you know, most of them, they are not all going to say the same thing, there is going to be these conflicts, just like we have in clinical trials data.

But if most of the compass arrows are sort of pointing in the same direction for particular NSAIDs, I think those are the ones that at least

that I sort of place on a suspect list.

DR. TEMPLE: So, very low hazards need at least multiple support before they are credible.

DR. GRAHAM: I think so, and I think that you want to try to encourage to collect that information sort of to test that out.

DR. TEMPLE: Alastair, could I take half a second to answer a question Larry raised before?

DR. WOOD: Sure, a second.

DR. TEMPLE: Well, it's a very good question, you know, if the drug is going to be used forever, why don't you study them forever. The only thing I would point out here is that what sort of started people thinking was VIGOR, and VIGOR didn't take 3 years to show anything, it showed up in 9 months.

So, what you have seen is for, say, lumiracoxib, a humongous study of about the same length, but, of course, they didn't know about APPROVe, did they, and whatever you think APPROVe means, whether Bob is right that it's late, or David is right that there weren't enough cases,

people were pointing toward a study that by every reasonable thought, if you think platelets are involved, ought to be long enough to show things up.

But then you form a new hypothesis once you have APPROVe, and you have to adapt it, and I think that goes on all the time. It would not be I must say for most things my first thought unless you are looking for cancer that you need a 3-year study to find it, but maybe you learned that it does.

Just for what is worth as an example, you can't get an anti-arrhythmic drug approved in this country without showing that you don't alter survival unfavorably. One result is there are hardly any being developed, but, you know, we had bad experiences, we didn't like the results of CAST, so you change.

I think there is no doubt that things evolve and you have to expect that, and APPROVe, depending on what you think of it, changes the nature of what you expect.

DR. GRAHAM: Bob, just one point on that. I think if the APPROVe study had been 5 or 10 times larger than it was--I am talking about retrospect

now--you would be able to answer with much greater confidence what is happening month 1 to 18. I guess what I am saying is that you could also shorten the latency to identification of a problem if it turns out that the risk is early on.

DR. TEMPLE: David, I think that is entirely possible, and if it involves platelets, I would believe you, but if it involves a small, long-term increase in blood pressure, then, I am not so sure.

DR. GRAHAM: Right, but we saw yesterday--

DR. TEMPLE: We don't know.

DR. GRAHAM: We don't, but if it's prostacyclin, that effect could occur immediately.

DR. TEMPLE: Yes, but the blood pressure effect could be delayed.

DR. WOOD: Right. So what, Bob, you are saying is that it is easy to be a Monday morning quarterback, but the data were not there before.

DR. TEMPLE: I would never be that rude.

DR. WOOD: I think you are right.

Dr. Stemhagen.

DR. STEMHAGEN: I would like to clarify a couple things. First, I am a little concerned in terms of the unpublished data. I appreciate that

we are able to get data very quickly, right at the minute that it is being generated, but none of us have had a chance to really review that, so I do have some concerns about the weight putting on this unpublished data when the rest of us haven't had a chance to look at it.

I think there needs to be some clarification. There was some discussion about the recall bias, and so on. Certainly, there is a major concern about that in case- controlled studies, and we don't have the questionnaires, but there were a lot of sort of subanalysis done in the Kimmel study, about trying to look at whether recall bias is a problem, and I am not sure that you have highlighted that enough that looking at all those different things, there were really no differences

found.

Similarly, in the Watson study, it's a GPRD study, it is different than a lot of the large databases, the automated databases.

There is a lot more personal involvement in terms of the data and the data collection and the adjudication of results, and I think it just needs to be clear that all of these studies are not the same in terms of a Medicare study where we can't go back and validate records. A lot of them had a much more careful review, and I am just not sure that that was totally clear and if you hadn't read each of the papers.

I would like to just ask a question in terms of your definition of the inception cohort, if you could just go over that again, because of your comments about the short-term use.

DR. GRAHAM: Inception cohorts are where people enter the cohort with their first-time use of a specific agent, so it's basically like an incident cohort, it's new users. That is to be distinguished from a prevalence cohort where

starting January 1st, everybody who was on an NSAID is in our cohort.

Some of those could be people who were on it before January 1st, and others could be people who start an NSAID after January 1st, so you are mixing people who are prevalent on the drug, who may have survived, or whatever, and people who are newly starting it.

In those types of cohort studies, a new user analysis was designed to focus on those people who, during the study window, were new initiators of the particular drug under study, so that time zero could be identified for those people.

That is what Alec Walker & Company did in their Ingenix study. It was a prevalence cohort, but they did a new user analysis in which they identified new users, and it was that new user analysis that showed the 1 to 30-day increased risk.

Wayne Ray did the same thing in terms of new user analysis, and in our study, the nested case control, everyone was an inception user in the

base population.

DR. STEMHAGEN: I guess just a comment in terms of people thinking about clinical trials where we have washout periods, is that people are really switching.

If they are RA or OA patients, they are not starting new with the drug, they have been on something for a long time, and they are switching. So, we have to think about those risks in terms of the weight we are putting onto that inception cohort, as well.

I guess the last point is based on the question that Ralph had about the other studies. I just want us to keep in mind also that a lot of those studies come from very unique populations - the randomized clinical trials, the colon polyp study, and the Alzheimer's disease patients, so are very different.

We can't tease out in any of these observational studies whether we have patients that meet those criteria or have those indications, as we also pointed out.

DR. WOOD: Tom.

DR. FLEMING: I think Drs. Platt's and Graham's presentations were informative, but with

certainly a lot of complexities for methodologic issues that I assume tomorrow, we will give our perspectives about, so let me ask a question and then a clarification.

The question relates to the slide on the 4 positive naproxen studies, I think slide 22. While you are getting that, just very quickly, these large linked databases certainly are very useful from the perspective of getting defined populations with numerators and denominators, but have many challenges that people have been talking about along the lines of lack of randomization, no confounder information, specificity and sensitivity.

Bob O'Neil got at a point that I think is critical, and that is the complexity of not having a time zero cohort with the ability to do what would be the analogous ITT analysis with complete follow-up or minimize loss to follow-up.

You bring out in the Solomon example there, David, a very nice illustration of this very point that you recognized, which is the selection bias that can go on when you are characterizing people into these groups, and it's misleading to think that you are really seeing the causal effect

of any use versus current, versus recent, versus remote, the causality could be going in the other direction.

Intrinsic differences in patients could be influencing whether they are, in fact, in those four categories. But don't you, in essence, even though your conclusion might be right, aren't you, in essence, doing the same thing at the top when you are looking at naproxen, say, when you are looking at other NSAIDs, it is protective, but you don't know whether it's, in fact, truly the harmful effect of the other NSAIDs, so you try to get in a non-use population, you are trying to simulate a placebo, but how do you know that those non-use people weren't intrinsically better? Isn't it the same issue?

DR. WOOD: I think we have had this discussion.

DR. FLEMING: But this is important, I want to get his views, because it's important for naproxen.

DR. WOOD: Okay.

DR. GRAHAM: There is no perfect reference group. It turns out that this non-use group is really they are remote users, but it is a question

and I can't answer it except to say that when you adjust for all the confounders you are able to measure, you try to remove those effects, but there still could be effects that you cannot remove.

The data are what the data are, and here what I was trying to show is that based on--if these data were looked at the way most of the other studies were done, it gives a very different result.

If it turns out that all of the NSAIDs increased the risk a little bit, the fact that naproxen doesn't increase it as much, could look protected, and you really don't know.

The real conundrum is to get an anchor point to help you interpret everything, and there is no perfect anchor point.

DR. FLEMING: Your motivation for wanting to know what the placebo-controlled result is, is clear and justified. This analysis, though, has the same potential flaws as the Solomon analysis. So, the motivation for the question is clear, as you are just restating, but the reliability of the conclusions are suspect for this very reason that you correctly noted, due to the selectivity in the Solomon categorization.

DR. GRAHAM: You need then to sort of generalize that to all of the observational studies, because all of them, you had--

DR. WOOD: Why don't we continue this conversation later, and, Tom, you can present discussion on that later.

DR. FLEMING: Well, there is much more to say, but I will defer to tomorrow.

DR. WOOD: I am sure there is.

Dr. Hennekens will be our last question

before the break. Just to encourage you, we will be back here just after 20 to, so make it fast.

DR. HENNEKENS: A question and a comment. Ten years ago, a large body of basic science, clinical studies, case-control, and prospective cohort studies consistently showed that patients with hypertension prescribed calcium blockers had 1.5 to 2-fold increased risk of MI even after controlling for a large number of available confounders.

I wrote a JAMA editorial asking for randomized evidence, but I assume, based on what I heard you say, that you would have asked the agency to withdraw the drugs. So, I would ask you to consider whether protecting the public from harm is an optimal goal.

It is far more simple and straightforward than trying to maximize benefit and minimize harm, which would do the most good for the most people, but doing the most good for the most people does not, strictly speaking, protect the public from harm.

DR. GRAHAM: Do you want a response to that? Okay. I think that when you are faced with a large risk that affects large numbers of people,

and has a large consequence, that you don't have the luxury of time to wait 10 years to get clarification on the issue, and you have to use what data you have available at the time.

I think that just as we have imperfect measures of risk, I would submit that we have even more imperfect measures of actual benefit. In the case of hypertension, I think, you know, that has been studied dramatically and we actually know that not all antihypertensives lowering blood pressure at the same amount, confer the same population benefit.

I would say that with this class of drugs, we really haven't even demonstrated--I mean yesterday, the question came up why would a company do a study on polyp prevention, had they thought about what the benefit of this was, and nobody had started to think, well, how many lives are we going to save by giving people these drugs, and I would

submit that if you were to ask the agency or ask the company on this, if you don't have a good measure on benefit, so you want to make a benefit-risk assessment.

We have measures of risk, they may be imperfect, but I would argue that from a population perspective, you don't really have nearly as good information as you might believe you do from the clinical trials, what the benefit in the population is, how many lives are actually saved by the COX-2s, for example.

DR. WOOD: On that note, I am told the lines are building at the men's room, so we need to be back here at exactly quarter to.

(Recess.)

DR. WOOD: Let's get going.

Arcoxia (etoricoxib)

Merck Research Laboratories

Sponsor Presentation

Sean P. Curtis, M.D.

DR. CURTIS: Mr. Chairman, members of the Joint Advisory Committee, FDA, ladies and

gentlemen: My name is Dr. Sean Curtis, Senior Director, Clinical Research, at Merck and Company, and I would like to thank you for the opportunity to review data from the Etoricoxib Development Program.

I believe the committee will find these data informative and contribute to the further evaluation of this therapeutic class, a goal we all share collectively.

Drs. Konstam and Loren Laine are serving as consultants today and are available as a resource to the committee.

Following an introduction, results from the development program will be summarized beginning with efficacy, followed by a review of the safety findings. I will first review the gastrointestinal and renovascular safety, followed by thrombotic cardiovascular safety.

I will then review the design of three studies, which together are designed to further characterize and assess the cardiovascular safety of etoricoxib in arthritis patients.

Cardiovascular safety data from the first of these three studies, the EDGE study, will be reviewed, and I will conclude with a summary.

My presentation will focus on the following points. Etoricoxib, as a selective COX-2 inhibitor, has a role among the current treatment options for patients with diseases and conditions characterized by pain and inflammation.

Supportive data will be reviewed, namely, efficacy that has been demonstrated to be similar and, in some cases, superior to NSAIDs, specifically naproxen 1,000 mg; gastrointestinal safety and tolerability, favorably differentiated from NSAIDs; and a renovascular safety profile, which is dose dependent and generally similar to the effects observed with comparator NSAIDs at therapeutic doses.

With regards to thrombotic cardiovascular safety, cardiovascular events occurred at a similar rate on etoricoxib as compared to non-naproxen NSAIDs over the course of approximately 1 year. Data are currently limited beyond 1 year of

treatment, and events occurred at different rates in comparison to naproxen.

The other key point for my presentation is that large, randomized clinical trials are currently ongoing to further characterize the long-term cardiovascular safety of etoricoxib as suggested by many members of this joint committee.

These results will provide a full characterization of the cardiovascular safety profile of etoricoxib in arthritis patients as compared to diclofenac.

These data are critical to the current scientific debate over cardiovascular safety. Specifically, we will address whether the long-term cardiovascular safety of a selective COX-2 inhibitor is similar to, or different, than that of a traditional NSAID.

Let's begin reviewing the data.

Etoricoxib represents a distinct chemical entity. It consists of a bipyridine ring with methyl sulfone side chain. In the clinical dose range, etoricoxib has demonstrated selectivity for

the COX-2 enzyme using human whole blood biochemical assays.

Its absorption is rapid with a peak plasma concentration achieved by approximately 1 hour and with an effective half-life of approximately 22 hours, it is suitable for once daily dosing.

Etoricoxib is currently approved in approximately 60 countries. Core indications include osteoarthritis at a once daily dose of 60 mg, rheumatoid arthritis at a once daily dose of 90 mg, and acute gouty arthritis. The dose is 120 mg for the acute symptomatic period only.

In the United States, the FDA issued an approvable action on our new drug application.

I would now like to summarize efficacy. The efficacy of etoricoxib has been demonstrated across a range of conditions and diseases characterized by pain and inflammation.

For these conditions, efficacy data have been published or accepted for publication including 3 diseases and conditions for which an indication is not currently granted in the United

States for a selective COX-2 inhibitor. These include studies in chronic low back pain, ankylosing spondylitis, and acute gouty arthritis.

As you will remember, the acute gouty arthritis data were discussed with the Arthritis Advisory Committee in June 2004 in the context of a committee meeting design to look at gout study designs.

Efficacy data are summarized in your background package, however, I would like to draw your attention to results obtained in three specific disease models.

The rheumatoid arthritis program included 2 pivotal double-blind, placebo and active comparator- controlled studies in approximately 1,700 patients. In one study, etoricoxib 90 mg demonstrated efficacy that was statistically superior to naproxen 1,000 mg for all primary endpoints and all additional endpoints including the ACR20.

In the other study, etoricoxib demonstrated efficacy that was similar to naproxen,

and in patient with the ankylosing spondylitis, we performed a single pivotal double-blind, placebo and active comparator-controlled study which enrolled approximately 390 patients.

Over the 52-week treatment period, etoricoxib demonstrated efficacy that was statistically superior to naproxen 1,000 mg for all 3 co-primary endpoints, and in patient with acute gouty arthritis, we performed 2 double-blind, active comparator-controlled studies enrolling approximately 350 patients in total.

In those studies, etoricoxib at a dose of 120 mg for 7 days demonstrated efficacy that was comparable to indomethacin.

I would now like to begin reviewing the safety data.

The gastrointestinal safety program, as summarized in your background package, was designed to evaluate the entire GI tract. Clinical outcomes based on pooled data from the entire development program were prespecified for analysis. These include a combined analysis of upper GI clinical

events, or PUBs, and a combined analysis of GI tolerability.

Here are summarized results from the prespecified combined analysis of upper GI clinical events which occurred in Phase IIB and III studies from the entire development program by displaying the cumulative incidence of confirmed events by treatment group over the entire duration of the studies involved in the analysis.

As you see, a statistically significant relative risk of 0.48 favoring etoricoxib was demonstrated. This represents a 52 percent risk reduction. It was observed early and maintained over the entire study duration. These results are largely driven by comparisons to naproxen.

For purposes of summarizing renovascular safety, we will focus on data from the osteoarthritis and the rheumatoid arthritis studies, which represent the majority of the data. Presenting results by disease types ensures the patient characteristics are similar among the treatment groups.

This slide displays the incidence of hypertension adverse experiences by treatment group observed over a 12-week treatment period, in OA

patients on the left, and RA patients on the right.

In the OA population, the dose response is observed most clearly from 30 to 60 and 60 to 120 mg, 90 mg is outlying likely due to the smaller sample size, and in the RA population, the dose response is also observed although less evident as compared to osteoarthritis.

Overall, the rates observed for etoricoxib, specifically the doses indicated for chronic use, that is, 60 and 90, are within the range observed with comparator NSAIDs, numerically higher than naproxen, numerically lower than that observed with ibuprofen, and in both patient populations, it was rare for patients to discontinue from this adverse experience with no clear difference observed between treatment groups.

In addition to hypertension, we looked closely at adverse effects related to edema and congestive heart failure. Tabulated here are the

incidence of congestive heart failure adverse effects as spontaneously reported by investigators in our placebo-controlled population of up to 12 weeks duration.

As you see here, incidences are low among the active treatment groups. I would like to show you the cumulative incidence of congestive heart failure adverse events which occurred over the entire duration of our chronic exposure studies.

We see here that etoricoxib as compared to comparator NSAIDs pooled are associated with similar rates of congestive heart failure adverse events. The grouping of terms is indicated on the bottom of the slide.

The data provided in your background package and summarized thus far support the improved gastrointestinal safety and tolerability of etoricoxib compared to non-selective NSAIDs, with clinical outcomes data including PUBs and GI intolerance endpoints, as well as endoscopic data.

These data also provide evidence of the renovascular profile of etoricoxib, that is,

hypertension, edema, and heart failure are dose related as would be expected, and generally similar to the effects observed with comparator NSAIDs, in some cases numerically higher and in some cases numerically lower.

I would now like to move on to cardiovascular safety data review. The process that Merck instituted for prospectively adjudicating all potential thrombotic events as described by Dr. Braunstein yesterday for rofecoxib, was operative for etoricoxib from the beginning of Phase IIB.

We prespecified an analysis of all such events using individual patient data from studies of at least 4 weeks in duration across the clinical development studies.

In total, there were 12 studies included in this analysis including approximately 6,700 patients and 6,500 patient years of exposure. For the analysis, comparisons of etoricoxib were made to placebo or active comparator NSAID using data only from the studies that contained the treatments

being compared.

The etoricoxib group and analysis you will be seeing shortly consists of data combined from doses of 60, 90, and 120 mg in order to improve statistical precision, and for the comparison to NSAIDs, naproxen was compared to etoricoxib separate from the other 2 NSAIDs, diclofenac and ibuprofen, based on the fact that naproxen is distinct pharmacodynamically from both ibuprofen and diclofenac, and because qualitative differences were observed in the comparison to naproxen versus the comparison to non-naproxen NSAIDs.

The endpoint specified as primary for the assessment of cardiovascular safety in the etoricoxib development program was a composite endpoint of all confirmed thrombotic events confirmed by the Adjudication Committee, and includes cardiac, cerebrovascular, and peripheral vascular events.

The primary results for the pooled analysis are summarized here by presenting the point estimate of the relative risk and the

corresponding 95 percent confidence interval for the comparisons of etoricoxib to placebo, to non-naproxen NSAIDs, and to naproxen for the composite primary endpoint of confirmed thrombotic events.

The naproxen-controlled data set is the largest of the 3 data sets, and the placebo-controlled data is the smallest of the 3. This is indicated numerically on the right in patient years at risk and correspondingly reflected by the size of the triangle representing the point estimate of the relative risk.

When comparing etoricoxib to placebo and to non-naproxen NSAIDs, the relative risk approximates 1.0 indicating no discernible difference in thrombotic cardiovascular events between those treatment groups.

However, it is important to keep in mind that the maximum duration of the placebo-controlled period was 12 weeks, and when comparing etoricoxib to naproxen, the relative risk is greater than 1, indicating a difference between the 2 treatment

groups in a trend favoring naproxen in that comparison.

Shown here are the cumulative incidence of confirmed thrombotic events in the non-naproxen-controlled data set. The amount of data are limited at longer term time points particularly for the non-naproxen NSAID group.

In total, the event rates are similar between treatment groups.

All individual events were categorized by the Adjudication Committee as either cardiac, cerebrovascular, or peripheral vascular. In reviewing the specific events in the non-naproxen-controlled data set, using this categorization, cardiac and cerebrovascular events were observed in both treatment groups.

Numeric differences between treatment groups trended in both directions and were observed at the level of individual events.

As indicated previously, the largest of the 3 data sets is the data set which compares etoricoxib to naproxen. As you can appreciate from

these cumulative incidence curves, the etoricoxib and naproxen groups separate early with a lower cumulative incidences observed on naproxen as compared to etoricoxib.

In the naproxen-controlled data set, the specific confirmed thrombotic events occurred in all 3 vascular events. In considering the overall difference between the naproxen-etoricoxib group, no single event predominates, however, a higher incidence of ischemic cerebrovascular strokes was observed on etoricoxib in this comparative data set.

Analyses were performed to explore the relation between dose of etoricoxib and rate of thrombotic events. The left two panels summarize the results of a pair-wise analysis, an approach that includes data only from studies that contained the doses being compared.

The righthand panel represents results using a summary approach, which incorporates rates by dose from all studies in the pooled cardiovascular analysis.

The data do not indicate evidence of a dose effect across the 60 to 120 mg etoricoxib dose range.

Summarized in your background package are results of subgroup analyses from the naproxen-controlled data set including patients at increased baseline cardiovascular risk and by arthritis disease type particularly OA versus rheumatoid arthritis.

These subgroup analyses, as well as additional analyses including those subgroups identified to be potentially at increased risk based on the rofecoxib APPROVe study failed to identify any specific patient subgroup at increased relative risk for thrombotic event.

It is important to remember, however, that the amount of etoricoxib cardiovascular safety data currently available do not allow us to make firm conclusions for any specific subgroup.

All-cause mortality in the etoricoxib development program is summarized here as rates per 100 patient years by treatment group. Included, as

well, are results from the EDGE study, a study of approximately 1 year's duration in over 7,000 osteoarthritis patients comparing the GI tolerability of etoricoxib to diclofenac.

Rates for etoricoxib and non-naproxen NSAIDs in the left panel are similar and numerically higher than those observed on naproxen and placebo, which are similar to each other. The rates here are represented as a point estimate with a corresponding 95 percent confidence interval.

As you see, the confidence intervals are broad and overlapping between the treatment groups. Based on these data, there is no evidence for a true difference in all-cause mortality between treatment groups.

In the EDGE study, on the right, rates were numerically similar between treatment groups in all-cause mortality again with confidence intervals that overlap the point estimates between treatment groups, at this point indicating no evidence of a difference.

The cardiovascular safety data from the

original development program can thus be summarized as follows. There is no clear evidence of a difference between etoricoxib and placebo based on limited amounts of short-term data.

There is no discernible difference in cardiovascular event rates between etoricoxib and non-naproxen NSAIDs. This comparison is limited, however, by the amount of active comparator-controlled data with both diclofenac and ibuprofen, and naproxen, at a regimented dose of 500 mg twice daily is associated with a lower rate of thrombotic events as compared to etoricoxib.

As you saw from the Kaplan-Meier curves, the cumulative incidences, a difference, separates early, and is, in fact, this is an observation that has been seen with the rofecoxib data and similar to the observations made from the lumiracoxib TARGET study, which we will be hearing about later.

Recent results from long-term placebo-controlled studies with rofecoxib and celecoxib have important implications for etoricoxib. Specifically, these recent data

showing a difference in cardiovascular safety in long-term studies versus placebo do, in fact, suggest a class effect.

Despite the large size of the original development program, over 10,000 patients, approximately 5,800 of which were receiving etoricoxib, there are limitations on the amount of accrued cardiovascular safety data. Specifically, the long-term data were limited in quantity, and limited primarily in comparison to naproxen.

Because of questions raised with respect to naproxen, we decided we needed a different approach to accrue additional data, and I would now like to review the strategic approach we took and then discuss the specific studies that resulted.

Our primary objective was to further establish the long term general and cardiovascular safety of etoricoxib in arthritis patients who required treatment. At the time the strategy to meet this objective was formulated, there were ongoing long-term placebo-controlled studies with other selective COX-2 inhibitors, largely focusing

on exploring novel indications for cyclooxygenase-inhibiting therapies. Examples include Alzheimer's disease and chemoprevention.

For etoricoxib, rather than explore novel indications with placebo-controlled studies, we chose to further evaluate the group of patients who required treatment for arthritis. Therefore, the plan we developed was to perform active comparator-controlled studies in osteoarthritis and rheumatoid arthritis patients.

Studying this patient population ethically precluded use of a placebo for more than a short period of time, because these patients require active treatment. Diclofenac was chosen as the active comparator, and I will review our rationale for that choice shortly.

Although the recent study results with rofecoxib and celecoxib were not available when we designed the studies that I will be describing shortly, our studies are extremely relevant as they compared etoricoxib to diclofenac and thus address the current clinical question of comparative

cardiovascular safety between a selective COX-2 inhibitor and a traditional NSAID.

In order to choose an appropriate comparator NSAID, we established criteria and evaluated numerous agents and ultimately determined that diclofenac was the most suitable choice.

Diclofenac is effective in treating both osteoarthritis and rheumatoid arthritis patients and can be dosed twice daily, which enhances compliance and convenience for the patient.

Secondly, it has been established that diclofenac does not interfere with low-dose aspirin's anti-platelet effects. Ibuprofen, on the other hand, does interfere with low-dose aspirin's anti-platelet effects.

This interaction posed two issues we felt precluded use of ibuprofen as the comparator. We were not comfortable enrolling patients who required low-dose aspirin with knowledge that its anti-platelet effects could, in fact, be inhibited, and secondly, we were concerned that interpretation of study results, which showed comparable

cardiovascular safety, to an agent that inhibits aspirin's anti-platelet effects could be problematic.

Diclofenac inhibits both COX-1 and COX-2 and confers partial inhibition on platelet-mediated COX-1 thromboxane. Since it lacks potent and sustained anti-platelet activity, we would not expect confounding effect on the interpretation of cardiovascular safety results as would be expected with naproxen based on the cardiovascular data from the development program which I presented.

Data from some of our clinical trials indicate that diclofenac's effect on blood pressure is generally similar and, in fact, in some cases more pronounced than the effect observed with etoricoxib.

In consideration of the established cardiovascular complications of elevations in blood pressure, a comparison of thrombotic cardiovascular safety between etoricoxib and diclofenac can, in fact, be considered conservative.

I wanted to briefly review some

pharmacodynamic data which supports diclofenac having COX-1 inhibiting effects. Represented on this slide are the ex-vivo COX-2 and COX-1 inhibiting effects of various agents.

Displayed on the X axis is the percentage of COX-2 inhibition as measured by inhibition of lipopolysaccharide-induced serum PGE 2. Displayed on the Y axis is the percentage of COX-1 inhibition as measured by serum thromboxane as a weighted average at steady state with 84 percent joint confidence regions around the point estimate of the mean.

Rofecoxib at 12.5 and 25 mg inhibits COX-2 on the order of 60 to 70 percent in this experiment. Diclofenac at a dose of 150 mg inhibits COX-2, but also inhibits COX-1.

Endoscopic data are also available which support the COX-1 inhibiting effects of diclofenac. Shown here are results from two endoscopy studies performed with valdecoxib which included a diclofenac treatment arm. In each case, the cumulative incidence of gastroduodenal ulcerations

observed at the end of the study period are displayed by treatment group in these two studies.

On the left are results of a 26-week study of rheumatoid arthritis patients. The incidence of gastroduodenal ulcerations observed on diclofenac was significantly greater than observed on either dose of valdecoxib in this study.

On the right are results of a 12-week study in osteoarthritis patients. The incidence of gastroduodenal ulcerations on diclofenac was significantly greater than placebo and valdecoxib, and, in fact, similar to the incidence observed on ibuprofen.

Lastly, I would like to point to some GI clinical outcomes data which also support the COX-1 inhibiting effects of diclofenac. Dr. Braunstein reviewed the cumulative incidence of confirmed upper GI clinical events of rofecoxib versus individual NSAIDs yesterday based on final data from the rofecoxib development program.

What I have done here is instead of looking at confirmed PUBs, I have also added the

confirmed plus unconfirmed results, which are very consistent with what Dr. Braunstein showed yesterday.

You see here the relative risk of confirmed plus unconfirmed upper GI events observed on rofecoxib is, in fact, significantly different than the effect observed with diclofenac, so again to provide some clinical data that support a COX-1 inhibiting effect of diclofenac.

The overall approach to further characterize etoricoxib that I have been describing consists of a prospectively designed analysis of cardiovascular safety data will accrue from three studies, which I am going to briefly review here.

All three studies compared etoricoxib to diclofenac. The first is the EDGE study, a study of 7,111 osteoarthritis patients with a primary objective to compare the GI tolerability of etoricoxib to diclofenac. This study is now complete.

Secondly, EDGE II, a study of approximately 4,090 RA patients with a primary

objective identical to that of EDGE. The dose of etoricoxib in EDGE II is 90 mg. This study is fully enrolled and ongoing. The predicted mean duration of this study is expected to be approximately 19 months.

Thirdly, MEDAL, a study of approximately 23,450 osteoarthritis and rheumatoid arthritis patients with the primary objective of comparing the cardiovascular safety of etoricoxib to diclofenac. This is an endpoint-driven outcome study. MEDAL is fully enrolled and currently ongoing. The predicted mean duration of therapy in MEDAL is approximately 20 months with some patients expected to be on therapy an excess of 3 years.

Although EDGE and EDGE II are designed as primary GI tolerability studies, the cardiovascular safety data that will accrue from those two studies are being adjudicated and will be combined with the cardiovascular safety data from the MEDAL study in order to improve the precision of the comparison.

The primary hypothesis for this analysis is that etoricoxib will demonstrate a

cardiovascular safety profile that is non-inferior to that of diclofenac. There are 2 key analyses that are designed to support this hypothesis.

The primary analysis will consider the minimum required 635 confirmed thrombotic events from all 3 studies combined, and the secondary analysis will consider the minimum 490 confirmed thrombotic events that are required from the MEDAL study alone.

As I mentioned, MEDAL was designed as an endpoint-driven outcome study and on its own represents a sufficiently powered assessment of cardiovascular safety. The patient population that has been enrolled in these studies consists of patients with a range of baseline cardiovascular risk and includes patients with pre-existing cardiovascular disease.

As clinically indicated, such patients, as well as others, are being prescribed aspirin, so we expect the total study cohort to include approximately 30 percent aspirin users.

MEDAL and EDGE II will generate a

tremendous amount of long-term cardiovascular safety data. As summarized on the previous slide, the predicted mean duration of therapies in EDGE II and MEDAL are 19 and 29 months respectively, and it is predicted that out of the 635 confirmed thrombotic events, approximately 200 of those events will occur in patients who have been on study therapy for at least 18 months.

In this cohort alone, the minimum between treatment group difference that would be statistically significant expressed as a relative risk is approximately 1.3.

An external Data and Safety Monitoring Board was chartered to monitor emerging data from MEDAL, EDGE, and EDGE II. Since 2002, they have been meeting regularly, most recently in November of 2004, at which time they reviewed a large amount of data. At that time, in total, there were approximately 21,000 patient years of exposure and approximately 300 confirmed thrombotic events were available at that time for their review.

In addition, there were approximately

3,000 patients who had been on study therapy for at least 18 months at that time. Based on their review, their recommendation was to continue the ongoing studies without interruption or without modification.

Of the 3 studies that we have been discussing, EDGE is the first to be completed, and I would now like to review the cardiovascular safety data from the EDGE study.

In this study, the 7,111 osteoarthritis patients were on study therapy for a mean duration of approximately 9 months, resulting in approximately 5,400 patient years of total exposure.

The study population included patients with a range of baseline cardiovascular risk. Here are summarized some selected baseline characteristics. As you see, approximately 38 percent of the patients in this study were at increased baseline cardiovascular risk defined as patients having 2 or more risk factors for cardiovascular disease or a documented history of

symptomatic atherosclerotic cardiovascular disease.

This slide summarizes the cardiovascular safety data from the EDGE study by presenting again the point estimate of the relative risk and the corresponding 95 confidence interval, for confirmed thrombotic events versus diclofenac, for events which occurred on therapy or within 14 days of study therapy discontinuation, on study therapy or within 28 days, and importantly, an all patients treated analysis.

In the EDGE study, all patients who discontinued were followed up closely with regular phone contact to ascertain any events that occurred long term off-of-study therapy, and this was done for all patients until all patients had completed the study.

The cumulative incidence of confirmed thrombotic events in the EDGE study are summarized here, and indicate no evidence of a difference between the treatment groups over time.

This slide summarizes the specific confirmed events by type in the EDGE study

beginning with events which occurred on study therapy or within 14 days of discontinuing study therapy.

As you see, there are events reported in all 3 vascular events with more cardiac event overall irrespective of treatment group. Evaluation of individual event types indicates that the absolute number of any event was small with numeric differences between treatment groups for certain events with some occurring at a higher rate on etoricoxib and some occurring at a lower rate.

For example, differences were observed in ischemic strokes numerically favoring etoricoxib, however, differences favoring diclofenac were observed for acute myocardial infarctions. Neither of these differences were statistically significant.

It is important to remember that even in a study of this size, results at the level of individual events should be interpreted cautiously. For example, when looking at events which occurred on study therapy or within 28 days, as requested by

the agency, the numeric differences between treatment groups has, in fact, narrowed slightly due primarily to an increase in the number of acute myocardial infarctions which occurred on the diclofenac group.

Data from ongoing randomized clinical trials will be critical to more precisely assess the comparative rates of myocardial infarctions on diclofenac versus etoricoxib.

Summarizing results of the EDGE cardiovascular safety data next to the results of the pooled analysis that I presented previously indicate that the EDGE data are, in fact, consistent with, and add precision to, the observations from the pooled analysis when comparing etoricoxib to non-naproxen NSAIDs.

I would now like to summarize. We have demonstrated efficacy with etoricoxib that is similar and in the cases I have pointed out, in fact, superior to comparator NSAIDs particular naproxen 1,000 mg.

We have a GI safety program that did

demonstrate improved GI safety and tolerability in relation to shift to non-selective NSAIDs primarily in relationship to naproxen, and the renovascular effects observed with etoricoxib are, as again would be expected based on the mechanism of action dose related, but at the doses recommended for chronic use are, in fact, generally similar to the effects observed for the comparator NSAIDs.

We saw numeric differences against naproxen favoring naproxen, but we also saw rates of hypertension that were very similar to those observed with ibuprofen even at their maximal chronic dose.

Based on thorough and ongoing reviews of cardiovascular safety data, there is no clear or discernible difference between etoricoxib and non-naproxen NSAIDs up to a year. As I said, we have limited amounts of data beyond 1 year at this time.

Differences were observed between etoricoxib and naproxen rates of thrombotic events. Based on the data we have, the limited amounts of

short-term placebo data, there is no clear difference between etoricoxib and placebo. That being said, emerging data from long-term placebo-controlled studies with rofecoxib and celecoxib showing a difference in cardiovascular safety versus placebo do, in fact, suggest a class effect.

MEDAL, the largest NSAID trial known, and EDGE II are currently ongoing and based on current cardiovascular event rates are expected to be completed next year. Results from these studies will further characterize the cardiovascular safety of etoricoxib, and we will have data to address numerous questions including cardiovascular safety in both osteoarthritis and rheumatoid arthritis patients, and cardiovascular safety in patients with a range of cardiovascular risk, and will include experience in aspirin users and non-users.

We will be able to further explore the effect of dose as both 60 and 90 mg are included in the study, and perhaps, most importantly, the long-term cardiovascular safety will be assessed as

we will have large amounts of data in patients who have been on study therapy for at least 18 months.

These studies directly address whether the cardiovascular safety including the long-term safety of a selective COX-2 inhibitor, such as etoricoxib, is similar to or different than that of a traditional NSAID.

In countries where etoricoxib is currently approved, Merck has consistently taken a proactive approach with regulatory agencies. From the time it was first approved years ago, the etoricoxib product label has, in fact, contained a precaution for use in patients with ischemic heart disease.

We continue to work aggressively with regulatory agencies and are currently actively engaged with European regulators, and have participated in a referral process in Europe. Our goal there is to ensure that the product label accurately reflects all accruing safety information that is relevant to prescribers based on data that are currently available.

In conclusion, etoricoxib has a role among

the current treatment options for patients with conditions characterized by pain and inflammation. However, it is critical to ensure its safe and effective use, that a product labeling continues to be revised to ensure that all currently available data are incorporated to help guide appropriate use.

We remain committed to help address public health questions and currently, with etoricoxib, largely through the conduct of the MEDAL and the EDGE II studies. These questions posed yesterday include, For patients who require chronic anti-inflammatory therapy for established indications, what is the risk and benefit of a selective COX-2 inhibitor as compared to an NSAID?

MEDAL and EDGE II will provide information to this question in comparison to diclofenac, and I have provided you the data we currently have available that provides information relative to naproxen.

Other questions which remain at this time include Can patients at increased cardiovascular

risk be identified, so the benefit is maintained and the risk minimized?

MEDAL, again due to its unparalleled size, and with the additional data from EDGE II, will provide information and data to allow further exploration to help answer this question.

Next, Is the increased cardiovascular risk a class effect of COX-2 inhibition, and if so, how large is the class, and what are the long-term cardiovascular effects of a selective COX-2 inhibitor and traditional NSAIDs?

Again, MEDAL, with its long-term direct comparison to diclofenac, will provide information to address both of these questions.

This concludes my presentation. I would like to thank the Chairman, members of the Advisory Committee, the FDA.

Thank you.

DR. WOOD: Thanks a lot. Let's go straight on to the FDA's presentation.

FDA Presentation

Analysis of Cardiovascular Thromboembolic Events with Etoricoxib

Joel Schiffenbauer, M.D.

DR. SCHIFFENBAUER: Thank you and good

morning. My name is Joel Schiffenbauer. I am going to be presenting an analysis of cardiovascular thromboembolic events with etoricoxib.

I will be presenting the results of trials for the following indications listed here in the NDA. In addition, I will be presenting results of the EDGE trial separately from those of the trials here.

I will first present briefly exposure data followed by mortality data and then spend the remainder of the time discussing the cardiovascular thromboembolic events data. Again, I will present data first for the NDA and separately for the EDGE study.

First, exposure. This slide summarizes the chronic exposure to etoricoxib across the NDA. As you can see for the 60, 90, and 120 mg doses, which were the proposed doses for the drug, the

total number of patients is shown here and the mean number of days is shown here.

For the EDGE study, there was approximately 3,500 patients in each arm, exposed for a mean of 9 months. Total patient years is shown at the bottom.

Let me turn now to the mortality data. This is the mortality data across the NDA. Rates are shown as per 100 patient years, and I have listed the comparators here, placebo, non-naproxen nonsteroidals, and naproxen.

If we first look at the first line of total deaths, we can see that the rate of deaths in the placebo group is similar to naproxen, followed by the non-naproxen nonsteroidals, and then etoricoxib.

Let me next draw your attention to the third line, thrombotic cardiovascular deaths. There were no deaths in the placebo group, followed by naproxen, etoricoxib, and then non-naproxen nonsteroidals.

These 2 events I would point out occurred

at greater than 36 months exposure to the non-naproxen nonsteroidals, and I will come back to this point when I present the Kaplan-Meier analysis looking at non-naproxen nonsteroidals.

The deaths in the EDGE study, the total deaths are similar, 8 and 6, for cardiovascular thrombotic related, it was 3 and 1.

Let me now move on to a discussion of the cardiovascular thromboembolic events.

The sponsor proposed a composite endpoint, which you have already heard about, which included events related to the cardiac, peripheral, and cerebrovascular system. I will present results for both the composite, as well as the components of the composite, and I think this is an important point because we do not yet know the effects of COX-2 inhibitors on each of these specific cardiovascular events.

In addition, I will not present data for APTC events or investigator-reported events. Although the numbers vary slightly, the trends are always in the same direction as the events that I

will show here.

These events were referred to an Adjudication Committee, that you have heard about already, and after being reviewed in that committee, were then described as confirmed cardiovascular thromboembolic events.

This slide shows an analysis of the confirmed thrombotic cardiovascular serious adverse events across the NDA. This is exclusive of the EDGE study. The sponsor performed 3 comparisons - etoricoxib to placebo, etoricoxib to non-naproxen nonsteroidals, and etoricoxib to naproxen.

The number of patients, the cases in patient years of exposure is shown here, rates, and relative risk. I will show this slide over again.

First, let me start on the first line. I draw your attention to the rate of events in the etoricoxib group 1.25 versus placebo 1.19 for the relative risk shown here, and an analysis of those events is shown in this slide.

These are the rates I showed you, 1.25 and 1.19. There were a total of 7 patients in the

etoricoxib group versus 4 in placebo, and this breaks down to 4 cardiac events, which are listed here - MI, fatal MI, unstable angina, and sudden death versus zero in placebo.

The number of events in peripheral and cerebrovascular are similar although the rates do vary slightly.

Let me point out here that in some of these slides, these numbers will not necessarily add up. That is for two reasons. One is an individual patient may have more than one event, and they would therefore be listed in more than one category, and, secondly, for the sake of clarity and brevity, I left out in some instances all the events.

This is the Kaplan-Meier estimate of time to event for the placebo comparison. Note that this is only 3 months in duration. There are very little differences between the two groups.

Let me move on then to the etoricoxib/non-naproxen comparisons. Here is the rate, 0.79 and 0.80, and I will show you that in

next slide. Here are the rates again, 0.79 and 0.80. These are composed of 12 patients in the etoricoxib group versus 4 in the combined, and by that I mean combined exposure to diclofenac and ibuprofen. You can see, however, exposure to ibuprofen is rather small and there were no events, so all of the events come from the diclofenac exposure.

If we examine the breakdown of these 12 events, you can see there were 11 cardiac events in the etoricoxib group for the rate shown here versus 2 in the combined for this rate, and that is further broken down to 3 MIs versus zero, 2 and 1 of fatal MIs, and then the rest you can see here. There are 2 and 2 events in the cerebrovascular system.

You have seen this previously, but let me make several points about this Kaplan-Meier analysis for the non-naproxen and nonsteroidal comparisons. First of all, you will note that the length of exposure is out to 36 months when there are relatively few patients still present in the

studies.

Secondly, there were 4 events in the non-naproxen nonsteroidals, which is shown by the solid line. Three of those events occurred at greater than 36 months exposure. Two of those 3 events were the deaths that I described in the earlier slide.

In contrast, there were 12 events in the etoricoxib group, 11 out of those 12 events occurred at approximately 26 months or earlier. So, there is a difference in the time to event as demonstrated by this Kaplan-Meier analysis.

Lastly, let me turn to the etoricoxib/naproxen exposure. Here are the rates, 1.37 and 0.81. Again, here are the rates, 1.37 and 0.81. There were 34 patients in etoricoxib versus 14 in naproxen, and that is broken down into 21 cardiac versus 9 for the rate shown here, 10 MIs versus 5, and you can see the remainder.

For peripheral, there was a slight imbalance, 5 events in naproxen versus 2 in peripheral, however, when we come back to the

cerebrovascular system, there were 12 versus 2, which included 10 ischemic strokes versus zero. Again, you have seen the Kaplan-Meier analysis, which shows a separation of the two curves almost throughout the entire exposure.

Let me turn now to the analysis of cardiovascular events in the EDGE study, and start by making a few points. There were 7,100 patients. It was designed as a GI tolerability study in which cardiovascular data was collected.

The sponsor defined a non-inferiority margin to diclofenac for cardiovascular events as the upper limit of the 95 percent confidence interval for the hazard ratio of 1.3.

In addition, there were several concerns that I would like to emphasize. First, it was designed as a non-inferiority trial, there was no placebo. Diclofenac was the only comparator, and as we have heard here, and there is data in the literature to support the relative COX-2 selectivity of diclofenac.

Next, there were only osteoarthritis

patients studied. There were no rheumatoid arthritis patients in this study. We know that rheumatoid arthritis itself confers cardiovascular risk.

The next two bullets relate to maneuvers that could potentially, in the context of a non-inferiority trial, make it difficult to identify differences between the two treatment groups.

So, for example, there was 30 percent aspirin use. If we believe that aspirin is cardio-protective even in the context of COX-2 inhibitor, this could make it difficult to discern any differences between the two groups.

In addition, previous COX-2 use was allowed, and I have listed here what that was, and this could potentially lead to depletion of susceptible individuals to a cardiovascular event.

Lastly, although it is important to study high-risk patients, if these high-risk patients are on aspirin, that may be a problem in differentiating the two groups. In addition, if

there are more events in these high-risk patients, it could increase the background events, and again in the context of a non-inferiority trial, may make it difficult to differentiate the two treatment groups.

So, you have seen this Kaplan-Meier analysis. Again, the two groups separate slightly, but the two curves do finally converge at approximately 12 months.

This is a breakdown of the events in the EDGE trial. There were 35 patients in the etoricoxib group versus 30 in diclofenac for the rates given here. If we look at a further breakdown of the components, we see there were 27 cardiac-related events versus 19 for the rates given here. For MI, there was 19 versus 11. For cerebrovascular events, there was 7 and 7 with a slight imbalance in ischemic strokes of 6 in diclofenac versus 3 in etoricoxib.

I think it is important, I mentioned earlier that aspirin use may be a problem. I broke down the number of events by aspirin and

non-aspirin users, and I have just provided the number of events, the patient years of exposure are fairly similar.

You can see that by aspirin users, there is little differences between the groups, 12 versus 9 here for cardiac events, 7 and 5. However, when you look at the non-aspirin users, the differences are more pronounced. There were 15 cardiac events in etoricoxib versus 10 in diclofenac, and 12 MIs versus 6.

There was some concern about hypertension. Some issues were raised about that yesterday. I show some data for hypertension-related adverse events in the EDGE trial. These types of adverse events could include anything from a hypertensive crisis, malignant hypertension to systolic blood pressure increase among other events.

This is an analysis of patients with serious hypertension-related adverse events. There were 5 in etoricoxib versus 2 in diclofenac, and then another category, hypertension-related AE associated with systolic blood pressure greater

than 180, or diastolic greater than 110, and there were 69 cases here versus 30 in diclofenac.

Then, this is a cumulative incidence of new use of anti-hypertensive medications. The upper line is etoricoxib, the lower line is diclofenac. You can see that the two curves separate almost throughout the entire 12-month period.

Lastly, a description of congestive heart failure-related adverse events. This is the incidence of CHF pulmonary edema-related or cardiac failure adverse events. There were 14 versus 6.

In summary, in the NDA, etoricoxib trends worse in terms of cardiovascular thromboembolic events, particularly cardiac and MI. The one common thread throughout all the comparators does appear to be the cardiac system.

There are differences in the cerebrovascular or peripheral system, but those are inconsistent depending on the comparator.

Comparisons of etoricoxib to naproxen for the cardiovascular events is similar to what you

have seen for rofecoxib and the naproxen comparisons.

I have outlined some trial design concerns in the EDGE study, which I presented, and as you have already heard, there are two ongoing trials of similar design, which I believe have similar concerns.

There are trends in the EDGE study for cardiac events, worse for etoricoxib, and that is seen mainly in the non-aspirin users.

Thank you.

DR. WOOD: Thanks very much.

Let's go straight on to the Novartis talk and we recognize that will finish a little late, but we will have a shorter lunch break.

Lumiracoxib

Lumiracoxib: Introduction

Novartis Pharmaceuticals Corporation

Sponsor Presentation

Mathias Hukkelhoven, Ph.D.

DR. HUKKELHOVEN: Thank you.

Dr. Wood, Dr. Gibofsky, Dr. Gross, members

of the FDA Advisory Committees, FDA, and Guests: Good morning. My name is Mathias Hukkelhoven and I am responsible for Global Regulatory Affairs at Novartis.

On behalf of Novartis, I would like to thank you for the opportunity to review the gastrointestinal and cardiovascular safety data that we have gathered in our clinical development program for lumiracoxib.

As a part of the program, we have also gathered one of the largest databases of clinical trial data with ibuprofen and naproxen.

Allow me to remind you of the reason that the COX-2 selective NSAIDs were developed. In the U.S. alone, there are approximately 100,000 hospitalizations, and as we heard yesterday, 16,000 deaths annually that are caused by GI adverse events. Deaths due to NSAIDs are among the leading causes of death in the U.S.

Our presentation will make the following key points. Each non-selective NSAID and COX-2 selective inhibitor has a benefit-risk profile that

must be considered individually.

The Novartis development program provides clinically informative safety data for lumiracoxib as well as for ibuprofen and naproxen.

The GI and CV safety profile for lumiracoxib differs from non-selective NSAIDs and other COX-2 selective inhibitors.

We have investigated the use of lumiracoxib for several indications, but our presentation today will focus on the safety data accumulated for chronic indications. We have conducted 22 clinical trials of 1 week or longer in which 34,000 patients were enrolled.

The largest of the clinical studies was the TARGET outcome study. This is the largest outcome study ever conducted for an NSAID or COX-2 selective inhibitor with 18,325 patients enrolled. It is important to note that this study was conducted at 400 mg daily dosing, which is 4 times the dose for which approval will be sought.

This 1-year study compared lumiracoxib to two different NSAIDs - naproxen and ibuprofen.

We will also present a meta-analysis of cardiovascular safety of all 22 long-term lumiracoxib studies.

Our presentation will demonstrate that there is a definitive GI benefit with lumiracoxib in the non-aspirin population. In addition, the CV meta-analysis of all lumiracoxib studies at no point revealed a significant CV risk.

I would like to introduce today's presenter Dr. Patrice Matchaba from our Clinical Research Department. In addition, we have a few advisers with us who will be able to answer specific questions. These are Dr. Michael Farkouh, a cardiologist from NYU; Dr. Raymond Hirschberg, a nephrologist from UCLA; and Dr. Thomas Schnitzer, a rheumatologist from Northwestern.

Drs. Farkouh and Schnitzer were the lead authors on the TARGET CV and GI publications that were published this past September in the Lancet.

I would now like to turn the podium to Dr. Patrice Matchaba.

Gastrointestinal and Cardiovascular Safety of Lumiracoxib, Ibuprofen, and Naproxen

Patrice Matchaba, M.D.

DR. MATCHABA: Thank you to the Chair, thank you to the Committee, the FDA, and the public for inviting us. Just to state that for this purpose, we will be discussing the cardiovascular

and GI safety data from the TARGET study, but we are certainly willing to answer any question related to an end organ, and that we have published the data in TARGET in the Lancet, two papers.

We have two of the key primary authors for the GI and other adverse events of safety profile, we have Dr. Schnitzer, and for the cardiovascular paper we have Dr. Michael Farkouh.

Before we got into the TARGET data for cardiovascular and CV, I think it is important underlie that when the TARGET study was designed, that the VIGOR study and the CLASS study had been completed, and that the discussion for the TARGET design occurred between health authorities including advice sought from the Arthritis Advisory Committee in September 2001, because there were

important public health questions that were asked after the CLASS study and the VIGOR study.

Some of the key issues or principles that then drove the design of the study, the first point was that we should designing studies to detect a difference in ulcer complications because that was the COX-2 promise.

As a result, more patients were required because this event, as Dr. Cryer had discussed yesterday, is a fairly rare event, about 1 percent of patients, that the patient numbers required increased to about 18,000 patients in TARGET.

The second point was that in this population of patients that we studied in terms of osteoarthritis, that they do take low-dose aspirin, so we stratified patients to low-dose aspirin, and we managed to get a 24 percent stratification, and obviously, because of the impact of low-dose aspirin on GI outcomes, this necessitated an increase in the size of the study.

The other point that had been made from the previous two studies, that the median duration

was short. If you recall, the VIGOR study had a median duration of about 9 months, and the data that we saw for CLASS was 6 months, whereas, in TARGET, we had a fixed term design of 12 months.

The other design principle that was important, and we have heard this data discussed extensively, was that not all NSAIDs are the same in terms of COX-1 and COX-2 activity and that we will see differential GI and CV effects because of that.

So, we chose two NSAIDs that should have a different impact on the GI and the CV, and addressed that question as to what is the difference between coxibs, and in this case, lumiracoxib between naproxen and ibuprofen.

Finally, there was a need to prospectively define an adjudicate all outcomes, so we had three Adjudication Committees, one for the cardiovascular outcome, the other one for the CV, and the other one for the hepatic events.

In terms of the objective, it was to compare lumiracoxib at 4 times the proposed OA

dose, 400 mg. to naproxen 500 mg bid, and the dose is important here, because this is the dose and the dosing frequency that people have discussed in terms of a possible anti-thrombotic effect, and ibuprofen at 800 mg 3 times a day.

Key inclusion criteria that I think are important for the endpoints is that patients who had a previous history of a cerebrovascular or ischemic event in terms of cardiac events were allowed into the study if the event occurred more than 6 months before they entered the study and if they had been on low-dose aspirin for 3 months in order to stabilize the patients, and this is the advice and the current thinking that was there in terms of patient safety if you are going to conduct a 1-year study.

From a GI perspective, a key exclusion criteria was that any patients who had active GI ulcerations 30 days previously were excluded, and any patients who had a GI bleed in the previous year were excluded because the thinking again was that with the availability of PPIs and high-dose H2

antagonists, that enrolling these patients that required long-term treatment would have been an unethical thing to do.

So, the study design were 2 studies that were identical, lumiracoxib compared to naproxen in 1 study, and compared to ibuprofen in the other study. You will note that the 2 studies are of similar size, about 9,000 patients in each study, and that the studies went on to 52 weeks or 1 year with a follow-up at 56 weeks or at 1 month.

The key thing to note also is that the naproxen sub-study started recruitment 4 to 5 months before the ibuprofen sub-study, and that different centers were used for the 2 studies. So, you may see differences in the baseline risk for the endpoints that we will be discussing.

For cardiovascular and for this particular discussion, as I said, we had a pre-defined and prospectively adjudicated CV endpoints that included important coronary cerebrovascular and also the peripheral events.

In terms of the patient demographics, the

majority were female an average age of 63. We managed the 24 percent aspirin stratification. Of importance is that within this cohort of 18,325 patients, about 12 percent of these patients had a high CV risk as defined by a previous cerebrovascular or cardiac history or by Framingham risk equations.

The patients were fairly representative of an OA population. We had hypertensive patients, diabetics, and patients with dyslipidemia. Very importantly, because it was fixed term design, 60 percent of the patients finished the 12 months, a total of about 11,000 taking treatment for 12 months.

For the primary endpoint, which was ulcer complications, or perforations, obstruction, and bleeds in the non-aspirin population, it was a relative risk of 0.21 or a 79 percent reduction if you compared lumiracoxib to all NSAIDs.

If you made that comparison by sub-study, it was an 83 percent reduction compared to ibuprofen, and 76 percent reduction compared to

naproxen.

So, although we have 2 different NSAIDs with different COX-1 and COX-2 activities, this the first GI outcome study that looked at ulcer complications as a primary endpoint and shows definitively a reduction in ulcer complications for lumiracoxib compared to the NSAID studied.

A lot of the discussion, because if you recall, we have stratified patients to low-dose aspirin in the 24 percent of patients, about 4,000, and the question was, and is, what is the impact of low-dose aspirin on this outcome, and we will also discuss the CV outcome.

Now, if you look at the ulcer complications in the low-dose aspirin population, and I have tried to show you an analytic figure here, is that for the upper GI ulcer complications, there was a relative risk of 0.79 with wide confidence intervals crossing the line of no difference with a point estimate showing a 21 percent reduction.

What we have done, however, for this

discussion is to say when we consider more events, ulcer complications and symptomatic ulcers, is the point estimate still favoring lumiracoxib and does the confidence interval tighten in terms of the precision, and you can see that the reduction increases to 27 percent, but the confidence interval certainly still crosses one.

In this context, it is important to remember that the TARGET study wasn't designed to show a difference in the low-dose aspirin population, but was designed to show a difference in the non-aspirin population, and it cascaded to the overall population if the first result was positive.

But what is encouraging is the consistent trend that we see in this population.

There was discussion yesterday about do coxibs, in this case lumiracoxib, does it still show benefit in patients who have a high GI risk, and this was prespecified in the TARGET analysis, and high GI risk, there were 5 categories of risk defined, age greater than 65, low-dose aspirin use,

a history of ulcers or bleeds in H. pylori-positive patients.

When we do the analysis, taking one risk into consideration, you see that the magnitude of about a 3-fold reduction in favor of lumiracoxib for ulcer complications is maintained. If we have time later on, we can also show you the data for patients greater than 65, for patients who were H. pylori-positive, but because of the exclusion criteria that I outlined beforehand for patients who had a previous bleed, the numbers become smaller and smaller when we look at further increasing risk for these patients.

So, in summary, for the GI data, the TARGET study definitively shows benefit for patients taking lumiracoxib compared to these 2 different NSAIDs, ulcer complications in the non-aspirin population. We have seen the high risk or high GI population as defined in TARGET, and we see a consistent trend although it is not significant because of the numbers in the patients taking low-dose aspirin.

The cardiovascular endpoint that was chosen at that time was the APTC endpoint. Certainly, all the other cardiovascular events were

also adjudicated, peripheral events, pulmonary embolism, deep vein thrombosis.

At the time we published the data, and as prespecified in the protocol, the plan was to compare lumiracoxib to all NSAIDs for the APTC endpoint, but for the purpose of this discussion, if we do that, we fail to disaggregate the relative results for lumiracoxib compared to naproxen and compared to ibuprofen.

So, we will discuss the separate studies, but, first, you will see that when you compare lumiracoxib and NSAIDs, that there is no difference in the APTC endpoint throughout the 12-month period, but there is greater data and more insight to be mined when you look at the 2 studies separately. That is the current debate.

Before we look at the data, look at the baseline demographics. If you recall, these were 2 parallel studies, recruiting at different centers,

different time points, identical in design, but what you can see is that for the endpoint that may have an impact on the rate of cardiovascular events in the 2 studies, that there seems to be differences in the low-dose aspirin use, for the naproxen sub-study, patients who were high CV risk and patients with baseline hypertension.

For the high CV risk patients, in terms of patient numbers, this translates to about 140 patients difference. Now, this may or may not be a factor in terms of looking at the differences in rates, and there are other factors certainly that we may not have measured that could impact on the differences in rates.

So, we will look at the ibuprofen sub-study first and look at the APTC endpoints, myocardial infarcts, look at stroke, look at the cardiorenal complications, congestive heart failure, and a combined endpoint, and just to state that in terms of all-cause mortality, there were 29 patients who passed away in the lumiracoxib study arm and 30 patients in the NSAIDs, and when you

split it up between the 2, there was essentially no difference.

So, for the APTC endpoint, looking at lumiracoxib versus ibuprofen, if you start off with the overall result, in other words, all patients including those who took low-dose aspirin, you can see that the hazard ratio for all populations studied are consistently less than 1.

The other point that I want you to see is that in the non-aspirin population, the number of events are the same with a hazard ratio of 0.94. There is certainly a lot of discussion and this was thought to be part of the value of looking at the TARGET data to ask what happens in the low-dose aspirin population where you have this possible interaction with ibuprofen.

You see in this population that there were 6 events in lumiracoxib and 10 in ibuprofen. This difference, however, was not significant, and you will see when we look at myocardial infarct, that the number of events in this population when you look down to myocardial infarcts, are not enough to

definitively contribute to this debate about the interaction of low-dose aspirin and ibuprofen, but certainly all the data in this 8,600 patients studied do not indicate that lumiracoxib is any different from ibuprofen in terms of the APTC endpoint or cardiovascular risk.

For myocardial infarcts, going through the same analysis, the overall population, 5 versus 7, again, you see the hazard ratio of consistently less than 1. The number of events are low. In the non-aspirin population, 4 versus 5, and as I pointed out, in this aspirin population, 1 versus 2, so difficult to comment and to contribute to the debate about myocardial infarct and ibuprofen interaction.

For stroke, again the number of events were low, 8 versus 9, no real difference, 6 versus 5, and 2 versus 4 in the aspirin population, lumiracoxib 2 events, and ibuprofen 4 events. So, again from this data, 8,600 patients treated for 1 year, no indication that lumiracoxib is any different from ibuprofen in this robust data set.

I think it is important to recall that this study, in terms of patient exposure and patient numbers, is larger than the VIGOR or the

CLASS study in itself in terms of exposure.

The real differences we see in the TARGET study is in hypertension, and there has been a lot of debate yesterday about the possible impact of hypertension as a risk factor in contributing to an increase in strokes and myocardial infarct, and cardiovascular morbidity.

If we look at the cumulative incidence of new onset hypertension or de novo hypertension, you can see that over the study period, 360 days, that the patients taking ibuprofen have a significantly higher incidence of new onset hypertension compared to the patients taking lumiracoxib. This is percentages, number of patients.

So, it is about 10 percent of patients with new onset hypertension with about 6 percent of patients.

For a similar analysis looking at aggravated hypertension, if you recall in our

demographic analysis, about 45 percent of the patients in the TARGET study were hypertensive. In terms of aggravation or worsening of the hypertension, you see exactly the same trend between lumiracoxib and ibuprofen, which was significant.

If we look at the mean difference over the entire study period, again comparing lumiracoxib and ibuprofen for blood pressure, we see a systolic of 2.7 for patients taking ibuprofen compared to 0.7, and we see almost a 1 millimeter increase in blood pressure for patients taking ibuprofen with a zero mean increase for patients on lumiracoxib, and these differences again are statistically significant.

There was a lot of debate yesterday as to the possible cardiorenal implications of this in terms of edema, congestive heart failure, and weight gain, and if you look at the data in TARGET for this sub-study in terms of edema, no significant differences between the comparators, but for edema and congestive heart failure, you see

that there are more patients taking lumiracoxib with edema, congestive heart failure, but no difference for weight gain.

There was discussion previously about how do we assess benefit-risk. There was discussion also yesterday that any advantage that was shown in terms of GI ulcer complication reduction with rofecoxib in VIGOR was negated by an increase in CV events.

We prespecified, and this is not a validated way of analyzing benefit or risk, but at least we prespecified this outcome to say if we combine ulcer complications as defined by perforation, obstruction, and bleeds, and combine them with the primary cardiovascular endpoint, of the APTC endpoint, what is the trend compared to the lumiracoxib and ibuprofen, and this is the endpoint that I am showing you for the non-aspirin population, that patients taking ibuprofen are significantly worse for this combination of the 2 endpoints of GI ulcer complications and APTC.

Certainly, this is the first time that

this has been done in an outcome study in arthritis, but we hope that this will contribute to the discussion in terms of getting an overall assessment for benefit for the patients with osteoarthritis.

If you look at the overall population, this difference is still significant with a 50 percent reduction, but if you look at the aspirin population alone, the significance disappears as would be expected.

So, in summary, in this patient population of more than 8,500 treated and randomized to treatment for 1 year with these doses of lumiracoxib and ibuprofen, if we look at the APTC endpoints, myocardial infarcts, and stroke, the hazard ratios are consistently less than 1.

We see significant differences in hypertension, and obviously, hypertension in the long term, as discussed yesterday and today, may be an impact on CV adverse events for patients with osteoarthritis.

We have also seen that there isn't an

increase compared to ibuprofen for congestive heart failure and for edema, and as for the combined safety endpoint, there is a significant benefit for patients taking lumiracoxib.

So, we will now look at the naproxen sub-study and go through the same analysis, APTC endpoint, myocardial infarct, stroke, cardiorenal, the combined endpoint.

What you see immediately is that for this sub-study, that the number of events is much greater than the ibuprofen sub-study. Also, what you see is that the hazard ratios are now in favor of naproxen, and there are more events with the lumiracoxib compared to naproxen.

You will see when we look at the next slide, and we look at myocardial infarcts, you will see that this is driven by the differences in myocardial infarcts particularly in the non-aspirin population.

So, if we look at the non-aspirin population, patients taking lumiracoxib, 10 myocardial infarcts, clinical and silent, compared

to 4 in the naproxen population, a hazard ratio of 2.37, but which is not significant over the 12-month treatment period.

But the robustness and I think the value that TARGET adds to the debate is that because we stratified 24 percent of the population to low-dose aspirin, when you look at the aspirin population, you see the numeric difference or the hazard ratio decreases in this population.

Now, low-dose aspirin we all agree has COX-1 activity, irreversibly binds to the platelet, and it may contribute to 10 to 30 reduction in myocardial infarcts.

The question then was asked when we look at this data, and this is the data that we present to you, is that if it's COX-1 activity of low-dose aspirin that is negating the differences in terms of myocardial infarct, the implication therefore that naproxen at 500 mg dose taken twice daily in a clinical trial situation to ensure compliance, and there is certainly pharmacological data that shows that this dose has got anti-thrombotic and platelet

aggregation activity, that naproxen must have significant COX-1 activity.

There has been extensive debate this morning about observational studies, the merits of them, and looking at the naproxen and non-naproxen data, but this paper published by June in Lancet last year, looking at all the studies, observational studies, and this is not the rofecoxib analysis, but just the observation studies looking at naproxen.

We can see that when you combine all the data, that the diamond at the end here shows a 14 percent reduction in myocardial infarcts with a confidence interval that doesn't cross the line of no difference or 1.

The point I think was made by a member of the panel that in observational studies, that the dose that is taken could be less than the 500 mg dose, and that the dosing interval would not be the regular dosing interval that you see in clinical trial situation.

I think Dr. Graham also made the point

that in that case, you would see the point estimates moving closer to 1 in terms of the real effect that you would see if it had anti-thrombotic activity.

So, you go back to the sub-study of naproxen and look at strokes, you see that in the non-aspirin population, small numbers, and the same thing in the aspirin population, so no significant differences, and the confidence intervals are crossing 1.

Now, again when we do the analysis for blood pressure, we see that there is significant difference in favor of lumiracoxib compared to naproxen. Now, if you recall in the VIGOR study, where they compared rofecoxib to naproxen, that the differences in blood pressure were the reverse, and that rofecoxib increased systolic and diastolic blood pressures, systolic by about 3 to 4 millimeters of mercury, and diastolic for this same comparator.

The caveats are there that these are different patient populations. The RA population

is a high-risk population, this is an OA population, but without the studies that compared directly COX-2s, this is the only way that we can make a cross-study comparison.

Again, hypertension may be significant as discussed in terms of long-term morbidity and mortality.

For the same analysis we did with the ibuprofen sub-study for de novo hypertension, and for new aggravated hypertension, no significant difference between lumiracoxib and naproxen although consistently, the lumiracoxib patients have less events over the 12 months.

This is again a revealing analysis if we look at the cardiorenal complications. For edema, slightly more patients having edema, 4.5 versus 4.2 percent, but we think what is encouraging is the no increase compared to naproxen for congestive heart failure.

Again, we saw in VIGOR, or if you look at the VIGOR data, that rofecoxib had more patients with congestive heart failure or pulmonary edema

compared to the same comparator, and we have not seen this is the naproxen sub-study, and weight gain, 8.1 percent versus 9 in favor of lumiracoxib.

For the same analysis we did for ibuprofen looking at this safety endpoint that we introduced and prespecified in TARGET, for ulcer complications and APTC in the non-aspirin population, again we see over time that notwithstanding the reduction that you get with myocardial infarcts with naproxen or when you add the 2 combined, that over time for patients with osteoarthritis, at the doses that we tested, that there is a significant reduction and benefit for patients taking lumiracoxib in the yellow line there.

So, in summary, these two studies, huge studies, 8- to 9,000 patients, randomized to 1 year, show interesting data, and the naproxen sub-study shows no significant increase compared to naproxen/lumiracoxib for the APTC endpoint, but we see these differences in myocardial infarcts with more events in lumiracoxib, but of key importance that when you consider the low-dose aspirin

population and you add COX-1 activity, that the numeric difference disappears.

From a public health perspective, still significant differences in blood pressure, no increase in cardiorenal or congestive heart failure with lumiracoxib as we saw in the other study, and the combined safety endpoint still significantly favor lumiracoxib.

Now, because the study included a certain number of high-risk CV patients, it allows us to look at a high-risk cohort within the TARGET study and follow them over the 12 months, and asked in this sensitive high-risk cohort of patients, what are the outcomes in terms of APTC and myocardial infarct, and we will discuss only the myocardial infarct for this high risk.

A total of over 2,200 patients, and these are patients who had a history of either coronary artery disease, a previous myocardial infarct, and other vascular events, and we added these patients to those who had a high Framingham, high risk, so over 2,200 patients treated for 1 year.

We look at the myocardial infarct data because we will probably glean more from looking at this specific endpoint than looking at APTC, but if

you have questions, we will address those questions.

But if you look at the overall population, these 2,200 patients, including those who were not taking aspirin and those who were taking aspirin, the naproxen sub-study, there were 7 myocardial infarcts in the lumiracoxib population compared to 5. Obviously, the number of events low, nonsignificant, and if you look at the ibuprofen sub-study, 1 in the lumiracoxib and 2 in the ibuprofen sub-study.

The question, and certainly there has been debate that by adding low-dose aspirin, which I think everybody thought it was a good idea in the year 2001 in terms of answering some of these biological questions on the impact of low-dose aspirin--

DR. WOOD: Hang on. You are getting well over time, so you can try and speed it up a bit.

Thanks.

DR. MATCHABA: Thank you.

But this population is an important population because these 646 patients have a high CV risk, but are not taking low-dose aspirin and are treated over 1 year. So, high CV risk and not on low-dose aspirin, and what you see is that in the naproxen sub-study, 2 versus zero, and 1 versus 1.

The last cohort are patients who had a previous myocardial infarct, randomized to treatment for 1 year, and there were 288 patients who had a previous myocardial infarct, and if you look at the repeat APTC events, for the naproxen patients, 6 events occurred versus 3 for the lumiracoxib, and certainly this is chance, because the number of events are low and the patient population is small.

But what we can comment is that we are not seeing an outstanding signal even in this high-risk population with all the limitations of the size of the analysis. So, that is the TARGET data.

Finally, we performed obviously a meta-analysis of all studies completed on the 30th of December last year. Math has already described

there were 22 of those studies. You can see from the analysis that 34,000 patients plus, 18,000 patient year exposure, that patients who were randomized to 1-year studies accounted for almost 90 percent analysis, so it's a fairly robust analysis.

If you look at the APTC endpoint, and notwithstanding all the discussion and comment that has come forth including from Dr. FitzGerald, that combining all comparisons is probably not the right thing to do, we did a comparison against all comparators.

Now, this is a cumulative meta-analysis and I will just quickly run through it. These are the studies that we have done from 2001 to 2004.

These are the cumulative patients you can see as we have added a trial, over 34,000. These are the events as events have occurred for APTC, 156, and we have added the events to try and get an

estimate as they have occurred, and you can see that the relative risk of 1.2 with a confidence interval crossing 1. This is against all comparators for the APTC.

We do the same analysis and we subtract naproxen, and when you do the same analysis without naproxen, you see the relative risk changes to 0.94, over 24,000 patients with cumulative event of 0.88. What you also see is that at no time in our development program have we seen a significant increase in risk.

If we look at myocardial infarct, same analysis against all controls, a relative risk of 1.28 crossing the line of no difference. A similar analysis minus naproxen again, and you see the relative risk goes to 1, 24,000 patients and 34 events.

For strokes, all controls comparison, a relative risk of 1.02, 62 events, and when we remove naproxen for the analysis, a relative risk of 0.84.

Now, this reduction that we are seeing in

the more robust data set with the meta-analysis is certainly within the bounds of the 10 to 30 percent benefit that you would expect from aspirin in the idea situation.

A specific question and the comparison has been made for the 2 studies, the naproxen sub-study versus the VIGOR, but just to point out, and we can have discussion if time permits, that the half-lives are different of this compound and the structure. Lumiracoxib has got a short half-life, and if the hypothesis that continuous prostacyclin inhibitor is important, this may be an important factor.

A median 9-month versus 12 months, seeing a significant difference with the caveats of the different populations, but not seeing it in a similar population not taking low-dose aspirin, and we have commented about the differences in the congestive heart failure and the hypertension, which we think plays a significant role with time.

The final slide I think has been discussed before in terms of prostacyclin, and if the Chair

and the committee decides we can discuss that more in detail, but the fact that the other NSAIDs also show a prostacyclin inhibition compared to the COX-2s.

So, in summary, we have seen that the meta-analysis is supportive of the data that we are seeing in TARGET. It's a robust meta-analysis, 34,000 patient. We are seeing that each time you removed naproxen from the comparison, you are getting your 10 to 30 percent difference and that at no time point during our development program have we seen a significant increase for the APTC endpoint.

Importantly, we are seeing no increase with lumiracoxib with congestive heart failure and hypertension.

The question was asked, and this obviously is the subject to further debate as to what do we think as a company going forward.

Thank you, Mr. Chair, and thank you, committee.

DR. WOOD: Great. Thanks very much.

We are going to break for lunch and I have to remind the members to turn in their dinner reservation form I guess to Kimberly, and we have a

table reserved for the committee members in the restaurant. We will be back here and start at 1 o'clock, so you had better grab it and eat.

(Lunch recess.)

A F T E R N O O N P R O C E E D I N G S

(1:04 p.m.)

Open Public Hearing

DR. WOOD: Let me begin by reading the conflict of interest statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsors of any products in the pharmaceutical category under discussion at today's meeting.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your

attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We are ready to go and let me give you the ground rules before we start, so that everybody understands. You get two minutes to talk. We have a light there that will go on. At 1.5 minutes it will be green, and then yellow, and then at zero, the microphone will go dead and only your lips will keep moving.

So, it is important at that point to sit down because the next guy is coming up to take that microphone.

Let's get started. I will be impolite enough to call you by number rather than by name because that is what I have here. If there are people who have registered to speak and have not

yet checked in, they need to go to the check-in desk outside and check in rapidly or someone else will get their spot.

Let's begin with Speaker No. 1.

MS. JOAN JOHNSON: Hello. I am Joan Brierton Johnson and this is my 7-year-old daughter Sabrina. She writes:

"Dear FDA:

When I was 6 years old, I had fun visiting my friends, playing computer games, and drawing lots of pictures. All of that ended when I came home from the first grade, not feeling very well.

My parents gave me Children's Motrin, but instead of getting better, I got Stevens-Johnson Syndrome.

Taking Children's Motrin is why I am blind today.

Now I wear a hat that covers my entire face - even indoors - because the light hurts my eyes. When I go outside, I get teased because of my hat. People say mean things to me about it and that really hurts my feelings.

I liked going to school, but my immune system is now so weak because of SJS that it is not safe for me to go anymore. I miss my friends.

Millions of kids all over the world are given Children's Motrin when they get sick. But it doesn't have a warning label on it about SJS.

I would like to ask the FDA to require a warning label about SJS on Children's Motrin and on any other drugs that can cause this horrible disease.

Thank you for considering my request.

Sabrina Brierton Johnson, age 7, Topanga, California."

Now, Sabrina would like to say a few words.

MS. SABRINA JOHNSON: Please do something so other children don't get hurt by Stevens-Johnson Syndrome like me. People really need to know about it. Thank you.

MS. JOAN JOHNSON: Thank you.

DR. WOOD: Thank you very much.

No. 2.

(No response.)

DR. WOOD: No No. 2. All right. Let's move on to No. 3, I know he will be here.

DR. WOLFE: Before the clock starts, I have no conflict of interest.

Four years ago, I testified before this

committee that FDA should require a black box warning on Vioxx and Celebrex because of significant evidence from the VIGOR study and trends in CLASS of increased cardiovascular risk.

What the FDA, the Advisory Committee, nor I knew then was that in the year 2000 Pfizer had finished a study, a placebo-controlled trial using Celebrex to prevent Alzheimer's disease progression and that the study had found increased cardiovascular risks for the drug.

What I did not know several weeks ago, when I made the results of this yet unpublished study public, was that the FDA had been provided the results of this study in June of 2001, even though they held back, Pfizer held back the study so that it wasn't discussed at the Advisory

Committee meeting four years ago, which would have presented a class effect for Vioxx and this drug.

FDA was concerned enough about this study that it presented it internally at a meeting in 2001, but never revealed the results to the public until yesterday in Dr. Witter's presentation, which acknowledged that in almost every type of adverse cardiovascular outcome, the cases occurred mainly in those using Celebrex, 3 cardiovascular deaths, non-fatal heart attacks, strokes, heart failure or angina out of 140 in the placebo group, 20 out of 285 in the Celebrex group.

Because of much prevarication, to put it mildly, by Pfizer yesterday, Pfizer testified under oath they might have been found to have committed perjury. I recommended today that Pfizer be criminally prosecuted for fraud to the U.S. Attorney's Office if they aren't already conducting such an investigation, and it appears that Senator Grassley's office will take up the investigation as to why FDA withheld this information for so long. I sent this testimony to them.

Given that Celebrex and Bextra are making an important contribution of the estimated 100,000 deaths and 2 million serious injuries a year from

adverse drug reactions, I hope you will recommend a ban of these drugs, not a don't use for more than 10 days.

DR. WOOD: Thank you.

No. 4.

MS. SUYDAM: Thank you for the opportunity to present an over-the-counter or OTC perspective on the safety of nonsteroidal anti-inflammatory drugs. The Consumer Healthcare Products Association is a national trade association representing manufacturers and distributors of OTC medicines and has a long history of working with FDA on important safety issues.

In considering the safety of NSAIDs, I ask the Advisory Committee to consider three important points.

First, the use of OTC NSAIDs clearly should be distinguished from long-term or chronic prescription use. OTC NSAIDs have a different

overall benefit-to-risk equation and a wider margin of safety because they are used at lower doses and are not intended to be used on a chronic basis unless directed by a physician and are used for mild, self-limiting conditions.

Second, OTC medicines differ from prescription drugs because the OTC label contains all of the information that consumers need to decide if the medicine is right for them, how to take the product, and when to see their doctor if needed.

OTC NSAIDs are not intended to be used for long durations unless directed by a physician, and this is clearly stated on the label.

Third, OTC NSAIDs are safe for consumer use when used according to label conditions. Every OTC NSAID has been extensively reviewed by FDA and FDA Advisory Committees. This review has confirmed that OTC NSAIDs are safe and effective and that the benefits of OTC use outweigh the risks.

In closing, it is important to clearly distinguish the benefit-to-risk equation for

prescription NSAIDs from that of OTC NSAIDs. The millions of consumers who rely on OTC NSAIDs for temporary pain relief should continue to feel confident that these medicines are safe and effective when used according to the label.

DR. WOOD: Thank you.

Jennifer Lo.

DR. LO: To facilitate the benefit and risk assessment of COX-2 inhibitor in each individual, we propose to the Committee a new test under development, iHAD test, used to assess the cardiovascular disease risk in patients taking COX-2 inhibitors.

Our test reveals the pathobiological effect of inflammatory mediators/inflammation related agents (IRAs) on each individual's vascular system ex vivo. Individuals found to be at high risk because they are likely to suffer the same pathobiological effect of IRSs if present under desirable conditions in vivo.

The ex vivo pathobiological effect may be quantified in the form of cytotoxicity which can be

revealed in 2 general categories: cytolysis and cyto-aggregation. The severity of cytotoxicity is used to determine the level of CVD risk of asymptomatic individuals. Individuals tested with a high risk may choose not to use COX-2 inhibitors. Others tested with a low risk may benefit from the use of COX-2 inhibitors with periodic retesting.

This picture depicts the cytolysis of cultured fibroblast induced by the basic nature of a protein like many inflammatory mediators.

The next picture depicts the cyto-aggregation of human blood cells induced by multiple IRAs. Phospholipase A2 is one of the many significant inflammatory mediators used in our assessment test.

This simplified proposed mechanism for Acute Coronary Syndromes (ACS) forms the basis of our new iHAD test, including the involvement of COX-2 inhibitors. Inflammation produces many IRAs and some of them are prothrombotic. PLA2 and other IRAs act on blood components to cause cell damage in the form of cytotoxicity.

Cytolosis may be responsible for rupturing atherosclerotic plaques, leading to thromboembolism, predisposing ACS.

Cyto-aggregation may lead to thrombosis, predisposing ACS.

COX-2 inhibitors prevent the synthesis of Prostaglandin (PGE2) that is responsible for triggering the pain, but they have no inhibitory effect on arachidonic acid (AA) a byproduct of phospholipase A2, which is also prothrombotic.

Our new iHAD test is intended to evaluate the response of individual blood cells to IRAs in assessing the baseline CVD risk based on the severity of cytotoxicity.

We urge all individuals taking the COX-2 inhibitors or considering taking the drug to take the iHAD test.

DR. WOOD: Thanks.

No. 6, Jim Tozzi.

MR. TOZZI: Thank you, Mr. Chairman, Distinguished members of the Committee. Having been a resident of New Orleans, I cannot speak that

fast, and I have burned up 10 minutes or 10 seconds

I am Jim Tozzi. I am the member of the Board of Advisors of the Center for Regulatory Effectiveness. The Center receives no funding from the pharmaceutical industry although a number of years ago we did receive grants from the industry.

The Center is a regulatory watchdog. To this end, we have a particular interest in the FDA compliance with the requirements of the recently passed Data Quality Act. When the agency makes determinations regarding the benefits and risks associated with the use of non-steroidal anti-inflationary drugs--sorry, I am an economist--anti-inflammatory drugs. They may be anti-inflationary, too.

The Data Quality Act required OMB and FDA to issue guidelines which would maximize the quality, the objectivity, the integrity, and the information FDA disseminates to the public.

So, you may be asking why am I here. Well, the guidelines require certain analytical results to be reproductive and

unbiased--reproducible and unbiased. The Data Quality Act places no requirements on the distinguished members of this committee, however, the FDA cannot rely upon the information it receives from the advisory committee unless the advisory committee information meets the requirements of the Data Quality Act.

Furthermore, any third party, such as CRA, can petition under this act for FDA not to use the results if they do not comply with the Data Quality Act, and I thank FDA for allowing--.

DR. WOOD: No. 7. Dianna Zuckerman.

MS. ZUCKERMAN: The National Research Center for Women and Families is an independent nonprofit organization with no conflicts of interest on this issue.

We focus on research, but we know that when Americans take medication, they don't expect to have to read the studies that have been conducted on the product, and their physicians don't expect to have to read them either, and the patients don't expect to have to carefully

scrutinize the fine print and personally weigh the risks and benefits.

They expect that medications that are FDA-approved are safe and effective for almost everyone and therefore safe for them.

So, please, when you vote tomorrow, please treat your votes as if they are the most important ones you will ever make, because there are a lot of people depending on you.

There is plenty to be concerned about regarding the medications that you are considering, but unfortunately, we don't have access to all the data that you have access to, so I am going to focus on the broader issue, which is the failure of the FDA to scrutinize long-term safety data.

This is a systemic problem and it will not be fixed by wishful thinking or by advisory panel instructions.

Unfortunately, drugs that are studied on a few hundred or even a few thousand people, for a few weeks or months, are then taken, as you know, by millions of people for many years. The FDA

really doesn't always know what the long-term risks are especially if the companies involved don't reveal all the information that they have.

The FDA should be requiring and carefully monitoring long-term studies of medical products that patients will rely on for a long time. Our Government needs to strengthen the FDA and other security checkpoints designed to protect us from those very real dangers.

In the meantime, please don't assume that the companies can be trusted to carefully conduct postmarket studies or that the FDA will enforce requirements to conduct such studies and act on their results in a--.

DR. WOOD: Thank you very much.

The next speaker is No. 8, Elizabeth Tindall.

DR. TINDALL: Good afternoon. I am Dr. Elizabeth Tindall and I am speaking today as a practicing rheumatologist from Portland, Oregon, and as President of the American College of Rheumatology. I have no consulting or financial

relationships with the companies or products being discussed at this meeting.

The ACR represents more than 6,000 physicians, scientists, and health care professionals who care for people with arthritis and other musculoskeletal diseases. Our members are actively involved in treating the estimated 70 million Americans who are affected by osteoarthritis, rheumatoid arthritis, and other musculoskeletal diseases for which traditional NSAIDs and COX-2 selective NSAIDs are used.

Limited and emerging data about the cardiovascular toxicity of COX-2 and non-selective NSAIDs, which has received widespread media coverage, has caused anxiety among the patients and the physicians who treat them. We are concerned that this controversy has damaged public confidence and trust in drug safety, and we believe the following points are central to the continued discussion of this issue.

First, the FDA should lead the effort to ensure that patients and the public are made much

more aware of the most common and serious toxicities of all medications including those of the traditional and COX-2 selective NSAIDs.

This information should be given to the public with information about what groups of patients may be at greatest risks including age and underlying comorbidities. That allows physicians and patients to make the best decision about their health care.

The American College of Rheumatology supports the FDA's efforts to ensure clarification of the most important drug toxicities in all direct-to-consumer advertising in print and broadcast media, and we also applaud the full disclosure of any advertising presented to the public as promotional educational material.

We also support the full disclosure of the test results of all industry-related trials for drugs that are FDA approved, so that public and scientific scrutiny may occur. We applaud the FDA in forming a new independent drug safety oversight board this week. This board must ensure that all--.

DR. WOOD: Thank you very much.

The next speaker is No. 9. Dimitra Poulos.

MS. POULOS: Good afternoon and I am here at my own expense.

Every time you take a drug, there is a risk factor to be considered. I believe it's important for the government to keep us informed on all drug findings and potential risks, so we are able to make informed decisions.

Cigarettes come with a warning label, there is no prescription needed for alcohol, yet taken by the wrong person, we are all at risk.

Liver is damaged from Lamasil and Lipitor, Coumadin is a risk of bleeding to death.

When I was diagnosed with rheumatoid arthritis in 1998, my life changed dramatically. Professionally, it had an impact on the quality of my work. Socially, I could no longer sit in a movie theater, take a walk, car trips to visit out-of-town family members was out of the question.

Personally, arthritis attacked my husband,

too. He had to assume most of my responsibilities for running the house. As daily functions became impossible for me, I needed his help to get dressed. On day he found me in the bathroom, on the commode, crying, unable to get off of it.

But that was before Vioxx. I have taken Vioxx for over 5 years with absolutely no side effects. Vioxx gave me my life back. We have no idea of the risks involved with any of the new drugs, but a known risk can be dealt with.

As I speak, I have 40 Vioxx left. I have 40 days before my life and my abilities will be severely altered.

I will assume all responsibility and sign any waiver. Please give me that option and thank you for allowing me this time.

DR. WOOD: Thank you very much.

The next speaker is No. 10, John Pippin.

DR. PIPPIN: Before the clock starts, may I mention my affiliations? I am here representing myself and the Physician's Committee for Responsible Medicine, a nonprofit. I have no

commercial affiliations.

While the primary focus of these meetings concerns whether the COX-2 inhibitors should be withdrawn from clinical use, we also must address the more fundamental problem regarding drugs developed and approved in the U.S., and that problem is how to identify safe and effective drugs before they are approved for human use.

The greatest obstacle to accomplish this goal is the continued use of animal testing to evaluate drug safety and efficacy. For reasons which are genetically based and immutable, drug testing in rodents, rabbits, dogs, and monkeys produces widely different results, none of which correlates with human results.

For example, 9 of 11 studies of vascular disease in mice and rats showed that COX-2 inhibitors, the very drugs we are talking about today, were beneficial for heart disease, and, in fact, some of the investigators suggested they would be useful drugs for heart disease. We know from the clinical trials that all three COX-2

inhibitors are dangerous for heart disease.

What I have just told you is no secret. Everyone involved, the pharmaceutical companies, their researchers, the FDA, we all know that animal testing is unreliable. However, we have been unreasonably slow to replace animal testing with newer and better tests for drug safety and efficacy.

First of all, we must eliminate animal testing from this process since this flawed method costs billions of dollars and tens of thousands of human lives annually in the U.S. In-vitro testing using human cells and tissues, computer-based modeling, microdosing studies in humans, stem cell technology to allow testing of human cells and tissues, and the burgeoning field of pharmacogenomics, which allows us to compare DNA and predict toxicity and efficacy of the drugs.

They are all superior to animal testing. We should be promoting these methods. As a group, these methods are light years ahead of our crude animal tests, they are safe, accurate, and cost

effective, and we must move toward these methods if we are to have safe and effective medicines in America.

DR. WOOD: Thank you.

No. 11. Major Grubb.

DR. GRUBB: I am Christopher Grubb, M.D. I am in the Army Medical Corps at Fort Bragg, North Carolina. I am supported by the Department of Defense and I have no financial interests. As a military physician, I have no other interests at heart but the health and safety of our men and women in uniform.

As a pain specialist, my mission is to conserve the fighting strength by treating acute and chronic pain in our active duty soldiers and returning them to the battlefield.

However, we don't like to send soldiers into harm's way on non-selective NSAIDs due to their anticoagulant effects and the potential for worsening bleeding after battlefield trauma. Instead, they go to war with COX-2 selective inhibitors or coxibs.

Consequently, the 82nd Airborne Paratroopers are required to carry a coxib drug to be taken in the event of a battlefield injury, one

of three drugs in what is called the soldier's pill pack.

Many soldiers are fearful of the bleeding risk with NSAIDs, so they ask specifically for coxibs. Since service members are young and very physically fit, the armed forces constitutes one of the lowest cardiovascular risk populations in our society, so the recent COX-2 risk data was of very little concern to the military.

So, in this meeting, we warn against using a broad brush when painting the portrait of risk. Military personnel suffer frequent injuries and have a higher incidence of chronic pain than civilians, further increasing our need for coxibs.

Coxibs have allowed the worldwide deployment of many previously disabled soldiers. Many are now in Iraq on daily regimens of coxibs. Without these products, we can't keep as many soldiers functional on the battlefield.

The study of coxibs for chronic pain is in its infancy. Although efficacy data for coxibs may be equivocal for arthritic conditions versus NSAIDs, the same can't be assumed for other types of pain. Indeed, most military personnel use coxibs for non-arthritic pain, such as low back

pain. We have found coxibs to be superior to NSAIDs for spine pain, so we are planning controlled trials of our own to compare these drugs head to head.

In summary, our bravest Americans are reaping benefits from coxibs without drug adverse events. This large population should not be disenfranchised here. Consider our military in this particular drug decision. Coxibs are essential in the global war on terrorism.

Thank you.

DR. WOOD: Thank you.

Dr. Arrowsmith Lowe, No. 12. Not here? Okay, we will go on to No. 13, Mark Einstein.

DR. EINSTEIN: My name is Dr. Mark Einstein and I am an Assistant Professor of

Gynecologic Oncology at the Albert Einstein College of Medicine, Montefiore Medical Center at Bronx, New York.

My academic department has supported my expenses to attend this meeting. I have not been asked to speak to you by any pharmaceutical company, however, one of my clinical trials is partially supported by an unrestricted grant from Pfizer.

As a gynecologic oncologist, I am committed to finding new therapies to prevent and treat women's cancers. Recent trend data suggest cancer is overtaking cardiovascular disease as the leading cause of death in the U.S.

COX-2 inhibitors are one of the promising class of agents used in cancer therapy, however, many current and planned cancer clinical trials using COX-2 inhibitors are on hold pending the results of these hearings.

Expression of COX-2 has been identified in many human cancers including gynecologic cancers. One of the COX-2-expressing cancers is endometrial

cancer, which is the second most common gynecologic malignancy in the U.S. after another COX-2-expressing cancer, breast cancer.

The number of deaths from endometrial cancer has risen 128 percent since 1987. Responses to toxic chemotherapy in women with recurrent endometrial cancer are dismal. These generally elderly women have comorbidities that also limit their tolerability of chemotherapy.

We identified high rates of COX-2 expression in the most chemo-refractory endometrial cancers. These data led us to begin a pilot trial using Celebrex in women with endometrial cancer that is grant supported by the American College of Ob-Gyn. This trial has been suspended.

Cervical cancer, the number 1 cancer killer of women in many countries also strongly expresses COX-2. Currently, two cooperative group trials that were designed to observe the effects of Celebrex in pre-invasive cervical cancer have also been suspended.

COX-2 inhibitors are one of the targeted

agents that are being used for prophylaxis in women at risk for ovarian cancer where survival using toxic chemotherapy regimens has not changed in over 15 years.

In summary, gynecologic cancers remain a critical issue in women's health and standard therapy are not very effective at limiting the death rate and are not well tolerated. The thought of using target agents, such as COX-2 inhibitors that have less toxicities than most chemotherapies have many--

DR. WOOD: We found No. 12.

DR. LOWE: My name is Janet Arrowsmith Lowe. I am a physician and epidemiologist and the president of a small consulting firm in a tiny town in New Mexico. I do want to state that some of my clients, my pharmaceutical clients include Bayer, Glaxo-Smith-Kline, Merck, Pfizer, and Wyeth, but today I am just representing myself and my firm.

It has been refreshing to hear discussion of risk and benefit, because I think too often in the press, concerning safety of marketed drugs only

risk is discussed, and I think as we all know, that when a product is approved, FDA weighs risk and benefit before approval.

Now, the calculus may change over time as new drugs or new information is available, but in my several years of experience at FDA, and since leaving, I am assured that the agency is still functioning, and I don't believe that FDA is broken.

It is not perfect. Is there a perfect institution? But it probably can be improved, but I think the proposals for a separate agency for the review of safety are not rational. I think that the premarket review really provides appropriate balance in deciding whether a product should stay on the market.

Now, I would like to see greater access to some drug development data including more user-friendly public access to the safety databases at FDA modeled along the lines of the MOD database in the Center for Devices.

So, in my opinion, the public health is

best served by a careful study of risks and benefits, and FDA, with the proper funding balance and authority, an engaged industry, and an educated public.

Thank you very much.

DR. WOOD: Thank you.

Next, we will go to No. 14, who is Dr. Abramson.

DR. ABRAMSON: Thank you for having me here. I do serve as an expert on cases involving Vioxx and Celebrex. I want to say that in order to get to the bottom of what went wrong with Vioxx, I think it is important to address first what went right.

At the February 2001 Advisory Committee meeting, the reports of the FDA reviewer showed conclusively that Vioxx caused significantly more cardiovascular complications in people with and without cardiovascular history, and overall, the people who took Vioxx developed 21 percent more serious complications.

So, the question before us is why do

American physicians prescribe $7 billion worth of Vioxx after Merck and the FDA knew that Vioxx was significantly more dangerous, no more effective, and far more expensive than naproxen.

In order to answer that question, we need to look at the sources of information that physicians trust most. That data was reported in the New England Journal of Medicine in 2000. The article acknowledged that there was a cardiovascular risk in theory and measured cardiovascular events, but the article did not report those cardiovascular events, nor did the article report serious adverse events overall.

It did report heart attacks. The heart attacks were reported as not statistically significant in people without a cardiac history, and therefore, the issue was not brought to physicians' attention. All 13 authors had financial ties to Merck.

We look at the clinical practice guidelines from the American College of Rheumatology. We see that first is Tylenol, and

next recommended is Vioxx and Celebrex. All four authors have financial ties to the manufacturers of both drugs.

The problem here is that the information that docs are getting is so heavily filtered through commercial sources that no matter what the FDA does with drug safety, unless the integrity or doctors' information is not improved and doctors and patients don't take good information into the exam rooms, this exercise is going to be for naught, and the quality of American medicine will not improve.

DR. WOOD: Thank you.

We will go to No. 15, Dr. Baraf.

DR. BARAF: I have consulted to and performed clinical trials for many of the companies whose drugs are being discussed today.

As a busy practicing rheumatologist, I have asked to be here to speak for my patients with arthritis. For four and a half months, their needs have been ignored in virtually every news report and medical journal editorial discussing NSAID

therapy.

Indeed, we have all learned that we must be more mindful of each patient's risk factors for cardiovascular disease in selecting COX-2s or other NSAID treatment, but data regarding this risk for COX-2 inhibitors is incomplete, sometimes contradictory, and begs further investigation.

The risk for cardiovascular disease with non-selective NSAIDs is unknown and untested. I urge this panel to give careful thought to the considerable benefits COX-2 inhibitors offer patients with arthritis especially those with GI risks.

For large numbers of my patients, COX-2 inhibitor diminish the threat of serious drug-induced gastrointestinal injury, thereby eliminating a major barrier to their treatment. How are we to balance the competing risks of cardiovascular and GI toxicity against real therapeutic need for patients with debilitating pain?

We must heed the advice that we give to

our patients. There are no completely safe drugs in any treatment category. It is my responsibility to weigh and risks and benefits of drugs with my patients, to make individualized decisions.

Sensationalizing and highlighting only the risks of these drugs based on scanty and incomplete information, as many of our colleagues have chosen to do, have created an atmosphere in which an informed discussion with patients is difficult, if not impossible.

For many patients with arthritis, these drugs are not superfluous as some have suggested, but greatly impact their quality of life. To withdraw one drug might put us on a slippery slope, leading to withdrawal of all NSAIDs. My patients must not be denied access to the widest variety of therapeutic options.

Thank you.

DR. WOOD: Thank you.

No. 16. Dr. Hamburger.

DR. HAMBURGER: I am a practicing rheumatologist and the President of the New York

State Rheumatology Society. I have been a speaker for several of pharmaceutical companies mentioned today.

I polled New York rheumatologists, State rheumatology society leaders, and I spoke to my patients, and we have remarkably consistent views. Events have reminded everyone of what rheumatologists and our patients already know. NSAIDs are important because of their role in the treatment of the pain of arthritis and because of the numbers of people who suffer from this pain.

We have seen recently far too many patients who have experienced the recurrence of their pain and their suffering because they stopped their medications out of fear or because of changes in managed care formularies.

None of us can emphasize enough the importance to these patients of reducing their pain and preserving their mobility. So, our consensus opinions are, number one, that access to anti-inflammatories needs to be preserved. Physicians and patients need to be provided with

the important information about these medications in a more rational and timely fashion, and the process for disseminating this information should be improved.

The coxibs, we have learned today, and we have known, have less GI toxicity, but their own side effects. Everyone wants an NSAID free of toxicity, but no one can say today to any patient that this NSAID has been tested and found to have no CV, GI, or renal toxicity.

So, we need to maintain access while deciding the best next research.

Patients act on what they read and hear, and they believe the information that appears in the media. The evidence on NSAIDs presented to the public has focused on only a small number of published studies, and the public is making its judgments without knowing all the information.

Juries in this country do not deliberate and reach a verdict based on the last three pieces of evidence.

DR. WOOD: Thank you.

The next speaker will be Dr. Qureshi, No. 17.

DR. QURESHI: Good afternoon. Before I

start I should let you know that I am being paid by Given Imaging to be here, but not enough to influence my results.

I am going to talk about NSAIDs and the small intestine injury they cause. The occasional findings of intestinal blood loss or anemia in the setting of normal upper and lower endoscopy led to the realization that NSAIDs cause significant disease in the small intestine.

We performed the first controlled study to look at NSAIDs using new technology that is a camera pill that takes a video wirelessly of the small bowel. We looked at 41 patients, half of them on NSAIDs for at least three months and half that took Tylenol or nothing.

This is a camera that you swallow.

Much to our surprise, we found small ulcers in the small bowel, large ulcers, and bleeding in the small intestine.

We found that 71 percent of NSAIDs takers had some form of injury in their small intestine, 20 percent had severe injury compared to none in the controls.

So, symptoms and signs of ill health among chronic NSAIDs users is often attributed to the

underlying disease, but we think that dyspepsia and not responding to acid suppression, vague abdominal symptoms, iron deficiency anemia, or hypoalbuminemia may result from small intestinal injury.

We have a new technology now that enables us to look at the small intestine. Video capsule endoscopy is very useful for diagnosing and for comparing the damage that different NSAIDs might cause on the small bowel, and in a subset of patients where we suspect small bowel injury, this technology is useful and shows promise.

Thank you.

DR. WOOD: Thank you.

We will go on to No. 18, Mr. Matthews.

MR. MATTHEWS: Thank you. My name is

David Matthews. I am a lawyer and I represent individuals who have been harmed by the drugs being discussed here today.

The fact that these hearings have become necessary to address the safety of COX-2 drugs is yet another tragic example of the continuing failure of the pharmaceutical industry to disclose the truth, the whole truth, and nothing but the truth to the FDA, prescribing physicians, and the citizens of this country.

Why is the whole truth not forthcoming? Simple. Billions and billions of profit dollars and absolutely zero individual accountability by company officers who submit drug safety data both before and after a drug is approved.

With the coxibs, the FDA has had to negotiate with the drug sponsors to change labels, conduct patient and physician education, limit advertising, modify approved indications, and to even complete studies.

The time for these negotiations should end. In response to a rash of corporate scandals

involving the likes of Tyco, WorldComm, Enron, and others, Congress passed the Sarbanes-Oxley Act of 2002. It provides criminal penalties of up to $5 million and 20 years in prison for knowingly submitting false finance information to the SEC.

These penalties are for lying about a company's financial status, not for causing injury or death to an individual. Because everyone deserves nothing less than the whole truth from pharmaceutical companies and complete disclosure about clinical trial data, there must be personal accountability for any individual who fails to do so.

I urge Congress, and I hope these hearings can be a springboard, to enact legislation which follows the Sarbanes-Oxley Act, but with more severe penalties for any drug company, officer, or employee who submits false, misleading, or deceptively modified drug safety data to the FDA, a physician, or to the public.

If someone who submits false financial information to the SEC can be filed $5 million and

sentenced to 20 years in prison, there is no compelling reason that the penalties for submitting false, misleading, or deceptively modified data to the FDA.

DR. WOOD: Next speaker will be No. 19, Dr. Wilson, and as you start, Dr. Wilson--we are not counting your time yet--try and step back a little bit from the microphone. Apparently, there is a lot of distortion from people being too close to the microphone, and that goes to the other speakers, as well. Thanks.

DR. WILSON: First of all, I have no sponsorship, I am here on my own recognizance. I am a practicing rheumatologist in Atlanta, Georgia, and my life is dedicated to alleviating the pain of arthritis.

Almost 2 million Georgians suffer from arthritis. In fact, the latest figures from the CDC are that 1 in every 4 Georgians has a chronic joint symptom, and arthritis is the number one cause of disability in America.

Pain matters. It may not kill you, but

you may wish that you were dead.

My patients are not concerned about living forever, they want to live well without arthritis pain. It is not surprise that the more experience we gain using medications, the more we learn when to use it and when not to use it. Patients do not take medications if they don't work, and millions of patients taking COX-2 selective medications evidence that they are effective. Indeed, this has been my experience.

I am concerned about safety. We should try to figure out what is unique about the 1 to 2 percent of patients with very serious side effects rather than depriving the 98 to 99 percent of patients with significant relief from their arthritis pain who have not experienced a serious side effect.

In a perfect world, I would have endless choices because all patients are not created equal. I believe that the choice to choose COX-2 selective medications is too important to answer for the patient. To limit choices based on evolving

knowledge is unfair to tens of millions of Americans with arthritis pain.

On average, 29 people a week die in a car in Georgia. I suspect that all of us came in a motor vehicle today and accepted a risk.

We must consider both sides of the equation when we decide how to treat patients and what to treat them with. Ideally, it should be a patient's decision to decide based on the information provided by their personal physician.

Most of my patients would take some significant risk for a better quality of life with relief from arthritis pain. Please thoughtfully consider our patients' pain when you make your decision.

Thank you for your time.

DR. WOOD: Thank you.

The next speaker is No. 20. Dr. Williams.

DR. WILLIAMS: I am Dr. Gary Williams. I am here on my own time and at my own expense.

It is generally accepted that COX-2 inhibitors are a safer alternative to patients with

arthritis. Cost containment has been a competing force. Those among us who feel these drugs are expensive or overused may be pleased with the recent changes in the market share of COX-2 specific drugs.

This shift has been caused largely by prolonged concerns regarding Vioxx, culminating in the decision by its manufacturer to withdraw the drug from the market.

Our current attention is directed to possible cardiovascular risks for two currently marketed drugs, celecoxib and valdecoxib. The data that concerns us is to date in non-arthritis trials designed to explore possible additional uses of these drugs beyond their current indications.

The largest effort to date to assess the impact of these drugs on cardiovascular risk in patients using them for their current indications is the FDA-sponsored Kaiser trial. This trial reinforces the cardiovascular risk for users of Vioxx and raises additional concerns for possible increases in cardiovascular risk in users of

nonsteroidal anti-inflammatory drugs including Naprosyn.

In this trial, Celebrex was not associated with increased risk compared to any other treatment option or even when compared to non-users or remote users of any of the treatment options.

On this background, we should be cautious in recommending that thousands, or even millions, of current users of COX-2 specific inhibitors move to other, older non-selective NSAID options.

We should be realistic and assume that they will continue to use anti-inflammatory drugs obtained either over the counter or by prescription. Since they would be moving away from the GI safety advantage demonstrated with the COX-2 selective drugs toward the options included in the Kaiser trial, they would be moving toward increasing GI risk.

Unfortunately, as it relates to the decisions facing this Advisory Committee, the same FDA Kaiser data suggests that the recommended movement--

DR. WOOD: Thank you.

The next speaker is Rebecca Burkholder, No. 21.

MS. BURKHOLDER: I am Rebecca Burkholder from the National Consumers League. In the interest of full disclosure, NCL occasionally receives unrestricted financial support from pharmaceutical companies for consumer education and research projects. The research cited below is one of those projects. My expenses for this meeting were not paid by an external organization and my statement reflects the interests of those NCL represents, consumers.

NCL urges the FDA to carefully weigh the risk and benefits of COX-2 inhibitors as it decides how best to protect the public. Whatever action this committee takes, NCL believes it is important to anticipate consumer response in the wake of the publicity surrounding COX-2 drugs.

Although COX-2 drugs were originally intended for use by those patients who had GI side effects with traditional NSAIDs, a much broader

population actually took the medications. Given recent events, some patients taking COX-2 drugs for arthritis for other pain will now likely turn back to traditional over-the-counter NSAIDs for relief, but consumers likely do not understand how to safely use these OTC NSAIDs.

A 2003 survey of over 4,000 adults commissioned by NCL on consumer use and attitudes towards OTC pain relievers found that 47 percent of those who take OTC NSAIDs take more than the recommended dose. Nearly half would not consult a doctor when taking for more than 10 days. Nearly half thought it was more important to control pain regardless of risk, and the survey revealed the following about arthritis sufferers - 85 percent take OTC for pain relief with 60 percent choosing OTC NSAIDs, 30 percent take pain relievers on a daily basis, and 70 percent do not discuss the risks.

Based on these findings, we believe consumers must be educated about the relative risks and benefits of all medications, OTC or

prescription. We call upon the FDA to engage with relevant partners in a broad-based educational campaign that would cover relative risks and benefits of various pain medications, appropriate pain management strategies, the importance of talking with a health care professional, and the role--.

DR. WOOD: Thank you. The next speaker is No. 22. Amye Leong.

MS. LEONG: My name is Amy Leong. Before I begin, I would like to say that while my funding here was as a result of the Foundation for Better Health Care, a nonprofit health education firm, I have had a role as a motivational speaker in previous years with several of the pharmaceutical companies mentioned today. However, my presence here today is as a concerned patient and a citizen.

As President and CEO of Healthy Motivation, a consulting firm in health education, and as spokesperson of the United Nation's endorsed Bone and Joint Decade, I am very concerned about the issues that you all are addressing today. I am

very pleased that you are addressing them, but I think that we need to look at the benefit-risk that you are all so diligently doing today.

I am that patient that you are addressing. I have got rheumatoid arthritis, I have had it for over 25 years. Within 8 years of diagnosis I ended up in a wheelchair, unable to feed myself. As a teenager, not being able to walk or feed herself, it is one of those frightening scenarios that we know should not ever happen.

Because of arthritis medications that did not work in my years, I ended up going through 16 surgeries, 12 of those were joint replacements. I have been hospitalized for over 312 days, and have indeed taken over 35 arthritis medications including every single nonsteroidal anti-inflammatory and the celecoxibs.

So, I am here today to just tell you and to share with you that while we look at risk, we really do have to consider the benefit. I am a standing benefit in front of you. It is my choice to work with my physician to determine what is at

higher risk for me and what is not.

Every single arthritis medication I have taken has come with some serious adverse effect - abdominal pain, fluid retention, gastric ulcers, upset stomach, nausea, vomiting, heartburn, indigestion, ringing in the ears, reduction in kidney function, increasing liver enzymes, rash, weakness, unusual tiredness, sleeplessness, sleepiness, respiratory infections, infections, sepsis, and it goes on and on.

This is what I deal with.

DR. WOOD: Thank you.

No. 23. Donna Fox-Keidel.

MS. ZUCKERMAN: My name is Diane Zuckerman. I am here on my own to read for Donna. She was unable to attend because her son is a juvenile RA patient, and he had a serious flare.

She writes:

"I am 39 years old and have lived with scleroderma and juvenile rheumatoid arthritis for 35 of those years. I began taking Celebrex in 2001 as part of my treatment plan. Prior to 2001, I had

been on almost every medication known to treat juvenile arthritis. I had endured many corrective and replacement surgeries. I have suffered setbacks and side effects too many to mention.

When my doctor spoke of this new medication called Celebrex, I was indeed skeptical, what would the side effects of this new medication bring to me, headaches, fatigue, and the dreaded gastrointestinal problems I had learned to despise, would it alter organ function, or, better yet, would it really even work, because so many medications I had experience had not shown any benefit, and my drug cocktails were never less than two medications and that is not counting the injections I received.

With my skepticism aside, I tried the new drug and within weeks saw a remarkable difference. I was able to attend school full time versus part time, I was able to manage my home better, and, most importantly, I was able to be a mom I wanted to be.

I was able to spend quality time with my

boys, maintain my home, and continue my work with a volunteer group I started for children with arthritis. My life was full for once and I was able to enjoy every moment of it.

For once, taking medication didn't mean chasing the pills with a bottle antacid. I could eat without fear of feeling nauseated. My then 90-pound frame was able to gain 15 pounds. For a brief period of time, I was taken off Celebrex due to insurance issues. I was borderline depressed because I was afraid my new-found life would disappear. Fortunately, this did not happen because my rheumatologist and I fought for my--."

DR. WOOD: Thank you.

The next speaker, Erika Umberger, is she here? No? All right.

Let's go to No. 25, Theresa Ray.

MS. SARAFIN: Hi. I am Judy Sarafin. I am here on my own and speaking for Theresa, who was unable to attend due to a last-minute emergency and she asked me to read her story.

"I am 35 with a history of osteoarthritis

starting in college. After the birth of my second child, my arthritis worsened. Advil wasn't working, my GP gave me Celebrex, which worked for about four months. When that was no longer sufficient, he sent me to Dr. Fleishman. Together, we worked through Mobic and Bextra before settling on Vioxx.

With the combination of Vioxx, multivitamins, glucosamine, and avoidance of caffeine, I became stable. For the first time in about five years, I could honestly say that I had periods of time where something didn't hurt. I could always feel pain somewhere prior to this point.

I reached stability with the Vioxx combination in August of 2004. When the FDA pulled Vioxx, I had no choice but to go back to the Bextra at least temporarily. Once again, Bextra failed to give me a sufficient quality of life. I hurt so badly I could feel it in my toes.

We are now trying to find something that will return me to my Vioxx quality of life. My

family has no history of heart disease or stroke, my blood pressure is perfect, and my cholesterol is ideal. I understand and do not wish to dispute that Vioxx can cause some serious complications in a certain portion of the population, however, what about someone with my medical history?

I completely agree that all new information, whether good or bad, should be disseminated to patients and physicians, but I believe the withdrawal of Vioxx was premature. Each patient and physician should be allowed to perform the risk-benefit assessment and further studies should be performed to fully understand the interaction before removing this drug from the marketplace."

DR. WOOD: Thank you.

The next speaker is No. 26, Judith Whitmire.

MS. WHITMIRE: Pfizer has paid my travel expenses. I came from Reno, Nevada. I contacted Pfizer, though, because I wanted to try to keep my drug of choice, Celebrex, on the market, so that is

why I am here today.

When I was a young teenager, I helped my grandfather in his home printing business. It was difficult for him to set type since his hands were even worse than mine are now. Certainly, I never did think that my hands would resemble his one day.

Now I face a similar challenge. When I retired at the end of 2002 from a 40-year career in public health microbiology, which was a problem with my hands, my husband introduced me to the wonderful world of woodturning. It seems I have a natural talent and my wooden bowls are in much demand if I can only keep my osteoarthritis under control, and this is what I do and love.

I will be 65 years old next week. Subsequent to a severe whiplash when I was 16, I developed osteoarthritis in my neck at the age of 30. It was then that I embarked on the search for an effective anti-inflammatory.

I started with Cliniril and have spent the next 30 years trying all of the new drugs as they became available. They either provided limited

relief or caused me gastritis, or both. I had a three-day run on Naprosyn before my stomach said no.

My new rheumatologist prescribed Celebrex last fall for the osteoarthritis in my hands, neck, and right knee. It gives me far better relief than all of the other anti-inflammatories, and no gastritis.

I do not have any risk factors for cardiovascular disease. Interestingly enough, most of my family has died of cancer. My rheumatologist is comfortable with my low dose regime of 200 mg per day. I urge you to keep this drug available for the clinicians to judge if it is appropriate for their patients like me.

Thank you.

DR. WOOD: Thank you.

The next is No. 27, Judy Fogel.

MS. FOGEL: My name is Judy Fogel. I drove myself here from my home in Ithaca, New York, to talk to you today. I found out about this hearing from inputting in Google the word Celebrex,

a drug I have been taking with great success for three years.

I feel like Celebrex was created for me. My OA started when I was in my early 20s. It started with pain and stiffness in my fingers. The symptoms continued to worsen. In the early '70s, a rheumatologist had me take increasing doses of aspirin, which led to gastric upset and ringing in my ears. Since there was no other drug available, I would sometimes take an aspirin and just pay the consequences.

We raised three children and being a soccer, football, and ice hockey mom, cold weather environments was especially difficult. In the '80s and early '90s, I tried about 10 of the NSAID drugs. As each new one came on the market saying it was better than the preceding one, I would take one pill and have gastric upset, bruising, and ringing in my ears.

Three years ago I went to my rheumatologist with an inflamed right arm and hand. He prescribed a new drug that would be easier on my

stomach, he said. It was called Celebrex. He gave me samples and a prescription form.

After taking the samples with no adverse aftereffects, I had the prescription filled and have taken 200 mg of Celebrex each day ever since.

It took several months to have the pain and swelling in my right hand and arm subside, so I could use them again, and gradually, the morning stiffness and pain in the rest of my body was remarkably better.

Most days I feel better than I did 30 years ago. I downhill ski, play golf, shuffle cards at bridge, sit through days of lectures and take notes, dig and clip in my gardens. I have regained the manual dexterity--.

DR. WOOD: Thank you very much.

The next one is Dr. Preston Mason, No. 28.

DR. MASON: Thank you. I would also like to acknowledge the contribution of my colleague, Professor Corey, Nobel laureate in Chemistry.

Both the studies I will discuss were conducted without interference from the

pharmaceutical industry. We both purchased the drugs used in our studies. I have received unrestricted grants from the manufacturers of these drugs.

Dr. John Vane, also a Nobel laureate, suggested as early as 2002 that differences in CV risk observed among COX-2 inhibitors may be attributed to their physico-chemical properties.

Confirmation of this hypothesis was provided by Professor Corey. He reported that rofecoxib readily formed potentially cardiotoxic metabolites under physiologic conditions. One of these metabolites would promote LDL oxidation, a well-known contributor to inflammation. Such toxic metabolites were not observed in the other agents he tested.

The findings of Professor Corey corroborate our own findings submitted before Vioxx was removed from the market. We showed that this drug dramatically damaged LDL and membrane lipids through oxidative modification. We saw this at pharmacologic levels.

In this figure, we also show an increase in isoprostanes, a mediator of inflammation, and we again report that this change in LDL oxidation was

not seen among other agents tested.

In the next slide, we contrast the pro-oxidant effects of Vioxx against a potent antioxidant. Remarkably, the combination only partially attenuated the effects of the rofecoxib.

We also saw that rofecoxib reduced the capacity of human plasma to defend against free radicals. We have seen, and others have reported, similar changes in patients with diabetes and a recent MI.

The next slide is a further explanation for the cardiotoxicity. We evaluated its molecular effects on lipid structure. Vioxx indeed altered lipid structure in a manner that we have seen consistent with increasing rates of oxidative damage.

We also saw adverse effects on lipid structure and oxidative damage with etoricoxib, another sulfone-type agent.

So, in summary, the last slide, we have seen increased reactive oxygen species with rofecoxib that contribute to mechanisms that lead to cardiotoxicity.

Thank you.

DR. WOOD: Thank you.

Is No. 29, Dr. Ross, here? No. All right. Let's move on to No. 30, Dr. Singh.

DR. SINGH: I am Gurkiepal Singh and I am here on my own. This morning you heard data from the collaborative study that David Graham and I did. I am also the lead author of the Estimate of NSAID GI Bleeds in the Country that Dr. Cryer referred to, and as a handout, I provided you our latest study on the hospitalizations because of complicated gastric and duodenal ulcers in the United States from 1988 to 2001 that I presented in a plenary session last year.

In the next 30 seconds, reviewing it very, very quickly, if you go on to page 3, the top slide on the right side shows you what we found, that there were a total of 493 million hospitalizations

in the U.S. and 3.6 billion patient years, and over the years, there has been a decline in the amount of gastric and duodenal ulcer complication hospitalizations in the country with two periods of remarkable decline, the first one '94 to '95, perhaps coinciding with the introduction of H. pylori guidelines by the NIH, and the second one in 1999, coinciding with, not necessarily caused by, the introduction of COX-2 inhibitors.

The last slide also shows you the same rate expressed for 100,000 NSAID prescriptions, and you would see that the 1999 decline was of 22 percent. We do not know what causes it, but here are the numbers.

One last point I would like to make on our Medi-Cal study, is that we did look at the recent exposures and current exposures and remote exposures. I know that issue came up, and the study was internally consistent and that the current exposure was always the highest followed by the recent exposure and then the remote exposure. So, internally, we were consistent in defining that

exposure.

Thank you very much, ladies and gentlemen, and I will be here to answer any questions that you want.

DR. WOOD: Thank you very much.

The next speaker is No. 39, Dr. Allan Fields.

DR. FIELDS: Good afternoon. My name is Dr. Allan Fields. I have been a physician practicing general and pelvic surgery and sports medicine for over 30 years. Presently, I am also the medical spokesperson for Swiss Medica, the maker of 024, Essential Oil Pain Neutralizer.

This is a potent, safe, and effective topical analgesic. It contains only natural ingredients that have been clinically studied and tested in the U.S. and around the world including double-blind studies. It carries a U.S. process patent.

As physicians, we have taken an oath to provide the most effective care while not knowingly harming the patient. To that end, I would like to

share some of my experiences with you.

I personally am asked on a daily basis what can patients do or take to control pain for a variety of medical conditions. I have been advising my patients to minimize the use of oral prescription OTC medications and instead to use the 024, which due to its purity, does no harm to the human body.

We also recommend that 024 be applied with massage therapies. This has provided pain relief that has often lasted 6 to 8 hours. These results have been very exciting. The patients have been using less of the aforementioned drugs and saving money in the process.

No serious adverse effects, such as GI bleed, hypertension, or cardiovascular problems have ever been reported. There is no interference with other medications that are necessary to maintain the patient's health because 024 is all natural.

It contains no binders, preservatives, or additives. Diet, exercise and work control are

also stressed, but in the future, we must strive to enhance our body's natural responses to pain and healing by safe and effective methods.

I am also a patient with diabetic neuropathy. I use it on a twice daily basis. I have had no pain since.

Thank you very much.

DR. WOOD: Thank you.

The next speaker is No. 32, Grant Johnson.

MR. JOHNSON: Thank you. I would like to start off by saying there is a little bit of a logistical mistake. The presentation packages will be circulated at the end of the public presentations.

My name is Grant Johnson. I am the present Chief Operations Officer at Swiss Medica, the manufacturer of 024. It's a topical pain relief medication that competes against the NSAIDs and the COX-2 inhibitor class of drugs.

We are all very aware of the huge potential negative side effects when certain high-risk patients take NSAIDs and COX-2 medicine

for any length of time. At Swiss Medica, we have compiled scientific evidence that powerful topical pain relievers, such as the 024, are as effective as many oral medications, but without the side effects, such as the bleeding ulcers, high blood pressure, or increased risks to the heart.

These claims are supported by three European medical studies, one American-based open trial, and a recently completed Canadian randomized, double-blind clinical study over an extended period of time.

Every one of these studies demonstrates that there was a 60 percent or greater quantifiable reduction in pain for those who suffer from chronic pain conditions.

The first study was conducted five years ago, the latest was concluded last month. In your presentation packet folders I have included the appropriate summaries and the five pages of professional endorsements, and you will also find anecdotal feedback from pain sufferers who switched to the 024 after failing to find relief from a wide

variety of pain medicine and magic solutions, particularly the NSAIDs and COX-2 inhibitors.

Consumers need to be better advised by the FDA, healthier eating choices, regular exercise. These are things that have worked for centuries on this planet. Does it make sense to allow multibillion dollar companies to spend tens of millions of dollars to persuade consumers to pop a pill instead of making a healthy lifestyle decision?

I propose the FDA consider a moratorium on all direct-to-consumer advertising until these drugs have been properly studied, and as of today, no one has a straight and honest answer to the question how many have really died from using these pain pills.

Thank you.

DR. WOOD: Thank you.

The next speaker is No. 33, Necole Kelly.

MS. KELLY: Hi. I am here speaking for the American Chronic Pain Association. We want to make sure that everyone here understands that

chronic pain also destroys lives.

People who have chronic pain fight to get their pain validated, to keep their jobs, to keep their health insurance, to maintain their homes and their families.

For 25 years, the ACPA has offered support and taught pain management skills to people with pain, to help them live more normal lives. Yet, in spite of their best efforts, many of these people still need medications including COX-2 inhibitors that come with both benefits and risks.

Imagine learning that one of the tools you need to live a normal life is not longer available. In recent weeks, we have received hundreds of letters and e-mails from people who have told us they have stopped taking their medications because they are afraid of heart attacks.

Others also have told us that they would rather live 10 years with manageable pain than live 20 in agony. Some people are getting their medications from Canada because they can't function without it.

The ACPA is not a research facility. We can't speak to the science behind these studies. We can speak for people with pain. What these

people want and need is to share with their doctors the medical decisions that affect their lives. They need to know the risks of taking any medications and weigh them against the benefits, to make intelligent personal treatment decisions. They need to retain the right to make these decisions for themselves.

People with pain need the FDA to continue helping the public to get the accurate science-based information they need to make good decisions, but we ask you to look beyond the science and see the human face of pain.

Imagine just one person who woke up today, as every day, with intractable pain, unable to function, and ask yourself what is best for that individual. We hope your decision will make a positive difference for that person.

DR. WOOD: Thank you.

The next speaker is No. 34, Karen Kaiser.

Is she here? No.

All right. Then, let's go on to No. 35, Robert Thibadeau.

DR. THIBADEAU: I am an experimental research scientist in a nonmedical field with no financial interests in the medical industry whatsoever.

I have had rheumatoid arthritis and ankylosing spondylitis since 1973, diagnosed by blood tests in 1983. Vioxx saved my life. It acts in an hour with no high or other perceptual side effects. It is like aspirin for headaches, it just makes the arthritis pain and stiffness go away.

I am here solely to reinforce the probability of an experimental confounding and ask for public analysis and full disclosure.

The confounding. You don't exercise for 25 years and now you have no pain and stiffness. You run upstairs because you are amazed you can. Risk of heart attack or stroke goes through the roof, not for bad reasons, but for good reasons.

Control. Since these are brief,

unpredictable episodes, electronic monitor all waking hours to see if patients show brief, spontaneous increases in aerobic physical activity over placebo controls. I have not seen this done or even mentioned for control by any study available to be read by the public.

I predict mentally incompetent people, Alzheimer's, much more likely to show this exertion side effect. People physically debilitated by joint damage should show less effect due to physically restricted mobility. Other predictions are in my longer paper.

I ask the advisory group to review for this confounding and ask the FDA to report the findings and justifications out publicly.

Thank you.

DR. WOOD: Thank you.

The next speaker will be Lois Humphrey, No. 53. No? Not here.

I beg your pardon, Glenn Eisen, No. 36, was 52.

MR. EISEN: Close enough. I would like in

the interests of full disclosure to acknowledge that I have done research and consulted with Pfizer, AstraZeneca, and Given, and like Dr. Qureshi, they are barely covering my expenses today.

Next slide, please.

I would like to discuss the fact that there has been accumulating data over the last decade as far as gastrointestinal toxicity that has gone beyond the ligament of trique (ph) to both the small and large bowel.

This is an autopsy study from the New England Journal approximately 10 years ago, which showed a greater than 10-fold incidence of nonspecific ulcers in an autopsy study.

Next slide.

A case-control study of hospitalized patients who presented with upper and lower GI bleeding found that patients within a week of admission had equal use of NSAIDs whether it was an upper GI bleed or a lower GI bleed, and this was twice of the control population.

Next.

As a secondary analysis in the VIGOR trial, you can see from these bars that there was

twice the risk of lower gastrointestinal bleeding for naproxen as compared to rofecoxib.

Next slide.

In another analysis from the CLASS study, showed that in an FDA-mandated outcome, having a greater than 10 percent drop or a drop in hemoglobin of greater than 2 grams per deciliter, there was double the risk of dropping the blood count in both diclofenac and ibuprofen as compared to celecoxib.

If we remove patients who have had overt bleeding, the trend continues.

Next slide.

So, because of this, we developed a study to show proof of principle for small bowel damage, and the combination of a nonspecific NSAID with a proton pump inhibitor should be associated with a rate of small bowel mucosal break that is significantly higher than the rate for placebo or

COX-2 selective agent.

Next slide, please.

We have already shown this.

Next slide. Dr. Qureshi showed some nice pictures.

Next slide.

This was a double-blind, randomized trial where healthy volunteers had a two-week run-in period, were randomized after a baseline capsule, which was normal, and then were given 1 of 3 treatment arms.

Next slide.

The primary endpoint was the mean number of small bowel mucosal breaks, and as you can see, naproxen with a PPI had 10 times the number of mucosal breaks as compared to celecoxib.

Next slide.

The secondary endpoint showed that there was 55 percent incidence of small bowel mucosal breaks for combination therapy as compared to 16 percent for celecoxib.

Next slide.

So, in conclusion, as in the upper GI tract, inhibition of COX-1 by naproxen, and not celecoxib, translated into significantly different

rates of mucosal injury in the small bowel, and these findings extend the original COX-1-sparing hypothesis beyond the upper GI tract and into the small bowel.

Next slide.

You can read it because I am out of time.

Thank you.

DR. WOOD: Thanks.

The next speaker is Susan Winckler. Is she here? Yes, No. 37.

MS. WINCKLER: I am here representing the American Pharmacist Association, and we did not receive funding to participate in today's meeting. The views I am presenting are solely those of the Association and its membership.

We are here because the safety profile of COX-2 selective NSAIDs has recently come into question. Some have suggested that these drugs are too risky to be marketed, but a consideration often

lost in comments and debates, such as this, is the reality that no drug has zero risk.

Every medication has benefits and risks, and those risks increase exponentially when the products are used inappropriately.

Unfortunately, patients have lost access to several medications because the health care system failed to appropriately manage risk. Patients should not lose access to these products because of the health care system's failure to reduce risk.

If the agency determines that the benefit-risk profile is insufficient for these products to remain on the market, that assessment must consider the responsibility of health care professionals and patients in making medications work.

By collaborating, pharmacists, physicians, and patients can mitigate some level of risk if we focus on identifying potential risks and determining systematically how best to manage those risks.

There are a few things that can help us with that risk management. First, is to increase the reporting of adverse events by pharmacists and

other health care professionals and to continue to encourage that reporting.

Providing pharmacists with complete information about the patients would also improve our ability to manage potential risks.

When products are identified as having a risk or requiring more attention, access to a more complete medical history would allow pharmacists to help assure that at-risk patients do not take medications that could exacerbate such a condition.

If the agency determines that there is a need for special oversight of COX-2 inhibitors or other NSAIDs, we urge the FDA and product sponsors to involve pharmacists in both the development and implementation of any risk management program.

Please avoid the misperception that only these products present a risk to patients when, in reality, every medication has benefits and risks.

Thank you.

DR. WOOD: Thank you.

The next speaker is No. 38, Virginia Ladd.

MS. LADD: My association is paying for my travel.

Good afternoon. My name is Virginia Ladd. I am President of the American Autoimmune Related

Diseases Association. We are a nonprofit health organization representing patients living with autoimmune diseases, which include rheumatoid arthritis, lupus, scleroderma, and over 80 other disorders sharing similar complications as the result of the body's attack on itself.

Autoimmune disorders are serious chronic and disabling conditions that often present with constitutional symptoms of joint and muscle pain, widespread inflammation, and fatigue.

We ask that the agency and its advisory committee respectfully consider the critical role of patient and physician dialogue in conducting risk-benefit analysis of any therapy at the level where it belongs - with the individual patient rather than a diverse clinical population as a

whole.

We believe that patients should have access to as broad an array of essentially safe and effective therapies as possible, with informed labeling, providing the means by which the provider and the patient can consider treatment options.

For many patients, the remote and even more common risk of a serious acute adverse event is, and would be, overweighed by the benefit of maintaining or regaining freedom from pain, mobility, and independence.

Since there has not been a new drug approved specifically for the use of most autoimmune disorders in the last 40 years, it is necessary that clinical reliance on off-label use of existing anti-inflammatories and immune-modulating drugs.

In particular, the COX-2 inhibitors have contributed to the improved life quality of many autoimmune patients to which I have personally spoken. Without COX-2 inhibitors, many autoimmune patients with sensitivities to other NSAIDs would

be relegated to the use of low-dose corticosteroids with therapy for the treatment of their debilitating symptoms, and as you are aware, such therapies carry--.

DR. WOOD: Thank you very much.

The next speaker is No. 39, Paola Patrignani.

MS. PATRIGNANI: I am Paola Patrignani, University of (inaudible) Italy. I am Professor of Pharmacology. I am in the field for 20 years.

This slide compares the therapeutic plasma concentrations of cyclooxygenase inhibitors, reported in pink, with the concentrations of the different drugs inhibiting by 80 percent the activity of platelet COX-1, a biomarker of gastrointestinal toxicity, shown in panel A, and monocyte COX-2, a biomarker of efficacy, shown in panel B, as determined in the whole blood assay that I developed. This is in vitro, reported in blue.

It should be pointed out that 80 percent inhibition of COX-2 is associated with clinical

efficacy.

Ibuprofen and naproxen therapeutic concentrations are proper to inhibit more than 80 percent platelet COX-1 and monocyte COX-2. Thus, these two drugs have similar pharmacodynamic traits and they should be placed in the same box.

Differently, therapeutic concentrations of COX-2 inhibitors are from 4 to 200-fold lower than those inhibiting platelet COX-1 by 80 percent, thus demonstrating a variable impact on COX-1 depending on the dose and selectivity.

The impact of COX-2 inhibitors on monocyte COX-2 is shown in panel B.

The therapeutic plasma concentrations of nemesulide, rofecoxib and etoricoxib are proper to inhibit more than 80 percent COX-2.

Diclofenac and lumiracoxib plasma concentrations are several fold higher than those inhibiting by 80 percent COX-2 while celecoxib and valdecoxib plasma concentrations are 2- to 4-fold lower.

In summary, ibuprofen and naproxen have

similar pharmacodynamic features towards COX isoforms, so they have to be in the same class.

Diclofenac and celecoxib have superimposable pharmacodynamic traits, but they are given at not comparable doses.

Lumiracoxib 440 mg is an overshooting dose.

Next slide, please.

This slide is very interesting because I compared, I gave different drugs, lumiracoxib, rofecoxib, celecoxib, ibuprofen, naproxen to healthy subjects or patients, and I compared the inhibitory effect on COX-1 and COX-2 and the synthesis of prostacyclin.

The most interesting part of the slide is that all the other coxibs gave a similar inhibitory effect of prostacyclin. Also, the other important--.

DR. WOOD: Thank you very much.

The next speaker will be No. 40, Betsy Chaney.

MS. CHANEY: Good afternoon. I am Betsy

Chaney. I am a Celebrex user. I took Vioxx before.

I am here to say would you all pick up your elbow and whack your funny bone and feel that pain that stops you in your tracks from doing what you are doing. All you want to do is say a bad word.

Well, I have cracked vertebras in my neck, and without Celebrex, I start to lose the feeling in my hand, and I can't grasp a paper, I can't hold onto something, I can't do things around my house.

I am concerned that you all will take my ability away to make a decision with my physician, my family, and my friends, to make an advised decision to take COX-2 inhibitors.

There is a lot of people here for profit, for many things, whether it be the drug companies or the lawyers, or whoever, but my issue is please don't take this medication that works so well for me.

I can't take other medication because I am taking two Nexium and a Xantac today. That is

maxed out on the stomach medication. They looked inside and said it looks like Barrett's esophagus. I have GERD and you all know I have NSAID, NSAID, NSAID. I could name 100 of them, but those names don't matter.

What matters is that I retain the right to make a decision, with my doctors and my family, to continue taking this medication even if there are risks.

I am willing for my quality of life to take those risks, and I thank you all very much for watching over us.

Thank you.

DR. WOOD: Thank you very much.

The next speaker is No. 41, David Peterson. Is he here? No.

Then, the let's go on to No. 42, Jack Klippel.

DR. KLIPPEL: Thank you, Mr. Chairman.

The Arthritis Foundation represents and is the voice of millions of Americans with arthritis. Our constituency is keenly interested and is a

major stakeholder in the discussions being held today.

They seek clear answers from us, you, their doctors, industry leaders, and regulatory authorities about the role of COX-2 inhibitors and other NSAIDs in the treatment of their arthritis.

The Arthritis Foundation believes there are two main factors that must be considered in these discussions of these drugs and similar discussions about other medications in the future.

First, there must be a more balanced discussion about the benefits, as well as the risks for these medications. Recent attention of COX-2 inhibitors and NSAIDs have focused almost exclusively on one particular risk, cardiovascular disease, with little mention of other risks associated with these drugs, or more importantly, the benefits of this class of drugs.

Numerous studies have documented that COX-2 inhibitors and other NSAIDs relieve pain and inflammation which has benefited millions of people with arthritis. Many have found COX-2 inhibitors

to provide greater pain relief than other medications. For some, COX-2 inhibitors have controlled pain when nothing else has worked.

They would ask you the question, whether their public health was made better or worse by the decision to withdraw Vioxx. Their greatest concern and risk is not about side effects of drugs, but that they live with arthritis.

Second, is the central role of informed patient choice in allowing patients with arthritis to make their own decisions about treatment. We believe that patients should be able to choose for themselves whether or not the benefits of a particular medication or treatment outweigh the risks.

Full disclosure of these benefits, side effects, and risks, and discussion with the patient's doctor--

DR. WOOD: Thank you.

The next speaker is labeled as No. 43. Kathy Pinkert. Is she here? No.

Then, No. 44, Carol Spitz.

MS. SPITZ: Hi. My name is Carol Spitz and my travel expenses have been paid for.

I have severe osteoarthritis. I have had

a knee replacement, shoulder replacement, and three back surgeries.

Bextra has allowed me to be able to function, some of the normal things that people take for granted like walking and dressing. I couldn't even do that before.

I am unable to take Motrin and Naprosyn and aspirin due to anaphylactic reactions. Other NSAIDs have given me adverse reaction of my stomach, and that's it.

Thank you.

DR. WOOD: Thank you.

The next speaker is No. 45, Eileen Lacijan.

MS. LACIJAN: Good afternoon. My name is Eileen Lacijan. I am grateful for the opportunity to be here today to speak to you about my experience with COX-2 inhibitors.

I would like to advise the committee that

I do not have any financial relationship with the sponsor, product, or competitors. I am here today representing myself on the advice of my cardiologist.

I am 57 years old and reside in Arnold, Maryland. I am a registered nurse and the Executive Director of a Hospice Program in Maryland.

I have osteoarthritis of the basal thumb joints of my hands. I was first prescribed Vioxx in March of 2000. My rheumatologist changed my prescription to Celebrex in June of the same year. I then took Celebrex for the next four years until July of 2004. Following a flare-up, the Celebrex was no longer effective and I was prescribed Bextra in July of 2004.

I have never smoked. I don't drink alcohol. I don't have diabetes or any family history of heart disease. I have never had high blood pressure. I exercise regularly. I am not overweight, and I have always maintained a health diet.

On the evening of August 12, 2004, I survived a myocardial infarction. A cardiac catheterization, which was performed the following

day at GW Hospital, revealed no blockages. My heart attack was thought to be caused by a coronary vasospasm, which affected the left anterior descending coronary artery and initially resulted in a moderately large amount of heart damage.

I received excellent cardiac care and was able to return to work full time a month after my heart attack. I continue to work out at cardiac rehab several mornings a week before work. I thank God every day that I am alive and have the love and support of my family and friends. However, I still have many unanswered questions about the cause of my heart attack as does my cardiologist.

DR. WOOD: Thank you very much.

The next speaker is No. 46, Gloria Barthelnes.

MS. BARTHELNES: I am Gloria Barthelnes and I am from South Grafton, Massachusetts.

When I was in my 30s, I was having

problems with my legs and my neck, didn't figure what it was. I figured it would go away. Finally, in 1984, I was living on a second floor apartment and I was carrying my grandson who was 10 months old up the stairs, got halfway up the stairs and couldn't finish, I had to sit down the pain was so bad.

I had contacted the doctor and had me go through several tests. Finally, he recommended a rheumatologist. They tried several medications on me, it didn't work. Then, finally, he had given me Vioxx. It was such a relief that I was able to go to work without any pain, without any problems.

To go to work, I had to travel like 37 miles one way, and sometimes there was a lot of traffic, and just to sit in the traffic was the hardest thing to do.

I have the arthritis in my neck, lower back, and in my legs. When they took the Vioxx away, I panicked and I tried using just the over-the-counter medication. It didn't work. So, finally, I had called the rheumatologist and I

said, "Can you help me?"

So, he put me on Bextra. I am hoping that you people can help me, and not take these medications away.

Thank you for your time.

DR. WOOD: Thank you very much.

The next scheduled speaker is No. 47, Rebecca Dachman. Is she here?

DR. DACHMAN: Hello. My name is Dr. Rebecca Dachman. I am an occupational medical physician, and I also have significant experience in clinical trial design.

There were a number of thoughts that came to my mind as I read in the papers about what was going on with the COX-2 inhibitors. One of them, as an occupational medicine physician, there are many people who only respond to COX-2 inhibitors, and that makes a difference between working and not working for them, which has significant effects both on disability and ultimately on their health, because nonworking, sedentary people are a setup for cardiovascular disease, as well.

As a clinical trialist, looking at the data, I know I was surprised that I didn't get more subgroup analysis of those who ended up having the

cardiovascular events, whether there were more diabetics in that group or whether there were any other ancillary factors that one could tell that would identify them, and I think that is important.

I also think that vis-a-vis drugs, we have to put it all in context, all drugs do have ADRs. Birth control pills are as extensively used as nonsteroidals and anti-arthritic drugs, and they all do cause increase in thrombotic events, yet, we haven't taken them off the market either.

I think we have to remind ourselves of that and what it means is not that they won't have events, but knowing about them and knowing how to subgroup the people in who those events occur.

I think from the FDA stance, they have to develop registries post licensure, so that for the first two years, you get all the adverse events that occur, and that is what is being done in Britain.

DR. WOOD: Thank you very much.

The next speaker is No. 48, Barrett Collins. Not here.

No. 49, Cynthia Lee. Not here.

No. 50, Robert Humphrey.

No. 51, Michael Paranzino.

MR. PARANZINO: I am Mike Paranzino. I am here on behalf of Psoriasis Cure Now, a patient advocacy group. We have no financial conflict. We receive no pharmaceutical industry funding or funding from their trial lawyer opponents.

I am here to represent the 6 1/2 million Americans with psoriasis, more than a million of those who have psoriatic arthritis, and many of those psoriatic arthritis patients take NSAIDs and/or the COX-2s.

Our written statement is on the FDA website. It is available at psoriasiscurenow.org, and there are some copies in the press room. Our central point there was that absent a scientific consensus against these drugs, that they continue to be available so that patients can decide, with

their physicians, if in their own particular set of circumstances, the benefits outweigh the possible risks.

But in the remaining time, I want to make a different point and I am amazed that in the last 50 people no one has made, and that is, that in some of the rhetoric surrounding some of the critics of FDA, some of the critics of the pharmaceutical industry, we are hearing even some buzz in Congress, that somehow the drug approval process is broken, and we think that is false.

Patients need expeditious approval of medications, and there are many still in clinical trials that need to get approved, and we are concerned that the FDA may become timid or gun-shy and flinch about approving those drugs that are coming down the pipeline that millions of Americans with disease desperately need.

Where it does appear--and I am just a lay guy, I am lay person, liberal arts guy--but where it does appear we need work is in postmarketing monitoring, post-FDA approval, that is where we

need long-term monitoring.

We can't wait 20 years to get long-term studies before drugs are approved, but when that data does become available, it does appear that the ball is being dropped on a lot of sides in adding that information to the mix.

So, please, keep approving the drugs. We need new treatment options, and I thank you.

DR. WOOD: Thank you.

The next speaker is Dr. Lawrence Goldkind.

DR. GOLDKIND: I would ask that I go over 20 or 30 seconds, I could use some of the time that some others didn't use.

DR. WOOD: No, you get two minutes. Good try.

DR. GOLDKIND: That's the Chair's prerogative, I understand.

DR. WOOD: Good try.

DR. GOLDKIND: From 2001 to 2003, I was the Deputy Division Director of the Anti-Inflammatory and Analgesic Drug Products Section at the FDA.

Over the past decade, there has been an evolution of what is considered feasible in the realm of clinical trials. Drugs, such as the

statins, beta blockers, ACE inhibitors have been developed to reduce mortality from cardiovascular disease. Demonstration of these benefits requires large and multi-year study.

Risk-benefit analyses are not so hard when there is superiority in an outcome of death, and placebo control, which is really add-on to standard care, is ethical and feasible.

What is unique about the COX-2 story is that the indication is pain relief, chronic in the case of arthritis, but the perceived value was a safety advantage compared to NSAIDs, which were known to have substantial risks that were reflected in the labeling.

In fact, everybody here knows that NSAIDs have been the poster child for problem drugs for over a decade. So, it seemed obvious that large outcome studies would adequately test the hypothesis of superiority of safety.

The concept of a large simple trial sounds simple, but, in fact, is not. We are now learning the limits of outcome studies. At the time that VIGOR and CLASS were done, they were the longest and largest trials by an order of magnitude of NSAIDs.

We can now say they were imperfect and lessons can be learned. One, therapeutic, super-therapeutic doses are not the best choice. They promote off-label usage, and you cannot extrapolate well back to the therapeutic dose levels.

Single comparator trials, when there are many standards of care available, likewise is hard to interpret and put into a context of therapies.

Allowing the duration and size to be driven by a single prespecified safety endpoint does not provide robust evidence necessarily of overall superiority, and yet it is impossible to power a study for unexpected or as yet uncharacterized safety problems.

Even today, the term "cardiovascular

outcome study" is bantered about as if it were cookbook simple. Well-known cardiologists have stated that the obvious population for study is the high risk patient--

DR. WOOD: Thank you very much.

The next speaker is Louis Humphrey, No. 53. Is she here? No.

Then, we will go through the ones that didn't respond to our call earlier.

Rakesh Wahi, No. 2. Erika Umberger, No. 24. Gilbert Ross, No. 29. David Peterson, No. 41. Barrett Collins, No. 48. Cynthia Lee, No. 49. Robert Humphrey, No. 50. Lois Humphrey, No. 53.

In the absence of them, we will take somebody off the wait list, who is Yvonne Shira. Is she here? Yes.

DR. SHIRA: Hi. My name is Yvonne Shira. I am a practicing rheumatologist, and while I have worked with all of the companies mentioned here, and many others, doing clinical trials and as a consultant, I am here today representing myself. I paid for this trip myself.

I am representing my patients and I hope most of the rheumatologists who are seeing patients day by day.

I ask the committee to consider that quality of life issues are as important as length of issues to many of our patients. When Vioxx was removed from the market, a number of my patients refused to discontinue the drug despite its risk, because they deemed the quality of life benefit to be greater than the risk.

One patient said to me regarding its removal, "Dr. Shira, they just don't understand how much we suffer."

So, I ask that you do not take away choices unless there is compelling evidence that the coxibs are substantially less safe than the available alternative NSAIDs.

The data you have presented so far does not suggest this, but that rather the traditional NSAIDs have not been sufficiently scrutinized in long-term trials.

Remember that real life data is more

consequential than theories no matter how good they sound. Rheumatologists have always been aware of the cardiovascular effects of all NSAIDs. That is why most of us monitor patients at high risk by having them come back within a week or so for blood pressure monitoring.

The problem has been that we have accepted blood pressure increases that we thought were insufficient, that in light of new cardiovascular information, may actually have hit long-term consequences.

It is likely, I believe, that all NSAIDs have cardiovascular risk, but they have not all been studied equally.

Please don't away our patients' choices without compelling evidence that the alternatives are truly safer.

Thank you.

DR. WOOD: Thanks very much. That was the last speaker in the public hearing. I am grateful to all of you for sharing your views with us. I am sure they will be helpful to the committee.

We are going to go straight back to the program, and Dr. Villalba.

MS. MALONE: Excuse me, Dr. Wood.

DR. WOOD: Sure, yes.

MS. MALONE: I am Leona Malone. I am the patient representative on the program. I just wanted to tell the people who did give testimony that--and this is not facetious at all--that I literally do feel your pain, and I think that everyone here is here because we are aware of the pain and the situation that you are in, and no one here is taking it lightly.

I know how much trouble especially for the patients it was to get here, to sit here, to listen, and to get up to speak, and I applaud you for that. I just want you to be assured and to be confident that all of us here will take it seriously and give a voice to everything that you have said.

Thank you.

DR. WOOD: Thank you, Leona. That was helpful.

Are we ready, Dr. Villalba?

DR. VILLALBA: I am ready.

DR. WOOD: Okay, let's go.

Lumiracoxib

FDA Presentation

Lourdes Villalba, M.D.

DR. VILLALBA: I am going to talk about the cardiovascular safety of lumiracoxib. I want to make some points before I am going to show the data, and this is that my talk is restricted to cardiovascular safety.

I will start again. I am going to talk about cardiovascular safety only in TARGET. So, this is a very focused presentation, and I am not going to discuss any other aspects of safety, such as hepatotoxicity, I am not going to discuss efficacy, so I would urge you not to jump into conclusions regarding the risk-benefits of lumiracoxib without having all the data on hand.

I am going to TARGET. I hope you remember everything that was presented before lunch, because I don't want to repeat everything. We know TARGET

was a large study, 52 weeks, 18,000 patients with osteoarthritis, that had two sub-studies, one comparing lumiracoxib and naproxen, the other, lumiracoxib and ibuprofen.

About 25 percent of patients were on low-dose aspirin, and they were two identically designed studies although there was a little less exposure in the second study, in the lumiracoxib and ibuprofen study, and there was some imbalance, slight imbalance in the cardiovascular risk factors between these two studies.

I want to point out that the dose of lumiracoxib that was used was 400 mg daily and that this dose has been mentioned before, that it is 4 times the recommended dose, however, that the effectiveness of this dose has not been demonstrated to the FDA's satisfaction yet.

So, we don't know exactly what this dose means. Initially, it was thought to be twice the recommended dose, now the sponsor is pursuing the 100 mg dose. So, again, this is hard to draw conclusion from this dose into what is going to be

in the final dose.

Regarding the cardiovascular safety, I want to point out that the primary endpoint here was confirmed and probable APTC endpoint. For example, Merck used only confirmed events. So, you cannot really cross-compare the numbers here to the other trials at Merck.

So, it includes cardiovascular and unknown cause of death, myocardial infarction, clinical or silent, and stroke, hemorrhagic or ischemic. Again, this specifically includes silent myocardial infarction, which was not particularly specified in the Merck definition. And then there were other variables, they were looking at everything.

So, here we have the same disposition of the slides that I showed yesterday. Here, you have the name of the study, the drugs used lumiracoxib, naproxen, ibuprofen, the number of patients randomized in this row. Before, I didn't have it up here, but now I have the patient years of exposure. As you see, there is a little less exposure of this study, but not that different.

Here we go to the APTC events. We have 40 events with lumiracoxib and 27 on naproxen as compared to 19 on lumiracoxib and 23 on ibuprofen.

So, the first thing that I think stands out is that there is a different number in the total number of events, and particularly the number of events on lumiracoxib is half in the study 2332 than in study 0117.

If you go through the different rows, the difference is driven by the non-fatal MI here in the lumiracoxib as compared to naproxen. This number, as I mentioned, includes silent MI.

Here, we have in this column the number of events and the rate expressed in 100 years of exposure, 100 patient years of exposure. This is a different way of presenting the data than the sponsor presented.

Here, in this column, we have the relative risk, which is the overall risk of lumiracoxib versus naproxen, and I did not include the confidence intervals here basically because it would make the slide so busy, but also there were

not statistically significant difference in any way you looked here.

So, again, if you look at the relative risk here of all the events to be increased. For lumiracoxib, it is increased, lumiracoxib compared to naproxen particularly driven by the number of non-fatal myocardial infarctions.

This is the Kaplan-Meier plot with the time to events information, with the percentage of patients with events, and here time and date. As you see, there is a separation between lumiracoxib and naproxen, that it starts early, before day 50, and seems to have a constant overall risk here.

However, if you remember, for example, in VIGOR we have the separation after a month, but if you think about APPROVe, the separation wasn't until after 18 months. So, this is only a year, so we didn't get into what we saw with APPROVe yet here.

These are the numbers for 2332, the number of confirmed and probable APTC events, and here you see that the numbers look pretty much the same.

The relative risks are all around 1 or below 1 for all categories.

Here, we have the Kaplan-Meier plot and they look pretty close here. This is lumiracoxib in red and this is ibuprofen.

Now, if we put the two lines together, we see that lumiracoxib in study 0117 was up here, and lumiracoxib in study 2332 was down here with ibuprofen and naproxen in the middle.

So, I think that is very difficult to interpret anything from this study, because lumiracoxib look like two different products in two sub-studies within the same study.

This slide shows the difference in the number of events by aspirin use. I am not going to give the relative rates, et cetera, but it is just to show you the numbers, how if you look in the lumiracoxib/naproxen sub-study, again, the number we said was driven by the number of non-fatal MIs, the non-fatal MIs among the non-aspirin users, because if you look at the number of aspirin users, the number is the same, 6 and 6.

This has to do with the size, because only 25 percent of the patients were on low-dose aspirin, so this may have something to do with

power, but again I think it is unclear what the role of aspirin is here, may be protecting, that is possible, but what I am concerned about is that the use of aspirin, if you have a substantial number of patients on aspirin in a trial that is evaluating cardiovascular safety, actually, that may blur a little bit the results.

Here, in 2332, we see that in the non-aspirin users, there is no difference, and if you look at the aspirin users, actually, there is a trend that goes, that the situation was on ibuprofen users who also use aspirin, and this trend is consistent with that hypothesis that actually ibuprofen depleted the anti-platelet effects of aspirin.

This is just to show the number of non-fatal myocardial infarctions in the first study, the lumiracoxib/naproxen. Here, we have all patients. The number was 18 versus 10. In the

non-aspirin population 10 versus 4, in the low-dose aspirin population 8 versus 6, and here you have the relative risks.

This is taken from the paper in the Lancet by Farkouh, et al.

Again, we see a signal here of lumiracoxib and naproxen, but this signal seems to start earlier than what we have seen before.

So, in conclusion, we cannot draw definitive conclusions regarding the COX-2 selective class effect. If anything, I think that this is consistent with what we have been discussing during the last two days, and that this seems to be a class effect.

We don't know that selectivity is a continuous variable, so different NSAIDs have different degrees of selectivity, and they are associated with different cardiovascular risks, and the same with the different so-called coxibs, but I never like that name, because to me they always were NSAIDs.

But anyway, I think that this adds some

information to the puzzle that we need to put together and decide what to do with this class of agents. I know that this was only one year. Now, we are expecting to see longer studies than one year now, this is up to a year, which at that time seemed to be a long time, but now that we look at it, we think, okay, we would like to see what happened in the next two years.

These included patients, some of the patients had increased cardiovascular risk as they were using low-dose aspirin, however, this was a study only in patients with osteoarthritis, it did not include patients with rheumatoid arthritis, and we know that rheumatoid arthritis is associated with higher cardiovascular risk than osteoarthritis.

So, that may have something to do with the findings, although we did see the findings really in the naproxen sub-study.

Again, I am not clear as to the role of aspirin here. Regarding blood pressure, for rofecoxib I think that blood pressure is an

important factor. I am not saying it's the whole explanation, but I think that is an important role.

However, here, I am not showing any data, but if you remember the data presented by the sponsor, ibuprofen affected blood pressure more than what lumiracoxib did. Actually, ibuprofen affected blood pressure more than what naproxen did. It was like a 2.7 change in mean blood pressure for ibuprofen. It was a 1.4 change in mean blood pressure for naproxen.

So, here, we see the association. There is not a big increase in blood pressure, but we are still seeing the signal. Again, we didn't have placebo here, so we don't know how these were compared to placebo.

Another thing that I want to mention is that lumiracoxib is structurally related to diclofenac, and we don't know how diclofenac would compare to lumiracoxib in this case.

This is it.

DR. WOOD: No back-up slides, good.

We are going to take a break and we are

going to be back here and start at five past 3:00, and then we will start with the discussion of the presentations of the two previous drugs, and then we will go to the general questions after we have dealt with that.

So, we will come back at five past 3:00 and start with the discussion of the Merck presentation and go on to this one second.

(Recess.)

Committee Questions to the Speakers

DR. WOOD: We have three tasks that we need to get through this afternoon, so pace yourselves as you think about that, colleagues.

We have got to deal with the questions and the issues that came up from the last two sets of presentations. We need to have Dr. Furberg address the Pfizer issues that he raised yesterday and give Pfizer the chance to respond to that, and we will come back to that in a second.

The third we need to do is start to address the questions that the FDA prepared for us. So, there are three tasks we need to get through.

It is just after five past 3:00, and we need to get started on that.

Let's begin with the questions for the speakers on etoricoxib.

Oh, Dr. Hennekens first.

DR. HENNEKENS: In the 1970s, I was in Oxford with Richard Peto. I had the privilege to help him put together the APT Collaboration. We prespecified non-fatal MI, non-fatal stroke, and all vascular deaths as the combined endpoint. We specifically excluded silent MIs in the first cycle in '88 and the second with Rory Collins leading in '93, and the third with Colin Baigent, now called the ATT.

So, Merck, in my view, has used the correct APT now ATT definition. It is Novartis and the FDA that are at variance with what the APT definition.

I had a question for the FDA presenter. One of the things Peto told me is if you torture the data enough, they certainly will confess, but with that as a background, the lumiracoxib

comparison versus ibuprofen is 0.76, against naproxen it's 1.46, and the conclusion is that the drug is behaving differently in the two studies.

Well, the alternative hypothesis based on the evidence we have seen so far is that there may be a protective effect of naproxen and perhaps some harm of the shorter acting NSAIDs, a hypothesis supported by the basic science showing some deleterious actions of all the NSAIDs, but this potential beneficial effect on platelets of the longer acting NSAIDs.

So, I think it may not be necessarily true that we need to conclude that this drug is behaving differently in two studies with two very different comparators.

DR. VILLALBA: My conclusion was that I really don't know what to make of it, and that is why I need the opinion of other people here.

The conclusion really was that this probably a class effect, this is a very heterogeneous class, and you have all the degrees of selectivity there. So, that is what we need to

determine.

DR. WOOD: We have got Dr. Stephanie Crawford.

DR. CRAWFORD: Thank you. I would like to ask Dr. Sean Curtis to please come to the microphone if you are in the room.

Dr. Curtis, this morning you stated that in global markets, Merck is currently revising its labeling for etoricoxib to address new safety information relative to the safety of selective COX-2 inhibitors, so I am intrigued. In what manner, specifically, what is the sponsor stating in its revised labeling worldwide on the safety of this product?

DR. CURTIS: We participated in the European referral. It has been basically a referral process for all the COX-2 inhibitors, and that is actually just wrapping up, as you know. I, of course, have been here, but I am aware of now that there has now been wording for the label that talks--and this is basically class labeling in terms of contraindications--but I think really what

it boils down to, you know, we have been informed from the CHMP that there will now be a classwide contraindication for all coxibs related to congestive heart failure.

It was previously classed as 3 and 4, it has been extended to Classes 2 through 4. In addition, there will be contraindications in patients with established ischemic heart disease and/or cerebrovascular disease, so that will be class contraindication, class labeling.

In addition, for Arcoxia or etoricoxib, there will be contraindication in patients with hypertension whose blood pressure has not been adequately controlled.

So, that is obviously new information as of today, and that is, in essence, what I mean by working with the regulators, based on new and evolving information, to come up with product labeling that accurately and adequately reflects current knowledge.

DR. WOOD: I think she was asking you--which I suspect is going to be the committee's

focus the rest of the afternoon for both the sponsors, for the committee at least to decide what the committee would need to see before they approve new drugs like this--I think what Dr. Crawford was asking was what were the studies you were proposing to do to do that. Is that right, Dr. Crawford?

DR. CURTIS: Could you restate the question? I couldn't hear you.

DR. WOOD: I think the question was what studies were you proposing to do, that you thought would help get this drug approved in the future.

DR. CURTIS: As I reviewed through my presentation, we feel the underlying safety information that is most relevant to ensure that we are all comfortable with the safe and effective use of the drug, is to proceed with the studies that I outlined this morning, namely, EDGE II and MEDAL, which are, as I reviewed, opportunity to assess the long-term safety of the compound in contrast to traditional care, namely, diclofenac.

I reviewed the reasons why we chose diclofenac. There is pluses and minuses of the

comparators, but that is our primary method to further assess the compound at this point in time.

DR. WOOD: Put on slide 31 again, would you. That was the slide that showed the relative potency on the COX-1 and COX-2.

Basically, I think Dr. FitzGerald said earlier that he saw this as rofecoxib lite or something. So, given that you presumably wouldn't have expected to see a difference between your new drug and rofecoxib, it seems like you picked the next best thing to do as your comparator.

Naproxen is up there higher up, and you picked the one that was closest to rofecoxib to make your comparator, so the chances of seeing a difference seemed to me extraordinarily small, and I am not sure what that will teach us.

DR. CURTIS: Could we go to slide 1115, please. The slide that I just showed as part of the core presentation was the weighted mean average. I did also want to point out that diclofenac here, what is plotted here is again at steady state and a percent inhibition from baseline again of a COX-1

assay looking at platelet, thromboxane, B2.

This is a plot of inhibition both at peak and at trough of the exposure in the blood. You see diclofenac at trough has about 60 percent inhibition of thromboxane, but at peak, achieves levels that are close to 90 percent, so there is some variability in the degree of thromboxane inhibition throughout the dosing interval.

I went through the reasons why. I showed some clinical data, too, that did suggest that at least from a GI tract perspective, which, of course, is ultimately one of the key safety endpoints, that there is a way to differentiate diclofenac from other NSAIDs--excuse me--from what we consider COX-2 selective inhibitors.

I showed you data with valdecoxib and rofecoxib. In thinking about other comparator choices, there are limitations to the use of the other NSAIDs that I reviewed, and I think fundamentally one needs to keep in mind that diclofenac at this point is, in essence, probably the NSAID used most worldwide currently.

So, you know, in acknowledgment of the limitations of choosing any single individual comparator, and in acknowledging some of the

limitations that were reviewed perhaps in the TARGET study even, where if you do start to do sub-studies, you do run the risk of showing different estimates even with one comparator, even with the same compound.

We felt that doing a large study of the magnitude that I described for MEDAL against one comparator, and I reviewed the reasons why we chose diclofenac, was as reasonable a choice given all the alternatives.

DR. WOOD: Garret, are you still here? Maybe the question to him is supposing that study turns out with no difference, are you going to hear from him that he doesn't believe that tells you anything because it is just another COX-2 selective drug, is that what we are going to hear, Garret?

DR. FITZGERALD: I would take a slight different tack. We have heard the words "continuous variables" used quite a lot, and I

think it is a continuum from as one extreme, very selective, very long-lived drugs, going through shorter lived, less selective drugs through to very non-selective drugs.

I would guess that the ease of detection and the size of signal would move across that spectrum from being very large to being very small or undetectable.

So, I won't reiterate the reasons why. I think diclofenac resembles remarkably Celebrex with respect to selectivity, and I would view this trial as actually a very useful trial, beginning to address for us information that we need to know. I would cast it as a within COX-2 selective trial in that respect.

It is like we have a surrogate for Celebrex. We saw a lot of little trials with many flaws in the blood pressure arena yesterday, setting up Celebrex against rofecoxib with arguments about timing of dosing, and so on.

Well, here the rubber meets the road. We actually addressed the question of whether a

commonly used, relatively selective drug, diclofenac, stacks up in a way that segregates from a longer lived, much more selective drug, etoricoxib, so I think it does provide useful information in that regard, although I might cast the reasons for why I think it is useful in a slightly different way.

DR. WOOD: Any other questions? Dr. D'Agostino.

DR. D'AGOSTINO: This is both for Joel and Sean.

You raised the question, Sean, about doing a non-inferiority study, and I am wondering--that certainly will be a discussion that we will have--and I am wondering if you realized the implications of that.

When you look at, for example, slide 44, in your presentation, and you look at the EDGE study, was the EDGE study a non-inferiority trial?

DR. CURTIS: I actually wanted to clarify something that Dr. Schiffenbauer mentioned. So, the answer is no. The non-inferiority criteria

that I identified in the presentation is based on cardiovascular safety data accrued from three studies: EDGE, EDGE II, and MEDAL. So, the cardiovascular non-inferiority criteria is to be applied to the minimum 635 confirmed thrombotic events that will accrue from three studies.

DR. D'AGOSTINO: From the three studies, not one at a time.

DR. CURTIS: That's correct, but I am providing you data that is coming available, and EDGE had finished, and it is an important piece of information.

DR. D'AGOSTINO: That is comforting in terms of what is possible, but just to point out that on that result, that would not be very positive for you if you did the 1.3. You would actually, in that case, say that the comparator could be better. I mean that would be a conclusion in that study.

I don't want to go into the details of that, but one has to be very careful when they go the non-inferiority route, and we will talk about

that more. This slide frightened me a bit.

The other is if you do go the non-inferiority route, what about the inclusion of the aspirin individuals, it probably won't be a constant hazard in the sub-groups, but what will happen then with your non-inferiority. This was raised by Joel, and I would like an answer. I would love to hear what your answer is.

DR. CURTIS: Aspirin, of course, it is hard to win with that, and I will tell you why. On the one hand, you want to include patients with a range of baseline risk, and certainly one criticism of some of the studies is that patients with cardiovascular risk have not been included in these studies.

Both us and the FDA felt it was important, as the data provided to included patients with baseline cardiovascular risk, but, of course, those patients should be on aspirin.

So, we, of course, allow patients to be on aspirin as per clinical guidelines. As I mentioned, we expect about 30 percent of the total

patient cohort in the cardiovascular analysis will be on aspirin.

But I want to be clear, the primary analysis will be based on all patients whether they are on aspirin or not.

DR. D'AGOSTINO: But are you going to be assuming in the 1.3 that the hazard ratio will be the same within that sub-group, but just that it will be a different level of absolute risk? We will talk about those things, but those are serious implications.

I would have to have a study design where the very first thing you do is say, well, gee, I couldn't do what I set out to do, I have to look at subsets, namely, I have to get rid of the aspirin users because they are confounding things.

Was that the concern that the FDA is having?

DR. SCHIFFENBAUER: Yes, as I expressed, in the non-inferiority design where we don't have the placebo background, this would be a maneuver to make the two groups look more similar. I mean if

you extrapolate it to 60 percent or 80 percent aspirin use, I think the two groups would look almost identical, so you would end up having to look at subsets, that is true.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: Yes, I have a question for Dr. Villalba

DR. WOOD: Can we just deal with the first presentation first.

DR. ABRAMSON: I am sorry. Then, I will wait.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: Dr. Curtis, I have a concern about the selective emphasis of data being presented in seeming replicate trials. If we go to slide 10, for example, and again in slide 46, you commented that etoricoxib was superior to naproxen in one of two pivotal studies, but similar in the other study, and based on that one study, you have used the term "superiority" at least twice in your presentation.

I guess I am kind of wondering, if you did

a back of the envelope calculation, like Dr. Fleming did yesterday afternoon when we were discussing two polyp trials, one of which we gave more focus to I think than the other, would you still be able to make this claim of superiority based on the meta-analysis with both trials?

DR. CURTIS: My point in highlighting the efficacy data was, of course, not to talk about a claim of superiority. The purpose was to provide data that provides you and all of us an opportunity to look at both the risks and the benefits of the compounds, and the data in RA were compelling, and I fully disclosed results from both studies.

Furthermore, the data, these really were the first studies that we are aware of that showed a statistically significant difference. So, my point was again in the context of an overall risk-benefit assessment, to claim--to not claim, but to show the data for this compound at the doses that were studied provide a level of efficacy that certainly should be part of the consideration.

I certainly would not be claiming any sort

of label claim or anything like that, because we are not here to talk about such things.

DR. GIBOFSKY: I take your point, but specifically, if you combine the second study with the first, would you use the word "superior" to naproxen, or would you use the word "equivalent" to naproxen?

DR. CURTIS: I can only talk about a clinical study within the context of that clinical study where patients were randomized evenly between treatment arms. I think it would be speculative to talk about combining the results.

DR. WOOD: Dr. Shafer.

DR. SHAFER: If you can go to slide 19, and we see here that once again the confidence bounds around the three groups do not really justify the breaking out of naproxen, it would appear to me, as a separate group.

Now, go to slide 44. Once again you have broken out naproxen as a separate group although it is not clear that the confidence bounds would support that either.

So, we have a pattern where you are constantly seeing a worse outcome compared to naproxen, and similar to rofecoxib, where the same

signal came up, you asked, I think, or you mean to imply to us that naproxen is intrinsically different, but we have heard multiple experts over the course of the last day and a half tell us that they don't believe that naproxen is intrinsically different.

We have seen observational trials in which there may be a modest effect of naproxen, but certainly nothing of the magnitude to explain a 1.5, 1.7 risk relative to naproxen that you have seen in your data, and even the sponsors themselves, Roche and Bayer, in their presentations, felt that naproxen did not have the cardio-protective effects that you have attributed to it.

So, first, I am disturbed that your primary analysis isn't versus NSAID comparisons, all NSAIDs, and then as a subgroup, you compare naproxen out. Instead, you pull naproxen out and

ask us, I mean the implication almost is that we should dismiss it, because it's naproxen, and then look at everything else. It concerns me that we aren't primarily looking at all NSAIDs as the comparison group.

Secondly, at this point in time, do you truly believe that naproxen and the postulated cardio-protective benefits of naproxen truly explain the difference that you are seeing, and that we are not actually seeing a very solid signal for intrinsic increased cardiovascular toxicity with the COX-2 antagonists?

DR. WOOD: And while you are answering that question, tell us why the right study wouldn't be to do a naproxen with omeprazole versus your drug. I mean you obviously believe naproxen beats the drug, right? And the only advantage of the drug over naproxen is a GI benefit.

Supposing omeprazole gave you the GI benefit and you still had the cardiovascular benefit, wouldn't that be the optimal therapy? And why, given your data here, did you choose to go

with the drug that has less benefit than naproxen? I still don't understand that.

DR. CURTIS: I am going to answer your second question first. Naproxen clearly is a very effective drug, however, as we heard repeatedly today, patients have different responses to therapies. Again, the reason people with arthritis take drugs is so they can have some relief. Not everybody responds to naproxen.

So, I think naproxen clearly is a very logical choice for many patients, but there are going to be patients who do not respond to naproxen, and when you factor in GI risk, adding a PPI certainly would appear to likely to mitigate some of the risk, but you are still going to be left with patients who don't respond to naproxen, who still are going to have a residual GI risk, and we have seen data that suggests even when you add a coxib or a PPI to an NSAID, there is still room to improve from a GI safety perspective.

So, I think that as a therapeutic option, selective COX-2 inhibitors, including etoricoxib,

still have a role. As to why we chose not to use naproxen as the comparator in our outcome study, I reviewed the reasons. We have now seen qualitative differences in cardiovascular outcomes against naproxen with three different COX-2 selective inhibitors: rofecoxib, etoricoxib, and lumiracoxib.

We felt that doing an outcome study against naproxen, we would likely replicate that observation again. We felt it was important to accrue additional data against another traditional NSAID that was used widely around the world to get a more firm estimate of what the cardiovascular risk looked like against another NSAID.

DR. WOOD: You looked at that data. You saw that naproxen beats your drug. So, you decided to pick one that didn't look like it would--because it is as selective as your drug is--and you are going to come back with that data and say wow, it doesn't produce any cardiovascular signal because it's the same as diclofenac. That doesn't make any sense.

DR. CURTIS: Again, I think it is important to remember that the qualitative differences that were observed against naproxen

were being seen at the same time that no differences were being observed with non-naproxen NSAIDs, and in a time frame like a year for which a difference from placebo with COX-2 inhibitors has not been appreciated.

So, I think all that data, to me, continues to say that there is something different about naproxen. I can't quantify that, I don't think the data allow that, but there clearly appears to be something different about comparisons to naproxen to the other NSAIDs.

DR. WOOD: I understand that, but the issue that has changed since hour initial studies with naproxen is that we now have three randomized trials against placebo in which placebo beat the drug. So, using an active comparator that you have chosen to match in terms of cardiovascular adverse events, etoricoxib, isn't acceptable in terms of showing that the drug doesn't have an effect on

cardiovascular mortality or morbidity.

It might have been acceptable in the days when you believed that naproxen was beneficial and that that was the total explanation, but by your own admission, you don't believe that anymore.

DR. CURTIS: So, if I understand the question, you are asking why we are not doing a large outcome study against naproxen?

DR. WOOD: I guess I am asking you what you are going to learn from the diclofenac study. You are certainly not going to be able to say that this drug does not produce cardiovascular problems given that you have deliberately chosen a drug that looks as similar to etoricoxib as you can get, and from your earlier studies, namely, this one, you have seen that it does produce a difference with naproxen, and it doesn't appear to produce a difference with this, and it has got a very similar pharmacology.

So, if you can imagine an imputed placebo arm here, and given what we know about placebo, you would predict that this drug would do worse than

placebo, and you won't be able to exclude that from the study you are designing.

DR. CURTIS: The data that are emerging, that we have all seen the APPROVe data, we have all seen the difference against celecoxib in the APC study, to us, that suggests a class effect. I have showed you our placebo-controlled data for etoricoxib, it's very limited.

With that being said, the class effect related to COX-2 inhibition, we would presume extends to etoricoxib, and, to us, the real clinical question is in patients who require chronic treatment, what is the cardiovascular safety against a standard of care, and for the reasons I reviewed, we chose diclofenac.

DR. WOOD: So, let me be sure I understand. So, we are going into this study saying that we know and believe that the drug will produce a cardiovascular signal, we are just trying to work out if it's better or worse than diclofenac.

DR. CURTIS: No, I think what we are

asking is--

DR. WOOD: Well, that is what you just said, isn't it?

DR. CURTIS: If I could rephrase what I said, I think what we are saying is we are suggesting there is a class effect, and we are not sure how big the class is, and we feel that the MEDAL study will help provide information to address that specific question, whether cardiovascular safety for selective COX-2 inhibitor is the same or different than that of a traditional NSAID, one that is the most widely used NSAID around the world currently.

DR. WOOD: Okay. Dr. Bathon.

DR. BATHON: I was going to say much the same thing. I have the same concerns about this especially since naproxen is the most widely prescribed NSAID in the U.S. and the most relevant to our practice, whereas, diclofenac has much more hepatotoxicity especially in RA patients where methotrexate is co-administered.

So, I think it would have added a lot more

to our clinical practice management to see another big trial against naproxen rather than diclofenac, plus you could have added these results to your prior trials and had more power to assess the effect of naproxen versus etoricoxib with all of your trials combined, but now, since you are using diclofenac, you don't have that extra power.

DR. WOOD: Dr. Reicin.

DR. REICIN: Let me just make one comment, and as all you start to talk about designing clinical trials, I think you will see, as many of you know, it is quite difficult and you cannot answer every question in every study.

MEDAL was started over two years ago, and at that time there was no placebo-controlled data to suggest that COX-2 inhibitor was different than placebo. Obviously, that has changed. The studies are fully enrolled and ongoing.

I can't disagree with you that the idea of doing a naproxen plus PPI study versus a COX-2 inhibitor isn't a good idea and isn't an important question. Unfortunately, we didn't design that

study, we designed this one, and I think, as Garret said, it will provide information about how big the class is.

While some of you may not be using diclofenac, it is the most widely used NSAID in the world, and therefore, I think it will provide beneficial safety data to see what a selective COX-2 inhibitor looks like versus a non-selective inhibitor albeit not as non-selective as naproxen.

DR. WOOD: Thanks.

Dr. Dworkin.

DR. DWORKIN: Yes, a simple question. You said that the CPMP had come up with class labeling, but you neglected to tell us CPMP defined the class. Is it all NSAIDs, is it COX-2 inhibitors, and if the latter, what drugs were included in that subclass?

DR. CURTIS: I am going to give my understanding as a clinician who has been here for the last 48 hours, but my understanding it is specific to what we consider the selective COX-2 inhibitors - celecoxib and etoricoxib, and that

that is how the class is being defined currently.

DR. DWORKIN: So, those two drugs, but not, for example, Meloxicam.

DR. CURTIS: Dr. Erb, would you like to comment on any additional agents?

DR. ERB: Yes, Dennis Erb from Regulatory Affairs.

The CHMP is included in the class, what we have been referring to today as the coxibs, lumiracoxib, celecoxib, and etoricoxib, and valdecoxib.

DR. WOOD: Dr. Platt.

DR. PLATT: More on the history of the choice of comparators. Dr. Schiffenbauer, could you tell us more about the conversations between the agency and the sponsor around the choice of comparators?

Your comments and the materials you presented to us suggested that you had reservations about that choice.

DR. SCHIFFENBAUER: Yes, we had extensive discussions with the sponsor. At the time we

appreciated the difficulties doing a placebo-controlled trial, but we had requested--and I can't quote you whether it was additional comparators or comparator--but we had recommended strongly that additional agents be studied to get a better handle on the true cardiovascular risk.

DR. PLATT: Was there discussion about naproxen as a comparator?

DR. SCHIFFENBAUER: Not specifically other than to mention that we recommended additional comparators.

DR. WOOD: Dr. Farrar.

DR. FARRAR: One of the things that strikes me about all of the studies that we have been looking at, and perhaps most in the comparison of studies that we are still waiting for some data on, namely, APC and CPAC, is the difference in the underlying risks between some of these different comparisons.

I noticed that in your particular study, the cardiovascular risk, you felt that 38 percent--I think that was the number--that in your

slide you had 38 percent at an increased risk of cardiovascular disease with 24 percent on aspirin and 10 percent of them as being diabetic.

I just wondered if you could comment on what the mix of the MEDAL study is likely to be or is. I mean you certainly would have the data at this point.

DR. CURTIS: Yes. 1103, please. The MEDAL study population is, as I mentioned, both OA and RA patients, so approximately 75 percent of the patients have OA and about a quarter have RA. What is represented here are the risk factors for the cohort, the entire cohort, and it is not dissimilar to what I highlighted for the EDGE study.

These are basically baseline medical diagnoses at the time of entry into the study, so about half have hypertension, which is a little higher than the EDGE study, which was about 40 percent, as you see here, the individual cardiac risk factors, and this 12 percent of history, that is documented atherosclerotic cardiovascular disease. The 38 percent that I quoted for the EDGE

study was patients with this or to primary risk factors.

So, that percentage, if I were to calculate that percentage for this study, it would probably be a little higher than EDGE, probably about 40, 42 percent. So, these are the patients in MEDAL.

DR. FARRAR: If I could just follow up and ask actually Garret FitzGerald, whether he has any comments on the relative risk of patients who have either high or low cardiovascular risk factors.

I mean we know from the study, the CABG study, that patients with very high risk clearly have a marked increased response to these drugs, and whether people who have cardiac risk factors are also in that category, or whether it really is restricted to sort of the release of active agents from the surgical procedure.

DR. FITZGERALD: Well, obviously, the actual information we have relevant to your very important question is conjecture. What we know mechanistically is that what we would expect would

be the response to thrombogenic stimuli would be enhanced, as would the predisposition to the other cardiovascular adverse manifestations of this mechanism, namely, hypertension and atherogenesis.

So, for example, if a population was enriched in patients with secondary hyperaldosteronism, they would be more prone, on average, to exhibit hypertension in response to an NSAID or particularly a selective COX-2 inhibitor.

Similarly, if they were at advanced risk of hemostatic activation, they would be prone to the thrombogenic complications, and I think with the CABG patients, we had an extreme phenotype of excessive hemostatic activation.

Now, as we move away from that extreme through what we call "heightened" cardiovascular risk, there is probably a continuum of predisposition that is a mix of predisposition to the various types of manifestation of this mechanism that could occur.

So, we have only crude indicators obviously, and to some extent, as I talked about

yesterday, it's in the eye of the beholder as to what defines heightened cardiovascular risk, but on average, the group defined as having higher cardiovascular risk, for example, RA compared to OA, on average would be expected to show a signal easier than in a group with low cardiovascular risk.

I mean I would think with this type of study, we may have had a premonition of the outcome from the EDGE result. For example, if we think of these two drugs as defining the limits of a class, just for fun, one could say like in the EDGE results, you wouldn't see a distinction in the hard GI endpoints or the hard cardiovascular endpoints, but what you might see a distinction in is their fringe surrogates, which might be easier to pick up, such as discontinuations because of hypertension or discontinuations because of GI side effects, and that is actually what was seen at the two ends of the spectrum in the EDGE result.

DR. WOOD: But we do know from the APPROVe study that the point estimate, even in the people

with no history of cardiovascular disease, which would be the only clinical measure we could reasonably use to distinguish that, it is still substantially greater than 1.

DR. FITZGERALD: Yes, I mean I did try to raise the issue yesterday that how we define underlying clinical substrate is an inexact science, on the one hand, and on the other, that many other factors that we discussed yesterday could play into the likelihood of manifestation of risk at the individual level.

DR. WOOD: Steve.

DR. NISSEN: I want to maybe bring us back to earth a minute and talk about the time horizon for such a trial. I feel compelled to point out that we have got a lot of history in cardiovascular medicine of studying drugs for atheroprotective effects.

Those trials are typically not one year or two years or even three years, they are typically five-year studies, and in many of them, let's take a blockbuster class of drugs like the statins.

Look at the CARE trial. The CARE trial, the Kaplan-Meier curves didn't diverge at all for two years, and so now we have got a drug here that

may be promoting atherogenesis, and so we are going to say, well, we are going to have a 20-month mean exposure, and if it doesn't produce a problem, then, there must not be a problem, and I am not sure that's right.

The problem we have is that what has been done here is the sample size has been increased to a large sample size in order to shorten the duration, but that may not be the same as studying a more modest size group of patient for three or four years.

It is assuming that the hazard is constant over time, and I am not so sure that it is here. If, in fact, Garret is right, and he has been right about a lot of things, that these drugs are potentially atherogenic, then, an atherogenic intervention may not produce an effect for several years.

So, how can you reassure us here that a

20-month mean exposure is enough to allow us to move forward with a drug like this?

DR. CURTIS: I think what you are touching on is--I am not going to disagree--what I am going to point out is the fact that I think running an arthritis study is perhaps different, and I have not designed outcome studies, cardiovascular, other than this--but to keep arthritis patients in studies is difficult, and that has to do with the treatment of the disease.

As the rheumatologists here can speak to, a traditional trial has 40 percent of the patients discontinuing after one year, and another 10 to 20 percent dropout rate every year subsequent, so there are significant practical limitations to keeping patients on study therapy into the time frame that you proposed, Dr. Nissen.

So, that is a practical limitation to running arthritis studies.

DR. NISSEN: I just would also point, however, that the patients that we studied initially with these atheroprotective drugs were

very high risk secondary prevention patients. These were not low risk people.

So, you are going to take a lower risk population and you are going to look for a signal at a 20-month mean duration, and that signal may actually take longer to show up in a lower risk population.

So, I am troubled by how long we have to look for with a drug like this before we really can say there isn't a problem. People may take these drugs for a decade. We heard that from people at the microphone here.

So, these are some of the things that trouble me about the whole question.

DR. WOOD: I have got a whole list of questions here, but I want to keep us moving here.

So, are there any people who have burning questions that they want to torture Dr. Curtis with before we let him off? It has to be specific. We will take Tom, we have not heard from you yet.

DR. FLEMING: Burning?

DR. WOOD: Burning.

DR. FLEMING: There are two or three issues I want to quickly review. You didn't mention in EDGE the new ischemic heart disease or

the heart failure, pulmonary edema, cardiac failure. I think the FDA indicated in their review, there was a 25-19, and a 14-6, so basically about a 30 percent relative increase and a doubling in those two, is that your understanding?

DR. CURTIS: The numbers, yes, Dr. Schiffenbauer quoted, those are the correct results, and that information was in your background package.

DR. FLEMING: And then very quickly, your slide 19 and then your slide 25. On your slide 19, do you have the analogous slide for the APTC results? If you don't, my understanding is the relative risks are less favorable than this or more unfavorable, depending on your perspective.

They are 1.8, 0.87, and 2.72?

DR. CURTIS: That is correct, yes.

DR. FLEMING: So, essentially, we are looking at with roughly a 3 to 2 randomization in

the aggregate, and the aggregation of these events here, we are looking at 43 versus 12, so a pretty substantial excess in the critical APTC measures.

DR. CURTIS: Well, again, as you know, the APT events in total are smaller than these numbers, so your confidence intervals around those point estimates are, in fact, much broader.

DR. FLEMING: But at 43 to 12, they are certainly well outside of unity.

The last thing is slide 25. You give the mortality results, but it is difficult to really see in this scale, but it appears that the relative risks are roughly in the range of 1.6 against placebo, also 1.6 against naproxen, and 1.2, and then in addition to that, it is also 1.33 in the EDGE trial.

So, it looks as though when you look in terms of relative risks, that you are looking at about a 1.5 relative risk on mortality across the aggregate of these data.

DR. CURTIS: Yes, this slide shows the rate with the confidence interval. I don't have

the relative risk.

DR. FLEMING: But those aren't relative rates is my point.

DR. CURTIS: That's correct, these are absolute rates here.

DR. WOOD: So, you are saying this stuff doesn't look it's good for you. Anyone else who has a burning question? Go ahead.

MS. MALONE: It's burning. I would like a simple answer. How much different--now, I heard him call this like Vioxx lite, I believe I heard him say that--how different is this from Vioxx, you know, chemically, and do you see it as a substitute for people who are perhaps taking Vioxx?

DR. WOOD: I think we are talking about diclofenac. It was the comparison to diclofenac which had been referred to.

MS. MALONE: He also did a presentation on etoricoxib. So, can he answer that?

DR. WOOD: You are asking me?

MS. MALONE: No, him. Okay, I am sorry, I thought you had said that about etoricoxib.

DR. CURTIS: Can you clarify the question, please?

MS. MALONE: I am just wondering how the

compound in etoricoxib compares to Vioxx.

DR. WOOD: You mean chemically?

MS. MALONE: Yes, but in simple terms.

DR. CURTIS: The human whole blood assay, if that is your specific question, the human whole blood, which is sort of the gold standard, that shows a degree of COX-2 selectivity that is greater for this drug, but in the clinical dose range, etoricoxib, just like rofecoxib, just celecoxib, just valdecoxib, are selective for the COX-2 enzyme in the clinical dose range, so in that regard, they are similar.

Does that answer your specific question?

MS. MALONE: I am just wondering, you know, I have heard people say that Celebrex or Vioxx was much more selective than Celebrex and Bextra, and where does this fit in, in that scheme?

DR. CURTIS: Again using the human whole blood biochemical assay, this drug would be

considered more selective, but I think the key concept, at least for me as a clinician, is that in the dose range that these drugs are used, they all selectively inhibit the COX-2 enzyme and do not inhibit COX-1.

DR. WOOD: Let's move on to the next set of presenters and let Dr. Curtis off the hook. Thank you very much.

Are there questions for the Novartis presenters from the committee? Some of the people who are still waiting for the questions, we will begin with them if they want to start with the other ones. Dr. Abramson had one, I know, and we punted.

DR. ABRAMSON: That was the TARGET presentation by Dr. Villalba. I would like to just throw slide 9 up, if we could, and follow up on a point that Dr. Hennekens made when we started this session.

In that slide, you combined the two component studies of TARGET and again said that lumiracoxib behaved differently in the two studies,

but I think that is probably incorrect to put up a slide like that. It is like putting up a CLASS and a VIGOR slide together, because these were, as I understand it, separate studies and separate populations.

That is the comment, but the other interpretation, as we heard, is that lumiracoxib performed less well than naproxen, maybe because it has a risk and maybe the naproxen has some protective effect, but was comparable ibuprofen, which again raises a question whether ibuprofen has some risk attached to it.

But my question is that you then said that you attributed these findings to a class effect, and since definitions are going to become very important for us going forward, I was wondering if you could tell us what you meant by a class effect and what you were referring to, is it the class of NSAIDs?

DR. VILLALBA: Yes, yes. First of all, this slide was made by the sponsor, we didn't make the Kaplan-Meier curve, so this was just a

different way of presenting the data. I don't think it was in the background package for you, and I thought it was an interesting way of looking at it, raising the issue that precisely you cannot just combine the two studies, because the sponsor also has presented the data of the two studies combined, lumiracoxib with NSAID, and you cannot just combine these two studies, because they are different studies.

I agree with you, you cannot cross-compare even within the same study that had two sub-studies, so we cannot compare to other studies that were done with different designs and different entry criteria, different endpoints, so that was the point of the slide.

Regarding the class effect I mentioned, I referred to the NSAID class effect. I think that if there is an effect, it is for the entire class, and that is a very heterogeneous class with different degrees of selectivity within the NSAID class. That is what I meant.

Actually, let me clarify. We also thought

that naproxen could be protective. I was seeing these data at the same time that I was reviewing all the other rofecoxib studies, so I guess you can understand what our position was at this time.

DR. WOOD: Dr. Furberg? No? All right.

Dr. Bathon?

DR. BATHON: This was a question for Dr. Matchaba.

I think there is an interesting observation about the TARGET trial. Before we even consider comparing lumiracoxib to the NSAID comparators, but just looking at the baseline APTC events in the two sub-studies of TARGET, there is an event rate of 0.43 percent in one trial and 0.84 percent in the other trial, in the lumiracoxib-treated individuals.

That is a 2-fold difference although the numbers are small. I am wondering if that could have been contributing also to the ultimate difference between lumiracoxib and the comparator drugs.

Even though you used the same inclusion

and exclusion criteria, could you tease out any differences in the two study populations that were enrolled into the studies that could have explained the baseline difference in events in the lumiracoxib groups? I don't mean baseline, I mean the accumulated events.

DR. MATCHABA: Thank you very much for the question. If I could have No. 8 and then could I have CV No. 67.

As we discussed, the TARGET study was a combination of two studies. The only thing identical about the studies is the design of the studies, but as I mentioned in the discussion today, that this study against naproxen started about 4 to 5 months before this study against ibuprofen, and that the centers that were used for this study were different centers even within the same country, and the staggering of the recruitment was to ensure that centers were not recruiting for the same study.

In some cases, countries that participated in one study did not participate in another study.

Can I see the CV67, please.

We have also asked this question to say why are we seeing differences in the rates of

cardiovascular events for the 1-1 study versus the ibuprofen sub-study. What we have done here is to look is it a center effect, and there is obviously a lot of reasons, we don't have all the answers or explanations, but if you see for the major recruiting countries, Argentina, Germany, and the U.S., that the naproxen sub-study, in terms of rates of APTC events, were always higher than for the ibuprofen sub-study even in the same country.

So, if you look at the demographic data that we also presented to you today, where 25 percent of the patients in this study were taking low-dose aspirin, where we had a difference of 14 percent versus 10 percent in high CV risk, that these populations are different in terms of baseline risk, and certainly that might be an explanation, it could be chance because the confidence intervals cross, but we don't have all the answers, but we think we have different study

populations.

I might ask Dr. Michael Farkouh to elaborate on that because he was involved in the design of the study and he was the primary author for the TARGET cardiovascular paper.

DR. WOOD: Have we got the question answered? I think we have. Let's move on. Dr. Abramson, did we answer your question already? Okay. Dr. Cryer.

DR. CRYER: Thank you. I have been trying to understand the differences in the results between the TARGET trial and previous outcome studies of COX-2 specific inhibitors. One very clear difference is in how the definitions were rendered.

One thing that concerns me is that in the lumiracoxib experience, both your CV and GI events are defined to include people that not only had definite MIs and definite GI events, but also included those people who had probable events.

Typically, I am more used to seeing trials in which we are looking at fully adjudicated

definite events. When I looked here, for example, at your CV events, and eliminate what you call silent MIs and look at just what would be considered clinical MIs, there is an apparent 3-fold increase with lumiracoxib for clinical MIs compared to NSAIDs, which dramatically differs from your other conclusion.

With respect to the GI events, I think that you actually studied a low GI risk population. We know that the relative risk of COX-2 specific inhibitors to have a GI benefit is greater in a population that has low GI risk.

Specifically, you didn't include anyone who had had a previous history of a GI bleed in the last year, and greater than 50 percent of your patients were less than 64 years of ago.

So, my question to you then is, have you re-evaluated your data using more conventionally accepted criteria, for example, fully adjudicated clinical events rather than include their probable events?

DR. MATCHABA: All the cardiovascular

endpoints, APTC, including silent MI, peripheral events, deep vein thrombosis, pulmonary embolism, TIAs were all predefined and prospectively adjudicated blindly by an adjudication committee before the study started.

This includes the GI or ulcer complications and PUBs with the different definitions that have been used, including clinically evident bleeds, were also predefined by a gastrointestinal committee.

DR. CRYER: I understand it may be predefined, but I am asking do you have data if you excluded the probable?

DR. MATCHABA: Yes. Perhaps Dr. Farkouh would like to comment.

DR. FARKOUH: Michael Farkouh from New York University. Our blinded adjudication committee, the definitions of probable or definite were purely on the basis of if we had all-source documentation versus our clinical judgment of the committee, which is many years of experience. I happen to be the most junior member. A probable

cardiovascular event really, in our mind, was a definite, that we just may not have had all the source documentation we needed, so it really was adjudicated as--probable was an element or a degree of definite is how I would put it.

DR. CRYER: With all due respect, I will ask the question a third time. Do you have data eliminating the subset of people who were classified as probable, and looking only specifically at those who you felt were definite events?

DR. FARKOUH: From our clinical cardiovascular committee, we did not feel there was any distinction between the two of them, so we did not mandate that. To be a probable event, I think any cardiologist that would be on this committee or anywhere else would have documented this as an event. So, it is a degree of definitiveness. We did not mandate that.

DR. MATCHABA: If I can just add to that, the answer is yes, and if you just look at confirmed cardiovascular events, the analysis is

the same, and just to add, that for silent MIs besides what Dr. Farkouh has added in terms of prospective definition, there was a total of 32 clinical MIs in TARGET, and there were 8 silent MIs.

Of those 8 silent MIs, 5 of them were in NSAIDs and 3 on the lumiracoxib. When we look at silent clinical MIs, we still see the same trends whether you compare the naproxen versus lumiracoxib with ibuprofen versus lumiracoxib.

DR. FARKOUH: There is a moving target here. The definition of MI has changed over the last five to six years. We have a much more enzymatic definition of MI which we have adopted, and also the definition of silent MI has been adopted into this modified anti-platelet trial.

I agree with Dr. Hennekens that it is not part of the sharp definition, but rather we were encouraged due to the signal of MI that has been seen in this class of drugs that we document silent MIs, and this was adjudicated through a blinded ECG core laboratory run at the University of

Pennsylvania.

DR. WOOD: Dr. Fleming.

DR. FLEMING: Could we go to slide 33. There, I think what you have tried to do is capture the aggregation of the favorable effects on reducing upper GI ulcer complication and the unfavorable effects on the APTC.

I guess my first thought is that since you didn't present the global data, I would assume the global data is your primary analysis, and by my crude calculation, the relative risk reduction is probably more towards 25 percent or so rather than the 41 percent that you are showing.

But I guess more to the point, is it not apples and oranges here as you are trying to look at the aggregation of evidence?

The ulcerative complication rate has been reduced from 1 percent to 0.4 percent, so we can think of it in terms of per 1,000 people, there are about 7 cases that are prevented, and the APTC is increased from 0.57 percent to 0.84 percent, so for 1,000 people, there are 3 of those cases.

Isn't it a little fairer to think of it in that context? We have got per 1,000 people, 7 of these ulcerative complications prevented, and while

those are substantial events, is it not true that predominantly patients recover and don't have long-term sequelae, while you are inducing 3 APTC events that are CV-strokes or MIs that have much more long-term effects?

So, isn't that a fairer question, and while this picture makes it look like it is a clear positive, I would have thought the answer is much less clear, if not clearly negative.

DR. MATCHABA: Thank you. It's a fair question. If we look at this combination of safety data for the overall lumiracoxib compared to NSAIDs, the reduction in the overall population is 35 percent. It was 25 percent in the naproxen population overall, and it was not significant.

DR. FLEMING: I am focusing on just the slide you are giving, which is the slide against naproxen, so just to keep it simple in the comparison against naproxen.

DR. MATCHABA: Yes. I think the first comment we will make is that the comment was made in the VIGOR study that any events that do occur in terms of ulcer reduction and complications are negated just quantitatively by the increase in cardiovascular events.

I also made the comment that this is certainly not validated, but it is an attempt on our part that using this unvalidated method for the first time and prespecifying it and stacking up the primary endpoints, what does the picture look like relative to comparators in the same study.

DR. WOOD: What Dr. Fleming is asking you, that there is a qualitative difference--

DR. FLEMING: Apples and oranges, yes.

DR. WOOD: And a GI bleed is not the same necessarily as a stroke. They don't compensate for one another. That is not a criticism, it is just a fact.

DR. MATCHABA: Yes, that is a valid point.

DR. WOOD: And I think that is what he is saying, am I right?

DR. FLEMING: Correct.

DR. WOOD: Any other questions for the sponsors? Before anyone thinks of any, let's move along.

DR. MATCHABA: Thank you very much.

DR. WOOD: One of the things that we left undone from yesterday was that Dr. Furberg raised some issues that he was unclear of some differences that he thought he saw in the Pfizer briefing book

and from his calculations.

I charged him with meeting with Pfizer and trying to resolve these. Dr. Furberg, did that get resolved?

DR. FURBERG: We met and I got some clarification, but I continue to be troubled.

DR. WOOD: So, the answer is no I guess. Why don't we do this then.

DR. FURBERG: I think there are five issues.

DR. WOOD: Why don't you tell us about the issues and let's give Pfizer an opportunity to respond.

Curt, why don't you go through the issues as you see these.

DR. FURBERG: The first one related to the number of trials included in the integrated safety analysis for the acute pain studies. There was in one place mentioned that there were 18 trials, in another place there were 20, and the explanation that was given was that the 18 trial analyses excluded 2 trials, the one using the highest dose of the drug, 60 mg--more than 60 mg a day.

That doesn't satisfy me. If you are looking at safety, the trials with the highest dose

are the ones that I am primarily interested in. I think the company did the proper thing, they included information about that, but they should have included that in the pooled analyses, as well, and that would have changed the message that you take away from that summary table. So, that was one issue.

DR. WOOD: Let me ask Pfizer, do you want to respond to each one in turn, is that the easiest way?

DR. HARRIGAN: That would be fine with me.

DR. WOOD: Let's do that, then, we can see what the issues are.

DR. HARRIGAN: Just one slide, slide D114, please. Ed Harrigan from Regulatory Affairs, Pfizer.

What we have done with this slide is basically pulled the two paragraphs from the briefing document that Dr. Furberg was describing. In Section 3.3, anybody who has the briefing document and who downloaded it from the web would be able to find these on pages 55 and 76.

In Section 3.3, as Dr. Furberg points out, we integrated safety data from acute pain studies, 18 of these studies, and as it says in the

paragraph, they represented 4,087 patients treated at a dose range of 20 to 60 mg total daily dose.

Later, in Section 3.6, we described 20 completed studies representing a larger number of patients treated with valdecoxib at a dose range greater than 20 mg total daily dose.

Now, the difference between these two

paragraphs is largely due to the CABG Study 035, which is described in great detail, in fact, six pages devoted to the CABG studies in the briefing document.

It is a matter of opinion as to whether one should have pooled this data. If one had pooled all the 80 mg data, then, one might have been accused of diluting the 80 mg treatment effect that was seen in the CABG 035 study. On the other hand, the 035 study was presented by itself with full representation of the safety issues in that study, which have been discussed in great detail here in the committee, appropriately so.

I think that is probably the end of response to that point.

DR. FURBERG: The second issue is to the mean consistency in the reported event data. Again, we are back to the same integrated safety analysis of the 18 studies, and Tables 19 and 20 indicate that there was a total of 4 to 6 MIs depending on how you define them, whether you include sudden death in the report.

Well, separately, there were data presented on two of the trials that were included among the 18, and I just added up the number of MIs

and I come up with the number 8 to 10 when I define it as non-fatal MI and fatal CHD. So, you already have a negative balance. What happened in the remaining 16 trials?

The explanation that was given was that in the second CABG trial that got involved in the analyses, they subtracted the number of events when the patient was on the I.V. formulation parecoxib. I looked it up and it turned out to be one case. So, that doesn't explain the discrepancy, so the explanation that was given was not satisfactory.

DR. HARRIGAN: Could I have slide D116, please.

This is Table 20 in the briefing document, I can't give you the page number. So, as Dr. Furberg points out, this is a table that shows placebo 2,468 and the 4,087 patients from the valdecoxib studies at doses of 20 to 60 mg. Three myocardial infarctions in the valdecoxib treatment

group.

Now, Table 22 is an illustration, it is a table titled from one of the tables, there are Tables 22 through 27 in the briefing document, which report on the adverse events in the rest of the studies described in that portion of the briefing document.

As Dr. Furberg points out, we reported to him earlier today that the myocardial infarctions that he saw in the general surgery study and in the two CABG studies, if they occurred to parecoxib, they were assigned to parecoxib. These are trials in which treatment with parecoxib took place for a certain number of days, and then patients were switched to valdecoxib.

If you assigned an event to both treatments, then, of course, you are going through tables until midnight, because they won't add up. You have to assign the event to one treatment or the other, they were appropriately assigned to parecoxib, and so they are not accounted for in the valdecoxib column.

A second reason for a difference is that the adverse events in the tables that Dr. Furberg was drawing them from are adjudicated adverse

events. So, these are events that were determined according to prespecified criteria in both of the CABG trials and in the general surgery trial.

So, aside from the parecoxib confound, you wouldn't expect those adverse events to add up to adverse events reported in a different way. This is frequently an issue in safety summary documents. There are a number of different ways to record adverse events.

You have serious adverse events, you have spontaneous adverse events reported to marketed drugs, you have adverse events recorded in case report forms in clinical trials. By presenting them several different ways, you are sure that you are giving the entire picture, because you don't want to select one picture and be accused of not showing the other two, but you can be guaranteed the columns will not sum up.

DR. WOOD: But parecoxib is the pro-drug

for valdecoxib.

DR. HARRIGAN: It is.

DR. WOOD: So, as far as my body knows when it gets parecoxib, it has got valdecoxib.

DR. HARRIGAN: Two points. One is that the events are described in the briefing document as you see, but they are assigned to parecoxib. I don't know if you are suggesting that all treatment groups that receive parecoxib, all patients that receive parecoxib be transformed to valdecoxib.

DR. WOOD: I guess the body transforms it to valdecoxib.

DR. HARRIGAN: It would obscure the data from the effects of parecoxib, which is given by different formulation. Some people consider that significant, so I think to describe it under parecoxib is appropriate. To not put it under valdecoxib is appropriate. The data is in the briefing document, it is not hidden, it is not suppressed, it is clearly available in the briefing document. The columns do not add up. We think there are good reasons why they do not add up.

There are alternative ways to present safety data. We are happy to, and frequently do, re-run safety data and safety tables with different algorithms and different rules.

DR. FURBERG: The numbers just don't add up.

DR. WOOD: Have you another point, as well?

DR. FURBERG: No.

DR. WOOD: I suggest that we are not going to resolve this this afternoon, so why don't we defer this to Dr. Temple and his staff to resolve. Is that fair, Bob?

DR. TEMPLE: Yes. Curt agreed earlier that he would write down exactly what the concerns are, and we, not me, will follow them up and pin down what is going on.

DR. HARRIGAN: It is important to us that members of this committee and the FDA, and other health agencies worldwide understand that we do not suppress safety data. We report safety data, we report it in a number of different ways, we do not

suppress safety data.

DR. FURBERG: But it would be much better if you explained why you did it differently and present the data in one way in one table, another way in another table, the numbers should add up if you have information from two trials and you have more events than you have in the pooled analysis of 18, that has to be explained.

I think there are some numbers that will be hard to explain away.

DR. WOOD: I think we have got it that there is still a bone of contention here. Let's move on to the three questions that we were charged with discussing this afternoon.

Dr. Gross, I think wanted to make some comments before we get to the first question.

Committee Discussion

DR. GROSS: On the first question, I would like to propose a construct to deal with the issue is the increase in cardiovascular risk a class effect. My proposal is to say yes, it is, but the degree of difference and the time of difference

varies and is different enough that one or more of the drugs that we have discussed should be marketable with a precaution and/or warning, and one or more of the drugs we have discussed should not.

A reasonable analogy is statins. As we know, they all have potential for liver toxicity and myopathy. That is a class effect, but the degree of this difference and the time when it occurs varies and is different enough that one or more of the drugs have been marketed with a precaution or warning, and one or more have not.

Tomorrow, we will discuss specifically the recommendations on celecoxib, valdecoxib, and rofecoxib, but I thought I would start off the discussion with this question about a class effect.

DR. WOOD: Okay. Dr. Nissen.

DR. NISSEN: Did you mean class effect for the COX-2s, or are you talking about NSAIDs, as well, because the question is asked for both here. So, I want to know which of those you mean.

DR. WOOD: Let me make a suggestion. I

think we should start with COX-2s. The data we have seen is by far the most convincing for that. Then, let's move on to any other issues.

DR. NISSEN: So, let me agree that is what we are talking about then.

DR. WOOD: Let's have a discussion around the COX-2s first and whether the available data support a conclusion that cardiovascular risk is a class effect for all--

DR. GIBOFSKY: Could I just interject and ask then that we discuss it in the context of patients with arthritis versus patients with other conditions?

DR. WOOD: Okay, that's fine, the committee can do that, but remember we are not discussing the relative risk-benefit at this point. We are discussing whether there is an effect, a signal, in other words.

DR. GIBOFSKY: I understand, but I think it is relevant to look at the populations in which the signal has been detected.

DR. WOOD: Do you want to comment on that

and save us going to back? Do you think that the arthritis population will be likely to have a lower risk than the other populations?

DR. GIBOFSKY: I am merely saying that I think that one looks at populations. As we have heard, there is variability in the population, and just as we wouldn't automatically extrapolate efficacy data from one population to another, I am not certain we can automatically extrapolate safety data from one population to another, and I think we need to discuss it in the context of the population studied.

DR. WOOD: Any other comments on this question?

DR. ILOWITE: I think you made the point that this was merely a discussion of safety, but I think the way the proposal was worded, there is implications about cost-benefit with regards to whether they should be approved or not. Could you repeat the--

DR. WOOD: You have the question in front of you.

DR. ILOWITE: The proposal.

DR. WOOD: Dr. Gross made a proposal, but the question we have got in front of us is to

discuss the available data supporting a conclusion of increased cardiovascular risk for COX-2 selective nonsteroidals.

I think we need to discuss that before we get to risk-benefit frankly.

Dr. Nissen.

DR. NISSEN: I think your proposal is an appropriate one and I would point out that we have at least one randomized trial for every drug that has been marketed in the class that shows an effect.

DR. WOOD: You mean a risk.

DR. NISSEN: That makes the grade in terms of calling it a class effect, but I think that there is clearly evidence of a gradient in risk, and that gradient is not only by drug, but also by dose.

So, saying it is a class effect means--let me tell you what it means to me. It means that if

you give a high enough dose of one of these drugs to a risky enough patient, you can produce an increased risk of adverse cardiovascular outcomes. But it doesn't mean that a particular dose in a particular population is risky.

DR. WOOD: Dr. Fleming.

DR. FLEMING: I think there is a great deal of data that is giving us a general sense, but there is an inadequate amount of information to really get at the specifics, and what I mean by that is certainly the indication, the dose, the duration of therapy, the nature of ancillary care, for example, aspirin use, these are all factors that obviously could influence the answer.

The approach that I took was to try to summarize the essence of what I think we have been presented in the randomized trials, and I focused in particular on those that were the major trials, many of them looking at somewhat longer term exposure and longer term follow-up.

There are about 15, and just to quickly run through them, in the Vioxx setting, there are

23,000 patients from four major trials. Those studies indicate something on the order of 1.4 to 1.5 relative risk, and driven heavily by VIGOR and APPROVe, and neutralized somewhat by the Alzheimer's 078-091 trial although that trial had surprisingly considerable excess deaths.

In the Bextra setting, the Nessmeier 071 trial, the 035, and 069 studies give about a 2 1/2 relative risk even though it is certainly heavily driven by this CABG setting.

In the Celebrex trials, the CLASS, the Alzheimer's 001, the APC, the PreSAP, now, we know there is the ADAPT, but we haven't been shown that, so I did the first four, and we are looking about a relative risk of 1.3, driven heavily by the APC trial and the 001 study, and neutralized by the CLASS study and the PreSAP that were more neutral.

The etoricoxib, the EDGE trial, and the other three that we were presented give us a relative risk of about 1.625, and in the lumiracoxib, it is about 1.18 relative risk from the TARGET trial.

Now, to put these into context, if we were trying to show--I am just going to give your four scenarios--a doubling. By the way, I am working

off a 1 percent background rate, and that is just about what these data show in the aggregate, in 73,000 patients, about a 1 percent aggregate rate for the primary cardiovascular endpoint of cardiovascular death, stroke, and MI.

If you were trying to show a doubling, it takes 88 events or about 5,000 people. If you were trying to show a 50 percent increase, it's 256 events, 20,000 people. If you are trying to show a 33 percent increase, it's 508 events, 40,000 people, and if you are trying to show just a 20 percent relative increase, from 1 to 1.2, it's 1,265 events or 115,000 people.

Where we are, if you ignore all those factors that I was arguing we can't ignore because the answer isn't the same, but if you put all this into a single pool, these add up to something in the neighborhood of a relative risk of about 1.4 to 1.45.

So, essentially, what it would have taken to discern that is an aggregate data of about 70,000, although the observed results that you would have to have, you would have to have a study on the order of about 5,000 people, because an observed result of 1.55 or 1.45 is statistically

significant when you have about 6,000 or 7,000 people.

So, the point is when you look at the aggregate, we have substantial data to say there is conclusive evidence here in the aggregate that there is the cardiovascular risk.

Now, what can we say individually? In the Vioxx setting, where the risk is about 1.43, one would need to have, with that observed rate, you would have needed to have data on about 6- to 8,000 people. We have data on 23,000. That is why the evidence there is very clear.

In the Bextra setting, we only have data on 3,000 in the Nessmeier 035 and 069 trials, but the relative risk is 2.58, and for a 2.58, you need less than 2,000 people, hence, that is why it is

statistically significant in that setting although it is only in the CABG setting.

It is also in the etoricoxib setting with the relative risk of 1.625, we would have needed less than 5,000 people. We have 17,000, so it is statistically significant in that category.

In the lumiracoxib setting, we have a relative risk of 1.18. That would have taken over 40,000 people for that relative risk to be detectable. We only have 18,000. So, it is suggestive of a modest or moderate excess, but it is not proven because of the smaller sample size or because of the smaller effect.

In the Celebrex, where it is about 1.29, it would have taken 20,000 people, if you observed that in 20,000, it would have been marginally significant. We observed it in approximately 12,000, so it is suggested, but not established.

Now, a lot of this, this is looking at things in a first pass. It is suggestive that there is something going on in all of these cases, but at very different levels is what at least the

data show, but the data aren't conclusive for us to be able to say in a reliable way what is the indication, what is the dose, what is the duration, is it in aspirin, not in aspirin, but globally, there certainly is an effect that is going on here, and for three of these five, it seems to be conclusively established, and for the other two, more modest effects that are suggestive.

DR. WOOD: Thanks. Dr. Shafer.

DR. SHAFER: I don't know that this will help our discussions at all, but I think one of the things we need to address is what is a COX-2. It has been assumed, I think, that we are going to go with the company's definitions when they way we have a COX-2 drug, COX-2 selective, but, in fact, if you go to Warner's review in FSAAB here, from 2004, we see that Meloxicam, Sulindac, and as we have heard, even diclofenac is potentially considered a COX-2.

Should we include these drugs in the discussions? We certainly won't have the evidentiary evidence that we have.

DR. WOOD: Let's stick to the drugs for which we have got evidence, otherwise, we will be here until midnight.

DR. WOOD: Charlie.

DR. HENNEKENS: I want to support the very crucial statements of Steve and Tom here. It does appear to be a class effect, which varies by drug and by dose, but the magnitude of that risk, which I also estimate to be 1.4 to 1.5, is lower than one would have guessed based on the early data-dependent stopping of some of these trials, based on the reported research, and the media coverage of all of this, so I think it is important to get Tom's quantitation and Steve's caveats about dose and drug and magnitude in there.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: I want to go back to this issue of definitions because I don't think that it is that simple to say that the coxibs that we are talking about are the only drugs that we need to discuss.

The concept of diclofenac lite, that

Garret proposed, or has stuck, but I think that term could be applied to Meloxicam, nemesulide. I think what we are stuck with is that assuming there is a class effect, we haven't excluded the fact that that class includes those other COX-2 preferential drugs, that we might agree that COX-2 inhibition is at fault here, and that is giving rise to some of these side effects, but it isn't precisely due only to those drugs.

Now, those drugs happen to have done the long-term studies, they have done them frankly at 2X dose compared to their comparators, and frankly, when you look at the randomized clinical trial development program with a relatively few placebo arms, the drugs look relatively comfortable.

So, if you conclude that there is an increased risk because of COX-2 effects and hypertension perhaps, then, I don't think it's really fair to restrict the discussion simply to those drugs that got marketed as coxibs, the randomized clinical trials, especially if you do agree that perhaps Naprosyn has a modest protective

effect, I think don't give a bye to these other drugs.

I think we have to look at certainly the case of celecoxib, that drug is relatively comparable pharmacodynamically to the other several drugs, so I think it is a much more complicated question than simply saying the COX-2 coxibs in this discussion, and we have to do apples to apples if we are going to make recommendations.

DR. WOOD: Dr. D'Agostino.

DR. D'AGOSTINO: My comment is very much the same. I am concerned about taking all these individual studies. I think, you know, sort of the potential is clear, but are we really lumping just because there is a direction on these here.

Tom, for example, the question about splitting the arthritis populations versus the other populations, the arthritis populations come basically from the old clinical trials where adjudication was a problem and things of that nature. So, how much do we believe that data and how much do we want to draw this inference?

So, I don't have a problem with sort of coming up with some sort of global statement that we are concerned, but I am concerned at this point

about quantification in a very heavy way, and we just may be overdoing it in terms of how we are sort of answering this question.

DR. WOOD: Just to make sure I understand your point, you are concerned about putting a number on it?

DR. D'AGOSTINO: I am concerned about this global, I mean for us to say that it's all COX-2.

DR. WOOD: But you would be comfortable naming names?

DR. D'AGOSTINO: I don't know what I would be comfortable with. I am uncomfortable with the sort of global statement that we have seen a number of studies--

DR. WOOD: I am just trying to draw out what you are saying. You would be more comfortable--

DR. D'AGOSTINO: The only thing we said in terms of separating was the arthritis studies. Are

we comfortable with the arthritis studies, do we have enough information, do we feel comfortable enough with the adjudication process, the recognition of the cardiovascular events in those studies? I mean I think I am much more comfortable when we come to these new studies.

DR. WOOD: So, what you are saying is that the dilutional effect of these old studies may be substantial.

DR. D'AGOSTINO: Exactly, and I don't know how we are actually dealing with that.

DR. WOOD: So, that is important for people to understand. Do you want to develop that a bit?

DR. D'AGOSTINO: What is that?

DR. WOOD: So, what you are saying is that the studies that didn't have a cardiovascular endpoint--

DR. D'AGOSTINO: And trying to get adjudication. They were showing a signal. We already there is a signal.

DR. WOOD: So, they may be diluting the

effects from when Tom adds on the back of the envelope--is that reasonable, Tom?

DR. FLEMING: Well, I fully agree that the best analysis of this is one that we don't have the time to summarize here right now, but it is one that will drill down in all of these dimensions as best we can.

Almost certainly, the answer is here, if we had unlimited data. We have about 75,000 people. That is a lot of insight, although we need far more than that. We do have another 30,000 coming along shortly.

In essence, though, what we really need, if we had the ideal, is that ability to drill down, as Ralph says, by indication, and by dose, by ancillary care, looking at whether or not it is an aspirin or not an aspirin, by duration of therapy. These are all things that we have seen the data suggesting that there is very likely these factors are influential.

So, essentially, my attempt was to say, in a very crude way, what do you see from 10,000 feet

here, but then acknowledge exactly, as Ralph said, that you really do need to drill down.

DR. WOOD: It is not likely to be less than the numbers you gave. It is likely to be more, right?

DR. FLEMING: Well, my own sense about this is this is the weighted average of the compilation of all these different settings, and so in all likelihood, in fact, with certainty, there will be settings where it is less, there will be settings where it is more.

Can you, for example, give Celebrex at a low dose with a short enough duration that in wide settings, it would be safe. That is still entirely possible within the context of what we have said. Those are issues that we really need to understand.

DR. D'AGOSTINO: And I am concerned somewhat that if we give this global statement, that we sort of can't get back to the question you just raised, can we look at Celebrex at a low dose, because somehow or other, we are saying it's in all the COX-2s.

So, I want to be just careful in how, the answer to this question, how it comes out quantitatively and what it locks us into in terms

of further discussion.

DR. FLEMING: What I would say is that--and I do agree that we need to look beyond these five or six products--but what I would say in several of these products, not just Vioxx, in the certain settings that we have looked at, in my view, there is evidence that establishes there is an excess risk.

There are other products where there is a suggestion, and we are underpowered, though, to discern whether or not that suggestion--it is not a suggestion of nothing, though, it is a suggestion of something, but it is more modest in size than the other agents although it could be a dose issue, it could be an indication issue that explains it.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: I think if one looks, there is really an attempt here to look very carefully in these quantitatives that we can. I think Dr.

Fleming provided a remarkable compilation just now for us.

But I think if one backs off to sort of high altitude and looks at these drugs, the signal, as people are using the term, it is pretty clear that there is an excess risk conferred by some or all of these drugs.

It seems to me the process is sort of turning around. We are trying very hard, you know, the idea is to demonstrate--and it's the sponsor who has to do it--to demonstrate safety and efficacy, and not necessarily the purpose of the FDA or its advisory committees to somehow demonstrate that the thing is unsafe.

It does look like they are unsafe, but the problem is that the studies presented really are not very good studies, and, in fact, one of the reasons that we probably didn't learn sooner that there is probably a real problem with these drugs is because of the relatively poor studies that were presented for approval.

So, I think it is important to remember

who has got what role. It is theirs to demonstrate safety and effectiveness, it is not ours to demonstrate it's unsafe.

DR. WOOD: Right, but I think the FDA is looking to us to give them some guidance here, right?

DR. DOMANSKI: Well, that is important for the future particularly, that is, what studies should be done next, and that is a legitimate concern.

DR. WOOD: Bob, do you want to say something?

DR. TEMPLE: Just that it is the company's job to show that it is safe, but we sort of have to say what would constitute adequate evidence, what sort of level of risk do you have to rule out, how long, and things like that.

Of course, we are in the process of learning about those things as these data come in. As I said before, I don't think anybody would have thought you need a four-year study, but that is sort of on the table now, and it wouldn't have been

before.

So, it is helpful to know what kind of risk is plausible to rule out and all the things that Steve said before, I mean you have got to worry about what doses to study.

We encouraged everybody to study high doses to rule out GI distress. Whether that was wise in retrospect, I am not sure, and I think I probably had something to do with it a long time ago. I am not sure that was the best thing. We want to be really sure you couldn't make an ulcer. I, at least, wasn't thinking about maybe making something else.

So, all of those questions are things we need help with even though, yes, it's the company's job to bring the data forth.

DR. WOOD: Dr. Farrar.

DR. FARRAR: In terms of the specific question that we are addressing, I also just want to point out that there is a second part to that, which it says, also, discuss the possible mechanisms of action for an increased

cardiovascular risk with these agents. I think that has bearing related to the fact that if we accept that the in vitro selectivity of the COX-1/COX-2 analyses at least have some bearing on at least their metabolic process.

What I am struck by is the variability of the agents with regards to other factors indicating that simply COX-1/COX-2 inhibition is not their only action, and that the ones with some of the higher risks are not necessarily the most COX-2 selective.

What that suggests to me is that we really don't understand the process yet well enough to be able to say that it is a group selective, because I am not sure what a COX-2 selective one is, where do you draw the line.

I think a more appropriate way to say this is to say that clearly, the role of COX-1 and COX-2 inhibition are important in the process of both anti-platelet and perhaps platelet aggregation, and that those with a more predominant COX-2 component need to be studied carefully for the potential

excess cardiovascular risk.

I have a great deal of difficulty, though, saying it is the group of drugs that have been called that by the pharmaceutical industry. I think that that is being very short-sighted about this.

In fact, the data that we have seen in these presentations make me want to go back and look at ibuprofen with regards to a whole host of issues that we hadn't thought of before. So, I think it is very important that we keep in mind that there is not a distinct relationship between those numbers specifically and that we need to be a little bit broader in terms of that look.

The other point I would like to make is that we clearly need to differentiate in terms of what we are considering between the placebo trials, which have been done primarily in cancer prevention, and the comparative trials with other agents. As has been brought up many times, none of the agents are the same, and so the comparisons there need to be carefully considered.

As such, I am in favor of a statement that says that we are consciously aware that COX-2 is an important component of this issue, but that all

agents that claim to have, really all agents that are developed in the future and all the current agents need to be carefully looked at for the balance between the cardiovascular, GI, and other risk factors including the hypertension, including the pulmonary edema that we have heard so much about.

DR. WOOD: Right. One pragmatic way perhaps that we could handle this is there are two drugs of whatever the class we are talking about is that are left on the market, and for which we have a number of randomized trials recently, and we could consider them as a sort of present tense evaluation, and for future tense, other drugs that may have signals that we don't really understand, and certainly drugs that were likely to be marketed in this area, this space, and whatever that means, and would need some sort of evaluation.

So, that would sort of divide up our work,

so that we would be considering what to do about the ones that are out there, what to do about the ones that are potentially out there, and I guess a third group is what to do about other drugs that may or may not fit into this class or may not be at some extreme of this class.

Is that sort of capturing the essence of what you are saying?

DR. FARRAR: That is certainly one way of dividing up the work.

DR. WOOD: Let's think of it in terms of that as we move forward.

Dr. Holmboe.

DR. HOLMBOE: Actually, a number of the things that I was going to say have been said. I would just add one caveat, Tom, to what you said, that if you look at these trials, over 40 percent of the patients never made it to the end of the study, which means that we probably don't have over 70,000 patient observations. We probably have about 20- to 30,000 less who actually made it to the end of the trial.

That, I am very concerned about, and you look at these trials also, although they look similar when they are first randomized, that is the

purpose of randomization, the populations that get to the end don't, so I think that we are also lacking some very important information, what happened to a fairly large number of individuals who started but never got to the end of the trial.

DR. FLEMING: Just to respond to that, that is a key point. Now, the analysis that I did yielded approximately 7- to 800 events, so we are getting the total number of events that we would have needed from a 70,000 person trial, but your point is still well taken.

We are not underpowered because of the lost to follow-up, but there may be a bias here that we all talked about earlier, that if you really wanted to get the most insightful, reliable assessment, you need to have high quality follow-up, so that is something that is still a relevant point. They are unequal in their quality of study conduct in the area of follow-up.

DR. D'AGOSTINO: This was part of my concern in terms of what I was trying to raise, that we have studies, but we don't have studies, there is a lot of problems with it.

DR. WOOD: Dr. Dworkin.

DR. DWORKIN: Ralph, I have a question to

follow up on what you were saying earlier. If I understood you, you were saying that you are uncomfortable with a global statement of the sort that Dr. Gross was making because you feel there is some kind of heterogeneity amongst the data, of the type that Tom summarized.

But then it seems to me you are between a rock and a hard place, because if you believe that there is a great deal of variability in the results with respect to risk, how could we possibly discriminate amongst the different drugs.

DR. WOOD: We have done that lots of times before.

DR. D'AGOSTINO: The qualities of studies are different. I think the arthritis studies is where we get the CV information, they weren't

designed to get the CV information, cardiovascular information, so I think there is a signal there, but I don't know how to interpret it.

I think there is the problem of lost to follow-up and things of this nature, and all of those things make me very uncomfortable, and sort of making a global statement and then living with that global statement.

I think it is clear or hopefully it is clear what I am concerned about. We don't want to be locked into, by making a global statement, later on saying that no matter what drug we look at, we have an answer for, and it may be low dose of Celebrex, that may be viable, and not unsafe.

We really need to worry about the studies that we are going to suggest, and if we absolutely thought there were safety problems, why are we suggesting them, why aren't we just saying stop the studies and get the drugs off the market. I think there is a lot of room for maybe there is something going on that is safe, and we want to really pin the issues down in good clinical trials.

DR. WOOD: Well, we have dealt with drugs within classes before. I mean a statin was removed, but the other statin is on the market, and

troglitazone was removed, but the other drugs stayed on the market.

I guess the difference here, which is only fair to point out, is that this is thought to be producing toxicity through the primary mechanism of action. At least that is one of the postulates, but we certainly should deal with them as individual drugs, I think, rather than as a class of drugs.

Dr. Abramson.

DR. ABRAMSON: I guess what I am thinking, it is possible to accept the fact that many of these toxicities are via the COX-2 mechanism, but recognizing that all of the class of NSAIDs, by definition, when they are effective, are inhibiting COX-2, and I am still troubled by the population data which shows signals with indomethacin and Meloxicam, and by older data which shows congestive heart failure particularly with the non-selective

drugs.

So, I think that we have to look at again the entire class, and particularly if you look at the CLASS and the TARGET trials, why is ibuprofen and diclofenac behaving pretty much like Celebrex and lumiracoxib, so if there is an assumption on our part that this class of drugs, even the highly selective COX-2s, increase by 1.4, 1.5 the relative risk, why is ibuprofen and diclofenac looking pretty comparable in those large population trials.

One answer is that they, in themselves, whether diclofenac is rofecoxib lite or not, but they themselves are imparting a risk, but they themselves have not been subject to these long-term placebo-controlled trials that we see in APPROVe and ADAPT.

So, therefore, I think the COX-2 mechanism may pertain, but it cuts across all degrees of relative selectivity.

DR. WOOD: Dr. Furberg.

DR. FURBERG: Well, I spent about five years looking for a definition of class effect, and

so far I have been unsuccessful. There is in the literature no definition of class effect. The closest I came was an FDA definition of class labeling, and that was not a good one.

So, I think the working definition of a class effect would be that members of a particular group or class share common actions in the broad sense, and I think that would apply to the COX-2s in my reading. They provide pain relief, GI protection, raise blood pressure, cause fluid retention, have the undesired effects on cardiovascular risk, so in my mind this is a class and sharing a lot of actions, and that would include the increased cardiovascular risk.

DR. WOOD: I am going to take two more questions on this topic and then I would like to move us to, I guess, considering which drugs, to answer Question 1, which drugs, rather than a class, which drugs we see a cardiovascular signal with, which is one way to approach the problem.

You are the next question, Steve.

DR. NISSEN: What I wanted to make sure we

got to is this issue of mechanism, which is actually in the question here, and the reason it's important is that I am not quite ready to accept the hypothesis that one can predict from the COX-2 selectivity and duration what is going to happen in these drugs.

Let me see if I can explain that because I think it is very important as we think about how to go forward here. I see a broad spectrum of blood pressure changes that don't seem to be as tightly linked to the COX selectivity as one would guess.

Lumiracoxib, for example, which is very COX selective, doesn't appear to have much effect on blood pressure. Rofecoxib has the largest effect on blood pressure by far and is relatively COX selective, and they are very different.

So, for the FDA, I think if you want to characterize the drugs, not only do we need clinical trials around looking for GI safety and cardiovascular safety, we need a standardized method to look at the effect of these drugs and their intended doses on blood pressure, and they

ought to all be subjected to similar scrutiny, so we can compare apples to apples and wherever possible with active comparators, let us understand that.

Now, why do I say that? Because Bob and I have sat at many a meeting and looked at blood pressure drugs, and I can tell you the data on the relationship between relatively small differences in blood and cardiovascular morbidity and mortality is rock solid across a huge number of drugs and interventions, and you almost can predict what will happen.

So, we need to know--and as I sit here, I can't tell you that drug X in this class has Y blood pressure effect and drug A has B blood pressure effect--and so we don't know, and we can't inform physicians about that unless we have better data on blood pressure.

So, I am making an appeal that we get to that level of specificity, and that is not a very big trial to do that. Bob, what do you usually ask for in the blood pressure study?

DR. TEMPLE: Well, if you use automated pressure monitoring, I think you can get a decent answer with 20 or 30 per group, maybe 40. It's

very easy.

DR. WOOD: Let's move on. I am going to give you the last word in a second. After we get Dr. Gross's comment, we are going to divide this first question into three things, which drugs do we see a cardiovascular effect of, and the secondly, we can ask whether we see a class effect, whatever we understand that at, and I am not sure we do, and then the third question that is in Question 1 is what do we see as a mechanism.

So, let's divide them into these three things and let's move to an answer.

Peter, last word.

DR. GROSS: What we say here today about these is going to have a significant impact in molding public perception, and if we conclude that there is a class effect for the selective COX-2 inhibitors, and don't say the same thing about non-selective NSAIDs in general, then people are

not going to want to use COX-2 inhibitors at all and they will be using the non-selective NSAIDs, which from the data presented, doesn't look as though many of them are better from a risk point of view.

So, I just issue that note of caution.

DR. WOOD: Does the FDA want us to go around the table asking people for an answer to each of these questions, the subsets of these, John?

DR. JENKINS: I think we really viewed these questions as things to stimulate your discussion, not necessarily things that are amenable to yes/no answer. The yes/no answers come tomorrow.

DR. WOOD: So, can we move on?

DR. JENKINS: If you think you are done with No. 1.

DR. WOOD: We are done with No. 1.

DR. TEMPLE: I just wondered if people could come to grips a little bit with some of what Steve said and some of what other people said. I

absolutely don't want to put words in anybody's mouth, but what I heard people say was they think the class has at least the potential for having this problem because of the imbalance and because of the stuff we have heard about before, and that you need to look at each drug to see whether that is manifested at a particular dose-dose interval and all the rest.

I just wondered whether that is getting close to what people are saying or not, and I absolutely am not giving my view on it, I am just suggesting it.

DR. WOOD: Let me try and answer that and then we will go around and ask other people.

I think what we are saying is almost the same as the GI effect before the GI effect or not was worked out for the so-called COX-2 inhibitors, that I see an effect, a cardiac effect from valdecoxib, certainly from Vioxx, and from celecoxib, and there is a dearth of data on the nonsteroidals, the other nonsteroidals at this stage in terms of cardiac safety, and we are not

going to be able to decide that even on Friday, it seems to me.

In the presence of that signal, the prudent activity would be to go look at it sometime in the future, but we can't do that between now and Friday night. So, that is sort of where I come down.

Dr. Abramson.

DR. ABRAMSON: I might have a slightly different view, because I mean I think of the class more broadly as it is defined now to include both the COX selective and non-selective drugs. I think that there is a signal probably for all of these drugs, maybe by different mechanisms perhaps. I think we have under-recognized that in the population, I think physicians have not been concerned enough about blood pressure changes.

So, my view is that maybe there will be different mechanisms, but that each of these drugs is suspect as having an increased relative risk when used chronically, whether it is ibuprofen or the most selective COX-2.

My own view is, as I said earlier, is this is not dissimilar to the late '90s, and until you prove otherwise, this is GI warning that these

drugs may cause cardiovascular risk or GI warning it may cause serious adverse events, and I think each of them should be held to that right now until someone proves otherwise, because I think it would be wrong based on the evidence to assume that three drugs have a cardiovascular risk, and several of the others don't, simply because we don't have the evidence.

I am also concerned about some of the research that was talked about by one of the public speakers. At most of our universities, these studies have actually stopped because of concern that these drugs are not as safe than the non-selective drugs.

I think, particularly in cancer and others, we are doing the public a disservice by prematurely picking out these drugs as being unsafe and stopping some very important research where the risk-benefit might even be more important than in

arthritis.

DR. WOOD: Dr. Shapiro, I missed you, I am sorry.

MS. SHAPIRO: That's okay. I think I agree with you, and I think it is hard to properly answer this question unless we ask ourselves why it is being asked, and if it's being asked because the FDA wants some broad-brush, uniform regulatory approach to this, what I hear people saying around the table is that that would not be appropriate for each and every one of the drugs that are in this possible class.

But if we are saying that we think that drugs that are related in composition, structure, this, that, and the other thing, should raise a red flag, which is what I think you are saying, that is what I think we want to say, and I think we are getting hung up on this class effect definition because we haven't gotten behind and asked why we are being asked the question.

DR. WOOD: Dr. Furberg.

DR. FURBERG: I think I disagree with

Steve Nissen, and I think it is a mistake to focus on one mechanism of action. Members of a drug class, they don't have to share all mechanisms of action. In fact, I don't know of any drug class where all the members share all mechanisms of actions, so the term is more loose and relative.

DR. WOOD: Dr. Shafer.

DR. SHAFER: Actually, I think Dr. Nissen said that it's not all one mechanism. I think that is exactly your point.

DR. NISSEN: Exactly my point. My point, Curt, was that these drugs do differ by some of them have much more of pressor effect than others, and that seems to be dissociated at least somewhat from their COX selectivity, and so I want to characterize the drugs individually, not necessarily collectively.

DR. SHAFER: Continuing that same line of argument, Bob, in answer to your question that you had raised, if there was all the FitzGerald hypothesis, then, the class effect makes a ton of sense, because you would say okay, you look at the

COX-2 selectivity, we kind of go on the list, and we do our cutoffs.

We have the blood pressure data. I point out once again we do have the aspirin data in some very big trials. The effect should have gone away in the presence of aspirin particularly I point out again to the APPROVe trial, the thrombotic risk was 3.25.

We have talked about this on and off, and you haven't been feeling well, so we haven't had a chance to really get together and discuss, at risk of my health, despite having lunch at Chuck E Cheese, but I am concerned because we haven't explained the aspirin effect, and aspirin, unlike the other drugs, doesn't go away, it doesn't have a pharmacokinetic component. I mean that should have clearly made a statement if the aspirin effect had reversed these prothrombotic effects.

Steve, I think that argues to your point that there are several mechanisms. One is certainly in part the FitzGerald hypothesis although there is partly a class effect, but the

aspirin also shows that there is something else going on.

DR. TEMPLE: Then, how do you characterize the class? I mean it sounds like most people think you are characterizing the class as one with a preference for the COX-2 receptor, for that one, and if you can't do that, it is hard to know how to go forward.

DR. SHAFER: Can I answer that?

DR. TEMPLE: But I agree with you about the aspirin, it's a fly in the ointment.

DR. SHAFER: It seems to me that you can look at where we have data that is consistent with the FitzGerald hypothesis, that is consistent with it, that you can say these drugs are behaving as in class, and certainly for the coxibs, as Dr. Fleming presented the data, it appears that they are all behaving in a way that is consistent with a class effect.

Where we don't have more specific data that would say they are behaving in this fashion, and I would point out these are the COX-2s that we

don't have data because they are older drugs, but they appear to be COX-2 selective, I am reluctant to include those in the class and sort of damn them because of where they show up on some table. At the same point in time, I am reluctant just to give them a get-out-of-jail-free card, if you will.

I think that something needs to be noted that they are potentially at risk for this effect.

DR. WOOD: Dr. Cush, then Dr. Hennekens.

DR. CUSH: I would support what Steve said and that I think that we came here with the spotlight focused on Class II specific agents, but we become more curious as we have seen all of them fall, but then seen all the other drugs, the non-selective drugs also seem to have some of the same failings, we don't want to focus solely upon the COX-2 specifics, but I think that we can start there and then extend our concerns to the other agents, as well.

It doesn't have to be, it can be linked to COX-2, and that may be where we start, but it obviously needs other investigation to look for a

mechanism of action.

DR. WOOD: If Raymond Pickey were here, he would say show me the data that tells you that these other drugs have this effect in published trials.

DR. CUSH: Well, one would be I guess some of the observational data.

DR. WOOD: Randomized, published randomized trials.

DR. CUSH: Well, I think the only one we really have is the Norwegian study.

DR. WOOD: Is that a randomized trial?

DR. CUSH: I believe it was. Well, they were randomized to--

DR. WOOD: That showed aspirin also had a negative effect.

DR. SHAFER: Alastair, that is the reason the Challenger blew up, the sort of show me it's safe, prove to me it's safe or I am not going to make a statement.

DR. WOOD: That is not the issue at all. I mean we have got to be careful, I think, rushing

ahead of credible data on the basis of rumors of war that are brought in from outside.

I mean we have got four randomized and controlled trials for three drugs, and we have got some news of other drugs, it seems to me, that are not--and documented very well. That is not giving anyone a get-out-of-jail-free card, but I think we have got to sort of go through this in an orderly fashion. Otherwise, we will be regulating on rumor forever, and I think that is a very dangerous step to take.

DR. TEMPLE: You do have some diclofenac data i comparison to some of the drugs that are of interest, so you have some. It's not the placebo-controlled trial you are dreaming of, but you do have that, and you have naproxen and several comparisons, as well.

DR. WOOD: And that looks pretty good.

DR. TEMPLE: Naproxen looks good, ibuprofen looks the same as--there are, I didn't count them up, three or four control groups of the older ones scattered around.

DR. FLEMING: Well, we can be specific because Bob is right, we do have--I mean basically, because of all of these other studies that were

done for the COX-2 inhibitors, there is a lot of data on naproxen and a lot of data on diclofenac, and diclofenac in the etoricoxib trial and in the CLASS trial more or less came out looking like the COX-2 inhibitors, while the winner is naproxen.

Basically, in the VIGOR trial, in the etoricoxib trial, very much in the lumiracoxib trial, it came out positive. Now, we are going to hear something tomorrow about the ADAPT, but looking at these others, it sure looks like naproxen is a winner, and it does look like the theory that was put forward that diclofenac is COX-2-like is at least supported by the trials where it was studied.

DR. WOOD: Right, but all we can say is they look the same as another drug where we are not absolutely certain of the effect of that other drug.

DR. FLEMING: That is true although we

have a lot of other studies on the other drug, and it is always you have got to be careful when you say A is better than B, and then B is the same as C, is C worse than A, but there is that kind of evidence.

DR. WOOD: Which is what I am concerned about.

Dr. Hennekens.

DR. HENNEKENS: I would say I am struggling with trying to gain this clarity, but as I view the drugs that either have been or are marketed with regard to cardiovascular risk, the picture that emerges, begins to emerge to me is that rofecoxib, ibuprofen, and possibly valdecoxib are in one bin, diclofenac and celecoxib in another bin, naproxen in a third bin, and then aspirin in the fourth bin, going from concerns about hazard to neutrality to benefit.

DR. WOOD: Other comments? Dr. Farrar.

DR. FARRAR: Two quick--well, I guess every time we mention aspirin, it never ends up being quick--but two quick comments, one of which

is that I am not as concerned about aspirin knocking out the issue of the COX-1/COX-2 problem primarily because, in fact, aspirin is a surrogate marker for people with cardiovascular disease.

If you look at the actual rates in all of the aspirin groups, they are at least, at least 2 to 3 times the rates in the non-aspirin groups to start with. So, I think that there is an issue there.

I think the second issue has to do with what was just discussed in terms of the comparison of drugs, and just to emphasize the fact that what we are talking about is we have data for there being a risk factor in the placebo-controlled trials, primarily the best data, which we will have a whole lot more of in two months or three months, of the cancer prevention trials to tell us what the level of risk is.

Then, we have the comparison data that Bob Temple was just talking about in terms of the non-selective versus the selective that say that they have very similar levels of risk.

The third point just to make is that all of this discussion about risk, I don't want to imply that I think that this risk is big enough to

actually warrant the continued hold on all the trials that we have going, and I think, in fact, what it suggests to me is that we need to continue with trials to understand better what the data is telling us.

DR. SHAFER: May I respond to the aspirin point? This confusion that you raise came up when I first raised it, I guess it was just yesterday, but the risk that we are talking about is not aspirin versus non-aspirin, because clearly, aspirin will be a marker for increased risk.

What we are talking about is the risk of rofecoxib in the case of APPROVe, the risk of rofecoxib versus the comparator in those patients taking aspirin, so that the increased risk of cardiovascular events has been evenly distributed between the two groups, because that is the blinded comparator variable.

So, we are talking about the risk of COX-2

versus non-COX-2 in those patients on aspirin. It is different from the risk of aspirin versus non-aspirin, which as you say is, of course, that risk is confounded. But in this case, that risk is evenly distributed between the two groups.

DR. WOOD: Go ahead, Dr. Farrar.

DR. FARRAR: I think the problem is that what you are saying is that aspirin is somehow only a COX-1 inhibitor and therefore it has a role there that somehow should balance the COX-2 or there should be some other process going on.

There is no question that aspirin and its indication of increased cardiovascular disease has an effect on the relationship of the COX problem. We have seen multiple examples in the cardiovascular risk, in the group who have the high cardiovascular risk, there is a different response to the COX-2 problem than in the lower group, so there is no question about that.

But I would argue that aspirin is as very different drug in terms of how it works, in terms of its binding to the sites, so all I am saying is

that I am not sure that that obviates the need to say that there is an issue there with COX-1/COX-2 that we need to look at more thoroughly.

DR. WOOD: Dr. Manzi.

DR. MANZI: I actually have a problem making inferences about diclofenac and naproxen in studies where I think we have a difficult time feeling comfortable with the results in relationship to the COX-2s. I mean the trials that are really driving the signal here are the placebo-controlled trials of long duration.

So, to feel that we don't have enough information to really feel comfortable with COX-2s, and then to try and extrapolate to the comparators in those, I think is dangerous.

DR. WOOD: That is what I was saying, too. You know, it's ten past 5:00, just to draw everybody's attention to that.

John, you are saying that you don't necessarily want a vote on this, is that right? So, I guess the question is, is there further discussion on this specific question that the

committee feels they can't hold until tomorrow? Tom?

DR. FLEMING: I share the caution in that last comment, but I will just note that methodologically, it is the exact problem we run into or situation we run into in non-inferiority trial designs, because you have placebo-controlled trial of agent A, and now you want to look at whether B is adequately safe, and you are looking at B against C, the new agent, and if C is the same as B, that was shown to be non-inferior, or you knew what its relationship was to no treatment, it is that non-inferiority issue.

Nevertheless, many of us have concerns with non-inferiority settings, but that is the methodologic challenge.

DR. WOOD: That is my concern, as well.

Let's move on Question No. 2. We may have discussed this a lot already, but this really addresses the contributions and limitations of the currently available observational studies to the assessment of cardiovascular risk for the

non-selective and COX-2 selective--and let's not bog down in what we mean by that. In particular, discuss the role of such observational studies in informing regulatory decisions about postmarketing safety issues.

Now, let me ask a clarification question. Does this mean we just sort of ignore the randomized trials here or take them as a given, or how do you want us to handle that?

DR. JENKINS: I think the idea here was to get your thoughts on how we should consider and weigh these studies in a mixture where we have some control trials, we have the observational trials. Sometimes they don't agree with one another. Sometimes the observational data come at a time when we don't have the control data.

We are trying to get your take on what weight should we place on these data as we are trying to make regulatory decisions.

DR. WOOD: So that we could modify the question to sort of include the randomized trials and say how do we relatively assess these and weigh

them up?

DR. JENKINS: Sure.

DR. WOOD: All right. So, that is a helpful clarification.

Comments on that question? Yes. Dr. Stemhagen.

DR. STEMHAGEN: A couple things. I think I want to make sure that it is understood, in my view, that they are definitely supplementary to the randomized clinical trials.

I think we all recognize that the value of randomized clinical trials is the randomization, that we don't have the selection bias that certainly takes place in observational studies, but nevertheless, when we think about the magnitude of the studies that we have, we have over many hundreds of thousands of patient years of exposure, we have in the cohort studies.

In the case-controlled studies we have more than 25,000 cases. We do have a very rich data set.

I think we have talked a lot about the

fact that we have got a number of studies and we see a lot of consistency in the results between those studies. There was an issue of maybe they are all biased in the same direction.

I think they were conducted in very different ways, many of them, and many very different databases. We also see some data on dose response, which is another suggestion that there is something going on and that the data should be believed.

I think if we talk about lost to follow-up in some of the randomized trials, in some of the very stable populations that we have in some of the databases, we actually do have long follow-up, although ideally, we would like these studies to go on longer. None of them are really as long as we would like, and part of that I think is the data being on the market or available within those databases at the times that the studies were done.

Another thing that really is different with these studies is we are not just talking about volunteers. When we do our clinical trials, we are

talking about volunteers. In our databases, we really have the totality of patients, of cases, of exposures.

So, I think we have got a somewhat different groups of patients. The clinical trial patients are essentially a subset to that. We also are looking at actual use doses, which are somewhat different doses perhaps than in a lot of these clinical trials where we have talked about high doses are pushing the dose.

So, I think they are different pieces of information. The endpoints that we are looking for are very hard endpoints, and I think we have talked about, and there was some evidence, that in some of these studies, there are adjudications, the same way there are in clinical trials when the medical records are collected.

There have been some validation studies looking at the ascertainment of MI and feeling that it is very complete. So, I think we can feel reassured that in these closed populations, we probably have identified the cases that we are

interested in, and we also have a lot of data, not necessarily exclusive, on the confounders, and there have been adjustment for confounders.

So, I really want to urge that when we look at the data, we don't just dismiss the randomized clinical trials, but they are telling us something. They do have some patterns, and they do show some differences between the products.

DR. WOOD: Dr. Cush.

DR. CUSH: I think there is obviously a value for observational studies, but one thing I keep hearing is that the FDA is not properly empowered to mandate that postmarketing trials be done until maybe a significant issue like this comes up.

This kind of public health issue sort of underscores some of the weaknesses of the current MedWatch system where common events like this are not going to get reported on new drugs, because people get heart attacks and heart failure and uncontrolled hypertension, and I think that one thing I would like to see come out of this is that

Congress and others empower the FDA, so they can do postmarketing trials that need to be done, either mandate it or as they need to occur, and if they can, mandate registries as they need to be done, as well.

That is certainly right now what I think is a big hole in our current safety system. We heard today from the patients, they want to know that we are going to help them. That mainly means they want to know that we are going to give them medicines that are safe.

DR. WOOD: Dr. Bathon.

DR. BATHON: I would like to take the example of naproxen for a minute where it seems like from observational studies, it has a neutral effect on cardiovascular risk, at least that was the overwhelming notion, whereas, in randomized trials it seems to be more protective.

I would like to explore for a minute why that discrepancy, if it is true, why it might be true. I would like to posit that in the randomized trials, we have people taking drug every day or at

least we think they are taking it, and they are taking it in the appropriate dose to have consistent COX-2 or whatever, COX-1 and COX-2 inhibition.

In observational data, those are driven, NSAID drug use is driven primarily by acute pain syndromes and osteoarthritis, where people, if we go to the acute, somebody has back pain for a few months, a lot of the people using those drugs might be on them for a few weeks or a few months.

The proportion of patients like the rheumatoids or the bad OA patients who might be taking them every day is probably relatively very small in that group. Even within the OA group, I think a lot of us probably have OA in here, some of us who have gray hair or getting gray, even the OA patients do not take the drug every day on average.

The rheumatoids tend to, the OA patients don't, and then the acute pain syndrome people or the back pain are more intermittent.

So, I wonder if the difference between observational data and the clinical trial is driven

by the fact that we are looking at very different treatment regimens, treatment durations, and so forth. So, I think the randomized trials are more valuable here than the observational data.

DR. WOOD: Dr. Holmboe.

DR. HOLMBOE: I would just make a couple of points. If we agree on No. 1 that there actually is harm, then, I think yes, you are going to have to do observational studies. I mean it is going to be hard to randomize somebody to study harm.

I think that we can take some comfort even though that the effects are different, that the observational trials were reasonably consistent with a lot of the randomized controlled trials that were presented today.

Second, I think a poor randomized controlled trial actually may be worse than a good observational study. As I mentioned earlier, a number of these studies had over 40 percent dropout with these patients not being followed, and I think that that is an opportunity for the FDA to follow

these people out to see if there is something inherently different about those populations who aren't continuing on the study drug.

The third point I would make, that with regard to meta-analysis, it is very important that the trials be fairly homogeneous in the way they were done. In all the stuff reported, I did not see anybody talk about a test of heterogeneity to see if they really truly could be combined.

While I understand that because the events are so low, you are trying to pool risk, there is some danger in pooling studies that are quite disparate. So, I think that is something that needs to be taken into consideration.

The last thing I would say is that I think there is a real lesson here potentially for the FDA. The comparator drugs were approved before we truly understood the biologic mechanism of these drugs. Our understanding of COX-1 and COX-2 occurred long after the original comparator drugs were approved.

So, it is a real challenge I think for the

FDA to go back and say wait a minute, could these comparator drugs potentially be a lot like the drugs that we are now studying, that we think are being proposed as different, but, in fact, may not. So, I think that that is real lesson, it has created a lot of the confusion we are now having to deal with, because a lot of the comparator drugs it turns out actually are very similar to the COX-2s that we are evaluating.

DR. WOOD: Dr. Day.

DR. DAY: Concerning the 40 percent dropout rate in the randomized trials, we have all the sponsors here, and they have lots of data and computers, and so on. Would it be useful to get the percentage dropout for each of the target drugs and the comparators and/or placebos in a giant chart before tomorrow to see, and then try to get a breakdown of what the reasons were for dropout?

Do they retain that information when a patient drops out, what the reason is, or is that on file somewhere?

DR. TEMPLE: They always provide it. The

question is how reliable it is. A lot of them say administrative reasons, and it really requires people to pursue that question, interview the patient, and while that is properly done sometimes, it isn't by any means always properly done.

DR. DAY: So, the breakdown isn't possible. What about the percentages for each of the groups that we have seen just in these studies?

DR. TEMPLE: Pretty much all studies know how many people stopped and completed and when.

DR. DAY: Do we know? Have we been given those data?

DR. WOOD: Well, I guess the Kaplan-Meier curves, and under each Kaplan-Meier curve, I think there is a number of patients at each point.

DR. D'AGOSTINO: Part of that was dropout, but part of that was the way they planned, you know, follow-up on the individual. The individual could, for some reason or another, say they are not going to take the drug anymore, and they only follow them 14 days, so that was legitimate in the study. A dropout that just disappears was sort of

illegitimate, that was not split up.

DR. WOOD: It is still a dropout, I mean the person didn't complete the study.

DR. D'AGOSTINO: Well, it followed the protocol. I mean you can't now go back and say they should have done something.

DR. WOOD: Dr. Paganini.

DR. PAGANINI: One of the things that I was surprised at here was the lack of information on the older NSAIDs, and that is one of the things that we are trying to deal with is what is the difference.

That then speaks to continued observational studies in the postmarket venue where if we had had that, we would have at least had some sort of observational anchor to put some of the newer drugs on.

Let me also add that while we always look at prospective randomized controlled studies as being the be-all and end-all, there is now an emerging--and I will ask some of the biostat folks to comment on this--a developing thought process of

having a wild arm, the wild arm being what is usually and customary done when doing something.

For example, if you do a dose of a drug, or you do an amount of O2 delivery or some sort of a respiratory issue in the ICUs, frequently, when you enter into a study which is randomly controlled, you have one arm versus the other arm, and they are fixed arms, but there is now a third arm that people are starting to ask for.

It's a wild arm, what do people usually do outside of the study, and I think that is a very important issue for when you are using drugs in a common, out-of-the-box way where everybody is using the drug. So, postmarketing observational studies might be considered the wild arm for some prospective randomized controlled trials in that same era.

DR. WOOD: Dr. Nissen.

DR. NISSEN: It is interesting. We like our observational studies when they show us what we want to see, and we just hate them when they show us what we don't want to see.

I have lived through this with the estrogen business. I had people tell me that it was absolutely unethical to do a trial of

postmenopausal estrogens because everybody knew they were beneficial, every observational study had shown it. So, it is important that we use observational studies as hypothesis-generating studies.

If you see a signal in an observational study, it is an indicator that you need to do a randomized controlled trial, and that is how we ought to use them. If we get too far beyond that, we are going to get into the women's health initiative kind of problem again.

It comes up every generation as another example of this, where every observational study tells us one thing until we do a randomized trial, we find exactly the opposite.

DR. D'AGOSTINO: I want you to recall that the Framingham studies said just the opposite, it was the observational study that didn't agree.

DR. NISSEN: Thank you, Ralph, you are

usually right.

DR. WOOD: You were down next to speak, Ralph, is that your question?

DR. D'AGOSTINO: Oh, is it my turn for my question?

DR. WOOD: Yes.

DR. D'AGOSTINO: When we have placebo-controlled trials, randomized controlled trials, I mean in some sense it is I think the gold standard, and when you have positive comparators, randomized controlled, it's the next level, I think that we have a lot of data that is well developed in terms of the studies.

We have questions about the dropout, and so forth, and I raised them also, but I think the randomized controlled trials have put us in the situation where we can minimized in some sense the observational studies.

Yesterday, I made my comment about torturing the data. We can torture the observational studies forever and ever, but I think our weight should shift on the placebo-controlled

trials.

DR. WOOD: I agree with that.

Dr. Fleming.

DR. FLEMING: Maybe just to be specific here about different kinds of observational studies, there is passive surveillance and active surveillance. Passive surveillance has been widely used, for example, in vaccines, childhood vaccines, and with the Veer system.

Essentially, it worked really well when you are trying to detect rare events and events that are proximal to the time of the intervention. So, introsusception with rotovirus and encephalitis, and anaphylaxis, et cetera, have been assessed fairly well.

The problem with those, and we heard naproxen experiences in what I would call passive surveillance, the problem is if you have events that occur with more regular frequency in the background, it is going to be almost impossible. There is under-reporting, you don't have denominators.

So, a step up is the large-linked databases or the active surveillance systems, and I think this is what a lot of what we have been

talking about with these observational studies. They give us numerators and denominators, they give us more complete ascertainment, but they still have unavailability often of confounder information on aspirin use, smoking, outcome specificity and sensitivities are less reliable.

We have talked earlier today about how it is extremely difficult in that context to do a valid ITT type analysis and have a time zero cohort and minimize lost to follow-up, and ultimately, you are not randomizing, and randomizing doesn't solve all problems, but it does, in essence, eliminate the systematic occurrence of imbalance.

It doesn't eliminate randomly occurring imbalances until you have large numbers, but you cannot, with covariates, go back and adjust for what is different in an observational study, because I always say the known and recorded covariates are just the tip of the iceberg, so you

are left with a great deal of uncertainty about bias.

Where they are very effective is understanding natural history, understanding event rates, understanding covariates, understanding how people are treated, but we really want to use them to understand causality, does intervention have an effect.

Essentially, if it is a very large effect, you can get some reasonable senses, but in most cases, I think they serve a very useful purpose, but it's hypothesis generation, it's development of clues.

So, if we look at the overview that David Graham gave, my sense is he was able to give us insights about a wide array of issues that we have not yet got adequate randomized trials, so specifically, the nonspecific NSAs, what does it look like there, and issues about dose, but I would call those hypothesis generation or clues.

I would be very reluctant for the majority of what we saw from those analyses to take those

results as established. It rather gives us a guide because we can't do randomized trials in every setting. It gives us a guide for how to design those trials and where the most pressing questions are.

So, the observational studies go hand in hand, but the ultimate answers in most cases really come from the randomized trials.

DR. WOOD: Right, and the estrogen studies shouldn't be forgotten, right?

Dr. Morris.

DR. MORRIS: I think Tom said a lot of what I wanted to say, but a lot better. In terms of causality assessment, living through what the Agency of Healthcare Policy and Research went through for outcomes, I think the conclusion is unless you randomize, you are never really sure.

In terms of observational studies, I think it is interesting that like event rates or something like that, where we think it is so much better, yet, I was struck in the discussion today of some of these drugs is how much the event rates

varied by center or study or country.

What isn't done in observational studies, what could be done, is more of a population-based sampling, so we have a better understanding of how much or how well that particular database is representative of the broader population of the U.S., so we can do some kind of sampling or extrapolation and get much better event rates, where I think observational studies can really do a much better job than clinical trials because they can measure naturally occurring events much better.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: You know, one always hates to admit ignorance, but I want to pursue this business of a wild arm. I mean I have seen some pretty wild arms in clinical trials, but never as a third one.

I don't understand where that is, I have not heard of that one, and I would like to learn more about it. Can you explain that?

DR. PAGANINI: I will give you an example of an NIH-VA study that is now ongoing looking at

dose of dialysis delivered in which there is a high dose delivered and then there is a low dose delivered. Then, there is the thought process of putting a third arm on there is what is everybody delivering anyway, so it is whatever the wild type is, to see if, in fact, people are artificially placed into one dose versus a second dose, and that, in and of itself, is an artificial placement of patients as opposed to what people usually do.

So, therefore, what is the comparison between one dose versus a second dose versus what is usually and customarily done.

DR. DOMANSKI: But don't you usually use a registry for that kind of question, that is, how well does it represent practice I guess?

DR. PAGANINI: It could be retrospective, but in effect now what they are doing is a prospective collection of data of what is normally done in that particular institution when people are off study.

DR. DOMANSKI: Again, registries can be prospective, of course. I am having trouble seeing

the difference. I mean are those people randomized, as well?

DR. PAGANINI: No.

DR. DOMANSKI: Okay, so it's a registry.

DR. PAGANINI: It's just a registry.

DR. WOOD: Dr. Hennekens.

DR. HENNEKENS: I would view the strengths and limitations of observational studies to be a function of the effect size. For the moderate to large effects, we can make safe clinical and policy decisions based on consistency of the data from the observational studies.

As the effect sizes get smaller, however, it's a two-fold problem because now the effect sizes we are seeking are as big as the amount of uncontrolled and uncontrollable confounding that is inherent in the designs.

There is a certain seduction from these large-scale databases because you have a large number of data you control confounding on, you could get very robust p values, so you begin to believe that you have really discovered something,

but I agree strongly with Tom that for small to moderate effects, they are useful to formulate, not test, hypotheses, so what Dr. Graham told us this morning are useful to formulate hypotheses.

If people took them as serious evidence that this indicated harm, he might be right, but it would have nothing to do with the data that we have seen. I conclude with the statement, I have the privilege to know Sir Austin Bradford Hill who, on this question, and I think Rich would agree with this, he said, "Don't let the glitter of the tea table detract from the quality of the fare."

DR. WOOD: Dr. Elashoff.

DR. ELASHOFF: Two comments. One, in this situation, especially when there is very specific evidence that the relative risk may vary over time, looking at the standard way that observational studies lump it all into patient years is bound to be misleading.

A second point has to do with the fact that in a randomized trial, when you are comparing events, the analysis per se tends to be pretty

transparent, but in an observational study, in order to understand it in detail, there are many covariates, pretty fancy footwork in the statistical realm, and it may not be very easy to tell exactly what was done or to think of reproducing it.

So, the observational study tends to be a lot less transparent in terms of the way it has been analyzed.

DR. WOOD: Dr. Friedman.

DR. FRIEDMAN: Two points. One, if I can follow up a little bit on this wild arm, if you will. As Dr. Wood knows well, this whole issue came up, to my dismay, if you will, about a year ago when we were dealing with the ARDSNet issue, and I think the general conclusion there was that it, in general, is not a very good way of answering a specific question. It might contribute in some fashion, but in general, it is not all that helpful.

Second, I am looking at the specific question here, and it says discuss the role of

observational studies in informing regulatory decisions about postmarketing safety. It seems to me that one of the things we might do is suggest ways that the FDA can improve some of the postmarketing surveillance issues.

For example, we have talked about all of the difficulties in using observational studies, and I don't disagree at all with any of them, but if some of them are planned ahead of time, with good ways of collecting data in consistent ways, we won't completely eliminate all of the problems, but we can reduce them, and I think we ought to at least consider that approach.

DR. WOOD: Dr. Platt, last comment on this.

DR. PLATT: To emphasize that point, taking everyone's thoughtful comments into account, it seems to me we have to be careful not to let the best be the enemy of the very good. I think that Tom Fleming's reference to the CDC's large databank for vaccines is quite on point. It seems to me that there is every reason for FDA to require, as

part of the approval process, that there be a substantial and organized observational set of studies that give at least a sense that generates hypotheses that would allow us to recognize the possibility that there is a signal of events that never be seen in clinical trials, events on the order of 1 or 2 or 3 per 1,000.

It is possible to do that with what in the scheme of these discussions we are having would be a relative small investment, and we wouldn't have to rely on the occasional observational trial or the clinical trial that shows up to start a discussion like this.

It seems to me that that is a very easy, relatively small step for CDC to take, to have every manufacturer of a new drug commit to doing a reasonable observational study.

DR. WOOD: But, Richard, isn't that the problem that Tom highlighted ages ago, that that sort of registry approach will pick up events that are relatively rare in the background, like devastating encephalitis or something like that

relatively easily.

But where you have got a background noise that is as high as MI, it is going to be extraordinarily difficult to pick that up from that kind of study.

DR. PLATT: Well, in the vaccine field, the large-linked database has been extraordinarily useful for things like febrile seizures after a DPT immunization, and that is a relatively common event. So, I don't take the point that you can't make reasonable observations about even relatively common events.

DR. WOOD: Bob, do you agree?

DR. TEMPLE: Well, just to make the same distinction you were making. You can look for introsusception or something that basically is very unusual, but how to find an increase in the rate in the rate of MIs requires a structured study and a plan to do it, and you sort of have to have a hypothesis or you don't know what to look for.

It is totally different from liver, you know, from gross hepatotoxicity, which comes in

through the AERS pretty well actually, maybe you could stimulate those, but it is totally different when you are looking at a change in something that has a high background rate.

DR. PLATT: The fact that it's challenging doesn't mean that you can't learn something useful, and it is pretty clear from the observational studies we have that we can learn something useful about that.

DR. TEMPLE: I was reacting to what you said, should we have the capacity or have the ability to get people to do studies once something emerges or once a question arises, or once you know something about the drug class, I am not challenging that at all, that's fine, but to have it in place as a mechanism for sort of automatically putting stuff up, I guess I don't know what that mechanism is.

There has been talk about encouraging places to report, and we have an arrangement with some liver centers, and those things are fine. Those might be ways to find hepatotoxins maybe

faster than we do now, but that still doesn't answer the question of a change in the rate of a common event, which is a fundamentally different problem, requires a study, not a report.

DR. PLATT: Well, the model of the large-linked databases I think gets around the idea of having to have active reporting. I think that there is a lot of ability to capture the outcomes that are of interest.

Obviously, you don't look for every outcome for every drug, but you can make up the list of things that you care about for certain classes of drugs, and it is possible to use automated systems to take you a long part of the way in understanding whether there is a problem that needs serious analysis.

DR. TEMPLE: Can I propose an alternative? I think what you are really saying is the thing you are worried about with drugs, where there is a high background rate of something, is always cardiovascular outcomes.

So, I think what you are saying is you

might want to look for any chronically used drug at cardiovascular outcomes, and that you could probably put in place.

DR. WOOD: Wait a minute. Are you suggesting that we insist on a cardiovascular study for every drug that we get approved? I mean that would make it prohibitive to approve any drug.

DR. TEMPLE: No, no. We used to fund more of them than we do now, that's a problem that other people will discuss, and certainly I won't, but we have access to databases, whether it's California Medicaid or whatever, and one can do that.

It doesn't seem inconceivable to me--and I am talking about something that other people know more about than I do, so I should probably shut up, but I won't--I can imagine that a couple of years into the approval of a drug that is widely used, you could ask the question at certain sites, can we see an increase in cardiovascular risk.

I am not sure how many other high background events it is that are common in the population that we are really that worried about.

Maybe that is something that we could think about.

DR. WOOD: So, if we could just sum up where we are, what the committee is saying, I think, is that we are impressed as the primary data source, and that the primary data source should be randomized and controlled trials, and observational studies may be good for hypothesis generation, and I guess the third point is that the AERS database is of almost no value in detecting adverse events that are common in the background in a situation.

Is that sort of fair for what we have sort of got out of this? Do people disagree with that? Yes, Dr. Farrar.

DR. FARRAR: There is one specific point to this question, which is that all of the non-experimental studies that have been presented here, I would certainly suggest, and I would hope people would agree, are hypothesis generating at best. Every single one of them is confounded by indication.

The best example is the indomethacin one where it is only used in people who are sicker than

people who aren't. So, I think there are clearly examples. What I was hearing before was a discussion about what we might do, and I just wanted to be clear that what we might do is very different than what we have right now.

DR. WOOD: You put it much better than I did. That is what I was trying to say.

Yes, Dr. Jenkins.

DR. JENKINS: I found this discussion to be very interesting because I think you all know there has been a lot of Monday morning quarterbacking about what FDA has or has not done in this class, and a lot of that has been based on observational study results, many of which fall into the range of what we have been calling small to moderate, I think, at best.

I don't think we need to revisit that here, but I think the questions we have going forward, first of all, we have to look at the data set we have today, and you have to look at the data set you have tomorrow on answering the questions about what do we do now, and observational studies

are part of that data set. We have controlled trials that are part of that data set also.

I think we are also interested in hearing your thoughts on going forward. I suspect that this going to be a mining exercise for everyone who does observational studies in the world probably. They are going to be looking to do another COX-2 or another NSAID observational study.

We are going to see more and more studies published, and as I think someone said, it often becomes attractive to say, "Oh, look at that, you have got a very small p value, yeah, the relative risk is only 20 or 30 percent or 40 percent, the p value is very small, the study was very large, FDA, you should take regulatory action, you should take this drug off the market, you should restrict its use, whatever."

You are telling us you view them primarily as hypothesis-generating, and that they should lead to controlled clinical trials. The reality is even if we have the authority that we might like to mandate those trials, it is going to take years to

get those controlled clinical trial data, and there is the pressure between people wanting you to act based on the observational data versus the scientific desire to wait until you get better controlled clinical trials.

I would be interested in having the committee say a little bit more of your thoughts about, you know, what do we do in the future in this class when we get the next observational study that is touted as wow, this really shows something, FDA, you should take action.

DR. NISSEN: Can I suggest some courses of action? One of them is that as people have pointed out, the strength of the association, I mean the hazard ratio is really important, and if somebody comes up with something which suggests 2 or 3, that is very different from a 1.3.

The other obviously is to have a rigorous process for looking at the quality of it. One of the things I have learned from several of you is that there is observational studies and then there is observational studies, and some of them are done

very well, and some of them are not done so well.

The FDA has the expertise to evaluate that. Now, the problem is, of course, if it gets into the political arena, you get a lot of political pressure, but what we would want you to do in the public interest is look at the strength of association, look at the quality of the study, and make a decision on whether there is enough there to put a warning out.

We have seen some strange things go on, like the warning around naproxen, that was clearly based upon pretty weak evidence. So, I think having a good standard is where you have to kind of hold your ground.

DR. WOOD: The other thing, in response to your question, is if we walk through the scenario here, the first signal was from a randomized clinical trial, and the question I guess then is what would we need to strengthen that observation because it wasn't against placebo and all the problems there were with it.

It would seem to me that we don't need is

a bunch of observational trials. That hardly is going to convince anyone, it seems to me. What we do need is an appropriately powered randomized trial that looks at the issue directly, and I am not so sure how long that would necessarily take.

It only took 2 1/2 thousand people and approved to get the data. The question to which we don't know the answer, in fairness, is would it have taken less time if we had done a larger study, and I don't know the answer to that, no one knows the answer to that, but it is certainly potentially possible that we could have gotten the data quicker if we had done a larger study and the effect appeared faster.

We don't know the answer to that, but that is one approach. I guess, responding to your question, it certainly seems to be in the public interest that you should have the power to ensure that that kind of a study gets done, and that is something certainly people should hear and hear loudly, I think.

DR. O'NEIL: Could I say something

relative to a point that Janet Elashoff had brought up? The general process for the review of randomized controlled trials, such as the ones we have been reviewing, is we have the data in, there has been a strong movement for prospective specification of events, even blind adjudication, we look at the protocol very seriously. We actually have the data in hand. We actually can re-analyze, regroup, adjust, stratify, do many things.

We are normally not in a position to do that on observational studies. We don't have the same level of process review for ran observational study. In fact, it is not even clear what the prespecified hypotheses were, even if you wanted to say the best that the observational study could do is to generate a hypothesis. However, there are many of them that have confirmed important things for us, the last of which was a protocol that we played a heavy role in, and that was propanolamine and its association with CVAs.

That was a five- or six-year prospective

case-controlled study that was done, that we reviewed the protocol. We had a heavy hand. In fact, David had a heavy hand in how that was designed, and that turned out to essentially support a regulatory conclusion.

The point I am making here is that if we do open the door for observational studies, we have to have a different way of actually having access to the data, the quality of the data, and give it the same level of attention that we do in the review of randomized trials but for the fact that it's not randomized.

Right now that is not in place, so we are talking about trials being balanced against observational studies where the standards for the trials are dramatically higher than the standards for the observational studies, not that they couldn't be better balanced, but I think that is an important issue.

There has been a society, ISPE, the International Society for Pharmaco-Epidemiology has tried to put good principles in place to sort of

say these are how you would do these studies, but we really don't have a process that would require that along the same ways that we would in these IND type studies or the larger randomized trials that we are seeing for the safety.

DR. WOOD: Tom.

DR. FLEMING: Just to reinforce some comments that Bob was just making, and Larry Friedman was making earlier, and Steve Nissen, as well. Not all studies are the same, we know that is true of randomized trials in terms of their quality, it is certainly true in observational studies.

Stuart Pocock more than 20 years ago put forward criteria for what you would want to do if you were doing an observational study that would be as reliable as possible.

Essentially, it is just like a randomized trial, it is very complicated and takes considerable effort to ensure that you are putting in the structures. You can then have the sensitivity and specificity issues assessed or

addressed by independent committees. You can do your best to try to define time zero cohorts.

You still don't have randomization, though, and ultimately, the level of reliability is increased, but it still doesn't match the reliability of a randomized trial, as Charlie Hennekens was saying, until you are persuaded that the signal exceeds the potential magnitude of the bias, you can't be confident that the result is reliable.

So often what we are looking at are effect sizes that aren't, in fact, larger than the magnitude of the bias, so that leads us down the pathway of needing randomized trials.

John, getting back to your point, if you have a profoundly low p value, this may be obvious, but it doesn't mean we know the truth. There are two fundamental aspects around the truth. One is variability and one is bias, and I can have 100 trials put together and give me a highly precise estimate. I mentioned yesterday, you just end up with a precisely biased estimate, and that is my

concern in the absence of randomized trials.

I believe these are very useful clues, we need these results, but just because you have profoundly low p value doesn't mean we got at the truth.

DR. WOOD: That is what happened with the estrogen studies, of course.

DR. HOLMBOE: I just want to make one point because we keep hearing about the estrogen study. There is one very important fundamental difference here. Estrogen had been posited to have a positive effect on cardiovascular mortality in observational trials, so it made a lot of sense to use randomized controlled trials to prove that hypothesis.

The hypothesis here is that COX-2 inhibitors are harmful, therefore, you are doing a randomized controlled trial that in investigating harm, not benefit, and I think we have to keep that in mind.

DR. WOOD: Good point.

Now, we are going to move on, Steve, to

the next question. The next question is discuss the available data regarding the potential benefits of COX-2 selective nonsteroidals versus non-selected nonsteroidals, whatever they are, and how any such benefits should be weighed in assessing the potential benefits versus the potential risks of COX-2 selective agents from a regulatory perspective.

DR. JENKINS: Dr. Wood, could I make a comment about that as you get started about this particular discussion point? We put this in here for a reason, because clearly, we didn't want a three-day meeting to just focus entirely on risk, because the decisions you need to give us advice on have to be balancing risk and benefit.

I think here we are particularly interested in hearing your views about benefit in a wide range of categories.

You know, this class of drugs was developed for the GI effect, so we are interested in hearing your conclusions about the benefit of these drugs on the GI toxicity, but there is also

other areas. Any input you have on their efficacy for pain relief for the treatment of inflammatory conditions will be useful.

I am also interested in hearing your comments about the value of choice. We heard that from some of the people in the public hearing today, that, you know, don't limit my choices, and we hear that a lot from physicians, we hear that a lot from patients, but we often are also hearing a competing view that if you have got one that looks like it is safer than the others, then, you don't need the others, but that is at odds with the idea that people like to have choice, because people don't respond the same to every drug, they may be allergic to one drug or whatever.

So, in this context of benefit, I would like you to cover a lot of different areas, and not just to gastrointestinal benefit, but that is clearly one of the major focuses of benefit here.

DR. WOOD: Okay. Dr. Nissen.

DR. NISSEN: A couple of things. One is I haven't seen any compelling evidence that in terms

of pain relief, that the drugs are actually more effective, and if such data is available, I would love to see it, but I don't find it there, so I think that is a little easier for me.

I don't think we can minimize the importance of the GI aspect. There is actually two things, one of which was talked about interestingly by the public, but not necessarily by us or the companies, and that is, you know, patient quality of life and patient preference.

Any of us, I have certainly taken NSAIDs and gotten gastritis from them, and it is not fun, you know, having your stomachache, and people who have that every day, you know, there is a suffering related to that, that we heard from the public, and that has to be taken into account as we think about these drugs.

In addition, I would be the first to say that a GI bleed is not a benign event. If these drugs were drugs that were better for treating acne, and they caused cardiovascular harm, that would be one thing, but the events, the GI events

here are serious events.

They are not as life-threatening as a stroke or a heart attack, but they can be, and they don't produce the permanent disability that a stroke or an MI does. You know, I take care of people with heart failure, and if you have had a big MI, and your pump doesn't work, your life is changed, the rest of your life is going to be different.

Most people with a GI bleed recover, and so as I weigh these events, I don't discount GI benefits, but I have to give them less credence than the kind of hard, permanently disabling effects of MI and stroke, and I also think we absolutely have to factor in here the sort of suffering of patients who just don't tolerate the conventional NSAIDs, and I think that compassion has to come into our decisions.

DR. WOOD: Dr. Fleming.

DR. FLEMING: A great deal of the focus on the data we have had presented to us relates to the cardiovascular risks and relates to the confirmed

complicated upper GI events, so if I start by focusing on that, it looks as though in a crude estimate that we might be having the rate of these events using the COX-2 inhibitors rather than the non-selective NSAIDs.

It looks as though that might be, in 1,000 people, preventing 5, 6, 7, 8 events, something on that order. If we took a relative risk of 1.4 as the relative risk for the increase in cardiovascular events, that would be about 4 events.

So, coming back to what Steve is saying, when you look at it in that context, yes, these ulcerations are important events, but 7 per 1,000, how is that up against 4 events that are strokes, MIs, or cardiovascular deaths, I don't think it adds up.

If that is the whole picture, I would have a concern, but in a number of settings, it isn't the whole picture. We have heard about the oncology setting. We have talked about, truly, we haven't talked about efficacy. We have only had a

number of comments stated that the pain relief seems to be about the same.

Well, if it is the same, then that balance that I was saying concerns me as not being a favorable balance, but we heard a lot of people testifying, and I will be the first to say open sessions at these meetings are not random samples of the entire public, but we still heard a lot of comments that reflected the fact that there seems to be some differential protection or pain relief in certain patients.

Can we quantitate that? Can we, in fact, more scientifically, rigorously establish certain subpopulations where there really is a differential relief? Then, the benefit to risk shifts, or in the oncology setting, the benefit to risk shifts.

The bottom line here, though, is to me the issue isn't so simple as choices. The issue is informed choices, and it takes the kind of scientific studies to reliably identify what are the true benefits and risks, so that patients are in a position to make an informed choice, and part

of the challenge to this, as one of the speakers at the public session pointed out, is it is not always the case that what might be learned by those people doing the studies is being effectively transmitted to the bedside or to the patients and their caregivers, and that is the other aspect, as well.

So, it is critical to follow a strategy here that allows us to reliably address benefit to risk and allow patients to make an informed choice.

DR. WOOD: Dr. Hoffman.

DR. HOFFMAN: I think for the last two days we have been hearing appropriate angst about damning a class of agents for which there is a measure of efficacy, both in regards to pain and GI events because of newly-discovered adverse events, but I feel like we are walking on eggs in trying to get away from a consistent observation that is the dose-response effects, relative risks that we are looking at in terms of cardiovascular endpoints.

We have heard this from experts at the FDA, independent investigators. We have even heard it from the thought leaders of industry, there

seems to be a consensus to the effect that there is a class effect.

I do take Steve Abramson's point that all of these drugs are not pure in their effects in terms of COX-1 or COX-2, but this is the data that we have, and it seems like there is a consensus about a class effect, and there also is a consensus in acknowledging that the patients that we enter into randomized controlled studies are probably the people least at risk that we may not see in our practices, who come in with 3 or 4 comorbidities that may have excluded them from being in this trial and actually having seen even a clear signal.

The data, of course, that we would like to have is something that we don't have, and that is, the old standards of treatment for pain, whether it's the arthritis pain of OA/RA or postoperative pain, with NSAIDs plus PPIs over a long, extended period of time.

We would all like to know the data for that over 2 or 3 years compared to the COX-2s, which I don't think any of us are saying should, as

a class, be taken off the market, but certainly should be used at the lowest safest dose.

Now, at the lowest safest dose we don't even know their efficacy qualities. We don't know whether at the lowest safest dose we have the same benefits in terms of preventing peptic ulcer disease, treating pain effectively, decreasing inflammation effectively, and that it seems is the data that we need to have.

I am a little concerned, as a footnote to that, about the issue of choice. I think it is our obligation to provide patients choice within the realm of relatively safe medications, but most of us would not give as a choice a narcotic analgesic to a patient with, say, fibromyalgia.

I don't think we should keep drugs on the market because of public pressure if we have a signal that we feel is a very strong one. We shouldn't give people a choice if we think that choice is uninformed and potentially does harm.

Now, I am not saying that for the class of COX-2 inhibitors, I am just saying that we need

more data to be able to provide for ourselves adequate information to make that choice and give our patients informed choice.

DR. WOOD: Dr. Cryer.

DR. CRYER: We were asked to kind more widely consider the potential benefits. As I see it clearly, one of the benefits is GI, and I will comment on it, but I do want to reiterate some of the comments that I personally don't see the benefit with respect to efficacy.

I think the clinical trial experience to date has pretty consistently indicated that the efficacy is similar to the traditional NSAIDs. We did see some provocative data with etoricoxib today suggesting greater efficacy in one trial than naproxen, but that wasn't replicated.

So, overall, I have to think that the efficacy is the same as we have with the traditional NSAIDs. I appreciated the testimonials of the patients about their individual efficacy responses, but my conclusion about that is those are anecdotes and it is consistent with the

clinical experience that we have with efficacy of NSAIDs, which is that there is variable and idiosyncratic, unpredictable responses between patients, and it is very common that you will have one patient who responds to one NSAID and does not respond to another.

I do think that we would still be giving these patients a wide range of choices given that there are 20 other NSAIDs available in the U.S. among which they can choose.

The benefits clearly I think are in the GI tract, but I will say that my conclusion is that the GI benefits are less than previously speculated.

If you look at the three outcome trials which we have, that looked at GI benefits, we have VIGOR, CLASS, and TARGET. The results in the VIGOR are clear, but I think that was clearly also of a manifestation of the comparator, and one of the things that I would like to be remembered is that the comparator NSAID matters.

One sees a greater degree of GI benefit

when one compares against naproxen than when one compares against diclofenac, so I do think there is value from the CLASS trial. I know that there was a GI benefit shown against ibuprofen.

In the TARGET trial, those GI estimates are overestimated primarily because they enroll a low risk group of individuals and in a lower risk. We have consistently seen in trials that when you have low risk GI group, the relative risk is higher although the absolute risk in a low risk population is very low.

So, the benefit is going to depend on the comparator. It is probably less than the 50 percent that you suggested it to be, because that 50 percent is based upon the VIGOR trial. It is probably closer to maybe a 30 percent benefit that I would estimate.

It also narrows when you consider low dose aspirin. In the face of low-dose aspirin, there is no apparent GI benefit. So, I think we also need to modify our estimates based upon the population that would be using or not using low-dose aspirin.

So, my conclusion about the GI events is that, yes, there is a benefit, it is not as large as we thought, the appropriate target population is

smaller with respect to the target group. It could be low risk people not taking low dose aspirin, but this event doesn't happen very commonly in low risk, and when you look at the high risk people in whom these drugs were originally targeted, several data sets suggest that the high risk people do not, in fact, have any appreciable benefit of GI risk reduction from a COX-2 specific inhibitor.

Final comments about other areas of benefit. Dyspepsia isn't one that is very convincing. When you look at the dyspepsia data from the clinical trial experience, it is only a few percentage points reduced. Dyspepsia, I consider mostly a nuisance symptom for which we have other very safe therapies to effectively deal with this.

Finally, from the GI perspective, the polyp story could be another potential benefit, but with regard to the polyps, we have to remember in

every trial we have seen, we are only modestly reducing the polyps and ultimately, we don't reduce cancer risk unless we eliminate adenomatous polyps, so it doesn't really change our algorithm in terms of how we would manage these patients, which would be colonoscopy and polypectomy.

DR. WOOD: Before you finish that, there are only two drugs on the U.S. market now, celecoxib and valdecoxib, so let's review the upper GI safety for them first.

Is there a study that you are aware of with valdecoxib looking at complicated ulcers that showed in randomized fashion that there was a safety signal?

DR. CRYER: No. Wait, what do you mean by safety signal?

DR. WOOD: GI benefit. Is there a VIGOR trial for valdecoxib?

DR. CRYER: No.

DR. WOOD: So, confining our discussion to the two drugs that are on the U.S. market, there is no VIGOR equivalent, if you will, in valdecoxib,

right?

DR. CRYER: Correct.

DR. WOOD: Now, for the other drug that is on the U.S. market, celecoxib, the published study didn't show the full data set. For the full data set for that, there wasn't benefit either.

DR. CRYER: Correct, but we did have the benefit of--

DR. WOOD: I understand, but there is always a benefit--I mean there is mortality problems halfway through, too, that disappear, that we ignore when we get to the end of the trial.

So, for the two drugs that are on the U.S. market now, we have no clear randomized data that show GI benefit given the endpoints that were predefined and the end of the trial, not the trial that was published without the complete data set.

The TARGET trial looks at a drug that is not on the U.S. market. So, our job is to evaluate the two drugs that are on the U.S. market, it seems to me.

DR. CRYER: So, I agree with your comments

about the fully published results in JAMA for the class, however, we did have the benefit of reviewing the full class results in the FDA hearing four years ago, and it is based upon that evaluation that I am deriving my conclusions of the full data set in which there did appear to be a demonstrable GI benefit when compare to ibuprofen in people who were not taking aspirin, certainly not when compared to diclofenac.

DR. WOOD: But the trial was not--that was a subsequent analysis taking out the aspirin. That wasn't the predefined endpoint.

DR. CRYER: Point well taken.

DR. WOOD: So, I mean just summarizing the point again, we have a benefit in a trial for a drug that is not on the U.S market, but we are not prepared to extend a class effect to cardiovascular risk necessarily, so I don't think we can just sort of step back and say that we are going to give a class benefit to GI benefit either extrapolating from studies of drugs that are not on the U.S. market.

DR. CRYER: Just because they are not on the U.S. market does not reduce the validity of the observation, for example, with lumiracoxib, and

just because this was not absolutely predefined, and the benefit was recognized in, let's say, a post-hoc perspective, I still think there is recognized benefit in the data that we see in terms of assessing the GI benefits of celecoxib versus ibuprofen, and lumiracoxib versus its comparators.

DR. WOOD: But the non-aspirin group also had a cardiovascular risk, right?

DR. CRYER: Absolutely.

DR. WOOD: I mean as we are doing Tom's sort of analysis, when we take out that aspirin group and say, wow, there is a GI benefit there, when we take out that aspirin group we find there is a cardiovascular risk. So, you know, we can't have it both ways.

DR. CRYER: Well, I would say that the cardiovascular risks extend to both groups, aspirin and non-aspirin.

DR. WOOD: Right, but it was clear

in--okay, Dr. Fleming.

DR. FLEMING: Just to pursue a bit further, Alastair, what Byron is saying, there are two aspects that I hear you saying that are really critical to the comments that I had made earlier.

One is that I might be overestimating the actual GI benefit when I say you are having maybe it's a 30 percent.

DR. CRYER: It depends on the comparator.

DR. FLEMING: But the other, even more important thing to me that you are saying is that in spite of what might appear in the open session, which we know is anecdotal, the scientific data you are saying repeatedly are showing in the RA, OA, CABG settings where we have done studies, that there is not a difference in the pain relief and the efficacy.

I would like to get more sense about that. If that is even close to true, then, there should be an incredibly low threshold for what you would accept in additional cardiovascular events, because the only thing you are getting relative to

nonspecific NSAIDs then would be a very small GI.

So, it seems like the efficacy here about the pain relief is a key issue.

DR. WOOD: I think the company wants to say something.

DR. KIM: Mr. Chairman, if I could, I will just make a comment, please. As I said yesterday, at the time that Merck withdrew Vioxx from the market, we based that decision on the available data that was available to us at that time, and we also stated that we thought that it would be possible to continue to market Vioxx with a labeling change that incorporated the results of the APPROVe trial.

But we decided and we concluded that the most responsible course of action to take, given the information that we had at that time, and the availability of alternative therapies, was to voluntarily withdraw the drug from the market.

We have heard over the past two days new data and we have seen in the New England Journal new data on some of these alternative therapies.

Merck's interpretation, as you have heard, of these data are that we are dealing with a class effect, and the major question on the table right now is how large is that class.

We are a data-driven company. If this committee and the FDA agree that what we are dealing with here is a class effect, then, I think it would be important for us to take the implications of that conclusion into consideration with regard to Vioxx, particularly given the unique benefits that Vioxx provides, one of which you are alluding to.

So, I just wanted to make that point.

DR. WOOD: So, just to understand, what you are saying is that if we think the cardiovascular effect is a class effect, you would consider putting Vioxx back on the market.

DR. KIM: What I am saying is that at the time we withdrew the drug from the market, we did so because of the availability of alternative therapies and the science that was available at the time. That science has progressed. We are now

engaged in a discussion around that science.

There are unique benefits to Vioxx, one of which is it is the only COX-2 inhibitor with proven reductions in gastrointestinal events, another one of which it is the only coxib which is not contraindicated for patients with allergies to sulfonamides, and the third is that we have heard numerous reports, and you have heard a few today, from patients, including patients with chronic debilitating pain that Vioxx was the only drug that relieved that pain.

DR. WOOD: Okay, good.

Dr. Farrar.

DR. FARRAR: I wonder if I could just be very clear that so far I don't think we have talked about benefits. The point I want to make is that what we are talking about with the GI, quote "benefit" is, in fact, a reduction of risk. No one that I know of takes coxibs of any kind for an upset stomach.

I think what we need to do is focus on the benefit to the patients, and we heard some of that

in the public forum today, and I want to be as clear as possible about the issue of that benefit.

There are two ways of measuring benefit, and, in fact, in outcome trials, there really are only two summary statistics that are possible. One is a mean or a median or some central tendency with a spread, standard deviation.

The second is a proportion, and it is a proportion of responders, it a proportion of people who die, which is the easiest, and in pain management, we get into all kinds of arguments about how much improvement you have to have to be a responder.

If you look at the data, we are used in most of our clinical trials to looking at means and standard deviations, and if you look at means and standard deviations, it is very hard to find a difference between any of the NSAIDs and acetaminophen, any of them.

If you ask patients about what works for them, in clinical practice, every patient will tell you that one works and that one doesn't. "I get

sick with that one, I don't get sick with the other one."

That is not something that we measure typically in our clinical trials. If you look at what level of drug is effective, with almost any NSAID, it is never, it is never above 50 percent in terms of patients who actually go on using the drug in a chronic process.

What we are talking about is trying to identify less than 50 percent of a population who respond to a drug, and I can tell you from clinical practice, as any of you who have taken patients with rheumatoid arthritis know, people like specific drugs because they don't cause side effects and because they do have an effect.

I think choice actually is a very important issue. Granted, we don't want to provide choice if there is an absolutely huge risk associated with that choice, but I think it is really important to understand that pain kills in the same way that the drug potentially can kill.

I think it is very important to understand

those two principles, the principles of the difference between a proportion and a mean value. Now, I am obviously talking to the converted here, but I think the issue really is looking at those issues.

We don't have any good trials, any that look at switching behavior within our patient populations, so there is no data that I know of that will help inform us about the need to and exactly how to go about this process, but I do know that in spite of all of our understanding of what goes on with the COX-1/COX-2 pathways and the inflammatory pathway, that when it gets down to using it in the patient, the issue is, is it absorbed, does it cause local effects, does it get to the active site, once it's at the active site, are there enough receptors for it to then cause the effect that we are looking for, a whole host of factors that we really can't measure and haven't measured yet in terms of metabolic process.

My honest sense from the data that we have heard here is that the drugs that we are

considering today, the two, perhaps three, has to do with the relative benefit of those drugs.

What is very clear is that there are people, and a large portion of people, who have trouble with the current list of what we call non-selective COX inhibitors, and that there is a very important role for the more selective COX-2 group, however we want to define that.

I think it is also, however, very important to understand that not everybody should be on a COX-2 predominant agent, and one of the problems that we are struggling with right now is the fact that because they were marketed as being safer, there was a very large push to switch people over who may not have needed to be switched.

So, I think that the issues that we need to consider are there is very good data that these drugs are effective at least in some segment of the patients in whom they are tried.

There is I think reasonable data to suggest that the potential risks is not clearly very different between them, at least not the data

that we have to date, and that from that perspective it is going to be important that we carefully think about how we then go about controlling those drugs.

I would end with just saying that I agree absolutely it is about informed choice, and that I think that there needs to be a fairly large amount of information in the label and information conveyed to patients and physicians to help them make those choices.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: I am particularly pleased about the nature of the conversation because as a student of medical history, it reminds me that the first treatment we had for arthritis was, of course, willow bark, and we told our patients to ingest willow bark in order to get salicylates, which, of course, have an anti-inflammatory effect. So, if only our patients could take aspirin, perhaps we wouldn't need the whole class of non-selective and selective COX-2s, but, of course, they can't. There are problems just with aspirin

in the treatment of arthritis at the doses they need it.

I am intrigued by the comments that, well, you know, an MI is an MI and you are dead, but a GI bleed, you get up, you get over it with no long lasting effect, and that may be true for the people who survive, but as Dr. Cryer showed us yesterday, and the best data set we have from Dr. Singh, 16 percent of patients who have a GI bleed die, so for them, it's a fatal event and one that they are not going to get up and continue on.

I don't want to get into a discussion of the GI benefit and whether, in fact, it was achieved with one agent versus another, but what is clear is something that hasn't been remarked yet, and that is for patients going to surgery, who are going to require anticoagulation following their surgery, and that is particularly in large part patients who have arthritis and are undergoing joint replacement surgery, the risk of a traditional nonsteroidal with an anticoagulant appears to be far worse in terms of bleeding later

on than the risk of being on a COX-2 because of the lack of platelet inhibition.

So, certainly there is a benefit for patients in that group who are going to go to surgery and require concurrent anticoagulant.

With regard to the issue of patient choice, there is several sets of data--and we heard one--showing that when you give a patient two different medications, in one study, the ACDA study, looked at acetaminophen versus diclofenac, another one, the PACES study, looked at celecoxib versus acetaminophen, and you asked patients without knowing which drug they were getting, in which arm, patients expressed a preference for either diclofenac or celecoxib over acetaminophen in the treatment of their arthritis.

The other issue with regard to choice is that we have also recognized, even in the pre-COX-2 days, that not infrequently, patients develop what is called a tolerance to the agent that they were on, that the latest data set we had suggested that inside of 18 months, patient who were taking

medication for their arthritis chronically had to be rotated among agents three to four times in that period of time.

So, the necessity for multiple agents in our armamentarium, the necessity for agents that allows for this individual idiosyncrasy that we have heard of is quite important.

As was alluded to, there can be two patients in the waiting room on the same drug, one will swear by it, one will swear at it, and so it is for that reason that we need to have, not just one agent in a class, whatever we define that class to be, but sometimes several. Sometimes they are agents of allergy or idiosyncrasy which necessitate having more than one agent available.

I think it is for all those reasons that we have to consider that in the benefit part as long as we are discussing benefit in the last part of the day.

DR. WOOD: I think we have to be really careful accepting this data, this 15-year-old data from Dr. Freis. I mean he has published, he

published multiple updates on that, and people keep showing that same data, and that data isn't what is in his latest revision.

DR. GIBOFSKY: Accepted. Dr. Cryer?

DR. CRYER: I would like to comment on that, and I think your point is well taken. While I showed the 16,500 data yesterday, at the same time I said that that estimate, based upon more recent evaluations, is probably an overstatement of the actual mortality risk, GI risk attributable to NSAIDs.

Dr. Singh has showed me more recent data which he has conducted in the U.S., which has shown that the risk has dramatically decreased in the U.S. That is probably related to several factors included in which is the eradication of HP, the introduction of PPIs into the U.S. marketplace, as well as the introduction of COX-2 specific inhibitors.

The most recent estimates that I have seen would suggest that the mortality is about half of what Dr. Singh previously suggested it to be.

DR. GIBOFSKY: Accepted, but even the mortality rate of 8 percent in a population is unacceptable.

DR. CRYER: It is not 8 percent, it would be 8,000.

DR. WOOD: It is much lower than that, and if you look at the curve, the fall occurred long before COX-2s were on the market.

DR. CRYER: You are correct.

DR. WOOD: The data are out to 2000 on his paper, and that fall had occurred by 1998, so that is before any of these drugs were on the market.

My point is that we keep throwing this 100,000 number around, including from the industry people, when the data is 15 years old, and the author has updated it multiple times, and that is not reasonable, guys.

Dr. Singh.

DR. SINGH: As the author of the papers that you are discussing--

DR. WOOD: I am talking about Dr. Freis's paper, which was actually published. Yours is an

abstract, I think.

DR. SINGH: Also, the 16,500 was from my paper that we estimated with the Aramis data set, and that, you are right, it is not 15 years old, but that is about '94, '95 data, and now that we have newer data sets, that was an estimate from the Aramis data.

The latest work now is actually on real hospitalizations based on the nationwide inpatient sample, which is a much better estimate of what is really happening than an estimate from a small patient population.

When we go back and look in '93, '94, of what the total number of deaths that the Federal Government said occurred in the United States, we were off by 32, that's it. It was like 16,486. That is how far we were off by, just to let you know in terms of an estimate.

This is also true that now, today, the latest data set that we have available from 2002, that has dropped significantly, and the death rates are more like 8,000.

But the other place where we underestimated was the hospitalizations. We underestimated the hospitalizations, they are not

108,000, there are a lot more than that.

The mortality rates today have gone down tremendously, and the mortality rates today are probably more in the 5 to 6 percent range, and that is where Byron is correct, as well.

Then, as far as the trend is concerned, the data that I showed you today is based on 483 million hospitalizations. We are not counting about 50 hospitalizations and then extrapolating it to the country. There are 483 million hospitalizations and 3.68 billion patient years.

Yes, the trend line started going down way before the COX-2s were introduced, but then there are two sharp years of decline. The trend line actually, if you look at my slide, is very interestingly correlated with PPI use, and I showed data to Byron from the same data set, that it also explains it very nicely because the duodenal ulcer rates have gone steadily downward, which would be

attributed primarily to PPI use and H. pylori eradication therapy.

The gastric ulcer rates and the gastric ulcer hemorrhage rate have not gone down in the same fashion. They went down when the '94-'95 H. pylori eradication campaign started. Then, they plateaued off pretty much, and PPIs haven't done very much to gastric ulcers until 1999, when the gastric ulcer rate dropped dramatically.

In 1999, there is a 22 percent drop per 100,000 prescriptions sold in this country. I don't know what it is because of. Coincidentally, in 1999, January 1, celecoxib was introduced. I don't know what it is because of.

DR. WOOD: Let's move on.

Dr. Dworkin.

DR. DWORKIN: Much of what I wanted to say has already been said, but I just want to emphasize that while there are no differences on average in pain relief amongst these drugs, certainly none that are replicated, as Byron pointed out, that there is a great deal of variability in response,

and I think there is every reason to believe that some patients respond better to one drug than another, so you have variability in the pain benefit, and you have to consider at the same time there is variability in the tolerability of the drug.

So, there are two sources of variability in patient response, which at least to my way of thinking provides a really solid basis for there needing to be a choice amongst several drugs, because you have the variability in the pain benefit amongst patients and the variability in their tolerability.

DR. WOOD: Dr. Cush.

DR. CUSH: I prefer to say that these drugs are equally potent between the COX-2 specific and the non-selective drugs. I think there is a variability, but that speaks to the need for choice.

Every rheumatologist at this table will tell you they cannot manage in any effective or compassionate way osteoarthritis or rheumatoid

arthritis using just Tylenol and aspirin and ibuprofen. That would be a gigantic step backwards.

So, they are equally potent. I think when it comes, however, to the risk, thankfully, this risk is incredibly low, but we would like to make it lower, and what we need to put forward is that we need a strategy for risk modification that is going to extend to all these drugs that we are examining here, much in the same that occurred with GGI, I think that we can start with some recommendations and then make it the responsibility of the manufacturers to come up with studies that will further define how we can best reduce the risk in people who may need to receive these medicines.

DR. WOOD: Dr. Morris.

DR. MORRIS: Let me focus on the question that asks about the weighting, because what we have is--I guess everybody interprets this question differently, but what I interpret it as is how do you look at these non-comparable outcomes and how you trade off a TIA from a gastric ulcer or

something.

I think what we can do is we can describe the effect and we can describe the probability of the effect, but what we don't know is what is the right way to weigh those things, and I would make a plea that probably the right way is to try to involve in some way the views of patients in that decisionmaking.

I don't mean that qualitatively, I mean that quantitatively, is in quality of life type data where people have looked at various outcomes, looked at it on a single scale, and apply some of those ways, so we understand how patients view it, and go beyond just medically what we think patients should evaluate it, but how they actually do evaluate it, and try to use some of the input of those data.

That literature suggests that we get it wrong, that there is things worse than death, and we always think of death as the worst thing to happen in a medical outcome, but yet from a patient's perspective, being paralyzed by a stroke

is perceived as worse, and we need to understand patients' evaluation of these outcomes, so we can make those weightings better for them.

DR. WOOD: Ms. Malone.

MS. MALONE: Obviously, this is complicated. I agree with most of what the previous speakers have said especially Dr. Cush, Dr. Gibofsky.

A big problem is like Dr. Gibofsky had said about having choice and trying different drugs, and having a period of time when they would work, and then they wouldn't be as effective and you would have to try something else.

That is why the need for choice is there. I have spent the last 35 years probably on each of the NSAIDs that are still available, and went through that, and the frustration and the pain, and just--it's very difficult, so when people give this anecdotal information and say that they have found something that works for them, they are going to fight for that.

We have to be able to prove to them that

the risk far exceeds the benefit, and we have to be able to show that, and we can decry anecdotal evidence as not being sufficient enough, but, in reality, it all comes down to anecdotal evidence. It all comes down to the personalization of it, what happens to me when I take this drug, what happens to me when this drug is not available.

But I think behind everything is the whole element of trust, and they place their trust in us, in FDA, and we can't give in to pressure, okay, but we can't give in to pressure either way. We have to keep an open mind about it and realize what they are going through and try to put yourselves in their shoes.

DR. WOOD: Dr. Platt.

DR. PLATT: In the spirit of supporting informed choice, it seems to me we could do a very much better job than we do by using the existing data that FDA already has to provide good information to patients about the risk stratum that they inhabit.

Saying that there is an overall 1 1/2 or 2

percent difference in the risk of a GI complication or myocardial infarction is not doing the best service to most people who take those drugs.

I would imagine that those data can be used to support predictive modeling that would allow a fair amount of discrimination so that individuals could be told that people like them can expect a risk of 1 in 1,000 or 1 in 100 or 10 in 100, and that would make it a lot easier, I think, for individuals and their doctors to make thoughtful decisions about the tradeoffs of the benefits and the risks.

It seems to me those data are there and it would be a straightforward thing to make them available. We do that with breast cancer all the time. The NIH did a tremendous service I think to the public by providing good predictive models that let women know what their risk of breast cancer is to help them decide whether to take preventive action. I think we could do it with these drugs.

DR. WOOD: Dr. Bathon.

DR. BATHON: It is interesting that you

would say that because that is, in fact, what most of us rheumatologists have been doing for the past four months with every single clinic visit, is weighing the benefits and the risks based on the data that exist right now, and it is a difficult endeavor.

I think that we are really hearing from our patients, and we heard this today, we are in a different era of patient-doctor relationships, and patients want to be a collaborator in these decisions, and they want to know the information.

I think that the way I am thinking about this problem right now is that these drugs, whether they are selective or non-selective, are another risk factor in the GI complications and the cardiovascular complications that we have to weigh along with their blood pressures, their diabetes status, their BMIs, their family history, and everything else to come to a final decision about what we recommend with their input.

Until we see an unequivocal cardiovascular risk that outweighs all those other factors, I

think that is the appropriate approach with the patient is to put the drug in with all the other risk factors and try to come up with the best benefit-risk ratio that exists for that individual.

DR. WOOD: Dr. Hennekens.

DR. HENNEKENS: I find Question 3 extremely complicated in a number of dimensions. I am attracted to Tom's formulation of benefit to risk, but I think we also have to consider these arthritis patients with regard to the use of selective coxibs.

As a group, they are at maybe a double the risk of heart disease of their non-arthritis counterparts. They are also suffering terribly with pain.

From that perspective, the data we saw over the last two days on naproxen was somewhat reassuring to me, but for the patient who has gastroesophageal reflux disease or an allergy to aspirin or non-selective NSAIDs, I think there the benefit-to-risk obviously shift although even here, I think they have to have their cardiovascular risk

factors managed aggressively, and I would add three more dimensions.

One is I am not reassured at all by the data that are available on the short-acting non-selective NSAIDs with regard to risks and benefits, and I think we need a lot more data there.

I am also not reassured by data we haven't reviewed that acetaminophen is either sufficiently efficacious or much safer, and then finally, the problems with high doses of aspirin are real.

I do point out, though, the UK TIA trial of 2,400 people that gave aspirin 1,200 mg in a placebo-controlled design for 5 years, the rate of GI side effects attributable to the aspirin was 14 percent, significant bleeding was 3.3 percent, but this flies in the face that 25 percent of the people on placebo had GI side effects and 1.6 percent of them had a significant GI bleed, so I think nothing is straightforward here.

DR. WOOD: Dr. Nissen.

DR. NISSEN: Just one brief comment, and

that is, one of the things I am struggling with for all of you, and maybe some of those that either deal with these diseases can help me with this, is that the people at greatest risk for GI bleeding are the older and more frail individuals who are also at the greatest risk for cardiovascular disease, and so finding the sweet spot for the drugs becomes a little bit harder.

There obviously are certain populations where it is obvious, but the big populations where there is risk, is it not true--I think I heard from Byron that older people are at greater risk for GI bleeding, and I can assure you they are at greater risk for coronary disease, so the question is how does it tilt in any given patient. It is not so easy to figure it out.

DR. PLATT: But you can quantitate it. I mean it seems to me you could tell the patients what individually, approximately what they could expect on both dimensions, and for a lot of patients, they would be high on both, but at least they could make an informed decision about that.

DR. CUSH: But it's the same situation as the GI problem. We know what the risk factors are, and age is a risk factor, and we counsel patients,

and we probably should tell the ones who might be willing to accept some small risk, because they don't seem like they are at risk just because of their age, but they don't have any other factors, and the same thing can happen here with regard to the cardiovascular risk if we have some appropriate guidelines.

DR. CRYER: Steve Nissen, I think you have got it exactly right and that there seems to be a great degree of overlap in those who are at GI risk tend to be, not uncommonly, the same patients who are cardiac risk. They are older, they may have a previous history of cardiovascular disease, and other risk factors which are common to both risk considerations, GI, and cardiovascular.

DR. WOOD: Ms. Malone, do you want to say something?

MS. MALONE: Yes, I do. Just what Byron has said, all of that brings in the importance of

the doctor-patient relationship, and today, with the health care climate that we have, I have heard patients say how difficult it is to go in and get an amount of time when you can talk to your doctor, have a relationship with him, and especially, as people become older, and where I live in South Florida, there are many elderly people who do not have family around, so they are going to their doctor by themselves, and they are dependent on that doctor's viewpoint.

They will say, "Well, what do you think?" I used to say if I were your child, and then it was if I were your wife, now it is getting to be if I were your grandmother, you know, with the age of everyone, and I hope I live to say if I were your granddaughter.

But that is very true, and again it is not a simple situation, and whether we need some sort of health educator to assist the doctor to be able to explain this to the patients, so that they are not taking valuable doctor-patient time, but something needs to be done.

DR. WOOD: Thanks.

Dr. Ilowite.

DR. ILOWITE: I wanted to talk to a few

pediatric issues about these agents, the granddaughter. First of all, about choice, there are far fewer choices in pediatrics. There is only three NSAIDs approved, only two liquids and none any longer that are available as once-a-day dosing regimens.

The second issue is about tolerability. Certainly, children have fewer serious gastropathic events, but they do have a lot of symptoms, and it is often difficult to get children to take medications that give them even bellyaches.

Third, is the risk of cardiovascular disease, which is very low in pediatrics. A new clinical research network called CARRA, Childhood Arthritis and Rheumatology Research Alliance, organization polled its 130 members of whom 92 or 71 percent responded, and there were no events of myocardial infarction or stroke that couldn't otherwise be accounted for easily that were

attributable to these agents.

Lastly, is the issue of exposure. It is likely that children with chronic rheumatic diseases are going to be on these agents longer even than adults, and the cumulative risk is of great concern.

I think it would be very important to try to get some insight into the pathogenesis of this, not just the frequency, so that early markers could be explored in children who are exposed before they exhibit the clinical endpoint.

MR. LEVIN: I haven't spoken for two days, so now I may go on. A couple of thoughts. One is I am all about informed choice, but the question is how informed is the choice, I think, as others have raised, and I want to point out that I think we have this sort of mythology of a changing environment which is patient-centered in which there is this sort of partnership.

With all due respect to the clinicians around the table in the room, I don't think that characterizes most people's experience in the

health care system today. I think it is totally unrealistic. We have 45- to 50,000 people who are uninsured, who have very haphazard access to care, certainly don't have an ongoing relationship probably with a practitioner who is going to sit down and run through the benefits and risks in the alternative therapies and help them make an informed decision.

We know from studies of how much time physicians have with patients and what they convey when they prescribe a drug, that is far from the role of the learned intermediary that is sort of I think mythic, and we need to get over.

I agree with Lou that we need to ask patients what they want and what their experience is, but on the other hand, we have a regulatory context here. We have 1906, we have 1938, we have 1962. For better or worse, the Congress has decided that there is a role for government to play in protecting the public from harm.

So, I don't think we can just sort of slide this all off on patients and physicians

supposed in this Nirvana good, up-to-date information, making intelligent choices through this very difficult, complex issue.

The Government does have a responsibility, and that is why we are here. We are being asked for I think advice on how government can best meets its responsibilities under statute to protect the public health and to do what it has to do.

We all recognize that there are lots of things that need to be improved, I believe, in the way new drugs come to market, because I have sat through this before when we are chasing the train. The train is out of the station, folks, it is going down the track very fast, and we are trying to catch up to it and figure out what do we do.

You know, it is heading for the crossing, there is a car on the track, how do we stop the train. It is too late. We are always going to hear from patients no matter what the drug, "This drug worked for me, it's wonderful, it changed my life."

I believe them, I certainly empathize with

them. There will always be that appeal. So, I guess we have a complex task, the train has left the station, but we can't abrogate our responsibility, and we can't pretend the Government, through the FDA, doesn't have a statutory responsibility here to protect the public health.

We can't just say put information out there, make it transparent, let this mythical doctor-patient relationship sort of bubble up and make things all right, because it's not going to happen that way.

DR. WOOD: Helpful comments from our consumer representative.

Dr. Manzi.

DR. MANZI: First, I would like to congratulate the members of the panel who I thought have brought some very relevant points to the table, and I agree with most of them, but it is interesting to me how many times I have heard the term "safe alternatives" used.

I look at our first question about

weighing the benefits of the COX-2s versus the non-selectives, and I think the assumption, as we are trying to deal with the coxibs, is that there is, quote "safe alternatives" in the non-selective agents that we would feel comfortable having our patients turn to in the event that these other COX-2s were not available.

My question would be, or I guess my challenge to my other panel members would be to provide data that has been obtained with the same rigor and had to undergo the same scrutiny as the drugs that we have just looked at to prove that the other non-selectives are safe alternatives.

I don't think we have it. I think we have signals actually to the opposite potentially. So, I just think we have to keep that in mind as we are making decisions that patients are going to have to turn to something, and do you feel comfortable saying that the alternatives are safe.

DR. WOOD: Another way to think of the same thing, though, is that if we were sitting here thinking about approving these drugs right now,

would we approve drugs with a clear cardiac risk in randomized clinical trials.

I think that is an important question for the committee to address because if we don't address that, we will either not be able to address it for drugs coming up in the future and/or we are going to apply a different standard to drugs that are on the market, and I understand all these points, but I think it's--maybe I am wrong--I think it's highly improbable that the committee would have approved any of these drugs given the safety signal we have got right now.

I think it is highly improbable that the FDA--I am talking about from randomized clinical trials--I think it is highly improbable the FDA would have approved drugs if they had had all the randomized studies they have right now.

That doesn't mean they wouldn't have approved them eventually perhaps, but they certainly wouldn't have approved them on that basis. Is that fair, Bob?

DR. TEMPLE: I think it varies depending

on how you view various collections of data, but some of them I think probably would not have made it.

DR. WOOD: All right, some of them we would not, but that is a fair comment.

DR. MANZI: Could I just comment?

DR. WOOD: Sure.

DR. MANZI: I would argue that that would depend on the need for the drug, and it would also depend on the alternatives available, and so I think it is hard to look at it in isolation.

DR. WOOD: Fair point.

Dr. D'Agostino.

DR. D'AGOSTINO: The Framingham study has generated many risk assessments. They are in the cholesterol guidelines. Cardiac risk assessment tools do exist. Would the physicians use them? I am not sure that cardiologists use them, nor other classes of physicians to automatically use them and sit with the patient and go through that, but they do exist, and if you could build a scenario for that, it would be possibly very useful.

But one of the things I wanted to really mention isn't just the existence of these tools, but there seems to be something synergistic about

taking the drug and your cardiac risk, so it is not just a matter of telling you you are diabetic and how likely you are to have a heart attack. This drug seems to double that or triple that, and so forth, so you will be presenting very high risk to the subjects, and I am not so sure how easy that is to do, but it should be kept in mind that there is an elevated risk beyond the normal cardiac risk.

DR. WOOD: Unless someone else has a burning question, I am going to give Ms. Malone the last word.

MS. MALONE: I feel the need to speak up for rheumatologists. I had been on this panel I believe starting in 1995, and as a consumer rep. I filled someone's term, and then I had my own term. So, I was on it for five years, and then I came on as a patient rep intermittently.

From my 35 years dealing with rheumatologists and being on the panel, I have to

say that rheumatologists, on a whole, are a unique set of doctors. They are in there for the long haul and I have always felt that when I was on this committee, if I were not here, that the voice of the patient would still be heard.

I find that I don't think there is one rheumatologist on here who would not spend time with their patient, who would not spend time educating them and listening to them albeit it it's not a half-hour, but I think they do have the ability to form a relationship with them, and I applaud them for that, and I disagree with Arthur on that point.

DR. WOOD: Stephanie, I will give you the last word and then we are stopping.

DR. CRAWFORD: Thank you so much, Mr. Chairman. I simply can't quite leave without at least attempting to address this stunning near cliffhanger that we were given about 40 minutes ago.

I am going to ask, if I may--and please forgive me if I get your name wrong, it's not

listed on my papers--I think it was Dr. Kim from Merck. Thank you.

Yesterday, I asked the question to Dr. Braunstein about what was or were the deciding factors in the extraordinary step that Merck made in deciding to voluntarily withdraw rofecoxib. I am not sure I heard a clear-cut answer, so I am going to ask you something very related to this last question we have been addressing from the opposite side.

Tonight, what considerations would you weigh or would you ask this committee to consider when we deliberate tonight or tomorrow in determining the benefit of potential re-introduction of rofecoxib, or if you wish to say this class, where the benefits would far outweigh any issues of safety concerns?

DR. KIM: Thank you for that question, and I will say that it has certainly been a very educational and informative day, two days actually, listening to these discussions. I think the issues are complex, and I think that all of the complex

issues are being brought up.

As I said, Merck believes, based on the new data that has just become available, that what we are dealing with here in terms of cardiovascular risk is a class effect.

The thing that we are struggling with, which you are all struggling with, is what does that mean in terms of the size of the class, and, in particular, is it limited to just inhibitors of COX-2 or does it include inhibitors of COX-2 that also now have an effect on COX-1.

The only point that I was trying to make was that at the time that we decided to withdraw Vioxx from the market, we did so based on the information that was available to us at that time, knowing that there were alternative therapies and that there were questions that were raised by the APPROVe trial.

Now, where the science has progressed to, where we see, we think, and we look forward to your decisions, but we think we are dealing with a class effect, then, I think we are no longer dealing with

a situation where Vioxx is unique in its cardiovascular risk, but instead is a member of a class.

Then, I think it is important for us--again, we are looking to you, this committee and the FDA, for your evaluation of whether or not you agree with our interpretation that this is a class-specific effect, but if that is the case, then, I think we need to take a look at the unique benefits that Vioxx provides, which I mentioned, and actually a fourth benefit which was already mentioned, that is, that Vioxx is the only COX-2 inhibitor which has been proven to reduce the events, serious GI events, as compared to naproxen.

Vioxx is the only COX-2 inhibitor that was approved that is not contraindicated in patients with allergies to sulfonamides, and Vioxx was the only COX-2 inhibitor with approval for juvenile rheumatoid arthritis in addition to the fact that we have heard numerous reports from patients, some with very chronic debilitating pain, that Vioxx was the only drug that worked for them.

With that, I will leave it to the committee. We really await your decision on this issue.

DR. WOOD: Okay. It's never the last word, is it.

DR. STRAND: May I finish the answer to a question that I was asked yesterday?

DR. WOOD: Who are you?

DR. STRAND: I am Dr. Strand and I responded to you yesterday about the use of COX-2s in patients, the benefit-risk profile. I simply to say that with Dr. Hochberg we authored an editorial in 2002 after the introduction of the data from CLASS and VIGOR to point out that there is benefit with these COX-2s, which is at least numerically preserved from a GI point of view, both from TARGET and CLASS data, with a baby aspirin, and, in fact, most of the cardiovascular risk may be abrogated by co-administration, and we certainly don't have to then worry about the potential interaction as has been demonstrated with ibuprofen.

So, I think it is important in your

deliberations to consider that point.

Thank you very much.

DR. WOOD: Kimberly tells me the committee has to meet in the lobby in 15 minutes. I think that is pretty optimistic, but good luck.

(Whereupon, at 7:00 p.m., the proceedings were recessed, to reconvene on Friday, February 18, 2005, at 8:00 a.m.)

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