

1 to be reflected. I said earlier in the day to Dr. Wofsy
2 that the main message to me is that all NSAIDs are not equal
3 and there definitely is a continuum. I did like the way Dr.
4 Sampson revised what Dr. Nissen had said about reporting of
5 what was actually found in the study and having the label
6 reflect the evidence that we do have out of this study.

7 DR. HARRIS: I am going to give a reserved no, I
8 don't think it should be changed. I think that as a
9 treating physician, if the label were just generally changed
10 like that, the sense that I would have is that this agent is
11 better than the non-steroidals, and I don't think that is
12 what has been proven.

13 Given the labels, such as they are with respect to
14 these agents, I, therefore, don't feel that there should be
15 a change. At the same time, I do think that this data, with
16 respect to naproxen in this particular group of patients
17 with this particular agent, is worth communicating in some
18 way within the label. But, I want to add one other thing.
19 I think too if I feel this way I would have wanted,
20 actually, the same thing to be done for celecoxib because,
21 again, these are two massive studies, the CLASS and the
22 VIGOR today and it just happened to be a choice of agents,
23 and so on, and I think if we are going to report, then let
24 us report the results such as they are.

25 The third point I am going to make is this we

1 respect to labeling, I really do think that the time has now
2 come for the FDA to look at this issue with respect to
3 comparator and non-steroidal agents because we are taking
4 one or two agents and generalizing, and there are obviously
5 issues with respect to that. I don't know if it is ever
6 going to be answerable but, nevertheless, I think it is
7 worth a discussion.

8 DR. WILLIAMS: I will give Dr. Wofsy's yes.

9 DR. SAMPSON: A cautious change is probably in
10 order. I think the continuum message has to be delivered.
11 I think the wording has to be done in such a way as to not
12 imply that this applies to all NSAIDs. Then, I made a
13 little note to myself, as Dr. Harris was speaking, about the
14 issue of celecoxib and whether there is some way of working
15 out in all of this class labeling for COX-2's that would be
16 equally applicable, and somehow summarize the information
17 gleaned from both very large studies.

18 DR. ELASHOFF: I agree with Dr. Pina that I don't
19 see any reason to delete anything that is already there. I
20 guess in view of that, I probably would feel that people
21 could learn about the results of this study in some other
22 way than the label but if it is strongly felt that the label
23 should include some very cautiously worded sentence about
24 the results of this trial, I wouldn't strongly object to
25 that.

1 DR. HARRELL: I would change it. I would be
2 narrow, be specific, report the good with the bad. I do
3 have to add though a p value is a technicality. It is a
4 mathematical convenience and allows you not to think. One
5 statistician, Herman Rubin, called the p value, next to the
6 atomic bomb, the worst invention of the 20th century.

7 [Laughter]

8 DR. HARRIS: Yes?

9 DR. DELAP: I think we spend a large amount of
10 time with sponsors on labeling, and it is a very important
11 mechanism for us to communicate with patients and
12 prescribes. It doesn't always communicate as well as we
13 would like but we do the best we can.

14 I think what drives us a lot in the labeling
15 negotiations is to try and serve the physicians and the
16 patients by giving them the information they need to choose
17 among products. So, if there is a distinction to be made or
18 that we think is pretty likely to be an important factor in
19 a decision of a physician and patient to use this drug
20 versus that drug, then we think it belongs there. If there
21 is terminology that could be misleading in terms of
22 appearing to indicate a distinction, we try to stay away
23 from things that appear to create distinctions or we are not
24 confident might actually exist.

25 It is coming up here because we had kind of a

1 generic way of labeling NSAID toxicities, and we recognize
2 increasingly as we get more data that there are distinctions
3 to be made. The struggle is to really accurately convey
4 that information, I think, for patients and physicians.

5 I think, again, the last thing I will say is that
6 we aren't captive, I think, to p values, to follow up on the
7 last speaker's comment. Although p values are a good way of
8 making decisions about data, they are not the only way.
9 Again, I think if we feel that there is information that is
10 relevant and important information we try and include that.

11 The very last thing I will say is that we struggle
12 with things like making comparisons against groups of drugs
13 where we haven't really studied all the members of the
14 group, and that has been a good part of the discussion here.
15 Again, it would not be fair to paint all of the other NSAID
16 products that are out there in the market that antedate
17 celecoxib -- we can't paint them all with the same brush.
18 In that sense, I am not satisfied that we can really say
19 that we know what we need to know, and just say all of those
20 are there and these two drugs are here.

21 DR. HARRIS: Thank you. Now I am going to raise
22 the cardiovascular question. What I am going to do this
23 time around, Dr. Pina, if you could give your opinion and
24 then maybe I will ask for one or two other comments and then
25 we could probably, if necessary, have a show of hands as to

1 whether or not they accept some of what you say.

2 DR. PINA: As far as the cardiovascular events, I
3 do think that we have seen some effects of naproxen on
4 platelet inhibition. I can't say that is not there. But
5 not withstanding that, it still leaves me the concern of a
6 greater rate of thrombotic events than I would have expected
7 in this population, and I value my rheumatology colleagues'
8 comments about the higher incidence of cardiac events in
9 this population but I am still not convinced that we know
10 that percentage well enough to tell me that this population
11 is at a rate that they should be for the amount of
12 rheumatoid arthritis. As I understand the disease, it is
13 also based on the duration of the disease and the severity
14 of the disease, both of which we are not certain about in
15 this trial.

16 I am also uncomfortable with the doses that are
17 higher. I don't know what the thrombotic events would be in
18 this population if the doses were lower. So, it still
19 leaves me with a fair amount of discomfort even though I do
20 think that some of the differences are due to naproxen. I
21 would put it in the label exactly as that, that the risk has
22 to be noted, that it may be there even in the patients that
23 you would not use aspirin for. That is why I was asking Dr.
24 Villalba about that table that she showed in patients who
25 would not have received aspirin otherwise, and that trend is

1 still there. Again, it may be rheumatoid arthritis. It may
2 be the disease that we are looking at but I can't say for
3 sure. I just don't have that data.

4 DR. HARRIS: Yes, Dr. Nissen?

5 DR. NISSEN: Briefly, I think what I would say in
6 the label is that there was an excess of cardiovascular
7 events in comparison to naproxen, that it remains uncertain
8 whether this was due to beneficial cardioprotective effects
9 of naproxen or prothrombotic effects of the agent, and leave
10 it at that, that basically we don't know the reason. We do
11 know there was a difference. That awareness should be made
12 available to the prescriber and to the consumer, but without
13 necessarily a final judgment as to the reasons for that
14 difference.

15 DR. WILLIAMS: I thought we addressed this in
16 question one, and I still don't think we have enough data to
17 make a statement. If we were going to make a statement, I
18 would favor the one done by Dr. Nissen but I still don't
19 think we have enough data to make a statement.

20 DR. HARRIS: Let me see if I can comment here, you
21 know, we have the label such as it is. The actual crafting
22 of the language -- it sounds very crafty, in fact, Dr.
23 Nissen, as to how it might be crafted and it may be crafted
24 the way you say. The question is whether or not there needs
25 to be some additional language, if you will, with respect to

1 that. So, I am going to ask yes or no, whether or not there
2 needs to be additional language, perhaps crafted along the
3 lines that Dr. Nissen suggested, or, no, there doesn't need
4 to be any additional language.

5 So, let me ask for those feeling yes, that there
6 needs to be something, some additional language perhaps,
7 along the lines of Dr. Nissen in terms of the label. I will
8 ask for a show of hands.

9 [Show of hands]

10 Is there anybody against?

11 [One hand raised]

12 One against. Any abstentions?

13 [No show of hands]

14 Again, let me emphasize this is merely advisory
15 and we are merely giving an opinion here. Thank you.

16 We are now going to move to question number four.
17 Please comment on the overall safety comparisons between
18 Vioxx and naproxen in the VIGOR study. We sort of commented
19 before, but whether or not --

20 DR. SAMPSON: There were some other pieces to
21 number three. There is the hepatic and skin.

22 DR. HARRIS: Thank you so much, Dr. Sampson. I
23 had actually wrongly come to the assumption that perhaps
24 there were no other issues with respect to that but, if
25 there are with respect to hepatic and skin and, in fact, any

1 organ system, is there any additional comment or any change
2 that one might expect?

3 DR. PINA: Let me make one comment simply because
4 clinically it is what we see and it is what it is. Down in
5 the labeling, where it has "additional adverse experience"
6 there is a mention of congestive heart failure and perhaps
7 there should be a statement about fluid retention in
8 congestive heart failure and about the incidence of
9 congestive heart failure as demonstrated in this trial,
10 rather than just lumping it down here because clinically it
11 is there; clinically we see it.

12 DR. HARRIS: Can you just quickly read the
13 statement for us?

14 DR. PINA: I am looking at the template and if you
15 go to page 11, they have additional adverse experiences
16 reported occasionally include congestive heart failure,
17 etc., listed under the cardiovascular system. I think that
18 as potentially this number of patients continues to grow, it
19 is the one cardiovascular disease going up in the country
20 instead of going down and there perhaps should be some
21 statement, and maybe the data from here can be quoted. The
22 sponsor has admitted to fluid retention and edema. I don't
23 it is anything that they haven't. But, I would like to see
24 it singled out somewhere because the sense that these agents
25 are quite safe in patients with volume repletion and volume

1 expansion is not the case.

2 DR. WOLFE: I have a question. Is that specific
3 for rofecoxib or for NSAIDs in general that we are seeing an
4 increase in congestive heart failure?

5 DR. PINA: I think it is for NSAIDs in general but
6 there is the common concept out there that these agents may
7 be a bit different in this population, and I think it should
8 be said that they are not different in this population. So,
9 one statement there would be reasonable.

10 DR. WILLIAMS: What we saw from the data was
11 edema, and that is listed under 1-10 percent and, based on
12 the data we saw today, I am not sure we can make that change
13 and if we did, it should be generic for all NSAIDs.

14 DR. PINA: But they did have a separate slide for
15 heart failure incidence. That is the one I am talking
16 about.

17 DR. WILLIAMS: It was not up to that level, or any
18 different than any other NSAID. That is why I say it should
19 be generic if you are going to do anything because, based on
20 the data we saw here, we shouldn't --

21 DR. PINA: I agree with the fact that it should be
22 generic. I would like to see it in there because it is not
23 a drug without its problems, all of them, in the heart
24 failure population. So, if we do it for one maybe we should
25 do it for all, but I think it should be here separately.

1 DR. HARRIS: I must say, from my own perspective
2 and I don't want to inference anything, I think this is a
3 general observations for NSAIDs and, I must say, based on
4 the data, it doesn't rise to any greater level than the
5 other NSAIDs requiring a separate statement. So, here is
6 what I am going to say, Dr. Pina, how many people agree
7 with Dr. Pina that with respect to congestive heart failure
8 there should be something additional written in the warning
9 label?

10 DR. PINA: I agree with Dr. Williams about all
11 NSAIDs, not just this drug, not Celebrex alone. I agree
12 that all of them should have some statement. I am not
13 trying to single this drug out at all.

14 DR. HARRIS: Do you think it is adequately
15 covered?

16 DR. DELAP: We are assiduously writing things down
17 here in the discussion and I think we can take that back and
18 think about it. Again, we do try and communicate what we
19 think are the most important points about all these products
20 to physicians and patients, and I think that what we hear
21 from you is that you feel that this may require a little
22 more prominence and we will take that back and look at it.

23 DR. HARRIS: Thank you. There were other organ
24 systems. Does anybody have any feeling as to whether there
25 should be changes with respect to any of the other organ

1 systems based on anything that we have heard today? I take
2 the shake of heads to mean no, and there doesn't appear to
3 be any yes. So, there seems to be a consensus; no other
4 change. Thank you.

5 Now, question number four is please comment on the
6 overall safety comparisons between Vioxx and naproxen in the
7 VIGOR study. I must say that this field has been plowed
8 quite extensively already. If there is some statement that
9 you feel might add to what has already been said, then I am
10 going to ask you, in fact, to comment.

11 DR. WILLIAMS: They actually had a slide that
12 showed serious adverse events and naproxen looked better
13 than rofecoxib in that area.

14 DR. HARRIS: Given that comment that, in fact,
15 apparently naproxen in overall respect to serious adverse
16 events looked better, is there anything else that one would
17 want to say other than that? Yes?

18 DR. WOLFE: There is something else I want to
19 bring up that was a little disturbing but, again, I learned
20 something new, that the p value isn't so holy after all.

21 [Laughter]

22 If that is the case, then in all fairness to
23 celecoxib, I think if you are going to be so circumspect on
24 the results of the VIGOR trial, saying it was only naproxen
25 that showed a difference, then divide their study up and

1 show the table -- you do it all the time in the PDR -- and
2 show the differences between celecoxib. Again, a lot of us
3 think this is probably a difference in study design that the
4 differences weren't shown in celecoxib. These are clearly
5 two different studies, with very different designs and
6 different results probably because of that -- I am going to
7 stress "probably." We are still not shown why the
8 differences were seen in these two studies.

9 DR. ELASHOFF: While I think that some mention
10 needs to be made of the overall difference in adverse
11 events, whatever is added for cardiovascular events and
12 whatever is added for GI events, make it clear that there is
13 somewhat compensating size of what is going on there. Then,
14 one wouldn't necessarily need to say anything about total
15 adverse events. But, one certainly wants to avoid a
16 sentence which implies that you get a lot of advantage in GI
17 and only a little extra worry in cardiovascular or something
18 like that, which would hide the overall total rise in
19 adverse events.

20 DR. HARRIS: Thank you for that remark, Dr.
21 Elashoff. I think it is a very important remark. Can I get
22 another comment or two as to whether or not there may be
23 some value to doing that?

24 DR. CRYER: This is a concept that actually has
25 been constructive for me over the last couple of days, that

1 while there are, or may be, clear benefits with respect to
2 organ-specific benefits physicians need to keep in mind the
3 overall, global safety. In follow-up to your comment, there
4 may be some reversal of organ-specific benefits when global
5 safety is considered, and I think that is an important
6 message which has been a new perspective for me, in fact,
7 because as a gastroenterologist I have somewhat had tunnel
8 vision with respect to these issues, but I think it is an
9 important message with regard to educating physicians.

10 DR. WOFSY: I would just concur. Since you are
11 asking for comments, I will bring back three messages to my
12 patients and students. One is that the study confirmed what
13 we thought we knew with respect to the relative benefit of
14 rofecoxib over at least some of the traditional NSAIDs with
15 respect to GI toxicity. I learned that there is reason for
16 concern about thrombotic events and probably the message
17 that you are both emphasizing and that I agree with very
18 much, that, in fact, what came out of that study was that
19 serious adverse events were at least as common, or more
20 common in the rofecoxib group. That is an important part of
21 the message.

22 DR. HARRIS: What I am going to do is just to
23 carry that message that, in fact, one does have to weigh the
24 benefits of one organ system compared to sort of the overall
25 risk-benefit, whatever. I will actually ask for a vote with

1 respect to whether or not we actually should advise that
2 there might be some way of framing that benefit in one
3 system and the issue of overall benefit. Do I get a sense
4 from the committee that we agree that there should be some
5 mention made of that? Let me have a show of hands, yes or
6 no.

7 [Show of hands]

8 Is there any disagreement?

9 [No show of hands]

10 Any abstentions?

11 [No show of hands]

12 So, that was unanimous.

13 There are two general questions that have been
14 posed, and I want to read the first of them -- yes, Dr.
15 DeLap?

16 DR. DELAP: I would just like to say one other
17 thing before you leave the individual drugs. You were
18 talking about the balance as seen in the studies and the
19 last thing I would like to say is that in looking at those,
20 of course, we will be looking also at the fact that both the
21 study today and the study yesterday used kind of high-end
22 doses of the COX-2 drug versus some more standard dose of
23 the comparator drugs. That does weigh in a little bit,
24 although we don't know exactly high, on the exact rates. It
25 is not a direct comparison of the usually prescribed doses.

1 So, we will have to factor that in as well in looking at
2 those kinds of numbers.

3 I guess we are moving into the general discussion
4 now which doesn't specifically concern the Merck product but
5 concerns all of the discussions over the last couple of
6 days. I guess we can kind of excuse the Merck folks unless
7 there is some further comment that they would like to make
8 before we move on in our agenda. I mean, you can continue
9 to sit there if you want but you don't have to do anything.

10 [Laughter]

11 DR. GOLDMANN: I would just like to thank the
12 advisory committee and members of the FDA for a really
13 stimulating couple of days. Thank you.

14 DR. HARRIS: I think maybe a ten-minute break
15 would be worthwhile. So, we will reconvene again at 3:25.

16 [Brief recess]

17 **General Questions**

18 DR. HARRIS: In this portion of the discussion we
19 are dealing with general questions, and I was asked whether
20 or not there might be brief comments invited, as we go along
21 here, from the audience. As long as they are kept very
22 brief and to the point being discussed, I think they
23 certainly would be welcome.

24 I want to read the first question for the
25 committee. Do these two large outcome trials suggest that,

1 (a) GI and, (b) overall safety should be addressed similarly
2 with large outcome trials before organ-specific safety
3 comparison and claims can be considered with new agents in
4 the future? That is quite a mouthful.

5 What I am going to do is invite comment first from
6 members of the committee.

7 DR. HARRIS: Dr. Harris, just a point of
8 clarification, when we think of new agents here we are
9 thinking of new COX-2? Is that correct?

10 DR. HARRIS: I am going to ask the FDA. I mean,
11 this was the question posed. I presume it is new COX-2 but
12 let me ask that question. It may be broader than that.

13 DR. GOLDKIND: I think we could look at it as
14 agents that are proposed to have safety benefits. So, we
15 are not really talking about efficacy; it would be whether a
16 sponsor feels that there is a safety advantage, and how
17 organ specific versus general safety -- how that balances,
18 and how strongly overall safety needs to be examined before
19 specific safety claims since it is not the way we typically
20 see it, typically we are looking for efficacy and then you
21 describe safety in whatever size database you have. The
22 paradigm is a little different here.

23 DR. SAMPSON: You are not suggesting that we
24 consider this statement for all types of compounds, are you?

25 DR. DELAP: I was just going to amplify on that

1 subject because the NSAIDs is where we have kind of a
2 template class labeling. So, I think the general rules are
3 that if you want to make a claim against some other
4 individual drug, you know, drug A versus drug B, forgetting
5 about the disease and the class of products for the moment,
6 then you have to study drug A against drug B. But, here we
7 are talking about within this NSAID class where we have some
8 kind of standardized labeling information where you might
9 want to make some modifications or comparative claims with
10 regard to that NSAID template kind of information.

11 DR. WOLFE: You said similarly and I feel very
12 strong some standards should be set. And, as long as I am
13 speaking first, I will tell you what I think the standards
14 should be.

15 Generally what has been done in the past is to use
16 the comparator which is the drug used most commonly. In
17 this country that is probably ibuprofen and naproxen, those
18 two drugs as the standard comparators in the most commonly
19 used doses. Additionally, in the case of COX-2 inhibitors
20 probably other drugs as well, but I would leave aspirin out
21 of it because, otherwise, you are not going to be able to
22 tease out aspirin very well unless you have very, very large
23 studies, really large studies which then take aspirin into
24 account as a separate group. If you want to look at
25 aspirin, make it a separate study. Otherwise, aspirin is

1 going to confuse your data very, very significantly.

2 The other point I would make is that having said
3 take aspirin out, in other studies put aspirin in because
4 that is more or a real-world situation but I would have
5 separate studies to assess whether aspirin is a risk factor,
6 and whether it is additive or whether it negates the
7 protective effect any drug might have.

8 DR. NISSEN: This is really a troublesome
9 question, and I was very persuaded by David Wofsy's comments
10 about the fact that we are talking about a class of drugs
11 that is basically a spectrum, with the COX-2 drugs on one
12 end and maybe naproxen and aspirin and ibuprofen on the
13 other. So, whenever you do a comparison you are picking
14 some point on that continuum between GI, cardiovascular,
15 renal and other effects. So, it becomes extraordinarily
16 difficult to do this.

17 So, it seems to me that the benchmark probably
18 should be overall safety because when you have competing
19 effects here -- you know, we have said, well, maybe
20 yesterday they used the wrong comparator. Well, you know,
21 the way to assess a drug before you say drug A is safer than
22 drug B, when you know you have that kind of a continuum of
23 benefit and risk is by showing that overall safety -- I
24 can't necessarily define that right now for you but that
25 overall safety is better for one drug than another. What I

1 might do there is classify serious adverse effects and say
2 you have to show that your drug in totality produces less
3 serious effects than another drug before any comparative
4 claim can be made. Otherwise what you do is you pick a drug
5 based upon the endpoint you want. You can pick the right
6 comparator and you can get it to show almost anything you
7 want to show.

8 DR. WOLFE: So what? Not all the patients are the
9 same. If we have a patient with a previous history of GI
10 bleeding from ulcer disease we want to use a drug that has
11 low ulcerogenic potential. If we have a patient with a
12 previous myocardial infarction, we want a drug that won't
13 cause myocardial infarction. I think the data is as it is.
14 We should know what the toxicity is specifically.

15 On the first day of pharmacology we learn that
16 every drug has toxicity to it. We have to know what that
17 toxicity is very specifically. I mean, the reason I
18 mentioned specifically naproxen and ibuprofen is because
19 they are the most commonly used NSAIDs right now and they
20 are not at the opposite ends or the spectrum. If you want
21 it for GI bleeding, let's put peroxicam back in there and we
22 will have plenty of really big differences then in almost
23 every drug.

24 DR. HARRIS: Dr. Wolfe, I am wondering if I could
25 pose a question to you. Suppose that there was some new

1 agent that, in fact, showed in terms of GI toxicity that it
2 was absolutely equivalent to placebo, however, that we found
3 -- and this is an extreme example -- should we ignore the
4 fact that, in fact, it increased renal toxicity to a degree
5 much more than one would expect?

6 DR. WOLFE: Absolutely now. That is the hole
7 point. There was an NSAID introduced -- I forget which one
8 it was -- that caused hepatotoxicity and the drug was never
9 approved by the FDA because of hepatotoxicity. We need to
10 know what the toxicity is. If it is unacceptable because of
11 other organ systems, then it shouldn't be approved. On the
12 other hand, if we have a drug -- let's pick drug X which has
13 complete cardiovascular sparing effects but has serious
14 gastrototoxicity because of ulcers both to the stomach and the
15 duodenum, that information is important for everybody to
16 know about.

17 I mean, basically what we are saying is pick your
18 poison. We know the NSAIDs are drugs which have serious
19 toxicity associated with them. We have seen the COX-2
20 inhibitors and it looks like they may be having a sparing
21 effect on the GI tract in exchange for an effect on the
22 cardiovascular system, thrombogenic events. But, again,
23 every patient is very different.

24 DR. HARRIS: I am going to invite more comments.

25 DR. WOFSEY:

1 DR. ELASHOFF: First of all, I would like to say
2 that I agree that the overall safety has to be the bottom
3 line and that I am not sure it makes much sense to talk
4 about it being more safe this way but might be more
5 dangerous in some other way. But, apropos of entering
6 people and now feeling that we could say that since it
7 looked a little safer in GI that our patient who has GI
8 problems would do better on this one versus somebody else
9 doing better on another one, I don't think the data have
10 been analyzed in enough detail, or perhaps even could be
11 analyzed in enough detail to really address the question of
12 whether that kind of assumption is true or not, that you
13 really could differentiate patients and what kind of
14 patients are going to do better on this and another kind of
15 patients are going to do better on that.

16 DR. SAMPSON: I want to speak just a little
17 speculatively for a minute. I am going to put on my
18 statistician's hat and start to think about models. I am
19 thinking about Dr. Wolfe's comments about a spectrum of
20 NSAIDs, I get the impression that you actually think of
21 things almost linearly laid out, at least not in the kinds
22 of responses they create but that somehow the spectrum is in
23 one dimension. I guess what I am wondering is, and I was
24 asking Dr. Williams about this, could you measure the ratio
25 of COX-1 to COX-2 inhibition for the different NSAIDs? I

1 gather that is different. Is that correct? Some NSAIDs are
2 much more COX-1 inhibiting and others are much more COX-2.
3 Is that number available for every NSAID now?

4 DR. WOLFE: There was a paper in Annals of
5 Internal Medicine last January, by Byron's colleagues,
6 Feldman and McMann, which was a meta-analysis looking at
7 about 20 different NSAIDs and looking at the COX-2-COX-1
8 relationship using in vivo assays. The information is
9 available but I am going to caution you, that doesn't always
10 correlate directly with the toxicity of the drug itself.

11 The other thing is that you are speaking as a
12 statistician, and the thing is that in so many ways so am I
13 because I am looking at the statistics. We do this every
14 day in medicine. We are looking at the chances of this drug
15 causing a good effect of you being such; the chances of
16 causing toxicity is such. On the other hand, in the
17 individual patient it could be 100 percent effective or 100
18 percent toxic or zero percent. I am exaggerating, but there
19 is a lot of individual variability. We are looking at a
20 statistic. This is called probability in every single
21 person we take care of that this drug may produce its
22 desired effect or cause a toxic effect.

23 DR. HARRIS: Yes, Dr. Cryer?

24 DR. CRYER: I would also like to comment. I think
25 that I would like to steer you away from that concept based

1 on differences in selectivity based upon preclinical data
2 which clearly show that there is a spectrum, probably not
3 linear, with respect to differences in selectivity. But
4 those concepts are flawed in that they are not entirely
5 applicable to clinical outcomes, and that was the entire
6 reason for the development of these outcome trials. We
7 really want to see how the differences fall with respect to
8 outcomes. Unfortunately, we have very few data that
9 actually give us this spectrum information with regard to
10 outcomes.

11 The other comment that I think is worth
12 emphasizing is that while I think it is important to
13 emphasize that there is a continuum, that concept with
14 respect to NSAIDs, I think there is also a continuum with
15 respect to patients and patients' risk for the development
16 of the problem, GI bleeding. I don't think that we can
17 discuss this issue of this continuum of NSAIDs with respect
18 to risk without discussing the difference in risk in
19 patients who may be given these agents. I think they go
20 hand in hand.

21 DR. HARRELL: I think we are making the problem a
22 lot simpler than it really is because when you are looking
23 at different safety outcome in acute MI studies, there is a
24 huge spectrum of safety events. Even when you are just
25 looking at stroke as an adverse event from thrombolytic

1 therapy, there is disabling stroke and there are milder
2 strokes. You can't just count strokes. You have to look at
3 the severity of the stroke.

4 Ever since I have been working for FDA, for 14
5 years now, I have heard the phrase risk-benefit assessment
6 and I have still never seen one done in 14 years. And, I
7 think we need to take some lessons from the cancer area
8 where they actually do this, and they have ways of trading
9 off toxicity with efficacy and quality of life, and the
10 assessment of patient utilities now is getting very mature
11 and we need to see some of this utility assessment and
12 disutility assessment for adverse events used and
13 incorporated in the tradeoff.

14 DR. WOF SY: It sees to me, and I may be wrong -- I
15 don't know the origin of this question, that this question
16 comes, at least in part, by some second thoughts based on
17 what has happened in the course of the development of COX-2
18 inhibitors, and did we do it the right way; should we have
19 done it a different way?

20 So, I might speak up actually for what was done.
21 It doesn't seem to me to be necessarily wrong. In fact,
22 this is a good example. This was rational drug development.
23 It was based on a biological principle that was important
24 and that addressed an important problem in clinical
25 medicine, and it led to a specific hypothesis and that

1 hypothesis had to do with GI toxicity. And, that is what
2 was looked at. It would be very hard to go back and try to
3 understand why you might have wanted to do anything
4 differently than that. In the course of doing thorough
5 examination of that question, other safety issues were
6 explored and came out that turned out to be important and
7 raised new questions for us. And, it seems to me that that
8 is okay too, that in this particular instance there was a
9 reason why organ-specific toxicity was the right thing to
10 look at first and it was, of course, appropriate then --
11 especially since this became such a widely used agent -- to
12 go beyond that and look broadly at other things.

13 It might be that for a different agent that wasn't
14 developed specifically focused on a single organ toxicity
15 that wouldn't be the right approach. But, in this case it
16 seems to me it is a rational approach and it would be hard
17 to even picture the discussion that would have led down a
18 different pathway from the beginning.

19 Having said that, however, I actually think it is
20 worth taking seriously the comments that were made in the
21 public session this morning about the thoroughness of a
22 safety review before approval. I don't think there was
23 anything wrong, anything that should be second-guessed, in
24 my own view, about the sequence of organ-specific evaluation
25 first and overall safety toxicity later but I do think that

1 the point that was made is very pertinent. That is, if a
2 drug doesn't have an efficacy advantage and is being put
3 forward primarily because of its safety advantage, a
4 particularly thorough safety evaluation needs to happen, in
5 whatever sequence, before a final decision is made. And, if
6 I were to sort of think back on the lessons learned on the
7 sequence of events with cyclooxygenase inhibitors, COX-2
8 inhibitors in particular, it would seem to me that that
9 might be more the lesson than the order in which this is
10 done.

11 DR. HARRIS: Thank you. In other words, if I am
12 hearing you correctly, the sense with respect to overall
13 safety is that there is a level of satisfaction with what
14 has been done and it is probably difficult to do anymore.

15 DR. WOFSY: My goodness, I must have misspoken!

16 DR. HARRIS: I must have misunderstood.

17 DR. WOFSY: No, I certainly didn't mean to imply
18 that there is no more to be learned here that is important
19 regarding the safety of this agent. I was more interpreting
20 -- maybe I have interpreted the question wrong -- about
21 whether we should focus first on overall safety and then
22 move to organ-specific safety or vice versa. I think it was
23 that question more that I was addressing. So, I didn't mean
24 to be implying that we are done.

25 DR. WOLFE: I want to echo what he said. Again,

1 we are looking through a retroscope. It is always easy to
2 do that. But, when I teach students, fellows and residents,
3 that this is the best example we have ever seen of the bench
4 to bedside. The discovery was made. The hypothesis was put
5 forth and it was tested. Indeed, in all the preliminary
6 studies it looked like the hypothesis was correct, that
7 these drugs were GI sparing. The next was to do a real-
8 world study, and that was done. Then, again, the prediction
9 was, after the objective was proven -- it definitely was
10 afterwards that there may be another issue regarding the
11 balance between thromboxane and prostacyclin and that was
12 examined and it came out in the trials.

13 So, I think everything done to date was really
14 appropriate, as you said, but there are other studies to be
15 done in the future and I think the advantage of some of the
16 newer drugs coming out will be that they have seen what
17 happened with the first drugs developed in this class.

18 DR. HARRIS: Let me just ask you again, so from
19 what I am hearing with respect to organ-specific safety is
20 that the way in which the trial was framed, with respect to
21 overall safety you are comfortable with what was required
22 and what was done?

23 DR. WOLFE: Overall safety ended up being
24 assessed, and I think that is very important if we are
25 looking to tell a patient or a physician is looking to tell

1 a patient here is a drug, we can't say that globally this is
2 going to be a much safer drug. I think we all agree with
3 that. On the other hand, we do know patients are all
4 different, and we know people have certain histories and
5 certain risk factors that would mandate or suggest a
6 different class of drug for that individual or different
7 drug within the class.

8 I mean, the future is going to be more than that
9 as well. There are drugs in every class that are
10 metabolized differently and we are going to have profiles on
11 cards which say which drug in which class we should be
12 using. It will be much easier than a guessing game because
13 these are being developed now.

14 DR. NISSEN: I am going to dissent here a little
15 bit just for the moment and say that I think that there are
16 some messages here. Let me see if I can articulate this.
17 You know, there is lots of history of drugs that were
18 designed well, designed for a specific purpose that had an
19 effect on another organ system that wasn't fully
20 anticipated. As a consequence of that, the potential does
21 exist to make a serious mistake when you focus all the
22 attention on the early development on this target organ and
23 kind of concept.

24 So, in pre-approval I really do think we don't
25 want to lose the FDA's focus on overall safety because, you

1 know, again, I can imagine a drug -- let's take a worst case
2 in this class. Let's take a case here where the GI safety
3 was improved but where the cardiovascular safety produced,
4 let's say, ten times as many myocardial infarctions -- that
5 sort of thing. Now, hopefully, that would come out in
6 general surveillance but sometimes when you do a target
7 organ oriented drug development the population you study may
8 be much narrower. It may not include so many patients at
9 risk and then the study gets out in general use and you find
10 out that there is an unforeseen toxicity involving another
11 organ.

12 So, I think there are some lessons here that maybe
13 ought to be revisited as we go forward in other areas, this
14 one included, where we put a pretty high priority on showing
15 the general safety issue, at least early on, concomitantly
16 with the specific organ safety with the idea that
17 postmarketing surveillance can pick up some of this but you
18 would sure like to know about that before you release the
19 drug. I would have liked to have known about the
20 cardiovascular issue here before these drugs got out into
21 general use, and we really didn't know that at the time.

22 DR. HARRIS: Can I ask a question here? I am
23 sorry to impose. Because perhaps the cardiovascular risk
24 rose in the course -- you know, it was after the event, can
25 one address overall safety with the same rigor that you can

1 organ-specific safety because overall safety is broad and
2 there are any of a number of things in overall safety? And,
3 if you are doing a safety study, the question is you have an
4 organ and you can be quite rigorous about that, but overall
5 safety, can you address it with the same rigor?

6 DR. NISSEN: You can't. So, if you know enough
7 about the drug you might be able to have some candidate
8 organs to look at. If you look back, there were some folks
9 that predicted this. I mean, Fitzgerald told us pretty
10 early on, he said, gee, there is this balance between
11 prostacyclin and thromboxane; I am worried here that you are
12 going to change that balance unfavorably. And, I think we
13 have to be really listening to folks like that. No, you
14 can't do every organ system with the same rigor you do the
15 target organ system, but maybe if there is a little bit of
16 anticipation maybe you can do some things early on that will
17 give you the signals you need to know whether or not there
18 is more risk there than you know about.

19 I mean, obviously, the retroscope is a wonderful
20 instrument here and we all have that advantage, but if you
21 go back and read what Fitzgerald wrote, he anticipated this
22 potential problem.

23 DR. CALLAHAN: To answer your second question, I
24 think it is difficult to do every organ system but, like Dr.
25 Nissen pointed out, if there is evidence for certain body

1 parts or candidate areas to at least study those. The
2 message I get over and over from today's message is we are
3 treating a whole patient, not just the muscoskeletal system
4 or the GI, and the overall toxicity is important in the
5 bottom line because it is the entire patient that these
6 drugs are treating, not just the one system.

7 DR. HARRIS: Let me again come in here. I think
8 the issue is not so much that one shouldn't monitor overall
9 safety. Should it be similarly monitored? I don't know if
10 I am over-interpreting what the FDA meant, but that is my
11 interpretation.

12 DR. GOLDKIND: The spirit of the question, in a
13 sense, is to give us guidance for future drugs that may be
14 in development, obviously most specifically COX-2 selective
15 agents, although conceptually it could extend to any drug
16 group where a product is developed with a safety advantage
17 in mind. And, there are minimum requirements for exposure
18 before drug approval but those requirements generally will
19 not pick up rare toxicities, nor will they give you robust
20 comparisons to any other drugs or placebo for even events
21 that are not that rare so that making a safety comparison is
22 difficult from the minimum database that is required for
23 approval of a drug. The question is aimed at soliciting
24 your thoughts on whether this is a good approach and, again,
25 preapproval versus postapproval for drug development where a

1 specific organ safety claim would be considered because this
2 would be a marked change from the past in terms of what we
3 would ask for preapproval, to have a large safety database
4 like this, particularly a comparative safety database.

5 DR. HARRIS: Thank you. I will take two more
6 comments.

7 DR. PINA: I think there are several levels here
8 that need to be examined. There is the level of possible
9 toxicities which the sponsor may know from their studies in-
10 house with the very early studies, and some of them may be
11 in vitro studies and some of them may be in animal studies,
12 that some toxicities may be expected.

13 I think you also have to look at the patient
14 population that it is going to be applied in, and if you
15 know the rates of certain concomitant co-morbidities and
16 diseases in that population it will help you focus on those
17 specific toxicities. In this group and yesterday as well,
18 for example, we are dealing with older patients where the
19 risk of cardiovascular disease is very high on the agenda,
20 particularly in the postmenopausal women, as we said
21 yesterday, the number one cause of mortality in the United
22 States. So, you are already focusing on a group that is
23 targeted to have a certain rate of accumulation of events in
24 a certain organ system. You could say the same for
25 malignancy.

1 What I think hasn't been discussed here, and I
2 kind of hinted at it yesterday, is that the majority of
3 these patients are on multiple drugs and I didn't see
4 anything today about drug-drug interactions, and I think
5 that is critical. And, in our cardiovascular arena, as
6 Steve has put well, we have had drugs that have been
7 released because of a very specific study that proved
8 improvement. I can name at least one in the heart failure
9 arena, and when it got out into public use very quickly the
10 FDA saw all the interactions with all the drugs that these
11 patients were on, for example, the statins. A lot of these
12 patients are also on statins. They are on aspirin; they are
13 on statins; they are on blood pressure medicines and I think
14 that is critical because the applicability of these data to
15 patients who are on multiple drugs -- we can't say. I don't
16 know it; it is not there.

17 DR. WOLFE: We are all saying the same thing but
18 in slightly different ways. None of us wants to put a drug
19 out there that has serious toxicity. The question is when
20 do you pick it up. Let's consider here a very specific
21 instance. Fitzgerald's lab article came out in January,
22 1999; celecoxib was approved a month earlier. You know, it
23 was already approved. That wasn't foreseen and also may not
24 have been picked up in studies leading to approval because
25 maybe aspirin was used in those studies and would have

1 masked that effect. Not only that but if it was a big, big,
2 you know, 20-fold increase it may have been picked up. That
3 is why you do have postmarketing surveillance. You have
4 Phase IV studies to pick up these possible toxicities and
5 the cardiovascular example is not exclusive. I mean, we
6 just had two drugs in GI this year -- excuse me, in 2000
7 taken off the market because toxicity was picked up that
8 wasn't seen initially when the drug was approved. That is
9 why we monitor drugs after they are approved as well.

10 MS. MCBRAIR: I think because of the increase in
11 the ability of the drug companies to market these drugs the
12 overall safety is important and needs to be done earlier
13 than perhaps used to be the case. There are a lot patients
14 now coming to doctors' offices with already preconceived
15 ideas of what they would like to be on; what they think they
16 should be on and that didn't used to be the case. So, the
17 overall safety seems to be a really important issue.

18 DR. HARRIS: Thank you. If there is anybody in
19 the audience -- and no more than two -- if there is anything
20 additional, anything that was not said earlier with respect
21 to this question that one feels might provide some more
22 information, then let me invite it. If not, I would like to
23 move on.

24 [No response]

25 Do you think you have gotten enough guidance here?

1 Let's go to the last question, both the VIGOR and the CLASS-
2 studies, as well as postmarketing data, confirm the higher
3 risk for complicated ulcers in elderly patients and in
4 patients with a prior history of ulcer disease. This
5 increased relative risk was seen across all comparators.
6 Current labeling notes these as a risk factor. Given that
7 COX-2 selective agents may be regarded by some as having a
8 better GI safety profile, does current labeling provide
9 adequate awareness for prescribers regarding the increased
10 risk in these populations? Dr. Nissen?

11 DR. NISSEN: I was very troubled by this question
12 and I am going to tell you why I was so troubled by it.
13 Those very same factors increase the risk of cardiovascular
14 morbidity and mortality. So, I don't know what to do
15 because the elderly are the ones that are most likely to
16 have unstable angina, acute MI or sudden cardiac death. So,
17 it is a mixed bag and I don't know whether the net benefit
18 here exceeds the net harm. You know, it actually would be a
19 lot easier for me to advocate a COX-2 inhibitor for a young
20 patient without cardiovascular risk because I can see where
21 the benefits would be outweighing the risks. But when you
22 consider that an atherosclerotic event is the cause of death
23 in about 50 percent of the American population, you are
24 talking about the potential for an awful lot of morbidity
25 and mortality as you treat those patients with agents that

1 may increase the risk of that endpoint. So, I think because
2 of the mixed data on GI safety and cardiovascular safety, it
3 is hard to make that recommendation.

4 DR. HARRIS: Dr. Nissen, do you get a sense that
5 that safety that we saw today was carried over? It was
6 equally safe in your mind with respect to patients who were
7 elderly and had a history of ulcer disease?

8 DR. NISSEN: I am sorry, I don't understand
9 exactly what you are asking.

10 DR. HARRIS: In other words, as far as COX-2
11 inhibitors used in these particular patient populations with
12 increased risks, the elderly and those who have had a
13 history of ulcer disease, do you have a sense here that the
14 COX-2 inhibitors were without risk? In other words, should
15 there be a labeling change?

16 DR. NISSEN: Well, they were certainly favorable
17 with comparison to the naproxen comparator. So, in that
18 sense, given the fact that if you have, let's say, a seven
19 percent chance of having a bleeding ulcer and you can reduce
20 that risk in half the absolute benefit to those patients is
21 relatively large in terms of the number of patients you
22 actually benefit. So, I did see some evidence of at least
23 proportionality in benefit among the elderly, if not greater
24 than proportionality.

25 DR. WILLIAMS: When I look at this question I

1 would say we all recognize that age is a risk factor for
2 many things besides just GI bleeding, however, the benefit,
3 as was just stated, of GI protection was extended to the
4 elderly. They were safer on a GI protective agent.
5 However, I would give the caveat, yes, but a healthy elderly
6 patient who has a risk for GI bleeding is going to be
7 benefited by a GI protective agent, however, if they have a
8 need for cardioprotection and they have to take daily
9 aspirin, like the elderly and the young, if they are on
10 aspirin I think you use the benefit of the GI protection
11 from a COX-2 specific drug. So, I think what needs to be
12 addressed is not the fact that the elderly are a risk factor
13 but, as we have already addressed earlier, aspirin and COX-2
14 agents together take away some of the benefit of the COX-2
15 agent.

16 DR. HARRIS: Could I interpose again? Is the
17 current labeling adequate?

18 DR. WILLIAMS: Yes, provided they accept what we
19 have said about aspirin earlier.

20 DR. HARRELL: This is one place where I think
21 statisticians have something unique to offer, and I would
22 like to say that in all the clinical trials that are done
23 the proportion of trials in which all the information that
24 could be obtained from the trial is obtained from the trial
25 is very low. There are so many opportunities for doing

1 modeling on good data, it is amazing. And, one of the
2 models that is needed is a model of who gets certain adverse
3 events but also who gets certain benefits.

4 There is one example in the literature which I
5 would like to see replicated in this area. It is tooting my
6 own horn maybe too much but in the GUSTO I study -- these
7 are acute MI studies where you have these huge numbers of
8 patients so it is easier to do. That study had 40,000
9 patients in it, but we had a risk model developed from the
10 clinical database, and published a paper that shows, in a
11 fairly easy to use scoring system, how you can estimate
12 absolute clinical benefit for an individual patient. You
13 could also, which we didn't do but you could also make that
14 net benefit after you subtract out hemorrhagic strokes and
15 certain adverse events. But if you look at that paper and
16 see the scoring system, to me, it is something that could
17 almost be in labeling some day. It is not that hard for a
18 physician to carry out and it is something that you could
19 make even easier with a computer program. But it is just a
20 table to go through and you add up certain points and, you
21 know, the bigger MI is or the older you are, or the more
22 anterior the infarct was, or whatever, you get more net
23 clinical benefit from TPA or streptokinase, and I would
24 encourage people to look at that.

25 DR. CRYER: With respect to the question that you

1 have asked, I think that there are three messages that need
2 to be relayed. One, which is one that we have overlooked to
3 a certain extent in our discussion, is that there is an
4 intrinsic risk to certain risk factors. GI bleeding in and
5 of itself, older age in and of itself in the absence of
6 NSAID exposure carry an intrinsic risk.

7 The second message that I think needs to be
8 transmitted is that in these patients it appears that they
9 certainly would benefit from a COX-2 specific inhibitor from
10 the perspective of risk reduction.

11 But, along those lines, the third message is that
12 the risk persists. So, there appears to be an intrinsic
13 risk. They will benefit but even in those who benefit there
14 is a persistent risk for complications.

15 DR. HARRIS: Can I ask, when one says about risk
16 here, does one say risk compared to the use of another non-
17 steroidal anti-inflammatory drug? In other words, if you
18 were to use a COX-2 it would be better than using perhaps
19 another COX-2 non-selective drug.

20 DR. CRYER: Well, I think those data were clearly
21 shown in the studies that we have seen. If you look at the
22 high risk populations from, let's say, the VIGOR trial,
23 their relative risk was clearly reduced in comparison to
24 naproxen. Did I answer your question?

25 DR. HARRIS: Yes, part of it. Is it reduced to

1 the intrinsic level? In other words, would you say that
2 there is no added risk?

3 DR. CRYER: I can't say that with any certainty.

4 DR. HARRIS: Okay. I think the labeling actually,
5 as it is right now, reflects the fact that there may be
6 added risk.

7 DR. CRYER: It does.

8 DR. WOLFE: But you have asked a question about
9 the elderly, and looking at the general warning, I don't
10 think there is anything about the elderly in there. Is it
11 in there? Is it in there about bleeding specifically? It
12 is in the hematologic and you want to add that the risk is
13 across the board. It is proportionally diminished, at least
14 in the VIGOR study by age, but there is still a risk. If
15 you look at an 80-year old on Vioxx, it is greater than a
16 20-year old on peroxicam.

17 DR. CRYER: If I may, Dr. Harris, for the purposes
18 of this discussion, I have underlined what the labeling says
19 with respect to this issue: NSAIDs should be prescribed
20 with extreme caution in patients with a prior history of
21 ulcer disease or gastrointestinal bleeding. Most
22 spontaneous reports of fatal GI events are in elderly or
23 debilitated patients and, therefore, special care should be
24 taken in treating this population.

25 DR. HARRIS: I get a sense here that most of us

1 feel this is adequate as it is, and perhaps there isn't a
2 need to do any more. If anybody objects, could they raise
3 their hand? I will take the absence of raising of hands as
4 the guidance you have gotten.

5 Are there any other burning issues to be raised?
6 If not, we come to the summary part of the proceeding.

7 DR. DELAP: Do you view the business as concluded
8 then? Is that what you are saying?

9 DR. HARRIS: To my knowledge, yes.

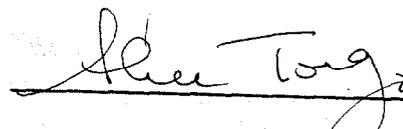
10 DR. DELAP: I would like to say thank you very
11 much for all your hard work over the last couple of days.
12 It has been a very enriching experience for us in terms of
13 all the comments and recommendations we have received, and
14 we thank you very much for your comments. That goes for the
15 sponsors as well. I think both the sponsors did a
16 tremendous job of preparing very massive databases in a very
17 thoughtful fashion.

18 DR. HARRIS: Thank you. Closed.

19 [Whereupon, at 4:10 p.m., the proceedings were
20 adjourned]

CERTIFICATE

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.


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