

# Question 1: Celecoxib

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

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

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## Highlights

- Voting for **Question 1A** (increased risk of cardiovascular events) was **Yes 32, No 0**.
- Voting for **Question 1B** (approval for marketing) was **Yes 31, No 1**.
- Around-The-Table 1C Recommendations (risk-management/suitable populations): Recommendations were allocated to 30 categories (see Attachment 1). Each category was scored for each member as “Yes”, “No” or “No Comment”. “No Comment” in many cases might just mean that someone else had made the recommendation earlier and the member felt no need to repeat the recommendation. There were 138 recommendations (an average of 4/member) for action (“Yes”), and 27 disagreements with prior recommendations by others (“No”). The categories and “Yes vs. No” tabulations were as follows:

Net Count (Yes - No)	Category
17	Patient Medication Guide (18 vs 1)
16	Black-box warning (22 vs 6)
12	Ban Direct To Consumer Adverts (17 vs 5)
11	Warning for High Dosage (11 vs 0)
6	Warning for Long Duration (6 vs 0)
6	Warning for High Cardiovascular Risk (6 vs 0)
6	Easier-To-Understand Explanation of Risk (6 vs 0)
5	Same labeling for NSAIDs (5 vs 0)
5	Postmarketing studies (5 vs 0)
4	Allow Black-box Removal if Adequate Trials Performed (4 vs 0)
4	Patient Consent/Attestation (5 vs 1)
2	Exclude if at High Cardiovascular Risk (4 vs 2)
2	High Dose Contraindicated (3 vs 1)
2	Academic Detailing (2 vs 0)
2	Educate Healthcare Professionals (2 vs 0)
1	Dear Healthcare Professional Letter (1 vs 0)
1	OTC Restrictions (1 vs 0)
1	Define Class (1 vs 0)
1	Define Mechanism (1 vs 0)
1	Comprehension Survey (1 vs 0)
1	Assess/Manage CV Risk (1 vs 0)
1	FDA Study of Medication Guides (1 vs 0)
1	Aspirin May Not Reduce CV Risk and May Increase GI Risk (1 vs 0)
1	Combine COX-2 & Framingham data (1 vs 0)
1	Do ALLHAT-Type Study (1 vs 0)
1	Contraindicated in CABG (1 vs 0)
1	Warn of Risk of Short-acting NSAIDs (1 vs 0)
1	Warn of Risk of COX-2 selective traditional NSAIDs (1 vs 0)
	Other (3)

**Question 1A:Discussion: Increased risk of CV events with celecoxib**

- **CELECOXIB HAS WEAKEST CV SIGNAL:** Dr. Abramson said that “My own view on celecoxib, just to lead off on my opinion, is that, if there is a cardiovascular

event, this, among the coxibs, is probably the weakest signal that we have seen...”. Dr. Nissen agreed and said “I think it depends on the dose .... there is no evidence in any trial

at the 200-milligram dose.” Dr. Nissen also said there was no celecoxib signal in the epidemiology data.

- **DEFINE “COX-2 SELECTIVE:** Dr. Abramson said that because diclofenac and other traditional NSAIDs were COX-2 selective “we need to circle back at the end to what we mean by COX-2 selective agents”.
- **QUESTION IS ABOUT ANY SIGNAL OF “SIGNIFICANT INCREASE”:** Dr. Furberg said that the “previous speakers were changing the question” and that “the way the question is posed, the answer is clear. We have evidence of significant increase in risk of cardiovascular events. I admit, it is in a select population, in a select dose, but that is not what the question is about.”
- **RISK RATIO OF 1.3 FOR CELECOXIB IS LESS THAN BEXTRA AND VIOXX:** Dr. Fleming made a detailed comment in which he estimated the relative risk for celecoxib at “about 1.3” and agreed “that this seems to be less than the other two approved agents” but that “the available data do support a conclusion that there is some level of increase in cardiovascular events”.
- **EXCLUSION OF HIGH RISK PATIENTS UNDERESTIMATES RISK:** Dr. Domanski made a general comment that the COX-2 trials had tended to exclude patients at higher cardiovascular risk, so that the level of risk seen in the trials might be underestimated. Dr. Wood agreed and said that “risk will probably be higher in patients with heart disease” as suggested by the Bextra CABG

studies in which subjects had high cardiovascular risk.

- **PLEA TO USE “SIGNIFICANT” AS SUBSTANTIAL, NOT STATISTICAL:** Dr. Farrar made a “plea” that the use of the word “significantly” during discussion should be considered as indicating “substantial benefit or substantial risk” rather than “significant risk in terms of a p-value”. He suggested that the sub-questions all be discussed before voting takes place so that benefit can be factored into the voting. Dr. Wood said that voting should be done for each sub-question in turn but that people should bring “the totality” of the issues into the discussion of each sub-question.
- **COXIBS INCREASE RISK 41% AND NO DIFFERENCES BETWEEN DRUGS:** Dr. Hennekens said that his impression was that the coxibs in general had about a 41% increased risk of vascular events and “that it doesn’t differ significantly by the drug being studied”.
- **OK TO EXTRAPOLATE RISK TO OTHER POPULATIONS:** Dr. Wood said that “there is clear evidence of risk from celecoxib” and he was not persuaded “that we can’t extrapolate that to other disease states”, particularly a population with “a higher risk of cardiovascular events such as rheumatoid arthritis”.
- **WHICH CV EVENTS SHOULD BE INCLUDED?** Dr. Friedman asked if hypertension and edema should be included as “major cardiovascular events”. Dr. Wood said that he had interpreted this to mean “hard endpoints such as” the vascular events that Dr. Hennekens had mentioned. Dr. Temple (FDA)

agreed that was “what we have been focusing on” and that heart failure while “of interest” is “a different kind of thing” and “potentially manageable whereas a heart attack and a stroke are not manageable”.

- **EVIDENCE OF CELECOXIB RISK MAINLY AT 800 MG/DAY:** Dr. Nissen said that it was important to realize “how much of the evidence” is based on the 800 mg/day celecoxib dose, “a dose that is two times the upper limit of the approved dose and four times the most commonly used dose”.
- **CELECOXIB HAS “MORE THAN A SIGNAL”:** Dr. D’Agostino said that “there is more than a signal” for Celecoxib so that he is “very comfortable” saying ‘Yes’ to Question 1A.
- **CELECOXIB SIGNAL IS “MARGINAL .. AT BEST”:** Dr. Cush said “there is a marginal signal at best” and that “when one considers the use of celecoxib at prescribed doses and for the approved indications, there really is no signal”.
- **IS THERE A SIGNAL AT 200 MG/DAY CELECOXIB?** Dr. Fleming said that there was evidence of a signal at the 200 mg bid dose of celecoxib, based on the low dose in the APC trial and the 001 trial and

asked “Are we challenging that the 200 BID dose isn't a dose level at which there is some evidence for excess?” Dr. Wood said he was not and said that another issue was “dose creep”. Dr. D’Agostino said that “it is the dose response that is going on here”. Dr. Fleming responded that “I thought I heard some comments that, if I interpreted it right, the 200 BID dose is one for which there isn't evidence of an excess and, it seems to me, there is.”

- **PPIs CAN REDUCE NSAID GI TOXICITY:** Dr. Temple said that some PPIs have been shown to improve the GI intolerance with some drugs and that lansoprazole and S-omeprazole are approved for “healing and risk reduction of NSAID-induced ulcers” and there is a “combination pill with lansoprazole and naproxen”.
- **SUGGESTION TO DIVIDE QUESTION INTO APPROVED AND UNAPPROVED DOSAGE DECLINED:** Dr. Gross suggested that they divide the question into two parts, for approved versus unapproved doses. Dr. Wood suggested the committee comes back to that when they make recommendations about doses.

### ***Question 1A: Voting: Increased risk of CV events with celecoxib***

- Dr. Abramson: Yes. “consistent with the COX-2 inhibition”.
- Dr. Nissen: Yes.
- Dr. Elashoff: Yes with respect to placebo. No with respect to the NSAID comparator.
- Dr. Gardner: Yes.
- Dr. Platt: Yes.

- Dr. Day: Yes “and I look forward to the discussion of dose effects”.
- Dr. Furberg: Yes.
- Dr. Fleming: Yes.
- Dr. Domanski: Yes.
- Dr. Boulware: Yes.
- Dr. Dworkin: Yes.
- Dr. Hoffman: Yes.
- Dr. Manzi: Yes.
- Dr. Farrar: Yes.
- Dr. Holmboe: Yes.
- Dr. Gross: Yes.
- Dr. Wood: Yes.
- Dr. Gibovsky: Yes “but”.
- Dr. Crawford: Yes.
- Dr. Cush: Yes.
- Dr. Bathon: Yes.
- Ms. Malone: Yes.
- Mr. Levin: Yes.
- Dr. Ilowite: Yes.
- Dr. D’Agostino: Yes.
- Dr. Morris: Yes.
- Dr. Cannon: Yes.
- Dr. Shapiro: Yes.
- Dr. Paganini: Yes.
- Dr. Friedman: Yes.
- Dr. Hennekens: Yes.
- Dr. Shafer: Yes.

### **Question 1B: Discussion: Support for marketing of celecoxib**

- **IMMEDIATE BENEFIT VS. POTENTIAL RISK:** Dr. Elashoff said that the present discussion involves an immediate benefit in pain relief versus a potential risk. Dr. Wood countered that there is no evidence that the immediate benefit with COX-2 drugs is superior to that with NSAIDs.
- **CELECOXIB GI SAFETY COMPARABLE TO NSAID+PPI:** Dr. Shafer said that Question 1B requires evaluation of the efficacy data. He mentioned two published studies comparing celecoxib to NSAID+PPI, both of which showed no difference between treatments.
- **NO GI RISK DATA WITH BACKGROUND STEROIDS:** Dr. Shafer said that there is no data available on GI risk in patients on background corticosteroid therapy.
- **LAST-RESORT OPTION:** Dr. Domanski said that COX-2 drugs in general and celecoxib in particular should continue to be available, although a “carefully drafted” black-box warning that says they should be used as a “last resort” is appropriate. Dr. Shapiro said that it was not her view that “they are a last-resort option”. Dr. Ilowite said that “last-resort” should not be considered to mean “you have to go through all 20 NSAIDs or wait until you have a serious gastropathic event before using them”. Dr. Domanski agreed that “last-resort” should not “imply some mechanical necessity to go through every drug known to man”.
- **DO COXIBS HAVE EFFICACY WHEN NO RESPONSE TO OTHER DRUGS?** Dr. Farrar said that a benefit of COX-2 drugs was in “patients who are not responsive to other drugs” either because of G.I. toxicity but also because “these agents work in a different manner.” He takes “serious issue” with saying that “we don’t know that they work better”. They may be comparable in “the mean value of the benefit” but

“certainly from the clinical experience, we know that there are patients who will respond to one and not to another” and he does not believe the data support use only as “last-resort medication”. Dr. Wood asked, “just for clarification to me”, if there are publications that “show there are patients who respond to these drugs who did not respond to traditional non-steroidals”. Dr. Farrar said no, and Dr. Wood said “Okay. That’s good.”

- **SIMPLE TRIAL TO ESTABLISH EFFICACY WHEN NO RESPONSE TO OTHER DRUGS:** Later in the discussion, Dr. Temple said that it is “very easy” to show that a drug “works when other drugs don’t work. You take failures on whatever the standard therapy is, and randomize people back to that therapy or to the new drug” as was done for clozapine and bepridil.
- **QUESTION 1B (SUPPORT FOR MARKETING) DIFFICULT IF DON’T CONSIDER QUESTION 1B (SUITABLE POPULATIONS):** Dr. Hennekens said that answering Question 1B is difficult without considering Question 1C (appropriate populations and risk-management) since appropriate candidates for the COX-2 drugs may include those allergic to naproxen, those with GI problems where NSAIDs+PPIs are contraindicated, or those patients who wish COX-2 therapy despite the cardiovascular risk.
- **CONCERN ABOUT SAFETY OF NSAIDS IN GENERAL:** Dr. Holmboe agreed that, with some restrictions, celecoxib should be made available but he was not “convinced” that “other available

agents” are “necessarily any safer”. Dr. Nissen said “That is exactly the same problem that I am having.... What I don’t know” is if celecoxib “increases risk over ibuprofen or diclofenac”. Dr. Bathon said that it seemed unfair to hold the COX-2 drugs to higher efficacy standards than the conventional NSAIDs, while at the same time not holding the conventional NSAIDs to the same GI and CV safety standards being applied to the COX-2 drugs. Dr. Wood asked Dr. Fleming to review “what you saw as the safety signals with conventional NSAIDs” since it “didn’t sound very convincing to me”. Dr. Fleming said that naproxen “looked more favorable than the coxibs it was compared to” and that diclofenac looked comparable to slightly worse and “seems to be in the range of what we were seeing with the coxibs”. Dr. Abramson pointed out that in “multiple randomized controlled trials from TARGET to CLASS and EDGE, that the comparator non-selective NSAID looked like the coxib...” so he was concerned about giving the non-selective NSAIDs “a pass”.

- **EMEA ESTIMATES OF COXIB RELATIVE RISK: OVERALL 1.41, VS. NAPROXEN 1.56, VS. OTHER NSAIDS 0.86:** Dr. Hennekens said that Dr. Baigent of Oxford had just made a presentation to the European Medical Evaluation Agency on “his preliminary analyses of 113 trials with 135,000 patients. Looking at the placebo-controlled trials, the relative risk was 1.41. In the naproxen comparator, it was 1.56. In the non-naproxen NSAIDs, it was 0.86.”

- **VOTING SHOULD BE ON CURRENT INDICATIONS:** Dr. Manzi wanted to be clear that they were voting on Question 1B for the “indicated use” and not the

“prevention population” and that while one might extrapolate risk from a different population, one could not extrapolate the risk:benefit. Dr. Wood agreed.

**Question 1B: Voting: Support for marketing of celecoxib**

- Dr. Shafer: Yes. “I, unexpectedly, cast my vote last night when my father, an 89-year-old man with no other risk factors for heart disease but a sensitive stomach, asked me if he should stay on his Celebrex I said yes”.
- Dr. Hennekens: Yes.
- Dr. Friedman: Yes.
- Dr. Paganini: Yes.
- Dr. Shapiro: Yes.
- Dr. Cannon: Yes.
- Dr. Morris: Yes.
- Dr. D'Agostino: Yes.
- Dr. Ilowite: Yes.
- Mr. Levin: No. During the subsequent discussion of Dr. Trontell’s talk, Mr. Levin said “One of the reasons for my no vote was this concern and that is the ability of FDA to insist on and enforce conditions which will limit the distribution and use of the drug to appropriate populations.”

- Ms. Malone: Yes.
- Dr. Bathon: Yes.
- Dr. Cush: Yes. “No ‘buts’.”
- Dr. Crawford: Yes.
- Dr. Gibofsky: Yes.
- Dr. Wood: Yes.
- Dr. Gross: Yes.
- Dr. Holmboe: Yes.
- Dr. Farrar: Yes.
- Dr. Manzi: Yes.
- Dr. Hoffman: Yes.
- Dr. Dworkin: Yes.
- Dr. Boulware: Yes.
- Dr. Domanski: Yes.
- Dr. Fleming: Yes.
- Dr. Furberg: Yes.
- Dr. Day: Yes.
- Dr. Platt: Yes.
- Dr. Gardner: Yes.
- Dr. Elashoff: Yes.
- Dr. Nissen: Yes.
- Dr. Abramson: Yes.

**Question 1C: General Discussion: Risk-management and suitable populations for celecoxib**

- Dr. Cush recommended: 1) suitable populations for celecoxib were “those that are currently indicated; osteoarthritis, rheumatoid arthritis and a few pain indications”, 2) additional studies should be done, 3) there should additions to the

warnings, 4) a risk-reduction strategy, and 5) no black-box.

- Dr. Shafer recommended: 1) a suitable population was “individuals who cannot tolerate NSAIDs with a proton-pump inhibitor”, and 2) no “standardized” black-box (because this might imply comparable risk

across the COX-2 class) but celecoxib should have a black-box “clearly stating the increased likelihood of cardiovascular adverse events including death” and stating that the drug is contraindicated following cardiopulmonary bypass (on the basis of the parecoxib/Bextra data).

- Dr. Domanski recommended “they all ought to get a black-box” that is “substantially the same” for each drug, reflecting the committee’s view that there is a class effect.
- Dr. Wood recommended 1) there should be a black-box, 2) there should be “severe restrictions” in both dose and populations, and 3) (frivolously) DTC advertising with “well-known skaters skating around an ice rink and then dropping dead”.
- Dr. Furberg agreed with Dr. Wood and recommended: 1) the populations should not include “high-risk people”, 2) that there should be warnings against high doses, and 3) there should be a black-box.
- Dr. Platt recommended: 1) celecoxib should be “a drug of second choice” (he was even “toying” with the idea that intolerance to naproxen be specifically mentioned as a requirement for use), 2) there should be a black-box, 3) there should be an “attestation requirement”, and 4) FDA and the NIH should collaborate to generate a better estimate of incremental risk..
- Dr. Nissen recommended: 1) there should be a black-box that describes the increased risk and the fact that this appears dose-related and duration-related, 2) that DTC advertising is not appropriate, 3) patient medication guide, 4) a

sponsor strategy to remove the warnings (e.g., adequately sized trial vs. a suitable comparator such as naproxen showing that celecoxib 200 mg/day at some defined level of confidence does not increase cardiovascular risk).

- Dr. Wood agreed with Dr. Nissen and restated his recommendation: 1) restricted black box warning with limitation of populations, dose and duration, 2) “absolutely” no DTC advertising, 3) specification of risk in a patient medication guide or in the package insert “in a more helpful way than we do that right now” (with multiple examples, for example: the same increased risk as from “smoking so many cigarettes a day”).
- Dr. Morris recommended: 1) no ban on DTC advertising (not enforceable, don’t ban information, and it won’t work), and 2) “break out the risk information” and put it in a single commercial and run this once for every three “benefit” commercials that are run.
- Dr. Day recommended, based on her as yet unpublished research, that DTC advertising can effectively communicate the safety message within a single advertisement by changing the placement of the safety information and adjusting the language.
- Dr. Bathon recommended: 1) that if a black-box is used there should not be a dose and duration warning in it because a dose warning would ignore the fact that efficacy is better in RA at high doses, and the duration warning would be inconsistent with the chronic indications, 2) the “underlying theme” of a black-box should be “avoidance in patients with high cardiovascular risk

profiles”. Dr. Wood commented that risk was also increased in those with low cardiovascular risk. Dr. Bathon implied that the absolute COX-2 risk was higher in those with high baseline risk.

- Dr. Manzi said she agreed with Dr. Bathon on “most of her comments” but recommended that the COX-2 drugs not be specified as second-line agents, because in some situations (such as GI risk or anticoagulation) they should be first-line agents.
- Dr. Abramson expressed his concern that “we are making fairly draconian recommendations for the drug that we thought had the least robust evidence”. Dr. Wood commented that the recommendations might be even “more draconian” for the other drugs. Dr. Abramson said that a black-box warning that celecoxib is a drug of last-resort is not “data-driven”. Naproxen may cause more GI bleeding and it does not seem rational to say that drugs such as diclofenac or meloxicam that are

comparable in COX-2 selectivity to celecoxib should be used before celecoxib. Dr. Dworkin agreed with Dr. Abramson and said there was no data to justify the “migrating away from this drug to other drugs” and that “none of us would feel comfortable enough” with the naproxen data to give naproxen “an indication of having less cardiovascular risk”.

- Dr. Gross suggested that they should first decide if all NSAIDs should receive a black-box, which would then make it easier to deal with individual drugs. Dr. Wood said “The problem with that is we have to vote...”.
- Dr. Gardner recommended: 1) FDA should “dig into all of the information we have on the various products” before specifying the populations suitable for the drug, and 2) put patient medication guides inside the containers distributed to patients.

### ***Question 1C: Around-the-table comments by committee: Risk-management and suitable populations for celecoxib***

- Dr. Abramson: 1) Define the class. 2) Define the mechanism. 3) Apply similar restrictions to drugs similar to celecoxib in COX-2 selectivity.
- Dr. Nissen: 1) Black-box with dose-dependent risk. 2) No DTC advertising. 3) Patient medication guide.
- Dr. Elashoff: No additional comments.
- Dr. Gardner: 1) No DTC advertising. 2) Patient medication guide. 3) Warnings appropriate to risk group.
- Dr. Platt: 1) Black-box. 2) Substantially upgraded postmarketing surveillance program. 3) Second-line drug (with specific mention of naproxen as preferred alternative). 4) Patient consent/attestation. 5) Describe risk in terms of “relatively easily understood risks”.
- Dr. Day: 1) Black-box with wording specific to each drug with celecoxib getting the “minimum”. 2) Patient medication guide. 3) "Dear Healthcare Professional" letter. 4)

- Don't suspend DTC advertising if risk:benefit balance can be achieved.
- 5) Patient consent/attestation, including a comprehension survey.
- Dr. Furberg: 1) Black-box. 2) Contraindication for high dose. 2) Contraindication with known coronary heart disease, stroke, and "patients at increased risk". 3) Patient consent/attestation. 4) No DTC advertising.
  - Dr. Fleming: 1) Black-box. 2) Caution with high cardiovascular risk, high dose and long duration. 3) No DTC advertising. 4) Patient medication guide.
  - Dr. Domanski: 1) Black-box. 2) Patient medication guide. 3) Second-line drug.
  - Dr. Boulware: 1) Black-box mentioning risk at dosage over 400 mg/day but stating lack of similar information for other NSAIDs.
  - Dr. Dworkin: 1) No black-box (unless given to all NSAIDs). 2) Detailed and comprehensive cardiovascular warning.
  - Dr. Hoffman: 1) Black-box (restricting dosage to 200 mg/day but not restricting duration). 2) No DTC advertising. 3) Patient medication guide. 4) Second-line drug.
  - Dr. Manzi: 1) Black-box stating the cardiovascular risk found at high dosage for long duration but "don't directly advocate low doses for short duration". 2) Patient medication guide. 3) Do not restrict it to being a second-line drug.
  - Dr. Farrar: 1) Black-box. 2) No DTC advertising. 3) Patient medication guide.
  - Dr. Holmboe: 1) Black-box if NSAIDs also get warning. 2) Patient medication guide. 3) FDA study of patient medication guides for "literacy" and "numeracy". 4) Academic detailing.
  - Dr. Gross: 1) Warning regarding "dose-dependent toxicity" provided similar warning for "all coxibs and nonselective NSAIDs". 2) Patient medication guide. 3) Patient consent/attestation for higher doses. 4) Don't ban DTC advertising if there is also "FDA-approved education on the putative risks". 5) Do not restrict it to being a second-line drug.
  - Dr. Wood: 1) Black-box. 2) Exclude people at risk for cardiovascular disease (known CV disease, elderly with high risk factors, others). 3) Ban DTC advertising. 4) Patient medication guide. 5) Describe risk in a way that related to risks in regular daily life. 6) Allow removal of black-box if well-designed trials establish that a drug, or a dose, or a particular group does not have these risks.
  - Dr. Gibovsky: 1) No black-box. 2) Patient medication guide. 3) Do not restrict it to being a second-line drug. 4) Populations should be as presently indicated in the labeling. 5) Use at lowest effective dose.
  - Dr. Crawford: 1) Black-box. 2) Need postmarketing studies. 3) Ban DTC advertising (if not possible, ensure adequate communication of risk). 4) Allow removal of black-box if justified by well-designed trials.
  - Dr. Cush: 1) No black-box. 2) General warning with strategy for risk reduction. 3) Don't ban DTC advertising if the major statement significantly outlines this cardiovascular risk. 4) Do further postmarketing studies.

- Dr. Bathon: 1) No black-box. 2) Warning on cardiovascular risk. 3) Ban DTC advertising.
- Ms. Malone: 1) No black-box, 2) Warning on cardiovascular risk and dose-dependency. 3) Limit on DTC advertising. 4) Do not restrict it to being a second-line drug (will make insurance companies say, “you have to try these other drugs first”). 5) Patient treatment guide that is understandable and easily accessible. 6) Very good education for doctors to permit the dialogue with the patient. 7) Patient consent/attestation (will improve doctor-patient communication).
- Mr. Levin: 1) Black-box. 2) Patient medication guide. 3) Patient consent/attestation. 4) Convey risk and benefit in ways that are meaningful to consumers. 5) Academic detailing. 6) Do further postmarketing studies. 7) Allow removal of black-box if justified by well-designed trials. 8) Suspend it for now until DTC advertising “can tell the truthful story about drugs”.
- Dr. Ilowite: 1) Black-box. 2) Warning on increased risk with high dose and long duration. 3) “Relatively contraindicated” with high CV risk. 4) Do not restrict it to being a second-line drug. 5) Ban DTC advertising. 6) Patient medication guide. 7) Don’t mention naproxen as preferred NSAID.
- Dr. D’Agostino: 1) Black-box. 2) Ban DTC advertising. 3) Do further evaluation of cardiovascular risk from available data (e.g., COX-2 clinical trial data and Framingham data combined).
- Dr. Morris: 1) Black-box provided there is the “broadest definition of class” with every drug in the class getting a black-box warning. 2) Black-boxes can vary between drugs in the class but include a statement about the class and “about what is not known as well as what is known”. 3) Don’t ban DTC advertising but restructure it. 4) Do further postmarketing studies. 5) Do Dr. Temple’s ALLHAT-like study. 6) No patient medication guide (instead have “unitive-use patient package insert” that is “broad and class-wide”). 7) Patient package insert for OTC drugs in this class.
- Dr. Cannon: 1) Black-box. 2) Warning about risk being dose- and duration- dependent. 3) Ban DTC advertising. 4) Patient medication guide. 5) Don’t prohibit use in patients with CV risk factors. 6) Say that concomitant aspirin will “likely” not reduce CV risk and may “negate the GI benefit”.
- Dr. Shapiro: 1) Black-box. 2) Ban DTC advertising. 3) Patient medication guide. 4) Restriction to “lowest possible dose”. 5) Second-line drug “not in the sense that something else would have had to have been tried, but that the physician would have had to have considered and then discounted a non-COX alternative”.
- Dr. Paganini: 1) Black-box. 2) Need to convey warning in “understandable terms”. 3) Warn of “probable dose and time relationship”. 4) Second-line drug. 5) Ban DTC advertising. 6) Patient medication guide.
- Dr. Friedman: 1) Black-box. 2) Warn of use in patients at high CV risk and with high dose. 3) Warn of uncertainties for all the NSAIDs. 4) Ban DTC advertising. 5) Enhance education for patients and the

medical community. 6) Do further postmarketing studies.

- Dr. Hennekens: 1) No black-box but have strong warning for all coxibs and all short-acting NSAIDs. 2) Inform healthcare providers and patients that a) coxibs increase CV risk about 40%, b) “in the comparator trials, naproxen compares favorably to all the coxibs” and c) “short-acting NSAIDs appear to be at least as hazardous as the coxibs”. 3) Assess cardiovascular risk in all arthritis patients or other NSAID candidates and aggressively manage cardiovascular risks. 4) Do

not restrict it to being a second-line drug. 5) Ban DTC advertising.

- Dr. Shafer: 1) Black-box. 2) Warn of dose- and duration- dependent CV risk. 3) Allow removal of black-box “for certain doses” if justified by well-designed trials. 4) Contraindicate following cardiopulmonary bypass. 5) Don’t ban DTC advertising. 6) Patient medication guide. 7) Don’t require physician attestation or patient consent/attestation.

## **Discussion Text: Question No. 1: Celecoxib**

### ***Question 1A Discussion***

DR. WOOD: Let me read the first part:

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

Since approval, additional data regarding the safety and effectiveness of these products has accumulated, in particular, new information regarding the potential cardiovascular risks of these products.

FDA must consider the impact of these new data on the benefit-versus-risk profile of each product in making

decisions about appropriate regulatory actions.

Although--and this is important--although Merck voluntarily withdrew Vioxx from marketing worldwide on September 30, 2004, questions relating to Vioxx are included below since it will be necessary for FDA to determine the appropriate regulatory action regarding the approval status of this product.

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

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

DR. ABRAMSON: I will just start. I wanted to start by questioning the premise of the first sentence which is that there are three COX-2 selective drugs on the market and just remember to point out that the drugs like Celebrex, there are four or five of them, diclofenac, et cetera, that have comparable pharmacodynamic profiles in terms of their COX-2 preferential effects and that in randomized controlled trials of these drugs, whether it is CLASS or the development program or TARGET have comparable cardiovascular adverse events in those comparator trials. So I think, just as a premise, as we go forward for each of these drugs, I think we need to circle back at the end to what we mean by COX-2 selective agents. That said--

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

DR. ABRAMSON: Right; exactly.

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

DR. ABRAMSON: I agree and I just wanted to frame my comments. My own view on celecoxib, just to lead off on my opinion, is that, if there is a cardiovascular event, this, among the coxibs, is probably the weakest signal that we have seen, that it is in the APC study but not in several other placebo-controlled, randomized trials--although there may be some trends in the PreSAP. We don't see it--and that there is a large

database in the randomized clinical-trial development program that does not show a signal that is excessive comparators. So, while I am tending to think that that is a cardiovascular signal that is COX-2-dependent, celecoxib does not--has the weakest amount of evidence that it, in itself, is significantly worse than the others.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I will support that. Let me say that I think it depends on the dose. The evidence from the APC trial at the 800-milligram dose is strong. There is no question about it. There is marginally statistically significant evidence at the 400-milligram dose and there is no evidence in any trial at the 200-milligram dose. We have a number of pieces of data that I consider supportive of that concept. In the epidemiological studies, while we recognize that they are flawed, there is no signal. There is really no signal at all for celecoxib and yet it has probably been the most widely prescribed agent in the class. Now, why would there not be a signal? Well, as we heard, the vast majority of use is at the 200-milligram dose. What happened here was in the colon polyp trial, in an effort to get efficacy, doses of 400 and 800 milligrams were the doses that were tested and we see a signal there. Interestingly, we don't see evidence in CLASS at an 800-milligram dose. We don't see evidence in PreSAP. So using, I think, Milton Packer's logic here, now you have to ask the question, does the evidence around rofecoxib and valdecoxib--to what extent does it support a conclusion around celecoxib. My view is that I can say that the 800-milligram dose is very likely to produce excess cardiovascular risk, that it is

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

DR. WOOD: Dr. Furberg?

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

DR. WOOD: That is a fair comment, actually. The question right now is just about the drug. So we are talking right now about the chemical entity, itself, and then we will get to issues of dose and patient subsets, perhaps, later--in fact, for sure, later, just to reassure everybody. Dr. Shafer?

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

panel rather than us all trying to flag you for attention. So clarification; what are we doing at this point?

DR. WOOD: We are discussing the question. So if you have got discussion on the question, by all means, say it. Eventually, we will reach a point where we vote on many of these questions. But the issue that we are trying to do is discuss the question right now to provide information to your colleagues that will help them inform their decision.

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

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

DR. SHAFER: Yes.

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

DR. SHAFER: Fine.

DR. WOOD: Other comments? Tom?

DR. FLEMING: Looking at the data, I am basing my sense predominantly on the CLASS trial, the Alzheimer's 001 trial, the APC and the Pre-SAP studies. The CLASS study is the largest and generally gives a favorable result of a lack of excess although one has to remember that is against diclofenac and ibuprofen. When one does look in the non-aspirin users and you are looking at atrial SAEs, anginal SAEs, MI and thrombophlebitis, we have got 30 events on celecoxib and 14 on the control. So I

am willing to take this as a relatively neutral study but there are elements of this that are consistent with some concern and we are also looking at a comparator group that is diclofenac and ibuprofen. The other three studies are placebo-controlled. The APC trial is probably an overestimate. In fact, I would--my sense in the totality of the data is that it is giving us an excess and it is giving a fairly persuasive sense that there is an excess and yet, when you look at this in the aggregate with the PreSAP trial, one gets a more tempered measure, although the aggregation of those two is in excess of a relative risk of 1.8. The Alzheimer's 001 trial is also suggesting an excess, 11 against 3 events, in a 2:1 randomization. So, if we use the three placebo-controlled trials, the aggregation of the evidence is in excess of about 1.6. My sense is, for all of these together, the excess is on the order of 1.4 to 1.5. If we fold the CLASS trial in and it is relevant to do so, but remembering that is not a placebo-controlled trial, one gets a sense of about 1.3. In that regard, I agree with some other comments that this seems to be less than the other two approved agents. Yet, there certainly is a suggestion, more than a suggestion, I would say. There is definite evidence that there is an increase, although potentially more modest than the other two agents. One, though, does need to factor in what you know about the totality of the data from the other agents in the class. In that sense, you live by the sword and die by the sword. If those other agents look favorable, it gives you less concern. If they look unfavorable, it is more concern. So, looking at the totality of the data, I don't like using the word "significantly" here, but I would say the available data do support a conclusion

that there is some level of increase in cardiovascular events using the totality of the data, particularly influenced by the placebo-controlled trials.

DR. WOOD: Okay. Dr. Domanski?

DR. DOMANSKI: I will pass again.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: Perhaps Dr. Fleming could elaborate on his response, his comments in regards to when one looks at the statistical analysis of each of the studies and there being possibly the risk of exaggerating the relative risk, we also spoke earlier of how, in most studies, we exclude people who have more serious illnesses that would, perhaps, subvert a clean trial, people who have serious cardiovascular disease that is obvious, serious congestive heart failure who, nonetheless, are people who wind up using these drugs once they are on the market. I don't recall, for each of these trials, the degree to which there was exclusion of those patients but we have agreed that, at least in some of those trials, those patients were excluded. If we acknowledge that, then the risk, in fact, for the general population, may be underestimated.

DR. WOOD: So, for many of these trials, people with heart disease were excluded, so you are right. The risk will probably be higher in patients with heart disease. Certainly, in the Bextra trial, that would suggest--that was certainly true. Did you want to address that question to Dr. Fleming? Did you want--okay. He addressed the question to you, Tom.

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

DR. WOOD: Okay. Dr. Farrar?

DR. FARRAR: One point and then a point of clarification in terms of our discussion so I know how to approach my second point. The first point is a plea for changing the word "significantly." Are we talking about statistical significance? I don't think so. But I think we need to be absolutely clear that we are talking about substantial benefit or substantial risk or important. Significantly continually gets confused and so I think that if we all agree what we are talking about is important, or substantial, risk, not significant risk in terms of a p-value. The second question is, in terms of discussion of these topics, are we talking--I think it would be useful, in fact, to talk about all three of the sub-questions here as part of the discussion as opposed to trying to discuss each of the sub-questions individually because, at the end, we have to take all of them into consideration in terms of our recommendations. So my question is whether, as a procedure, can we talk about benefit at this point or would you prefer to restrict it currently to--

DR. WOOD: I think it will be easier to manage with the size of the committee if we actually stick to each sub-question and then we can vote on that. Obviously, if people think there are other issues--as you look at each sub-question, you should bring the totality of whatever issues relate to that to bear on it. If there are discussion points you want to bring to bear on that then, by all means, raise them.

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

DR. WOOD: Any other comments? Charlie?

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

DR. WOOD: I passed myself by. I agree with what Tom said. I think there is clear evidence of risk from celecoxib and we will come back to the subgroups later. I am not persuaded in the absence of data that we can't extrapolate that to other disease states. It seems highly improbable to me that the risk of cardiovascular events would be less in situations where we know that that population have a higher risk of cardiovascular events such as rheumatoid arthritis. So just focusing on the risk right now, it seems improbable to me that we can't extend this information to these other settings. Bear in mind why we have only placebo-controlled trials from non-arthritis patients. The reason we only have placebo-controlled trials from non-arthritis patients is you can't give placebo to patients for 18 months who have got pain. So, stepping back from that and sort of seeing a safety benefit in patients who have not been studied in

placebo-controlled trials seems to me a very hazardous thing to do, particularly when we have non-placebo-controlled trials that seem to show the same thing. Other comments on the question? Yes?

DR. FRIEDMAN: Do you include hypertension or edema as major cardiovascular events? If so, I think it is clearly there as well.

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

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

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

DR. NISSEN: I just wanted to comment for the statisticians here. It is important to understand how much of the evidence comes from the 800-milligram dose which is not a dose that is approved. So, what we have to understand and we have to filter into our thinking here is the fact that the best signals come from a dose that is two times the upper limit of the approved dose and four times the most commonly used dose. Now, that may or may not reassure individuals but it is, I believe, relevant to our considerations and I would like you all to think about that.

DR. WOOD: I think that comes under 1.c. That is where we should deal with that. Right now, we are just addressing whether the drug, itself, can cause events. Any other comments? Dr. D'Agostino?

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

DR. CUSH: I would concur with the original statements of Dr. Nissen and Steve Abramson in that there is a marginal signal at best. But, again, when one considers the use of celecoxib at prescribed doses and for the approved indications, there really is no signal.

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

DR. TEMPLE: No. I just want to correct something I said before that is wrong and might make a difference. I was unaware that some proton-pump inhibitors had actually been shown to improve the G.I. tolerance of some drugs and are actually approved for that purpose. Lansoprazole is approved for healing and risk reduction of NSAID-induced ulcers and there is a combination pill with lansoprazole and naproxen. S-omeprazole has a similar claim. So I don't know if that is going to affect anything but I wanted to correct what I had said before.

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

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

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

DR. FLEMING: Just for clarification, as we look at dose and we look at the three randomized trials, certainly in the APC trial, the signal was greater at 400 compared to the 200. The signal was a relative risk of 3.4 at the 400 although it was still a relative risk of 2.5 at the 200. The second piece of information was the Alzheimer's 001 trial which also was the 200 BID dose that showed basically almost a doubling. So I am a little uncertain. Are we challenging that the 200 BID dose isn't a dose level at which there is some evidence for excess?

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

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

DR. FLEMING: That's right. I would certainly stop short of saying dose isn't important. That is not my issue. My issue is I thought I heard some comments that, if I interpreted it right, the 200 BID dose is one for which there isn't evidence of an excess and, it seems to me, there is.

DR. WOOD: Yes; I agree.

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

DR. WOOD: Let's go back to that. The reason we don't have evidence in the approved indications is because the studies couldn't be done in the approved indications. So that shouldn't wrap us in warm, fuzzy feelings, I don't think. That is a reflection of the nature of art rather than the science. Any other discussion? Great. Let's go, now--now, I have got strict instructions as to how to do this. So we have to go around the room and everybody has to say their name and then vote yes or no. So you precede your vote with your name. And we are dealing with Question 1.a.

### ***Question 1A Voting***

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

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

DR. NISSEN: Steve Nissen. Yes.

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

DR. GARDNER: Jacqueline Gardner. Yes.

DR. PLATT: Richard Platt. Yes.

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

DR. FURBERG: Curt Furberg. Yes.

DR. FLEMING: Fleming. Yes.

DR. DOMANSKI: Domanski. Yes.

DR. BOULWARE: Dennis Boulware. Yes.

DR. DWORKIN: Robert Dworkin. Yes.

DR. HOFFMAN: Gary Hoffman. Yes.

DR. MANZI: Susan Manzi. Yes.

DR. FARRAR: John Farrar. Yes.

DR. HOLMBOE: Eric Holmboe. Yes.

### **Question 1B Discussion**

DR. WOOD: Let's move on to Question 1.b.; does the overall risk versus benefit profile for celecoxib support marketing

DR. GROSS: Peter Gross. Yes.

DR. WOOD: Alastair Wood. Yes.

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

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. CUSH: Jack Cush. Yes.

DR. BATHON: Joan Bathon.

MS. MALONE: Leona Malone. Yes.

MR. LEVIN: Arthur Levin. Yes.

DR. ILOWITE: Norm Ilowite. Yes.

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

DR. MORRIS: Lou Morris. Yes.

DR. CANNON: Richard Cannon. Yes.

DR. SHAPIRO: Robyn Shapiro. Yes.

DR. PAGANINI: Emil Paganini. Yes.

DR. FRIEDMAN: Larry Friedman. Yes.

DR. HENNEKENS: Charles Hennekens. Yes.

DR. SHAFER: Steve Shafer. Yes.

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

in the U.S.? So this is the question for which everybody is waiting, I guess. Discussion? Dr. Elashoff?

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

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

DR. SHAFER: I would submit for Question 1.b. that we really don't have the efficacy data. There are no data on G.I. risk with concurrent steroid use which is a common co-administered drug in patients with arthritis, particularly rheumatoid arthritis. I asked the Pfizer representative if there were data about celecoxib versus NSAID plus PPI. He said he didn't know of any. In fact, there are two such studies both published by Dr. Chen, one in New England Journal 2002, one in Gastroenterology, 2004, with an editorial by Dr. Cryer. Neither was sponsored by a drug company and both showed no net benefit. So I don't know what, if anything, we can conclude about the efficacy of celecoxib given that--versus what is likely the alternative therapy which is PPIs plus NSAIDs.

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

DR. DOMANSKI: I think that what I am about to say is true not only for Celebrex but for all of them, but certainly for

Celebrex. I think that the data presented support the view that the COX-2 inhibitors are effective for their intended use, probably not uniquely so in any group that we can define right now but almost certainly in some individuals. Secondly, these drugs, Celebrex and all of them, in fact, do place patients at increased risk for a heart attack or death but the absolute increase in risk is not such that these drugs should be taken out of the hands of wise physicians and their well-informed patients in whom these drugs were a last resort for achieving an acceptable quality of life. So I think that, with this drug as with the others, we need a black-box warning that is carefully crafted. But taking them out of the hands, as though they were a smoking gun, is probably too extreme.

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

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

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

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

DR. DOMANSKI: Are you asking me for an explanation? I think that is how they should be used. I think there is clearly a significantly increased risk. I think many people will derive benefit from other drugs that probably are less--

place them at less risk. But I think there also exists a group of people who don't derive benefit. There clearly are differences among people in which drug they respond to. Somebody who is leading a very poor quality of life, who understands the risk they are taking and is willing to take it, I think is a reasonable candidate for that drug and I don't think it ought to be pulled out of the hands of the physicians to prescribe it.

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

DR. WOOD: Right.

DR. DOMANSKI: And I would certainly second that.

DR. SHAPIRO: Okay.

DR. WOOD: Dr. Farrar?

DR. FARRAR: I need to bring up a couple of points here that I think are vital to our discussion. First of all, again, for clarity perspective, the lack of G.I. side effects is not the benefit we are talking about. I agree with Dr. Shafer that some of the benefit that they may provide to our patients is in a reduction of the side effects that are seen in the G.I. tract. But the benefit that we are talking about here is the benefit to patients who are not responsive to other drugs perhaps because of G.I., known G.I., toxicity but, perhaps, also for another reason which is that these agents work in a different manner. Dr.

FitzGerald laid out very carefully for us the complexity of the COX-1/COX-2 story and it is not clear to me, as a pain specialist, that we yet understand all of the complexities of that. What we have heard from and seen from patients that we have all treated and heard some comments yesterday is that these drugs work very effectively in certainly some of those patients where other drugs did not work. I would take serious issue with the comment that we don't know that they work better. For sure, if you look at trials and you look at the mean value of the benefit, these drugs cannot be shown to be of superior benefit in an overall population. However, certainly from the clinical experience, we know that there are patients who will respond to one and not to another. I would argue, in fact, that there is a very strong reason for allowing drugs, as long as the risk is not abhorrently high, that these drugs be allowed to be available so that patients and clinicians can make decisions understanding all the risks in moving forward. The last thing is, with regards to it being a last resort, I think if you looked at the comparison of lumiracoxib with ibuprofen, what we see there is that there is a reduction in the cardiovascular--or a lower cardiovascular risk in one group compared to what we would normally consider and is even over-the-counter as a therapy, so one that we would sort of consider more safe. I don't think that we have data yet that tells us that these are a last-resort medication.

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

to published studies where that has been done?

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

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

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

DR. WOOD: All right. Dr. Hennekens?

DR. HENNEKENS: I find answering b. difficult without at least thinking about c. because those patients who are allergic to naproxen, those with GERD or other G.I. toxicities for whom NSAIDs and PPIs are deemed contraindicated by their doctors, those who wish to take it despite knowing that there is a 40 percent higher risk of CVD, these are things which drastically alter the risk:benefit equation, in my view.

DR. WOOD: Okay. Dr. Domanski?

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

DR. WOOD: Dr. Holmboe?

DR. HOLMBOE: I agree that I think with some restrictions that this should be

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

DR. WOOD: Dr. Nissen?

DR. NISSEN: That is exactly the same problem that I am having. It would be very easy if we knew that ibuprofen and diclofenac were placebo. See; I answered yes to the question, does celecoxib increase risk over placebo. I am convinced by all the statistical arguments that it does. What I don't know is if it increases risk over ibuprofen or diclofenac. So, you know, it is a moving target, everybody, and I think your point is an extremely important point here. So how you answer that question depends on whether you accept the premise that all the other NSAIDs are at 1.0 for hazard, and I am not convinced that they are. I am worried that some of them may be at 1.3, 1.4, 1.5 where we think celecoxib is, in which case our decision could be irrational. So it is a really big problem.

DR. WOOD: Dr. Temple?

DR. TEMPLE: I don't want to participate in this discussion but I did want to point out to people, however, that where you are very worried about a side effect of a drug, it is possible, in a very easy way, to show that it works when other drugs don't work. You take failures on whatever the standard

therapy is, and randomize people back to that therapy or to the new drug. That is how clozapine got into the marketplace. That is how bepridil got into the marketplace. So, if that was really an important question, that is not that hard a study to do.

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

DR. TEMPLE: Not to my knowledge.

DR. WOOD: If the data is as compelling as people would have us believe, it should have been very easy to do. Any other discussion? Yes?

DR. BATHON: I am very strongly in agreement with the last few comments about safety. I wanted to throw out one other comment for consideration. If a pharmaceutical company brings a conventional NSAID to the market, they don't have to prove that it is better than the existing agents. When the COX-2 drugs were brought to study, their initial studies were 6 weeks, 12 weeks, long. They were shown to be effective in reducing pain and so they were approved on that basis. It was later, in the following studies, that they used the biology to then work towards an indication of safety from the G.I. perspective. But, as we are deliberating, I don't think it is entirely fair to hold them to higher efficacy standards because we don't hold conventional NSAIDs to that basis. Now, if we then add in the safety perspective--if they are not more efficacious, then we have to prove that they are less safe. The last few comments are relevant because of the safety signals that we might be seeing with conventional NSAIDs. We are in a quandary, I think, saying that

they are more safe at the point. So I would just like to put that perspective.

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

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

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

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

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

DR. FLEMING: My sense was that the evidence for naproxen, in relative comparisons here, was, overall, quite favorable and that was based on the positive result in the VIGOR trial and the positive results in the etoricoxib setting and the lumiracoxib setting. The ADVANTAGE trial was fairly neutral. So it seemed from those data that the naproxen experience looked more favorable than the coxibs it was compared to. The diclofenac was compared in the CLASS trial and in the etoricoxib setting. In the etoricoxib setting, it was neutral to slightly worse. In the CLASS trial it was what I might call comparable to the Celebrex.

DR. WOOD: So we are not hearing from you a lot of evidence-based concern

about the other non-steroidals. That doesn't mean they are not there, obviously.

DR. FLEMING: Certainly the data are much more limited. My own sense about this is that the diclofenac seems to be in the range of its experience seems to be in the range of what we were seeing with the coxibs that it was compared to while my own sense, in looking at the tally of the data, is that the naproxen does look more favorable, in the aggregation of evidence, compared to the coxib comparators.

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

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

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

DR. CRYER: Okay.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: On Tuesday of this week, Dr. Colin Baigent of Oxford presented to the European Medical Evaluation Agency his preliminary analyses of 113 trials with 135,000 patients. Looking at the placebo-controlled trials, the relative risk was 1.41. In the naproxen comparator, it was 1.56. In the non-naproxen NSAIDs, it was 0.86. So we were fortunate to have

Tom here with what he has done because, in effect, Tom has given us the same perspectives that were reported to the European authorities.

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

DR. ABRAMSON: Just, Alastair, I wanted to address your point that there is no evidence in randomized trials to be suspicious of the nonspecific non-steroidals. The nature of the evidence, I think, is that they were no different in many of these trials from the drugs that we were imputing some cardiovascular risk. I guess Dr. Fleming, yesterday, one of the members of the panel, was talking about if a coxib is worse than placebo. We have multiple randomized controlled trials from TARGET to CLASS and EDGE, that the comparator nonselective NSAID looked like the coxib than b. looks like c., and b. is different from a. I think that is the nature of the evidence in the randomized clinical trials that gives a lot of us some concern about giving those drugs a pass.

DR. WOOD: Arthur?

MR. LEVIN: Not to be wordsmithing but I am somewhat uncomfortable with the wording of b. and c. and how it may be interpreted, and I would say not only for 1., but 2. and 3. as well. I guess I would interpret b. as a question asking does it support the marketing as "at present" in the U.S. I mean, that is how I would interpret that. When we start nuancing that and modifying and saying, yes, but with a black-box warning or yes, but with this risk management strategy, that is for later discussion.

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

DR. JENKINS: I can address that. The intent of these questions were that the questions would be the same for the three approved products. So the first question, we wanted to hear your view on is: Are there data to suggest that there is an increased cardiovascular risk for the individual product? That is why we put that first. If you were to answer no to that question, it might make the second question less important. We also wanted you to answer the question which is b., which is essentially, should the product be withdrawn from the market. It is not stated that way because, in a desire to keep the answers all the same for the three questions, it made it odd for the Vioxx, which has already been voluntarily withdrawn. So that is why we asked, do the data support marketing. The third part of the question really gives you the opportunity to say, yeah; I think it should be on the market but we think you should make the following changes to manage the risks that we saw in a.

DR. WOOD: I mean, given what we heard yesterday about Vioxx not being on the market but maybe being back, do you want to change it? Should they be withdrawn?

DR. JENKINS: No. I think it is fine to leave the questions the way they are because, you know, Merck has stated their perspectives on this but, presumably, if you find that these products have a cardiovascular risk and should stay on the market, you are going to give us advice about what we should

do to change the labeling, the marketing, et cetera, et cetera, for these products. So Vioxx could not just reappear back on the market on Tuesday like a question we got last night in the press briefing. There would need to be substantial agreements to move forward on how to revise the labeling which we would have to approve.

DR. WOOD: Right. Okay. Does that help, Arthur? All right. Dr. Cush?

DR. CUSH: I'll pass.

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

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

DR. WOOD: We don't have that data. I would like to be reassured, too. Bob Temple designed the study. We would all want reassurance. But we are sitting here at whatever time it is, 11:00, 12:00-

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

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

tough. Okay. In the absence of any other comments--oh; I'm sorry. Dr. Manzi.

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

DR. WOOD: Right. I mean, if someone comes in and demonstrates that this drug cures cancer 100 percent of the time, then, obviously, they will come back and have a very different risk:benefit ratio than we would be discussing here. So I think all we can discuss right now are the indications for which it is being used right now. If someone comes back with colon polyp prevention or some other, a curing of Alzheimer's, the individual risk:benefit analysis that people would take into account then I think would be different. Then I think that would be reasonable.

DR. MANZI: I just think it is important because, although we are extrapolating

risk from a population that it wasn't indicated as far as usage, we can't extrapolate risk:benefit.

DR. WOOD: The population--I mean, one question is do you think, as you take this into account, you should consider is, do you think the outcome for risk would be fundamentally different based on some biologically plausible probability in different populations. If it does, you might take that into account, I guess.

DR. MANZI: I don't think we have the answer to that. I think it is unknown. But I think the benefit may be very different.

DR. WOOD: It is not entirely unknown. The studies that were done in arthritis patients which were not placebo-controlled, done against active controls, showed the same kind of signal. Now, we impute in them a placebo which is always risky, of course. But we would have to come up with some very convoluted kind of argument, I think, to do. But I hear your point.

### **Question 1B Voting**

DR. WOOD: Any other comments? Are we totally satisfied, as the auctioneer would say? Then let's start the vote and we will start it on the other side this time. I would remind you, again, to state your name.

DR. SHAFER: Steve Shafer. I, unexpectedly, cast my vote last night when my father, an 89-year-old man with no other risk factors for heart disease but a sensitive stomach, asked me if he should stay on his Celebrex. I said yes.

DR. HENNEKENS: Charles Hennekens. Yes.

DR. FRIEDMAN: Larry Friedman. Yes.

DR. PAGANINI: Emil Paganini. Yes.

DR. SHAPIRO: Robyn Shapiro. Yes.

DR. CANNON: Richard Cannon. Yes.

DR. MORRIS: Lou Morris. Yes.

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

DR. ILOWITE: Norm Ilowite. Yes.

MR. LEVIN: Arthur Levin. No.

MS. MALONE: Leona Malone. Yes.

DR. BATHON: Joan Bathon. Yes.

DR. CUSH: Jack Cush. Yes. No "buts."

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. GIBOFSKY: Allan Gibofsky. Yes.

DR. WOOD: Alastair Wood. Yes.

DR. GROSS: Peter Gross. Yes.

DR. HOLMBOE: Eric Holmboe. Yes.

DR. FARRAR: John Farrar. Yes.

DR. MANZI: Susan Manzi. Yes.

DR. HOFFMAN: Gary Hoffman. Yes.

DR. DWORKIN: Robert Dworkin. Yes.

DR. BOULWARE: Dennis Boulware. Yes.

DR. DOMANSKI: Michael Domanski. Yes.

DR. FLEMING: Fleming. Yes.

DR. FURBERG: Furberg. Yes.

DR. DAY: Ruth Day. Yes.

DR. PLATT: Richard Platt. Yes.

DR. GARDNER: Gardner. Yes.

DR. ELASHOFF: Janet Elashoff. Yes.

DR. NISSEN: Steve Nissen. Yes.

DR. ABRAMSON: Steve Abramson. Yes.

DR. WOOD: Okay. To allow everybody to go off and file their stories now, we will break for lunch and be back to start again promptly at 1 o'clock. Thanks a lot. (Lunch recess.)

### **Question 1C Discussion**

DR. WOOD: Let's go on to Question 1.c. which is, if yes, and it was yes, please describe the patient populations in which the potential benefits of celecoxib outweigh the potential risks and what actions you would recommend. The reason that we had the immediately preceding talk was it seemed to me, at least, as I looked at that question, that the potential actions obviously included a raft of the various options that we heard from the last speaker. So, do we have discussion on this point? Dr. Cush?

DR. CUSH: The populations where the potential benefits outweigh the risks were, I believe, those that are currently indicated; osteoarthritis, rheumatoid arthritis and a few pain indications. I do think that we should make a call for additional study. I do think that there should be additions to the warnings within the label under Precautions or Warnings, although not a black-box for celecoxib. I do think that there should be, in those warnings, or in the study

designs that have come forward, a risk-reduction strategy so that patients who may be at risk, that risk is minimized as much as possible.

DR. WOOD: Other discussion? Arthur?

MR. LEVIN: Could I just ask why you oppose a black-box warning?

DR. CUSH: In this instance and this compound, I don't think there is a preponderance of evidence that argues in favor of that.

DR. WOOD: I didn't hear that last comment.

DR. CUSH: I believe, for this compound, there is not a preponderance of evidence that would suggest the need for a black-box warning for this compound.

DR. WOOD: All right. Other comments? Dr. Shafer?

DR. SHAFER: I think for indications the drug should be indicated for individuals who cannot tolerate NSAIDs with a proton-pump inhibitor. I think the drug should be started at the lowest possible dose as part of the indications. I oppose a standardized black-box warning for the class because I think that can result in a dilution of the message by implying that the risk across the class is identical. But I think each drug should be evaluated individually. In the case of celecoxib, I think the FDA should mandate a black-box warning clearly stating the increased likelihood of cardiovascular adverse events including death. But I also think there should be a black-box warning that contraindicates the drug following cardiopulmonary bypass based upon the parecoxib, valdecoxib data. I think that

part--these drugs should all not be used following cardiopulmonary bypass. Pfizer has voluntarily suspended marketing of celecoxib. I believe they should continue to do that, although it is not in our purview, until the FDA has implemented the recommendations.

DR. WOOD: Other comments? Dr. Domanski?

DR. DOMANSKI: You know, I wonder--this is a small point, probably. I think they all ought to get a black-box. I think there is something to be said for--you know, if the message is substantially the same for having substantially the same message in that black-box, though, because it underscores the fact that we think there is a class effect, admitting that there is probably some variation among the drugs.

DR. WOOD: I think we may have to circle back to the class effect at the end. So I think, right now, we should just focus on the risk-management strategy for celecoxib and not take in the other ones. I also think there should be a black-box warning. I think there should be severe restrictions on the prescribing of the drugs at both the dose and the patient population. Curt?

DR. FURBERG: I agree with that. I think if you are consistent. We unanimously said the drug carries risks. So we have an obligation to be more specific obligation to be more specific about that, and the way to do it is to have a black-box warning and warn against use in high-risk people and in the use of high doses.

DR. WOOD: I mean, we could have direct-to-consumer advertising that had

people, well-known skaters skating around an ice rink and then dropping dead, or something rather than just--okay.

DR. PLATT: So yes to black-box warning. I am very impressed by the seeming consensus we have had that naproxen appears to be a relatively safe drug. So I would favor considering the label and the instruction to clinicians being that this be a drug to be used as a drug of second choice; that is, for individuals who have either failed a comparator--and I am toying with the idea of suggesting the we actually name naproxen--or who are intolerant for some reason. I favor the attestation requirement because I think there is an important piece of risk communication that we could do but I think we won't do without having that. I think there is a lot of information living in the datasets that were presented to us that hasn't been put in a form that is most useful to patients and that is I think that I would have the attestation actually specify the incremental risk that patients might expect based on the accumulated literature and that incremental risk would be patient-specific based on fairly standard risk factors. So I would really hope that the committee would support a request to FDA to collaborate with NIH to use the accumulated data to develop much more informative information for patients and physicians to allow them to estimate their incremental risk. I think there is a huge difference between a patient agreeing to take an incremental risk that might be a half a percent per year versus an incremental risk that might be 10 percent per year. We have the information to allow patients to know what size risk they are taking on.

DR. WOOD: Dr. Nissen?

DR. NISSEN: The problem with that, of course, is we don't have robust enough data to actually know that in an individual patient's situation. But let me come back--the thing is what do we really want here? What we want is to make certain that therapy is available for those people in whom it is appropriate and to make certain that people in whom it is inappropriate don't get it. Now, a black-box is a good way to communicate things. The question is what does it say? I think what it has to say is that there is evidence of an increased risk of cardiovascular and cerebrovascular and, obviously, in language that is very clearly written. I also think that it is important to discuss--we have seen some pretty good evidence of a dose-response relationship with cardiovascular toxicity. So, to say to physicians, you should limit the dose and you should limit the duration whenever possible is also very important to communicate. I don't think direct-to-consumer advertising is appropriate at this point, given the fact that direct-to-consumer advertising tends to stimulate the use of a drug, excessive use of the drug. I think a patient guide is very helpful here. I think that patients--you have to respect the ability of patients to also make decisions. I think a patient guide that explains in lay language what our conclusions are about the extent of risk that must be dispensed with the drug is a very helpful way to educate the public about what these risks look like. I would also say that we ought to offer a strategy for the sponsor here for getting these warnings removed. In my view, an adequately sized trial against a comparator that we are comfortable with--namely, naproxen, at the 200-milligram dose--would be--we can set

what those upper bounds are, but I think if someone can demonstrate, if the sponsor can demonstrate, that the 200-milligram dose does not produce excess cardiovascular risk versus naproxen, that we ought to give that option. That would be an incentive, a strong incentive, to do that very pivotal trial because what we don't have is we don't have good data on what the 200-milligram dose, what its risks look like, compared to a very good comparator. So those are some of the thoughts I had.

DR. WOOD: I agree with that. I would say that, from my personal perspective, that it should have a restricted black-box warning. It should be given to very restricted patient populations in limited dose and for limited duration. There should be absolutely no direct-to-consumer advertising. I would add that if a patient guide or even if the package insert, itself, was to try to specify risk, we should do that in a more helpful way than we do that right now. I don't know what 1 percent increase means to me, even. So we should put it in some contextual basis like it is the same increased risk as you would get from smoking so many cigarettes a day. Or it is the same increased risk as you get from whatever it is, having diabetes or something. You could give multiple different examples. So patients have some kind of sense of what they are talking about here because I don't see how any of us, certainly not people who don't think about risk every day, can really put that into a meaningful contextual basis. You know, people worry about flying and then get in their car and drive drunk. So people have a relatively poor ability, I think, to assess risk and we need to help them do that with meaningful statements rather than

other risks. Are there any other--I'm sorry. Yes?

DR. MORRIS: Let me argue against a ban on DTC. Firstly, I am against a ban for three reasons. One is I am not sure it is enforceable. Secondly, philosophically, I am against the idea of banning information. Thirdly, it won't work. There are too many other ways of getting to the patient and I think what you will have is a big influx of money into public-relations efforts in which we won't even see what is being communicated to patients. On the other hand, I would argue very strongly for a totally different way of communicating the risks of these drugs to patients. Right now, what you have in all these commercials, is about a third of the ad having some kind of message that no one understands and nobody takes away. It clearly just isn't coming across to people. What I would suggest is that what we do is we break out the risk information on this drug into a single commercial and that, for every three benefit commercials, we play this risk commercial so people can have a whole story in which we can put this into a better context, not put together by people whose job it is to market and sell the drug but let these commercials be put together by an independent group reporting to the FDA that meets the standards of fair balance for both the company and the FDA but which provides a full message to people about how the risks and benefits of the drug have to be carefully understood and whatever other message it is. But I think that we need to think of--I mean, I have been--of all this whole story, the public reaction to the withdrawal of Vioxx just astounded me. I have to believe that part of their reaction was due to the direct-to-

consumer advertising that was done for this class of drugs. I think, unless we have a fundamental change and do a better job of educating the public and communicating better risks in the same way we communicate benefits, I think this is going to happen again in another class of drugs.

DR. WOOD: People who look at consumer ads apparently interpret toxicity statements as implying the drug is more potent. The surveys of the effects of the erectile dysfunction ads and the ones that have, because of the way they chose to advertise them--the ones that say, beware of a four-hour erection, are assumed by patients to imply more potency. No pun intended.

DR. MORRIS: But if there is a very vivid risk, like, for Xenical, or, for some reason, I have learned people love their livers. If you say it causes liver disease, it really upsets people. But, for the most part, this--if you look at the research on consumer takeaways, what they remember from seeing an ad, risk information is way down on the list. It just doesn't get through to people with the same prominence as the benefit information. If we really want a balanced ad, I think we have to have a dedicated ad that balances all the benefit information.

DR. WOOD: Dr. Day?

DR. DAY: I agree with Dr. Morris' intended outcome but I do not think we need to go to separated ads at this time. I apologize for bringing in results that are not yet published but I feel morally obligated to at this time. We have produced our own t.v. ad for a fake drug and, after analysis of what is going on in

all the t.v. ads--for example, the location of where they put the side effect and showing that that is the least optimal place for memory and comprehension based on separate laboratory studies on other kinds of materials--we then did experiments where you put the side effects in where they normally come and people don't remember or understand them. You relocate them somewhere else where all the lab studies say people will remember and you at least double what they take away. In some of our experiments, it has been even higher than that. So if we look at what the nature of cognitive processing is for a 60-second, 45-second ad, amount of information and put the information in an appropriate location, as well as adjust the language--we have done an extensive analysis of the readability level of what is being said for the benefits versus the risks. We found that you need to have three grade levels more education to understand the risks than the benefits. If we can have fair balance on these two things I have mentioned as well as others that we have looked at, then we will have more of a chance to have all the information at the same point in time.

DR. MORRIS: Ruth, I am not saying you could not build an ad to do this. When we first did the initial experiments on DTC, we actually varied different ways of presenting risk information and, yeah; you can communicate risk information. But if you look at the way ads are produced, it is clear that the people who create these ads, their primary goal is to market the drug. It is not to produce information that is equally balanced. I don't think you can set up a structure that people can't get around. It would be fairly easy for them

to figure out a way to get around it. Also, this was a t.v. ad you did, or print?

DR. DAY: This is a t.v. ad.

DR. MORRIS: So, okay; you can do it. It just won't work.

DR. WOOD: We are getting--I understand. Let's move on. Dr. Elashoff?

DR. ELASHOFF: No.

DR. WOOD: No? Let's look at my list here. Dr. Bathon?

DR. BATHON: If we do recommend the black-box, I am pretty strongly opposed to the idea of putting a dose and duration warning in that. I would say that, if you consider the four indications right now for these drugs, some don't have all four indications, three of the four conditions are chronic; R.A., O.A., and FAP. The exclusion is acute pain. So, to come in and say, use for the shortest duration possible, contradicts the indications. Secondly, if you put in an indication to use the lowest dose possible, you are negating the fact that efficacy is better for some of these drugs at the higher doses for people with rheumatoid arthritis in particular, and they need those higher doses. That is one of the four indications. I would suggest, if we decide on a black-box, that we ought to have the underlying theme be avoidance in patients with high cardiovascular risk profiles. That would be the underlying unifying theme.

DR. WOOD: Although the risks also appear in people with low underlying risk profiles in the studies.

DR. BATHON: The studies do show, the ones that we reviewed over these past few days, pretty clearly, in a number of them, that those people who have higher cardiovascular risk profiles, and who are on aspirin, have higher event rates than those not.

DR. WOOD: Right. They have higher event rates, but the others had a significant effect as well.

DR. BATHON: We have to play probability somewhere. We can't cover all of our bases.

DR. WOOD: Okay. Let's go on. Dr. Gibofsky?

DR. GIBOFSKY: No.

DR. WOOD: Dr. Manzi?

DR. MANZI: First of all, I agree with Joan on most of the comments but I wanted to get back to the suggestion that we regulate the order in which we are recommending prescribing the medications where they have to fail the tradition or "nonselective, nonsteroidal" first. I would say I would be opposed to that because I think, for various reasons, there may be reasons to go to these agents first-line, whether it is G.I. issues or anticoagulation issues or whatever the situation may be.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: Yes. I just want to express an overall concern that we are making fairly draconian recommendations for the drug that we thought had the least robust evidence, although we all agreed it had evidence.

DR. WOOD: We might make more draconian recommendations for the others.

DR. ABRAMSON: I understand that. But I think we are doing it out of context because the notion that you put a black-box to say that you can't use this primarily without failing other drugs is not data-driven. We saw in, even ADAPT, that there was increased negative outcomes on the Naprosyn group. So, while I agree with the consensus that Naprosyn does seem to be protective, an unintended consequence of making Naprosyn the first choice without being very careful is more G.I. bleeding. We all understand the PPIs might protect but this becomes a very complex risk:benefit decision. I also think that, to say that, therefore, diclofenac, meloxicam, et cetera, look very much like the celecoxib, should be used before celecoxib is not data-driven. So I think we have to be careful not to make decisions that are driven by our sense that there is something terribly wrong with this class that supports the use of other drugs that is going to give us unintended consequences. So I think we are going to end up needing a very serious warning, maybe a black-box warning. I think it is hazardous to discuss each of these drugs right now without defining what the nature of the class is because I am going to suggest that whatever we say for celecoxib it is going to be hard not to say for diclofenac and a couple of other drugs.

DR. WOOD: Dr. Domanski?

DR. DOMANSKI: I think that saying that something is a second-line drug doesn't necessarily mean that you have got to try a different drug if it is clear to

the physician that that drug is inappropriate. I mean, it forces you to consider it as a second-line drug only but not necessarily to give something else. I do think these should be a second-line drug, though, and I would just reiterate that I think that the warning should be a strong one and I entirely agree that that should apply to the other drugs in this class.

DR. WOOD: Dr. Dworkin?

DR. DWORKIN: I completely agree with Dr. Abramson. I am really uncomfortable with the notion of giving this drug a black-box warning or considering it second-line because we have seen no data in the last two-and-a-half days that would warrant the huge migration of patients away from this drug to traditional NSAIDs. We just don't know that the cardiovascular risks of traditional NSAIDs are less than celecoxib, but there will be a huge number of patients, both because of clinical and patient decisions, migrating away from this drug to other drugs where we don't have an evidence base in support of that. Now, while we have seen some data suggesting that naproxen has less of a risk than these other drugs, I think none of us would feel comfortable enough with that data to give naproxen, for example, an indication of having less cardiovascular risk. So I think we have to be very aware of the kind of very meager evidence base that we have here and the risk that we are going to bring about an enormous migration of patients from one drug to other drugs where we don't really know much.

DR. WOOD: Dr. Gross.

DR. GROSS: I sense a discomfort in the group about committing ourselves to celecoxib and whether there should be a black-box warning or not. Maybe the solution is to consider what we want to say about all the NSAIDs including the coxibs, do we want to have a warning for all of them or a black-box warning for all of them, and then it might be easier to deal with the individuals.

DR. WOOD: The problem with that is we have to vote, first of all, whether-- what the actions we take for each of the drugs. I think we should do that first because we haven't done that yet with the others. Dr. Nissen?

DR. NISSEN: The reason everybody is uncomfortable, of course, is that we know so much less about the comparator drugs. We don't have robust cardiovascular safety data, for example, for diclofenac. One of the things that is really troubling me about this, and I think you made some very good points, Steve, is that if you look at a trial like CLASS, you see, basically, the same cardiovascular event rates with diclofenac as you see with 800 milligrams of celecoxib. So if, in fact, we do precipitate a migration away from celecoxib to diclofenac, we may not actually be doing good. We may actually be doing potentially harm. I am concerned that we don't have the evidence. So I think we have to keep our warnings to what we know. What we do know is, and we have agreed, that celecoxib, compared to placebo, has excess risk. But we don't know whether that risk is excess in comparison to ibuprofen or diclofenac. So any statement that would tend to suggest using those alternative agents first is probably not warranted by the data

because we simply don't have the data to make such a conclusion. So I think we have to limit our statements to what has been proven within a reasonable doubt here and that is that celecoxib is probably riskier than placebo.

DR. WOOD: Dr. Gardner.

DR. GARDNER: I am having similar discomfort about the benefit side when we look at all of these drugs in a group like this. So my comments will apply to everything that we are doing here today. I think that we are not, this afternoon, going to get a whole lot more information about benefit. We have been focused on risk. But I would echo Rich Platt's request to the FDA to dig into all of the information we have on the various products including the observational data which can be very helpful here in helping to specify. For example, we are all, now, very sensitive to the fact that R.A. patients and elderly patients tend to be, thanks especially to Dr. Cryer's presentations--we know that they are at higher risk both of cardiovascular and of G.I. bleeds. We know that. But the observational studies, at least in some of the clinical trials, were done on much younger folks. We heard yesterday from the Military that they have got very fit people who need these drugs. So I would like to--before we start specifying who are the populations that have need and what we should do to help them restrict, I would like to ask that, at least the FDA if not we, this afternoon, pay attention to better specification of the risks and benefits for communication of risks to other people besides the elderly R.A. patients whom we know are at higher risk and then find ways to communicate them appropriately. I am in favor of med

guides. I just want to comment, as someone who fills prescriptions, that when you put a med guide in a packaging, the way to get it to the patients is to have it packaged in the containers that you are going to distribute to the patients. That affects bulk packaging. Any time you design a med guide that is supposed to be handed out by a pharmacist in a chain pharmacy after you have taken bulk drug out and repackaged it is not going to get there. So think, as well, when we are talking about med guides, that you want to individualize them to the dispensing.

DR. WOOD: I think we have exhausted the discussion. Do we want to move to the vote on this.

DR. CRYER: Dr. Wood, over here in the corner.

DR. WOOD: I have been told that, as you are not a voting member of the committee, you are not allowed to comment during the discussion at this stage. Thanks.

DR. CUSH: Should not the first vote, then, be whether this is no warning, warning or black-box?

DR. WOOD: I think what we could do--let me ask the FDA. It seems to me that

there are multiple issues here so I would suggest that we go around the panel and ask each panel member what they think should be done, what is their kind of list of things that they would like to see done. Is that reasonable?

DR. JENKINS: The intent of Question c. was not to have a specific vote. It was more to give a sense, from the committee, about the goals for the risk-management program and any specific ideas you have about how that should be implemented but not to take a vote on the exact wording of a box or whatever.

DR. WOOD: Sure. But would it be helpful to go around and ask each person what they think or have you got a sense of that already, John?

DR. JENKINS: Wait a minute, one of my colleagues is telling me--I don't know that you have to go around to every individual member, but if that is what you choose, that would be fine. We are always interested in hearing everyone's ideas.

DR. WOOD: Okay. Let's do that. Was that acceptable to the committee? Let's start with Dr. Abramson.

### ***Question 1C Around the Table Recommendations by Committee Members***

DR. ABRAMSON: I guess my bias on this is that we have to, as I have said several times, define what we mean by the class and what we think the pathophysiology is here. I think we all

agree that there is a risk from sustained, high-level COX-2 inhibition. I think the challenge before us, and I will ultimately believe in some sort of serious warning, perhaps a black-box warning, is that we agree that we are talking apples to

apples. My bias will be, as I have said, to include drugs other than the coxibs, drugs that fall into COX-2 preferential categories similar to celecoxib. Just as a final point, I would remind the panel that when meloxicam was first marketed, in the U.S., it was marketed as a COX-2 inhibitor. After VIGOR, the company was prescient enough to stop marketing that way. It is, I believe, still the only COX-2 selective drug available in Japan. So, had they continued to market that drug as a COX-2 inhibitor, that would be among our four drugs of discussion. So my plea is that we decide first, before we get into too much detail on the individual warnings and labeling, what it is we mean as a group as COX-2 and try and draw a line somewhere that extends, in my view, beyond the three coxibs that we are discussing.

DR. WOOD: Let's just go around. And let's try and just list the things and not discuss it all again. Otherwise, we will take forever. Just list your recommendations.

DR. NISSEN: I am in favor of a black-box warning which basically says that there is dose-dependent increase in cardiovascular risk with the drug. I am in favor of no DTC advertising and I am in favor of a patient guide, a patient handout, that would inform the patient about the risks of the drug.

DR. ELASHOFF: I have no additional comments.

DR. GARDNER: I am in favor of no DTC advertising, a patient guide, a med guide, to communicate to the patient as well as the physician, and warnings that are appropriate to the risk group.

DR. WOOD: Richard?

DR. PLATT: I favor a substantially upgraded postmarketing surveillance program, black-box warning. I would favor recommending this drug be treated as a second-line drug and I would favor mentioning the suggestive evidence about naproxen possibly being a preferred alternative. I personally would favor attestation that requires the patient to acknowledge the magnitude of the risk and I was persuaded by the argument about putting that risk in the context of other easily, relatively easily, understood risks.

DR. DAY: I am for a black-box warning and I think that they can be differential across the different products and whatever the minimum is, this one might get that. The upper limit may still be high but I don't think we need to decide on this one, given defining the class and so forth, at this time. I would be in favor of the medication guide. Also, I know a lot of people say the "Dear Healthcare Professional" letter isn't read, but sometimes it is, so I think that both physicians, healthcare providers and patients should get this information. I am not necessarily in favor of suspending DTC at this time as long as it is done in a way that provides fair balance between benefits and risks if that can be achieved. I am open to having the patient attestation part, perhaps with a small survey for comprehension.

DR. FURBERG: I am for the black-box. I agree with the contraindication for high dose. I would like to be more specific about the population by contraindicating the drug for patients with known coronary heart disease and stroke and for patients at increased risk. I am also in

favor of some form of patient agreement or consent. If we had any way of barring direct-to-consumer advertising, I would be in favor of that because I think that action, in itself, would prevent more serious adverse events than anything else we can do other than taking that drug off the market.

DR. FLEMING: I favor a black-box warning regarding the increased cardiovascular and cerebrovascular risks. I am inclined to also agree with noting the particular concerns with those patients that have high cardiovascular risk and toward encouraging minimizing dose and duration, appreciating the comment that that is more challenging in certain settings, and yet it still doesn't preclude use for a longer term but it just notes that there are potentially increased risks with that. I am in agreement with barring direct-to-consumer advertising unless Dr. Morris strategy that could be more effective is achievable--I don't have a clear sense about that--and the concept of the patient guide as well.

DR. WOOD: Okay. Let's just keep going. Dr. Domanski.

DR. DOMANSKI: Black-box warning that puts for the increased cardiovascular risk of the drug, patient pamphlet, second-line drug.

DR. BOULWARE: I favor a black-box warning expressing the known cardiovascular risk when used in the doses that were excessive of the approved levels of 400 milligrams but also stipulating it is not quite clear what the relative risk is to the other known non-steroidals.

DR. WOOD: Next?

DR. DWORKIN: I am not in favor of a black-box warning unless it is given to all NSAIDs, traditional and selective. I am in favor of a detailed and comprehensive cardiovascular warning for celecoxib. I will pass on the other stuff.

DR. WOOD: Dr. Hoffman.

DR. HOFFMAN: I am in favor of a black-box warning to be in place until more definitive studies are done and that warning should--well, we are not supposed to address the direct wordage but it was mentioned that there should be a limitation on duration. I think that is impractical because most of the patients using this drug have chronic diseases that don't go away. But there definitely should be, within the guidances, doses not to exceed 200 milligrams a day. I would be against direct-to-consumer advertising and I would advocate a patient guide with this being second-line therapy.

DR. WOOD: Dr. Manzi.

DR. MANZI: I am not opposed to a black-box warning. I think it should clearly state the cardiovascular risk with higher doses for longer duration but not directly advocate low doses for short duration. I am vehemently opposed to it being a second-line agent and I think a patient guide is sufficient.

DR. WOOD: Dr. Farrar.

DR. FARRAR: I am in favor of a black-box warning specifying cardiac risk factors. I am vehemently against direct advertising on this and all of the COX drugs. I feel strongly that a patient guide

should be designed so that it can be read and understood by patients. I will pass on the rest.

DR. WOOD: Dr. Holmboe.

DR. HOLMBOE: I am in favor of a black-box warning. Again, I had some discomfort with regard to the nonselective NSAIDs. There should be a warning for those as well. I am in favor of a patient medication guide, particularly one that should try to address not only health literacy issues but also health numeracy issues. I hope that the FDA will undertake study of these guides as well as, say, the medication themselves. I am also in favor of also adding to this some academic detailing to make sure the word gets out to the physicians who are using these drugs. I will pass on the others.

DR. WOOD: Peter?

DR. GROSS: I am in favor of a warning related to the dose-dependent toxicity and that a similar warning should be on all coxibs and nonselective NSAIDs. I favor a medication guide for patients and a consent for patients when they will be taking higher doses. I would favor direct-to-consumer advertising only if combined with FDA-approved education on the putative risks and I am opposed to it being a second-line agent.

DR. WOOD: Thank you. I am in favor of the black-box warning. I am in favor of a very restricted patient group to exclude people who are likely at risk for cardiovascular disease. It is not just those who have previously identified themselves by having cardiovascular disease. It would include the elderly

patients with high-risk factors and probably some others. I am against direct-to-consumer advertising, strongly. I think a patient guide has to be useful and should be done. I think however we articulate risk to patients, it needs to be done in a way that is immediately obvious what we are talking about. I think it is hard for me and for most people to understand what a 1 percent increase in risk means to me or to anyone else. So I think it needs to be put in some contextual way that relates to people's regular daily lives. I think one other thing I am in favor of that has not been said is I am in favor of the company having the opportunity to have the black-box warning removed if they can demonstrate in well-designed, well-controlled, double-blind trials that the drug, at any particular dose or on any particular group, does not, indeed, have these risks. So I think I am favor of viewing this as a step that we are taking right now based on the evidence we have but we are prepared to consider changing that if they come up with evidence, good evidence, excellent evidence, that overwhelms what we have got right now.

DR. GIBOFISKY: There are four indications for celecoxib, two short-term and two long-term. I think the population should be the intended populations, the indicated populations, to be used at the lowest effective dose. I oppose a black-box warning. I am in favor of patient handout. I oppose the use of or designation as a second-line agent. I am not opposed to DTC advertising so long as it is informative and educational and consistent with the message above.

DR. WOOD: Dr. Crawford.

DR. CRAWFORD: Thank you. I am strongly in favor of a black-box warning about the cardiovascular risks. Also, I feel strongly the need for postmarketing commitment studies. I share the Chairman's thoughts about the possibility of such studies removing the need for a black-box warning in the future. Also, I am very much against direct-to-consumer advertising, but if it is not possible to make that a regulatory action, to say that there needs to be appropriate communication of the risk in that direct-to-consumer advertising.

DR. WOOD: Dr. Cush.

DR. CUSH: Jack Cush. I am opposed to a black-box warning. I am in favor of a general warning that stipulates some strategy for risk reduction and risk minimization. I am strongly in favor of direct-to-consumer advertising as long as the major statement significantly outlines this cardiovascular risk and that D.V.MAC take particular attention and making sure that that is highlighted. I am also in favor of further study of cardiovascular risk in the target population.

DR. WOOD: Dr. Bathon.

DR. BATHON: I am opposed to a black-box warning but I am in favor of a strong warning that advises the association of cardiovascular risk and in the target population. I am very opposed to DTC advertising and I think that, if there were not DTC advertising and a strong warning, we would be more likely to target these drugs to the appropriate populations.

DR. WOOD: Ms. Malone.

MS. MALONE: Yes. I am opposed to a black-box warning. I think there should be a serious warning about cardiovascular risk and dose-dependency. I think there should be a limit on direct-to-consumer advertising. I don't like the idea of calling this a second-line drug. I think what that is going to do is have insurance companies require--it is not going to leave the decision with the physician and the consumer. It is going to make insurance companies say, you have to try these other drugs first. I think there should be a patient guide that is readable, understandable, easily accessible and I think there should be very good education for the doctors so that this dialogue can take place. And I am not opposed at all to a patient consent or attestation and I actually think that that will lead to a better communication between the doctor and the patient.

DR. WOOD: Arthur?

MR. LEVIN: Black-box with the cardiovascular risk; medication guide, of course; some sort of informed consent or assent or agreement. But I agree with the Chairman that we have to learn how to convey risk in ways that are meaningful to consumers. I would also argue that we have to learn how to convey benefit. We are only talking conveying risk. We need to figure out how to convey realistically what we know about the benefits so that the balance can be made. Academic detailing, I think, has been shown to be effective and it would be intriguing. I just think it is an intriguing idea to tie black-box removal as a stick and carrot to encourage further study. Until we figure out how direct-to-consumer advertising can tell the truthful story

about drugs, I would at least suspend it for now.

DR. WOOD: Dr. Ilowite.

DR. ILOWITE: I favor a black-box warning advising of the increased cardiovascular risk which is duration and dose-dependent. I favor a statement saying that it is relatively contraindicated in patients with high cardiovascular risk. I am opposed to calling it a second-line drug. I am opposed to direct-to-consumer advertising. I am in favor of a medication guide. And I wouldn't mention Naprosyn as the preferred NSAID.

DR. WOOD: Ralph?

DR. D'AGOSTINO: I am in favor of a black-box warning. I don't think there should be direct-to-consumer advertising. I think the evaluation of the cardiovascular risk is important and, as a matter of fact, I don't think it would be very hard to do with the clinical-trial data plus some things like we have at Framingham. There are comparators compared to--sort of the optimal person compared to your average population. It is equivalent to being diabetic. There are lots of ways of doing this and I think it should definitely be done.

DR. WOOD: Dr. Morris.

DR. MORRIS: I am in favor of a black-box warning. I would like to see it for the broadest definition of class and every drug get the black-box warning in this class. Information can vary, but within that, there should be statements about the class because I am real concerned about switching when there is nothing

known and I would like to include some kind of statement in that black-box warning about what is not known as well as what is known. Obviously, I am in favor of DTC but restructuring it. In favor of a really strong postmarketing-surveillance program and probably studies like Dr. Temple suggested. I am actually not in favor of a medication guide but I am in favor of a unitive-use patient package insert. I think some of the information in that should also be broad and class-wide so people can understand that the concerns extend beyond just COX-2s as they think of COX-2s. I am also in favor of an insert for over-the-counter drugs in this class that also talks about the use of this drug. I guess that is it.

DR. WOOD: Dr. Cannon?

DR. CANNON: I am in favor of a black-box warning, a warning of increasing cardiovascular risk that is dose- and duration- dependent. I am also in agreement no DTC. I think a medication guide for patients is fine. I don't think this drug, though, should be prohibited for use in patients who have cardiovascular risk factors. I don't think we have the data to say that they are at particularly higher risk than those without risk factors. I would say something that hasn't been mentioned and, in my view, should be included and that is, for those patients who do have cardiovascular risk factors, that the concomitant use of aspirin will likely not reduce the risk that may be imparted by the use of Celebrex and that, in fact, it may negate the G.I. benefit of the drug.

DR. WOOD: Dr. Shapiro?

DR. SHAPIRO: I, too, favor a black-box warning; no direct-to-consumer; a patient guide; and prescribing restrictions that would assure lowest possible dose; and, also, second-line not in the sense that something else would have had to have been tried, but that the physician would have had to have considered and then discounted a non-COX alternative.

DR. WOOD: Dr. Paganini?

DR. PAGANINI: I favor a black-box. I believe that it should contain a cardiovascular warning in understandable terms. I believe that there should be a statement of probable dose and time relationship, that it should be a second-line for those with G.I. failure to other options; there should be no direct advertising and there should be developed a patient brochure.

DR. WOOD: Dr. Friedman.

DR. FRIEDMAN: I favor a bar to direct-to-consumer advertising. I favor enhanced education both for patients and, frankly, for the medical community. I favor a black-box warning mentioning the high-risk group, the problem with cardiovascular disease, the concern with the high dose. I also favor mentioning the uncertainties with regard to all of the NSAIDs. I assume that, under Question 5, we will discuss additional research activity which I see as absolutely essential.

DR. WOOD: Charlie?

DR. HENNEKENS: I would want all healthcare providers and patients to be aware that coxibs increase

cardiovascular risk by about 40 percent. I would want them also to know that, in the comparator trials, naproxen compares favorably to all the coxibs. I would also want them to know that the short-acting NSAIDs appear to be at least as hazardous as the coxibs. I would want basically that all arthritis patients and all other patients treated with coxibs or the short-acting NSAIDs, especially, as well as naproxen, should have their global cardiovascular risk assessed as the NHLBI has recommended in general, and they should have aggressive management of all their cardiovascular risks. I am not in favor of this being a second-line drug. I am not in favor of direct-to-consumer advertising. I am not actually in favor of a black-box but I am in favor of a strong warning that should be applied equally to all coxibs and all short-acting NSAIDs.

DR. WOOD: Steve?

DR. SHAFER: I believe it should be indicated for second-line therapy. I favor a black-box warning on dose- and duration-dependent cardiovascular risk. I concur with potentially removing the black-box for certain doses in comparator NSAIDs as is supported by clinical-trial data in the future. It should be contraindicated following cardiopulmonary bypass. I would actually permit DTC advertising as we have understood what that would mean with the black-box warning. I like the idea of the patient guide and I would oppose to mandatory physician and patient attestation.

DR. WOOD: Okay. Just in case you thought you had finished, let's move on to Question No. 2.

## Slide with Text of Question 1

### Question 1, 2, 3

Do the available data support a conclusion that celecoxib, rofecoxib and valdecoxib significantly increase the risk of cardiovascular events?

Does the overall risk versus benefit profile for each of these support marketing in the US? If yes, please describe the patient population(s) in which the potential benefits of celecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use.

# Attachment 1: Tables of Question 1C Recommendations Committee: Member by Category

Committee 1C Celecoxib Recommendations (Populations/Risk Management): Committee members are listed in order of voting. Recommendations are listed in order of net score.

Surname	Patient Med Guide	Black-box	Ban DTC Adverts	Warn for High Dose	Warn for High CV Risk	Warn for Long Duration	Better Explanation of Risk	Same for NSAIDs	Postmarketing studies	Allow black-box removal	Patient Consent/Attention	Exclude for High CV Risk	Exclude for High Dose	Academic detailing	Educate healthcare Professionals	Dear Healthcare Professionals Letter	OTC Restrictions	Define Class	Define Mechanism	Comprehension Survey	Assess/Manage CV Risk	Study of Med guides	ASA does not reduce risk	Combine COX-2 & Framingham data	Do ALLHAT Type Study	Contraindicate in CABG	Warn of risk of Short-acting NSAIDs	Warn of COX-2 selective NSAIDs	Mention Naproxen is safer	Exclude for Long Duration	Second-Line Drug	Other							
Abramson																		1	1															1					
Nissen	1	1	1																																				
Elashoff																																							
Gardner	1		1		1																																		
Platt		1					1		1																										1		1		
Day	1	1	-1								1										1																		
Eurberg		1	1								1	1	1																										
Fleming	1	1	1	1	1	1																																	
Domanski	1	1																																			1		
Boulyware				1				1																															
Dworkin		-1			1																																		
Hoffman	1	1	1										1																										
Manzi	1	1		1		1																																	
Farrar	1	1	1																																				
Holmboe	1	1						1							1								1																
Gross			-1	1				1			1																												
Wood	1	1	1				1			1		1																											
Gibovsky	1	-1		1									-1	-1																									
Crawford		1	1							1	1																												
Cush		-1	-1						1																														
Bathon		-1	1		1																																		
Malone	1	-1	1	1	1		1				1					1																							
Levin	1	1									1	1			1																								
Ilowite	1	1	1	1		1						1																											
D'Agostino			1	1																					1														
Morris	-1	1	-1						1	1								1																					
Canon	1	1	1	1		1							-1																										
Shapiro	1	1	1											1																									
Paganini	1	1	1	1		1	1																																
Eriedman		1	1	1	1		1	1	1																														
Hennekens		-1	1																																				
Shafer	1	1	-1	1		1				1	-1	1																											
Yes	18	22	17	11	6	6	6	5	5	4	5	4	3	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
No	1	6	5	0	0	0	0	0	0	0	1	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
No Comment	13	4	10	21	26	26	26	27	27	28	26	26	28	30	30	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	31	
Net Score	17	16	12	11	6	6	6	5	5	4	4	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Rank by Net S	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	-	-	-	-	-	-		

**Committee Voting (in order of members voting) For Question 1C: POPULATIONS & RISK-MANAGEMENT WITH CELEBREX**

Surname	1st Name	Expertise*	Member Comments
Abramson	Steven	Rheumatology	COX-2 selectivity
Nissen	Steven	Cardiology	Dr. Nissen: 1) Black-box with dose-dependent risk. 2) No DTC advertising. 3) Patient medication guide.
Elashoff	Janet	Statistics	Dr. Elashoff: No additional comments.
Gardner	Jacqueline	DSRMAC (Epidem.)	Dr. Gardner: 1) No DTC advertising. 2) Patient medication guide. 3) Warnings appropriate to risk group.
Platt	Richard	DSRMAC (Epidem.)	Dr. Platt: 1) Black-box. 2) Substantially upgraded postmarketing surveillance program. 3) Second-line drug (with specific mention of naproxen as preferred alternative). 4) Patient consent/attestation. 5) Describe risk in terms of "relatively easily
Day	Ruth	DSRMAC (Psychol.)	Dr. Day: 1) Black-box with wording specific to each drug with Celebrex getting the "minimum". 2) Patient medication guide. 3) "Dear Healthcare Professional" letter. 4) Don't suspend DTC advertising if risk/benefit balance can be achieved. 5)
Furberg	Curt	Epidemiology	Dr. Furberg: 1) Black-box. 2) Contraindication for high dose. 2) Contraindication with known coronary heart disease, stroke, and "patients at increased risk". 3) Patient consent/attestation. 4) No DTC advertising.
Fleming	Thomas	Statistics	Dr. Fleming: 1) Black-box. 2) Caution with high cardiovascular risk, high dose and long duration. 3) No DTC advertising. 4)
Domanski	Michael	NIH Research	Dr. Domanski: 1) Black-box. 2) Patient medication guide. 3) Second-line drug.
Boulware	Dennis	Rheumatology	Dr. Boulware: 1) Black-box mentioning risk at dosage over 400 mg/day but stating lack of similar information for other
Dworkin	Robert	Anesthesiology	Dr. Dworkin: 1) No black-box (unless given to all NSAIDs). 2) Detailed and comprehensive cardiovascular warning.
Hoffman	Gary	Rheumatology	Dr. Hoffman: 1) Black-box (restricting dosage to 200 mg/day but not restricting duration). 2) No DTC advertising. 3) Patient
Manzi	Susan	Rheumatology	Dr. Manzi: 1) Black-box stating the cardiovascular risk found at high dosage for long duration but "don't directly advocate low doses for short duration". 2) Patient medication guide. 3) Do not restrict it to being a second-line drug.
Farrar	John	Statistics	Dr. Farrar: 1) Black-box. 2) No DTC advertising. 3) Patient medication guide.
Holmboe	Eric	DSRMAC	Dr. Holmboe: 1) Black-box if NSAIDs also get warning. 2) Patient medication guide. 3) FDA study of patient medication guides for "literacy" and "numeracy". 4) Academic detailing.
Gross	Peter	DSRMAC	Dr. Gross: 1) Warning regarding "dose-dependent toxicity" provided similar warning for "all coxibs and nonselective NSAIDs". 2) Patient medication guide. 3) Patient consent/attestation for higher doses. 4) Don't ban DTC advertising if there is also "FDA-approved education on the putative risks". 5) Do not restrict it to being a second-line drug.
Wood	Alastair	Pharmacology	Dr. Wood: 1) Black-box. 2) Exclude people at risk for cardiovascular disease (known CV disease, elderly with high risk factors, others). 3) Ban DTC advertising. 4) Patient medication guide. 5) Describe risk in a way that related to risks in regular daily life. 6) Allow removal of black-box if well-designed trials establish that a drug, or a dose, or a particular group does not
Gibovsky	Alan	Rheumatology	Dr. Gibovsky: 1) No black-box. 2) Patient medication guide. 3) Do not restrict it to being a second-line drug. 4) Populations should be as presently indicated in the label. 5) Use at lowest effective dose.
Crawford	Stephanie	DSRMAC (Pharmacy)	Dr. Crawford: 1) Black-box. 2) Need postmarketing studies. 3) Ban DTC advertising (if not possible, ensure adequate communication of risk). 4) Allow removal of black-box if justified by well-designed trials.
Cush	John	Rheumatology	Dr. Cush: 1) No black-box. 2) General warning with strategy for risk reduction. 3) Don't ban DTC advertising if the major statement significantly outlines this cardiovascular risk. 4) Do further postmarketing studies.
Bathon	Joan	Rheumatology	Dr. Bathon: 1) No black-box. 2) Warn on cardiovascular risk. 3) Ban DTC advertising.
Malone	Leona	Patient Representative	Ms. Malone: 1) No black-box. 2) Warning on cardiovascular risk and dose-dependency. 3) Limit on DTC advertising. 4) Do not restrict it to being a second-line drug (will make insurance companies say, "you have to try these other drugs first"). 5) Patient treatment guide that is understandable and easily accessible. 6) Very good education for doctors to permit the
Levin	Arthur	DSRMAC (Consumer)	Mr. Levin: 1) Black-box. 2) Patient medication guide. 3) Patient consent/attestation. 4) Convey risk and benefit in ways that are meaningful to consumers. 5) Academic detailing. 6) Do further postmarketing studies. 7) Allow removal of black-box if justified by well-designed trials. 8) Suspend it for now until DTC advertising "can tell the truthful story about drugs".
Ilowite	Norman	Rheumatology	Dr. Ilowite: 1) Black-box. 2) Warning on increased risk with high dose and long duration. 3) "Relatively contraindicated" with high CV risk. 4) Do not restrict it to being a second-line drug. 5) Ban DTC advertising. 6) Patient medication guide. 7)
D'Agostino	Ralph	Statistics	Dr. D'Agostino: 1) Black-box. 2) Ban DTC advertising. 3) Do further evaluation of cardiovascular risk from available data (e.g. COX-2 clinical trial data and Framingham data combined).
Morris	Louis	DSRMAC	Dr. Morris: 1) Black-box provided there is the "broadest definition of class" with every drug in the class getting a black-box warning. 2) Black-boxes can vary between drugs in the class but include a statement about the class and "about what is not known as well as what is known". 3) Don't ban DTC advertising but restructure it. 4) Do further postmarketing studies. 5) Do
Cannon	Richard	NIH Research	Dr. Cannon: 1) Black-box. 2) Warning about risk being dose- and duration- dependent. 3) Ban DTC advertising. 4) Patient medication guide. 5) Don't prohibit use in patients with CV risk factors. 6) Say that concomitant aspirin will "likely" not
Shapiro	Robyn	DSRMAC (Ethicist)	Dr. Shapiro: 1) Black-box. 2) Ban DTC advertising. 3) Patient medication guide. 4) Restriction to "lowest possible dose". 5) Second-line drug "in the sense that something else would have had to have been tried, but that the physician would have had
Paganini	Emil	Nephrologist	Dr. Paganini: 1) Black-box. 2) Need to convey warning in "understandable terms". 3) Warn of "probable dose and time relationship". 4) Second-line drug. 5) Ban DTC advertising. 6) Patient medication guide.
Friedman	Lawrence	NIH Research	Dr. Friedman: 1) Black-box. 2) Warn of use in patients at high CV risk and with high dose. 3) Warn of uncertainties for all the NSAIDs. 4) Ban DTC advertising. 5) Enhance education for patients and the medical community. 6) Do further
Hennekens	Charles	Epidemiology	Dr. Hennekens: 1) No black-box but have strong warning for all coxibs and all short-acting NSAIDs. 2) Inform healthcare providers and patients that a) coxibs increase CV risk about 40%, b) "in the comparator trials, naproxen compares favorably to all the coxibs" and c) "short-acting NSAIDs appear to be at least as hazardous as the coxibs". 3) Assess cardiovascular risk in all arthritis patients or other NSAID candidates and aggressively manage cardiovascular risks. 4) Do not restrict it to
Shafer	Steven	Anesthesiology	Dr. Shafer: 1) Black-box. 2) Warn of dose- and duration- dependent CV risk. 3) Allow removal of black-box "for certain doses" if justified by well-designed trials. 4) Contraindicate following cardiopulmonary bypass. 5) Don't ban DTC