

HIGHLIGHTS

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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This report was prepared by TMT (Taylor MicroTechnology, Inc.). Additional materials on the COX-2 meeting are available at TMT’s website (www.masterdocs.com/cox-2.htm).

Welcome (FDA): Steven Galson MD

- **FOREIGN REGULATORY AUTHORITIES PRESENT:** Special guests included “representatives from the drug regulatory authorities of the member countries of the European Union and six separate countries--Canada, Japan, Singapore, Australia, Switzerland and Mexico”.
- **ANXIOUS TO HEAR ALL POINTS OF VIEW:** “I want to emphasize that we are anxious to hear all points of views from the advisory committee and, of course, from agency staff. It goes without saying that all FDA staff are free to make any presentation without fear of any retaliation.”
- **COMMITTEE MEMBERS SCREENED FOR CONFLICT OF INTEREST:** “I want to remind the public that all members of this committee have been carefully screened for conflicts of interest and we have used the same standards in this process that we have used for other committees and similar meetings.”
- **CHANGING INFORMATION ENVIRONMENT:** “You will be assessing the risk/benefit balance of these products this week in the midst of a changing information environment.....”. “We are aware of at least a half dozen ongoing meta-analyses and huge population-based studies, in addition to several of the studies you will hear about this week for which data analysis continues as we speak.”
- **CAUTION IN INTERPRETING PRELIMINARY, NON-PEER-REVIEWED DATA:** “We must be very cautious about interpreting data for regulatory decision-making that has not been thoroughly vetted and peer reviewed, and even more cautious about interpreting data of preliminary studies that are not even complete.” “As scientists, we have all seen examples of ongoing studies whose findings have changed as analysis is in the final stages, or examples where inadvertent errors have led to misclassification in epidemiologic studies, or when data that comes in at the end of the data gathering stage influences results.”

Regulatory History (FDA): Jonca Bull, MD

- **1986:** Public Advisory Committee Meeting: Discussed GI Paragraph & databases.
- **1994:** Celebrex IND.
- **1995:** Revisions to NSAID class label.
- **1998:** Advisory Committee Meeting to discuss “new science of the COX-2s”.
- **DECEMBER 1998:** Celebrex NDA approval.
- **MAY 1999:** Vioxx NDA approval.

- **2001:** Advisory Committee Meeting to discuss relevance of endoscopic studies.
- **NOTHING IS RISK FREE:** No improvements in drug development can completely eliminate the risk of unexpected events”.
- **QUESTIONS ON COX-2S:**
 - In what ways are they different from traditional NSAIDs in GI, CV, renal, hepatic, allergy risk?
 - What additional science is needed?
- What risk management options are appropriate?
- What is the impact of “aggressive marketing”?
- **PRESENTATION SCHEDULE:** Dr. Cryer and Fitzgerald; Vioxx; Celebrex; NIH polyp; Bextra/parecoxib; naproxen; observational studies; ADAPT trial; Dr. Packer, Dr. Temple, Dr O’Neill and Dr. Hertz; Questions to Committee members.

Gastrointestinal Effects of NSAIDs and COX-2 Specific Inhibitors: Byron Cryer MD

- **MAIN GI COMPLICATIONS:** The main upper GI effects of NSAIDs are clinically significant ulceration (~2% with NSAIDs), bleeding, perforation & obstruction. These are associated with considerable morbidity, mortality and cost.
- **LOWER & UPPER GI EFFECTS:** NSAIDs may cause lower GI as well as upper GI adverse effects.
- **ENDOSCOPIC RESULTS VS. GI COMPLICATIONS:** Endoscopic ulcerations “are predictive of what one might expect to see in outcome trials” and “we have come full circle in our understanding”.
- **GI RISK FACTORS:** Risk factors for adverse GI effects of NSAIDs include age, history of GI complication, concomitant corticosteroids or anticoagulants, cardiovascular disease, multiple NSAIDs, high NSAID dosage.
- **GASTROPROTECTIVE DRUGS:** Concomitant misoprostol or proton pump inhibitor therapy reduces GI effects of non-selective NSAIDs, making them comparable to COX-2 inhibitors in GI safety.
- **GI EFFECTS OF ASPIRIN:** Concomitant low dose aspirin therapy increases the risk of endoscopic ulceration and of clinical GI events from NSAIDs.
- **ENTERIC COATING/BUFFERING:** Enteric coating or buffering does not reduce GI effects of NSAIDs.
- **LESS GI TOXICITY WITH COX-2 INHIBITION:** COX-2 inhibitors have shown less GI adverse effects than non-selective NSAIDs in some but not all trials, and may be a

function of the non-selective NSAID comparator. Some traditional NSAIDs such as non-acetylated salicylates, nabumetone, diclofenac and etodolac may have less GI toxicity and this could be related to moderate COX-2 selectivity.

- **GI PROTECTION IS NOT ADEQUATE WITH COX-2**

INHIBITOR + ASPIRIN: From a GI perspective, “COX-2 specific inhibitor plus aspirin equals the effects of a non-selective traditional NSAID”. But neither approach gives adequate gastroprotection in high risk patients.

Discussion Cryer Paper – GI Toxicity

- **TWO-THIRDS REDUCTION IN GI ULCER COMPLICATIONS SINCE 1990:** Dr. Woods (Chairman) pointed out that Dr. Cryer showed a slide illustrating high GI ulcer complication rates through 1990, but that Dr. Fries had published data through the year 2000 showing that ulcer complications have been reduced by two-thirds since 1990, and that this decrease preceded the introduction of COX-2 inhibitors. Dr. Cryer agreed.
- **CLASS STUDY REDUCED GI COMPLICATIONS AT 6 MONTHS BUT NOT 1 YEAR:** Dr. Woods also pointed out the apparent loss of GI protection of celecoxib 400 mg bid v. diclofenac by one year of therapy in the CLASS study. Dr. Cryer agreed. Dr. Cush asked a subsequent question on this issue and Dr. Cryer said that “there does appear to be a plateauing” in event reduction which could be related to early dropout of the most vulnerable patients. Dr. Fleming pointed out that in the CLASS trial celecoxib after 6 months reduced GI complications in non-aspirin patients

(by two-thirds) but not in patients on aspirin (aspirin therapy not being randomized but given if clinically indicated); however, at one year this effect in non-aspirin patients had disappeared, suggesting that the GI complications are delayed but not prevented in this subset. Again, Dr. Cryer said that “susceptible people” are removed from the study early. Dr. Cryer was asked about the choice of diclofenac as the celecoxib comparator, as diclofenac appears moderately COX-2 selective. Dr. Cryer said that studies have been completed but not yet published showing that celecoxib and naproxen plus a proton pump inhibitor (PPI) have similar GI effects.

- **PREDICTORS OF HIGH RISK OF GI COMPLICATIONS:** Dr. Cryer said that the most important risk factor was a history of a previous GI bleed, and that PPI therapy did not reduce this risk in NSAID users. Next in importance was anticoagulant therapy such as warfarin. Age was also an important risk factor but the effect was “variable”; risk increases about 2%

per age decade so that most patients in their 80s are at increased risk. The more risk factors a patient has, the higher the risk. Dr. Cryer did not provide definitions for “low”, “medium” and “high” risk but said that about 20-25% of patients are at elevated GI risk and suitable candidates for COX-2 inhibitors.

- **MORBIDITY/MORTALITY ASSOCIATED WITH GI COMPLICATIONS:** Dr. Cryer was asked how dangerous NSAID-induced GI complications were. He replied that a significant GI bleed requires hospitalization and can be fatal. However, most “are reversible”.
- **INITIAL HIGH GI RISK MAY BE REDUCED OVER TIME:** Dr. Cryer was asked if patients considered at high GI risk who show no GI complications by 1 year can be considered no longer at high risk. Dr. Cryer replied that the data were not consistent but that the highest risk occurred in the first 3 months.
- **COXIB GI COMPLICATIONS VS. NON-SELECTIVE NSAIDS WITH LOW-DOSE ASPIRIN:** Dr. Nissen (cardiologist) said that he routinely gives low dose aspirin to

patients at elevated cardiac risk and asked if COX-2s were GI protective in this setting. Dr. Cryer said that the data were not clear but that GI events in this population were too high for us to be “comfortable”.

- **NSAID DYSPEPSIA:** In response to a question, Dr. Cryer said that NSAID dyspepsia was common (10-30%, depending on the definition) and that dyspepsia was not correlated with major GI complications. Although patients could discontinue therapy because of dyspepsia, it was considered more of a “nuisance”. Trials suggested that COX-2s reduced dyspepsia vs. NSAIDs “by a few percentage points” but results were not consistent.
- **LOWER GI COMPLICATIONS:** Dr. Cryer said that a COX-2 (Vioxx vs. naproxen) reduced lower GI endoscopic erosions whereas PPIs did not. These erosions are probably not clinically significant, although chronic reduction in hemoglobin could be an important result of lower GI erosions. In population studies, about 10-20% of clinically relevant GI complications of NSAIDs were in the lower GI tract.

Mechanism Based Adverse Cardiovascular Events and Specific Inhibitors of COX-2: Garrett Fitzgerald MD

- **BASIS OF PRESENTATION: ANIMAL & EX VIVO DATA:** Most of the presentation was based on animal and ex vivo studies.
- **ARACHIDONIC ACID METABOLISM:** Arachidonic acid is metabolized by COX-1 and COX-

2 enzymes forming a number of lipids called prostaglandins.

- **BIOLOGICAL EFFECTS OF METABOLITES DEPEND ON HOW THE METABOLITES ARE GENERATED:** Prostacyclin and prostaglandin E2 (PGE2) are

prostaglandins that may be formed by either COX-1 or COX-2 enzymes. Arachidonic metabolism is “complex” and the biological effects of inhibition may depend on whether the inhibition is caused by COX-1 inhibition or COX-2 inhibition.

- Prostaglandins formed by COX-1 provide gastroprotection.
- “But it turns out that when the very same lipids” are formed by COX-2, they mediate pain and inflammation and also have cardioprotective effects such as limitation of the proliferative and platelet activation response to vascular injury.
- **BOTH COX-2 SELECTIVE INHIBITORS AND MIXED INHIBITORS INHIBIT PROSTACYCLIN:** Prostacyclin formation is inhibited to a similar degree by “COX-2 inhibitors” and “mixed inhibitors” such as ibuprofen and indomethacin.
- **THROMBOXANE:** Prostaglandins formed by the COX-1 enzyme include thromboxane which enhances platelet aggregation and increases the proliferative and platelet activation response to vascular injury. Prostaglandins formed by the COX-2 enzyme (which do not include thromboxane) do not enhance platelet aggregation.
- **COX-1 INHIBITION/PLATELET EFFECT RELATIONSHIP NON-LINEAR:** The “relationship between inhibition of the capacity of platelets to make COX-1 derived thromboxane and inhibition of thromboxane-dependent” platelet aggregation is “very non-linear”. It

requires about 98% “inhibition of capacity” to “get into the red zone for inhibition of platelet function” but the relationship between the degree of prostacyclin inhibition and the loss of “protective cardiovascular function” is not known. Inhibition by at least 98% of the capacity to “make COX-1 derived thromboxane by platelets” results in “rescue from arachidonic acid induced thrombosis or, indeed, the time to complete occlusion induced by the thrombogenic stimulus”.

- **HAZARD GREATEST WITH HEMOSTATIC ACTIVATION:** The clinical finding that a cardiovascular hazard with a COX-2 inhibitor was detected “faster and in a smaller study” in a setting of “hemostatic activation” (CABG surgery) “is perhaps unsurprising”. “Suppression of prostacyclin does not cause spontaneous thrombosis but augments the response to thrombogenic stimuli in vivo. So, the hazard from coxibs would be expected to be particularly evident in those otherwise predisposed to thrombosis and we have evidence that this hazard is modulated by inhibition of COX-1 in the appropriate zone.”
- **SAME MECHANISM FOR HYPERTENSION FROM NON-SELECTIVE NSAIDS AND COX-2 INHIBITORS:** Hypertension from traditional NSAIDs and COX-2 inhibitors results “from the same mechanism” and “Hypertension on NSAIDs would be expected to relate to the inhibition of COX-2 and the selectivity with which it is attained.”
- **COX-2 IMPACT ON ATHEROSCLEROTIC PLAQUE AND PLAQUE STABILITY? A**

“buffering capacity between COX-1 and COX-2” affects development of atherosclerosis, and an apparent interaction with estrogen “raises a whole new set of questions about the use of these drugs in premenopausal women.” Such an effect could be enhanced by drug-induced hypertension. In mice, combining a thromboxane antagonist with a COX-2 inhibitor results in loss of the fibrous cap of an atherosclerotic plaque “consistent with destabilization of the plaque”.

- **ASPIRIN WILL DAMP BUT NOT ABOLISH COX-2 INDUCED CARDIOVASCULAR HAZARD:** Aspirin “acts as a general constraint on any agonist that acts harmfully on these systems. So, one would expect aspirin, in a perfect world, to damp rather than abolish the signal.” Aspirin “leads to complete and sustained inhibition of COX-1” as well as some inhibition of prostacyclin even at low dosage.
- **NON-SELECTIVE NSAIDs LESS CARDIOPROTECTIVE THAN ASPIRIN BECAUSE OF LOSS OF COX-1 INHIBITION AT END OF DOSING INTERVAL:** Traditional NSAIDs may act like “dilute aspirin” because adequate COX-1 inhibition is not maintained throughout the dosing interval.
- **SLIGHT COX-1 INHIBITION WITH COX-2 INHIBITORS DOES NOT AFFECT PLATELET FUNCTION:** COX-2 inhibitors reversibly inhibit COX-2. They cause some COX-1 inhibition but not the degree that causes “inhibition of COX-1 dependent platelet function” so that “effectively this makes these drugs selective for COX-2”. By COX-1 and COX-2 IC-50s in whole

human blood, “celecoxib and diclofenac look remarkably similar” and “diclofenac is probably a selective COX-2 inhibitor like Celebrex” and “we can start thinking of diclofenac as Celebrex with hepatic side effects.”

- **NON-SELECTIVE NSAIDs CAN BLOCK EFFECTS OF ASPIRIN:** A non-selective NSAID such as ibuprofen blocks “access of aspirin to its target acetylation site” because of “prior occupancy of the COX-1 site” and “may undermine the benefit from aspirin”. This does not occur with a selective COX-2 inhibitor such as diclofenac.
- **GASTROPROTECTION AND CARDIOVASCULAR TOXICITY GO HAND IN HAND:** The level of COX-2 inhibition results in “superimposition” of gastroprotection and increased cardiovascular risk.
- **LOOK AT NON-SELECTIVE NSAIDs INDIVIDUALLY:** To group together all “non-naproxen NSAIDs, which is really diclofenac plus ibuprofen” is not “legitimate lumping.” There is “some suggestion that naproxen achieves sustained platelet inhibition in some individuals.”
- **DISMISS DEAD DRAGONS:** Some “dead dragons” that are “worth dismissing” are:
 - Naproxen is not the full explanation of VIGOR.
 - Hypertension is not a different mechanism.
 - The “strange chemical interactions” currently “touted” to explain a drug-related effect are “off-target fantasies”.

- Avoiding hazard in an individual patient is not “just a matter of reducing the dose” (for the population) since “we all have our own dose-response curves”.
- COX-2 inhibitor trials in acute coronary syndrome or in other patients at high cardiovascular risk are “ethically questionable”.
- **WHERE TO GO FROM HERE:**
 - Strategies to identify patients at high risk of thrombosis, for example by measuring prostacyclin excretion, ex vivo COX-1 or COX-2 inhibition, or genetic polymorphisms.
 - Don’t be misled by the “simple message” of “dose reduction”.
 - Subject new and marketed COX-2 drugs to “significant hurdles”.
 - Restrict the duration of dosing for COX-2 drugs until safety has been established.
 - Restrict use of COX-2 drugs to those at higher GI risk.
 - Identify “risk transformation” as a function of duration of therapy.

Committee Questions to Dr. Fitzgerald

IS LOW-DOSE ASPIRIN CARDIOPROTECTIVE IN COXIB SETTING?

- **URNS COXIB INTO NON-SELECTIVE NSAID?** Dr. Schafer (and several others over the course of the meeting) asked why addition of 100% COX-1 inhibition with low dose aspirin does not seem to prevent the cardiovascular toxicity of Vioxx – by turning it into a non-selective NSAID.
- **IMPACT OF LONG-LASTING ASPIRIN PLATELET EFFECT:** Dr. Fitzgerald, on this occasion and on other later occasions, did not give an answer that appeared satisfactory to all the Committee members. On this occasion, Dr. Fitzgerald said this was a function of time and that the long-lasting effects of aspirin meant that aspirin plus a COX-2 inhibitor would have longer-lasting COX-1 inhibition than a non-selective NSAID like ibuprofen plus a COX-2 inhibitor. Dr. Schafer said that this “cut in the opposite direction” because the long-lasting COX-1 selectivity of aspirin should give long-lasting protection against the adverse effects of COX-2 inhibition.
- **NOT “YING & YANG”:** Dr. Fitzgerald said that this was not a “Ying and Yang” situation and that “a priori one would expect that aspirin would damp rather than abolish the signal” and that the number of events on aspirin is “so vanishingly small that it is really conjecture”. In later discussion, he seemed to imply that prostacyclin has wide-ranging effects, not all of which are antagonized by thromboxane; thus the adverse effects of COX-2-inhibitor-induced

inhibition of prostacyclin would not be fully counteracted by simultaneous COX-1 inhibition of thromboxane.

- **DOES COX-2 INHIBITION BY NON-SELECTIVE NSAIDs IMPLY THEY WILL BE CARDIOTOXIC?** Others later in the meeting suggested that this explanation would imply that non-selective NSAIDs should share the

OTHER:

- **ARE NON-SELECTIVE NSAIDs SAFE FOR HEART?** Dr. Wood asked if non-selective NSAIDs are safe for the heart; Dr. Fitzgerald implied that he considered this to be the case.
- **UNCLEAR WHICH DRUGS ARE COX-2 SELECTIVE:** Dr. Abramson pointed out that, based on in vitro studies, COX-2 selectivity was a continuum and that there was a “cluster of 5 or 6 drugs” such as diclofenac, celecoxib, miloxicam and etodolac that are “comparably COX-2 selective” and a “complex story of what one might call functional COX-2 selectivity” because of “transient COX-1 inhibition” in the face of prolonged COX-2 inhibition. Dr. Fitzgerald responded by saying that individuals vary in the amount of COX-2 selectivity and that “the class is the mechanism by which the selective inhibition of COX-2 is attained”. He did not state which drugs should be considered COX-2 selective.
- **DOSE-RESPONSE: INDIVIDUAL OR POPULATION FEATURE?** Dr. Nissen asked Dr. Fitzgerald to clarify that what he was saying was that there was sufficient

cardiovascular toxicity demonstrated with the "COX-2 inhibitors".

- **IS IT PROSTACYCLIN OR COX-2 EXPRESSION WITH WIDE-RANGING EFFECTS?** Pfizer, in a subsequent presentation, seemed to imply not that prostacyclin has wide-ranging effects, but that COX-2 expression has wide-ranging effects, not all of which are mediated by prostacyclin.

dose overlap so that a low dose in one patient could be a high dose in another, but that he was not suggesting that the higher dose of a drug was not associated on a population basis with more cardiovascular toxicity. Dr. Fitzgerald did not respond directly but agreed that there was “a dose-related effect for populations”.

- **ARE BP DIFFERENCES BETWEEN COXIBS COX-2-DEPENDENT?** Dr. Nissen also asked if Dr. Fitzgerald was suggesting that the “striking” differences between celecoxib and rofecoxib seen in blood pressure effect were related to COX-2 selectivity. Dr. Fitzgerald said that with the available data selectivity and duration of action are confounded and you can’t differentiate between the two. However, studies should be done to standardize the COX-2 selectivity seen and then see if blood pressure effects are purely a function of selectivity.
- **IDENTIFICATION OF PATIENTS AT HIGH-RISK FROM COX-2s:** Dr. Wood, Dr. D’Agostino and others asked how

one could determine which patients should avoid COX-2 inhibitors. Dr. Bathon asked if the higher cardiovascular risk in patients with rheumatoid arthritis could be attributable to the high dosage of NSAIDs required to treat this condition. Dr. Fitzgerald did not have definitive answers.

- **STANDARDS FOR NON-COXIB COX-2 SELECTIVE DRUGS:** Dr. Cryer asked if diclofenac-like drugs with similar COX-2 selectivity to celecoxib (he recalled that Dr. Fitzgerald had called diclofenac “celecoxib with hepatic side effects”) should meet the same safety testing

standards. Dr. Fitzgerald said that this was one of the unanswered questions and that the same question applies to other drugs such as meloxicam.

- **EXTRAPOLATION BETWEEN DISEASES:** Dr. Gibovsky suggested that it was difficult to extrapolate from one disease to another.
- **COMPARE COX-2 INHIBITION IN PATIENTS WITH AND WITHOUT CV EVENT:** Dr. Manzi suggested that it might be useful to compare the level of COX-2 inhibition in patients with and without cardiovascular events.

Sponsor Presentation (Merck): Vioxx (Rofecoxib)

Introduction: Peter Kim MD

- **3-STUDY CV SAFETY PLAN:** After cardiovascular safety concerns with Vioxx emerged, Merck deliberated with its outside advisers and developed in discussions with FDA a plan to evaluate cardiovascular safety in three large placebo-controlled trials.
- **VIOXX 2004 WITHDRAWAL:** Following preliminary data from one of these trials, Merck voluntarily withdrew Vioxx.
- **WITHDRAWAL COULD BE RE-EVALUATED:** The decision to withdraw Vioxx was based on “the science available at that time”. However, since that time, “new cardiovascular safety data for other COX-2 inhibitors have become available” and will be discussed and interpreted at this meeting.

Rofecoxib Safety: Ned Braunstein MD (Merck)

- **CENTRAL QUESTION:** The “central question of this meeting” is how big is the class of NSAIDs that increases thrombotic cardiovascular risk? Because of limited data with traditional NSAIDs, this question cannot be currently answered.

- **ALL NSAIDs INHIBIT COX-2:** All NSAIDs cause dose-dependent inhibition of COX-2, and no COX-2 inhibitors “inhibit COX-1 at clinical doses”.
- **ROFECOXIB CONSISTENTLY GASTROPROTECTIVE:** With rofecoxib “reduction in clinical upper GI events is consistently seen with rofecoxib versus diclofenac, ibuprofen and naproxen”.
- **INCREASED CV RISK VERSUS NAPROXEN BUT NOT OTHER NSAIDs:** Rofecoxib has shown an increase in cardiovascular events versus naproxen (rofecoxib 50 mg QD versus naproxen 500 mg BID in the VIGOR rheumatoid arthritis trial) and placebo (rofecoxib 25 mg QD in the APPROVe colorectal polyp trial) but not versus other NSAIDs.
- **ALZHEIMER & OA DATA EXCLUDE 2-FOLD INCREASE IN CV RISK:** Pooled analyses of Alzheimer’s Disease trials and osteoarthritis trials were sufficiently powerful to exclude the 2-fold increased cardiovascular risk seen in VIGOR.
- **BASIS FOR STOPPING APPROVe TRIAL:** The APPROVe trial was prematurely discontinued by the safety monitoring committee because of increased cardiovascular risk, even though the original plan had been to determine cardiovascular safety on the basis of pooled analyses of the APPROVe, VICTOR and ViP trials.
- **LUMIRACOXIB ALSO HAS SIMILAR CV RISK TO TRADITIONAL NSAIDs BUT HIGHER RISK WITH NAPROXEN:** The TARGET study with lumiracoxib showed results similar to those with rofecoxib, with a thrombotic cardiovascular event rate similar to that with a traditional NSAID (ibuprofen) but higher than that with naproxen.
- **POST HOC ANALYSES:** Merck performed numerous post hoc exploratory analyses to identify factors associated with increased cardiovascular risk.
 - **CV DISEASE & DIABETES:** Two factors (history of atherosclerotic cardiovascular disease and history of diabetes) approached statistical significance ($.05 < p < .10$).
 - **BP INCREASE:** Average blood pressure statistically significantly rose (by 4/2 mmHg). Of the multiple BP analyses performed, only a rise in systolic BP to 160 mmHg showed a statistically significant relationship with increased cardiovascular event rates; however, this finding was not confirmed in similar analysis of other datasets such as VIGOR and the pooled placebo-controlled data.
 - **RISK AFTER 18 MONTHS:** The APPROVe trial suggests that relative risk increases after 18 months of therapy.
 - **DATA INSUFFICIENT TO ADDRESS DOSE-RESPONSE FOR CV EFFECT:** “With regard to dose, our data cannot definitively address this.”
- **ROFECOXIB REDUCES COLON POLYP RECURRENCE:** The final APPROVe analysis showed that rofecoxib was associated with a highly statistically

significant 24% reduction in the risk of colon polyp recurrence.

- **PLANNED META-ANALYSIS:** No definitive conclusions are yet available from the previously-planned pooled analysis of APPROVe, VICTOR and ViP.
- **MORTALITY DATA:** All-cause mortality rates were generally similar between rofecoxib and comparators in the multiple datasets examined. Rofecoxib had a significantly lower death rate than the active comparator in the osteoarthritis Phase IIb/III database. In the Alzheimer Disease dataset there was a statistically significant increase in mortality with

rofecoxib versus placebo, with increases in deaths due to thrombotic cardiovascular events but also increases in deaths due to non-cardiovascular causes.

- **COX-2 CLASS EFFECT:** The available data “strongly suggest an effect of COX-2 inhibition on increasing cardiovascular risk”. “If the committee agrees that this is a class effect, the next critical question will be determining the size of the class” (for example, determining if ibuprofen and diclofenac are members of the class).

FDA Presentation: Vioxx (Rofecoxib): Lourdes Villalba MD

- **GOAL OF PRESENTATION:** To show that FDA was not “sleeping behind the wheel”.
- **DATA DIFFICULT TO INTERPRET:** There was an “enormous amount of data” on rofecoxib that “was not always that clear to interpret”.
- **ENDPOINTS:** FDA routinely looks at all cardiovascular adverse events, including SAE and those causing discontinuation. Merck used a blinded adjudication committee and determined if cardiovascular events met an APTC definition. FDA used some additional cardiovascular classification systems.
- **CV SAFETY AT TIME OF NDA APPROVAL:** At the time of NDA approval cardiovascular safety appeared to be “between ibuprofen and diclofenac”, except that for hypertension “there was a very clear

dose response with the 50 mg being greater than the 12.5 and 25.”

- **BASIS FOR INCREASED CARDIOVASCULAR HAZARD:** After the increased cardiovascular hazard was found with rofecoxib versus naproxen, Merck took the position that “this was the cardioprotective effect of naproxen. However, we did state clearly at the advisory committee back in 2001 that we were very skeptical about that interpretation...”
- **PLANNED META-ANALYSIS OF THREE LONG TERM STUDIES:** Merck proposed that the cardiovascular issue be addressed by a meta-analysis of three long term studies (one ongoing at the time) that would provide a 25,000 patient placebo-controlled database. FDA “agreed with the concept of pooling these studies” and “there were a lot

of discussions regarding the data analysis plan for these pooled analyses.” Prior to this meta-analysis being done, the APPROVe study was prematurely discontinued and rofecoxib was withdrawn from the market.

- **OBSERVATIONAL STUDIES:** For “epidemiologic studies in general” results were conflicting. “What was consistent was that there was increased cardiovascular/thrombotic risk for Vioxx 50 and that was in the label already..... There was no clear evidence with the 12.5 and 25 mg dose.”
- **IMPACT OF ASPIRIN ON RELATIVE RISK:** For APTC endpoints, “the difference in cardiovascular and thrombotic events or in APTC events is driven by the

non-aspirin users. In the aspirin users the relative risk decreases, particularly because there is an increase in the patients in the comparator.”

- **IMPACT OF BLOOD PRESSURE ON RELATIVE RISK:** Relative risk was greatest in those who developed on-treatment hypertension, although increase in risk was also seen in patients who maintained “normal” BP.
- **ALL-CAUSE MORTALITY:** All-cause mortality was increased in Alzheimer’s Disease trials but not in other patient populations.

Committee Questions on Rofecoxib to Dr. Braunstein & Dr. Villalba

NEED TO PRESENT ALL SIGNIFICANT RISKS:

- **SHOW PULMONARY EDEMA DATA:** Dr. Wood said that “since the primary object of this Committee is to evaluate all the risks and benefits that these drugs can produce” he was “very surprised” not to see the Kaplan-Meier curve for pulmonary edema from the APPROVe study. Dr. Nissen added that “heart failure and pulmonary edema would be helpful”. Dr. Braunstein showed the slide and said that this was a recognized NSAID side effect and was in the labeling.
- **SHOW HAZARD RATIOS OF 4.6 & P<.05 IN PRESENTATIONS:** Dr. Wood pointed out that this had a hazard ratio of 4.6 and a p value of <.004. Dr. Wood said “It’s important for the Committee, and this goes for all the speakers I think, that if there are other hazards with a hazard ratio of 4.6, that we see these as they are presented, so that we can make a cumulative estimate of what the hazards are from these drugs”.

CONCOMITANT ASPIRIN:

- **RELATIVE RISK WITH ASPIRIN ON BOARD:** Dr Schafer followed up an earlier question from Dr. Nissen and asked about the relative risk with rofecoxib when aspirin was on board. Dr. Schafer pointed out that in the APPROVe trial with aspirin on board the relative risk is 3.25 “with a confidence interval which is wide, as Dr. Fitzgerald had suggested it might be, because of small numbers” but it goes from 0.98 to 13.81. Merck interpreted the VIGOR results as based on an “aspirin-like effect” of naproxen but Dr. Schafer suggested that these APPROVe results “essentially disprove the Naprosyn hypothesis”.
- **EARLY AND LATE CV EFFECTS MAY HAVE DIFFERENT MECHANISMS:** Dr. Braunstein suggested that the mechanism for the cardiovascular effect may be different in VIGOR (where the effect occurred earlier) and APPROVe and that if one looks at the APTC endpoint “the difference actually seems to go away”.
- **ROFECOXIB WORSE THAN NAPROXEN EVEN IN ASPIRIN SUBSET: COULD BE BP EFFECT:** Dr. Temple commented

that the aspirin group was a “baseline subgroup” of about 1,000 patients and they were randomized to either rofecoxib or naproxen. With combined aspirin and rofecoxib “there is plenty of COX-1 inhibition” so that the combination represents non-selective NSAID therapy. Thus, the difference in cardiovascular hazard ratio between rofecoxib and naproxen does not seem to be explained by the COX-2 hypothesis, and he wonders if the increased risk could be related to something like a blood pressure effect which would not be prevented by aspirin. Dr. Wood pointed out that patients were not randomized to aspirin. Dr. Braunstein said their aspirin data “were not robust enough” and there were not many events (Dr. Temple interjected that there were 16).

- **IN CV EFFECT, NAPROXEN-ROFECOXIB DIFFERENCE MUCH GREATER THAN WITH ASPIRIN-PLACEBO:** Dr. Nissen pointed out that naproxen would have to be a lot better than aspirin in preventing cardiovascular events to explain the increased events on rofecoxib on the basis of a beneficial effect of naproxen – and that this seemed unlikely.

BLOOD PRESSURE:

- **BP EFFECT INSUFFICIENT TO EXPLAIN CV EFFECT?** Dr. Braunstein said that the blood pressure effects “would not appear to explain the magnitude of the cardiovascular findings”. Dr. Temple

responded that “one of the reasons to worry is that people with diabetes or heart disease are probably more susceptible to the blood pressure effect”. Dr. Nissen also expressed concern about the greater blood

pressure effect of rofecoxib compared with other coxibs.

- **MORE BP DATA PRESENTED:** Merck provided more blood pressure data on rofecoxib since they had only shown data from APPROVe (which showed the "expected" NSAID difference from placebo) (see end of this section for slides).
- **BP EFFECTS OF ROFECOXIB & CELECOXIB SIMILAR IN ONE TRIAL:** Merck described a 14-day trial in the elderly that

compared the BP effects of rofecoxib 25 mg/day and celecoxib 400 mg/day (that "at that dose have similar inhibition of COX-2") as well as naproxen 500 mg bid and placebo and showed similar mean changes in systolic and diastolic blood pressure with each NSAID that was greater than that seen with placebo.

HEART FAILURE:

- **OA DATABASE SHOWS HEART FAILURE SIMILAR WITH ROFECOXIB AND NSAIDS:** Merck showed an additional slide from their osteoarthritis database that showed that "the incidence of heart failure was low and was generally similar to ibuprofen" and also diclofenac. However, there was one epidemiology study that suggested a higher rate with rofecoxib.
- **HEART FAILURE IS AN EARLY EVENT:** Dr. Abramson asked if heart failure was an early or a late event in the study. Dr. Braunstein said that it was an early event.
- **SHOULD HEART FAILURE BE INCLUDED IN COMPOSITE CV ENDPOINT?** Following the presentation by Dr. Villalba (FDA), Dr. Furberg suggested that heart failure should be included together with myocardial infarction and stroke in evaluating "the cardiovascular signal". Dr. Villalba said that apart from an increase in heart failure with rofecoxib versus naproxen in the Vigor study, we do not have heart failure data on other NSAIDs.

MORTALITY:

- **INCREASE IN TOTAL MORTALITY:** Dr. Hennekens expressed concern about the increase in total mortality with rofecoxib in addition to the increased cardiovascular risk. Following the presentation by Dr. Villalba (FDA), Dr. Fleming pointed out that more than half of all-cause mortality occurred in the VIGOR and Alzheimer's studies which is where "we are seeing the signal". However the Advantage study "still had one more death" and the cardiovascular events were 4 to 0 in the wrong direction.

OTHER:

- **PROBLEM INTERPRETING ROFECOXIB CARDIAC SAFETY LABEL:** Dr. Wood and later Dr. Shapiro expressed concern about the wording of the rofecoxib cardiac safety label change, and how a physician was supposed to interpret it.
- **BASIS FOR ROFECOXIB WITHDRAWAL:** Dr. Crawford asked about the level of signal that made Merck decide to withdraw rofecoxib. Dr. Cush asked whether, if Merck had known that the cardiovascular risk was a “class effect” at the time the decision was made to withdraw rofecoxib, “would you have made the same decision” Dr. Braunstein said “I couldn’t go back and speculate”.
- **INCLUDE/EXCLUDE NAPROXEN FROM POOLED NSAID ANALYSIS:** Dr. Schafer asked about the justification of doing a separate analysis of rofecoxib and naproxen rather than including all comparative NSAID groups together.
- **RISK-BENEFIT:** Dr. Gibovsky asked if Merck had calculated the risk-benefit profile in colorectal polyps. Dr. Braunstein said they had not done this. Dr. Fleming asked if Merck had tried to compare the risk-benefit profile for gastrointestinal versus cardiovascular toxicity. Dr. Braunstein said no.
- **LACK OF FOLLOW-UP MIGHT UNDERESTIMATE RISK:** Dr. Fleming and Dr. D’Agostino expressed concern that the absence of follow-up beyond 2 weeks post-discontinuation might be underestimating the level of risk. Dr. Villalba (FDA) said “that is a good question for the sponsor” but that they did try to follow-up the patients.
- **PRECIPITANTS OF MI:** Dr. Cannon asked if myocardial infarction appeared to be precipitated by some intervention such as CAPG surgery. Dr. Braunstein said this did not appear to be the case.
- **ROFECOXIB INDICATED FOR JRA:** Dr. Ilowite pointed out that rofecoxib was one of the few drugs indicated for Juvenile Rheumatoid Arthritis and that without it patients had fewer options.
- **ABSOLUTE RISKS IMPORTANT AS WELL AS RELATIVE RISKS:** Dr. Platt emphasized that it was important to consider absolute risks in different populations, rather than just relative risks.
- **IS GI SAFETY CLAIM WITH ROFECOXIB RELATED TO COMPARATOR?** Dr. Cryer asked that, since rofecoxib’s unique labeling for increased GI safety was based on the VIGOR trial (which compared rofecoxib with naproxen) the GI safety difference might have been a result of the comparator selected rather than the degree of COX-2 inhibition – particularly since the rofecoxib comparisons with diclofenac did not show a clear GI safety advantage. Dr. Braunstein said that he thought rofecoxib would have been superior to diclofenac in GI safety “in an adequately powered study”.

Sponsor Presentation (Pfizer): Celebrex (Celecoxib): Introduction: Joseph Feczko MD

- **APC TRIAL:** Recent preliminary findings from the APC trial should be evaluated in the context of the “large body of prior data on Celebrex.”
- **EXTENSIVE DATABASE AND ANALYSIS:** Pfizer has been extensively studied in clinical trials and epidemiologic studies, and a large meta-analysis of Pfizer’s randomized trials database has been performed.
- **COMPARISONS BETWEEN DRUGS:** The Pfizer presentation will discuss similarities and differences between COX-2 compounds, and also similarities and differences between celecoxib and non-selective NSAIDs.

Cardiovascular Safety and the Risk/Benefit Assessment of Celecoxib: Kenneth Verburg PhD

CELECOXIB SAFE AND EFFECTIVE IN ARTHRITIS

- “Improved GI safety compared to NSAIDs”.
- “Cardiovascular safety of celecoxib is similar to NSAIDs for up to 1 year”. Beyond one year little is known for “any of these agents”.
- “Rofecoxib appears to be distinct from celecoxib and NSAIDs with respect to cardiovascular safety”.

RISK OF GI COMPLICATIONS LESS WITH CELECOXIB THAN NSAIDS

- A gastrointestinal safety meta-analysis (to be published February, 2005) evaluated 31 arthritis randomized controlled trials with over 39,000 patients and a mean exposure of 9 months. This analysis evaluated: 1) symptomatic ulcers and GI bleeding, 2) clinically significant blood loss (reduction in hemoglobin of ≥ 2 G/dl) and 3) withdrawal due to GI intolerance. Celecoxib was compared with NSAIDs (mainly naproxen, ibuprofen and diclofenac) “We see that the relative risk for any of these events, it favors celecoxib, significantly so”.
- Data from observational studies also suggested that patients on celecoxib had fewer GI complications compared with patients on non-selective NSAIDs.

CARDIOVASCULAR SAFETY

- In the CLASS trial cardiovascular safety with celecoxib was comparable to that with NSAIDs (diclofenac and ibuprofen combined).
- A cardiovascular safety meta-analysis of over 44,000 patients from 41 completed, Pfizer-sponsored, short term controlled studies did not demonstrate an increased cardiovascular risk with celecoxib. The main cardiovascular safety endpoint used was based on the APTC endpoint, a “well recognized endpoint” comprised of “non-fatal myocardial infarctions, non-fatal strokes or vascular deaths”. However, because these trials were not prospectively defined as cardiovascular safety trials, a modified APTC index was obtained from non-adjudicated, serious adverse events reported by investigators.
- The colorectal polyp studies APC and pre-SAP were scheduled for later presentation at the meeting. “Just to sum the results though, there was a significant cardiovascular risk associated with celecoxib in the APC trial and no such risk was observed with celecoxib in the pre-SAP trial”. “Use of concomitant aspirinwas nearly twice as great in the APC trial as in the pre-SAP trial”.
- Calculation of relative risk in observational studies showed an increased cardiovascular risk with rofecoxib but comparable cardiovascular risk with celecoxib and non-selective NSAIDs.

POSSIBLE MECHANISMS OF CARDIOVASCULAR TOXICITY WITH COXIBS AND NON-SELECTIVE NSAIDS

- A “unifying hypothesis” of prostacyclin/thromboxane imbalance “that would attribute increased cardiovascular risk to the coxib class only” could explain the results in the VIGOR, APPROVe and APC trials but not the results of the Pfizer meta-analysis, the observational studies, the pre-SAP trial or the ADAPT trial.
- A different unifying hypothesis is that both coxibs and non-selective NSAIDs “may not provide effective blockade of platelets, even though thromboxane production is reduced throughout their entire dosing interval.”
- “This would be more or less a unifying hypothesis across all the classes. It would unify the coxibs and the NSAIDs together if this was the case, to some degree What all those compounds have in common is that they inhibit COX-2, but by doing so, they not only inhibit the formation of prostacyclin but they also inhibit the formation of other prostaglandins that are formed by COX-2 activity and subsequent enzymatic activity”.
- Non-selective NSAIDs could act as selective COX-2 inhibitors “during a portion of their dosing cycle”.
- “Alternately, COX-2 ... in the vasculature has been linked to several cardiovascular disease states, and the up-regulation of COX-2 expression not only results in the

production of prostacyclin, which would then lead to downstream beneficial effects on endothelial function and prevention of platelet aggregation, but has also been shown to increase the production of prostaglandin E2 which again through a cascade could result in a reduction in plaque stability, ultimately. Also COX-2 could lead to the formation of thromboxane A2 which would obviously have effects opposite to prostacyclin”.

- “So, that particular scheme would suggest that the results of COX-2 inhibition might be more complicated than just focusing on prostacyclin, and also that the clinical outcomes of such effects might be more difficult to predict than we would envision.”
- “If we move this consideration of mechanism a step further and then ask the question: ‘Well if that may be the case that the coxibs and the NSAIDs are all alike, then what may account for the differences that are seen with rofecoxib as compared to the other agents in terms of cardiovascular risk?’, we should not forget in this conversation ... that

each of these compounds has unique pharmacological activity, unique pharmacokinetics, and other properties that could mitigate or worsen a cardiovascular risk profile that is embedded in a mechanism-based effect”.

- “Rofecoxib and/or some of its metabolites may have a pro-oxidant effect which could ultimately lead to an increase in blood pressure or thrombosis. Do we know this for sure? No. Do we know what the contribution of this is to the overall effect of rofecoxib? No. But it is clear from the clinical literature that rofecoxib is associated with elevations of blood pressure that are not seen to that degree with other agents, whether they be non-selective NSAIDs or celecoxib”.
- In a comparative study of rofecoxib, celecoxib and naproxen, rofecoxib had significantly greater effect on systolic blood pressure than the other agents and this was of a magnitude from outcomes studies that “can have a significant impact on cardiovascular mortality and morbidity.”

Committee Questions to Dr. Verburg on Celecoxib

- **RISK RATIOS:** Dr. Furberg said that Table 4 in the Pfizer briefing document showed risk ratios of 1.7 & 1.8 for thromboembolic events. Dr. Verburg responded that the rates for the composite endpoint in the meta-analysis with average duration of therapy of 1.7 months were 1.4 for placebo and 1.8 for celecoxib, a non-significant difference. Dr. Furberg

said that the relative risk for “any myocardial thromboembolic events” was 1.77 in the briefing document, but that the slide presented by Dr. Verburg had “much lower relative risks”. Dr. Verburg said this was because he had used the “more meaningful endpoint and that was the APTC” but that the differences in

endpoints do not “in any way change the overall conclusions”.

- **HEART FAILURE:** Dr. Furberg said that Table 6 shows a 6-fold, statistically significant increase in heart failure. Dr. Verburg said that with “hypertension and peripheral edema and heart failure” celecoxib “is associated with a significant increased incidence of all these events, as are all non-selective NSAIDs”. Dr. Furberg said ‘So, the patients didn't even have a chance to develop heart failure. You raised their blood pressure and caused fluid retention and you followed them for a few weeks.’
- **APC TRIAL:** Dr. Wood suggested that Pfizer show a slide of the Kaplan-Meier curve from the APC trial. Dr. Verburg said that he did not have the data for that study and the APC trial would be discussed later by Dr. Hawk.
- **ADAPT TRIAL:** Dr. Cryer said that Dr. Verburg’s comment that naproxen was associated with a “significant” increase in cardiovascular risk in the ADAPT trial was “misleading”. Dr. Verburg said that this had been his interpretation of what “was put into the public domain ... but without having the data to review I can't answer that.”
- **SHORT-TERM NATURE OF DATA IN META-ANALYSIS:** Dr. D’Agostino pointed out that the short term results presented by Dr. Verburg did not exclude an increased risk that did not become apparent until 18 months of therapy. Dr. Verburg said that Pfizer had reviewed all data available to it, and that other speakers would discuss longer term data in other indications

currently being explored. Dr. Wood commented that saying that Pfizer did not have the data published in the New England Journal of Medicine “just doesn’t pass the laugh test”. Dr. Feczko (Pfizer) then said that “We are not privileged to the data. We were just given some top-line commentary about the data”.

- **CELECOXIB-INCREASED CV RISK PERSISTS IN ASPIRIN SUBSET:** Dr. Schafer said that Table 4 in the APC trial publication shows that the increased cardiovascular risk with celecoxib persists even in the low dose aspirin group. <Note: the hazard ratio in this paper was 3.8 for those taking aspirin and 2.4 for those not taking aspirin, with a p value of 0.63 between subgroups.> Rofecoxib data and Pfizer’s slide 48 appear to show similar lack of protection of low dose aspirin to the increased cardiovascular risk of COX-2 inhibitors. He therefore suggested these data “actually pretty strongly support your contention that there are other mechanisms besides the COX-1 and COX-2 balance at play here”. Dr. Verburg said that other possibilities include blood pressure-related or drug molecule-related mechanisms. Dr. Fitzgerald called this issue a “straw man” since one would expect aspirin to diminish but not abolish the risk (because thromboxane inhibition only partially reverses the effects of prostacyclin inhibition). He thought that “the in vivo basis for the molecule specific effects are tenuous to non-existent” as was the suggestion of a “pro-oxidant effect of rofecoxib”.

- **SAFETY FOR APPROVED INDICATIONS:** Dr. Gibovsky commented that drug safety concerns generated outside “the context of intended uses” may not apply to the approved indications. “Many drugs, when tested for unapproved uses, will turn out not to be safe, whereas they may very well be for the indications for which they are approved...”
- **BP EFFECTS:** Dr. Dworkin asked about BP effects of celecoxib 200 mg BID. Dr. Verburg said there were “very minor differences” compared to placebo. Dr. Friedman asked about BP effects of celecoxib in longer term studies in larger numbers of people. Dr. Verburg asked Dr. Welton, a Pfizer consultant, to comment. Dr. Welton said that NSAIDs increase BP on average by 5 mmHg and that this effect is primarily seen in patients on antihypertensive therapy, raising the question of a drug-drug interaction. The celecoxib database showed “that there really isn't much in the way of hypertension adverse events reported” but with rofecoxib there was a “very obvious dose-correlated increase in hypertension events”. To resolve this he and his colleagues did a double blind ambulatory BP comparison of celecoxib and rofecoxib in patients receiving antihypertensive drug therapy. This trial showed that rofecoxib but not celecoxib showed “early disruption of blood pressure”. Other studies have shown that BP changes of even 2 mmHg are associated with differences in mortality. <See slides at end of this document for BP data shown by Dr. Welton> Later, Dr. Nissen commented that, since celecoxib has a shorter half life than rofecoxib, “the effect of the drug may be gone toward the end of the dosing interval, which would tend to bias the study in favor of celecoxib”.
- **COMBINED ANALYSIS OF SEVERAL NIH STUDIES:** Dr. Furberg commented that information on cardiovascular outcomes was supposed to have been collected from a number of NIH studies with celecoxib and he was concerned that “the NIH has dropped the ball”. “So, I think we should request that information and, if necessary, even go to the director.”
- **SHOULD FOCUS ON PLACEBO-CONTROLLED STUDIES:** Dr. Furberg said that the focus should be on placebo-controlled rather than active-controlled trials.
- **FOCUS ON LONG-TERM STUDIES:** Dr. Fleming suggested the focus should be on “on the half a dozen studies that have longer-term follow-up “. If one groups “atrial SAEs, anginal SAEs, MI and thrombophlebitis” in non-aspirin users in the CLASS trial, there were “four times as many events on Celebrex than ibuprofen”. The APC trial shows “a three-fold increase in the rate of CV death, MI and stroke” versus placebo. The 97-02-001 trial “had I think a doubling in the rate of targeted events”. “The PreSAP and the ADAPT trials will also be very informative.” Dr. Verburg said that the Pre-SAP results were to be reviewed in the afternoon by Dr. Levin and that he (Dr. Verburg) had no non-public information about the ADAPT trial. Dr Verburg said that the 97-02-001 trial was difficult to interpret because of small numbers

and a lack of stratification by risk factors. However, “we didn’t entirely dismiss it” and performed a “blinded adjudication process” of all serious cardiovascular events.

- **CELECOXIB VS. NSAID+PPI:** Dr Shafer asked if there were data comparing celecoxib alone with a combination of a non-selective NSAID with a proton pump inhibitor. Dr Verburg said he was not aware of any data “with respect to whether patients stay on therapy longer with celecoxib alone versus the combination of an NSAID and, say, a proton pump inhibitor”.
- **CELECOXIB/VIOXX EQUIVALENT DOSES FOR BP, EFFICACY AND COX-2 INHIBITION:** Dr. Nissen said that “I have certainly heard is that the equivalent dose of celecoxib to 25 mg of rofecoxib is 200 mg BID, not once a day. “ He asked if there were data comparing efficacy and BP effects of celecoxib 200 mg daily and rofecoxib 25 mg daily. Dr White (Pfizer consultant) responded that he did 2 controlled studies. One ambulatory BP study of celecoxib

200 mg bid and placebo in patients on ACE inhibitors showed no statistically significant difference with a mean systolic BP difference of 1.3 mmHg. With regard to efficacy, a 500-patient, 12-week controlled OA study in hypertensive diabetics receiving an “angiotensin blocker” compared the effects of celecoxib 200 mg daily, rofecoxib 25 mg daily and naproxen 500 mg BID showed equivalent efficacy whereas rofecoxib alone showed an increase in blood pressure (4.2 mmHg). At the end of this discussion, Dr. Braunstein asked to show a slide of the rofecoxib and celecoxib dose-response curves for 24-hour COX-2 inhibition (as measured by ex vivo PGE-2 inhibition). This showed equivalence of rofecoxib 25 mg/day with celecoxib 200 mg BID, and equivalence of rofecoxib 12.5 mg/day with celecoxib 200 mg once/day. Another clinical study showed equivalent efficacy (as measured by Patient Global Assessment) between rofecoxib 12.5 mg/day and celecoxib 200 mg once daily.

FDA Presentation: COX-2 CV Safety: Celecoxib: James Witter MD

- **LONG TERM PLACEBO NOT FEASIBLE IN CHRONIC PAIN:** Since a placebo group is not feasible in patients with chronic pain, most controlled data is versus active controls.
- **PARADIGM SHIFT:** The COX-2 drug findings have resulted in “a dramatic shift in terms of looking at safety events and the kinds of data that we have”.
- **PREVIOUS NSAIDs HAD LITTLE DATA:** The NDA for diclofenac (approved in 1988) had less than 100 patients with 1 year therapy, with most studies of 12 weeks or less. The diclofenac NDA had 324 patient-years of exposure compared with 16,208 (50x greater) in the celecoxib NDA. Two myocardial infarctions occurred on

diclofenac and none on the comparators.

- **ENDPOINTS:** In the celecoxib NDA GI events but not cardiovascular events were prespecified and adjudicated. There are “different ways to look at cardiovascular events. We are all familiar with the APTC”.
- **CELECOXIB IQ5-97-02-001 TRIAL:** Dr. Witter quoted from a letter FDA received from the data safety monitoring board for this study. The letter expressed concern that “at final review there was an excess of cardiovascular-related and other risks but it was difficult to interpret” because of “the small sample size” (425 patients) which “made relative risk and odds ratios unreliable”, was conducted in “a frail and fragile population”, and a somewhat greater baseline cardiovascular risk in the celecoxib group suggested “failure in randomization”.
- **FDA POSTS ON INTERNET:** Celecoxib information is on the web.
- **“DOSE CREEP” IS A PROBLEM:** “patients tend to increase their dose if they are allowed to.”

- **FDA TEAM EFFORT:** FDA includes many people with different areas of expertise when reviewing a large NDA like that for celecoxib.
- **DOSE-RESPONSE AND MORTALITY:** An extension trial suggested a trend towards increase in cardiovascular mortality with increasing doses of celecoxib. However, patients were not randomized to the different dose levels and the data were difficult to interpret.
- **FDA SKEPTICAL OF ENDOSCOPY AS SURROGATE:** FDA was concerned that endoscopy data might not translate to a reduction in GI complications.
- **OTC AVAILABILITY:** Some of the marketed NSAIDs are available over the counter and can be a complicating factor when taken concomitantly in controlled trials.

Committee Questions to Dr. Witter on Celecoxib

- **APC TRIAL NOT DISCUSSED:** Dr. Wood’s expressed surprise that the FDA presentation had also not discussed the APC trial.
- **STUDY IQ5-97-02-001 ADJUDICATION:** Dr. Fleming expressed concern about the

adjudication process in the IQ5-97-02-001 study in which “it is certainly noteworthy that there is a pretty consistent excess across all of these key categories for Celebrex”. “It is kind of hard to adjudicate something in a blinded way when all the events are in the one arm”. Dr. White

(Pfizer consultant) said “The adjudication committee was not aware of the results when they looked at the data at all.”

- **STUDY IQ5-97-02-001 P-VALUE:** Dr. Nissen asked Dr. Fleming if he had calculated a p value for an endpoint of “APTC-like or just the serious AEs” in the IQ5-97-02-001 trial. Dr. Fleming said that it would

be “probably borderline”. *<Note by TMT: a Fisher’s Exact Test on celecoxib (11/285) versus placebo (3/140) on “Any CV Event” gives a 2-sided p value of 0.5638 so that the basis for the Pfizer study report statement of a “statistically significant difference favoring placebo in adverse events” remains unclear.>*

The APC Trial (Prevention of Sporadic Colorectal Adenomas with Celecoxib): Ernest Hawk MD

- **APC TRIAL STATUS:** Drug administration in the APC trial was stopped in December 2004 but in other respects the trial is continuing with collection of efficacy and safety data.

COLO-RECTAL CANCER:

- Colorectal cancer remains a significant problem with 145,000 new US cases per year and 55,000 deaths. NSAIDs including COX-2 inhibitors show promise in preventing/treating this condition because of:
- 1) activation of mechanisms that retard carcinogenesis (apoptosis of neoplastic clones, reduction in angiogenesis, inhibition of proliferation, stimulation of immune surveillance),
- 2) “profound benefits” in animal models (reduced cancer incidence, delay in time to progression, reductions in advanced features of tumors),
- 3) observational studies showing 30-40% reduction in intestinal neoplasia, and

- 4) three controlled aspirin studies show 30-40% reduction in recurrent adenoma.

- **PATIENTS WITH BONE MARROW SUPPRESSION:**

Coxibs, which do not inhibit platelet function, are useful in cancer patients with bone marrow suppression.

- **CELECOXIB APPROVED FOR FAMILIAL ADENOMATOUS POLYPOSIS:**

Celecoxib is currently the only approved agent for familial adenomatous polyposis. Endoscopic improvement with celecoxib was “more profound and robust” at dosage of 400 mg BID but some patients “respond quite dramatically” to lower doses.

- **APC TRIAL DESIGN:** The APC was a 3-year double blind trial of celecoxib 200 mg bid, celecoxib 400 mg bid and placebo in 2035 patients with prior sporadic adenomas. Most of the 91 sites were in the US but there were also sites in Canada, Australia and the UK.

- **CARDIOVASCULAR SAFETY ANALYSIS:** Following marketing withdrawal of Vioxx, the data safety

monitoring board (DSMB) initiated cardiovascular adjudication of cardiovascular serious adverse events followed by statistical analysis by Dr. Janet Wittes of Statistics Collaborative, Inc., a distinguished statistician and former Editor-in-Chief of *Controlled Clinical Trials*.

- **PUBLICATION IN NEJM:** The results were published on-line in the New England Journal of Medicine in February, 2005. A “Supplementary Appendix” accompanied the on-line article and described the cardiovascular adjudication procedure in detail, but not the underlying rationale or level of pre-specification for the analytical procedure. <TMT Note: Some issues regarding the analysis are discussed in Attachment 1>.
 - **HIERARCHY OF ENDPOINTS:** The analysis was based on point estimates of hazard ratios with 95% confidence intervals for a hierarchy of endpoints. In the hierarchy, subsequent endpoints subsumed the data from the endpoints earlier in the hierarchy. The hierarchy was: cardiovascular death, non-fatal MI, stroke, heart failure, angina and CV procedure.
 - **CONCOMITANT THERAPY:** Use of aspirin and lipid-lowering drugs was about 30% and equal between the treatment groups.
 - **DIFFERENT HIERARCHICAL ENDPOINTS IN DIFFERENT PRESENTATIONS:** An earlier presentation used the third level in the hierarchy (cardiovascular death + non-fatal MI + stroke) whereas Dr. Hawk presented data on the fourth level (cardiovascular death + non-fatal MI + stroke + heart failure).
- The fourth level ‘is the one that the steering committee and the safety assessment team chose to focus upon, which includes cardiovascular death, myocardial infarction, stroke or heart failure because we feel these are all clinically relevant and important outcomes that could be considered together.’”
- **EVENTS INFREQUENT:** Events “are quite infrequent”. For all groups combined, the percentages of patients having an event for hierarchical categories 1-6 were 0.5, 1.5, 2.0, 2.3, & 2.7%. The actual number of events varied from 10 in category 1 rising to 54 for category 6.
 - **OVERALL MORTALITY:** Data were not presented on non-cardiovascular death but Dr. Hawk made the comment that for “death from any cause, overall mortality, there is really no significant difference across these arms, with the 200 mg group and placebo being equivalent in this study”.
 - **EFFECT OF BASELINE RISK FACTORS:** Analysis of baseline cardiovascular risk factors did not suggest a “differential hazard by any of those baseline factors. Of course, the analyses are limited by few events and, therefore, limited power.”
 - **TIME-TO-EVENT ANALYSIS:** Time-To-Event analysis showed “relatively slow event rates”. If the Y axis was changed to “focus specifically on a probability up to 5 percent, we see the diverging curves similar to what was seen previously with rofecoxib, but the divergence coming somewhere arguably around 12-14 months.” <TMT Note: No

justification was provided for this Y axis change>

- **PLANNED META-ANALYSES:** There are plans to analyze the ASP and Pre-SAP trials together, and to analyze these 2 trials together with 4 other NIH-funded celecoxib trials, all of at least 2 years duration of therapy, “and it is simply a matter of trying to do this in an expedient manner”.
- **NEW DATA ON INCREASED CV RISK WITH NSAIDS:** Dr.

Hawk also mentioned a Scandinavian nested case control study in patients with oral cancer that suggests that increased cardiovascular risk “may extend to other NSAIDs” and he said that “other observational data and the experimental data from the National Institute's of Aging study, may very well raise questions about other NSAIDs”.

The PreSAP Trial (Prevention of Colorectal Sporadic Adenomatous Polyps): Bernard Levin MD

- **PreSAP TRIAL STATUS:** Drug administration in the PreSAP trial was stopped at the same time drug administration was stopped in the APC trial. It is assumed that in other respects the trial is continuing with collection of efficacy and safety data.
- **PreSAP TRIAL DESIGN:** The PreSAP was a 3-year double blind trial of celecoxib 400 mg QD and placebo in 1561 patients with a history of sporadic adenomas. It was conducted at 106 sites in 32 countries.
- **CARDIOVASCULAR SAFETY ANALYSIS:** The same data safety monitoring board (DSMB) as for the APC trial initiated cardiovascular adjudication of cardiovascular serious adverse events but “...some of this information is still in a preliminary status.”
- **HIERARCHY OF ENDPOINTS:** The analysis is using a hierarchy of endpoints similar to the APC trial. In the APC trial hierarchy, subsequent

endpoints subsumed the data from the endpoints earlier in the hierarchy. The hierarchy was: cardiovascular death, non-fatal MI, stroke, heart failure, angina and CV procedure.

COMPARISON WITH RESULTS IN THE APC TRIAL:

- **BASELINE:** Baseline characteristics were “somewhat similar to the APC trial in terms of age and gender. What is different is that the smoking status is higher, 25 percent, and baseline aspirin use is lower.” Treatment groups at baseline were “somewhat similar in age, gender and baseline cardiovascular risk”.
- **CARDIOVASCULAR EVENT RATES:** Compared with the APC trial, the placebo cardiovascular event rate was 6.4 (“about double that in the APC trial”) and the hazard ratio was non-significant at 1.1.
- **EFFECT OF BASELINE RISK FACTORS:** As in the APC trial, there was “no statistical evidence of

a differential hazard ratio by baseline risk groups. Of course, there are few events and it has limited power.”

- **REASONS FOR DIFFERENCES IN RESULTS:** “What, of course, is most tantalizing to everyone involved is: Why is there a difference in this trial compared to the APC trial? At this point, all we have to go on is the frequency of the schedule of administration of celecoxib.”
- **EVENTS INFREQUENT:** “The number of events is low” and “and when this is magnified, similar to

what Dr. Hawk showed, the curves are essentially similar.”

- **OVERALL MORTALITY:** Not discussed.
- **PLANNED META-ANALYSES:** As Dr. Hawk mentioned, there are plans to analyze the ASP and PreSAP trials together, and to analyze these 2 trials together with 4 other NIH-funded celecoxib trials, all of at least 2 years duration of therapy.
- **EFFICACY:** No efficacy results are yet available from the PreSAP trial.

Committee Questions to Dr. Hawk and Dr. Levin on APC and PreSAP

- **BASELINE DIFFERENCES BETWEEN ASP AND PRE-SAP TRIALS:** Dr. Farrar said that the ASP and Pre-SAP trials differed in baseline diabetes (2x in Pre-SAP), smoking (“substantially higher” in Pre-SAP), lipid-lowering drugs (“remarkably lower”) and these differences may be relevant to the different findings in the two trials. Dr. Levin agreed that the Pre-SAP population was “potentially a higher risk group” but that the “data is still a little bit preliminary”. Dr. O’Neill suggested that another difference between the trials might be the proportions of US to non-US patients; Dr. Hawk said he did not have those data.
- **COX-2 SUPPRESSION AS FUNCTION OF DOSING INTERVAL:** Dr. Gross suggested that the different dosing regimen

(QD vs. BID) could have resulted in loss of sustained COX-2 inhibition over 24 hours and might explain the difference in cardiovascular hazard. Dr. Seibert (Pfizer) commented that AUCs are similar and steady state C-mins are “about 20% different” and “still exceed that which is necessary to inhibit COX-2” so that “we don’t see a clear differentiator there in the dosing regimen”.

- **EFFECT OF ASPIRIN:** Dr. Wood said that the APC/Pre-APC data suggest that cardiovascular risk was increased by aspirin. Dr. Hawk commented on a study by John Baron (NEJM) suggesting dose-dependent increase in events with aspirin but that “there are a lot” of trials showing that aspirin lowers cardiovascular risk.
- **ASP TRIAL STOPPING RULES:** Dr. Hennekens expressed concern

that the “statistical stopping guideline” used may have resulted in the APC trial being stopped prematurely without adequate statistical justification. Dr. Hawk said that the data safety monitoring board had recommended halting drug administration but “that is my level of insight into the issue.”

- **CONSISTENCY OF ASP AND PRE-SAP CV DATA:** Dr. Furberg said that the 95% confidence interval for Pre-SAP cardiovascular results is consistent with “a 40 percent benefit and a 2.34-fold increase in risk” and are thus compatible with ASP. Dr. D’Agostino, Dr. Nissen and Dr. Wood agreed with Dr. Furberg’s comment.
- **CELECOXIB VS. ASPIRIN FOR COLORECTAL POLYPS:** In response to Dr. Cryer, Dr. Hawk said that celecoxib is more effective than aspirin in animal models but it is premature to speculate how effective celecoxib will be in the ASP/Pre-SAP trials, or whether there is a dose that is effective without an increased cardiovascular hazard.
- **POOLING DATA FROM ASP AND PRE-SAP TRIALS:** Dr. Nissen suggested that pooling the

data from these two similarly designed trials each at 400 mg/day might “give us more stable estimates of the hazard ratio”. Dr. Hawk said that a combined analysis “has been done based upon preliminary data that were analyzed back in December”. Dr. Fleming said that he had done a “back of the envelope calculation” that gave a “relative risk of about 1.82” for the meta-analysis which was of “borderline statistical significance” (apparently for the pooled data from the low and high dose levels).

- **CANCER TRIAL SHOWING INCREASED NSAID CV RISK VS. ACETAMINOPHEN:** Dr. Andrew Dannenberg (Cornell and a Pfizer consultant) described a not-yet-published study of acetaminophen versus non-selective NSAIDs in preventing oral cavity cancer that showed a reduced risk of oral cavity cancer with NSAIDs but this was accompanied by an increased cardiovascular risk with NSAIDs (hazard ratio 2.06).

Sponsor Presentation (Pfizer): Valdecoxib and Parecoxib Cardiovascular Safety and Risk/Benefit Assessment of Valdecoxib and Parecoxib, Kenneth Verburg PhD

- **REGULATORY HISTORY:** US approval for valdecoxib was in November 2001 at dosage of 10 mg once daily. The NDA had 15,000 patients.
- **POST-APPROVAL FOCUS:** Post-approval, Pfizer focused on acute pain and non-arthritic chronic pain.
- **GI SAFETY:** “We have data to suggest that valdecoxib provides improved GI safety compared to NSAIDs.”

- **CARDIOVASCULAR SIGNAL IN CABG SETTING:** There is a “cardiovascular signal in the CABG surgery setting” but this “does not appear to extrapolate to the arthritis population based on the data at hand.”
- **RISK OF STEVENS-JOHNSON SYNDROME:** Valdecoxib does show a higher rate of Stevens-Johnson syndrome than celecoxib or rofecoxib and has a black box warning to this effect.
- **PARECOXIB:** Parecoxib is the prodrug of valdecoxib.

CABG STUDIES:

- In the first CABG study, patients “received parecoxib at 40 mg IV Q 12 hours for a period of at least 3 days, and then once they were able to transition to oral treatment they received valdecoxib at the same dose”. Patients also received concomitant aspirin 80-325 mg/day. Versus placebo, there was an increased risk of the composite cardiovascular endpoint, “driven primarily” by an imbalance in stroke/TIA.
- The second, larger (1500 patient) CABG trial had three groups (parecoxib followed by valdecoxib, valdecoxib, and placebo). The composite cardiovascular endpoint (over 10 days therapy and 30 days post-surgery follow-up) showed versus placebo a statistically significant increase for parecoxib/valdecoxib, and a statistically non-significant increase

for valdecoxib alone. As in the first CABG study, stroke was a “major driver” of the increase in the composite endpoint. Stroke tended to occur in the early post-surgical period whereas cardiac arrest and cardiovascular death tended to occur later in treatment.

- **RISK FACTOR ANALYSIS:** Risk factor analysis was not fruitful because of the small number of events.
- **MECHANISTIC BASIS OF CARDIOVASCULAR EFFECT:** The mechanism underlying the increased cardiovascular risk in the CABG setting is not clear but the following factors may play a role: 1) activation of platelets, leukocytes and endothelial cells, 2) aortic cross-clamping-induced ischemia, re-perfusion injury and emboli formation, 3) prostacyclin and thromboxane effects, and 4) platelet aspirin resistance.
- **SAFETY IN NON-VASCULAR SURGERY:** In parallel with the CABG studies, Pfizer did general surgery trials that suggested that the cardiovascular hazard is not present outside a vascular surgery setting.
- **EFFICACY IN POST-OPERATIVE PAIN:** On the benefit side, significant reduction in post-operative pain was seen as well as significant reductions in opioid use.

Concluding Remarks by Pfizer: Joseph Feczko MD

- **PATIENTS WITH CHRONIC PAIN NEED TREATMENT:** In the treatment of arthritis, “placebo is really not an alternative”. Arthritis patients need therapeutic options. “Not everything works for everyone.”
- **CARDIOVASCULAR SAFETY OF NON-SELECTIVE NSAIDS IS UNKNOWN:** Non-selective NSAIDs have known GI risks, but their long-term cardiovascular safety (compared with placebo or no therapy) has not been established.
- **CARDIOVASCULAR SAFETY OF CELECOXIB IS COMPARABLE TO NON-SELECTIVE NSAIDS:** Pfizer believes that “the cardiovascular safety of celecoxib is at least on a par with therapeutic alternatives such as the non-selective NSAIDs”.
- **A LARGE CARDIOVASCULAR SAFETY STUDY OF CELECOXIB AND NON-SELECTIVE NSAIDS IS PLANNED:** Pfizer is committed to performing a study to establish the comparability of the cardiovascular safety of celecoxib with non-selective NSAIDs. A protocol has been discussed with outside cardiologists and is currently filed with FDA.
- **EVALUATION OF CELECOXIB IN CANCER WILL CONTINUE:** Pfizer is also committed to continuing evaluation of celecoxib in cancer.
- **VALDECOXIB IS SAFE OUTSIDE A VASCULAR SURGERY SETTING:** The valdecoxib database is smaller than with celecoxib but no increase in cardiovascular risk has been seen outside the CABG surgery setting.
- **PARCOXIB IS EFFECTIVE AND SAFE OUTSIDE A VASCULAR SURGERY SETTING:** Parecoxib is a “highly effective” parenteral drug which appears to be safe in a setting of non-vascular surgery.

Questions from Committee to Dr. Verburg on Valdecoxib and Parecoxib

- **RISK WITH DIFFERENT TYPES OF SURGERY:** Dr. Wood questioned the safety of valdecoxib in general surgery. Dr. Nessmeier (Pfizer consultant) said that valdecoxib should “be avoided in patients undergoing coronary revascularization” and by extension “any other revascularization” but that does not apply to other surgical procedures. Dr. Fleming expressed concern about a conclusion of safety in general surgery because of the low event rate in general surgery trials.
- **DATA INCONSISTENCIES:** Dr. Furberg was “troubled by some inconsistencies” in Pfizer’s briefing document. It was agreed that Pfizer

would review Dr. Furberg's concerns and would give a 10 minute presentation the following day on these issues.

- **RUPTURE OF UNSTABLE ATHEROSCLEROTIC PLAQUE:** Dr. Hoffman expressed concern that one mechanism for the increased cardiovascular risk in the CABG setting might be related to rupture of unstable atherosclerotic plaque; if this were the case, valdecoxib might be dangerous in non-surgical patients with unstable plaque. Dr. Verburg said "we are left with a lot of unknowns" and that Pfizer is "mindful of the concern that you raised".
- **WOUND HEALING:** Dr. Hoffman asked about wound healing studies in animals. Dr. Seibert (Pfizer) said that valdecoxib did not affect incisional wound healing but Pfizer does not have data "in a vascular setting".
- **RECOMMENDATION TO PROCEED CAUTIOUSLY:** Dr. Platt commented that the data are inconsistent and "the question is what is the cautious way to proceed while acquiring the additional information that we need to have? How important is it to think about the way these drugs are used while the additional information is being collected?"
- **VALDECOXIB PATIENTS NEEDING EMERGENCY VASCULAR SURGERY:** Dr. Friedman expressed concern that patients on valdecoxib might need emergency vascular surgery and asked if such patients would have to delay surgery for some time while valdecoxib was discontinued. Dr. Verburg said he did not have an answer.
- **SPEED OF ONSET OF ADVERSE CARDIOVASCULAR EFFECT:** Dr. Nissen expressed concern that the CABG studies showed that "potent COX-2 inhibitors" can "produce events quickly even in patients taking aspirin" and over 10 days is a "pretty rapid emergence of the problem".
- **POSSIBILITY THAT EFFECT MIGHT BE SHARED BY NON-SELECTIVE NSAIDS:** Dr. Abramson interpreted the CABG data as indicating that "if you inhibit COX-2 to a high degree you may get this result" and because aspirin was also on board, this might not be a selective COX-2 effect but might result from any of the non-selective drugs that also inhibit COX-2. Dr. Seibert (Pfizer) agreed with this comment and said "What we really don't know is the effect of an NSAID in the same CABG setting". <Note: There is a double blind CABG study of naproxen vs. placebo that did not show a hazard of naproxen (Kulik et al, Eur J Cardiothorac Surg. 2004 Oct;26:694-700) to which TMT alerted Pfizer by email on 10/26/04.>
- **SELECTION OF PATIENTS FOR VALDECOXIB THERAPY:** Dr. Wood asked Dr. Seibert if she would take it if she "were at high risk of a platelet-driven problem". Dr. Seibert referred the question to Dr. Strand, a Pfizer consultant, who said that he would not recommend valdecoxib for "a patient with high cardiovascular risk" but that valdecoxib is still needed as an "alternative for the patients who need chronic pain relief". Dr. Wood asked if he meant that valdecoxib should be used in "patients who have failed other therapy". Dr. Strand said

“I see it in patients who have high GI risk” and “In patients who have not already responded to celecoxib or may have been forced to discontinue Vioxx.”

- **MI DIAGNOSIS:** Dr. Furberg said that one should not use standard diagnostic criteria (particularly chest pain and enzyme changes) in diagnosing acute myocardial infarction in the post CABG setting. Dr. Nessmeier said that standard MI diagnostic criteria were not used (they used more rigid CK-MB and troponin criteria). Dr. Wood pointed out that the criteria were equally applied to the placebo and valdecoxib groups.
- **PROBLEM GIVING ANY DRUG WITH CV EFFECTS POST CABG:** Dr. Hennekens said that “any drug, regardless of its class, that

would increase blood pressure, fluid retention and risk of heart failure, if given during or after CABG, would pose very difficult research and clinical challenges.”

- **THROMBOGENIC STIMULUS IN CABG TOO INTENSE TO BE REVERSED BY ASPIRIN:** Dr. Hennekens said “I would say to Dr. Shafer, regardless of the mechanism that is proposed, this is far beyond the powers of aspirin.”
- **NEED FOR THERAPEUTIC OPTIONS:** Dr. Shafer commented that the CABG setting is “an area where we do need improved therapeutic options and I would just encourage the committee to keep that in mind.”

FDA Presentation: COX-2 CV Safety: Valdecoxib-Naproxen: James Witter MD

- **VALDECOXIB 40 MG BID INCREASES BP:** Valdecoxib 40 mg bid (but not 20 mg bid) increased BP significantly more ($p < .05$) than naproxen in a 6 month osteoarthritis study.
- **CABG TRIALS HAD NO POSITIVE CONTROL:** The CABG studies only used placebo as a control. In retrospect, it would have been useful to have had one non-selective NSAID arm (e.g. toradol).
- **PARECOXIB/VALDECOXIB DOSAGE IN CABG SETTING:** It is possible that “the dosing was too high” in the first CABG study.
- **CABG TRIALS COMPLEX TO INTERPRET:** Although parecoxib/valdecoxib clearly increased cardiovascular hazard in a CABG setting in the doses used, “there is a lot there that we still need to know.”

Valdecoxib Discussions: Dr. Furberg and Pfizer

- **INCONSISTENCIES:** During the valdecoxib discussion period on Day 1, Dr. Furberg said he was ‘troubled by some inconsistencies that I have found in the briefing document from Pfizer’. It was agreed that Pfizer would review these issues and respond during the Day 2 proceedings. After the end of the Day 1 proceedings, Dr. Furberg and Pfizer met to go over the issues.
- **LACK OF RESOLUTION REPORTED DAY 2:** At the discussion of the matter on Day 2, Dr. Furberg said that “We met and I got some clarification, but I continue to be troubled.” Dr. Wood, the Chairman, suggested that Dr. Furberg ‘tell us about the issues and let's give Pfizer an opportunity to respond.’ Dr. Furberg said that there were 5 issues.
- **ISSUE 1:** Dr. Furberg’s first issue was the number of trials reported in the acute pain integrated safety analysis. Dr. Harrigan (Pfizer) responded that Pfizer presented two separate data groupings (on pages 55 and 76 of the briefing document). One grouped 18 studies with a daily dose range of 20-60 mg. The other grouped 20 studies with a daily dose “greater than 20 mg total daily dose”. The difference between these two groups of studies was “largely due” to the fact that one grouping did not include “the CABG Study 035, which is described in great detail, in fact, six pages devoted to the CABG studies in the briefing document.”
- **ISSUE 2:** Dr. Furberg’s second issue dealt with the number of cardiovascular events reported in the integrated safety analysis. This depends partly on the definition (whether you include sudden death as well as fatal CHD) but the numbers did not seem to add up. Pfizer told him that “in the second CABG trial that got involved in the analyses, they subtracted the number of events when the patient was on the I.V. formulation parecoxib”. However, “I looked it up and it turned out to be one case. So, that doesn't explain the discrepancy, so the explanation that was given was not satisfactory.” Dr. Harrigan responded that since patients received parecoxib first and then valdecoxib, you “have to assign the event to one treatment or the other, they were appropriately assigned to parecoxib, and so they are not accounted for in the valdecoxib column.” Another reason for the discrepancy depends on whether adverse events were adjudicated or not.
- **EVENT ALLOCATION TO VALDECOXIB OR PARECOXIB IF DURING PARECOXIB THERAPY:** Dr. Wood commented that since ‘parecoxib is the pro-drug for valdecoxib’, “as far as my body knows when it gets parecoxib, it has got valdecoxib”. Dr. Harrigan asked if Dr. Wood was suggesting that “all patients that receive parecoxib be transformed to valdecoxib”. Dr. Wood responded ‘I guess the body transforms it to valdecoxib’. Dr. Harrigan said ‘It would obscure the data from the effects of parecoxib, which is given by a different formulation’.
- **PFIZER STATEMENT ON SAFETY DATA REPORTING:**

Dr. Harrigan said ‘It is important to us that members of this committee and the FDA, and other health agencies worldwide understand that we do not suppress safety data. We report safety data. We report it in a number of different ways. We do not suppress safety data.’

- **ISSUE DEFERRED TO FDA FOR RESOLUTION:** Dr. Furberg commented ‘The numbers just don't

add up’. It was agreed that the issues would be deferred to FDA for resolution. Dr. Furberg said ‘... it would be much better if you explained why you did it differently ...’. ‘I think there are some numbers that will be hard to explain away.’ Dr. Wood said ‘I think we have got it that there is still a bone of contention here.’

Sponsor Presentation (Bayer & Roche): Naproxen Introduction: Leonard Baum MD

- **REGULATORY HISTORY:** Naproxen was approved for marketing in 1976 and for OTC use in 1994.
- **ANTI-PLATELET EFFECTS:** Naproxen inhibits platelet aggregation.
- **ESTIMATED EXPOSURE:** Exposure is estimated at 110 billion Rx and 550 billion OTC courses of therapy (assuming 2 tablets a day for 10 days). Over 22 million patients use naproxen each year.
- **ADAPT STUDY:** The ADAPT study in patients with a familial history of Alzheimer’s or dementia was suspended in December 2004 “in part due to the APC findings and this was released as part of the NIH statement”, “based on preliminary findings”.

Sponsor Presentation (Bayer & Roche): Safety Data: Martin Huber MD

- **ANTI-PLATELET EFFECTS:** “it is a known property of naproxen to inhibit platelet aggregation and this has been substantiated by studies demonstrating an increase in bleeding time, etc.”
- **LONG TERM RANDOMIZED TRIALS:**
- The VIGOR trial was already discussed (increase in CV risk with Vioxx compared with naproxen).
- The TARGET trial was 2 sub-studies one with naproxen and one with ibuprofen. Versus lumiracoxib, naproxen “had a lower incidence” of stroke and myocardial infarction, whereas “ibuprofen actually had a higher rate than lumiracoxib”. However the incidence with lumiracoxib was higher in the naproxen comparison which “makes this a little tricky”.

- There was also a randomized trial comparing rofecoxib, naproxen and placebo (results not discussed).
- **META-ANALYSIS:** The White meta-analysis of celecoxib data did not show “an increased risk of myocardial infarction or stroke” with naproxen “compared to either celecoxib or placebo”.
- **OBSERVATIONAL STUDIES:** Observational studies, despite their limitations, did not suggest increased risk with naproxen. Of 11 studies, only one (the Graham Lancet study) suggested increased risk (14% increase, but the lower confidence limit “did hit 1.0”).

Committee Questions to the Naproxen Speakers

- **EVENT CLASSIFICATION:** Dr. Furberg was concerned about lack of prespecified event definitions and lack of event adjudication in the ADAPT trial.
- **INTERPRETATION OF DIFFERENT CV HAZARD RATIOS OF NAPROXEN AND ROFECOXIB:** Dr. Hennekens asked if the results in VIGOR were because naproxen was beneficial, because rofecoxib was harmful, or a combination of the two. Dr. Huber said “I don’t know”.
- **INTERPRETATION OF OBSERVATIONAL STUDIES:** Dr. Fleming said it was difficult to rule out a doubling of a common event such as MI from the naproxen exposure data. Dr. Huber responded that for the observational studies “there is some weight to that evidence. It shouldn’t be completely put aside.” Dr. Fleming replied that observational studies make it difficult to detect an increase in a common event “unless you are looking for a ten-fold increase”.
- **INTERPRETATION OF LONG TERM CONTROLLED DATA:** Dr. Fleming focused on the long term controlled studies and there are only three. Two (VIGOR and TARGET have a coxib comparison) and the third (ADAPT) has a placebo control group for which there was a suggestion that the data monitoring committee stopped the trial due to and increase with naproxen in “GI bleeds, cardiovascular and cerebrovascular events”. Dr. Huber said that in “the NIH press release there were approximately 70 cases, and what was stated about it was that there was--I can’t remember the exact wording of the text, but it was an increased risk of stroke or MI.” Dr. D’Agostino said that the comments that Dr. Fleming was making “are very important.”
- **RISK BY DURATION OF NAPROXEN THERAPY:** Dr. Morris asked about the effect of duration of therapy. Dr. Thacker (Roche epidemiologist) responded that “None of the studies really gave us any data on duration of use.”
- **ADAPT TRIAL NAPROXEN DOSE WAS THE OTC DOSE:** Dr. Witter said that “in the ADAPT trial naproxen was the OTC dose.”

Interpretation of Observational Studies of Cardiovascular Risk of Nonsteroidal Drugs: Richard Platt MD

OBSERVATIONAL STUDY LIMITATIONS:

- **APPLES AND ORANGES:** In observational studies one can never be sure that the groups being compared are comparable in risk for the outcome of interest. One can only adjust for the confounders that one knows about, and the presence of other confounders can never be excluded. If the difference in estimate of risk between the unadjusted and the adjusted result using known confounders is small, one can have somewhat more confidence in the result. Similarly, the presence of a dose-response relationship imparts more credibility.
- **IS SYSTEMATIC BIAS A REASONABLE EXPLANATION FOR THE RESULTS?** Since differences between drug groups may reflect factors unrelated to the drugs being compared, one may be tempted to conclude that the magnitude of the apparent effect is so large that any systematic bias could not be enough to explain the findings. However, the estrogen “protection” story in post-menopausal women provides a cautionary tale.
- **DIFFERENTIAL PROBABILITY OF ASSIGNMENT TO DIFFERENT DRUGS:** Political, economic, standard-of-care or geographic factors may influence the probability of assignment to different drugs.
- **DIFFICULT TO MONITOR DRUG ADHERENCE AND DATA COLLECTION:** identifying adherence to treatment and making sure that events and other data items are properly collected is often difficult.
- **IMPACT OF PRIOR DRUG THERAPY:** It is difficult exclude an impact of prior drug therapy on outcomes occurring on subsequent therapy.
- **FOLLOW-UP OFTEN INCOMPLETE:** In cohort studies, initial drug status may change during follow-up and adequate follow-up is difficult.
- **EXTRAPOLATION TO DIFFERENT POPULATIONS:** One has to be careful about extrapolating from the population you study to the other populations or the general population with the disease. Case-control studies may not provide patients who are representative of the “group that you are trying to study” although this is less of a problem in cohort studies. The outcome to be evaluated may be limited by the need to get information on drug therapy from a patient surviving the outcome of interest.

- **BIAS:** Recall bias and reverse recall bias is a common problem.
- **LESS GOOD FOR COMMON EVENTS:** Common events are harder to study in observational studies than rarer events.
- **LACK OF STANDARDS FOR OBSERVATIONAL STUDIES:** The lack of uniform standards for designing, documenting, analyzing and interpreting observational studies is a major problem.

OBSERVATIONAL STUDY ADVANTAGES:

- **QUICKER & CHEAPER:** Observational studies are quicker, cheaper and less resource-intensive.
- **MORE REPRESENTATIVE OF POPULATION ON DRUG:** Subjects in some types of observational studies are more likely to be comparable to the actual population of users for the drug and to use the drugs as they are used in the general population.
- **GOOD FOR RARE EVENTS:** They are particularly useful when evaluating rare events.

CLINICAL TRIAL LIMITATIONS:

- **SLOW & EXPENSIVE:** Clinical trials give slower answers than observational studies and can be very expensive and resource-intensive.
- **NOT REPRESENTATIVE OF POPULATION ON DRUG:** Subjects in clinical trials are “different from the actual population of users” of a drug.
- **LESS GOOD FOR RARE EVENTS:** For very rare events clinical trials may not be practical.
- **LACK OF STANDARDS FOR CLINICAL TRIALS:** Although clinical trials standards are better documented than the standards for observational studies, deficiencies remain in 1) adjusting p values for multiple testing and other factors, 2) exact pre-specification of primary and secondary hypotheses, 3) documenting and displaying the results of analysis, and 4) designing and documenting valid trial stopping rules.

CLINICAL TRIAL ADVANTAGES:

- **STUDY GROUPS MORE LIKELY TO BE COMPARABLE:** The “tremendous advantage” of randomized trials is that the different groups being compared have a known probability of being within certain limits of comparability at baseline, without systematic bias in

group assignment. However, even in properly randomized trials, major baseline inequalities can sometimes happen by chance.

- **RANDOMIZED TRIAL MORE CREDIBLE:** Overall, “all things being equala randomized trial is more credible than an observational study.”

- **GOOD MONITORING OF DRUG ADHERENCE AND DATA COLLECTION:** Randomized trials are better at identifying adherence to treatment and making sure that events and other data items are properly collected.

OTHER ITEMS:

- **OBSERVATIONAL STUDY DESIGNS:** If observational studies are to be done to evaluate a common event, case-control, nested case-control or cohort designs are best. For the present COX-2 issue, Kimmel was case-control, Graham and Solomon were nested case-control, and Ray and Aramis were cohort designs.
- **COHORT STUDIES:** A cohort study identifies if a patient has been exposed to the drug or not and then follows the patient to record an outcome. Inception cohorts are people who had to be members of a population (e.g., members of a particular health plan) from its inception (or for a defined period before beginning the drug of interest).
- **CASE-CONTROL STUDIES:** A case-control study starts with people who have the outcome we care about (e.g., MI) and matches them to comparable patients who did not have that outcome.
- **NESTED CASE-CONTROL STUDIES:** A nested case-control study is a “hybrid” that “draws many of the strengths from both designs” (cohort and case-control). It is a case-control study that is “nested” in

a defined population, thus combining the strength of a cohort study with the efficiency of a case-control study.

- **REASONS FOR LACK OF POWER:** As with randomized trials, observational studies may have insufficient events, insufficient duration of therapy, or not-at-risk patients that prevent identification of the outcome of interest.
- **INTERPRETATION OF RISKS:** “I think that observational studies are best at finding relative risks that are more than 2. I think that I would pay some attention to relative risks of 1.5. I get very nervous about adjusted relative risks of 1.2.” Calculating other risk estimates such as absolute risk, person-level risk and population-level risk is also important when making individual patient-physician decisions, and in making public policy decisions.
- **APOLOGY:** Note that some of the “Highlights” above were derived from related comments made by other committee members during the COX-2 meeting. It was felt to be important to try to draw together some of the common threads comparing observational studies and clinical trials. The reader’s (and Dr.

Platt's) forbearance is requested. This is the only "Highlights" section

in the COX-2 meeting summary in which this approach has been taken.

Review of Epidemiologic Studies on Cardiovascular Risk with Selected NSAIDs: David Graham MD

- **SEVEN STUDIES WILL BE REVIEWED:** He will review seven epidemiology studies of hospitalized MI – 3 "stronger" published studies that were "done better", 2 published studies that were "less strong" and two unpublished studies (Ingenix and MediCal).
- **CONSISTENCY ACROSS STUDIES:** Consistency in results across studies suggests "a real effect".
- **NON-USERS MAY NOT BE VALID COMPARISON:** Ideally one would compare with non-users as well as other drugs, but "people

who don't use drugs tend to be healthier than people who do use drugs".

- **ADJUSTMENT MAY NOT ADJUST FOR ALL INFLUENCES:** To account for differences between groups we "can try to adjust for confounding and the like, but you are still left with that concern that they may be, in some way that we can't measure, different..".

ROFECOXIB:

- **INCREASED RISK IN 3 OF 4 STUDIES:** In three of 4 evaluations of rofecoxib "there is an elevation in the point estimate. In the Graham study, it included one." In the Ingenix study (sponsored by Merck) there is a "a result that goes in a very unexpected direction." Preliminary data from the California Medicaid study shows "a dose-response to rofecoxib from 12.5 mg up to and through 50 mg" with "very narrow confidence intervals in the 12 to 25 mg and in the 25 to 50 mg".
- **INCREASED RISK WITH ROFECOXIB VS. CELECOXIB:** In rofecoxib comparisons with

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

- **ONE ROFECOXIB MI PER 100-200 USERS?** The typical COX-2 users are in their 60s. The MI rate for 65-74 year old men in the US is 2% per year. Although the risk ratios for rofecoxib varied between studies, a ballpark estimate would be that one rofecoxib-induced MI would occur

in every 100-200 rofecoxib users. With high dose rofecoxib, risk would be higher.

- **PUBLIC HEALTH PERSPECTIVE:** One should also look at the risk from a public health perspective and estimate how many additional MIs will occur in the population of rofecoxib users.
- **TIME OF ONSET OF EFFECT:** Although the APPROVe trial showed clear increase in risk after 18 months of therapy, he suggests that the apparent lack of increased risk at earlier time points in randomized studies may be because of the small number of events and “low statistical power”. He believes this because the observational studies show early

increase in risk. In the “Graham study” half of the cases “occurred within 2 to 3 months of starting the drug.” And no one in this study that showed increased risk with rofecoxib had treatment for “more than about 15 months”. The Solomon, Kimmel and Ingenix studies also showed increased rofecoxib risk early in therapy.

- **ROFECOXIB CONCLUSIONS:** He concluded: “For rofecoxib, we believe that there is evidence of increased risk at both the lower doses and the higher doses, and that risk begins early in therapy and is apparent during the first 30 days of use.”

CELECOXIB:

- **NO EVIDENCE OF INCREASED RISK OVERALL:** For celecoxib, the observational studies either suggested no effect or (in the Kimmel study) a “substantial protective effect”.
- **SUGGESTION OF DOSE-RESPONSE:** Two unpublished studies showed “evidence of a dose response” with celecoxib. The risk ratio for MI was “1.18 or so at 400 mg” in the Ingenix study. In the Medi-Cal study low dose risk ratio was 1.01 and high dose risk ratio was

“about 1.24”. However, he also said in his talk that for risk ratios “above 2 you feel really comfortable, above 1.5, you can believe it, below that you begin to get really edgy.”

- **CELECOXIB CONCLUSIONS:** “Celecoxib, we believe that based on the evidence we have at hand, that there is no apparent effect of risk at doses of 200 mg or less. Above 200 mg, we think that there is evidence of increased risk.”

VALDECOXIB:

- **SMALL DATABASE DOES NOT SUGGEST RISK:** For valdecoxib, the only data came from the unpublished Medi-Cal study which

“found a point estimate of 0.99” with “mostly 10 and 20 mg use”.

- **VALDECOXIB CONCLUSIONS:** “With valdecoxib, there is a paucity

of information, but the information we have at this time suggests that the

risk is not increased at doses of 20 mg or less.”

NAPROXEN:

- **TWO SLIDES ON NAPROXEN STUDIES:** He presented two slides on naproxen studies. One slide showing studies with either no protective effect or, in several studies, “the possibility of a small increased risk with naproxen”. The other slide showed four studies that “found a protective effect”.
- **PROBLEMS WITH “POSITIVE” STUDIES:** Dr. Graham has problems with the four studies with protective effect. 1) The Rahme study compared naproxen with ibuprofen and since ibuprofen may increase risk, lesser risk with naproxen may still represent increased risk versus a hypothetical placebo. 2) The Kimmel study had low participation, reverse recall bias and few cases. 3) The Solomon study defined exposure as having taken naproxen any time in the last 6 months so that a patient could have stopped naproxen and still be included in the study; if one looks at

“remote users” (whose naproxen use ended at least 2 months before), the apparent protective effect of naproxen is still present, which suggests to him “selection bias” rather than a long-lasting benefit after stopping naproxen. 4) The Watson study “was sponsored by Merck, and it was authored by Merck investigators” and claimed “a 39 percent reduction in cardiovascular risk.” However, the endpoint included inappropriate events such as subarachnoid hemorrhage and subdural hematoma. In addition, after adjusting for smoking and baseline cardiovascular risk, the effect was no longer statistically significant. He concludes that of the four “positive” studies, “none of them provide credible evidence of a protective effect.”

- **NAPROXEN CONCLUSION:** “... naproxen is not cardio-protective.”

IBUPROFEN:

- For ibuprofen, in “preliminary” data from his unpublished California Medicaid study “for ibuprofen we

found a small but statistically significant increased risk”.

INDOMETHACIN:

- For indomethacin, also in the California Medicaid study, “we found a risk of 1.7” and they also

“found an increased risk with indomethacin in our Kaiser

Permanente study. It was 1.3 and it was highly statistically significant.”

- “In at least two other studies that I reviewed in preparation for this

advisory meeting, indomethacin is noted to have an increased risk of myocardial infarction.”

MELOXICAM:

- For meloxicam, “we are presenting these data just to say that we found

an increased risk. It is one study, but I think it is the only study.”

SULINDAC:

- For sulindac, “there was an increased risk”.

DICLOFENAC:

- For diclofenac, “overall did not have an increased risk, but at the high

doses there is a suggestion of a dose response.”

RISK ESTIMATES DEPEND ON MODEL ASSUMPTIONS:

- “FDA will present its estimation of the number harmed by rofecoxib, modeling randomized clinical trial survival curves”.
- The model assumes a “grace period” early in therapy, an assumption which he thinks is “unreliable due to low statistical power early on” and conflicts with his epidemiology data.

- The model also does not take into account the fact that “the patients enrolled in randomized clinical trials are generally healthier than patients in the real world” so that this assumption results in an underestimate of the number harmed.

OVERALL CONCLUSIONS:

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

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

Questions to Dr. Graham

- **WAS ALL NECESSARY INFORMATION PRESENTED?**

Dr. Wood asked if Dr. Graham had presented all the information the committee needed to here. Dr. Graham said that he had “been able to present what I thought was important to present” and said that the controversy arose because he was initially asked to present the unpublished Ingenix study from Merck but was told not to present his own unpublished California Medicaid study. This was resolved when it was agreed that he would present both unpublished studies.

- **POPULATION IMPACT OF A SMALL INCREASE IN RELATIVE RISK FOR A COMMON EVENT VS. LARGE INCREASE IN RELATIVE RISK FOR A RARE EVENT:**

Dr. Wood asked Dr. Graham to put the “excess population risk” that he estimated in

the context of “other drugs that have been withdrawn from the market.” Dr. Graham said that the “leading cause of drug withdrawals” was “acute liver failure” which has a background rate in the general population of about 1 million a year – similar to the risk of being struck by lightning. Thus, if a drug increased this risk 5-fold or even 100-fold the actual number of people affected would be fairly small on a population basis and be “measured in the tens and the hundreds”. In contrast, a small increase in risk for a common event can result in much larger numbers of people affected – for example he estimates that the high dose of Vioxx would increase the 1 in 50 yearly chance of heart attack for a male aged 65 to 74 to a chance of 5 in 50.

Committee Questions to Dr. Platt and Dr. Graham

- **MAKING INDIVIDUAL DRUG RECOMMENDATIONS WHEN DATA ON SOME DRUGS ARE RANDOMIZED AND ON OTHERS IS OBSERVATIONAL:**

Dr. Shafer said that coming up with “some sort of common warning as a class” would communicate “no relevant information”. However, to give “individual drug-specific recommendations” would have to be on the basis of controlled trials for

the COX-2 drugs and on the basis of the less convincing observational studies for the older drugs. Dr. Graham gave a detailed answer that implied that one has to make decisions on the data that are available, even if these data are from observational studies. One should “weed the garden of the bad actors” (he mentioned indomethacin as a bad actor) and “shift the market” towards those that appear to have less “risk in

the totality of their evidence”. Later in the discussion, Dr. Abramson said that it is not necessarily bad to “call attention to this class effect” since it may stimulate doctors to do “the simple thing of checking blood pressures”.

- **POSSIBLE BIAS IN INTERPRETING DIFFERENT OBSERVATIONAL STUDIES:** OF Dr. Friedman commented that because of the known limitations of observational studies, “it is easy after the fact to critique away those whose results you don't much care for”. Dr. Elashoff later commented that “just because you put a lot of variables in some model doesn't necessarily mean that you have adequately removed the confounding effects even of those variables”. She also pointed to the omission of the Ingenix data in slide 13 on “excess population risk” that makes it “a biased presentation”. Dr. Graham said “OK, fair enough”. Later in the discussion, Dr. D'Agostino later expressed concern that Dr. Graham criticized some studies as bad because of confounding but not others that had the same potential confounding, saying “Why do you throw out a result you don't like and keep all the results you like?”
- **PATIENT YEARS ARE DIFFERENT FROM ACTUAL DURATIONS OF THERAPY:** Dr. Friedman also that using “patient years of exposure” can obscure the fact that most of the patients may only have a few weeks of therapy. So his preference is for randomized studies that do have long exposure in individual patients. During another detailed answer, Dr. Graham said “I think the epidemiologic data, in my

mind at least, answers the question about when the effect begins” but he did not elaborate on this position.

- **RANKING ROFECOXIB RISK VERSUS OTHER CV RISK FACTORS:** Dr. Bathon asked where the cardiovascular risk of the high dose of rofecoxib ranked among the known cardiovascular risk factors. Dr. Graham said his “ballpark” would be “probably more significant than smoking or diabetes or hypertension, maybe more important than the combination of several of those factors in a patient.” For the lower dose he estimated “probably more than hypertension, a little less than diabetes, and a little less than smoking”. He conceded that Dr. Bathon and Hennekens knew the risk factors “much better than I do.”
- **NASAIDS APPEAR AS RISKY AS COXIBS FROM OBSERVATIONAL DATA:** Dr. Abramson challenged Dr. Graham on his assertion that “the coxibs were more risky” since Dr. Graham also said that both indomethacin and meloxicam have “a risk” (Dr. Abramson also mentioned the McDonald & Way paper that ibuprofen had a 2-fold higher mortality). The message he got from Dr. Graham's presentation was that cardiovascular risk is dose-related for both coxibs and non-selective NSAIDs. Dr. Graham said “I think your observation is correct” and “you do need to look at it drug by drug”.
- **RECALL BIAS AND REVERSE RECALL BIAS:** Dr. Day commented about “recall bias” (“flashbulb memory” can be “notoriously false” and there are problems with “eyewitness

testimony”) and “reverse recall bias”. She said “it is not trivial how you ask people questions”. The actual questions asked are often not included in the publications.

- **ADJUSTMENT FOR INDICATION AND DOSE-INDICATION INTERACTION:**

Dr. Gibovsky asked if Dr. Graham stratified by indication (rheumatoid arthritis has increased cardiovascular risk) and factored in dose-indication relationships (since higher coxib doses are used in rheumatoid arthritis). Dr. Graham said that in most of the studies there were very few patients with rheumatoid arthritis so that it would not “materially affect things”. The California Medicaid study was “limited to patients who had diagnoses of osteoarthritis or rheumatoid arthritis” and rheumatoid arthritis did not “seem to affect things”. He did not respond to the question on dose-indication relationships.

- **SURVIVOR BIAS:** Dr. Gibovsky asked Dr. Platt about “the concept of survivor bias” in relation to differences in the amount of previous NSAID exposure and the recent study “suggesting that discontinuation of an NSAID may itself be a risk factor for a thrombotic event”. Dr. Platt agreed with the point saying that “if we start the clock after a person has already been exposed to a drug or to one that has the same effect, then, it is very much less likely that those individuals will have a problem.”

- **TIME FROM NEW USE VS. TIME ZERO:** Dr. O’Neill (FDA) asked Dr. Graham if the observational studies were able to

“identify new initial use, and then track continued use for that individual” so as to allow comparison of the hazard in randomized trials with the hazard in the observational studies. Dr. Graham said that “time on drug” was available for some cohort and nested control studies, and the Wayne Ray cohort study included “prevalent and incident users” allowing a “new user” subanalysis. However, none of the studies presented data as “a survival analysis” which he thought “is what Dr. O’Neil would like to see”. Dr. O’Neill said “my question is not so much in survival” but he does not think that these studies were designed to “define any time from new use, which is essentially critical to when those risks start”. Dr. Graham said that “time zero for rofecoxib was identified” and that looking only at the data in the 30 days since time zero, the increased risk with rofecoxib was still seen. One could also know that an increased risk seen occurred before 18 months if no one in a study had 18 months of therapy.

- **RISK MIGHT BE BASED ON RISK FROM DISCONTINUING PRIOR NSAIDS:** Dr. O’Neill said that if “discontinuation from an NSAID alone raises risk”, the increased risk following initiation of coxib therapy could merely reflect the discontinuation from the NSAID. This would not be a problem in randomized trials where there is a comparator group that has similar NSAID discontinuation. Dr. Graham said that “even in the clinical trials, study 090 was 6 weeks long, 12.5 mg, and it had a cardiovascular effect”.

- SIGNIFICANCE OF LEVEL OF RISK:** Dr. Farrar asked Dr. Graham “what level of risk is acceptable” bearing in mind that “treating pain or not treating pain and not treating the disability of arthritis also has very serious risks, even of death”. Dr. Graham said that a reduced GI risk would contribute to such a decision but that the data are conflicting – although only rofecoxib has the GI protective claim, in two “large” published studies celecoxib was associated with a “lower rate of hospitalization for GI than rofecoxib”. We “actually know very little about the actual population benefit of any of these products” but “The case fatality rate for myocardial infarction in the United States approaches 40 percent. The case fatality rate for hospitalized GI bleeding is probably somewhere around 5 or 10...”. Dr. Nissen said that a ‘hazard ratio of 1.5 to 2’ is “equivalent to raising a cholesterol from 200 to 260, or taking up smoking”. The drugs that are most effective in reducing cardiovascular morbidity and mortality are the statins, and they ‘reduce risk about 35 percent. So, a hazard ratio of 1.5 to 2 is really a very, very big effect when you are talking about the most common cause of mortality”. Dr. Boulware later suggested that even with a risk approaching 2.0, there might be some patients for whom that risk is acceptable, for example patients for whom physical impairment as a result of a lack of pain drug therapy could increase risk. He mentioned data showing that mortality increases with increasing functional impairment in rheumatoid arthritis patients.
- IS RISK RATIO A FUNCTION OF DURATION OF THERAPY?** Dr. Nissen asked if the lower apparent risk in the observational studies might represent a somewhat increased hazard with short term therapy, but that the larger degree of risk in the long term randomized studies might represent an increasing hazard ratio with longer duration of therapy. Dr. Graham thought it was “more likely” that the “hazard is the same” but there are insufficient events early to show the effect. He also suggested that the lower apparent risk in the observational studies might reflect the higher “misclassification of exposure” (with more intermittent therapy) and “misclassification of outcome” than in randomized trials.
- STRONG SIGNAL IN RANDOMIZED STUDIES REDUCES VALUE OF OBSERVATIONAL STUDIES:** Dr. D’Agostino said he had “spent a good part of my career in the Framingham Heart Study” which is a cohort observational study but he was concerned that, since we already had “very strong” randomized studies (the APPROVe study and the APC study), the observational studies did not add much. Dr. Graham said that the observational studies were the only ones with adequate power to demonstrate the increased risk during early therapy.
- RISK AS A FUNCTION OF AGE:** Dr. Boulware asked if there was evidence that the level of risk was age-dependent. Dr. Graham said that “Nobody in any of the studies where they have looked at it” suggested “that the level of risk differs at different ages”.

- **IMPACT OF MISSED DOSES ON RISK:** Dr. Cryer asked if there was a way in observational studies to take into account missed doses, since a missed dose results in antiplatelet and other effects being “immediately reversed”. Dr. Graham said “No, there isn’t” and the impact of missed doses would be to bring the risk ratio closer to 1.
- **NSAID COMPARISONS VALID BECAUSE PATIENTS NEED TREATMENT:** Dr. Temple made two points: The first was that people were going to get “one drug or another” for their chronic pain so that “comparisons with other NSAIDs seems like as good a comparison as we should make”.
- **OVER-INTERPRETATION OF SMALL RISK RATIOS:** Dr. Temple’s second point was that differences of less than 2 (or even less than 3 according to “Jerry Cornfield, who sort of invented all this stuff”) are generally agreed to be hard to interpret, but “we are talking about differences here that are 0.1 differences, not that they wouldn’t be hugely important if they were true”. Yet “just as an example, there is a very great consistency that you cite that celecoxib looks sort of okay, but you found one study where there is a little hint that maybe the higher dose is a problem, and since probably we all think dose response is likely, that looks good to you.” Dr. Platt said “a relative risk of 3 in an epidemiologic study, as David found” (for high dose rofecoxib) “is meaningful”. Dr. Temple said “I would not dispute that at all”. Dr. Platt said that data on lower doses “gains weight by borrowing” from the clearer data at higher doses, and that replication of

results “in a number of different environments” where similar biases are less likely is also important. Dr. Graham said that we are reaching the limits of “the available tools we have to define the levels of risk that we are talking about”. He agreed with Dr. Platt that “consistency across different studies” was important but that “some light in a storm is probably better than no light in a storm”. Dr. Temple asked if Dr. Graham was saying that “very low hazards need at least multiple support before they are credible”. Dr. Graham agreed.

- **INCREASED RISK RATIO WITH LONGER DURATION REQUIRES LONGER STUDIES:** Dr. Temple said that new data alters one’s thinking. He gave the analogy of the antiarrhythmic drugs which after the CAST study had to show “that you don’t alter survival unfavorably” with the result that “there are hardly any being developed”. So, if you form a new hypothesis that the risk ratio increases with long term therapy, you have to study drugs for longer durations. Dr. Graham said that larger short term studies could provide the same precision in evaluating risk. Dr. Temple said that this would not be the case if the increased risk involved something like “a small, long-term increase in blood pressure” for which the effects would take longer to develop.
- **CONCERN ABOUT UNPUBLISHED NON-PEER-REVIEWED STUDIES:** Dr. Stemhagen expressed concern about interpreting unpublished studies without peer review.

- **DEFINITION OF INCEPTION COHORT:** Dr. Stemhagen also asked about Dr. Graham’s definition of “inception cohort”. Dr. Graham said that “Inception cohorts are where people enter the cohort with their first-time use of a specific agent, so it’s basically like an incident cohort, it’s new users. That is to be distinguished from a prevalence cohort where starting January 1st, everybody who was on an NSAID is in our cohort.”
- **MOST PATIENTS ARE NOT DE NOVO NSAID USERS:** Dr. Stemhagen said that most patients “are really switching” from previous drug therapy rather than first time users of NSAIDs.
- **OBSERVATIONAL STUDIES DID NOT ADDRESS IMPACT OF UNDERLYING DISEASE:** Dr. Stemhagen also pointed out that the observational studies did not “tease out” the impact of the underlying disease, such as colon polyps or Alzheimer’s in which increased risk versus placebo had been shown in the controlled trials.
- **EVALUATION OF ABSOLUTE RISK DIFFICULT IN OBSERVATIONAL STUDY:** Dr. Fleming said that it is difficult to conclude that there is increased hazard of a drug (and he specifically mentioned naproxen) versus no therapy in an observational study since the “non-use people” may have been “intrinsically better”. Dr. Graham agreed that this was an issue and “you adjust for all the confounders you are able to measure” but “there still could be effects that you cannot remove”.
- **CCB SAGA ARGUES AGAINST PREMATURE RESPONSE TO APPARENT RISKS IN OBSERVATIONAL STUDIES:** Dr. Hennekens pointed out that 10 years ago “a large body of basic science, clinical studies, case-control, and prospective cohort studies consistently showed that patients with hypertension prescribed calcium blockers had 1.5 to 2-fold increased risk of MI” and he interpreted Dr. Graham’s position as being that “you would have asked the agency to withdraw the drugs” (even though later randomized studies showed no increased risk). “Protecting the public from harm” is “simple and straightforward” but may not have the effect of “doing the most good for the most people”. Dr. Graham responded that “when you are faced with a large risk that affects large numbers of people, and has a large consequence, that you don’t have the luxury of time to wait 10 years to get clarification on the issue, and you have to use what data you have available at the time.”

Sponsor Presentation (Merck): Arcoxia (etoricoxib): Sean Curtis MD

- **ETORICOXIB: MARKETED OUTSIDE U.S, COX-2 SELECTIVE, LONG 1/2-LIFE:** Etoricoxib is COX-2 selective with a half-life of 22 hours. It is marketed in ~60 countries outside the US.
- **EFFECTIVE:** In various arthritic conditions, etoricoxib 90-120 mg/day was comparable or superior in efficacy to naproxen 1,000 mg/day and indomethacin.
- **LESS GI TOXICITY:** Etoricoxib was associated with a 52% reduction in the risk of upper GI complications compared with NSAIDs (results being “largely driven by comparisons to naproxen”).
- **DOSE-RELATED INCREASE IN HYPERTENSION AE:** Etoricoxib caused a dose-related increase in the incidence of “hypertension adverse experiences”. At doses of 60 & 90 mg/day (i.e., “doses indicated for chronic use”) these effects but these effects “are within the range observed with comparator NSAIDs, numerically higher than naproxen, numerically lower than that observed with ibuprofen...”
- **COMPARABLE TO NSAIDS IN HYPERTENSION, CHF & EDEMA:** “...hypertension, edema, and heart failure are dose related as would be expected, and generally similar to the effects observed with comparator NSAIDs...”. “...etoricoxib as compared to comparator NSAIDs pooled” was “associated with similar rates of congestive heart failure adverse events.”
- **CLASS EFFECT:** The etoricoxib data together with recent results from rofecoxib and celecoxib studies “suggest a class effect”.

META-ANALYSIS:

- **CV EVENTS IN 6,700 PATIENTS IN STUDIES OF AT LEAST 4 WEEKS THERAPY:** A meta-analysis including 6,700 patients from 12 studies of at least 4 weeks duration compared cardiovascular event rates with etoricoxib (60, 90 and 120 mg doses combined), naproxen and non-naproxen comparators.
- **THROMBOTIC CV EVENTS COMPARABLE TO NON-NAPROXEN NSAIDS:** Relative risk estimates indicated “no discernible difference in thrombotic cardiovascular events” between treatment groups in studies comparing etoricoxib and non-naproxen NSAIDs.
- **THROMBOTIC CV EVENTS HIGHER THAN WITH NAPROXEN:** However, “when comparing etoricoxib to naproxen, the relative risk is greater than 1, indicating a difference between the 2 treatment groups in a trend favoring naproxen in that comparison.”

- **NO DOSE-RESPONSE FOR CV EVENTS:** “The data do not indicate evidence of a dose effect across the 60 to 120 mg etoricoxib dose range”.
- **RELATIVE RISK NOT A FUNCTION OF BASELINE**

FACTORS: Subgroup analyses did not suggest that relative risk was related to the baseline factors examined.

MORTALITY:

- **NO TRUE DIFFERENCE IN ALL-CAUSE MORTALITY VERSUS COMPARATORS:** All-cause mortality excluding the EDGE study was “numerically higher” with etoricoxib and non-naproxen NSAIDs than with naproxen and

placebo, but “there is no evidence for a true difference in all-cause mortality between treatment groups.” All-cause mortality in the EDGE study was “numerically similar” between the etoricoxib and diclofenac treatment groups.

FURTHER EVALUATION OF CARDIOVASCULAR SAFETY:

- **CV SAFETY TO BE EVALUATED IN ARTHRITIS:** For further evaluation of the finding of increased cardiovascular events with etoricoxib versus naproxen, Merck decided to focus on patients with arthritis.
- **ACTIVE COMPARATOR IS DICLOFENAC:** The focus on arthritis necessitated active drug comparators rather than placebo. Merck selected diclofenac as the comparator for several reasons: Firstly Merck wanted to compare “a selective COX-2 inhibitor and a traditional NSAID”. Diclofenac was the “traditional NSAID” selected because it 1) is effective in arthritis, 2) has the convenience of twice daily dosing, 3) “does not interfere with low-dose aspirin’s anti-platelet effects” (which ibuprofen does), 4) would not have the “confounding effect expected from naproxen”

(based on naproxen’s superior cardiovascular safety from the earlier results in the development program, and 5) has “generally similar, and in fact, in some cases more pronounced” blood pressure effects to etoricoxib. Merck “established criteria” to “choose an appropriate comparator NSAID” but do not appear to have considered COX-2 selective drugs such as diclofenac as inappropriate choices under these “criteria”.

- **DICLOFENAC INHIBITS COX-1 AS WELL AS COX-2:** Merck believes that diclofenac has “COX-1 inhibiting effects” on the basis of ex vivo inhibition of PGE2, on a clinical trial that showed a “significantly greater” incidence of endoscopic GI ulcers with diclofenac than with Bextra, and on a significantly greater incidence of the totals of “confirmed plus

unconfirmed” “upper GI clinical events” with diclofenac than with Vioxx.

- **PLAN TO SHOW NON-INFERIORITY TO DICLOFENAC:** The “overall approach” to evaluation of cardiovascular safety will be to show non-inferiority to diclofenac in a “prospectively designed analysis ... from three studies” comparing etoricoxib and diclofenac: 1) EDGE (a completed 7,111-patient osteoarthritis trial with a mean of 9 months therapy_ , 2) EDGE II (fully enrolled 4,090-patient RA trial using etoricoxib dosage of 90 mg/day with

a predicted mean duration of 19 months per patient), and 3) MEDAL (fully enrolled ~23,450-patient OA & RA trial with a predicted mean duration of 20 months per patient; MEDAL is an “endpoint-driven outcome” trial that is “sufficiently powered” “on its own” to allow an individual study analysis). An external DSMB is monitoring the data from these three studies and as of the last DSMB meeting in November 2004 there were 300 confirmed thrombotic events from 21,000 patient-years of exposure with about 3,000 patients on therapy for at least 18 months.

FDA Presentation: Analysis of Cardiovascular Thromboembolic Events with Etoricoxib: Joel Schiffenbauer MD

CV ENDPOINTS:

- **COMPOSITE VS. INDIVIDUAL COMPONENTS OF ENDPOINT:** Merck proposed a composite cardiovascular endpoint but FDA also looked at the components of the composite endpoint.
- **CONFIRMED EVENTS:** FDA will present data for “confirmed thrombotic cardiovascular serious adverse events” 1) for the entire NDA excluding the EDGE study, and 2) for the EDGE study alone.

NON-EDGE DATA:

- **RISK RATIOS FOR NON-EDGE DATA:** “Across the NDA” (exclusive of the large EDGE study) the risk ratios, based on small numbers of events, were calculated:
- **VS. PLACEBO:** Etoricoxib 1.25 (7 patients) versus 1.19 for placebo (4 patients).
- **VS. NON-NAPROXEN NSAIDs:** Etoricoxib 0.79 versus non-naproxen comparators 0.80 (all on diclofenac). The Kaplan-Meier graph showed a shorter time-to-event for the etoricoxib group.
- **VS. NAPROXEN:** Etoricoxib 1.37 versus naproxen 0.81. The Kaplan-Meier analysis “shows a separation of the two curves almost throughout the entire exposure.”

EDGE TRIAL:

- **NON-INFERIORITY DEFINED AS <1.3 HAZARD RATIO:** For the 7,100-patient EDGE study in osteoarthritis, the “sponsor defined a non-inferiority margin to diclofenac for cardiovascular events as the upper limit of the 95 percent confidence interval for the hazard ratio of 1.3”.
- **30% ON ASPIRIN:** Aspirin was used in 30% of patients which might have reduced cardiovascular risk in a COX-2 setting.
- **PREVIOUS COX-2 USE ALLOWED:** “previous COX-2 use was allowed and this could potentially lead to depletion of susceptible individuals to a cardiovascular event.”
- **K-M CURVES CONVERGE AT 12 MONTHS:** In the Kaplan-Meier analysis of CV event rates, “the two groups separate slightly, but the two curves do finally converge at approximately 12 months”.
- **CV RISK SAME IN ASPIRIN USERS BUT SOMEWHAT HIGHER IN NON-ASPIRIN SUBSET:** CV event rates were comparable in aspirin users (12 versus 9 total, and 7 versus 5 cardiac). However, in non-aspirin users there were 15 cardiac events on etoricoxib versus 10 on diclofenac, and 12 MIs versus 6 on diclofenac.
- **MORE HYPERTENSION ON ETORICOXIB:** Hypertension-related risk was higher with etoricoxib: 5 versus 2 for hypertension-related SAE, and 69 versus 30 for “hypertension-related AE associated with systolic blood pressure greater than 180, or diastolic greater than 110”. Similarly, a graph over 12-months therapy of the “cumulative incidence of new use of anti-hypertensive medications” showed that “the two curves separate almost throughout the entire 12-month period.”
- **MORE HEART FAILURE ON ETORICOXIB:** There was also an increase in “congestive heart failure-related adverse events”, 14 versus 6.

MORTALITY DATA:

- **PLACEBO = NAPROXEN < NON-NAPROXEN NSAIDs < ETORICOXIB:** Looking at mortality data across the NDA, “the placebo group is similar to naproxen, followed by the non-naproxen non-steroidals, and then etoricoxib”.

CONCLUSIONS:

- **TREND TO INCREASE IN CV EVENTS:** In the NDA “etoricoxib trends worse in terms of cardiovascular thromboembolic events, particularly cardiac and MI. The one common thread throughout all the comparators does appear to be the cardiac system.”
- **ETORICOXIB & ROFECOXIB SHOW SAME INCREASE IN CV EVENTS VS. NAPROXEN:** “Comparisons of etoricoxib to naproxen for the cardiovascular events is similar to what you have seen for rofecoxib and the naproxen comparisons.”
- **UNFAVORABLE TRENDS IN NON-ASPIRIN USERS IN EDGE TRIAL:** “There are trends in the EDGE study for cardiac events, worse for etoricoxib, and that is seen mainly in the non-aspirin users.”

Lumiracoxib Introduction Mathias Hukkelhoven PhD

- **LARGE DATABASES ON LUMIRACOXIB, IBUPROFEN & NAPROXEN:** The Novartis lumiracoxib program also provided large ibuprofen and naproxen databases.
- **EACH DRUG HAS A UNIQUE BENEFIT-RISK PROFILE:** Each non-selective and COX-2 selective NSAID has an individual benefit-risk profile, and lumiracoxib has a unique “GI and CV safety profile”.
- **PRESENTATION TO FOCUS ON CHRONIC USE DATABASE:** Lumiracoxib has been investigated for several indications, but the Novartis presentation will focus on chronic indications, with data on 34,000 patients in 22 clinical trials of 1 week or longer.
- **LARGE (>18,000 PATIENT) TARGET TRIAL:** These data include the TARGET trial in over 18,000 patients (the largest NSAID trial ever performed) and a trial that used “400 mg daily dosing, which is 4 times the dose for which approval will be sought”.
- **LARGE META-ANALYSIS (34,000 PATIENTS):** In addition, the results of a meta-analysis of all 22 clinical trials will be presented.
- **GI BENEFIT WITH NO SIGNIFICANT GI RISK:** The results show “a definitive GI benefit with lumiracoxib in the non-aspirin population. In addition, the CV meta-analysis of all lumiracoxib studies at no point revealed a significant CV risk”.

Gastrointestinal and Cardiovascular Safety of Lumiracoxib, Ibuprofen, and Naproxen: Patrice Matchaba MD (Novartis)

- **PRESENTATION IS ON TARGET TRIAL:** The presentation is based on the TARGET 1-year osteoarthritis lumiracoxib study (already published in Lancet). TARGET included 18,000 patients to give adequate power to demonstrate superiority for GI ulcer complications (which occurs in only 1% of patients). Patients were stratified by need for low-dose aspirin (which was expected to increase GI events).
- **EVENT ADJUDICATION:** There were three Adjudication Committees – GI, CV and hepatic.
- **DOSAGE & COMPARATORS:** TARGET compared lumiracoxib (at 400 mg once daily - 4x “proposed OA dose”) with naproxen (500 mg bid) and ibuprofen (800 mg tid) in two separate trials of comparable design. The naproxen trial began 4-5 months before the ibuprofen “substudy” and used different trial centers. Duration of therapy was the full 12 months in the protocol in 60% of patients.
- **BASELINE VALUES:** At baseline, most were female, average age was 63 years, and 12% had high CV risk.
- **FAVORABLE GI SAFETY:** GI complications were reduced by 79% with lumiracoxib compared with the pooled naproxen and ibuprofen groups (83% for ibuprofen and 76% for naproxen). In the aspirin subset, there was a 21% non-significant reduction in GI complications.
- **MORTALITY:** Mortality in the pooled naproxen and ibuprofen substudies was comparable (29 lumiracoxib and 30 NSAID deaths).
- **SHORT HALF-LIFE, POSSIBLY WITH ONLY INTERMITTENT PROSTACYCLIN INHIBITION:** “Lumiracoxib has got a short half-life, and if the hypothesis that continuous prostacyclin inhibition is important, this may be an important factor”.
- **RISK-BENEFIT INDEX:** Novartis devised and prespecified a procedure for assessing benefit-risk (although this is not “validated”) in which “we combine ulcer complications as defined by perforation, obstruction, and bleeds, and combine them with the primary cardiovascular endpoint, of the APTC endpoint”.

CARDIOVASCULAR SAFETY PARAMETERS:

- **PRIMARY CV ENDPOINT:** The protocol prespecified that the primary cardiovascular safety endpoint would be the APTC

composite index for which lumiracoxib would be compared to the pooled naproxen and ibuprofen data.

- **SECONDARY CV ENDPOINTS:** However, Novartis also did APTC

endpoint comparisons for naproxen and ibuprofen separately and looked at the individual components of the APTC index.

CARDIOVASCULAR SAFETY OVERALL:

- **COMPARABLE CV SAFETY OVERALL:** Cardiovascular safety was comparable between

lumiracoxib and the pooled naproxen and ibuprofen data.

IBUPROFEN SUBSTUDY:

- **NO INCREASE IN APTC, MI, STROKE, CARDIORENAL COMPLICATIONS OR HF:** In the ibuprofen substudy, there was no increased cardiovascular hazard (in terms of the APTC endpoint, MI, stroke, cardiorenal complications or heart failure) for the total patients or for the aspirin or non-aspirin subsets individually.
- **LESS BLOOD PRESSURE EFFECT:** However lumiracoxib was associated with significantly less (6%) new-onset hypertension than ibuprofen (10%). Similarly, lumiracoxib was associated with significantly less aggravation of preexisting hypertension. For mean change in blood pressure, systolic and diastolic BP rose significantly less with lumiracoxib (0.7 mmHg vs.

2.7 mmHg for systolic BP and 0 vs. ~1 mmHg for diastolic).

- **EDEMA AND HEART FAILURE:** There were no significant differences for edema and congestive heart failure but “you see that there are more patients taking lumiracoxib with edema, congestive heart failure, but no difference for weight gain” but “there isn't an increase compared to ibuprofen for congestive heart failure and for edema”.
- **BENEFIT IN RISK-BENEFIT INDEX:** The risk-benefit index showed “that patients taking ibuprofen are significantly worse for this combination of the 2 endpoints of GI ulcer complications and APTC” for all patients but no significant difference is seen in the aspirin subset.

NAPROXEN SUBSTUDY:

- **HIGHER BL CV RISK IN NAPROXEN SUBSTUDY:** The

naproxen substudy population had higher baseline cardiovascular risk than the ibuprofen substudy

population, as assessed by low-dose aspirin use, CV risk factors and hypertension.

- **HIGHER CV EVENT RATES THAN IBUPROFEN SUBSTUDY:** In the naproxen substudy, cardiovascular event rates were higher than in the ibuprofen substudy.
- **LUMIROCOXIB HAS UNFAVORABLE RELATIVE RISK VERSUS NAPROXEN:** “Hazard ratios ...are now in favor of naproxen, and there are more events with the lumiracoxib compared to naproxen”.
- **INCREASED CV RISK DRIVEN BY MI:** This increased cardiovascular risk is ‘driven by the differences in myocardial infarcts particularly in the non-aspirin population’ (10 MIs vs. 4 for a “hazard ratio” of 2.37 which is “not significant over the 12-month treatment period”). In the aspirin subset, “the hazard ratio decreases” so that “when you consider the low-dose aspirin population and you add COX-1 activity”, “the numeric difference disappears”.
- **NAPROXEN OBSERVATIONAL STUDIES OF MI:** A meta-analysis of naproxen observational studies (Lancet, June 2004) reported a significant 14% reduction in MI. In addition, dosage in observational studies might involve lower dosage and wider dosing intervals than in clinical trials.
- **NO DIFFERENCE IN STROKE:** There were no significant differences in stroke rates.
- **BLOOD PRESSURE:** For blood pressure, “we see that there is

significant difference in favor of lumiracoxib compared to naproxen” but there was no significant difference for new onset hypertension.

- **EDEMA & HEART FAILURE:** There were “slightly more patients having edema” (4.5% vs. 4.2%) but “no increase compared to naproxen for congestive heart failure”.
- **BENEFIT IN RISK-BENEFIT INDEX:** The risk-benefit index showed a significant benefit for lumiracoxib versus naproxen.
- **RESULTS IN HIGH CV RISK SUBSET:** In a subset of 2,200 patients treated for 12 months who were at high cardiovascular risk (based on history of coronary artery disease, previous MI or vascular events, or a high Framingham risk score), there were 8 MI on lumiracoxib and 7 MI on NSAIDS (7 vs. 5 in the naproxen substudy, and 1 vs. 2 in the ibuprofen substudy). In the 646 patients (30%) of that 2,200 patient subset who were not on low-dose aspirin, there were 3 lumiracoxib vs. 1 NSAID myocardial infarcts (2 vs. 0 in the naproxen substudy, and 1 vs. 1 in the ibuprofen substudy). In 288 patients “who had a previous myocardial infarct, randomized to treatment for 1 year” there were 3 lumiracoxib vs. 6 naproxen myocardial infarcts but “certainly this is chance”. The above data indicate that “we are not seeing an outstanding signal even in this high-risk population”.

META-ANALYSIS:

- **34,000 PATIENT META-ANALYSIS:** Over 34,000 patients were included in a meta-analysis of all studies completed by the end of 2004. Patients “who were randomized to 1-year studies accounted for almost 90 percent”.
- **NO SIGNIFICANT INCREASE IN RELATIVE RISK IN META-ANALYSIS:** For the APTC cardiovascular endpoint, the relative risk versus all comparators was 1.2 (non-significant), and versus non-

naproxen comparators the relative risk was 0.94. For myocardial infarct, the relative risk versus all comparators was 1.28 (non-significant), and versus non-naproxen comparators the relative risk was 1.24. For stroke, the relative risk versus all comparators was 1.02, and versus non-naproxen comparators the relative risk was 0.84.

FDA Presentation on Lumiracoxib: Lourdes Villalba MD

- **PRESENTATION CONFINED TO TARGET TRIAL:** TARGET was an 18,000-patient, 1-year osteoarthritis study with two separate comparisons with lumiracoxib (naproxen and ibuprofen).
- **LUMIRACOXIB DOSE:** The lumiracoxib dose was 400 mg/day (four times the 100mg dose that “now the sponsor is pursuing”).
- **CONCOMITANT ASPIRIN:** Aspirin was used by about 25% of patients.
- **BASELINE CARDIOVASCULAR RISK:** There was slight baseline imbalance in cardiovascular risk between the naproxen and ibuprofen components.
- **CV ENDPOINT:** Merck used confirmed APTC events. Dr. Villalba will use confirmed and probable APTC events.
- **APTC EVENT RATES:** There were 40 lumiracoxib events versus 27 on naproxen in the naproxen component, and 19 lumiracoxib

events versus ibuprofen in the ibuprofen component.

- **NON-FATAL MI IN NON-ASPIRIN USERS DRIVE EVENTS:** The lumiracoxib/naproxen difference in APTC event rates was “driven” by non-fatal MI (which includes silent MI) among the non-aspirin users. The numbers of non-fatal MIs in the lumiracoxib/naproxen comparison were 18 versus 10 on naproxen.
- **EARLY SEPARATION OF LUMIRACOXIB & NAPROXEN:** The Kaplan-Meier plot shows “a separation between lumiracoxib and naproxen” that starts before day 50 and continues. The study was 1 year in duration and in APPROVe the Vioxx effect versus placebo did not become obvious until 18 months.
- **EVEN EARLIER ONSET OF SIGNAL IN LANCET PAPER:** In the Farkouh Lancet paper, the signal for lumiracoxib versus naproxen “seems to start earlier than what we have seen before.”

- **IBUPROFEN MAY INHIBIT ASPIRIN PLATELET EFFECT:** In the ibuprofen comparison, aspirin users showed a trend supporting other data suggested that ‘ibuprofen depleted the anti-platelet effects of aspirin.’”
- **BP INCREASE MORE WITH IBUPROFEN:** In the prior presentation by Novartis, ‘ibuprofen affected blood pressure more than what lumiracoxib did’”.

Committee Questions to Merck (Etoricoxib), Novartis (Lumiracoxib) and Dr. Villalba (FDA)

Etoricoxib Discussion:

- **NON-US LABELING CHANGES FOR ETORICOXIB:** Dr. Crawford asked what specific revisions in labeling are being made for etoricoxib in non-US markets. Dr. Curtis (Merck) that this will reflect a CHMP-mandated class-wide contraindication in heart failure, ischemic heart disease and cerebrovascular disease. In addition, etoricoxib will have a non-class-wide contraindication in patients with hypertension whose blood pressure has not been adequately controlled”. Later Dr. Dworkin asked how the CHMP defined the “class”. Dr. Erb (Merck) said that the class is “the coxibs, lumiracoxib, celecoxib, and etoricoxib, and valdecoxib”.
 - **DICLOFENAC COMPARATOR FOR NEW MERCK ETORICOXIB STUDIES:** Dr. Wood asked what studies Merck would do to get US approval. Dr. Curtis said Merck would proceed with the EDGEII and MEDAL comparisons with diclofenac. Dr. Wood said since diclofenac appeared to be a COX-2 selective drug also, “I am not sure what that will teach us”.
- Dr. Curtis said that diclofenac is “probably the NSAID used most worldwide currently”. Dr. Fitzgerald said that diclofenac could be considered as a “surrogate for Celebrex” in the “continuum” of COX-2 selectivity and increased cardiovascular risk, and accordingly these trials would be “very useful” as a comparison of a relatively selective versus a highly selective COX-2 inhibitor.
- **NON-INFERIORITY CRITERIA:** Dr. D’Agostino asked about what would be adequate to be considered a “non-inferiority” trial of etoricoxib. Dr. Curtis said that this would be the combined data from three trials (EDGE, EDGEII and MEDAL) which would provide a minimum of “635 confirmed thrombotic events”. Dr. D’Agostino asked if people on aspirin in these studies would be part of the non-inferiority evaluation. Dr. Curtis said that “the primary analysis will be based on all patients whether they are on aspirin or not”. Dr. D’Agostino suggested that he would “get rid of” the aspirin users, who don’t have the same hazard as non-

aspirin users and “are confounding things”. Dr. Schiffenbauer agreed that aspirin use could reduce the signal of increased cardiovascular risk.

- **META-ANALYSIS OF TWO ETORICOXIB STUDIES VERSUS NAPROXEN:** Dr. Gibovsky asked if etoricoxib would be superior to naproxen in a meta-analysis of the two naproxen studies, only one of which showed “superiority”. Dr. Curtis said that “it would be speculative to talk about combining the results”.
- **NAPROXEN SHOULD NOT BE SEPARATED FROM OTHER NSAIDS IN POOLED COMPARATOR ANALYSIS:** Dr. Shafer said that the data did not support breaking out the etoricoxib comparators into naproxen as a separate group and all other comparators. The results in the etoricoxib trials versus naproxen are similar to those in the rofecoxib-naproxen comparisons but any beneficial effect of naproxen is “certainly nothing of the magnitude” needed to explain a “1.5, 1.7 risk relative to naproxen”. The naproxen manufacturers in their own presentation “felt that naproxen did not have the cardio-protective effects that you have attributed to it”. He asked if we are “not actually seeing a very solid signal for intrinsic increased cardiovascular toxicity with the COX-2 antagonists?” Dr. Curtis did not answer this question directly but said “We have now seen qualitative differences in cardiovascular outcomes against naproxen with three different COX-2 selective inhibitors: rofecoxib, etoricoxib, and lumiracoxib.”

- **NAPROXEN+OMEPRAZOLE AS COMPARATOR:** Dr. Wood asked why Merck did not choose to compare etoricoxib to a combination of naproxen and omeprazole which could reduce the GI toxicity of naproxen. Dr. Curtis said that “we have seen data that suggests even when you add a PPI to an NSAID, there is still room to improve from a GI safety perspective”. Dr. Wood said “You saw that naproxen beats your drug. So, you decided to pick one that didn't look like it would That doesn't make any sense.” He said that randomized trials showing more cardiovascular toxicity than with placebo means that it is not enough to pick a comparator that may be comparable in cardiovascular toxicity. It sounded to him that “we are going into this study saying that we know and believe that the drug will produce a cardiovascular signal, we are just trying to work out if it's better or worse than diclofenac.” Dr. Curtis said that the MEDAL study would help to answer the question of “how big” is the class of drugs that increase cardiovascular toxicity.
- **NAPROXEN MORE RELEVANT THAN DICLOFENAC TO U.S. PHYSICIANS:** Dr. Bathon said that “naproxen is the most widely prescribed NSAID in the U.S. and the most relevant to our practice, whereas, diclofenac has much more hepatotoxicity especially in RA patients where methotrexate is co-administered”, so that it would “have added a lot more to our clinical practice management to see another big trial against naproxen plus you could have added these results to your prior trials and had more power

to assess the effect of naproxen versus etoricoxib with all of your trials combined”.

- **ETORICOXIB DICLOFENAC STUDIES ALREADY FULLY ENROLLED:** Dr. Reicin (Merck) commented that the “studies are fully enrolled and ongoing. I can't disagree with you that the idea of doing a naproxen plus PPI study versus a COX-2 inhibitor isn't a good idea and isn't an important question. Unfortunately, we didn't design that study. We designed this one...” and “it will provide beneficial safety data to see what a selective COX-2 inhibitor looks like versus a non-selective inhibitor, albeit not as non-selective as naproxen.”
- **FDA DID RECOMMEND ADDITIONAL COMPARATORS TO MERCK:** In response to a question by Dr. Platt, Dr. Schiffenbauer said that FDA “recommended strongly” to Merck “that additional agents” (other than diclofenac) “be studied to get a better handle on the true cardiovascular risk” with etoricoxib.
- **UNDERLYING CV RISK IN MEDAL STUDY:** In response to a question by Dr. Farrar about “the difference in the underlying risks between some of these different comparisons”, Dr. Curtis said that in the MEDAL study is 75% osteoarthritis, 50% hypertensive, and 12% “documented atherosclerotic cardiovascular disease”.
- **IS THERE A CONTINUOUS GRADATION OF RELATIVE RISK ACROSS DIFFERENT LEVELS OF BASELINE CARDIOVASCULAR RISK?** Dr. Farrar asked Dr. Fitzgerald to comment on whether relative risk is

increased in all groups with cardiac risk factors or whether it is restricted to those with “release of active agents from the surgical procedure”. Dr. Fitzgerald said that it was “conjecture” but that “as we move away from that extreme” (CABG surgery) “through what we call ‘heightened’ cardiovascular risk, there is probably a continuum of predisposition” based on the “predisposition” to such factors as hemostatic activation and hypertension induction. Dr. Wood pointed out that there was increased risk “even in the people with no history of cardiovascular disease”.

- **IF COX-2 DRUGS PROMOTE ATHEROGENESIS, FIVE-YEAR TRIALS MAY BE NEEDED:** Dr. Nissen expressed concern that if the COX-2 drugs are “promoting atherogenesis” randomized trials may have to be of 5 years duration, and you would not be able just to increase the “sample size in order to shorten the duration”. Dr. Curtis said “I am not going to disagree” but that arthritis trials tend to have 40% dropout by 1 year and an additional 10-20% yearly thereafter, which would make a valid 5 year study very difficult in this population.
- **MORTALITY APPEARS INCREASED IN EDGE ETORICOXIB STUDY:** Dr. Fleming said that in the EDGE study (with a 3:2 randomization) APTC events were 43 versus 12 which is “certainly well outside of unity”, and that the mortality results shown are “difficult to really see in this scale” but mortality appears increased and “it looks as though ...you are looking at about a 1.5 relative risk on

mortality across the aggregate of these data.”

- **ETORICOXIB IS MORE COX-2 SELECTIVE THAN VIOXX:** Ms. Malone asked for a “simple answer” about how different etoricoxib was from Vioxx. After some clarification

of the question, Dr. Curtis said that etoricoxib is more selective for the COX-2 receptor than Vioxx but that “in the dose range that these drugs are used, they all selectively inhibit the COX-2 enzyme and do not inhibit COX-1”.

Lumiracoxib Discussion

- **LUMIRACOXIB RISK RATIO A FUNCTION OF THE COMPARATOR:** Dr. Hennekens suggested that the different risk ratios for lumiracoxib versus ibuprofen of 0.76 and versus naproxen of 1.46 could be a result of the different comparators and of a protective effect of naproxen.
- **POSSIBLE INCREASED CARDIOVASCULAR RISK OF IBUPROFEN:** Dr. Abramson referred to a slide shown by Dr. Villalba (FDA) in which she suggested that lumiracoxib “behaved differently” in the two components of the TARGET study. He does not think this is a valid interpretation. He suggested that lumiracoxib could be worse than naproxen because of some mix of naproxen protection and lumiracoxib toxicity, but that the comparability of lumiracoxib and ibuprofen suggests that “ibuprofen has some risk attached to it”. Dr. Villalba agreed with his point.
- **REASON FOR 2-FOLD DIFFERENCE IN CV LUMIRACOXIB EVENT RATES IN TWO COMPONENTS OF TARGET:** Dr. Bathon asked why the two components of the TARGET trial had a 2-fold difference in cardiovascular event rates on lumiracoxib despite “the same

inclusion and exclusion criteria”. Dr. Matchaba (Novartis) responded that these differences “could be chance” but could be related to the different countries contributing sites, to differences in the time scales for the two components, or to differences in baseline cardiovascular risk.

- **INCLUDING SILENT MIs IN TARGET CV EVENT DEFINITION OBSCURES 3-FOLD INCREASE WITH LUMIRACOXIB:** Dr. Cryer suggested that some of the differences between TARGET and previous COX-2 outcome studies could be related to not using “fully adjudicated definite events” in the TARGET study. If you exclude silent MIs and just look at clinical MIS there is “an apparent 3-fold increase with lumiracoxib for clinical MIs compared to NSAIDs, which dramatically differs from your other conclusion.” Dr. Matchaba said that all events were prospectively adjudicated. Dr. Cryer said that he was asking for data that “excluded the probable”. Dr. Farkouh (Novartis consultant) responded that “probable was an element or a degree of definite”. Dr. Cryer said “With all due respect, I will ask the question a third time”. Dr. Farkouh said “we did not feel there was any distinction

between the two of them, so we did not mandate that.” Dr. Matchaba added that when you look at silent MIs alone, the same lumiracoxib-naproxen and lumiracoxib-ibuprofen trends are seen.

- **SUPERIOR GI SAFETY PROFILE OF LUMIRACOXIB MAY BE BECAUSE PATIENTS WERE AT LOW GI RISK:** Dr. Cryer also suggested that the superiority in GI safety might have been because of a “low GI risk population” since we “know that the relative risk of COX-2 specific inhibitors to have a GI benefit is greater in a population that has low GI risk”.
- **WEIGHTING OF FAVORABLE GI AND UNFAVORABLE LUMIRACOXIB CV EVENTS:** Dr. Fleming said that Dr. Matchaba’s comparison of favorable GI events

with unfavorable CV events in the naproxen comparison was misleading. His calculation was that for GI events “in terms of per 1,000 people, there are about 7 cases that are prevented” whereas for CV events “for 1,000 people, there are 3 of those cases”. This way of looking at the data changes “a clear positive” to “much less clear, if not clearly negative”. Dr. Matchaba said that “it is an attempt on our part that using this unvalidated method for the first time and prespecifying it and stacking up the primary endpoints, what does the picture look like relative to comparators in the same study?” Dr. Wood said “And a GI bleed is not the same necessarily as a stroke. They don’t compensate for one another. That is not a criticism, it is just a fact.”

Discussion of FDA Presentations

- **APTC DEFINITION:** Dr. Hennekens coauthored the APTC criteria which “prespecified non-fatal MI, non-fatal stroke, and all vascular deaths as the combined endpoint” but excluded silent MI. He thinks that Merck’s definition is correct and that Novartis and FDA have used a different one.
- **DEFINITION OF “CLASS” EFFECT:** Dr. Abramson also asked what Dr. Villalba meant by “class effect”. Dr. Villalba said that she was referring to the “entire class ... with different degrees of selectivity within the NSAID class”.

Open Public Hearing

PRESENTERS INCLUDED:

- Many patients who said that COX-2 drugs were the only ones that controlled their pain.
- A few patients in whom major adverse events such as myocardial infarction occurred.
- Vioxx, Celebrex and Bextra patients with good and bad experiences.
- Many types of physicians, including rheumatologists, other pain specialists, gastroenterologists, and an epidemiologist.
- Representatives of many professional, patient and advocacy organizations.
- Scientists with new tools to evaluate GI ulcers, COX-2 selectivity, cardiovascular risk or pro-oxidant effects of Vioxx and etoricoxib.
- A manufacturer of a topical pain relief medication.
- A litigation lawyer.
- Theorists on mechanisms of COX-2 toxicity.

ORGANIZATIONS REPRESENTED INCLUDED:

- American Autoimmune Related Diseases Association
- American Chronic Pain Association
- American College of Rheumatology
- American Pharmacist Association
- Arthritis Foundation
- Center for Regulatory Effectiveness
- Consumer Healthcare Products Association
- National Consumers League
- New York State Rheumatology Society
- Physician's Committee for Responsible Medicine
- Psoriasis Cure Now
- Public Citizen
- U.S. Army Medical Corps

NOTABLE PRESENTERS:

- A colleague of 1990 Chemistry Nobel Laureate EJ Corey (Preston Mason).
- A former FDA Deputy Division Director (Lawrence Goldkind).
- A prominent Vanderbilt gastroenterologist (Glenn Eisen).
- A Stanford co-author of FDA's David Graham (Gurkiepal Singh).
- The Director of the Health Research Group, Public Citizen (Sidney Wolfe).
- The President of the American College of Rheumatology (Betsy Tindall).
- The President of the Arthritis Foundation (Jack Klippel).

Call to Order, Shortening of Agenda, Request for Sponsor 2-Min. Summaries – Day 3

- **AGENDA SHORTENED:** Mr. Levin suggested that the agenda be modified to make sure sufficient time was available for committee discussion, voting and advice to FDA. This was agreed. Dr. Temple and Dr. O’Neill from FDA agreed to give their talks from their seats. With regard to the talk by Dr. Hertz from FDA, Dr. Wood suggested that she remove some of the 45 slides she had

planned and commented ‘it is very unusual for the FDA to summarize the meeting for the committee, which is partly what the committee is here to do, I guess’.

- **TWO-MINUTE SUMMARIES BY SPONSORS:** It was also agreed that the sponsors could have 2 minutes each to “make some summary comments”.

Investigator Presentation: Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT): Constantine Lyketsos, M.D

- **DR. LYKETSOS IS STEERING COMMITTEE MEMBER:** He and his colleague Dr. Piantadosi (who is in the audience) are both on the steering committee of the ADAPT trial.
- **ALZHEIMER’S AFFECTS 4+ MILLION PEOPLE IN US:** Alzheimer’s disease affects 4-4.5

million people in the US and this number may increase with the expected aging of the population to 12-15 million people. Observational studies suggest “substantial reductions of risk of Alzheimer’s disease” with NSAIDs.

PREPARED STATEMENT:

- **TREATMENTS SUSPENDED ON 12-17-04:** The ADAPT study steering committee suspended the NSAID treatments on December 17, 2004.
- **MISUNDERSTANDING ABOUT SUSPENSION:** There “is much public misunderstanding about our decisions and their rationale”.
- **RISK: BENEFIT BALANCE IS DIFFERENT IN PREVENTION TRIALS:** The risk:benefit balance is different in a prevention trial from a treatment trial because “risks are

typically not balanced by any promise of tangible near-term benefit”.

- **SAFETY ANALYSIS NOT YET AVAILABLE:** Auditing and tabulation of the ADAPT trial’s cardiovascular safety data is not “quite completed” so that he cannot present the trial safety results today.
- **UNUSUAL CIRCUMSTANCES: DATA NOT SUFFICIENT TO SUSPEND: EXTERNAL DATA RAISED CONCERNS ABOUT TRIAL “PRACTICALITIES”:**

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

- **ADAPT TRIAL DESIGN:** The ADAPT trial is a double blind trial of celecoxib 200 mg bid, naproxen 220 mg bid, and placebo in subjects at least 70 years of age in the prevention of Alzheimer’s dementia and age-related cognitive decline. Subjects with “preexisting uncontrolled hypertension, anemia or a history of gastrointestinal bleeding, perforation or obstruction” were excluded.
- **DATA SAFETY MONITORING BOARD:** The ADAPT DSMB (ADAPT calls this the “TEMC”) meets twice a year. In addition “the ADAPT study officers and consultants also conduct reviews of safety data at intervals between TEMC meetings”. Dr. Bruce Psaty “a physician with expertise in evaluation of cardiovascular risks in clinical trials” was recently added to the DSMB. The ADAPT study officers had been “relatively reassured” by the “periodic reviews of the celecoxib safety data” and the “study chair communicated this information in a telephone conversation on 15 October 2004 with Dr. Sharon Hertz at FDA”.
- **DSMB TOLD 12-10-04 OF WEAK NAPROXEN SIGNAL BUT TREATMENTS CONTINUED:** Analyses of the available data (in

2,528 subjects with average duration of 20 months) were presented to the TEMC on December 10, 2004, and “suggested a weak signal suggesting increased risks of cardiovascular and cerebrovascular events with naproxen. Reviewing the data, however, we understood well the TEMC's evident conclusion that this signal was not sufficiently compelling or definitive to warrant a recommendation to suspend the treatment or to otherwise alter the protocol”.

- **TREATMENTS SUSPENDED ON 12-17-04, THE SAME DAY CELECOXIB APC RESULTS RELEASED:** On December 17, 2004, the APC and PreSAP trials were suspended because of “increased cardiovascular risks” in the APC trial.
- **BASIS FOR TREATMENT SUSPENSION:** The news of the APC results “led to extensive discussion among the steering committee on that day centering on the following considerations one arm of the APC trial had used the same celecoxib dosing as ADAPT, 200 milligrams twice daily, but over a longer period of time. News reports cited a relative risk of 2.5 for cardiac events in this arm of APC. Although this risk was reported as only ‘marginally significant,’ a greater cardiac-risk signal was reported with the higher APC dosage of 400 milligrams twice daily. Thus, we took seriously the possibility of harm over time to ADAPT participants receiving celecoxib. Especially in a prevention trial with no strong prospects of immediate benefit, we had strong misgivings about continuing celecoxib treatments”.

- **CELECOXIB CONTINUATION WOULD HAVE NEEDED CONCURRENCE OF IRBs:** If they had “discounted the APC data and continued celecoxib we would clearly have needed the concurrence of the seven IRBs that oversee ADAPT. These IRBs began almost immediately to question us about implications of the APC results and seemed likely to question a decision to continue. Even if we had persuaded them to permit continuation of celecoxib using a revised consent process, we would surely be involved in lengthy discussions with these IRBs. In the meantime, we would be unable to offer much explanation to our participants, thereby endangering the relationship of trust that is vital to the success of long-term trials.”
- **EXPECTED INCREASE IN DROPOUTS FOLLOWING APC RESULTS:** “Number three” on the list of concerns was that “ADAPT was experiencing some difficulty with adherence to treatments” following the Vioxx withdrawal and they “expected the announcement of the APC results to exaggerate the problem further with scores of participants stopping treatment...”. “Thus, even though the ADAPT safety data did not, themselves, warrant suspension of celecoxib treatments. There seemed little practical choice but to do so.”
- **NAPROXEN CARDIAC SAFETY WAS “CONCERNING”:** “We next confronted the dilemma of what to do about naproxen and its placebo. The “accumulated naproxen safety data” was “somewhat more concerning than the celecoxib safety data”. Some “post hoc data composites barely reached statistical significance for naproxen versus placebo” but “no singular vascular event was clearly more frequent with naproxen versus placebo.”
- **CHANGE TO TRIAL OF ONLY NAPROXEN AND PLACEBO COULD CONFUSE SUBJECTS:** They could have revised ADAPT to “a two-armed trial of naproxen versus placebo” but subjects “might end up getting confused and taking the wrong pills and many would stop taking their treatments altogether.”
- **“NOTABLE” INCREASE IN GI BLEEDING WITH NAPROXEN:** In addition, this would have given the “misleading” impression that the ADAPT data suggested that “celecoxib was risky but naproxen was ‘safe’ ”. In fact, even though they attempted to reduce the G.I. risk of naproxen “by excluding participants with prominent risk factors other than age, the ADAPT data showed a notable increase in G.I. bleeding with naproxen versus placebo.”
- **TOTALITY OF ARGUMENTS RESULTED IN SUSPENSION DECISION:** “Especially amid concerns that ADAPT was exposing its participants to potential risks that were immediate, while the trial's hoped-for benefits lay in the future, the totality of the above arguments lead the steering committee to suspend both treatments and to also suspend enrollment into ADAPT.”
- **PAPER TO BE SUBMITTED FOR PUBLICATION IN FEW WEEKS: WILL NOT HAVE FULL SAFETY ANALYSIS:** They “expect, within a few weeks, to submit a scientific paper for peer review and publication. The paper's

focus will be on the process and rationale underlying the decision to suspend treatments and enrollment in ADAPT. Because these decisions did rely, in some measure, on the ADAPT safety data as of 10 December, the paper will, also, disclose some of these data.”

- **FOLLOW-UP OF SUBJECTS AND EVENT CLARIFICATION/**

ADJUDICATION IS PLANNED:

Subjects in the ADAPT study will have “a further two years of additional safety monitoring”. In addition, additional information will be collected on some of the adverse events, and “all information” will be submitted for “expert adjudication”.

Committee Questions for Dr. Lyketsos on ADAPT Trial

- **FIRE IN AUDITORIUM:** Dr. Nissen commented that the initial NIH announcement was “the medical equivalent of screaming ‘fire’ in a crowded auditorium” and it would have been preferable to have said that the trial was being stopped for “for futility rather than for hazard, when there was a non-statistically significant hazard”. Dr. Wood and Dr. Gibovsky agreed with this comment.
- **GI BLEED COMPONENT:** Dr. Farrar asked about the advisability of a trial that put ‘patients at risk of serious complications from the G.I. bleeding’. Dr. Lyketsos said that the GI risk was considered in the context of the high risk of these subjects for the “devastation that Alzheimer’s disease brings”.
- **USE OF PREVENTION DATA TO RESTRICT TREATMENT USAGE:** Dr. Gibovsky asked about restriction of drug use for treatment purposes being based on results in a trial for prevention of disease. Dr. Lyketsos said that on this point he would “defer” to “people who are more expert in that”.
- **BASIS FOR DOSING DECISION:** Dr. Fleming said that it was his understanding that the “driving issue” behind the steering committee recommendation came from “the external data on the APC trial for Celebrex” and not “some emerging trends that happen to be in the unfavorable direction on naproxen”. He put this in the context that “one has to be extremely cautious, when you are looking at data continually over time, not to over-interpret emerging trends that can easily ebb and flow”. Dr. Wood said: “Just to develop that question, what I understood you to say was you hadn’t passed some stopping boundary; is that correct?”
- **PRACTICALITIES VERSUS EVIDENCE:** Dr. Lyketsos responded that “the issue really was one of practicalities more than our internal data” including talking to “IRBs and participants”. Dr. Fleming asked that Dr. Lyketsos clarify “what your sense of the evidence was” before discussing practicalities. Dr. Lyketsos said that in the context of the “climate” created by the removal

of Vioxx from the market and “the widely publicized APC results”, they “had to stop and take stock and get more information” even though their own results “did not compel us to stop treatment based on our own data”.

- **EXTERNAL NAPROXEN DATA MIGHT HAVE ALLOWED CONTINUATION:** Dr. Fleming said that they did have access to the “VIGOR data which was very reassuring for naproxen” and he was “perplexed” as to why the steering committee decided not to continue the study when “your data-monitoring committee, in looking at the data, looking at the benefit as well as the risk, indicated the study should continue”. Why did they not pursue a strategy of notifying investigators, IRBs and patients “that the monitoring committee has carefully looked at benefit and risk and that the totality of the data is beyond the APC trial” since the concern in the ADAPT trial was a possible safety problem with naproxen and not celecoxib.
- **STEERING COMMITTEE ACCESS TO DATA IS VIOLATION OF TRIAL MONITORING PRINCIPLES:** Dr. Lyketsos said that “some members of the steering committee did have access to the data that the DSMB had seen” and that such “very difficult judgment calls” have to take into account “evidence, but also practical aspects of continuing to conduct this sort of a prevention trial”. Dr. Fleming said that he was “dismayed to hear ... some steering committee members, had access to the data. That is also a violation of the principles of monitoring trials. It

should have been in the sole possession of the data-monitoring committee. I am also distressed because I am not hearing that the monitoring committee was front and center in terms of having these issues brought back to it for reassessment”.

- **DROPOUT RATES AFTER VIOXX WITHDRAWN:** Dr. Wood asked for clarification if “one of the perceptions was it was no longer possible to continue the trial” because “of a very large number of dropouts from the trial after the Vioxx withdrawal”. Dr. Lyketsos said that “adherence” had been declining annually and “that now there were data about one of the study drugs”, “that would further erode adherence”.
- **CLARIFICATION: DRUGS STOPPED FOR OPERATIONAL PROBLEMS RATHER THAN SAFETY:** Dr. Wood said that the initial announcement “was that this trial was being stopped for a safety signal” but what “I heard in your statement and what I hear from you now is that the trial was being stopped for operational problems...”. Dr. Lyketsos responded that “I think my statement should speak for itself. In terms of what the data were, as I have pointed out, they will be submitted very soon so that you can judge for yourselves”.
- **NAPROXEN MAY HAVE CARDIOVASCULAR RISK AND ADAPT TRIAL RESULTS MAY CLARIFY THIS ISSUE:** Dr. Farrar said that the ADAPT study will “provide some vitally important information” on naproxen and he questioned Dr. Fleming’s comment about the VIGOR trial providing

“some reassurance about naproxen” since VIGOR provided no information against placebo. Dr. Farrar said that “I have assumed, based on all the data that we have, that every NSAID will not fare well against a placebo” in terms of cardiovascular safety, and “this study

is likely to provide the data to support that”.

- **LESSONS FOR THE FUTURE:** Dr. Nissen made the final comment that “it caused a panic that was unnecessary and it shouldn't have happened, and I hope it doesn't happen again”.

Interpretation of Observed Differences in the Frequency of Events When the Number of Events is Small: Milton Packer MD

- **DEFINITION OF “SMALL”:** For the purposes of his talk he arbitrarily defines “small” as providing “less than 70% power to have detected a true treatment difference, assuming an effect size similar to that generally encountered in clinical research”.
- **CONFIDENCE IN P-VALUES IS HIGHEST FOR A PRIMARY ENDPOINT IN A COMPLETED CLINICAL TRIAL:** One has most confidence in a particular calculated p-value if it refers to a predefined primary endpoint in an adequately powered clinical trial. Even then, however, a p-value less than 0.05 has only about a 50% probability of being seen again in a second identical trial. For this reason, FDA requires 2 trials at the 0.05 level or one trial with a much smaller p-value (at the 0.001 level for one trial, there is 90% probability of seeing a p-value of less than 0.05 in a second identical trial).
- **P-VALUES FOR ENDPOINTS THAT ARE SECONDARY OR NON-PRESPECIFIED GIVE LESS CONFIDENCE:** If the p-value refers to a secondary endpoint, or “was not even precisely defined before the start of the trial” one should have much less confidence in the p-value.
- **BY CHANCE, A P-VALUE OF 0.05 WILL BE OBTAINED ONE TIME IN 20:** A clinical trial generates data on large numbers of safety or efficacy parameters and calculating a p value for each results in a known estimate of false positive results for p-values at the 0.05 level – 5% of all tests. Thus, if one calculates p-values for each of 500 individual adverse event terms, one should expect 25 events (5%) to show “significance” at the 0.05 level purely by chance.
- **AE RECORDING AND CATEGORIZATION OF ADVERSE EVENTS POOR, EVEN WITH ADJUDICATION:** Another issue is the accuracy in which adverse events are recorded by the investigator and then translated into standardized terms. One can pre-specify a blinded adjudication process to evaluate the adverse events, but if this is done after the unadjudicated data has been examined and a problem identified, the adjudication can magnify or

dilute the effect. In addition, adjudication usually addresses only patients who were specified as having had one of the events to be adjudicated – and does not address any under-reporting in remaining patients.

- **NON-PRESPECIFIED ADVERSE EVENT GROUPINGS CAN INVALIDATE P-VALUES:** A further issue is the fact that “some signals are apparently only if adverse events are grouped together”. Such groupings are often constructed after the fact, and are capable of being influenced by whether the investigator is trying to confirm or exclude the presence of an adverse drug effect. If the investigator does not find evidence of an effect with a particular grouping, there may be a temptation to broaden or narrow the grouping until a p-value of 0.05 is obtained. Since p-values are being calculated for many different groupings, “these differences may be related to the play of chance”. Even when a group of investigators creates a “uniform definition to be used across all studies”, they may have already examined some of the data, so that the definition may be based on what is “required to capture the events of interest”.
- **MAGNITUDE OF TREATMENT EFFECT REQUIRED FOR STATISTICAL SIGNIFICANCE IS A FUNCTION OF THE NUMBER OF EVENTS:** The smaller the number of events, the larger must be the estimated treatment effect in order to get a formal significance value of $p=0.05$. This means in a calculation of relative risk that 1) the point estimate of relative risk is very far from the

point of no-effect (a risk ratio of 1.0), and 2) the confidence limits are very wide. As the number of events increases, the ability to detect smaller effects increases, and the confidence limits narrow.

- **INTERIM ANALYSES NEED DIFFERENT STANDARDS OF SIGNIFICANCE COMPARED TO COMPLETED CLINICAL TRIALS:** The confidence with which one interprets ongoing safety data in a clinical trial or a clinical program is less than the confidence with which one would interpret prespecified endpoints in a completed clinical trial. Fortunately, “we know a fair amount of how to interpret interim analyses in a clinical trial”. One “plots the treatment difference represented by a z-score against the amount of information that we have, and that is generally represented by the fraction of expected events”. For the primary endpoint at the end of the trial, “an alpha of about 0.05 ... generally corresponds to a z-score of about 2.0”. However, “things tend to bounce around a lot” during the early stages of a trial so that it is quite likely that any one interim evaluation will have a p-value that would be considered “statistically significant” if it had been found for a primary endpoint at the end of a trial. Accordingly, if one does not adjust one’s definition of the threshold for statistical significance to take into account the repeated analyses being performed in a series of interim analyses, one will over-interpret the significance of a z-value of 2.0.
- **STOPPING BOUNDARIES:** The statistical community has proposed stopping boundaries that “must be

crossed before we can feel comfortable that an effect seen early is likely to be present at the end of an experiment". Several different boundaries have been proposed. The O'Brien/Fleming boundary commonly used in the US is curvilinear – so that the z-value at the boundary is more extreme early in the study, and curves towards the end-of-study p-value of 0.05 as we approach the end of the study. Dr. Packer presented a number of examples where, if one had not used appropriate stopping boundaries, one might have concluded from an interim analysis that a drug effect was present. The cardiovascular field is "replete with examples" of apparent effects on major cardiovascular endpoints, and he mentioned trials of clofibrate, omapartilat, amlodipine, vesnarinone, losartan, magnesium and metoprolol.

- **APPROACH NEEDED THAT REFLECTS THE TRUE IMPRECISION OF FINDINGS:** He thinks that "the most important first step" is to "develop an approach to analyzing data in trials with small numbers of events which actually accurately reflects the true imprecision of the treatment effect estimate and its statistical significance".
- **BIOLOGICAL PLAUSIBILITY SHOULD BE EVALUATED BUT PHYSICIANS CAN ALWAYS PROPOSE AN EXPLANATORY BIOLOGICAL MECHANISM:** For "worrisome trends in imprecise data" we should consider if they are "biologically plausible" – but the danger is that physicians are always capable of proposing a "biological

mechanism to explain the validity of an unexpected and potentially preposterous finding...".

- **WHERE DATA ARE IMPRECISE, LOOK FOR REPLICATION & CONSIDER "CUMULATIVE META-ANALYSIS":** For "worrisome trends in imprecise data" we should also look for confirmatory evidence in other studies, but remembering "that we shouldn't be selective". Salim Yusef and others have proposed a "cumulative meta-analysis in which each trial is considered to represent an interim analysis on the way to a final judgment". Dr. Yusef has proposed that because of the different populations and trial designs necessarily included in a cumulative meta-analysis the stopping boundaries should require more stringent z-values than for a set of comparable trials.
- **MOST COX-2 CV SAFETY RESULTS DON'T MEET REQUIRED CRITERIA:** In terms of the present COX-2 meeting, "most of the effects the committee has seen over the past two days would not come even close to meeting these criteria".
- **SPONSORS SHOULD BE OBLIGATED TO FOLLOW-UP SAFETY CONCERNS:** He also suggested that sponsors should have an obligation to follow-up safety findings of concern, just as they do for promising efficacy findings. He also felt that criteria for establishing efficacy and safety should be similar.
- **CONCLUSIONS:** "In conclusion, the findings of controlled trials are most easily interpreted when they represent the principal intent of the

study. A non-principle finding is subject to many interpretive difficulties many of which we have reviewed; ascertainment biases, inflated false-positive rates due to multiplicity of comparisons and, the one I have emphasized the most, the

imprecision of estimates inherent in the analysis of small numbers” and “it is critical to understand the limitations of what we know and to resist the temptation to reach conclusions before we are justified to do so”.

Committee Questions to Dr. Packer

- **UNADJUSTED P-VALUES OF <.05 MAY NOT TRULY BE “SIGNIFICANT”**: Dr. D’Agostino asked how the APPROVe study, that had a small number of events (45 vs. 25) but good identification of events, should be interpreted. Dr. Packer said that you have to be “a lot more careful” but that “doesn’t mean you can’t make judgments”; his main point was that clinical investigators rely on p-values and that these may be less valid than we think. A trial can have “prespecified, adjudicated endpoints” but with “small-number events” you have “very imprecise estimates”.
- **PRACTICAL PROBLEM OF DOING A TRIAL LARGE ENOUGH TO RULE OUT A CLINICALLY IMPORTANT EFFECT**: Dr. D’Agostino asked if “we could live with” a result in a non-inferiority trial that ruled out a “1.3 relative risk” since with such a risk “people may be dying”. Dr. Packer said “I wish I knew the answer to that” but that “one learns very little from doing a lousy trial”.
- **HANDLING DROPOUTS**: Dr. D’Agostino asked how to deal with dropouts in long-term trials, both patients that can be followed up for possible delayed effects, and those that “just stop coming”. Dr. Packer said that with an efficacy trial everything reasonable is done to maintain adherence, but that in a non-inferiority trial investigators and sponsors may be “less motivated” on adherence since they realize that an adherence problem “works in their favor”.
- **SHOULD SAFETY AND EFFICACY DATA BE INTERPRETED USING DIFFERENT STANDARDS?** Dr. Shapiro asked about Dr. Packer’s comment that safety and efficacy data should be evaluated in comparable fashion, as she felt that it is not just a question of whether a problem occurs but also its prevalence and severity. Dr. Packer said that it was a question of the “risk-to-benefit relationship” and that it might be reasonable not to pursue evaluation of a minor safety issue with a drug that prolongs life, whereas one would want to pursue the same issue with “a drug for a symptomatic or cosmetic condition”. Prevalence and severity are just part of the risk-to-benefit equation.
- **WHAT IS A “WIDE” CONFIDENCE INTERVAL?** Dr. Cush asked about how one decides that a confidence interval is “wide”. Dr. Packer said that this is a function of the extent to which the upper or lower bound crosses the point of 1.0 relative risk, and that one looks at “wide” differently for confidence intervals below 1.0 (where the lowest

possible value is zero) and above 1.0 (where there is no limit on the upper bound).

- **COMBINED IMPRECISION OF CONFIDENCE INTERVAL AND DIFFERENT POPULATION:** Dr. Cush asked how one takes into account the combined imprecision of a wide confidence interval, and the application of this confidence interval to a different population. Dr. Packer said that “we do that all the time” and that “There is a general sense that efficacy is not extrapolatable across diseases but safety that is not disease-specific is extrapolatable.... If we didn't do that, the problem that I put forward would be really impossible...”.
- **URGENCY OF SAFETY DECISIONS AFTER DRUG ON MARKET:** Dr. Shafer said that how to evaluate small number events depends on whether they occur before or after marketing approval. In the post-approval situation, “clinical and regulatory decision making” is “based on imprecise information” and “a daily decision is being made by patients and their physicians as to whether or not they need to take the drug”. Dr. Packer said that efficacy estimates are “almost always” more precise than safety estimates. So one can have a situation with a precise estimate of a small efficacy effect and an imprecise estimate of a possible safety effect with “a big risk”. Although one might think of a “statistical model” to address this issue, he is “much more comfortable with people doing that” as “people have the ability to integrate all of this, especially a group of people” and we should not replace “the

human, very important human, element here”.

- **HOW CAN WE HAVE CONFIDENCE OF ABSENCE OF EFFECT?** Dr. Farrar asked about “thinking about it the other way around” , where “you have ten studies that show no safety issue with a well-measured process, whether you can then say, well, maybe the 11th study is going to show it somehow”. Dr. Packer said that one should determine if it is valid to “combine the data across the studies” and, if so, come up with a more precise estimate with smaller confidence intervals.
- **SOME EXAMPLES OF TRIALS INAPPROPRIATE:** Dr. Domanski questioned some of the trials Dr. Packer presented as examples (e.g., ISIS 4). Dr. Packer conceded that not all of his examples might be appropriate and that others might know more than him about specific studies. However, “the number of examples here is just overwhelming”.
- **REPLICATION WITH COX-2 DRUGS:** Dr. Wood said that for the COX-2 drugs “we have replication” of the safety signals.
- **EARLY TRENDS MAY CORRECTLY PREDICT PROBLEM:** Dr. Furberg said that there are “examples showing the other side, how trends in smaller studies were confirmed in definitive trials”. Dr. Packer agreed but said he was not saying that early trends are “worthless” but such a finding “is just not as reliable as we think it is”.
- **SHOULD STATISTICAL THRESHOLD FOR ACTION BE DIFFERENT FOR SAFETY AND EFFICACY?** Dr. Wood suggested

that Dr. Packer was saying that the level on which we act for an efficacy endpoint (say, 2 studies with $p < .05$) should be less stringent than for a safety endpoint. Dr. Packer disagreed, saying that “when you have a p less than 0.05” on the primary efficacy endpoint in two trials, that is not the same as “having a p less than 0.05 on two imprecise estimates which are combined together”. Dr. Wood said that Dr. Packer was “overselling the point a bit. Let's move on”.

- **STOPPING DECISIONS NOT BASED ON PRE-SPECIFIED STOPPING RULE:** Dr. Jenkins asked how one should interpret the stopping of the APPROVe trial when the actual stopping rule was supposed to be based on the combined data from APPROVe and two other trials. Dr. Packer said “I don't come with any answers” but “I am very comfortable with the human process of doing so, as long as the human process incorporates an understanding of how difficult and imprecise this is, and the fact that, in the past, although it has led to predictions that came true, it also led to predictions that did not come true.” “Any time you deviate from your preplanned attack on the conduct of analysis of a trial, you weaken, to varying degrees, the precision of the estimate and the confidence you have in the data that you are looking at”.
- **REPLICATION ACROSS DRUG CLASS RATHER THAN INDIVIDUAL DRUG:** Dr. Nissen

said that “an additional subtlety here” is that the committee is trying to assess the totality of the data for “a class of agents” and not just for “a single agent”, and trying to evaluate replication data occurs across different drugs. Dr. Packer said “that is why the process works best when there are human beings involved in the thinking process”. “In the absence of precision, you have got to do that. But don't forget” that the data are imprecise.

- **SAFETY JUSTIFIES LESS STATISTICAL RIGOR:** *<The following is an extract from Dr. Fleming's comments during the introductory statements by individuals and committees before Questions 1-3. It is provided in that document but also here because of its relevance to Dr. Packer's paper.>* Dr. Fleming said that it is important to take into account, as Dr. Packer had said, multiplicity in testing individual safety parameters over time, and multiplicity in the actual safety parameters. However, “when you are looking at safety” it is less acceptable to apply conservative statistical procedures such as “monitoring boundaries” because there is a multiplicity of safety issues, and because you have to take into account both the “severity of those safety issues” and “benefit to risk”. Ultimately, the statistical procedures can “provide some guidance” but “there has got to be informed judgment”.

Issues in Projecting Increased Risk of Cardiovascular Events to the Exposed Population: Robert Temple MD

- **MAIN CONCERN:** The main concern is an adverse effect of the COX-2 drugs on “cardiovascular outcomes, notably death, stroke and heart attack” and whether such an effect is a “class” effect.
- **DOUBTS ABOUT CV SAFETY OF NON-SELECTIVE NSAIDS:** Non-selective NSAIDs have little long-term data and some are “sort of selective anyway”.
- **IDENTIFY RISK DIFFERENCES BETWEEN POPULATIONS:** There is major interest in identifying subpopulations at different risk.
- **POSSIBLE MECHANISMS FOR INCREASED RISK:** Possible mechanisms include platelet effects and blood pressure. If these are present, how should they be managed (“conceivably, you could manage a blood pressure effect”).
- **DOSE AND DOSE INTERVAL MAY AFFECT RISK:** Both total daily dose and dose interval may influence the level of risk.
- Some studies show early effects but some effects may not be seen until much later.
- **REASONS FOR LACK OF CONSISTENCY ACROSS TRIALS:** The lack of consistency between the different studies may reflect several things, including differences between drugs, doses or patient populations. In addition, even good studies are not always consistent, particularly where the effects are small.
- **INCREASED BP POSSIBLE MECHANISM FOR INCREASED CV RISK:** Increase in blood pressure may be a significant factor and Vioxx may cause larger increases in blood pressure (an effect that is dose-related so that I doubt you could write a proper informed consent” for a trial with the 50 mg dose). However, comparative data on blood pressure effects is not adequate (in terms of dose-response, effect over the entire dosing interval, effect on average blood pressure, incidence of drug-induced hypertension, incidence of hypertension-induced adverse events, and interaction with concomitant antihypertensive drugs). The CAMELOT trial suggests that a reduction of 5 mmHg systolic and 3 mmHg diastolic can reduce by one third “the kinds of events we are talking about” in people with moderate hypertension.

ALLHAT-TYPE TRIAL:

- **UNDERLYING ASSUMPTIONS FOR ALLHAT-TYPE TRIAL:** He described a proposal for an “ALLHAT study for anti-inflammatory drugs” that might be done if “you believe”:

- 1) certain things about celecoxib (“the cardiovascular risk of 200, 400, of celecoxib is not entirely clear”, “One polyp study says yes and other studies are not so clear”),
- 2) “... a class effect is uncertain.”,
- 3) if a class effect exists “...the effect might not apply to certain doses and certain dose intervals”,
- 4) “...more needs to be known about the long-term use of all NSAIDs, including those that are nominally COX-2-selective”
- 5) “new COX-2-selective agents conceivably could be developed with appropriate information”, and
- 6) “...the pharmacology gives hypotheses that need to be tested..”.
- **MASSIVE UNDERTAKING BUT WE NEED THE DATA:** Such a study would be “a massive undertaking” but it would provide “information we all collectively need as a community”.
- **DRUGS COMPARED:**
- 1) ibuprofen (“probably ought to be neutral, not bad” although “It may not have the platelet effects you want”).
- 2) naproxen (which “sort of looks good. You might even say it is at least a placebo, but I am not quite ready to say that”). After his presentation, Dr. Wood suggested that one could use naproxen + PPI and Dr. Temple agreed that “would be okay”.
- 3) diclofenac (a “regular NSAID that is really COX-2 selective”).
- 4) celecoxib (“possibly at more than one dose”; perhaps for caution “the lower dose first”).
- 5) high dose aspirin in combination with a proton pump inhibitor (with a preceding short-term study to “show that proton pump inhibitors really do block the ulcerogenic effects of aspirin”).
- 6) acetaminophen in combination with codeine (used widely outside the US; possibly adding codeine only as needed, with management of any resulting constipation; this “would be as close to a true placebo group as I think you can get” in this setting).
- **STRATIFY BY DISEASE:** Patients would be stratified by disease (OA or RA).
- **BASELINE CV RISK:** Patients would initially be at lower cardiovascular risk, but as safety data accumulated, patients at higher CV risk could be included (but would probably need background low-dose aspirin).
- **SAMPLE SIZE:** The sample size would depend on the question asked. If you wanted to pick up a small (say 20-30%) difference in risk between drugs, you would need about 50,000 patients per group which “is beyond my hopes even for ALLHAT 2”.
- **OUTCOMES:** The major outcomes should be cardiovascular death, stroke MI and GI complications. He thinks that heart failure should be looked at separately.
- **BP MONITORING:** Blood pressure would have to be monitored and treated if it rose above some defined threshold (perhaps 130/90 mmHg – although one could argue for 120/80 mmHg).

STUDY DESIGN FOR NEW NSAIDS:

- **NEW SINGLE AGENT TRIAL DESIGNS:** A new single agent could be compared with 1) naproxen and 2) either aspirin+PPI or acetaminophen+codeine (and perhaps the study could also include ibuprofen and naproxen groups).
- **CELECOXIB + ASPIRIN:** He suggested trying “celecoxib with the addition of aspirin” to mitigate any adverse CV effects (the data suggesting that aspirin does not mitigate the adverse CV effects of COX-2 drugs “doesn’t make much sense” and could be tested).

Questions to Dr. Temple

- **“REFERENCE STANDARD” AN ALTERNATIVE TO ALLHAT:** Dr. Nissen said that it would be difficult to do Dr. Temple’s proposed ALLHAT-type study, and suggested as an alternative having an active agent “reference standard” to which all other drugs would be compared, and that naproxen would be the best candidate. Dr. Temple responded that he actually said the same thing at the bottom of one slide but that he would still like to know if naproxen is “less bad” or “really good”. The sponsors used different comparators in different trials so that, for example, one did not have a direct naproxen-ibuprofen comparison.
- **IF NAPROXEN+ PPI SAFE FOR GI, COX-2 SELECTIVE DRUGS ARE OF LESS VALUE:** Dr. Temple asked if naproxen alone or naproxen together with a PPI should be used as a comparator. His own feeling is that some more data on this question is needed, but if the PPI protects against naproxen’s GI adverse events it raises “the fundamental question of how much help you get from being COX-2-selective”.
- **NO DATA ON GI SAFETY OF ASPIRIN+PPI:** Dr. Cryer thought that use of “full-dose aspirin” (if this means 3.9 grams a day) would be “non-practical”. Dr. Temple asked what would happen if you added a PPI to aspirin, even short term using endoscopic ulcers as an endpoint. Dr. Cryer said “I don’t know and I don’t think that it will ever be known”.
- **COX-2+ASPIRIN = NSAID IN ENDOSCOPIC ULCERS, = NSAID+ASPIRIN IN GI EVENTS, AND LESS THAN NSAID+ASPIRIN IN GI HOSPITALIZATIONS:** Dr. Cryer commented on Dr. Temple’s suggestion of how a combination of celecoxib and 80 mg aspirin would look in terms of the GI effect. “With respect to endoscopic ulcer, COX-2 plus aspirin equals traditional NSAID”. With regard to

hospitalizations, an unpublished Canadian study shows that with “COX-2 plus aspirin ... hospitalizations ... are less than hospitalizations for non-selective NSAIDs plus aspirin”. Abstracts of outcome studies indicate that GI events “on COX-2 plus aspirin are similar to events on non-selective NSAID plus aspirin”.

- **IS THERE A (COX-2 + ASPIRIN) COMBINATION WITH CV SAFETY AND GI BENEFIT?** Dr. Temple suggested that it might be possible to combine some level of COX-2 selectivity (from one of several drugs with different degrees of COX-2 selectivity, or different doses of a COX-2 selective drug) with some dose of aspirin so as to mitigate the adverse cardiovascular effect while retaining some of the benefit of less GI safety problems. He conceded that “the data so far don't show that. But they didn't seem definitive to me”.
- **PROBABLY HIGH DROPOUT RATE IN 1-2 YEAR OA ALLHAT-TYPE TRIAL:** Dr. Cush said he liked the idea of an ALLHAT-type study but it would be hard to keep OA patients on the assigned treatment over a 1-2 year trial period. Drugs to be compared could range from highly selective COX-2 inhibitors to less COX-2 selective drugs, to non-selective NSAIDs to pure analgesic drugs.
- **“LARGE SIMPLE TRIAL” MAY BE PREFERABLE TO ALLHAT-TYPE DESIGN:** Dr. Hennekens expressed a preference for a “large simple trial” rather than an ALLHAT-type trial.
- **“COLLABORATIVE” ALLHAT-TYPE TRIAL WITH FDA, NIH &**

SPONSORS: Dr. Abramson suggested that the ALLHAT-type study might be feasible if FDA, NIH and sponsors all contribute to “collaborative study” that includes biomarkers, pharmacogenomics, and blood pressure. Dr. Temple agreed but said that some of the drugs are generic and unlikely to get sponsor support – “you noticed I didn't have a slide on how to do this”.

- **HIGH-DOSE ASPIRIN AND THROMBOSIS:** Dr. Ilowite mentioned a study in Kawasaki disease in which high-dose aspirin appeared prothrombotic, possibly because of prostacyclin inhibition at these high doses. Dr. Hennekens said that in 135 randomized trials in over 212,000 subjects, all aspirin doses between 75 mg/day and 2 grams/day had “significant cardiovascular benefits” and there is no cardiovascular “reversal of benefit” at high doses. Ongoing randomized trials are evaluating beneficial effects of high-dose aspirin on endothelial function, nitric oxide formation and other measures of anti-atherogenic effects.
- **FULL ANALGESIC DOSE OF ASPIRIN LESS THAN FULL ANTI-INFLAMMATORY DOSE:** Dr. Cush suggested that the aspirin dose might be selected to provide analgesic effect rather than anti-inflammatory effect.
- **“GATE” STUDY SHOWS NO INCREASED CV RISK WITH CELECOXIB 200 MG QD:** Dr. Cush mentioned that the completed GATE study is a 1,588-patient, 6-month, OA trial that is presently being analyzed. One of the 5 arms of the trial uses celecoxib 200 mg once daily and the DSMB has found no

“increase in cardiovascular events including M.I., any difference

between the Celebrex group and the other four control groups”.

Issues in Projecting Increased Risk of Cardiovascular Events to the Exposed Population: Robert O’Neill PhD

- **PROBLEM NOT WELL STUDIED:** There is very little published on projecting risk to an exposed population so that he will just try to identify a logical framework to address the issue.
- **PROBLEM DIFFICULT AND ASSUMPTION-DEPENDENT:** It is “a very difficult problem” to get an estimate, and any estimate is not

precise but sensitive to “all the assumptions you have to make”.

- **INFORMATION NEEDED:** We need to know how many people are on drug, for how long, at the level of the national population. And we have to integrate information from both clinical trials and epidemiology studies. Terms such as “event definitions” are important.

TIME MATTERS:

- **BOTH TOTAL RISK AND RISK PER UNIT TIME MAY BE A FUNCTION OF TIME ON DRUG:** His most important point is that “time matters”. With a hazard ratio that is constant over time, the total risk increases with increasing time. In addition, if the hazard per unit time increases with time, there is “escalation” of risk as duration of therapy increases. He pointed out that, when risk escalates with increasing time, as appeared to be the case in the VIGOR (RR 2.28) and APPROVe (RR 1.92) trials, the calculated relative risk is an average risk over the entire time period, but the relative risk during the latter part of the time period is higher than this average.
- **OBSERVATIONAL DATA CANNOT IDENTIFY EARLY**

RISK BECAUSE OF “TIME FROM NEW USE” PROBLEMS AND LACK OF A PARALLEL GROUP TO EXCLUDE EFFECT OF PRIOR NSAID: With regard to identifying increased risk early when there is a “power issue”, he does not believe that Dr. Graham’s observational data with increased risk in a population that only had short-term therapy “adds anything to our knowledge about early risk, for the points I made yesterday” <Note: His comments the previous day questioned whether “time from new use” was correctly identified, and that, without a parallel group, an early effect might just reflect the effect of discontinuing the previous NSAID>.

- **VERY LIMITED DATA ON NUMBERS OF PEOPLE IN U.S.**

POPULATION EXPOSED AND ON DURATION OF THERAPY:

Unfortunately, “we have no data in the United States” that provides information on “how many people are exposed for how long a period of time”. However, they were able to do a “projection based upon the IMS National Prescription data” that examined this question, and this showed “Surprisingly enough, a very small percentage of the millions of people that are prescribed the drug are on the drug for more than a year”.

- **IMS PRESCRIPTION DATA USED TO GENERATE VERY CRUDE AND UNRELIABLE ESTIMATE:** They used the IMS

information and a “number of assumptions many of which are not verifiable” to come up with a “crude estimate” which we “probably don’t believe” but which is definitely “very variable”.

- **ESTIMATE OF “PATIENT-YEARS” NO GOOD FOR NON-PROPORTIONAL HAZARDS:** He thinks that we need to move “away from summarizing non-proportional hazards in person-years. It is not a good idea. It begs the question as to whether the risk is constant or whether the risk is dependent on time”. This is a major problem with the epidemiology literature.

OTHER POINTS:

- **NO EASY WAY OF COMBINING DATA FROM DIFFERENTLY DESIGNED CLINICAL TRIALS:** A major problem with clinical trials is trying to integrate the information from several clinical trials that may differ in the patient population or the dosage used.
- **HIS CONCLUSION:** “So the point here is that this is a very difficult exercise to project. This was just a

framework to say, here is how you might think about it”.

- **HIS “ESTIMATE” BASED ON NUMBER AT RISK AND RISK IF EXPOSED:** After Dr. O’Neill’s talk, Dr. Wood asked him to clarify what he meant by “estimate”. Dr. O’Neill said he meant: “An estimate of the absolute numbers of individuals that might have been at risk, and had these events if they were exposed”.

Summary of Meeting Presentations (FDA): Sharon Hertz MD

- **SOME COX-2s NOT APPROVED BY FDA:** FDA has not approved all

COX-2 NDAs, in some cases because of cardiovascular concerns.

- **INCREASED RISK BUT RESULTS NOT CONSISTENT:** This meeting has identified “increased risk for cardiovascular events” but results “are not consistent across studies and across situations”.
- **MULTIPLE MECHANISMS POSSIBLE:** “It is possible there is more than one mechanism”.
- **TIME TO ONSET OF RISK IMPORTANT:** Another important issue is “time to onset of risk”.
- **DECISIONS REQUIRED DESPITE UNCERTAINTIES:** Despite all the uncertainties, “we have to move forward” and decide the role of currently approved products, and what new studies to do.
- **COMMITTEE QUESTIONS:** For Questions 1-3 (celecoxib, valdecoxib, rofecoxib) – CV risk, support for marketing, appropriate populations, risk-management) the answers will depend on whether there is considered to be a “fairly uniform” class effect. Question 4 asks if aspirin mitigates a cardiovascular risk of COX-2 drugs. Other questions address the “potential G.I. benefits for these same products”, labeling and risk-management recommendations (and the extent to which these should be “class”-based), additional trials for non-selective NSAIDs, and approval requirements for new drugs.

Sponsor Two-Minute Statements

- **PFIZER:** Celebrex has received more extensive safety evaluation than non-specific NSAIDs, and is effective in arthritis and familial adenomatous polyposis. The daily dose of Celebrex is 200 mg/day or less in three-quarters of patients. Celebrex has a favorable GI profile. Celebrex has not shown an increased cardiovascular risk in arthritis patients. In three long-term placebo controlled trials, increased cardiovascular risk was noted only in the APC study. The final results of the ADAPT trial will clarify the relative cardiovascular safety of Celebrex and naproxen.
- **MERCK:** New data show that increased cardiovascular risk is not unique to Vioxx and appears to be a class effect. The large MEDAL study will compare the relative risks of COX-2 inhibitors and traditional NSAIDs.
- **NOVARTIS:** Cardiovascular risk, GI risk, heart failure, cardiorenal profiles, and blood pressure effects are not well correlated with the degree of COX-2 selectivity. Lumiracoxib was associated with significantly less blood pressure effect and a 79% reduction in GI complications in the TARGET study. Duration of use should be restricted to that supported by the data. There should be a robust risk-management program, including firm post-marketing commitments.
- **BAYER:** Bayer’s Aleve brand of naproxen is a safe and effective pain reliever suitable for OTC use. Bayer appreciates the comments by the

committee that the public reports on the ADAPT trial may have caused

significant physician and consumer confusion.

FDA's Regulatory Armamentarium: Presentation by Anne Trontell (FDA) & Committee Discussion

THE FDA ARMAMENTARIUM:

- **VOLUNTARY LIMITATION OF MARKETING:** Voluntary limitation of marketing (e.g., no Direct-To-Consumer advertising, restriction to certain specialty groups, restriction to certain specialty journals).
- **LABELING RESTRICTIONS:** Labeling restrictions (e.g., black-box, second-line use, contraindication in certain patient populations).
- **TARGETED EDUCATION:** Targeted education or outreach that goes to doctors and/or patients (e.g., Dear Doctor letters, patient medication guides, other academic detailing that targets prescribers with information about safe use).
- **REMINDER SYSTEMS:** Reminder systems that prompt people on appropriate use (e.g., patient agreements or informed consents where patient acknowledges and accepts risks, attestation by physician that appropriate-use conditions have been met such as is used for Lotronex).
- **DISPENSING RESTRICTIONS:** Limitation of amount dispensed or number of refills.
- **PERFORMANCE-LINKED ACCESS SYSTEMS:** Performance-linked access systems that defines a population of providers or patients to whom access is restricted (e.g., the clozapine patient registry in which patients are required to show proof of an adequate WBC count - "no blood, no drug"; proof that woman is not pregnant before dispensing thalidomide).
- **SUBPART H RESTRICTIONS:** Subpart H can restrict distribution "for drugs that are important and that you could only be satisfied that they were safe for use in that setting". Dr. Temple said that that, to his knowledge, this had not been imposed after approval but "I don't think it is impossible".
- **MANDATED POST-APPROVAL STUDIES:** FDA can mandate new safety studies to address a new safety issue.

DISCUSSION:

- **EFFECTIVENESS OF BLACK-BOX WARNINGS:** Dr. Platt asked how well black-box warnings work, and cited the example of cisapride that was withdrawn after black-box warnings did not work. Dr. Trontell

said that the effectiveness of these programs was not well tested, but that in the case of the black-box for ketorolac “there is actually very high conformance”. With Seldane, the black-box for torsades de pointes eliminated about 90% of inappropriate prescribing but not entirely and “there were still unacceptable levels persisting”. “So, it is a mixed picture...”. Dr. Wood cited Rezulin and bromfenac as examples where the black-box did not work but “That is not to say we shouldn't do them...”. Dr. Dworkin asked about different levels of warning. Dr. Trontell said that one can have different levels within the black-box category.

- **MANDATORY ACADEMIC DETAILING:** Dr. Platt asked what “mandatory academic detailing” means with regard to who develops the content, who delivers it, and who oversees compliance. Dr. Trontell said that this system, to her knowledge, is “not in place”.
- **WRITTEN AGREEMENT BY PATIENT MAY NOT INDICATE COMPREHENSION:** Dr. Day pointed out that even though people may “sign a piece of paper we don't know that they really understand until we give them a comprehension test” as has been tried with Accutane. When a survey was voluntary, only 20% of patients filled it out.
- **DTC ADVERTISING WITH BLACK-BOX WARNING:** Dr. D’Agostino asked if there were circumstances where a black-box still permitted Direct-To-Consumer advertising. Dr. Temple said that a black-box makes reminder ads impossible, but it is conceivable that

a Direct-To-Consumer advertisement would be acceptable if it conveyed the “black-box in all its full unpleasantness”. Dr. Wood suggested that “restricting DTC should be a separate or additional issue to black-box warnings” and that although FDA cannot mandate a DTC restriction, “it is within the rubric of the commission's recommendations”.

- **DTC BY FDA WITH PDUFA FUNDING:** Dr. Gross suggested that FDA does “direct-to-consumer education from the FDA's point of view, either pairing it with the ad from the pharmaceutical companies, doing it separately”. Dr. Temple said “That takes money beyond what we usually feel we have.” Dr. Gross said “That is why I suggested PDUFA funding”.
- **EDUCATION THROUGH MEDWATCH AND PUBLIC HEALTH ADVISORIES:** Dr. Trontell said that FDA can educate through MedWatch and Public Health advisories.
- **PROMPT NEGOTIATION AND IMPLEMENTATION OF VOLUNTARY RESTRICTIONS:** Mr. Levin asked if a “voluntary” restriction could be “imposed” by FDA because of the threat of removal from the market. Dr. Trontell said that was “a difficult question” but that “to my knowledge, these agreements that have been put in place relative to marketing have been ones that have been offered by the drug companies”. Generally, in matters of “risk management or risk minimization, there is a back-and-forth process that is directed to the feasibility of actually putting some of these systems into place”. Dr.

Wood said it the committee makes “strong recommendations that something should be done, it would be pretty tough not to follow them”. Dr. Morris expressed concern about “the ability of FDA to insist on and enforce conditions which will limit the distribution and use...” but, that said, some risk-management results have been positive (e.g., Lotrinex). However, he is concerned about the time it takes to negotiate with the sponsor, and that “whatever we do recommend today”, it is going to be a “long haul”. Dr. Wood said that the committee should “light a fire under these guys that will provide ammunition to the FDA in their negotiations....”. Dr. Jenkins said “we are committed to making our decision on your recommendations on these applications and these products very quickly after this meeting”. Dr. Wood said “There is nothing beats setting a time line...”.

- **REMOVAL OR RESTRICTED USE OF HIGH DOSE CAPSULES:** Dr. Nissen asked if the marketed doses could be changed (e.g., market the 100 mg celecoxib capsule but not the 200 mg capsule

so as to make it difficult for a patient to take the number of capsules required for an 800 mg dose). Dr. Trontell agreed that this could be done. Dr. Jenkins pointed out that an unintended consequence could be that patients might have to pay more for the same number of milligrams. Dr. Wood suggested that one could have different restrictions for the different capsule strengths.

- **NEW POST-MARKETING STUDIES:** Dr. Crawford asked if one could mandate “definitive, well-designed postmarketing surveillance studies”. Dr. Jenkins agreed and said that “postmarketing commitments are not only made at the time of approval, they can also be made after approval when a new issue comes up”. Dr. Wood suggested that “your success in getting these studies completed has not been terrific” but Dr. Jenkins said “the record is much better than it is portrayed often in the media” and that FDA posts information on its website “so you can see if companies are meeting their obligations or if they are falling behind”.

Committee Preliminary Discussion on Questions 1-3: End of Day 2

QUESTION 1: DO COX-2 DRUGS INCREASE CARDIOVASCULAR RISK?

- **DESPITE A CLASS EFFECT THERE ARE DIFFERENCES BY DRUG AND BY DOSE:** Dr. Gross said that, although there may be a “class effect”, the drugs to be discussed are sufficiently different so

that “one or more of the drugs should be marketable and one or more of the drugs ... should not.” Dr Nissen said that there was a ‘class effect, but I think that there is clearly evidence of a gradient in risk, and

that gradient is not only by drug, but also by dose.”

- **SEPARATE QUESTION INTO ARTHRITIS AND NON-ARTHRITIS:** Dr. Gibovsky interjected to ask “that we discuss it in the context of patients with arthritis versus patients with other conditions”
- **POINT ESTIMATES OF RISK WITH EACH COX-2:** Dr. Fleming gave an overview of the statistical evidence and concluded: “There certainly is an effect that is going on here...” Although the point estimates are not precise, he estimated hazard ratios of 1.4-1.5 (rofecoxib), 2.5 (valdecoxib), 1.3 (celecoxib), 1.6 (etoricoxib) and 1.2 (lumiracoxib). Dr. Hennekens said that Dr. Fleming’s estimates of hazard ratio are “lower than one would have guessed based on the early data-dependent stopping of some of these trials”. Dr. Wood suggested that the favorable results in the arthritis studies might be “diluting the effects” when Dr. Fleming made his hazard ratio estimates. Dr. Fleming responded that “the best analysis is one that will drill down in all of these dimensions as best we can.” Dr. Wood’s response was: “It is not likely to be less than the numbers you gave. It is likely to be more, right?” Dr. Fleming responded that “There will be settings where it is less. There will be settings where it is more.”
- **LOW DOSE CELECOXIB:** Dr. Fleming said “Can you, for example, give celecoxib at a low dose with a short enough duration that in wide settings, it would be safe. That is still entirely possible within the context of what we have said”. Dr.

D’Agostino expressed concern that “if we give this global statement” we “can’t get back to the question you just raised: Can we look at Celebrex at a low dose?” Later, Dr. D’Agostino said “it may be a low dose of Celebrex, that may be viable, and not unsafe”.

- **DEFINITION OF COX-2 DRUG:** Dr. Shafer asked “What is a COX-2?” and suggested that this might include meloxicam, Sulindac and diclofenac. Dr. Wood said “Let’s stick to the drugs for which we have got evidence.” Dr. Abramson echoed Dr. Shafer’s concern and pointed out that the newer drugs are the only ones with long-term studies and that the doses used in those studies were higher than the usual doses of comparators. Dr. D’Agostino said his “comment is very much the same”.
- **IF IT IS JUST COX-2, THEN ALL NSAIDS IMPLICATED:** Dr. Abramson pointed out that all the NSAIDs, including the older non-selective ones, inhibit COX-2, so that if the increased cardiovascular risk is related to COX-2 inhibition per se, it should occur with all NSAIDs. Dr. Gross expressed concern that “if we conclude that there is a class effect for the selective COX-2 inhibitors then people are not going to want to use COX-2 inhibitors at all and they will be using the non-selective NSAIDs, which from the data presented, doesn’t look as though many of them are better from a risk point of view”.
- **DIFFERENTIAL RISKS WITH DIFFERENT DRUGS:** Dr. Fleming’s take on the traditional NSAIDs was that “naproxen is a winner” and that “the theory that was put forward that diclofenac is COX-

2-like is at least supported by the trials where it was studied". Dr. Hennekens said that "the picture that ... begins to emerge to me is that rofecoxib, ibuprofen, and possibly valdecoxib are in one bin, diclofenac and celecoxib in another bin, naproxen in a third bin, and then aspirin in the fourth bin, going from concerns about hazard to neutrality to benefit." Dr. Manzi commented that she had "a problem making inferences about diclofenac and naproxen in studies where I think we have a difficult time feeling comfortable with the results in relationship to the COX-2s..... So, to feel that we don't have enough information to really feel comfortable with COX-2s, and then to try and extrapolate to the comparators in those, I think is dangerous".

- **IMPORTANCE OF BLOOD PRESSURE EFFECTS:** Dr. Nissen emphasized the importance of blood pressure effects and pointed out that lumiracoxib and rofecoxib, both very COX-2 selective drugs, have very different effects on blood pressure and that "the relationship between relatively small differences in blood and cardiovascular morbidity and mortality is rock solid across a huge number of drugs and interventions, and you almost can predict what will happen". Dr. Temple said that comparative studies of blood pressure effects with these drugs could be done with 20-40 patients per group.
- **ASPIRIN DATA MAKES MECHANISM UNCLEAR:** Dr. Shafer again expressed concern about the fact that risk did not seem to be reduced by concomitant aspirin

which seemed to raise doubts about "the Fitzgerald hypothesis". Dr. Temple agreed that aspirin is "a fly in the ointment".

- **HIGH COX-2 DOSES IN TRIALS MAY NOT HAVE BEEN WISE:** Dr. Temple commented that "We encouraged everybody to study high doses to rule out GI distress. Whether that was wise in retrospect, I am not sure, and I think I probably had something to do with it a long time ago. I am not sure that was the best thing."
- **CORRELATES OF INCREASED RISK:** Dr. Farrar said that "the ones with some of the higher risks are not necessarily the most COX-2 selective". Dr. Cryer said that increased GI risk and increased CV risk go together in the same patient. Dr. Cryer said that lumiracoxib which is not yet on the US market showed GI benefit. Dr. Wood pointed out that such benefit was seen at doses that had an increased cardiovascular risk.
- **PROBLEM WITH LACK OF FOLLOW-UP:** Dr. Holmboe and Dr. Fleming expressed concern that we don't have cardiovascular safety data collected for the patients who dropped out early.
- **RISK NOT LARGE ENOUGH TO CONTINUE HOLD ON ONGOING TRIALS:** Dr. Farrar said that with "all of this discussion about risk, I don't want to imply that I think that this risk is big enough to actually warrant the continued hold on all the trials that we have going, and I think, in fact, what it suggests to me is that we need to continue with trials to understand better what the data is telling us."

- **CHART TO COMPARE DRUG DROPOUT RATES:** Dr. Day suggested that “a giant chart” be prepared “before tomorrow” that lists the percentage dropout rates for each

drug together with the reasons for drop-out. Dr. Temple said “The question is how reliable it is..... it isn't by any means always properly done”.

QUESTION 2: OBSERVATIONAL STUDIES

- **OBSERVATIONAL STUDIES ARE ONLY HYPOTHESIS GENERATING:** Dr. Nissen said that we should only “use observational studies as hypothesis-generating studies. If you see a signal in an observational study, it is an indicator that you need to do a randomized controlled trial..”. Dr. Fleming agreed that observational studies should be considered hypothesis generation; passive surveillance can detect rare events but active surveillance is needed to detect a change in frequency of common events; however, in all observational studies “recorded covariates are just the tip of the iceberg, so you are left with a great deal of uncertainty about bias” and these studies can give “us a guide because we can't do randomized trials in every setting.... but the ultimate answers in most cases really come from the randomized trials.” Dr. Wood also agreed and emphasized the point made earlier by Dr. Nissen that observational studies had fooled everyone into thinking that estrogen therapy prevented heart disease in post-menopausal women. Dr. Hennekens also agreed and in this respect quoted Bradford Hill who he had the privilege of knowing. Dr. Farrar said that “Every single one of them is confounded by indication. The best example is the

indomethacin one where it is only used in people who are sicker than people who aren't.”

- **DESPITE LIMITATIONS, OBSERVATIONAL STUDIES HAVE ADVANTAGES:** Dr. Stemhagen made some general comments on observational studies: Despite their limitations, they do provide additional information not available from the randomized trials: dose-response data, data in a setting of adequate follow-up, real-world patients and real-world doses. Dr. Holmboe said that “a poor randomized controlled trial actually may be worse than a good observational study” and randomized studies can have poor follow-up and other problems. Similarly, meta-analyses of randomized trials need “a test of heterogeneity to see if they really truly could be combined”.
- **FDA EMPOWERMENT TO MANDATE STUDIES:** Dr. Cush suggested that Congress empower FDA to mandate post-marketing trials, including observational studies.
- **LOWER RISK BECAUSE OF INTERMITTENT DOSING IN OBSERVATIONAL STUDIES:** Dr. Bathon suggested that the risk of drugs in observational studies might be lower than in randomized trials since patients tend to take their drugs only on an intermittent basis.

- **“WILD ARM” OBSERVATIONAL ANALOG IN CLINICAL TRIALS:** Dr. Paganini suggested that randomized trials include a “wild arm” that consists of patients receiving “what is usually and customary done” when prescribing the drug. This would provide an observational study analog in a controlled setting. Dr. Domanski was intrigued by the “wild arm” concept. Dr. Paganini gave the example of an ongoing NIH-VA dialysis study which has three arms: high dose, low dose, and “what is usually and customarily done”. However, in further discussion with Dr. Domanski, he said that the “wild arm” was really just a prospective registry and that patients were not randomized to this third arm. Dr. Friedman thought that the “wild arm” concept was not a good idea “when we were dealing with the ARDSNet issue”.
- **VARYING RISK LEVEL ACROSS TIME NOT EVALUATED IN OBSERVATIONAL STUDIES:** Dr. Elashoff pointed out that where the risk level varies across time “the standard way that observational studies lump it all into patient years is bound to be misleading”.
- **SHOULD RECOMMEND GOOD OBSERVATIONAL STUDY DESIGN TO FDA:** Dr. Friedman suggested that it would be useful to advise FDA on the best use of observational studies rather than just focusing on “all of the difficulties in using observational studies”.
- **DETECTING COMMON VS. RARE EVENTS IN OBSERVATIONAL STUDIES:** There was discussion between Dr.

Platt, Dr. Wood and Dr. Temple about the ability to detect a change in the frequency of common events if one were to mandate post-marketing observational studies. Dr. Platt felt that if one used an automated recording system in “the model of the large linked databases” to identify certain pre-specified common events, the problem of under-reporting could be handled. Dr. Temple felt that this issue with chronic use drugs was always cardiovascular and agreed that Dr. Platt’s system could probably be put in place. Dr. Wood expressed concern about mandating such a study for every chronic use drug but Dr. Temple felt that “we have access to databases, whether it’s California Medicaid or whatever, and one can do that”. “Maybe that is something that we could think about.”

- **OUTSIDE PRESSURE TO BAN DRUGS ON BASIS OF INVALID OBSERVATIONAL STUDIES:** Dr. Jenkins (FDA) expressed concern that, going forward, “this going to be a mining exercise for everyone who does observational studies in the world probably. They are going to be looking to do another COX-2 or another NSAID observational study” and he was interested in what the committee thought FDA should do with “the next observational study that is touted as wow, this really shows something”. Dr. Nissen suggested that “We have seen some strange things go on, like the warning around naproxen, that was clearly based upon pretty weak evidence. So, I think having a good standard is where you have to kind of hold your ground.” Dr. Wood said that “...it

certainly seems to be in the public interest that you [FDA] should have the power to ensure that that kind of a study gets done, and that is something certainly people should hear and hear loudly...". Dr. O'Neill

said that one of the problems was that observational studies are often poorly designed and "it is not even clear what the prespecified hypotheses were".

QUESTION 3: COX-2 BENEFITS VS. NON-SELECTIVE NSAIDS

- **QUESTION 3:** Discuss the available data regarding the potential benefits of COX-2 selective non-steroidals versus non-selective non-steroidals, and how any such benefits should be weighed in assessing the potential benefits versus the potential risks of COX-2 selective agents.
- **FDA PERSPECTIVE:** Dr. Jenkins (FDA) asked for the committee views on the GI advantages of COX-2 drugs, efficacy in pain relief, and about "the value of choice" by making multiple drugs available.
- **EFFICACY, RISK WEIGHTING & COMPASSION:** Dr. Nissen said "I haven't seen any compelling evidence that in terms of pain relief, that the drugs are actually more effective..."., that "the GI events here are serious events" but that "I have to give them less credence than the kind of hard, permanently disabling effects of MI and stroke", and that "compassion has to come into our decisions" for "patients who just don't tolerate the conventional NSAIDs". Dr. Fleming said that in "a crude estimate" the COX-2 drugs might be preventing "7 per 1,000" GI events but that "how is that up against 4 events that are strokes, MIs, or cardiovascular deaths?" However, the benefit-risk may be different in certain patients and it would be important to "more scientifically, rigorously establish

certain subpopulations where there really is a differential relief". Dr. Fleming said that if there is no efficacy advantage to the COX-2 drugs, "there should be an incredibly low threshold for what you would accept in additional cardiovascular events, because the only thing you are getting relative to nonspecific NSAIDs then would be a very small GI."

- **COMPARE TO NSAIDS + PPI:** Dr. Hoffman said that it is important to obtain 2-3 year data comparing the GI safety of non-selective NSAIDs in combination with proton pump inhibitors to COX-2 drugs alone.
- **IS LOWEST SAFE DOSE STILL EFFECTIVE?:** Dr. Hoffman also said that If COX-2 drug dosage is going to be reduced to "the lowest safe dose" it needs to be established that such doses have adequate efficacy and retain the GI protective effect of higher doses. In addition, although "it is our obligation to provide patients choice" we "shouldn't give people a choice if we think that choice is uninformed and potentially does harm".
- **MANY OTHER CHOICES AVAILABLE:** Dr. Cryer said that even without the choice of COX-2 drugs, patients would still have the choice of "20 other NSAIDs available in the U.S".

- COX-2 GI BENEFITS SMALL:** Dr. Cryer also said that he thinks that “the GI benefits are less than previously speculated”. The GI advantage of COX-2 drugs versus non-selective NSAIDs may be greatest in patients at low GI risk and less in those patients who are at greatest GI risk. In addition, in “the face of low-dose aspirin, there is no apparent GI benefit”. Dr. Wood said that for the two drugs presently on the US market (celecoxib and valdecoxib) “we have no clear randomized data that show GI benefit”.
- MERCK’S VIEW:** Dr. Kim (Merck) said that rofecoxib has “unique benefits” and that the increased cardiovascular risk appears to be a “class effect”. Dr. Wood asked if he was saying that “if we think the cardiovascular effect is a class effect, you would consider putting Vioxx back on the market”. Dr. Kim did not answer directly. Later in this session, Dr. Crawford asked Dr. Kim about the “potential reintroduction” of Vioxx by Merck. Dr. Kim again responded ambiguously, seeming to link any reintroduction decision a decision by the committee that the increased cardiovascular risk is a class effect. At the two minute Sponsors’ summary presentations on Day 3, Merck appeared to be on the point of clarifying this point, but the two minutes allotted were up and the microphone went dead – to the accompaniment of considerable laughter from the audience.
- DIFFERENTIAL EFFICACY IN INDIVIDUALS & CHOICE:** Dr. Farrar said that the discussion so far had not really addressed benefit (a relative lack of GI toxicity is not an absolute benefit but a reduced risk). Clinically, he has patients who say one drug is effective whereas another drug is not – although no controlled studies have substantiated such an effect. He thinks choice is important. Dr. Dworkin commented that there is “a really solid basis for their needing to be a choice amongst several drugs, because you have the variability in the pain benefit amongst patients and the variability in their tolerability”.
- GI MORTALITY RISK IS SUBSTANTIAL:** Dr. Gibovsky pointed out that, although myocardial infarction can be fatal, Dr. Singh’s data show that 16% of GI bleeds are also fatal. In addition, COX-2 drugs are preferable in patients on anticoagulants post-surgery because of their lack of platelet inhibition. He also mentioned the ACDA and PACES trials in which patients preferred celecoxib or diclofenac over acetaminophen. Another point is that tolerance to NSAIDs is common (the latest data set shows that patients switch therapy 3-4 times within 18 months) and that patients may not tolerate a given drug because of allergy or idiosyncrasy. This argues for maintaining a choice of drugs. Dr. Wood expressed concern that the most recent estimates of GI complication rates indicated that this was less of a problem than was being suggested. Dr. Singh said that the more recent figures did show that the death rate and duodenal ulcer rates have dropped. However, the hospitalization rates had been underestimated in the earlier studies and “there are a lot more than that”, and the “gastric ulcer rates and the

gastric ulcer hemorrhage rate have not gone down in the same fashion”.

- **INVOLVE PATIENT IN RISK ASSESSMENT:** Dr. Morris said that it was difficult to weigh the relative importance of events such as TIA or a gastric ulcer but “we need to understand patients' evaluation of these outcomes”. Dr. Platt said that “we could do a very much better job than we do by using the existing data that FDA already has to provide good information to patients about the risk stratum that they inhabit.” Dr. Bathon commented “that is, in fact, what most of us rheumatologists have been doing for the past four months with every single clinic visit”.
- **NEED FOR AGGRESSIVE MANAGEMENT OF CARDIOVASCULAR RISK:** Dr. Cush said that using only traditional agents such as “Tylenol and aspirin and ibuprofen would be a gigantic step backwards” and “what we need” is “a strategy for risk modification”. Dr. Hennekens said that arthritis patients are at increased cardiovascular risk and that their cardiovascular risk factors should be “managed aggressively”.
- **NO PROOF THAT ACETAMINOPHEN IS SAFER OR AS EFFECTIVE:** Dr. Hennekens expressed concern that it was not clear that acetaminophen “is either sufficiently efficacious or much safer”.
- **NEED FOR DRUGS IN PEDIATRICS:** Dr. Ilowite expressed concern about the limited choice of agents in pediatrics. Also “the risk of cardiovascular disease ... is very low in pediatrics” but that because duration of therapy is

“longer even than adults”, it is important to “to get some insight into the pathogenesis of this ... so that early markers could be explored in children...”

- **FDA INTERVENTION OR DOCTOR/PATIENT RELATIONSHIP FOR RISK MANAGEMENT:** Mr. Levin said that we should not “just sort of slide this all off on patients and physicians supposed in this Nirvana good, up-to-date information” and that we “can't abrogate our responsibility, and we can't pretend the Government, through the FDA, doesn't have a statutory responsibility here to protect the public health.” Ms. Malone disagreed, saying that the rheumatologists on the committee “do have the ability to form a relationship with” patients and “I applaud them for that”.
- **NON-SELECTIVE NSAIDS MAY NOT BE SAFE ALTERNATIVES:** Dr. Manzi expressed concern about those suggesting there are “safe alternatives” to the COX-2 drugs since “I think we have signals actually to the opposite patients are going to have to turn to something, and do you feel comfortable saying that the alternatives are safe?” Dr. Wood said that on the other hand “I think it's highly improbable that the committee would have approved any of these drugs given the safety signal we have got right now”. Dr. Temple agreed that “some of them I think probably would not have made it”. Dr. Manzi responded that such a decision would depend on the need for the drug and what alternatives

were available rather than looking

“at it in isolation”.

Questions to Advisory Committee – Introduction, General Discussion & Committee Statements

DR. WOOD’S VIEW:

- **CV RISK: MULTIPLE TRIALS:** There are 4-5 randomized trials that show a cardiovascular hazard, with replication of results for two drugs – rofecoxib (VIGOR and APPROVe trials) and valdecoxib (two CABG trials). For celecoxib there is one study (APC trial).
- **LARGE SAFETY SIGNAL:** This is “a far larger randomized safety signal than we have seen for any of the drugs that have been withdrawn for safety reasons”.
- **RISK IS FOR COMMON EVENT:** The present situation is unusual in that it deals with an increased incidence of a common event rather than an unusual event.
- **OBSERVATIONAL STUDIES SUPPORT DRUG RANKING:** The observational studies, with “all the caveats that we heard” tend to show the same results as the randomized trials, and can help in ranking “drugs by toxicity, and toxicity by dose”, with rofecoxib being “the most toxic”.
- **NO CLEAR GI BENEFIT FOR CELECOXIB & VALDECOXIB:** No individual trials with celecoxib and valdecoxib established a better safety profile for GI clinical events.
- **NO CONTROLLED DATA SHOWING BETTER RESPONSE IN INDIVIDUAL PATIENTS:** Despite “moving” testimony at the open public hearing, no controlled trials have been done to evaluate better response in individual patients. We need to be able to identify patients who “uniquely benefit” from a coxib.
- **EASY-TO-UNDERSTAND RISK DESCRIPTION NEEDED:** We need an understandable way to describe the possible associated risk.
- **ADAPT TRIAL STOPPED FOR OPERATIONAL REASONS:** The ADAPT trial now seems to have been stopped because of “operational reasons” and not because of “safety signals”.
- **CLEAR RECOMMENDATIONS NEEDED:** It is “wonderful” to “pontificate” but FDA needs clear recommendations to act on.

DR. FITZGERALD’S VIEW:

- **FOCUS SHOULD BE PLACEBO-CONTROLLED TRIALS:** Dr. Fitzgerald suggested that the “focus of our deliberations” should be the

placebo-controlled trials – because of better quality and more biological plausibility.

- **TARGET TRIAL & PLATELET HYPOTHESIS CONSISTENT:** The lumiracoxib TARGET study (which showed no significant increase in risk) is not “inconsistent with plausibility of the mechanism”, and that the trial had low-risk patients and was underpowered to detect an increased cardiovascular risk (even then, non-aspirin users had a CV hazard ratio of 1.47).
- **TARGET TRIAL BLOOD PRESSURES UNRELIABLE:** The blood pressure in TARGET was not a pre-specified endpoint and he

doubts the reliability of the 1-2 mmHg lower values on lumiracoxib since “it would indeed be amazing if an even more selective drug was less effective on blood pressure”.

- **PLATELET HYPOTHESIS EXPLAINS BOTH ACUTE AND CHRONIC RISKS:** The hypothesized platelet effects are “entirely consistent with an acute and chronic time-dependent evolution of risk”.

DR. FLEMING’S VIEW:

- **SAFETY JUSTIFIES LESS STATISTICAL RIGOR:** Dr. Fleming said that it is important to take into account, as Dr. Packer had said, multiplicity in testing individual safety parameters over time, and multiplicity in the actual safety parameters. However, “when you are looking at safety” it is less acceptable to apply conservative statistical procedures such as “monitoring boundaries” because there is a multiplicity of safety issues, and because you have to take into account both the “severity of those safety issues” and “benefit to risk”. Ultimately, the statistical procedures can “provide some guidance” but “there has got to be informed judgment”.
- **DATA ACCESS FOR DATA MONITORING COMMITTEE:** Data monitoring committees are “critical” and should have “have sole access to emerging data on safety and efficacy during the course of the trial”.

- **VIGOR WAS HYPOTHESIS GENERATION: LATER TRIALS WERE CONFIRMATORY:** The first study to show the CV safety signal was VIGOR and it is appropriate to view this as hypothesis generation that requires “confirmatory” data. He thinks that confirmation has been obtained since there are “at least a dozen trials and at least half of those trials show an indication of excess risk and the majority of those are placebo-controlled trials”.
- **INFORMATION SUFFICIENT FOR MEASURED RESPONSE:** The information “is clearly sufficient for a measured response”.
- **SAMPLE SIZE ISSUES:** He does agree that “we need greater insight”. Drilling “down to the numbers”, to rule out a doubling in risk takes 2,500/arm versus 10,000/arm to rule out a 50% increase in risk (his best point estimate of the coxib effect is a risk of 1.4-1.5). He thinks that 10,000/arm is “conceivably doable”

in view of the 23,000 people in the METAL trial.

- **LONG DURATION WILL INCREASE EVENT RATES:** Since it is important to evaluate

long-term risks, the higher event rates resulting from longer duration of therapy would give more power with a given sample size.

ARTHRITIS ADVISORY COMMITTEE VIEW:

- **ENJOYABLE INTERACTIONS BETWEEN COMMITTEES:** Dr. Gibovsky said that he, and his “colleagues on the Arthritis Advisory Committee”, “very much enjoy the interactions with our colleagues in Drug Safety”.
- **SAFETY IN APPROVED INDICATIONS, WHEN USED AS LABELED:** While “safety for patients in the absolute is important”, marketing approval for the coxibs was given by FDA on the basis that “the potential benefits of each product outweigh the potential risks, when used for the approved indications, according to the directions included in the product labeling”.
- **WITHDRAWALS USUALLY FOR AE IN POPULATION WITH INDICATION:** We may be “at the dawn of a new paradigm” and “when we leave here tonight” we

should “provide some clarity” – but it is his understanding that where “drugs have been withdrawn it has usually been in the context of adverse events in the group for which the drug was approved and not based on adverse events in a prevention or proposed group”.

- **FOCUS ON SAFETY IN PATIENTS WITH ARTHRITIS & PAIN:** He thinks that “we need to look at our questions both in terms of absolute safety, which is critical, as well as relative safety as we define the populations which are going to get these drugs, namely the patients with arthritis and pain”.

DR. WOOD’S “CORRECTION”:

- **TROGLITAZONE IS EXAMPLE OF AE IN NON-APPROVED INDICATION:** Dr. Wood asked to “provide some correction” to Dr. Gibovsky’s comment about the reason for prior drug withdrawals, and gave the example of troglitazone which was withdrawn because of adverse effects in prevention of

diabetes rather than the indication (treatment of diabetes).

- **CAUTION IF EXTRAPOLATE TO OTHER POPULATIONS:** Dr. Gibovsky agreed (“I think that is absolutely correct and it is not a uniform finding.”). He said his “concern is the extrapolation from trials of prevention to trials of

treatment, and I merely indicate that

we cannot be universal about that.”

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE VIEW:

- **REVIEW REASONS FOR PRIOR DRUG WITHDRAWALS:** Dr. Gross made a suggestion on behalf of the Drug Safety and Risk Management Advisory Committee that data on drugs previously withdrawn from the market be reviewed for “commonalities and differences that could guide policy decisions in the future”:
 - The nature of the adverse events.
 - When they were first recognized.
 - The pre-marketing signals.
- The extent to which the nature of the decisions was dependent on the availability of other drugs in the class.
- **REVIEW WOULD BE GOOD FOR COMMITTEES, PUBLIC AND PRESS:** This would facilitate risk:benefit decisions by Advisory Committees, would give the public a “better perspective”, and give the Press “a better sense of relativity of all these activities”.

NO NDAC VIEW:

- Dr. Wood said that they would be “glad to hear” that he was “not going to make a statement on behalf of the NDAC Committee” (Nonprescription Drugs Advisory Committee).

Question 1: Celecoxib

- 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. 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

underestimates. 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 be 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 "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.

Question 2: Valdecoxib

- Voting for Question 2A (increased risk of cardiovascular events) was **Yes 32, No 0**.
- Voting for Question 2B (approval for marketing) was for the **First Vote: Yes 15, No 8, Abstain 9**. For the **Second Vote, voting was: Yes 17, No 13, Abstain 2**.
- Around-The-Table 3C Recommendations (risk-management/suitable populations): Recommendations were carried over from the prior celecoxib recommendations since only incremental recommendations were recorded. They were allocated to 37 categories). 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 **175 recommendations (an average of 5/member) for action (“Yes”), and 20 disagreements with prior recommendations by others (“No”)**. The categories and “Yes vs. No” tabulations were as shown on the following page:

Net Count (Yes - No)	Category
22	1. Black-box warning (25 vs 3)
17	2. Patient Medication Guide (18 vs 1)
16	3. Contraindicated in Cardiovascular Surgery (16 vs 0)
15	4. Ban Direct To Consumer Adverts (19 vs 4)
11	5. Warning for High Dosage (11 vs 0)
7	6. Warning for Long Duration (7 vs 0)
6	7. Warning for High Cardiovascular Risk (6 vs 0)
6	8. Easier-To-Understand Explanation of Risk (6 vs 0)
6	9. Postmarketing studies (6 vs 0)
5	10. Same labeling for NSAIDs (5 vs 0)
5	11. Postmarketing studies (5 vs 0)
4	12. Allow Black-box Removal if Adequate Trials Performed (4 vs 0)
4	13. Second-line Drug (9 vs 5)
4	14. Patient Consent/Attestation (5 vs 1)
2	15. Exclude if at High Cardiovascular Risk (4 vs 2)
2	16. High Dose Contraindicated (3 vs 1)
2	17. Academic Detailing (2 vs 0)
2	18. Educate Healthcare Professionals (2 vs 0)
2	19. Marketing contingent on LT study forthwith (2 vs 0)
2	20. Don't know long-term CV risk (2 vs 0)
1	21. Third-line drug,
1	22. Dear Healthcare Professional Letter,
1	23. OTC Restrictions,
1	24. Define Class,
1	25. Define Mechanism,
1	26. Comprehension Survey,
1	27. Assess/Manage CV Risk,
1	28. FDA Study of Medication Guides,
1	29. Aspirin May Not Reduce CV Risk and May Increase GI Risk,
1	30. Combine COX-2 & Framingham data,
1	31. Do ALLHAT-Type Study,
1	32. Contraindicated in CABG,
1	33. Warn of Risk of Short-acting NSAIDs, &
1	34. Warn of Risk of COX-2 selective traditional NSAIDs.
1	35. Say that Naproxen is Safer than Coxibs (1 vs. 1)
1	36. Long Duration of Therapy Contraindicated (0 vs 2)
	Other (3)

Question 2A: Discussion: Increased risk of CV events with valdecoxib

- **PARECOXIB CONSIDERED WITH VALDECOXIB:** Dr. Shafer asked if they should discuss parecoxib while discussing valdecoxib. Dr. Wood said yes, since

“parecoxib is converted to valdecoxib in the body”.

- **CLEAR SIGNAL ONLY IN CABG SURGERY:** Dr. Shafer said that valdecoxib increases cardiovascular risk in

cardiopulmonary bypass (of which CABG is one type) but “I don’t think the signal is clear otherwise” since “the signal has been weaker than

other studies of approximately the same size” although in “Study 047, there was some increase in C.V. events versus naproxen.”

Question 2A: Voting: Increased risk of CV events with valdecoxib

- All 32 members voted “Yes” without additional comments.

Question 2B: Discussion: Support for marketing of valdecoxib

- **IS CELECOXIB PREFERABLE TO VALDECOXIB?** –

DIFFERENT VIEWS: **Dr. Wood** said that the current data “probably does not” support continued marketing because 1) clear cardiovascular signal in two studies, 2) lack of clear benefit for GI complications, 3) the committee has already “approved” celecoxib that “appears to have a lower signal than the others”. Later he said “it seems highly improbable to me that this drug is safer than celecoxib. It is almost inconceivable to me why somebody would prescribe this drug over celecoxib if you were going to use that”. “....given the size of the signal and somebody used the expression before, the CAB studies may be a canary in a coal mine. It is a high platelet-activated group and that may be just reflecting a model in which it is easier to see a signal than it is in other models”. **Dr. Hennekens** said that while there is no evidence that valdecoxib is safer than celecoxib, “there is also no evidence that it is more harmful”. **Dr. Nissen** agreed as did **Dr. Abramson**. **Dr. Furberg** disagreed and said “we need to face up to the fact that we don’t have good

evidence and take it off the market”. **Dr. Cush** said that since valdecoxib is “equipotent to available drugs” there is “obviously, demonstrated benefit” and he is not convinced of a “significant risk, when the drug is used as indicated”.

- **LITTLE DATA AND NO CLEAR HAZARD IN INDICATED POPULATIONS:**

Dr. Nissen said that valdecoxib was “really tough” because of the absence of data in the indicated populations. The CABG signal was only really strong in the component that included parecoxib.

- **CABG MAY NOT PREDICT SAFETY IN ARTHRITIS: CABG DATA MAY APPLY TO OTHER NSAIDS:**

Dr. Abramson said “it would be not a good precedent, in my view, to remove a drug because there is an alternative without a more serious safety signal”. Because of low-dose aspirin, in the CABG trials patients “had both COX-1 and COX-2 inhibition” and in the CABG setting, the platelets may be “so intensely clotting that the aspirin may have been overridden. But, in effect, these patients were given a COX-mixed inhibition. So since there was no comparator arm in that valdecoxib/parecoxib study, I don’t

know that we can draw a lot of conclusions about the intrinsic safety of this drug in arthritis use over time. I think that was a flawed study to draw specific conclusions about isolated COX-2 inhibition”. Later he suggested that if “high dose Motrin” had been studied in the CABG setting, similar results might have been obtained.

- **VALDECOXIB ALREADY HAS SKIN BLACK-BOX:** Dr. Elashoff pointed out that valdecoxib already has a black-box for skin problems, so that it already has increased risk versus the other drugs.
- **SHOULD MARKETED DRUGS HAVE RENEWAL DATE?** Dr. Farrar said “it is much harder to take a drug off the market without evidence than not to put it on without evidence” and this suggests “that drugs ought to have a renewal date” and he would “strongly recommend consideration of that”.
- **DOUBLE STANDARD FOR CELECOXIB VS. VALDECOXIB?** Dr. Manzi said that the same standard as with celecoxib (keep on market but with black-box and remove black-box when adequate safety data available) should be applied to valdecoxib.
- **CABG RELATIVE RISK 2 FOR VALDECOXIB & 3.7 FOR COMBINATION: CHRONIC DATA LIMITED AND SAFETY DIFFICULT TO ASSESS:** Dr. Fleming responded to Dr. Nissen’s comment that the safety signal was strongest when combined valdecoxib and parecoxib were given, saying that the relative risk in that setting was 3.7 compared with 2 with valdecoxib alone. Both the lack of long-term safety data and the

uncertainty about extrapolating the CABG findings to the arthritis setting is what “we are struggling with”. Dr. Gibovsky expressed concern about Dr. Fleming’s interpretation of the data “in light of what Dr. Packer taught us this morning”. Dr. Fleming said he “just was looking at the evidence in the totality” and “to my way of thinking, that is strong evidence”.

- **ENORMOUS PHYSIOLOGIC DERANGEMENT IN BYPASS:** Dr. Shafer emphasized the “level of physiologic trespass imposed by cardiopulmonary bypass” and the effects “on the entire immune and thrombotic systems”. So he was concerned that if a company studied analgesia in a bypass setting and had a bad outcome, those findings would be applied in other settings – and he had difficulty extrapolating the findings to arthritis.
- **NAPROXEN STUDIES SHOULD BE PART OF NSAID GROUP ANALYSES:** Dr. Shafer also commented “I totally rejected the concept that the naproxen studies should be separated out...”.
- **PROPOSAL TO VOTE ACCOMPANIED BY NEGATIVE SUMMARY:** Dr. Wood then suggested they move to the voting, first noting “remember, the question asked does it support marketing in the U.S., not just is it neutral” and “the question we are being asked here is does the data support marketing the U.S. So it is not just a question-if we have no data at all, that surely wouldn’t support marketing in the United States. So, absence of data is important here, I think, particularly in the presence of

- a safety signal, a strong safety
- **DISCUSSION CONTINUED:** However, several members wanted to continue the discussion. Dr. Hennekens commented that he interprets the valdecoxib data to say “these classes of agents should not be used in cardiac-surgery patients, but they don't bear directly on their utilization in arthritis patients”.
- **SUPPORT WITHDRAWAL VS. SUPPORT MARKETING:** Dr. Ilowite pointed out that the only reason the question says “support marketing” is that FDA wanted to provide the same question for all three coxibs and rofecoxib is not presently marketed; accordingly, the question might easily have said “does it support withdrawal?” “The hurdle is lower if you say, ‘Does it support marketing?’ than if you say, ‘Does it support withdrawal?’”.
- **HURDLE TO WITHDRAW APPROVED DRUG VS. NOT APPROVING UNAPPROVED DRUG:** Dr. Wood asked Dr. Jenkins (FDA) “do you think the hurdle to remove a drug from the market should be higher than the hurdle to get it on the market?” Dr. Jenkins’ comment was unclear. Dr. Wood said “let’s call the question”. Dr. Temple commented that the “standard for approval” is “fairly clear” but that although you can withdraw a drug from the market if the “risk:benefit calculus” changes, these rules are not “quantitative”. In part because of the legal ramifications, he implied that more evidence is required to take a drug off the market.

Question 2B: Voting (in order)(First Vote on 2B): Support for marketing of valdecoxib

- Dr. Abramson: Yes.
- Dr. Nissen: Yes.
- Dr. Elashoff: “I am concerned that we are adding a new risk to something that already has a black-box warning. So I am unclear here.”
- Dr. Gardner: “Pass:
- Dr. Platt: Yes
- Dr. Day: “Abstain”.
- Dr. Furberg: No.
- Dr. Fleming: “Abstain”.
- Dr. Domanski: “Abstain”.
- Dr. Boulware: Yes.
- Dr. Dworkin: Yes.
- Dr. Hoffman: “Abstain”.
- Dr. Manzi: Yes.
- Dr. Farrar: Yes.
- Dr. Holmboe: No “because of the sulfonamide issue and the other black box for cardiovascular”.
- Dr. Gross: No.
- Dr. Wood: No.
- Dr. Gibofsky: Yes.
- Dr. Crawford: No. “ based on the paucity of evidence”.
- Dr. Cush: Yes.
- Dr. Bathon: Yes.
- Ms. Malone: Yes.
- Mr. Levin: No.
- Dr. Ilowite: “Abstain”.
- Dr. D’Agostino: “Abstain”.
- Dr. Morris: Yes.
- Dr. Cannon: Yes.
- Dr. Shapiro: No.
- Dr. Paganini: “Abstain”.

- Dr. Friedman: “Abstain”.
- Dr. Hennekens: Yes.
- Dr. Shafer: Yes.

Question 2C: General Discussion: Risk-management and suitable populations for valdecoxib

- **REQUEST TO JUST ADD VALDECOXIB RESTRICTIONS:**
Dr. Wood suggested that they “go around the table again and ask for suggestions as to how you would manage this”. “I will assume that we would do at least what we would do with celecoxib unless someone sees an objection to that. Let’s only produce incremental changes, if any, that you would like to see to this”.
- **STUDIES-TO-DO DISCUSSION:**
Dr. Temple suggested that the

committee might care to consider here “what studies people should do” even though this will be discussed later in Question 5. Dr. Wood declined this suggestion “because I want to keep us moving”. He asked members to add “to your previous comments .. if there are things you want to add, add them. Otherwise, we will just stay with what you said before”.

Question 2C: Around-the-table comments by committee (only comments additional to those for celecoxib included): Risk-management and suitable populations for valdecoxib

DR. SHAFER: “in anesthesia, we do desperately need better options in the immediate post-operative period for which the intravenous form is an intriguing opportunity”.

DR. HENNEKENS: Same as for celecoxib.

DR. FRIEDMAN: Same as for celecoxib.

DR. PAGANINI: “alter the black box to include only post-cardiac surgery”.

DR. SHAPIRO: “exclude its use ever in post-cardiac surgery”.

DR. CANNON: Same as for celecoxib.

DR. MORRIS: “I would suggest a medication guide. I would also suggest a contraindication that would be both in the contraindications section and the black box in cardiac surgery. I would also try to develop some kind of special program that would be coordinated with patients undergoing cardiac surgery that would have some kind of extra warning.”

DR. D'AGOSTINO: Same as for celecoxib.

DR. ILOWITE: “discussion of the CABG data”.

MR. LEVIN: Same as for celecoxib.

MS. MALONE: “emphasize the need for postmarketing surveillance”.

DR. BATHON: “black-box warning for this drug with the advisory about the CABG patients and against chronic use until further safety data are available in the target populations”.

DR. CUSH: “change the warning to a black box regarding CABG and any other acute cardiac situation”.

DR. CRAWFORD: Same as for celecoxib.

DR. GIBOFSKY: Same as for celecoxib.

DR. WOOD: “triple black-box warning”.

DR. GROSS: “make valdecoxib a second-line selective COX-2 inhibitor”.

DR. HOLMBOE: “contraindicate this drug for use in post-CABG surgery”. Ban for “consumer advertising”. “I clearly would make this a second-line drug”.

DR. FARRAR: In the black box: “an absolute contraindication in cardiac surgery”, “a contraindication stating that the long-term-use risk is unknown” and “second-line”. Clear indication that, “if the company produces data obviating those, then those could be removed.”

DR. MANZI: “contraindication in any revascularization procedure”.

DR. HOFFMAN: “whereas I was not in favor of a duration limitation for Celebrex, I am in favor of a duration

limitation for this agent for which we only have six-month data”.

DR. DWORKIN: “black-box warning”, “third-line” and “with the contraindications that other people have mentioned”.

DR. BOULWARE: “contraindication for CABG surgery” and “listing that we don't know the long-term use in cardiovascular risk”.

DR. DOMANSKI: “Number one, I am going to ask that I be allowed--I am given pangs of conscience by Dr. Nissen. I think he is right. I don't think the data are there and I would like to change my abstain to a no, if I am permitted to. With regard to the box, same as Celebrex but would add that it is contraindicated in the setting of post-bypass.”

DR. FLEMING: “contraindicated in cardiac surgery”, “mandated requirement ... for trials that would give us the broader insight that we are lacking. I am troubled by the fact that when we look at the other four coxibs, they have all had, on average, 20,000 patients. We have three here. Dr. Nissen has persuaded me that we do need to be more forthcoming. We can't probably be as persuasive in mandating that as we can in voting no. So, with that logic, I would like to also change my ‘Abstain’ to a ‘No’.”

DR. FURBERG: “limitation in use to 1 to 2 weeks”, “mentioning in the black box or somewhere in the labeling that there is a lack of evidence for short- and long-term benefit and safety in low-risk patients”.

DR. DAY: “contraindications that others have mentioned”, “no DTC”.

DR. PLATT: “contraindication for patients undergoing cardiovascular surgery”, make “continued marketing of this drug conditional on an appropriately designed randomized trial being undertaken forthwith”.

DR. GARDNER: “I will join my colleagues in converting from an ‘Abstain’ to a ‘No’ and, therefore, not make recommendations for continued”.

DR. WOOD: That was another change in the vote. Did you get that? You can

see how hanging chads come; right? Dr. Gardner changed her vote from an ‘Abstain’ to a ‘No’.

DR. ELASHOFF: “limitation to second-line therapy”.

DR. NISSEN: “stronger warning than we put on celecoxib which particularly emphasizes that longer-term safety has not been established and that the drug should not be used long-term until further data are forthcoming”.

DR. ABRAMSON: Same as for celecoxib.

Question 2B: Valdecoxib: Clarification of Dr. Elashoff’s vote

Dr. Wood announced that “Dr. Elashoff’s vote was not properly recorded because it was unclear what she said, apparently. Would she like to vote?”. Dr. Elashoff said “I was told I

had to say something other than “unclear,” so I said no.” Dr. Wood then said “the vote is 14 yes, 5 abstain and 12 no”.

Question from Dr. Hennekens about Class Effect in CABG Patients

Dr. Hennekens wanted to make sure that people would know that they should not substitute “another coxib or another NSAID instead of valdecoxib “. Dr.

Wood and Dr. Jenkins seemed to agree that FDA would “contraindicate all of them in cardiac surgery”.

Question 2B: Valdecoxib Revote

The initial vote on the marketing of valdecoxib was disregarded, and voting was performed a second time. All 32 valdecoxib votes had been recorded before a decision was made to vote again. 31 votes were clearly stated at the initial vote. A few minutes later, Dr. Wood (the Chairman) announced that “Dr. Elashoff’s vote was not properly recorded because it was unclear what she said, apparently”. When she was asked to make a clear vote in response to this problem, she voted “No”.

Following this, the first valdecoxib 2B vote, as given to and announced by Dr. Wood was: “14 Yes, 5 Abstain, and 12 No” which did not provide a majority in favor of marketing valdecoxib. Note that, based on both the audio record and the official transcript, this tally is incorrect – the actual vote was 15 Yes, 10 Abstain, and 7 No.

The Committee then went on to discuss labeling restrictions for valdecoxib (Question 2C) and then Vioxx (Questions 3A and 3B). During these discussions, and prior to the 3B vote and repeat 2B vote, the following interaction between Dr. Wood and Dr. Nissen took place:

Dr. Nissen: You know, I’m disappointed in the abstentions. You know, we’ve all sat here and listened to the evidence, you know, we have. ...

Dr. Wood: Steve, I don’t think we should, should badger people into voting...

Dr. Nissen: Well, I actually I do want to ask people as we move forward to think about making a commitment one way or the other. Because, what you have is a minority of us making a decision. And I think it is appropriate that people weigh in. So, one man’s opinion....

After voting on Questions 3A and 3B, the following discussion took place:

Dr. Wood: The hanging chads are... have raised their head. They want to go back. We can't agree on the vote apparently for 2B. That was... So, the Question for 2B was, em, "Does the overall risk versus benefit profile for valdecoxib support marketing in the US". Even though we announced the vote and everybody rushed out to file a story, em, <Dr. Wood laughs> it was premature. We're going to have to retake the vote because we're not sure what the vote was, apparently. So, so, em, I've forgotten which side we started on now. Who started? All right, Steve. So, <a Committee member laughs> let's go round again, and you'll vote. And let me remind everybody what we're voting here. We're voting for valdecoxib: Does the overall risk versus benefit profile for valdecoxib...

Questions to Dr. Wood: (inaudible).

Dr. Wood: Yes. We're.. Vald... We're going back to retake the vote for valdecoxib for question 2B, em, because there's some discrepancy apparently in the vote counting. Remember Florida? You thought I was kidding, right?

Questions to Dr. Wood: (inaudible).

Dr. Nissen: Where, where's Katherine Harris now that we need, need her?

Dr. Wood: Right. So we're going to go back to retake. Isn't that right? (obviously asking for confirmation from some person he was looking at). We're going back to 2B. We're going back to the question 2B. And we're taking the, the vote on 2B. So the question is: For valdecoxib, Bextra, does the overall risk versus benefit profile for valdecoxib support marketing in the US? A Yes would keep it on the market. A No would take it off the market. And Steve, were you the... which one was it?

Question from a Committee Member: Is it not on the tape recorder?

Abramson: Abramson, Yes.

<Voting proceeds to completion. The Committee votes in favor of valdecoxib marketing.>

<Further discussion and voting on Vioxx>

Dr. Wood: OK. And I'm now in a position to read you the votes for the, for t.. Question 2B and 3B, at least for now. Em, the, the, em vote for 2B, which was the vote on valdecoxib (for those of you who've forgotten already) em was 17 Yes, 2 Abstain and 13 No....

The actual revote regarding support for valdecoxib marketing proceeded as follows:

DR. ABRAMSON: Yes.

DR. NISSEN: Yes.

DR. ELASHOFF: No.

DR. GARDNER: No.

DR. PLATT: Yes.

DR. DAY: Abstain. "the hanging chad. I have to abstain because the question is based on the available evidence. That is the basis for my abstention."

DR. FURBERG: No.

DR. FLEMING: No.

DR. DOMANSKI: No.

DR. BOULWARE: Yes.

DR. DWORKIN: Yes.

DR. HOFFMAN: Yes. “with restrictions on dose and duration”.

DR. MANZI: Yes.

DR. FARRAR: Yes. “with limitations on dose and duration”.

DR. HOLMBOE: No.

DR. GROSS: No.

DR. WOOD: No.

DR. GIBOFSKY: Yes.

DR. CRAWFORD: No.

DR. CUSH: Yes.

DR. BATHON: Yes. “I had restrictions, also”.

MS. MALONE: Yes.

MR. LEVIN: No.

DR. ILOWITE: Yes “I am one of the abstainers before. I will change it to yes”.

DR. D'AGOSTINO: No. “I will balance that and change it to no”.

DR. MORRIS: Yes.

DR. CANNON: Yes.

DR. SHAPIRO: No.

DR. PAGANINI: Abstain. “Paganini continues abstaining”.

DR. FRIEDMAN: No. “I will go to a no”.

DR. HENNEKENS: Yes.

DR. SHAFER: Yes.

Question 3: Rofecoxib

- Voting for **Question 3A** (increased risk of cardiovascular events) was: **Yes 32, No 0**.
- Voting for **Question 3B** (approval for marketing) was: **Yes 17, No 15**. Six of the “Yes” votes were accompanied by reservations.
- Around-The-Table 3C Recommendations (risk-management/suitable populations): Recommendations were carried over from the prior celecoxib and valdecoxib recommendations since only incremental recommendations were recorded. They were allocated to 46 categories. 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 **225 recommendations (an average of 7/member)** for action (“Yes”), and 20 disagreements with prior recommendations by others (“No”). The categories and “Yes vs. No” tabulations were as follows:

Net Count (Yes - No)	Category
22	1. Black-box warning (25 vs 3)
17	2. Patient Medication Guide (18 vs 1)
16	3. High dose contraindicated (17 vs 1)
16	4. Contraindicated in cardiovascular surgery (16 vs 0)
15	5. Ban Direct To Consumer Adverts (19 vs 4)
11	6. Warning for High Dosage (11 vs 0)
9	7. Patient Consent/Attestation (10 vs 1)
8	8. Warning of Increase in Blood Pressure (8 vs 0)
7	9. Warning for Long Duration (7 vs 0)
7	10. Second Line Drug (12 vs 5)
6	11. Warning for High Cardiovascular Risk (6 vs 0)
6	12. Easier-To-Understand Explanation of Risk (6 vs 0)
6	13. Postmarketing studies (6 vs 0)
5	14. Same labeling for NSAIDs (5 vs 0)
5	15. Allow Black-box Removal if Adequate Trials Performed (5 vs 0)
5	16. Patient Registry (5 vs 0)
3	17. Long Duration of Therapy Contraindicated (5 vs 2)
3	18. Don't use in adults (3 vs 0)
2	19. Exclude if at High Cardiovascular Risk (4 vs 2)
2	20. Academic Detailing (2 vs 0)
2	21. Educate Healthcare Professionals (2 vs 0)
2	22. Assess/manage cardiovascular risk (2 vs 0)
2	23. Marketing contingent on LT study forthwith (2 vs 0)
2	24. Insufficient data on LT risk (2 vs 0)
2	25. Third-Line drug (2 vs 0)
1	26. Dear Healthcare Professional Letter (1 vs 0)
1	27. OTC Restrictions (1 vs 0)
1	28. Define "class" (1 vs 0)
1	29. Define mechanism (1 vs 0)
1	30. Comprehension survey for patient consent (1 vs 0)
1	31. FDA study of patient medication guides (1 vs 0)
1	32. Aspirin May Not Reduce CV Risk and May Increase GI Risk (1 vs 0)
1	33. Combined analysis of COX-2 & Framingham data (1 vs 0)
1	34. Do ALLHAT-Type Study (1 vs 0)
1	35. Warn of Risk of Short-acting NSAIDs (1 vs 0)
1	36. Warn of Risk of COX-2 selective traditional NSAIDs (1 vs 0)
1	37. Lack of Safety Data in Long-Term patients (1 vs 0)
1	38. Special program to prevent use in Cardiac Surgery (1 vs 0)
1	39. Contraindicated in ANY revascularization procedure (1 vs 0)
1	40. Reexamine pediatric dosage (1 vs 0)
1	41. Study blood pressure and atherogenesis in children (1 vs 0)
1	42. Reminder every 6-12 months of LT therapy (1 vs 0)
1	43. Mention risk of heart failure (1 vs 0)
1	44. Mention lack of data on cardiovascular effects in children (1 vs 0)
0	45. Say that Naproxen is Safer than Coxibs (1 vs. 1)
	Other (3)

Question 3A: Discussion: Increased risk of CV events with rofecoxib

- Dr. Ilowite wanted to “remind everybody” that rofecoxib is the only COX2 inhibitor that is approved for juvenile rheumatoid arthritis, and also that it is available as a liquid.

Question 3A: Voting: Increased risk of CV events with rofecoxib

- The voting was 32 to 0.
- There were no additional comments other than from Dr. Elashoff who said “Yes. Both against placebo and against naproxen”.

Question 3B: Discussion: Support for marketing of rofecoxib

- **ROFECOXIB & CELECOXIB HAVE SIMILAR RISK VS. PLACEBO:** Dr. Hennekens said that the point estimate for risk of rofecoxib versus placebo is “practically identical to that for celecoxib.” The “discrepancy” only occurs when naproxen was used as a comparator in rofecoxib trials.
- **BLOOD PRESSURE EFFECT MORE WITH ROFECOXIB:** Dr. Nissen said, “however”, the blood pressure effects of rofecoxib “are clearly outside of other drugs in the class including celecoxib...” and “a 5- or 6-millimeter average blood-pressure increase over a period of time is very undesirable since there are other drugs in the NSAID and coxib class that do not appear to have that very large signal on blood pressure”. He was also concerned about the “heart-failure signal” with rofecoxib compared to “the APC and approved trials. What you see is almost no heart-failure events”. Dr. Hennekens asked why, in view of what Dr. Nissen said, the APTC cardiovascular index did not show “a higher risk estimate”. Dr. Nissen said “there may be a latency issue here” and “it takes a while for hypertension to yield an excess of events”.
- **VERY LARGE EARLY HEART FAILURE RISK: ROFECOXIB WORSE THAN OTHERS?** Dr. Wood said that “the data here are very compelling” with the “cardiovascular risk in the APPROVe trial” and “the very large risk from heart failure which separates very early”. “So there is a clear signal this drug appears substantially worse than the others. I can’t see any reason to keep it on the market.” Dr. Furberg disagreed with these heart failure conclusions and said that celecoxib versus placebo had a risk ratio of 6 as compared with a risk ratio of 4 in the rofecoxib APPROVe trial.

- **STRONG DOSE-RESPONSE FOR ROFECOXIB SAFETY SIGNAL:** Dr. Paganini said that rofecoxib had a “much stronger dose relationship” than the other coxibs with 50 mg “probably not very good”, 25 mg “a little better” and 12.5 mg “back to where the other NSAIDs seemed to be”.
- **ADVANTAGES OF ROFECOXIB:** Dr. Manzi commented that not only is rofecoxib “the only drug approved for “juvenile rheumatoid arthritis “as Dr. Ilowite pointed out”, but it is the “only one with a G.I. safety proven indication”, and because of its once-daily dosing has favorable patient compliance. Dr. Bathon said that rofecoxib was the only coxib available for those who are sulfa-allergic.
- **IS ROFECOXIB TOXICITY RELATED TO LONG HALF-LIFE?** Dr. Wood suggested that the once-daily dosing might contribute to the cardiovascular toxicity of rofecoxib.
- **ALL 3 LT STUDIES HAVE SAFETY PROBLEM:** Dr. Fleming said that each of the three long-term rofecoxib trials had a safety problem: cardiovascular events in APPROVe and VIGOR, and increased mortality in the Alzheimer’s trial.

Question 3B: Voting: Support for marketing of rofecoxib

DR. SHAFER: No. (“overwhelmingly no, although if individual patients can petition the company under some mechanism, I would support that”).

DR. HENNEKENS: Yes.

DR. FRIEDMAN: No.

DR. PAGANINI: Yes.

DR. SHAPIRO: No.

DR. CANNON: No.

DR. MORRIS: Yes “but”.

DR. D'AGOSTINO: No.

DR. ILOWITE: Yes.

MR. LEVIN: No.

MS. MALONE: Yes. “with reservation”.

DR. BATHON: Yes. “but at lower dose, no 50 milligrams”.

DR. CUSH: Yes.

DR. CRAWFORD: Yes.

DR. GIBOFSKY: Yes.

DR. WOOD: No.

DR. GROSS: No.

DR. HOLMBOE: Yes. “but only for children”.

DR. FARRAR: Yes.

DR. MANZI: Yes.

DR. HOFFMAN: No.

DR. DWORKIN: Yes. “with restrictions”.

DR. BOULWARE: Yes.

DR. DOMANSKI: No.

DR. FLEMING: No.

DR. FURBERG: No.

DR. DAY: No.

DR. PLATT: Yes.

DR. GARDNER: Yes. “with restrictions”.

DR. ELASHOFF: No.

DR. NISSEN: No. “but with a possible compassionate-use program”.

DR. ABRAMSON: Yes.

Question 3C: General Discussion: Risk-management and suitable populations for Rofecoxib

- **JRA PATIENTS HAVE LOW CV RISK:** Dr. Holmboe said that rofecoxib’s indication in juvenile rheumatoid arthritis applies to a population at “very low cardiovascular risk”.
- **HYPERTENSION & EDEMA COMMON TO CLASS: MONITORING NEEDED:** Dr. Farrar suggested that the risk of hypertension and edema is shared with the other drugs, so that there should be monitoring for these events as well as a “more formal warning” as effects might otherwise not be noted in a “young, healthy person”.
- **TOP DOSE AND LONG DURATION UNACCEPTABLE:** Dr. Morris said that the highest dose of rofecoxib should be removed from the market and “really bold warning” is needed on “duration of use”. Dr. Paganini agreed.
- **HYPERTENSION AND DOSE-RESPONSE OF CONCERN:** Dr. Abramson said the concern with rofecoxib is hypertension and the dose-response and the maximum dose should be addressed.
- **BLOOD PRESSURE CONCERN IN CHILDREN:** Dr. Hoffman said that he was concerned about even slight increases in blood pressure in chronic use in children. Dr. Nissen said that blood pressure is a “continuous risk factor”, that the increase in blood pressure occurs even with the 25 mg rofecoxib dose, and there is no reason to suppose that other agents could not be developed for juvenile rheumatoid arthritis.
- **CHANGE IN BP ON STOPPING ROFECOXIB NOT KNOWN:** Dr. Morris asked what happens to the blood pressure when patients are taken off rofecoxib. Dr. Nissen believed “that it would be likely, at

least in large part reversible, but I am not sure anyone has such data”.

- **DO BP AND ATHEROGENESIS STUDIES IN CHILDREN:** Dr. Ilowite suggested that approval in children could be made contingent of long term blood pressure and atherogenesis effects. Dr. Nissen said this would be difficult to study because of the long latency for events to occur. Dr. Ilowite said that blood pressure should be “easy to study” and other trials use “surrogate early markers of atherosclerosis”. Dr. Farrar mentioned that the NIH is getting “a billion dollars worth of money to study pediatric diseases” and they might be persuaded to look at these issues.
- **NO BP CHANGES IN ROFECOXIB JRA TRIALS:** Dr. Manzi asked if there were blood pressure changes in the rofecoxib JRA trials. Dr. Ilowite said there were no such issues.
- **CAN ROFECOXIB-INDUCED HYPERTENSION BE “MANAGED”?** Dr. Temple said that blood pressure “is something we

ordinarily think of as treatable” and asked if rofecoxib’s effect on blood pressure could be managed. Dr. Wood and Dr. Nissen pointed out that blood pressure was managed in APPROVe and there was more use of anti-hypertensive drugs, but the blood pressure was still higher and there were increased dropouts because of hypertension. Dr. Nissen said that, in addition, “treated hypertension still confers a risk over no hypertension”; Dr. D’Agostino agreed, based on the Framingham data.

- **HIGHER ROFECOXIB DOSES MAY BE MORE EFFECTIVE AND MORE TOXIC:** Dr. Hennekens (during 3C voting) said “I share Steve's concern that blood pressure is a greater potential issue here but Richard's that it is likely that higher doses of this drug lead to greater benefits. This may offer one plausible explanation for the higher risk seen in observational studies.

Question 3C: Around-the-table comments by committee: Risk-management and suitable populations for Rofecoxib

DR. ABRAMSON:

“stronger label in terms of hypertension and potential cardiovascular outcomes”,

“restriction of upper dose to be determined”,

“leave open the possibility of some change of this with future studies”,

“second choice” drug.

DR. NISSEN:

Restrict dose to 12.5 mg “if anything is done with the drug),

“I don't want to go there. But, if we do go there, I would put the most difficult and most complex warning on there possible”.

DR. ELASHOFF:

“Stronger than either of the two previous cases”.

DR. GARDNER:

“Stronger”,

“register patients or otherwise bring attestation into the risk-management program”,

“good, strong postmarketing” evaluation.

DR. PLATT:

“dose restriction”.

DR. DAY:

“More restriction”.

DR. FURBERG:

“Stronger black-box warnings”.

DR. FLEMING:

“same conditions and concerns that Steve Nissen indicated”.

DR. DOMANSKI:

“underscore second-line drug”.

DR. BOULWARE:

Same as for celecoxib.

DR. DWORKIN:

“third-line” drug

“a patient will have had to have failed two NSAIDs, whether selective or not, before they try this drug.”

DR. HOFFMAN:

“restriction in dose to 12.5 mg”.

DR. MANZI:

“restrict only the 50-milligram dose”,

“have patient consent” better than not having the drug available.

DR. FARRAR:

“strong black-box warning including an indication of ongoing monitoring of blood pressure in all patients including children”,

“I am conflicted about the idea of registration”,

“some sort of patient consent”,

“restriction in dose”.

DR. HOLMBOE:

“I agree with what has been said previously”,

if used in adults “there should be some sort of informed-consent process”.

DR. GROSS:

“strong black-box warning”,

“second-line drug”,

“restricted to 12.5 mg dose”.

DR. WOOD:

“black-box warning”,

“very restricted access program”,

“attestation and some clear ability of patients to consent”,

“be careful not to” put children “at even greater risk with their lifelong hypertension risk, their lifelong exposure to cardiovascular risk factor”.

DR. GIBOFSKY:

restrict dose to 12.5 mg “for chronic use, not for acute use”,

“very strong black-box warning to emphasize the hypertension, cardiovascular, at the higher dose”,

“second or third choice”,

consider “Subpart H where there would be very strong restrictions on who would have access to it”.

DR. CRAWFORD:

“stronger black-box warning”,

“dose limits as appropriate”,

“duration limits”,

“second-line”

“informed consent”.

DR. CUSH:

“removal of the 50-milligram dose from the market”,

“black-box warning”.

DR. BATHON:

“strong black-box warning”,

“elimination of the 50 mg” dose,

“second choice”.

MS. MALONE:

“ongoing studies”,

“patient consent”,

MR. LEVIN:

“Black-box warnings”,

“I am intrigued by the notion of a Subpart H approach”.

DR. ILOWITE:

“strong black-box warning”,

“elimination of the 50 mg dose”,

“reexamination of the dose in children”,

“studies of blood pressure and atherogenesis”.

DR. D'AGOSTINO:

“Stronger black-box warning”,

“dose restriction to 12.5” mg,

“restricted access”.

DR. MORRIS:

“Black box”,

“withdrawal of the highest dose”,

patient “consent”,

“reminder sent to the patient about either six months or a year, depending upon issues related to duration to remind them about the risks of long-term use”.

DR. CANNON:

“strong black-box warning”,

“no direct-to-consumer advertising”,

limit use “to a short-term use for pain in adults and for chronic use in children and young adults with JRA with careful monitoring of blood pressure”.

DR. SHAPIRO:

“I agree with what Dr. Cannon just said”,

“some dose limitations”.

DR. PAGANINI:

“Black box to include very strong and severe dose and time restrictions as well as cardiovascular”,

“spell out the cardiovascular clearly to include blood pressure and congestive heart failure”,

“no direct advertising”,

“move from a patient brochure as a patient consent”.

DR. FRIEDMAN:

“elimination of the high 50” mg dose.

DR. HENNEKENS:

“global risk assessment and aggressive management of cardiovascular risk”,

DR. SHAFER:

“If it is to be marketed, I think it should only be indicated for children not adequately treated with conventional NSAIDs”,

“The black-box warning should state that the cardiovascular effects in children are unknown and that the use in adults is not recommended”,

“The adult use should be limited to compassionate use only which, I believe, is the Subpart H restriction”.

Question 4: Low Dose ASA and CV Events

- **“CLASS” TRIAL SUGGESTED ASPIRIN REVERSED COX-2 GI AND CV EFFECTS:** Dr. Wood said that the CLASS trial “wasn't a randomized comparison, although it does give some evidence that the G.I. benefit was antagonized by aspirin and the cardiovascular benefit was reversed as well...” Dr. Bathon said that the available data suggest that aspirin “seems to undo the GI benefit”.
- **ASPIRIN DATA LIMITED:** Dr. Nissen said “the amount of data we have ... is limited. It would be useful ... to study this in a more formal way with larger sample sizes whether, in fact, aspirin is an effective antagonist to the toxicity of this class of drugs”. Dr. Gross said “there is just not enough good evidence to comment on this one way or the other..” Dr. Wood said he agreed with Dr. Gross that there is insufficient evidence to answer the question.
- **ASPIRIN HAS LIMITED EFFECTS IN PREVENTING CARDIAC DISEASE:** Dr. Farrar said “Aspirin is not a panacea for cardiac vascular disease.” And in the COX-2 setting “it is clear to me that it doesn't work”.
- **COX-2 INHIBITORS NOT SUITABLE FOR HIGH CV RISK PATIENTS:** Dr. Cush said that if you “need aspirin for cardiovascular prophylaxis ... then you certainly shouldn't be on a COX-2 inhibitor.”
- **GI HOSPITALIZATIONS MAY BE LESS FREQUENT IN PATIENTS ON ASPIRIN+COX-2s THAN ASPIRIN+NSAIDS:** Dr. Nissen asked if any study compared GI toxicity with conventional NSAID+aspirin with a COX-2 inhibitor+aspirin. Dr. Cryer said there was only epidemiology data and this suggested hospitalizations are reduced with the COX-2 inhibitor+aspirin; however, with regard to “the traditional characterization of G.I. events” the two regimens appear equivalent.
- **LUMIRACOXIB CV RISK WAS REDUCED IN ASPIRIN SUBSET:** Dr. Villalba said that with lumiracoxib, the aspirin subset had no difference in MIs, whereas in the non-aspirin subset lumiracoxib had more MIs than naproxen (“like, 10 to 2 myocardial infarctions”).
- **TARGET TRIAL:** Dr. Cryer said that in the TARGET trial in the 18,000 patients, there were no statistically significant differences with respect to low-dose aspirin and G.I. events”.

Question 5: Future Trials for Coxibs

- **GET EXPERT GROUP TO DESIGN STUDY:** Dr. Farrar suggested that a group of experts get together to develop a “really good design” and have an “ongoing process with a group of academic advisers”.
- **TWO TYPES OF STUDY – VS PLACEBO AND VS ACTIVE COMPARATORS:** Dr. Wood said that there could be two groups of studies – against placebo and against active comparators. One would choose the comparator based on the indication, and also on “information on what the comparator looks like on its own”. He suggests that it would be good to know how naproxen+PPI versus placebo affects CV risk.
- **COMPARABILITY TO IBUPROFEN MAY NOT BE ADEQUATE:** Dr. Temple questioned how acceptable an ibuprofen comparison would be.
- **WILL PLACEBO-CONTROLLED TRIALS BE FEASIBLE?** Dr. Temple asked how feasible it would be to do additional placebo-controlled trials. If you have to wait until you have a definitive naproxen-placebo trial “we are talking almost never...”.
- **APPARENT COX-2 RISK REQUIRES CAUTION IN TRIALS:** Dr. Wood said a concern is that the COX-2 drugs may be risky, so that “you would be cautious” about doing a trial that would reproduce the toxicity already seen.
- **CELECOXIB/NAPROXEN STUDY SUGGESTED:** Dr. Temple suggested a 1-3 year comparison of naproxen and celecoxib.
- **DON'T USE ANOTHER COX-2 INHIBITOR AS YOUR CONTROL:** Dr. Wood would be “unimpressed” with a “study against another selective COX-2 inhibitor. I think that is likely to be negative”.
- **USE NAPROXEN CONTROL, NOT PLACEBO OR ACETAMINOPHEN:** Dr. Nissen said you could not do a placebo-controlled trial in arthritis, and he did not think an acetaminophen-codeine control group would be “practical”. It will be difficult to interpret the data if every sponsor uses a different comparator, and he favors using naproxen.
- **CELECOXIB 200 MG/ NAPROXEN 500 MG BID/ DICLOFENAC COMPARISON:** Dr. Nissen suggested a study of celecoxib 200 mg/day versus naproxen 500 mg bid – and it would “make a lot of sense” to add diclofenac as a third arm.
- **ADD IBUPROFEN TO CELECOXIB/NAPROXEN/DICLOFENAC:** Dr. Dworkin largely agreed with Dr. Nissen but suggested a fourth arm using ibuprofen.
- **MULTIPLE COMPARATORS NEED FUNDING BY LARGER GROUP:** Dr. Temple said that a single company might reasonably say that a single comparator such as naproxen should be adequate, so that studies with multiple comparators might have to be funded by “a larger group”.
- **NON-INFERIORITY TRIAL OF COX-2 INHIBITOR:** Dr. Fleming suggested a 2-3 year, OA/RA, non-inferiority comparison of celecoxib and either naproxen or aspirin+PPI

using 10,000 patients/arm to provide 90% power of picking up a 50% increase (i.e. an excess risk of 17%) with only a 2.5% false positive error rate. If results were favorable that should be enough to remove the celecoxib black-box. For valdecoxib and rofecoxib where the safety signal is higher, a comparable study would be needed within an acceptable time frame “if they are going to be on the market”. In the case of rofecoxib which may have been studied at excessive dosage, the dose should be lower.

- **NEED TO SHOW SAFETY OF SHORT-ACTING NSAIDs:** Dr. Hennekens said that “the short-acting NSAIDs” appear “at least as hazardous as the coxibs” and are OTC drugs with DTC advertising. Accordingly, they should not be ignored when planning future studies.
- **NEED TO FOLLOW-UP DROPOUTS:** Dr. D’Agostino said that follow-up is important for patients dropping out of the study “because their blood pressure is building up, they are getting hypertensive, or because of G.I. problems”.
- **OA BETTER POPULATION THAN RA:** Dr. Hoffman suggested that the proposed study should be done on OA(since in RA patients are sicker, are at greater CV risk, and an “analgesic arm” would not be feasible). He suggests that the groups consist of: 1) acetaminophen (with addition of codeine if necessary), 2)

an NSAID (such as naproxen or ibuprofen) plus a PPI, 3) the COX-2 drug.

- **PRACTICALITIES OF ALLHAT-TYPE DESIGN:** Dr. Cush supported a 2-year trial using Dr. Temple’s proposed ALLHAT approach. However, he expressed concern about the “impracticalities” of the study suggested by Dr. Temple and Dr. Fleming. He does not think patients would stay on high dose aspirin for the duration of the study and “to provide some modicum of protection by putting a PPI on top of that is not going to be practical”.
- **SAMPLE SIZE OF 10,000/GROUP ANTICIPATES POINT ESTIMATE OF RISK NOT MORE THAN 15% TO PROVIDE CONFIDENCE THAT TRUE VALUE IS LESS THAN 50%:** Dr. D’Agostino expressed concern that the suggested sample size would only be sufficient to pick up a 50% increase in risk. Dr. Fleming responded that to increase the ability to detect smaller effects would increase the sample size from the 10,000/group he had suggested to 20,000 for a 33% increase and 60,000 for a 20% increase. However, he pointed out that the point estimate of risk would have to be within about 15% of zero effect in order to have the upper confidence limit be below the 50% increase in risk that must be excluded.

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

- **100% VOTE FOR ADDED LABELING:** All 28 members voting on Question 6 voted for added safety labeling for approved NSAIDs.
- **OBSERVATIONAL STUDIES: MORE DATA NEEDED:** Dr. Pratt said that in the absence of clinical trial data on the traditional NSAIDs, we need to get more observational data “pronto”.
- **LABELING OF NSAIDs WOULD BE USEFUL TO NON-RHEUMATOLOGISTS:** Dr. Domanski approved of having additional safety information (as a warning or a precaution) in the labeling, especially for non-rheumatologists.
- **NON-COXIB COX-1 SELECTIVE DRUGS SHOULD HAVE SEPARATE LABELING:** Dr. Nissen’s concern (“Houston, we have a problem”) is with the “so-called COX-2-selective NSAIDs that are not called coxibs” and thinks that these agents should be specifically identified and given their own set of warnings. Dr. Shafer suggested that the same black-box warning for the coxibs should be given to four other COX-2 selective drugs (etodolac, miloxicam, diclofenac and sulinac). Dr. Wood disagreed with Dr. Shafer’s suggestion because it would “undercut the strength of black-box warnings”.
- **OTC DRUG LABELING A PROBLEM:** Dr. Wood asked how to handle the OTC drugs (naproxen, ibuprofen and ketoprofen). Dr. Temple said that the “nominal labeling” says “short-term use – not that we believe that anybody limits it. So that has to be coped with.” Dr. Ilowite said that FDA had told him that giving an OTC drug a black-box means it is no longer OTC.
- **BLACK-BOX PRESENCE MORE IMPORTANT THAN CONTENT:** Dr. Morris said that a black-box should be used for all NSAIDs and that the important thing was the symbolic value of a black-box, and not necessarily the information inside the black-box. Dr. Gross agreed with a black-box for all NSAIDs.
- **LABELING OF SAFETY: DISPLAY OPTIONS:** Dr. Temple gave a brief overview of where safety information can reside in the label – black-box, description and clinical trials, warnings, and precautions. In a draft proposal, the latter two are combined into a section called “Warnings and Precautions”. A black-box “absolutely bars reminder ads.”
- **WILL NAPROXEN BE EXCLUDED FROM WARNING LABELING?** Dr. Platt said “it would be a mistake” to have the same warning for all NSAIDs “absent naproxen which I think we have excluded from any warning”.
- **SHOULD QUESTION 6 BE FOR TWO SEPARATE GROUPS?** Dr.

Wood suggested that they break Question 6 into two parts, one for COX-2 selective non-coxibs and one or the rest of the traditional NSAIDs. Dr. Jenkins (FDA) said that the concern with this is that there is not

agreement as to which drugs should be designated as “COX-2 selective”. Dr. Temple said that FDA could later “refine” the decision as to which drugs should be considered “COX-2 selective”.

Voting on Question 6

DR. ABRAMSON: Yes.

DR. NISSEN: Yes.

DR. ELASHOFF: Yes.

DR. GARDNER: Yes.

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

DR. DAY: Day. Yes. “I echo Platt”.

DR. FURBERG: Yes. “to precaution”.

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

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

DR. BOULWARE: Yes.

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

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

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

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

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

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

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

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

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

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

MR. LEVIN: Yes. “to the first”.

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

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

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

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

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

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

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

Voting Results on Question 6

Yes 28, No 0, Abstentions 0.

Question 7: Trials for CV Effects of Non-Selective NSAIDs

- **NEW STUDIES NEEDED:** All participants agreed that additional cardiovascular safety studies of non-selective NSAIDs are required.
- **INCLUDE NSAIDS IN ALLHAT-TYPE TRIAL:** Dr. Fleming said that ibuprofen and diclofenac should be included in the Temple ALLHAT-type trial if possible.
- **PRACTICE-LEVEL RANDOMIZATION IN LARGE SIMPLE TRIAL:** Dr. Platt suggested a variation of the ‘large simple trial’ in which randomization to a particular drug would be on a practice-level rather than a patient-level basis to provide large-scale randomized studies of drugs “as they are used in regular practice”.
- **TRACKING DEATHS IN OBSERVATIONAL STUDIES:** Dr. Wood asked about tracking deaths in the Medi-Cal database.. Dr. Graham did not respond directly but said that California Medicaid, Kaiser Permanente, Tennessee Medicaid, and several Canadian databases all have linkage to death certificate data.
- **TOUGH WARNINGS GIVE INCENTIVE TO SPONSORS:** Dr. Nissen said that the best way to get the randomized safety trials of non-selective NSAIDs it to provide the incentive of losing the “cardiovascular warning” if the results are good – which argues for “tough” warnings to provide more incentive. Dr. Wood said that this could be an opportunity to differentiate their drug from the competition because of a better safety profile.
- **ANY NEW OTC APPROVALS NEED GOOD SAFETY DATA:** Dr. Wood said that no new OTC NSAID approvals should be given without “really good safety data”.

Question 8: CV Evaluation of New NSAIDs

- **SIMILAR STANDARDS AS FOR MARKETED NSAIDs:** Dr. Wood said that the standards for trials of new NSAIDs should be just as stringent as for marketed NSAIDs. Dr. Fleming said that the previous sample size recommendations (“rule out a 50 percent increase in the relative risk for cardiovascular events”) should be applied to new NSAIDs.

- **DO TRIALS IN SETTING OF CV RISK REDUCTION STRATEGIES:** Dr. Holmboe reiterated, for trials with new NSAIDs as well as marketed drugs, that standard cardiovascular risk reduction strategies be employed, since this is a setting where the drugs might be increasing cardiovascular risk.
- **SWITCH CURRENT COX-2 PROGRAMS AWAY FROM DICLOFENAC:** Dr. Nissen said that the current investigational COX-2s should change their development programs to use naproxen as the comparator rather than a non-coxib COX-2 selective drug such as diclofenac.
- **POWER FOR SUB-GROUP & DURATION ANALYSES:** Dr. Gardner commented on the need for adequate power for subgroup analyses and duration-of-use analyses.
- **TARGET POPULATIONS BUT NOT HIGH CV RISK PATIENTS:** Dr. Farrar said that the trial populations should be those in which the drugs will be used, while “obviously limiting it to” mild cardiovascular risk.
- **COMPARATOR SHOULD UNCLUDE NSAID+PPI:** Dr. Farrar also said that one of the comparisons should be of GI toxicity versus a comparator that has a gastroprotective component such as a PPI.
- **NEW SAFETY PARADIGM WILL SLOW DRUG DEVELOPMENT:** Dr. Cush said that for new drugs, low-risk patients with the indication being sought should be studied versus an active control for 1-2 years. He also pointed

out that a requirement to complete an adequate long-term safety trial before a new NSAID can be marketed is a “departure in process” and “may take a longer time to do”. Dr. Jenkins confirmed that this is what he thought the committee was advising. Dr. Cush expressed concern that future drug development not only for NSAIDs but in other therapeutic areas might be “delayed and curtailed” because of “this new paradigm”.

- **DRUG DEVELOPMENT MAY BE SLOWED IN OTHER AREAS ON CASE-BY-CASE BASIS:** Dr. Nissen thought that the NSAIDs were a special case and similar standards need not necessarily be imposed for other drug classes. Dr. Temple agreed but also said that similar special situations existed (because of “priors”) with heart failure drugs (where long-term survival trials are needed) and with anti-arrhythmic drugs (in which the CAST trial showed that these drugs could have “a disastrous outcome”). Dr. Wood said another example was phosphodiesterase inhibitors.
- **INCREASED SAFETY REQUIREMENTS ARE NOT JUST CARDIOVASCULAR:** Dr. Wood said it was not just cardiovascular risk that had to be evaluated satisfactorily but also “heart failure”, “GI bleeds” and “complicated ulcers”. Dr. Temple commented that some sponsors of coxibs have “seen that particular handwriting on the wall” and are trying to do studies of this type.

Announcements of Voting Results

- **QUESTION 1A:** The Question 1A announced vote (Celebrex CV toxicity) was: Yes 32, No 0.
- **QUESTION 1B:** The Question 1B announced vote (Support for marketing Celebrex) was: Yes 31, No 1.
- **QUESTION 2A:** The Question 2A announced vote (Bextra CV toxicity) was: Yes 32, No 0.
- **QUESTION 2B:** The Question 2B announced vote (Support for marketing Bextra): The initial vote was “not properly recorded” for 1 member. When this was done the vote was reported as: Yes 14, Abstain 5, No 12. A discussion of the inadvisability of abstaining then took place. Following this, the vote was retaken and was reported as: Yes 17, Abstain 2, No 13.
- **QUESTION 3A:** The Question 3A vote (Vioxx CV toxicity) was: Yes 32, No 0.
- **QUESTION 3B:** The Question 3B announced vote (Support for marketing Vioxx) was: Yes 17, No 15.
- **QUESTION 6:** The Question 6 announced vote (Modified labeling for approved NSAIDs) was: Yes 28, No 0. <Not all voting members present>.