Trends-in-Medicine

March 2005
by Lynne Peterson

SUMMARY

Pfizer's Bextra and Celebrex will remain on the market, but get a black box warning, if the FDA follows the advice of its advisory committee, which also determined that Merck's Vioxx is safe enough to return to the market, with an even stronger black box warning and other restrictions. However, the outlook for Cox-2 inhibitors still in development is doubtful. Panel members were very negative on the prospects for Novartis's Prexige, and Merck's Arcoxia likely would have to start another large (at least 20,000-patient) trial vs. Bayer's Aleve (naproxen), which appears to be the new gold standard against which Cox-2s will be compared. Traditional non-selective NSAIDs also have become suspect, and the panel recommended they get warning labels as well.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Advisory Committee Determines Cox-2 Inhibitors and NSAIDs Safe Enough to Remain on the Market

After three days of review and discussion, an FDA advisory committee recommended on February 18, 2005, that a black box be added to all Cox-2 inhibitors and that a warning or precaution be added to all marketed non-selective NSAIDs except Bayer's Aleve (naproxen). FDA officials promised to act quickly on the panel's recommendations. Dr. John Jenkins, Director of the FDA's Office of New Drugs, said, "We will have a meeting with our review staff and senior staff to come to conclusions…We are committed to reaching conclusions in the next few weeks, and then we will make announcements about our decision. But it will take time to put them into place. You can't change labeling over night and have it show up in the pharmacy the next day…We are committed to making our decisions very quickly after this meeting."

The FDA's Drugs Safety & Risk Management Advisory Committee and its Arthritis Drugs Advisory Committee jointly met to review the cardiovascular safety profile of Cox-2 inhibitors on February 16, 17, and 18, 2005. There were 32 experts on the panel, including rheumatologists, cardiologists, drug safety experts, epidemiologists, a statistician, and a patient advocate.

Pfizer appeared the big winner at this panel meeting. The panel clearly felt that Pfizer's Celebrex (celecoxib) should stay on the market. Responding to the panel's vote, the head of Pfizer's global R&D said, "Patients and doctors now have a better understanding of the benefits and risks (of Cox-2s). Before this week, there was a lot of confusion which created a lot of doubt about the safety (of these drugs)."

The panel's recommendations about the future of Pfizer's Bextra (valdecoxib) and Merck's Vioxx (rofecoxib) were less clear, but the panel opened the door for Merck to bring Vioxx back on the market in a restricted way. There was a bare majority in favor of continued marketing of Vioxx and Bextra, but the FDA traditionally views a close positive vote as a neutral vote. Panel chair, Dr. Alistair Wood, Professor of Pharmacology at Vanderbilt University Medical Center, said, "At a personal level, I think I see the risk of Bextra substantially greater and better documented than celecoxib…but patients need to evaluate that risk in conjunction with their doctor and decide whether they are in a group that has failed other drugs and might benefit from that drug for some reason." An FDA official said, "Close votes obviously are challenging to interpret, but then we look at the comments of members of the panel…We got a very narrow margin of members who felt it (Vioxx) should be on the market. We will have to take that into consideration. Currently, Vioxx is voluntarily withdrawn…If Merck continues to have interest (in re-introducing Vioxx), we will welcome them to come talk to us about various pathways forward…We consider committee member comments, and we factor in the comments of people who voted no…If we decided to keep (Vioxx) on the

market, we would try to incorporate a mechanism to address those concerns." If Vioxx comes back, it won't happen quickly because the FDA has to approve a new label. The panel recommended a black box, an indication for second-line therapy, and perhaps other restrictions. The panel's recommendation should help Merck with the Vioxx lawsuits, but it may not eliminate them since the panel characterized Vioxx as the most dangerous of the Cox-2s, and there could still be charges that Merck did not act quickly enough on the early evidence of a CV risk. An FDA official said, "We hear a message that the committee thought Vioxx had a CV risk that is possibly larger than the other selective Cox-2 inhibitors – or better documented than the others."

The bad news for Merck was that its follow-on Cox-2, Arcoxia (etoricoxib), is likely to have to do another large, two-year, 20,000+-patient trial before approval. The large MEDAL and EDGE-II trials, with diclofenac as the comparator, most likely will not be sufficient. A panel member commented, "It is costly to redesign that trial, but…if (it's) right that diclofenac is similar to Celebrex, then the comparator to etoricoxib could be a non-neutral comparator…so we may not have the clarity we need." An FDA official said, "The committee thought they should rule out rigorously a 1.5 increased risk vs. naproxen, which requires about 10,000 patients per arm and should run a couple of years. How big the trial is depends on how many other arms you put in." The panel chair said, "You could do a relatively large, short-term (1-2 year) study that excluded effect size...That would get you a (CV safety) answer relatively quickly."

Novartis also appears to be a loser. Panel members were very negative on the outlook for Prexige (lumiracoxib), which is more Cox-2 selective than Vioxx.

The FDA appears determined to find a way to make NSAID and Cox-2 sponsors do additional post-marketing studies, even for the already approved and marketed drugs. An official said, "We could clearly have companies agree to a post-marketing study based on your (the advisory committee's) recommendation. Post-marketing commitments are made not only at the time of approval but after approval when an issue comes up…We probably haven't used those as much as possible in the past in the post-approval arena, but we could do that…The success of these has been better than portrayed in the media…Part (of the problem) was record-keeping, and the Agency was not as diligent as it could have been on timelines…We are better about that now."

While the FDA doesn't have the authority to ban direct-to-consumer advertising as many panel members would like, an FDA official indicated the agency does have some muscles it can flex. The panel chairman said, "The committee, I think, wanted to send a very clear message that they thought direct-to-consumer advertising was inappropriate…and it would be a brave company that would start a direct-to-consumer advertising campaign right now for these drugs." An FDA official said, "We clearly can reach agreements with companies that they will agree not to do so…We can ask companies (to do additional trials) and ask them to commit in writing…Ultimately if we think another study is necessary, one option is to take the drug off the market…That is always a kind of trump card in working with companies to get the data we think we need. Our authority short of taking the drug off the market is much more uncertain and less clear."

Late last year, Pfizer voluntarily suspended its DTC at the request of the FDA. A senior Pfizer official said the company would continue to forego DTC advertising – for now. He explained, "There will be no Celebrex DTC over the next few weeks. We will work with the FDA over where we go from here…Allowing DTC with caveats is fair, but the same caveats need to apply to OTC drugs (NSAIDs)…Celebrex and even Bextra are as safe as an NSAID in arthritis…We need to see what (advertising) we can do. Labeling discussions with the FDA are important. It is a partnership with the FDA. We would follow any (advertising) guidelines they give us."

All the non-selective or less-selective NSAIDs – except perhaps Bayer's Aleve (naproxen) – will be negatively impacted by the panel action, too. An FDA official said, "There was a clear vote that they (the panel) felt the labeling needed information on the CV risk or possibly about the absence of data to evaluate the CV risk…I think there was more confidence on the data on naproxen as a comparator. Naproxen seemed to do better than other (NSAID) drugs...That does not mean it is the same as placebo…and we don't think it is the same as placebo…I thought there was a sense of wishing there were other data on the other NSAIDs, but that's life." Another FDA official said, "The committee was divided on whether drugs that appear to be selective deserve special treatment…That is complicated because not everyone trusts the tests...We will have to grapple with that."

Asked how, based on the information available now, the patient population for naproxen would differ from that for a selective Cox-2 inhibitor, the panel chair said, "Naproxen is better for you than the NSAIDs right now – at least in terms of CV risk…It may not be as safe for GI side effects, which is a reversible problem in the vast majority of patients…so many patients should probably start with naproxen, perhaps with a proton pump inhibitor (PPI)…There are data in other settings that say that is not a bad thing to do...And then perhaps progress to something else…It would be a brave man or woman who started someone on these drugs without some strong reason."

Asked if the re-labeling will be different for each of the approximately 20 NSAIDs on the market, the panel chair said, "We hear that there are data on at least one – naproxen. That will be an evolving situation…We don't have all the facts right now…The data we have right now suggest naproxen is more beneficial than some of the others." An FDA official said, "This is complex…We had a situation like that with the antidepressants, and working through the efforts to get those medication and patient guides, we learned something about the

complexities of maneuvering through this process, and we can apply that to the NSAIDs…But it is clearly more complicated to have a different label for each drug…That is why on antidepressants we have essentially a class label and a class medication guide…We will have to take that into consideration…Not all members of the class have the same data…We have to decide if we should use standardized labeling or variable labeling…If there is no innovator, it makes it more complex, but the generics have to have an approved label, too. Then, we will have to work with the generic makers. We faced that same complexity with the antidepressants, where some innovators were no longer marketing."

An FDA official pointed to three key messages the FDA is taking away from this panel meeting:

1. "There was a clear ranking of the drugs…A uniform vote to leave Celebrex on the market, a split vote for Bextra and Vioxx…And I think that fit reasonably well with the pharmacology response which was that the hazard had clearly been shown with Vioxx and Bextra, and if a hazard had been shown with Celebrex, the hazard was relatively low…But none of that data is cast in stone."
2. "There is no great comfort in rapidly approving any other drugs in this class until we get safety data."
3. "There are real questions about what the overall safety of the individual drugs is. A lot of the focus was on the CV risk, but there was also a clear signal for some in heart failure."

INTERNATIONAL ACTION ON COX-2S

During the FDA panel meeting, the European Medicines Agency (EMEA) announced that it was restricting the use of Cox-2 inhibitors in Europe. The agency said Cox-2s should not be given to people with ischemic heart disease or stroke and that the lowest dose and shortest course should be prescribed.

Shortly after the FDA Advisory Committee meeting, New Zealand's Health Ministry advised patients taking any Cox-2 inhibitor to see a doctor for advice about whether to continue with the Cox-2, accepting an increased risk of heart attack and stroke, or to switch to another drug. The ministry said it could not quantify the level of risk associated with the drugs, but an adviser reportedly said "preliminary conclusions" were that all of the Cox-2s increase CV risk, at least in some patients.

HealthCanada is expected to make a decision soon about the fate of Vioxx and other Cox-2 inhibitors in that country. Officials of HealthCanada attended the FDA panel meeting to get a better understanding of what U.S. experts and regulators thought.

Following is a detailed review of the advisory committee meeting, discussion, debate, and votes.

NSAIDs and Cox-2 Selectivity

Cox-1 Selectivity *(least down to most)*	Cox-2 Selectivity *(most down to least)*
	Novartis's Prexige (lumiracoxib)
	Merck's Vioxx (rofecoxib)
	Merck's Arcoxia (etoricoxib)
	Pfizer's Bextra (valdecoxib)
	Etodolac
	Boehringer Ingelheim/Abbott's Mobic (meloxicam)
	Pfizer's Celebrex (celecoxib)
Diclofenac	
Ranbaxy's Nalfon (fenoprofen)	
Ibuprofen	
Naproxen	
Aspirin	
Merck's Indocin (indomethacin)	
Pfizer's Ansaid (flurbiprofen)	
Ketorolac	

SETTING THE STAGE

Dr. Steven Galson, Acting Director of the FDA's Center for Drug Evaluation and Research (CDER), opened the meeting and set the stage for the three days of discussions. He emphasized:

- "We are anxious to hear all points of views from the advisory committee and from agency staff. It goes without saying that all FDA staff are free to make any presentation without fear of retaliation."
- "Although you've all heard strong opinions in the media about the drugs we're considering, your job is to consider both the risks and benefits…and the impact on real people of any changes you make."
- "We are aware of at least a half dozen meta-analyses and huge population-based analyses for which data analysis continues as we speak. Three days is not long enough to hear details on every ongoing, incomplete study. Leaving them out has nothing to do with keeping information from you and everything to do to allowing you to focus, to let you get to our critical advisory questions."

Dr. Jonca Bull, Director of the FDA's Office of Drug Evaluation V, Office of New Drugs reminded the panel that:

- No improvements can completely eliminate the risk of unexpected events.
- Large NDA databases are helpful but continued monitoring is essential to assess the evolving risk profile for a new product.
- Aggressive marketing can play a role.

EXPERT OPINIONS

Gastrointestinal side effects

When Cox-2 inhibitors were introduced, it was thought they would have fewer gastrointestinal (GI) side effects than traditional, non-selective NSAIDs (tNSAIDs). Dr. Byron Cryer, a gastroenterologist with the University of Texas Southwestern Medical School, reviewed the GI safety of NSAIDs for the panel.

NSAID Gastrointestinal Effects

	Deaths	Hospitalizations
Risks: GI, kidney, platelet inhibition	16,500/year	107,000/year
NSAID-Induced GI Effects		
Upper GI	**Small Intestine**	**Colon**
GERD	Ulcers	Colitis
Subepithelial petechial hemorrhages	Strictures	Ulcers
Erosions	Diaphragms	Strictures
Ulcers of stomach and duodenum	Enteropathy	Diverticular bleed/perforation
Bleeding of stomach and duodenum		Collagenous colitis
Perforation/obstruction		Relapse of IBD
Mean prevalence of NSAID-Induced Ulceration		
Gastric ulcer	15%	
Duodenal ulcer	5%	
Clinically significant ulcers	2%	
Time to complicated ulcer	**Celebrex (CLASS Trial) n=7,882**	
Cox-2 vs. NSAIDs	Nss	
Cox-2 vs. diclofenac	Nss	
Cox-2 vs. ibuprofen	Nss	

Risk Factors for GI Complications with NSAIDs
History of prior GI ulceration (highest risk factor)
Age >65 (~2% increased risk per decade)
History of upper GI ulcer complication
Concomitant drugs (e.g., steroids, Coumadin)
Multiple NSAID use
CV disease

Dr. Cryer's conclusions:

- The GI effects of tNSAIDs result in considerable morbidity, mortality, and costs.
- Adding a proton pump inhibitor (PPI) to a tNSAID does not provide sufficient protection.
- Cox-2 inhibitors have been widely used by patients not at high risk of NSAID GI effects.
- There is no great need for Cox-2s in patients at low GI risk, and there is no GI benefit to Cox-2s in patients concurrently taking aspirin.
- COX-2 inhibitors are an attractive option for patients at greatest GI risk.

Points that came out during panel questioning of Dr. Cryer included:

- There has been a decline in GI bleeds, but that decline began before Cox-2 inhibitors were introduced.
- The risk of GI events with NSAIDs may be highest in the first three months of use, but the risk continues throughout use.
- The prevalence of dyspepsia is much more common than GI complications, but dyspepsia was described as a "nuisance" side effect that is not predictive of GI complications.

Mechanisms

Dr. Garret FitzGerald, a cardiologist at the University of Pennsylvania, explained mechanism-based adverse cardio-vascular (CV) events with Cox-2 inhibitors. His key points included:

- Coxibs are not platelet inhibitors.
- Inhibition of Cox-1 removes the Cox-1 protection against thrombosis.
- The hazard from Cox-2s would be expected to be particularly high in those otherwise pre-disposed to thrombosis, and this hazard is attenuated by inhibition of Cox-1.
- An increase in MI and/or stroke has been seen in five placebo-controlled trials with three structurally distinct Cox-2 inhibitors.
- Diclofenac is actually a Cox-2 inhibitor. He said, "I contend diclofenac is probably a select Cox-2 like celecoxib…We can start thinking about diclofenac as Celebrex with hepatic side effects."
- The following are myths:
  - There are non-naproxen-NSAIDs that are safer. He said, "People will parse naproxen vs. non-naproxen-NSAIDs. I don't think that is legitimate. I think they all have to be considered individually."
  - Reducing the dose solves the problem.
  - A study of Cox-2s in acute coronary syndrome (ACS) is needed.
- Duration of use of Cox-2 inhibitors should be restricted until the parameters of safety for extended dosing have been established.
- Cox-2s should be restricted to individuals intolerant of tNSAIDs+PPIs.

- Existing NSAIDs and Cox-2 inhibitors should be subject to the same trial requirements as any new drugs in these classes. He said, "It seems likely that existing drugs should meet the same hurdles as new drugs, particularly for extended dosing…I think diclofenac is one of the unanswered questions on the table. I think there are other drugs – like meloxicam (Boehringer Ingelheim/Abbott's Mobic) – with questions where we don't have the information."

Imprecise measurements

Dr. Milton Packer, a cardiologist with the University of Texas Southwestern, offered a provocative review of the problem with imprecise measurements, as in the APPROVe trial that led to the withdrawal of Vioxx. He said, "The precision people think we have here (in the APPROVe trial) isn't as precise as it could be…but that doesn't mean you can't put together your own idea of the totality of the data and decide if it reaches the level of concern…but don't forget that inherently the data are imprecise."

Among the key points Dr. Packer made were:

- The interpretation of observed differences in the frequency of events can vary when the number of events is small.
- With a small number of events, even the finding of an observed difference does not prove the existence of a true difference.
- Analyses that depend on group of events are subject to bias. When the process of developing a definition (of adverse events) has been raised, those creating the definition have frequently already looked at the data and know (subconsciously) what kind of definition is needed to capture the events of interest.
- Imprecise estimates are fine if the intent is to withhold judgment until more data are collected to make the estimates more precise. Imprecise estimates are problematic if the intent is to stop and reach a conclusion.

What should be done with worrisome trends in imprecise data? Dr. Packer recommended:

1. Looking for confirmatory evidence in other studies.
2. Carrying out a definitive trial with the adverse event as a primary endpoint, powered to detect a meaningful treatment difference.

Probability a Second Trial Would Find P<.05 if the Second Trial Were Identical to the First Trial

P-value in first trial	Probability of p<.05 in second trial
0.10	37%
0.05	57%
0.01	73%
0.005	80%
0.001	91%

3. Believing in observed differences that are biologically plausible. However, he cautioned, "Be wary of differences that are deemed 'real' based on biological plausibility because physicians can always be relied upon to propose a biological mechanism to explain the validity of an unexpected (and potentially preposterous) finding that happens to have an interesting p-value."

MERCK'S Vioxx (rofecoxib)

Dr. Ned Braunstein, Senior Director of Merck Research Laboratories, reviewed the history of what Merck knew about the CV risk of Vioxx, concluding there is a need for more studies, "We believe long-term studies are needed, in particular comparator studies between Cox-2s and NSAIDs, to better understand the risk profiles." He said that when Merck withdrew Vioxx, the company believed this was a Vioxx problem, not a class problem – and there were other Cox-2s on the market.

The panel's key questions/issues for Merck officials included:

- The length of time it took – 14 months – to get a change in the Vioxx label after an FDA advisory committee recommended new safety warnings. The Merck official responded, "After the advisory committee meeting, there were a lot of discussions with the FDA and data requests which we provided. We submitted the NDA supplement for rheumatoid arthritis at that time…We worked diligently with them, and collaborated in that way to make sure they had that information, and then we worked deciduously with them to be sure they had the information."
- The value and interpretability to clinicians of the added label warning, which says, "Caution should be exercised with Vioxx used in patients with ischemic heart disease." The panel chairman asked a Merck official, "What am I supposed to do with that information? That label doesn't seem to me to be helpful. What did you intend for me to do with that information?"
- Lack of an intent-to-treat analysis, suggesting that the dropouts could have masked the CV risk of Vioxx in earlier trials.

A Vioxx investigator, speaking on behalf of Merck, said he no longer believes there was a cardioprotective effect of naproxen in the VIGOR trial: "We didn't 'buy' the naproxen theory, but we didn't have data that it is worse than placebo. We were confused until today…I believe the difference now is exposure time…From APPROVe, we see no evidence of a hazard in thrombotic events through 18 months, and then there is a separation. The mean time in the pooled analysis was months – not the 9 months of VIGOR or 2.4 years in APPROVe…To me, that may be the explanation for why the pooled analysis in 2001 and as it went forward showed no problem, but then APPROVe showed a problem."

Merck Presentation on GI and CV Risk of Vioxx

Measurement	Relative risk	p-value
VIGOR Trial		
CV thrombotic events of Vioxx vs. naproxen	2.38	.002
Time to confirmed upper GI event	0.46	<.001
Pooled analysis of Alzheimer's Trials: Thrombotic CV events *(investigator-reported)*		
Vioxx vs. placebo	.84	---
Vioxx vs. non-naproxen NSAIDs	.79	---
Vioxx vs. naproxen	1.69	---
Pooled analysis of APPROVE, VICTOR, and ViP trials: GI safety		
Vioxx vs. NSAIDs	.36	---
Vioxx vs. naproxen	.27	---
Vioxx vs. diclofenac	.52	---
Vioxx vs. ibuprofen	.32	---
Thrombotic events in Alzheimer's Trials PN-078 and PN-091		
Vioxx vs. placebo	1.01	p>.05
Pooled analysis of APTC		
Vioxx vs. placebo	1.14	---
Vioxx vs. non-naproxen NSAIDs	.93	---
Vioxx vs. naproxen	1.61	---
APPROVe: Confirmed thrombotic CV events – Vioxx vs. placebo		
In all patients	1.92	.007
In patients at increased CV risk	2.71	---
In aspirin users	3.25	---
In patients with a history of symptomatic ASCVD	9.59	---
In patients with a history of diabetes	6.10	---
Confirmed thrombotic CV events: Vioxx vs. placebo		
CV Outcomes Study (interim pooled analysis)	1.67	---
APPROVe	1.92	---
ViP	0.87	---
VICTOR	3.14	---

Asked what the next step is, a Merck official said, "In the near term, to better understand the data and which patients are at increased risk for events…We also are working with people in the basic field to understand the data…And we are working with people who are studying the data across all the drugs…Hopefully, by pooling the data we will get a better feel for this...And lastly, we think we need comparative outcome studies to understand selective Cox-2s with tNSAIDs. There is no long-term data on tNSAIDs, and we think things like the MEDAL trial are one thing in the right direction." Data on ≥23,000 MEDAL patients are expected in 2006.

Merck also issued a press statement during the panel meeting which included these comments:

- "The data suggest an increased CV risk vs. placebo that is a class effect. Our data suggest the CV risk is time dependent."
- "It is unclear if the class of medicines is limited to Cox-2 selective inhibitors, all NSAIDs, or NSAIDs without potent antiplatelet effects."
- "There are risks and benefits with every medicine, and Cox-2s and NSAIDs are no different."
- "We believe it is important to study these medicines not only against placebo, but against the standard of care (traditional NSAIDs)."

A Merck official hinted that the company may consider re-introducing Vioxx if the panel did not recommend removing other Cox-2 inhibitors from the market: "At the time we withdrew Vioxx, we based our decision on the available data at that time…We stated we thought it would be possible to continue to market Vioxx with a labeling change...but we concluded the most responsible course, given the information at that time and the availability of alternative therapies, was to voluntarily withdraw the drug from the market…We've seen new data on some of these alternative therapies. Merck's interpretation of this data is we were dealing with a class effect, and the major question is how large is that class. If the committee and the FDA agree this is a class effect, then I think it would be important to take the implications of that conclusion into consideration...There are unique benefits to Vioxx."

Dr. Peter Kim, President of Merck Research Laboratories, said, "Based on the new data, Merck believes what we are dealing with as a CV risk is a class effect...We are struggling with what it means for the size of the class. Is it just Cox-2 or does it include Cox-2s that also have an effect on Cox-1? At the time we withdrew Vioxx from the market, we did it based on information that was available at the time, knowing there were alternatives, and that there were questions raised by APPROVe…Now where the science has progressed, we see that we are dealing with a class effect…Then, we are no longer dealing with a situation where Vioxx is unique in CV risk but instead is a member of a class…If that is the case, then we need to take a look at the unique benefits of Vioxx – Vioxx is the only Cox-2 to prevent or reduce serious GI events vs. naproxen, Vioxx is the only Cox-2 approved that is not contraindicated in patients with allergies to sulfonamides, Vioxx is the only one with approval for junior rheumatoid arthritis, and there are numerous reports from patients that Vioxx was the only drug that worked for them."

In a written statement, Merck further addressed this issue: "Merck is a data-driven company…In the past few days, we have seen new clinical data on the medicines in this class. Merck believes that these data suggest a class effect, but the size of the class is uncertain…If the advisory committee and the FDA conclude that the benefits of this class outweigh the risks on some patient populations, then we would have to consider the implications of the new data given the unique benefits Vioxx offers…Merck has not altered its position on the withdrawal of Vioxx. Anything further would be speculation. We look forward to hearing the committee's thoughts and concerns and to discuss the outcome of this meeting with the FDA and other regulatory authorities."

The FDA presentation

Lourdes Villalba, FDA Medical Officer, Office of Drug Evaluation V, the Vioxx reviewer, made a long presentation, taking the panel through the review timeline, defending the FDA for not recognizing the CV risk of Vioxx sooner, which she blamed in part on the confounding effect of the naproxen comparator. Her point: "We were not sleeping behind the wheel…This has been a very challenging application, a very complicated process, reviewing a lot of information that was not always that clear to interpret…I am not clear even today of the role of naproxen. It is possible that there is a pro-thrombotic effect of Vioxx. I think naproxen does have a role, but it doesn't explain everything."

Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs) warned the panel about relying too heavily on intent-to-treat analyses: "I want to remind people that an ITT analysis is loved because it is a conservative analysis. It makes effects go away – if you are worried about censoring. But it also makes efficacy go away, and it can make side effects go away…It isn't that you shouldn't follow people up...but an analysis that includes people long after the drug has a high likelihood of not showing the effect of the drug – before we get too enthusiastic (about ITT) – it might make the effect lower…There is so much emphasis on how many events (occur)…I'm always bothered by that…I want to be sure people have taken the drug long enough…and length is where you can see if something happened."

FDA Review of Vioxx Safety by Time Period

Measurement	Vioxx	Comparator
1998: VIGOR Trial – Vioxx (25 mg) vs. naproxen		
CV events by investigator	64	32
CV events – adjudicated	45	19
CV events – APTC	35	18
CV deaths – APTC	6	6
1998: Vioxx NDA Database – Vioxx vs. ibuprofen		
CV events at 6 weeks	0.7 at 25 mg 1.1 at 50 mg	0.4
CV events at 24 weeks	1.1 at 25 mg 1.1 at 50 mg	0.5
2001: Vioxx Studies – risk per 100 patient years vs. naproxen		
APTC events in RA efficacy database	6.9 at 12.5 mg 1.0 at 25 mg 1.4 at 50 mg	0.6
APTC events in ADVANTAGE Trial	1.56 at 25 mg	1.11
2001: Alzheimer's Disease – Vioxx vs. placebo		
APTC events	17 events (rate 1.34 at 25 mg) (relative risk = 0.37)	27 events (rate 1.84)
2004: Alzheimer's Trials PN-091+PN-078 – Vioxx vs. placebo		
APTC events	32 events (rate 1.88) (relative risk = 0.91)	40 events (rate 2.07)
2004: APPROVe Study		
APTC events in all patients	Relative risk = 2.25	---

* APTC=Antiplatelet Trialists Composite Endpoint

FDA Summary of Safety of Vioxx in Trials

Measurement	Vioxx (events/rate)	Comparator (events/rate)
APTC events		
VIGOR Trial	35 / 1.30	18 / 0.77 naproxen
Alzheimer's Trial	32 / 1.88	40 / 2.07 placebo
APPROVe Trial	34 / 1.11	18 / 0.54 placebo
MI (fatal and non-fatal)		
VIGOR Trial	20 / 0.74	4 / 0.14
Alzheimer's Trial	14 / 0.88	15 / 0.77
APPROVe Trial	21 / 0.68	9 / 0.27
All-cause mortality (on drug)		
VIGOR Trial	22 / 0.82	15 / 0.56
Alzheimer's Trial	36 / 2.12	19 / 0.98
APPROVe Trial	10 / 0.36	10 / 0.30

MERCK'S Arcoxia (etoricoxib)

With respect to efficacy, Dr. Sean Curtis, Director of Clinical Research for Merck, told the panel Arcoxia is:

- Superior to naproxen in rheumatoid arthritis.
- Superior to naproxen in ankylosing spondylitis.
- Comparable to indomethacin in acute gouty arthritis.

On safety, he claimed that pooled data from the entire Arcoxia development program vs. NSAIDs have shown:

- Upper GI events in Phase IIb-III – the relative risk was 0.48 in favor of etoricoxib, a 52% risk reduction, and this was observed early and maintained over the study duration, driven largely by comparison to naproxen.
- Dose-related incidence of hypertensions was generally similar to NSAIDs.
- The congestive heart failure (CHF) incidence is low and similar to the rate of the pooled comparators.

Pooled Analysis of Arcoxia CV Events

Measurement	Odds Ratio
Arcoxia vs. placebo	1.11
Arcoxia vs. non-naproxen NSAIDs	0.83
Arcoxia vs. naproxen	1.70

Merck chose to present the EDGE trial data on Arcoxia to the panel in a slightly different way than the company presented it at the American College of Rheumatology meeting in October 2004: in terms of relative risk instead of CV rate per 100 patient years.

1-Year Results of the EDGE Trial of Arcoxia

Measurement	Arcoxia	Diclofenac
Within 14 days of treatment discontinuation		
ACR: Cardiac and cerebral event rate (all cardiac events) – rate per 100 patient years	0.97	0.73
FDA: Relative risk of a CV event	1.07	---
Within 28 days of treatment discontinuation		
ACR: Cardiac and cerebral event rate	0.96	0.77
FDA: Relative risk of a CV event	1.02	---
Regardless of time after treatment discontinuation		
FDA: Relative risk of a CV event	1.01	---

Other points Dr. Curtis made included:

- "These recent data showing the difference in CV safety…do suggest a class effect."
- "Despite the large size and development program of etoricoxib…there are limitations on the amount of CV safety data…specifically, the long term data were limited and mostly vs. naproxen." Thus, Merck has undertaken the larger MEDAL and EDGE-II trials, with diclofenac as the comparator, in which the mean duration of treatment will be 18-20 months.
- After the latest review, the DSMB recommended that the MEDAL and EDGE-II trials continue. With ~21,000 patient-years of exposure, there were ~300 confirmed CV events available for review, and ~3,000 patients on study for 18 months.

Panel members wanted to know why Merck chose to use diclofenac instead of naproxen in the MEDAL and EDGE-II trials for Arcoxia, **despite the FDA's request for another comparator in those trials.** A Merck official said it was because the company wanted to explore other NSAIDs, since not all patients will respond to naproxen, "We felt doing an outcome study against naproxen would likely replicate the same outcome (as EDGE)…So, we wanted to see what the outcome was against another comparator…Diclofenac is the most widely prescribed NSAID in the world."

PFIZER'S Cox-2 Inhibitors: Celebrex (celecoxib), Bextra (valdecoxib), and Dynastat (parecoxib)

Pfizer officials defended their Cox-2 inhibitors with a detailed presentation, and attempted to prove that:

- The Vioxx CV risk is unique to Vioxx, not a class effect.
- There is no CV risk increase with Celebrex.

Dr. Kenneth Verburg, Pfizer's Vice President of Inflammation and Immunity, Clinical R&D contended:

- In the APC trial, Celebrex is associated with an increased CV risk after one year of continuous therapy.
- In the Pre-SAP trial, there is no added risk with Celebrex out to three years.
- In the ADAPT trial, naproxen lowered the CV risk over 1.5 years vs. placebo.
- Additional studies are needed and Pfizer plans to conduct them.
- There is no dose-related increase in CV risk with Celebrex.
- There is no increased CV risk with Celebrex use at either high or low dose out to one year, and the MI risk is similar to non-Celebrex users – but Vioxx is "systemically associated with an elevated risk vs. non-users."

Pfizer Meta-analysis of the CV Safety of Celebrex

Measurement	Celebrex	NSAIDs
Composite of CV death/MI/stroke	3.4 Relative risk: 0.86	3.8
CV death	Relative risk: 0.72	16%
Relative risk of Celebrex		
vs. placebo	1.26	---
vs. NSAID	.86	---
vs. naproxen	1.11	---
CV Death, MI, Stroke by risk factors (Celebrex ≥200 mg)		
With concomitant aspirin use	Non-fatal stroke favors Celebrex, otherwise Nss	

A Pfizer consultant said he worked on NIH-funded research that may shed additional light on the CV risk question of NSAIDs. His study was designed to see whether NSAIDs could protect against tobacco-induced oral cancer. The study found that oral cancer was significantly reduced with NSAIDs but not acetaminophen, but there was no difference in survival between the two groups, "That lead us to interrogate the data-set to look at all causes of death. We saw a 2.06 HR with NSAIDs – due to CV disease – vs. no impact by acetamino-phen."

Pfizer's Dr. Verburg discussed the CV safety of Bextra, which is FDA-approved, and Dynastat, which is currently under review by the FDA. Among the points he made were:

- "Our view is that valdecoxib remains a viable treatment alternative for OA and RA…We have data to suggest it has improved GI safety compared to NSAIDs…The valdecoxib database is smaller than for celecoxib at present, but the profile appears similar to NSAIDs for up to six months, and the CV incidence in the CABG setting does not appear to extrapolate to the arthritis population."
- "The choice of parenteral therapeutics for acute pain are fairly limited, so there is additional need for agents that improve post-op pain control."

- Parecoxib has shown a higher rate of CV events than placebo. "As a result of those findings…we quickly went to those countries where parecoxib is marketed and have modified the product labeling to contraindicate parecoxib+Bextra in CABG or in other revascularization procedures since those settings have not been studied. In the U.S. we include a contraindication for Bextra in the CABG setting or revascularization setting, even though Bextra doesn't carry an indication for acute pain."
- "Parecoxib offers unique benefits over existing parenteral analgesic medications and has a favorable risk:benefit ratio in the surgical settings other than CABG/revascularization…It is administered in controlled settings under physician observation. The CV risk is found only in the CABG surgery setting, not in other surgical settings."

Measurement	Valdecoxib	NSAIDs
Death from CV causes, MI, stroke, or heart failure	0.8%	1.5%
MI	0.4%	0.8%
Hypertension	3.5%	3.2%
Cardiac failure	0.1%	0.3%
Valdecoxib relative risk		
vs. placebo	1.28	---
vs. NSAID	.49	---
10 mg	.27	---
40 mg	1.36	---
80 mg	No events	---

The FDA presentation

The FDA panel had several concerns with Pfizer's data, including:

- **Completeness.** Dr. Curt Furberg of Wake Forest University said, "I am troubled by your presentation …You did comparative studies and placebo-controlled studies are better…What you talked about doesn't help us answer that question…There is information in the Pfizer briefing document that you didn't bring out…In addition, you did not address at all the issue of heart failure…We were informed that in APPROVe there was a four-fold increase in heart failure…For Celebrex, if anything, it is worse…a six-fold increase that is statistically significant."
- **Missing data.** Pfizer did not have some of the data the committee wanted.
- **Lack of long-term data.** For instance, Pfizer officials emphasized a meta-analysis of 44,307 patients on Celebrex (mostly for OA/RA) at a range of doses (50-800 mg/day), but only 4% of these patients (803) were on Celebrex ≥1 year, and most of the other trials were even shorter.
- **Hypertension.** A Pfizer expert countered, "In the OA trial (in the NDA), you can see there really isn't much in the way of hypertension adverse events reported…In the CLASS trial, there wasn't much in the way of blood pressure increases. (In comparison), in the OA trials for Vioxx, then we see an obvious dose-correlated increase in hypertensive events…My colleagues and I decided the only way to resolve this was to do a head-to-head trial of Celebrex vs. Vioxx, and the logical subset was in patients being treated for hypertension…Our first trial found an early disruption of blood pressure with Vioxx, and that was not seen with Celebrex…So, we repeated it in >1,000 patients…and there are differences with the drugs over 24 hours and by doses."
- **Lack of data on CV safety in patients on Celebrex plus a PPI.** Pfizer officials said the company didn't have any data to offer on that.
- **No clarity as to the CV risk with traditional NSAIDs.** Dr. Ernest Hawk, a medical oncologist with the National Cancer Institute (NCI), said, "The absence of evidence doesn't prove they (traditional NSAIDs) are safer, and that is an important context issue for us." Dr. Temple asked for data on how many of the APC trial patients were U.S. vs. OUS, saying that it would be useful, but that information was not available.
- **The Celebrex dose equivalent to 25 mg Vioxx.** A panel member argued that 200 mg Celebrex BID is equivalent to 25 mg Vioxx, but a Pfizer official claimed that 200 mg QD is a better comparator.

FDA Review of Bextra Safety

Measurement	Placebo	Bextra in CABG	Bextra outside CABG	NSAIDs
CV events in high risk patients	1.9%	1.7% - 2.4%		2.4%
CV events in at-risk patients	0	0.2% - 0.4%		0.6%
Deaths	0	6 patients	4 patients	2 patients
Mortality rate	0	0.47%	0.35%	0.35%
CV adverse events				
		Bextra 20 mg BID	**Bextra 40 mg BID**	**Naproxen**
Edema	---	2.2%	0.7%	1.4%
Worsened blood pressure	---	5.8%	7.7%	3.2%
Cardiac failure	---	0	0.5%	0
Thrombosis	---	0	0.25%	0
Cerebrovascular disorder	---	0.3%	0.3%	0

FDA Review of Celebrex Safety

Measurement	Placebo	Celebrex	NSAIDs
Total serious cardiorenal events	1.6%	1.5%	1.9%
Heart failure	<.1%	<.1%	<.1%
MI	0.1%	0.1%	0.1%
Hypertension	0	<.1%	0
CLASS Trial			
CV mortality rate	0	0.1%	0.37%
All know cardiac deaths	0	0.2%	0.37%
Mortality in CLASS Trial			
	Diclofenac	**Celebrex**	**Ibuprofen**
Total	0.8%	0.8%	0.7%
In aspirin users	0.4%	1.2%	1.6%
CV death	0.5%	0.5%	0.4%
MI	0.8%	0.9%	1.0%
Serious CV events in the CLASS Trial			
	Diclofenac	**Celebrex**	**Ibuprofen**
MI in non-aspirin users	0.2%	0.3%	0.2%
MI in aspirin users	0.8%	2.5%	2.8%
Serious thromboembolic CV events in non-aspirin users	Rate=0.97%	Rate=0.77%	Rate=0.45%
Alzheimer's 001 Trial EQ5-00-06-002			
	Placebo	**Celebrex**	---
Deaths	2.0%	4.6%	---
Cardiac deaths	1.4%	2.8%	---
Serious adverse events	2.1%	8.4%	---
MI	0	0.7%	---
CHF	0	1.8%	---
AF	0	1.1%	---
Hypertension	0	0.4%	---

Expert opinions

Dr. Hawk discussed the APC (Adenoma Prevention with Celebrex) trial. He made a pretty strong case that there is real potential for Cox-2 inhibitors in general, and Celebrex in particular, to reduce the risk of colorectal cancer. He said, "There is a profound amount of data that traditional NSAIDs and Cox-2 inhibitors may be beneficial in reducing the colorectal cancer risk...We still believe they hold great potential…We don't know if CV events are occurring in patients with efficacy or without efficacy...and we don't know if it (Celebrex) is efficacious at all…but in the FAP (familial adenomatous polyposis) setting, there was a small Vioxx trial, and there was ~10% adenoma reduction, and we saw ~30% reduction (in APC)."

Dr. Bernard Levin, an oncologist with M.D. Anderson Cancer Center, reviewed the Pre-SAP trial. He said, "We don't have the efficacy data yet for the Pre-SAP trial…The Vioxx (colorectal) data is tantalizing…One trial showed ~30% reduction (in adenomas), but what is interesting is the effect on advanced adenomas – a 49% reduction. The question will be, in my opinion, relevant to the impact of this or any therapy on lesions who have propensity to develop into cancer." A panel member commented, "I hope we don't make too much of the Pre-SAP trial…It doesn't add much to our knowledge."

A statistician on the panel did a quick, back-of-the-envelope calculation of the CV risk if the APC and Pre-SAP trials were combined, "I came out with a 1.82 relative risk. It is borderline statistically significant."

The Advisory Committee view

Panel members did not dismiss the CV risk of these two drugs as quickly as Pfizer. A panel member said, "There is a very striking increase across a wide range of adverse events in the CABG setting for both trials." Another panel member commented, "I'm troubled by inconsistencies in the Pfizer briefing document…What happened to the (other) data…They disappeared? Is this suppression of information? Error?… There is clearly an underreporting of events, as I interpret it. We all make mistakes…(but) I raise the question whether

National Cancer Institute Presentation on Celebrex Colorectal Cancer Trials

Measurement	Placebo (rate per 1,000 patient-years)	Celebrex 200 mg BID (rate per 1,000 patient-years)	Celebrex 400 mg BID (rate per 1,000 patient-years)
APC Trial			
Death from CV causes	0.1% (0.5)	0.4% (1.4)	0.9% (2.9)
Death from CV causes, MI, stroke, or heart failure	1.0% (3.4)	2.3% (7.8)	3.4% (11.4)
Death from non-CV causes	0.7%	0.4%	0.4%
Death from any cause	0.9%	0.9%	1.3%
Pre-SAP Trial			
	Placebo	**Celebrex 400 mg QD**	**Hazard ratio**
Death from CV causes	0.6% (2.1)	0.2% (0.7)	0.3
Death from CV causes, MI, stroke, or heart failure	1.9% (6.4)	2.0% (6.8)	1.1

these are honest mistakes." A third panel member posed a question Pfizer officials couldn't answer, "Sometimes CABG is emergency…How do you handle those patients (on Bextra)?…What policy are you advocating?" The Pfizer official responded, "We have not envisioned that…I don't know that anyone thought through the implications of that." The panel chairman added, "What we learned from the CABG study is that a sufficiently high dose of a Cox-2, given only 10 days, for group of people also taking aspirin is capable of producing a highly significant increase in CV events. What is unique is the rapidity of the events with relatively short-term exposure. Doesn't it tell us the potential exists for a potent Cox-2 to produce events quickly even in patients taking aspirin? This is pretty rapid emergence of the problem. We heard of 18 month delay in another study (APPROVe)…This is only 10 days of therapy."

NOVARTIS'S Prexige (lumiracoxib)

Mathias Mukkelhoven PhD, Senior Vice President and Global Head of Drug Regulatory Affairs for Novartis, discussed the GI and CV safety of lumiracoxib. He noted that in the TARGET trial, the lumiracoxib dose is four times the recommended chronic osteoarthritis (OA) dose.

Dr. Patrice Matchaba, Global Medical Director of the lumiracoxib program for Novartis, gave a detailed presentation on the TARGET trial. He defended Prexige, but he did it by separating the TARGET trial into a comparison of Prexige against each of the comparators separately, instead of pooling the comparator NSAIDs.

TARGET Trial Results

Measurement	Hazard ratio lumiracoxib 400 mg QD vs. ibuprofen	Hazard ratio lumiracoxib 400 mg QD vs. naproxen
GI complications		
Upper GI ulcer complications in aspirin population	0.79	
Symptomatic ulcer and upper GI ulcer complications in aspirin population	0.73	
APTC endpoint		
Overall	.76	1.46
Non-aspirin population	.94	1.49
Aspirin population	.56	1.42
MIs		
Overall	.66	1.77
Non-aspirin population	.75	2.37
Aspirin population	.47	1.36
Stroke		
Overall	.82	1.11
Non-aspirin population	1.16	1.12
Aspirin population	.47	1.53
Hypertension		
De novo hypertension	39% reduction with lumiracoxib	Nss
Aggravated hypertension	33% reduction with lumiracoxib	Nss
Combined CV and GI endpoints		
Non-aspirin population	56% reduction with lumiracoxib	41% reduction with lumiracoxib

FDA Review of Prexige CV Safety from TARGET Trial

Measurement	Lumiracoxib	Naproxen	Lumiracoxib	Ibuprofen
APTC events				
Overall APTC	40 (rate =1.1)	27 (rate=0.76)	19 (rate=0.58)	23 (rate=0.74)
CV death	11	8	8	10
Non-fatal MI	16	9	5	5
Non-fatal ischemic stroke	13	11	6	6
Non-fatal hemorrhagic stroke	0	0	0	2
APTC events based in non-aspirin users				
CV death	7	5	5	6
Non-fatal MI	10	3	4	3
Non-fatal stroke	5	6	4	2
APTC events based in aspirin users				
CV death	4	3	3	4
Non-fatal MI	6	6	1	2
Non-fatal stroke	8	5	2	4
Incidence of confirmed or probable MI events: lumiracoxib vs. naproxen				
Overall population	1.77	---	---	---
Non-aspirin population	2.37	---	---	---
Low-dose aspirin users	1.36	---	---	---

FDA perspective

Dr. Lourdes Villalba who reviewed Vioxx for the FDA was also the FDA reviewer on CV safety for Prexige. The FDA was critical of the Prexige data in the TARGET trial, and Dr. Villalba said, "We can't make conclusions about the Cox-2 class effect from this (study) because it looks like two studies within the same study."

In effect, her point was that Prexige performed differently against the two comparators. While the comparators might be expected to perform differently, Prexige was expected to perform the same in the different arms – but it didn't.

TARGET Trial Results for Prexige

Adverse events	Lumiracoxib 400 mg QD	Ibuprofen 800 mg TID	Naproxen
Edema (pre-specified)	5.0% vs. ibuprofen 4.5% vs. naproxen	5.6%	4.2%
CHF (ad hoc analysis)	0.27% vs. ibuprofen 0.34% vs. naproxen	0.34%	0.34%
Increase in weight from baseline >5%	8.5% vs. ibuprofen 8.1% vs. naproxen	8.5%	9.1%
APTC events in patients with prior MI	1.8% vs. ibuprofen 3.2% vs. naproxen	0	8.2%

BAYER/ROCHE'S Aleve (naproxen)

By the end of the meeting, panel members and FDA officials appeared convinced that naproxen is relatively safe. In fact, naproxen is the new "gold standard" comparator for NSAID and Cox-2 trials.

On December 17, 2004, the ADAPT trial, a study of Celebrex 200 mg BID vs. naproxen vs. placebo in the prevention of Alzheimer's Disease, was halted by the Steering Committee, casting doubt on the safety of Aleve. Leonard Baum, RPh, Vice President of Regulatory Affairs at Bayer, and Dr. Martin Huber, Vice President and Global Head of Drug Safety Risk Management at Hoffman-La Roche, both defended the safety of naproxen. Dr. Huber said, "There is no signal for MI or stroke in our NDA trials…And we reviewed our safety database back to the 1970s, and there was no signal for an MI or stroke in over one million patient years…We didn't see a signal even looking retrospectively."

Dr. Huber cited the TARGET and VIGOR trials as well as observational studies that found no increased CV risk with naproxen. However, panel members indicated they strongly prefer randomized clinical trials to observational studies. One panel member also noted that there isn't good long-term data in naproxen with respect to CV events. Dr. Huber responded, "I would be careful in observational studies; there is a wide number of patients who've been exposed to naproxen, which gives us what we believe is important information. There are 80,000 person years in the observational studies…We should give some weight to that...and for MI we see a consistent finding of 1.0 (relative risk) or lower…The data are telling us there probably isn't an increased risk."

Dr. Constantine Lyketsos of Johns Hopkins University said there is much public misunderstanding of the ADAPT Steering Committee's decision to halt the trial. Just a week before ADAPT was halted, the TEMC (Treatment Effects Monitoring Committee, the equivalent of a DSMB) for ADAPT reviewed the safety data and determined the trial could continue. Dr. Lyketsos did not present the safety data to the FDA advisory committee, explaining, "We cannot present the safety data we had at the time the decision was made…We defer that to a peer-reviewed publication at a future date…In reality, the decisions were made in very unusual circumstances…that raised concerns about the practicality of continuing the trial."

He cited four factors that played into the Steering Committee's decision:

1. No likelihood of an early benefit to Celebrex in Alzheimer's prevents, and strong misgivings about Celebrex.
2. IRBs raising safety questions, and few answers to those questions.
3. Adherence problems had already arisen in the trial, and those worsened after Vioxx was withdrawn.
4. The data on the naproxen arm in ADAPT appeared "somewhat more concerning" than the Celebrex safety data, though it did not reach statistical significance. Dr. Lyketsos said, "ADAPT showed a notable increase in GI bleed with naproxen vs. placebo."

Panel members took strong exception to how the ADAPT trial was handled – and to the fact that some Steering Committee members not on the TEMC had access to the data. Panel member Dr. Steve Nissen, a cardiologist at the Cleveland Clinic, said, "That trial was fundamentally stopped for futility …The problem is that a warning was issued on naproxen, which was the medical equivalent of screaming fire in a crowded auditorium. Many of us got calls from patients who wanted to stop naproxen for CV risk. It would have been far better to announce the trial was stopped for futility rather than hazard when it was a non-statistically significant hazard." Dr. Tom Fleming, a statistician at the University of Washington, said, "There were some emerging trends that, in my words, were in an unfavorable direction, but in the context of monitoring trials we know one has to be cautious not to over-interpret emerging trends that can easily ebb and flow…My understanding is not that there were emerging trends that were unfavorable on naproxen but, rather, the external data were the driving factor in the decision…I'm distressed to hear that some (Steering Committee) members had access to the data…To me, what I'm hearing raises very significant concerns about putting at risk the integrity of studies with pre-judgments with only access to partial information...This warning was inappropriate. We can't operate in this fashion. We need to assure we don't do this again…It caused a panic that should not have happened, and I hope it doesn't happen again." The panel chair said, "What I hear now is that the trial is being stopped for operational problems, and this was a convenient moment to stop."

ADDITIONAL FDA PERSPECTIVE

FDA epidemiologist Dr. David Graham presented a review of Medi-Cal (California Medicaid) data on Cox-2 inhibitor and NSAID use. His conclusions were:

- Naproxen is not cardioprotective.

- Vioxx:
  - ≤25 mg = probable increased risk.
  - >25 mg = definite increased risk.
  - Risk begins early in therapy and is apparent during days 1-30 of use.
- Celebrex:
  - ≤200 mg = no apparent CV effect.
  - >200 mg = probable increased risk.
- Bextra: ≤20 mg = no apparent effect.
- As a class, non-coxib NSAIDs may increase risk, but differences exist between non-coxib NSAIDs with respect to risk.

Dr. Graham noted that the FDA has concerns that this is a new database for research purposes, and there are possible dose misclassifications. Other limitations of the data include no access to medical records because of HIPAA and complicated data. He said there are several advantages to the Medi-Cal data, including: size (>7 million persons per year), includes OTC aspirin data, includes people over age 65, has long durations of follow-up with low drop-out rates, and has a sicker population than private payors. His conclusion: "There is no strong evidence of systemic bias that interferes with trusting the (Medi-Cal data)."

Dr. Graham described the typical Cox-2 user as someone in his/her 60s with other health problems, so his Medi-Cal analysis focused on this subgroup. Some of the points he made were:

- **Non-coxib NSAIDs,** as a class, may increase risk, but differences exist between non-coxib NSAIDs with respect to risk. He commented, "Meloxicam (Mobic) is now the No. 1 selling branded NSAID…We know there has been a shift in the marketplace to meloxicam…The company recently raised the price…We found an increased risk. It is one study but the only study. We looked at it in Kaiser, but meloxicam is almost not used in Kaiser, so we couldn't study that."
- **Naproxen is not cardioprotective.** He explained the "cardioprotective" effect seen with naproxen in four trials as selection bias. He said, "Here we have what I think is classic selection bias. It is not naproxen that protects you, but some other factor. Patients treated with naproxen had lower CV risk. I can't explain why that happened, but it is not due to naproxen…When I look at the four positive studies, I find no credible evidence of a protective effect (of naproxen)."
- **The Vioxx risk** (and probably other Cox-2s) begins early in therapy and is apparent during Days 1-30 of use.

Dr. David Graham's Conclusions on the Safety of Cox-2 Inhibitors

Drug	Conclusions
Bextra ≤20 mg	No apparent effect
Vioxx ≤25 mg	Probable increased risk
Vioxx >25 mg	Definite increased risk
Celebrex ≤200 mg	No apparent CV effect
Celebrex >200 mg	Probable increased risk

Individual Excess Risk of AMI or Sudden Cardiac Death

Trial	Risk per year in average 65-74-year-old man	Excess population risk in 1 million U.S. Men age 65-74 treated with Vioxx per year
Vioxx ≤25 mg		
Ray	1 in 2,500 patients	400
Graham	1 in 217 patients	4,600
Ingenix	1 in 93 patients	10,800
Medi-Cal	1 in 172 patients	5,800
Vioxx > 25 mg		
Ray	1 in 54 patients	18,600
Graham	1 in 25 patients	40,000
Medi-Cal	1 in 89 patients	11,200

Preliminary Medi-Cal Data on AMI Risk

Drug	Odds ratio
Cox-2 inhibitors	
Bextra	0.99
Celebrex	1.09
Vioxx	1.22
Cox-2 inhibitors vs. non-coxib NSAIDs	
Bextra	0.88
Celebrex	0.97
Vioxx	1.18
Non-coxib NSAIDs	
Ibuprofen	1.11
Indomethacin	1.71
Meloxicam (Mobic)	1.37
Nabumetone	0.83
Sulindac	1.41
Naproxen	~ 1.1

The panel had a lot of questions for Dr. Graham, and the key points that came out of those exchanges were:

- The typical drug that has come off the market in the U.S. has been due to acute liver failure – e.g., Warner Lambert's Rezulin (troglitazone) and Duract (Wyeth, bromfenac) – but the background rate of acute liver failure is 1 per million per year. The background rate of MI is 1:50 for the average male aged 65-74.
- Dr. Graham does not have any relevant data that has not been presented.
- The differences in the hazard ratios are very small, and the panel is struggling with understanding how to interpret these.

- Asked by a panel member if the panel should look at individual drugs or a class effect, Dr. Graham said, "I believe, based on the evidence, that there is a Cox-2 effect and that it is dose-dependent…My advice would be to see if we can identify bad actors – and I believe indomethacin is clearly a bad actor – we should weed the garden of the bad actors...Try to identify drugs that, based on the evidence we have, appear to have less risk in the totality of their evidence, and then suggest these are the drugs we think the public should use…Then, you have to decide if you want the others on the market…I'd identify the bad actors and get rid of them…and shift the market to the ones that 'appear to be safe.'"
- The Medi-Cal study was an observational study, and at least one panel member had serious reservations about putting too much weight on that, but Dr. Graham's position was that the randomized clinical trials of Cox-2 inhibitors were not large enough to have the power to detect an early increased risk. This exchange was interesting:

  FDA's Dr. Bob Temple: "We are talking of differences here of 0.1. It's not that they wouldn't be important if true…but I want to know what you (speakers) make of all this."

  Dr. Graham: "If most compass arrows point in the same direction for a particular NSAID, those are the ones I would put on the suspect list."

  Dr. Temple: "So, a low hazard ratio needs multiple support before it is credible?"

  Graham: "Yes."

PUBLIC WITNESSES

Each public witness was allowed precisely two minutes to speak, and the time limit was strictly enforced; the microphone shutdown at exactly two minutes. Several patients made short but poignant speeches in support of the Cox-2 inhibitors. They described how the drugs had favorably changed their life or the life of a loved one, and they urged the panel not to eliminate them. A consumer said, "All drugs come with dangers. Vioxx saved my life…I've hoarded it …Please give it back to me." The mother of a child with juvenile arthritis declared, "Vioxx is great." A Celebrex user said, "I feel like Celebrex was created for me."

However, Dr. Sidney Wolfe of Public Citizen urged that all the Cox-2s be withdrawn from the market. He said, "If Pfizer had testified under oath yesterday, they might well have been found to have committed perjury. I recommended today to the U.S. Attorney's Office in New Jersey that they start an investigation of Pfizer for fraud if they have not already begun to do so. I also spoke with Sen. Charles Grassley's (R-IA) office today and requested an investigation concerning the FDA's dangerous suppression of data from this study (the Celebrex Alzheimer's study) for more than 3.5 years…I hope you recommend a ban (of Celebrex and Bextra). Label limitations to short-term use will fail just as they did with the now-banned NSAID, Duract."

Dr. Max Hamburger, President of the New York Rheumatology Society, said he had polled his members, "We have remarkably similar views. NSAIDs are important. Far too many patients have had recurrence (of their pain) because they stopped their meds out of fear or changes in managed care formularies. Our consensus: Access to anti-inflammatories needs to be preserved, physicians need information in a more rational and timely fashion, and the process for disseminating information should be improved."

THE ADVISORY PANEL DISCUSSION

The FDA posed several points for the panel to discuss before they voted on the actual question the FDA wanted answered.

DISCUSSION POINT #1: Discuss the available data on the potential CV risk for non-selective NSAIDs and Cox-2s.

Among the interesting comments made and concerns expressed by panel members were:

- Concern over the safety of traditional NSAIDs, particularly indomethacin.
- Current Cox-2 trials should be continued, not stopped, and those that have been temporarily suspended should resume.
- *Panel member:* "It is up to the sponsor to demonstrate efficacy and not up to the FDA to show drugs are unsafe…It does look like they (Cox-2 inhibitors) are

FDA Panel Member Assessment of CV Risk of Cox-2 Inhibitors

Drug	Relative risk	Notes	Size of trial needed to detect an increased CV risk (assuming a 1% CV background rate)	Size of database available
Vioxx	1.4-1.5	Driven heavily by VIGOR and APPROVe and neutralized some by the Alzheimer's trial	6,000 – 8,000	~23,000
Bextra	2.58	Heavily driven by the CABG setting	<2,000	3,000
Celebrex	1.3	Driven heavily by the APC trial and the Alzheimer's study, and neutralized by Pre-SAP and CLASS, which were more neutral	N/A	N/A
Arcoxia	1.625	---	<5,000	17,000
Prexige	1.18	From the TARGET trial	>40,000	18,000

unsafe, but the studies presented are really not very good studies." Another panel member said, "That is the reason the Challenger blew up – the prove-to-me-it-is-safe approach."

- *Panel member:* "If we say there is a CV risk for Cox-2 inhibitors and not for (traditional) NSAIDs, then people won't want to use Cox-2s and will use NSAIDs, and from the data presented, it doesn't look as if many of them are better from a risk point of view."
- *Chair:* "There is a dearth of data on other NSAIDs…We will not be able to decide that…The prudent activity would be to look at it in the future."
- *Panel member:* "I think there is a (CV risk) signal for all these drugs…It is wrong to assume the three drugs (Celebrex, Vioxx, and Bextra) have a CV risk and the others don't because we don't have the evidence."
- *Panel member:* "It sure looks like naproxen is a winner – and that naproxen is Cox-2-like."

DISCUSSION POINT #2: Discuss the contributions and limitations of the currently available observational studies and randomized in the assessment of CV risk for non-selective NSAIDs and Cox-2 inhibitors.

Among the interesting comments made and concerns expressed by panel members on this issue were:

- There was consensus that randomized clinical trials are more valuable than observational data, but a signal in observational data is a sign that a randomized clinical trial is needed.
- *Panel member:* "I would like to see Congress empower the FDA to mandate post-marketing trials and registries."
- *The FDA's Dr. Temple:* "I'm not challenging that we should have the capacity to make people do studies."
- *Chair:* "The committee is saying, I think, that they are impressed that the primary data source should be randomized clinical trials, and observational studies may be good for hypothesis-generation…The AERS (Adverse Event Reporting System) database is almost no good in detecting adverse events that are common in the background."
- *FDA official:* "You are saying they should be hypothesis-generating, and lead to randomized clinical trials...but even if we had the authority to mandate (trials), it would take years to get that data…and there would be pressure to act and significant concern about waiting for the data."
- *Panel member:* "It would seem to me what we don't need is a bundle of observational trials...but an appropriately-powered randomized clinical trial that looks at the issue directly."
- *Another FDA official:* "If we do open the door for observational studies, we have to have a different way of having access to the data, the quality of the data, and give it the same level of attention we do in the review of randomized clinical trials…Right now that is not in place."
- *Panel member:* "The hypothesis here is that Cox-2s are harmful…Therefore, you are doing randomized clinical trials to investigate if there is harm, not benefit, and we have to keep that in mind."

DISCUSSION POINT #3: Discuss the available data regarding the potential benefits of Cox-2 inhibitors vs. non-selective NSAIDs and how any such benefit should be weighed in assessing the potential benefits vs. the potential risks of Cox-2 agents from a regulatory perspective.

- *Panel member:* "I think the clinical experience to date pretty much indicates the efficacy (of Cox-2s) is similar to NSAIDs…We did see provocative data on etoricoxib today that suggests it has better efficacy than naproxen, but that was not replicated…My conclusion is the GI benefits are less than previously speculated...closer to a 30% benefit…and in the face of low-dose aspirin, there is no apparent GI benefit."
- *Panel member:* "I think choice is an important factor...Obviously, you don't want to offer choice if it is dangerous...but pain kills the same way the drug potentially can kill…There is a lot of evidence these drugs are safe…and reasonable data to suggest the potential risk is not really very different between them."
- Deaths and hospitalizations from GI bleeds has been trending down for many years – and the trend started before the introduction of the first Cox-2 inhibitor.
- *Panel member:* "I'm not reassured at all by the data that are available on the short-acting non-selective NSAIDs …I think we need a lot more data there."
- *Panel member:* "There seems to be an assumption that there are 'safe alternatives' in non-selective agents we would feel comfortable having our patients turn to if Cox-2s were not available…My challenge to panel members is to provide data with the same rigor and the same scrutiny as the drugs we just looked at and prove the non-selectives are safe alternatives…I think we have signals to the opposite…and we have to keep in mind that patients have to turn to something."
- *Asked whether the FDA would approve the currently-approved Cox-2s if they came before the agency today, given the recent information, Dr. Temple said,* "I think it varies depending on how you view various collections of data…but some of them probably would not have made it."

Before the panel voted, the FDA outlined the options available to ensure safe use of a drug. Officials explained that it is difficult for them to withdraw a drug from the market without strong evidence. One official said, "To take a drug off the market against a company's will, you have to go through a set of legal proceedings…So, there is a firm amount of evidence needed to take a drug off the market."

- **Voluntary limitations on marketing** – no direct-to-consumer (DTC) advertising and detailing and ads only to selected specialists. An FDA official said the agency doesn't have the authority to ban DTC advertising. However, the advertising has to be fair, balanced, and not misleading.
- **Labeling**
  - **Black box** which limits reminder ads. An FDA official said, "A black box makes reminder ads impossible…How big a deal that is depends on how much reminder advertising there is…But the ad has to convey the contents of the black box...It is hard to write an appealing ad when you are telling all the bad news…And it has to be right upfront; you can't put it in the small print…I won't say all black boxes make it impossible to do (advertising). Even without a black box you have to say the bad news, but the content of a black box are bad and scary." The panel chair said, "A black box affects promotion of a drug. I don't think it works in terms of physicians following the recommendations in the label, but it may decrease usage of the drug – penetration of the drug in the market."
  - Change in indication to second-line.
  - Contraindicate in select patients.
- **Education /outreach**, such as:
  - **Medication guide.**
  - **Dear Health Care Professional (DHCP) letters.**
  - **'Academic detailing'** to targeted prescribers. An FDA official said he was unaware of any cases in which the Agency had mandated this.
- **Reminders** – Patient agreement or informed consent.
  - Physician attestation of appropriate use (e.g., second-line use).
  - Limited amount supplied or limit refills.
- **Performance-linked access** – as with Novartis's Clozaril (clozapine) or Celgene's Thalomid (thalidomide) – in which the drug is not dispensed/shipped unless defined conditions are met.

THE ADVISORY COMMITTEE VOTES

1. PFIZER'S Celebrex (celecoxib)

a. ***Do the available data support a conclusion that Celebrex significantly increases the risk of CV events?***

YES, unanimously

Cardiologist Dr. Nissen said, "It depends on the dose. The signal at 800 mg is strong, no question. There is marginally statistically significant evidence at the 400 mg dose, and no evidence at the 200 mg dose. The 800 mg dose is very likely to produce excess CV risk, and probably at 400 mg, but no evidence at 200 mg…So, the answer to this question has to be based on dose."

b. ***Does the overall risk vs. benefit profile for Celebrex support marketing in the U.S. (Should the product be withdrawn from the market)?***

YES, by a vote of 31 yes to 1 no

The sole dissenting vote was consumer representative Arthur Levin, director of the Center for Medical Consumers in New York.

c. ***If yes, please describe the patient populations in which the potential benefits of Celebrex outweigh the potential risks and what actions you recommend the FDA consider implementing to ensure safe use of Celebrex.***

The panel overwhelmingly favored a black box, with several members recommending that the black box be able to be removed if new data proves Celebrex not to have an increased CV risk. They recommended a patient guide that clearly explains the risks of this and other coxibs and maybe all short-acting non-selective NSAIDs (e.g., diclofenac and ibuprofen, but not naproxen). Many panel members also oppose direct-to-consumer advertising, though they generally recognized the FDA's ability to enforce that. It was ***not*** the majority view that Celebrex should be relegated to second-line status, that patient attestations should be required, or that academic detailing should be instituted.

The discussion included these comments:

- *Panel chair:* "There are ways to do print ads with a black box…It might not be a pretty girl skipping through a field, but it won't be skull and crossbones either… I think there should be a black box and severe restrictions on prescribing – both dose and patient population…and absolutely no DTC advertising…If the package insert tries to specify risk, we should do it in a more helpful way than we do now – in some contextual basis, as in the same increased risk for smoking, having diabetes, etc. And you could give multiple examples so patients have some sense of what we are talking about."
- *FDA official:* Asked if Celebrex could be limited to 100 mg capsules as a way to avoid patient exposure to higher doses, an FDA official warned: "We have to be careful we don't have unintended consequences. Drug prices are not based on the number of milligrams in a capsule. 100 and 200 mg are often the same price…So, you could have the unintended consequence of substantially increasing the cost by limiting the available dosage."

- *Dr. Steven Shafer, Professor of Anesthesia at Stanford University:* "It should only be indicated for individuals who can't tolerate a non-selective NSAID plus a PPI, and it should be started at the lowest dose…I oppose a black box for the class…because it would make it seem all the same…I think there should be a black box for Celebrex …but also one to contraindicate it in CABG based on the parecoxib/valdecoxib data…Pfizer has voluntarily suspended marketing of Celebrex, and I think they should continue to do that until the FDA implements our recommendations."
- *Ruth Day PhD, a psychologist from Duke University:* "I favor an attestation requirement…I think there is a lot of information in the datasets presented that is not in a form most useful to patients…I would have the attestation actually specify the incremental risk patients might accept."
- *Dr. Nissen:* "A black box is a good way to convey the message…We know so much less about the comparators. We don't have robust CV safety data for diclofenac…If you look at a trial like CLASS, you see basically the same CV event rates with diclofenac as with 800 mg Celebrex ...If we do a migration from Celebrex to diclofenac, we may not be doing good; we may be potentially doing harm. We have to keep the warning to what we know – that Celebrex vs. placebo has excess (CV) risk. We don't know if that is excess vs. ibuprofen or diclofenac. So, any statement that suggests using them first is probably not warranted by the data…From what we know: Celebrex is probably riskier than placebo."
- "Unless we do a better job communicating the risks, this will happen again in another class of drugs."
- "The idea that diclofenac and meloxicam…should be used before celecoxib is not data-driven…While I think we need a serious warning and perhaps a black box, I think it is difficult to discuss this without discussing the class. Whatever we say for celecoxib, we probably have to say for diclofenac and others."
- "The data we've seen don't warrant a huge migration of patients away from this to traditional NSAIDs…While we've seen some data that naproxen has less risk than the others, none of us would feel comfortable enough with that data to give naproxen an indication of less CV risk (than placebo)."

2. PFIZER'S Bextra (valdecoxib)

a. *Do the available data support a conclusion that Bextra significantly increases the risk of CV events?*

YES, unanimously

b. *Does the overall risk vs. benefit profile for Bextra support marketing in the U.S.?*

YES, by a vote of 17 yes, 13 no, and 2 abstentions

The vote initially was closer, but the panel was re-polled and some of the abstentions decided to vote after all. The FDA does not generally consider a close vote to be a positive vote, and an FDA official commented in the past that an 8 to 6 vote is viewed as neutral, not necessarily positive, so 16 to 12 (or 17 to 13) might also not necessarily indicate a positive vote. Since it is tougher for the FDA to justify its decision to pull a drug already on the market, the agency would look for a strong signal from its advisory panel – and a 17 to 13 vote is not strong.

Among the panel comments were:

- *Chair:* "This was a pretty strong signal in a small number of patients…What we are lacking are large outcome trials…It is not a good precedent to remove a drug because there is an alternative without a more serious safety signal."
- *Dr. Nissen:* "We don't have the data…I voted no…I'm troubled that there is only data on 3,000 patients on Bextra."
- *Rheumatologist:* "I don't see a significant risk when the drug is used as indicated."
- "We should do the same with this as with Celebrex."
- *Statistician Dr. Fleming:* "I realize there is less data here, and it is predominantly in CABG…but the magnitude of the signal really impresses me here."
- "It is a very strong signal…but it is hard for me to extrapolate this in this patient population…I know giving 40 mg right after CABG is not a good idea…I know that for certain...but I don't know what that means in giving 10-20 mg for arthritis."

c. *If yes, please describe the patient populations in which the potential benefits of Bextra outweigh the potential risks and what actions you recommend the FDA consider implementing to ensure safe use of Bextra.*

The panel also recommended a black box for Bextra, with special contraindications in cardiac surgery (e.g., CABG). The panel's other recommendations for Bextra otherwise mirrored the recommendations for Celebrex. A few members restricting it to short-term use, and one member would require additional studies.

3. MERCK'S Vioxx (rofecoxib)

a. *Do the available data support a conclusion that Vioxx significantly increases the risk of CV events?*

YES, unanimously

b. *Does the overall risk vs. benefit profile for Vioxx support marketing in the U.S.?*

YES, by a vote of 17 yes to 15 no

However, Vioxx is unlikely to return to the market quickly. The FDA's Dr. Jenkins said, "Vioxx could not just reappear back on the market (immediately)…There would need to be substantial agreement on moving toward labeling, which we would have to approve."

Panel comments included:

- *Chair:* "I can't see any reason to keep this on the market."
- *Epidemiologist:* "There is no indication Vioxx is worse than Celebrex for causing heart failure."
- "I think this drug has a stronger dose relationship than the others."
- "It's the only Cox-2 approved for JRA (juvenile rheumatoid arthritis), the only liquid, and the once-a-day dosing is a benefit. And Vioxx can be used in patients with a sulfonamide allergy."

c. *If yes, please describe the patient populations in which the potential benefits of Celebrex outweigh the potential risks and what actions you recommend the FDA consider implementing to ensure safe use of Celebrex.*

The panel favored allowing Vioxx back on the market, preferably at the 12.5 mg dose, with a stronger black box warning than for either Celebrex or Bextra. Panel members agreed that the 50 mg dose should not be re-introduced, but some felt the 25 mg dose would be acceptable. A significant number of panel members also thought Vioxx should be restricted to second-line use. Panel members also thought that, like Celebrex and Bextra, there should be a patient guide that clearly explains the CV risks of this drug. Some panel members also recommended patient consent be required. The clear message was that this drug should be able to come back – but in a limited way.

4. *What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential CV risk of Celebrex, Bextra, and Vioxx?* What additional clinical trials or observational studies, if any, do you recommend as ***essential*** to further evaluate the potential benefits?

The panel basically agreed with the FDA that an "ALLHAT-like" trial is a good idea. The FDA's Dr. Temple had suggested an ALLHAT-like trial with several arms, for example: ibuprofen, naproxen, Celebrex+81 mg aspirin, and full-dose aspirin+PPI (if a PPI is shown to prevent ulcers). Dr. Nissen said, "The (Temple) design makes a lot of sense…and it could lead to evidence to remove the black box…I urge the comparator be naproxen or aspirin+PPI…A non-inferiority design, essentially ruling out…a 50% increase…with 90% power, 250 event, and 10,000 patients per arm is the basic target, with probably two or three year follow-up in the OA/RA setting. That target is positive if the observed increased risk is <17%…That would provide considerable reassurance." A rheumatologist on the panel said, "We need a team of drugs to manage people…To expect people to stay on aspirin for two or three years is not going to happen…81 mg/day aspirin might work as a control." Dr. Fleming said, "Naproxen is an option to use as a control instead of aspirin."

After the meeting, a senior Pfizer official said Pfizer "would endorse an ALLHAT-like trial with Celebrex and Bextra." He suggested the trial should run for two years, have sufficient numbers for meaningful results, and include arms with ibuprofen, diclofenac, naproxen, perhaps Mobic, Bextra, and Celebrex. He said, "We will fund our share as we did in the (original) ALLHAT trial."

Non-selective NSAIDs

5. *Do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical trial data to assess the potential CV effects?*

YES, unanimously

If so, please describe how you recommend that information be conveyed (e.g., warning, precaution).

The panel offered a range of opinions on this, with less than a third advising a black box, others recommending a warning label, and others saying a precaution was enough.

- *Dr. Nissen:* "'Houston, we have a problem.' If you read the literature...they will tell you the biggest beneficiary of this controversy has been the Cox-2 selective NSAIDs that are not called coxibs…meloxicam (Mobic) doubled market share in the wake of the Vioxx controversy…Do we know that an agent like meloxicam that is approximately the same in Cox-2 selectivity as Celebrex won't produce exactly the same outcomes? The answer is, 'We don't know.' If we don't have a big enough database to keep Bextra on the market, isn't that true for other agents…So, at the very least we have to tell prescribing doctors and the public that we don't know…At least we need the same warnings and evidence. Otherwise, we could shift people from celecoxib to meloxicam, and they would have false reassurance there is not a problem, and we just don't know. There has to be equality in labeling across this class until proven otherwise…We know more about naproxen…Naproxen beat the Cox-2s pretty heavily in randomized clinical trials, and we have good epidemiological data on it, so I don't put it in the same class…I'm guessing you don't have enough data inside the FDA not to document a CV risk (with the partially Cox-2 selective drugs). We could be hiding the problem under a great big rug unless we act more broadly."
- "If we walk out with just a black box for Cox-2s and not all the NSAIDs, it will extremely limit Cox-2 use, and a lot of people who would benefit will not get the benefit...I think we need a black box for all of them."

- *Dr. Shafer:* "If we put a black box on all the Cox-2s, we will dilute the message we give…We know four drugs that are Cox-2 like…I recommend the same warning should apply to those drugs specifically."
- *Chair:* "I am dead against that…It is one thing to put a black box on something we have data on, but to use it when we don't have data undercuts the strength of black box warnings."
- "We don't have enough data on some of these others…It would be a mistake to attach the same warning to all NSAIDs except naproxen, which we excluded from any warning."

6. *What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential CV risk of the non-selective NSAIDs?*

Dr. Fleming said, "Naproxen does look more favorable than other comparators."

7. *With regard to the evaluation of CV risk, what studies do you recommend as essential to be completed and reviewed prior to approval of a new NSAID?*

- *Dr. Nissen:* "I just think you need a comparator that is neutral or better than neutral…so I want new drugs (like) naproxen, and that has a high enough standard to protect the public…I am willing to accept naproxen is no worse than neutral…and if you are not 50% worse than naproxen, then you meet standard that is acceptable. That is a safe and secure way to proceed. That means restarting some development programs…but being better than diclofenac is not correct."
- *A rheumatologist:* "It is important to be practical…So, for new drugs not yet on the market…they should be required to do trials like APPROVe…and in the indication being sought…Those trials should be done in low-risk individuals, not in high risk individuals and with active control over a long period of time – at least a year, and preferably two years. That's expensive but necessary for those to come into the market. For those on the market, they could be helped a good deal by ALLHAT or a derivation thereof."
- *Dr. Fleming:* "I want to see a placebo-control or naproxen control."

8. *If the pre-approval studies recommended as essential in Question 7 do not demonstrate an increased risk of CV events for a new NSAID, please comment on how the FDA should handle the issue of CV risk in labeling.*

Dr. Fleming said, "The failure to establish a statistically significant increase does not rule a problem…If you do trials that fail to show a significant increase, that is not an assurance of no increase. You want a trial ruling out an unacceptable increase…What we want is sufficient evidence to rule out an unacceptable increase, which could be a relative risk of 1.5." Dr. Temple added, "If you want a drug for heart failure, we will expect an outcomes study because so many drugs have adverse events while improving exercise tolerance…Similarly, any anti-arrhythmic must prove outcomes…It is not good for drug development (to require an outcome study), but it is necessary because we had a problem." The panel chair said, "That is where we are here."

♦