

# Open Public Hearing

## **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.

### **Highlights**

#### **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).

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## Presenters

### **DR. WOOD (Chairman, Conflict of Interest Statement):**

Let me begin by reading the conflict of interest statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsors of any products in the pharmaceutical category under discussion at today's meeting.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in

connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We are ready to go and let me give you the ground rules before we start, so that everybody understands. You get two minutes to talk. We have a light there that will go on. At 1.5 minutes it will be green, and then yellow, and then at zero, the microphone will go dead and only your lips will keep moving.

So, it is important at that point to sit down because the next guy is coming up to take that microphone. Let's get started. I will be impolite enough to call you by number rather than by name because that is what I have here. If there

are people who have registered to speak and have not yet checked in, they need to go to the check-in desk outside and check in rapidly or someone else will get their spot.

Let's begin with Speaker No. 1.

**MS. JOAN JOHNSON (Daughter has Stevens-Johnson Syndrome):** Hello. I am Joan Brierton Johnson and this is my 7-year-old daughter Sabrina. She writes: "Dear FDA: When I was 6 years old, I had fun visiting my friends, playing computer games, and drawing lots of pictures. All of that ended when I came home from the first grade, not feeling very well. My parents gave me Children's Motrin, but instead of getting better, I got Stevens-Johnson Syndrome. Taking Children's Motrin is why I am blind today. Now I wear a hat that covers my entire face - even indoors - because the light hurts my eyes. When I go outside, I get teased because of my hat. People say mean things to me about it and that really hurts my feelings. I liked going to school, but my immune system is now so weak because of SJS that it is not safe for me to go anymore. I miss my friends. Millions of kids all over the world are given Children's Motrin when they get sick. But it doesn't have a warning label on it about SJS. I would like to ask the FDA to require a warning label about SJS on Children's Motrin and on any other drugs that can cause this horrible disease. Thank you for considering my request. Sabrina Brierton Johnson, age 7, Topanga, California." Now, Sabrina would like to say a few words.

**MS. SABRINA JOHNSON (7-year old daughter of Ms. Johnson):** Please do something so

other children don't get hurt by Stevens-Johnson Syndrome like me. People really need to know about it. Thank you.

MS. JOAN JOHNSON: Thank you.

DR. WOOD: Thank you very much. No. 2. (No response.) No. 2. All right. Let's move on to No. 3, I know he will be here.

**DR. SIDNEY WOLFE (Public Citizen):** Before the clock starts, I have no conflict of interest.

Four years ago, I testified before this committee that FDA should require a black box warning on Vioxx and Celebrex because of significant evidence from the VIGOR study and trends in CLASS of increased cardiovascular risk.

What the FDA, the Advisory Committee, nor I knew then was that in the year 2000 Pfizer had finished a study, a placebo-controlled trial using Celebrex to prevent Alzheimer's disease progression and that the study had found increased cardiovascular risks for the drug.

What I did not know several weeks ago, when I made the results of this yet unpublished study public, was that the FDA had been provided the results of this study in June of 2001, even though they held back, Pfizer held back the study so that it wasn't discussed at the Advisory Committee meeting four years ago, which would have presented a class effect for Vioxx and this drug.

FDA was concerned enough about this study that it presented it internally at a meeting in 2001, but never revealed the results to the public until yesterday in

Dr. Witter's presentation, which acknowledged that in almost every type of adverse cardiovascular outcome, the cases occurred mainly in those using Celebrex, 3 cardiovascular deaths, non-fatal heart attacks, strokes, heart failure or angina out of 140 in the placebo group, 20 out of 285 in the Celebrex group.

Because of much prevarication, to put it mildly, by Pfizer yesterday, Pfizer testified under oath they might have been found to have committed perjury. I recommended today that Pfizer be criminally prosecuted for fraud to the U.S. Attorney's Office if they aren't already conducting such an investigation, and it appears that Senator Grassley's office will take up the investigation as to why FDA withheld this information for so long. I sent this testimony to them.

Given that Celebrex and Bextra are making an important contribution of the estimated 100,000 deaths and 2 million serious injuries a year from adverse drug reactions, I hope you will recommend a ban of these drugs, not a don't use for more than 10 days.

DR. WOOD: Thank you. No. 4.

**MS. SUYDAM (Consumer Healthcare Products**

**Association):** Thank you for the opportunity to present an over-the-counter or OTC perspective on the safety of nonsteroidal anti-inflammatory drugs. The Consumer Healthcare Products Association is a national trade association representing manufacturers and distributors of OTC medicines and has a long history of working with FDA on important safety issues.

In considering the safety of NSAIDs, I ask the Advisory Committee to consider three important points.

First, the use of OTC NSAIDs clearly should be distinguished from long-term or chronic prescription use. OTC NSAIDs have a different overall benefit-to-risk equation and a wider margin of safety because they are used at lower doses and are not intended to be used on a chronic basis unless directed by a physician and are used for mild, self-limiting conditions.

Second, OTC medicines differ from prescription drugs because the OTC label contains all of the information that consumers need to decide if the medicine is right for them, how to take the product, and when to see their doctor if needed. OTC NSAIDs are not intended to be used for long durations unless directed by a physician, and this is clearly stated on the label.

Third, OTC NSAIDs are safe for consumer use when used according to label conditions. Every OTC NSAID has been extensively reviewed by FDA and FDA Advisory Committees. This review has confirmed that OTC NSAIDs are safe and effective and that the benefits of OTC use outweigh the risks.

In closing, it is important to clearly distinguish the benefit-to-risk equation for prescription NSAIDs from that of OTC NSAIDs. The millions of consumers who rely on OTC NSAIDs for temporary pain relief should continue to feel confident that these medicines are safe and effective when used according to the label.

DR. WOOD: Thank you. Jennifer Lo.

**DR. JENNIFER LO (iHAD test to assess CV risk of COX-2 inhibitors in individuals):** To facilitate the benefit and risk assessment of COX-2 inhibitor in each individual, we propose to the Committee a new test under development, iHAD test, used to assess the cardiovascular disease risk in patients taking COX-2 inhibitors.

Our test reveals the pathobiological effect of inflammatory mediators/inflammation related agents (IRAs) on each individual's vascular system ex vivo. Individuals found to be at high risk because they are likely to suffer the same pathobiological effect of IRAs if present under desirable conditions in vivo.

The ex vivo pathobiological effect may be quantified in the form of cytotoxicity which can be revealed in 2 general categories: cytolysis and cyto-aggregation. The severity of cytotoxicity is used to determine the level of CVD risk of asymptomatic individuals. Individuals tested with a high risk may choose not to use COX-2 inhibitors. Others tested with a low risk may benefit from the use of COX-2 inhibitors with periodic retesting.

This picture depicts the cytolysis of cultured fibroblast induced by the basic nature of a protein like many inflammatory mediators.

The next picture depicts the cyto-aggregation of human blood cells induced by multiple IRAs. Phospholipase A2 is one of the many significant inflammatory mediators used in our assessment test.

This simplified proposed mechanism for Acute Coronary Syndromes (ACS) forms the basis of our new iHAD test, including the involvement of COX-2 inhibitors. Inflammation produces many IRAs and some of them are prothrombotic. PLA2 and other IRAs act on blood components to cause cell damage in the form of cytotoxicity.

Cytolysis may be responsible for rupturing atherosclerotic plaques, leading to thromboembolism, predisposing ACS. Cyto-aggregation may lead to thrombosis, predisposing ACS.

COX-2 inhibitors prevent the synthesis of Prostaglandin (PGE2) that is responsible for triggering the pain, but they have no inhibitory effect on arachidonic acid (AA) a byproduct of phospholipase A2, which is also prothrombotic.

Our new iHAD test is intended to evaluate the response of individual blood cells to IRAs in assessing the baseline CVD risk based on the severity of cytotoxicity.

We urge all individuals taking the COX-2 inhibitors or considering taking the drug to take the iHAD test.

DR. WOOD: Thanks. No. 6, Jim Tozzi.

**MR. JIM TOZZI (Center for Regulatory Effectiveness):** Thank you, Mr. Chairman, Distinguished members of the Committee. Having been a resident of New Orleans, I cannot speak that fast, and I have burned up 10 minutes or 10 seconds

I am Jim Tozzi. I am a member of the Board of Advisors of the Center for Regulatory Effectiveness. The Center receives no funding from the pharmaceutical industry although a number of years ago we did receive grants from the industry.

The Center is a regulatory watchdog. To this end, we have a particular interest in the FDA compliance with the requirements of the recently passed Data Quality Act. When the agency makes determinations regarding the benefits and risks associated with the use of non-steroidal anti-inflammatory drugs--sorry, I am an economist--anti-inflammatory drugs. They may be anti-inflammatory, too.

The Data Quality Act required OMB and FDA to issue guidelines which would maximize the quality, the objectivity, the integrity, and the information FDA disseminates to the public.

So, you may be asking why am I here. Well, the guidelines require certain analytical results to be reproducible and unbiased--reproducible and unbiased. The Data Quality Act places no requirements on the distinguished members of this committee, however, the FDA cannot rely upon the information it receives from the advisory committee unless the advisory committee information meets the requirements of the Data Quality Act.

Furthermore, any third party, such as CRA, can petition under this act for FDA not to use the results if they do not comply with the Data Quality Act, and I thank FDA for allowing--.

DR. WOOD: No. 7. Dianna Zuckerman.

**MS. DIANNA ZUCKERMAN (National Research Center for Women and Families):**

The National Research Center for Women and Families is an independent nonprofit organization with no conflicts of interest on this issue.

We focus on research, but we know that when Americans take medication, they don't expect to have to read the studies that have been conducted on the product, and their physicians don't expect to have to read them either, and the patients don't expect to have to carefully scrutinize the fine print and personally weigh the risks and benefits.

They expect that medications that are FDA-approved are safe and effective for almost everyone and therefore safe for them.

So, please, when you vote tomorrow, please treat your votes as if they are the most important ones you will ever make, because there are a lot of people depending on you.

There is plenty to be concerned about regarding the medications that you are considering, but unfortunately, we don't have access to all the data that you have access to, so I am going to focus on the broader issue, which is the failure of the FDA to scrutinize long-term safety data.

This is a systemic problem and it will not be fixed by wishful thinking or by advisory panel instructions.

Unfortunately, drugs that are studied on a few hundred or even a few thousand people, for a few weeks or months, are then taken, as you know, by millions of

people for many years. The FDA really doesn't always know what the long-term risks are especially if the companies involved don't reveal all the information that they have.

The FDA should be requiring and carefully monitoring long-term studies of medical products that patients will rely on for a long time. Our Government needs to strengthen the FDA and other security checkpoints designed to protect us from those very real dangers.

In the meantime, please don't assume that the companies can be trusted to carefully conduct postmarket studies or that the FDA will enforce requirements to conduct such studies and act on their results in a--.

DR. WOOD: Thank you very much. The next speaker is No. 8, Elizabeth Tindall.

**DR. ELIZABETH TINDALL (President of the American College of Rheumatology):** Good afternoon. I am Dr. Elizabeth Tindall and I am speaking today as a practicing rheumatologist from Portland, Oregon, and as President of the American College of Rheumatology. I have no consulting or financial relationships with the companies or products being discussed at this meeting.

The ACR represents more than 6,000 physicians, scientists, and health care professionals who care for people with arthritis and other musculoskeletal diseases. Our members are actively involved in treating the estimated 70 million Americans who are affected by osteoarthritis, rheumatoid arthritis, and other musculoskeletal diseases for which

traditional NSAIDs and COX-2 selective NSAIDs are used.

Limited and emerging data about the cardiovascular toxicity of COX-2 and non-selective NSAIDs, which has received widespread media coverage, has caused anxiety among the patients and the physicians who treat them. We are concerned that this controversy has damaged public confidence and trust in drug safety, and we believe the following points are central to the continued discussion of this issue.

First, the FDA should lead the effort to ensure that patients and the public are made much more aware of the most common and serious toxicities of all medications including those of the traditional and COX-2 selective NSAIDs.

This information should be given to the public with information about what groups of patients may be at greatest risks including age and underlying comorbidities. That allows physicians and patients to make the best decision about their health care.

The American College of Rheumatology supports the FDA's efforts to ensure clarification of the most important drug toxicities in all direct-to-consumer advertising in print and broadcast media, and we also applaud the full disclosure of any advertising presented to the public as promotional educational material.

We also support the full disclosure of the test results of all industry-related trials for drugs that are FDA approved, so that public and scientific scrutiny may occur. We applaud the FDA in forming a new

independent drug safety oversight board this week. This board must ensure that all--.

DR. WOOD: Thank you very much. The next speaker is No. 9. Dimitra Poulos.

**MS. DIMITRI POULOS (patient with rheumatoid arthritis):** Good afternoon and I am here at my own expense.

Every time you take a drug, there is a risk factor to be considered. I believe it's important for the government to keep us informed on all drug findings and potential risks, so we are able to make informed decisions.

Cigarettes come with a warning label, there is no prescription needed for alcohol, yet taken by the wrong person, we are all at risk.

Liver is damaged from Lamasil and Lipitor, Coumadin is a risk of bleeding to death.

When I was diagnosed with rheumatoid arthritis in 1998, my life changed dramatically. Professionally, it had an impact on the quality of my work. Socially, I could no longer sit in a movie theater, take a walk, car trips to visit out-of-town family members was out of the question.

Personally, arthritis attacked my husband, too. He had to assume most of my responsibilities for running the house. As daily functions became impossible for me, I needed his help to get dressed. On day he found me in the bathroom, on the commode, crying, unable to get off of it.

But that was before Vioxx. I have taken Vioxx for over 5 years with absolutely no side effects. Vioxx gave me my life back. We have no idea of the risks involved with any of the new drugs, but a known risk can be dealt with.

As I speak, I have 40 Vioxx left. I have 40 days before my life and my abilities will be severely altered.

I will assume all responsibility and sign any waiver. Please give me that option and thank you for allowing me this time.

DR. WOOD: Thank you very much. The next speaker is No. 10, John Pippin.

**DR. JOHN PIPPIN (Physician's Committee for Responsible Medicine):** Before the clock starts, may I mention my affiliations? I am here representing myself and the Physician's Committee for Responsible Medicine, a nonprofit. I have no commercial affiliations.

While the primary focus of these meetings concerns whether the COX-2 inhibitors should be withdrawn from clinical use, we also must address the more fundamental problem regarding drugs developed and approved in the U.S., and that problem is how to identify safe and effective drugs before they are approved for human use.

The greatest obstacle to accomplish this goal is the continued use of animal testing to evaluate drug safety and efficacy. For reasons which are genetically based and immutable, drug testing in rodents, rabbits, dogs, and monkeys produces widely different results, none of which correlates with human results.

For example, 9 of 11 studies of vascular disease in mice and rats showed that COX-2 inhibitors, the very drugs we are talking about today, were beneficial for heart disease, and, in fact, some of the investigators suggested they would be useful drugs for heart disease. We know from the clinical trials that all three COX-2 inhibitors are dangerous for heart disease.

What I have just told you is no secret. Everyone involved, the pharmaceutical companies, their researchers, the FDA, we all know that animal testing is unreliable. However, we have been unreasonably slow to replace animal testing with newer and better tests for drug safety and efficacy.

First of all, we must eliminate animal testing from this process since this flawed method costs billions of dollars and tens of thousands of human lives annually in the U.S. In-vitro testing using human cells and tissues, computer-based modeling, microdosing studies in humans, stem cell technology to allow testing of human cells and tissues, and the burgeoning field of pharmacogenomics, which allows us to compare DNA and predict toxicity and efficacy of the drugs.

They are all superior to animal testing. We should be promoting these methods. As a group, these methods are light years ahead of our crude animal tests, they are safe, accurate, and cost effective, and we must move toward these methods if we are to have safe and effective medicines in America.

DR. WOOD: Thank you. No. 11. Major Grubb.

**DR. CHRISTOPHER GRUBB (Army Medical Corps):** I am Christopher Grubb, M.D. I am in the Army Medical Corps at Fort Bragg, North Carolina. I am supported by the Department of Defense and I have no financial interests. As a military physician, I have no other interests at heart but the health and safety of our men and women in uniform.

As a pain specialist, my mission is to conserve the fighting strength by treating acute and chronic pain in our active duty soldiers and returning them to the battlefield.

However, we don't like to send soldiers into harm's way on non-selective NSAIDs due to their anticoagulant effects and the potential for worsening bleeding after battlefield trauma. Instead, they go to war with COX-2 selective inhibitors or coxibs.

Consequently, the 82nd Airborne Paratroopers are required to carry a coxib drug to be taken in the event of a battlefield injury, one of three drugs in what is called the soldier's pill pack.

Many soldiers are fearful of the bleeding risk with NSAIDs, so they ask specifically for coxibs. Since service members are young and very physically fit, the armed forces constitutes one of the lowest cardiovascular risk populations in our society, so the recent COX-2 risk data was of very little concern to the military.

So, in this meeting, we warn against using a broad brush when painting the portrait of risk. Military personnel suffer frequent injuries and have a higher

incidence of chronic pain than civilians, further increasing our need for coxibs.

Coxibs have allowed the worldwide deployment of many previously disabled soldiers. Many are now in Iraq on daily regimens of coxibs. Without these products, we can't keep as many soldiers functional on the battlefield.

The study of coxibs for chronic pain is in its infancy. Although efficacy data for coxibs may be equivocal for arthritic conditions versus NSAIDs, the same can't be assumed for other types of pain. Indeed, most military personnel use coxibs for non-arthritic pain, such as low back pain. We have found coxibs to be superior to NSAIDs for spine pain, so we are planning controlled trials of our own to compare these drugs head to head.

In summary, our bravest Americans are reaping benefits from coxibs without drug adverse events. This large population should not be disenfranchised here. Consider our military in this particular drug decision. Coxibs are essential in the global war on terrorism. Thank you.

DR. WOOD: Thank you. Dr. Arrowsmith Lowe, No. 12. Not here? Okay, we will go on to No. 13, Mark Einstein.

**DR. MARK EINSTEIN (gynecological oncologist):** My name is Dr. Mark Einstein and I am an Assistant Professor of Gynecologic Oncology at the Albert Einstein College of Medicine, Montefiore Medical Center at Bronx, New York.

My academic department has supported my expenses to attend this meeting. I have not been asked to speak to you by any pharmaceutical company, however, one of my clinical trials is partially supported by an unrestricted grant from Pfizer.

As a gynecologic oncologist, I am committed to finding new therapies to prevent and treat women's cancers. Recent trend data suggest cancer is overtaking cardiovascular disease as the leading cause of death in the U.S.

COX-2 inhibitors are one of the promising class of agents used in cancer therapy, however, many current and planned cancer clinical trials using COX-2 inhibitors are on hold pending the results of these hearings.

Expression of COX-2 has been identified in many human cancers including gynecologic cancers. One of the COX-2-expressing cancers is endometrial cancer, which is the second most common gynecologic malignancy in the U.S. after another COX-2-expressing cancer, breast cancer.

The number of deaths from endometrial cancer has risen 128 percent since 1987. Responses to toxic chemotherapy in women with recurrent endometrial cancer are dismal. These generally elderly women have comorbidities that also limit their tolerability of chemotherapy.

We identified high rates of COX-2 expression in the most chemo-refractory endometrial cancers. These data led us to begin a pilot trial using Celebrex in women with endometrial cancer that is grant supported by the American

College of Ob-Gyn. This trial has been suspended.

Cervical cancer, the number 1 cancer killer of women in many countries also strongly expresses COX-2. Currently, two cooperative group trials that were designed to observe the effects of Celebrex in pre-invasive cervical cancer have also been suspended.

COX-2 inhibitors are one of the targeted agents that are being used for prophylaxis in women at risk for ovarian cancer where survival using toxic chemotherapy regimens has not changed in over 15 years.

In summary, gynecologic cancers remain a critical issue in women's health and standard therapy are not very effective at limiting the death rate and are not well tolerated. The thought of using target agents, such as COX-2 inhibitors that have less toxicities than most chemotherapies have many--

DR. WOOD: We found No. 12.

**DR. JANET LOWE (physician and epidemiologist):** My name is Janet Arrowsmith Lowe. I am a physician and epidemiologist and the president of a small consulting firm in a tiny town in New Mexico. I do want to state that some of my clients, my pharmaceutical clients include Bayer, Glaxo-Smith-Kline, Merck, Pfizer, and Wyeth, but today I am just representing myself and my firm.

It has been refreshing to hear discussion of risk and benefit, because I think too often in the press, concerning safety of marketed drugs only risk is discussed, and I think as we all know, that when a

product is approved, FDA weighs risk and benefit before approval.

Now, the calculus may change over time as new drugs or new information is available, but in my several years of experience at FDA, and since leaving, I am assured that the agency is still functioning, and I don't believe that FDA is broken.

It is not perfect. Is there a perfect institution? But it probably can be improved, but I think the proposals for a separate agency for the review of safety are not rational. I think that the premarket review really provides appropriate balance in deciding whether a product should stay on the market.

Now, I would like to see greater access to some drug development data including more user-friendly public access to the safety databases at FDA modeled along the lines of the MOD database in the Center for Devices.

So, in my opinion, the public health is best served by a careful study of risks and benefits, and FDA, with the proper funding balance and authority, an engaged industry, and an educated public. Thank you very much.

DR. WOOD: Thank you. Next, we will go to No. 14, who is Dr. Abramson.

**DR. ABRAMSON (“expert on cases involving Vioxx and Celebrex”):** Thank you for having me here. I do serve as an expert on cases involving Vioxx and Celebrex. I want to say that in order to get to the bottom of what went wrong with Vioxx, I think it is important to address first what went right.

At the February 2001 Advisory Committee meeting, the reports of the FDA reviewer showed conclusively that Vioxx caused significantly more cardiovascular complications in people with and without cardiovascular history, and overall, the people who took Vioxx developed 21 percent more serious complications.

So, the question before us is: Why do American physicians prescribe \$7 billion worth of Vioxx after Merck and the FDA knew that Vioxx was significantly more dangerous, no more effective, and far more expensive than naproxen?

In order to answer that question, we need to look at the sources of information that physicians trust most. That data was reported in the New England Journal of Medicine in 2000. The article acknowledged that there was a cardiovascular risk in theory and measured cardiovascular events, but the article did not report those cardiovascular events, nor did the article report serious adverse events overall.

It did report heart attacks. The heart attacks were reported as not statistically significant in people without a cardiac history, and therefore, the issue was not brought to physicians' attention. All 13 authors had financial ties to Merck.

We look at the clinical practice guidelines from the American College of Rheumatology. We see that first is Tylenol, and next recommended is Vioxx and Celebrex. All four authors have financial ties to the manufacturers of both drugs.

The problem here is that the information that docs are getting is so heavily filtered through commercial sources that no matter what the FDA does with drug safety, unless the integrity or doctors' information is not improved and doctors and patients don't take good information into the exam rooms, this exercise is going to be for naught, and the quality of American medicine will not improve.

DR. WOOD: Thank you. We will go to No. 15, Dr. Baraf.

**DR. BARAF (practicing rheumatologist):** I have consulted to and performed clinical trials for many of the companies whose drugs are being discussed today.

As a busy practicing rheumatologist, I have asked to be here to speak for my patients with arthritis. For four and a half months, their needs have been ignored in virtually every news report and medical journal editorial discussing NSAID therapy.

Indeed, we have all learned that we must be more mindful of each patient's risk factors for cardiovascular disease in selecting COX-2s or other NSAID treatment, but data regarding this risk for COX-2 inhibitors is incomplete, sometimes contradictory, and begs further investigation.

The risk for cardiovascular disease with non-selective NSAIDs is unknown and untested. I urge this panel to give careful thought to the considerable benefits COX-2 inhibitors offer patients with arthritis especially those with GI risks.

For large numbers of my patients, COX-2 inhibitors diminish the threat of serious

drug-induced gastrointestinal injury, thereby eliminating a major barrier to their treatment. How are we to balance the competing risks of cardiovascular and GI toxicity against real therapeutic need for patients with debilitating pain?

We must heed the advice that we give to our patients. There are no completely safe drugs in any treatment category. It is my responsibility to weigh and risks and benefits of drugs with my patients, to make individualized decisions.

Sensationalizing and highlighting only the risks of these drugs based on scanty and incomplete information, as many of our colleagues have chosen to do, have created an atmosphere in which an informed discussion with patients is difficult, if not impossible.

For many patients with arthritis, these drugs are not superfluous as some have suggested, but greatly impact their quality of life. To withdraw one drug might put us on a slippery slope, leading to withdrawal of all NSAIDs. My patients must not be denied access to the widest variety of therapeutic options. Thank you.

DR. WOOD: Thank you. No. 16. Dr. Hamburger.

**DR. HAMBURGER (President of the New York State Rheumatology Society):** I am a practicing rheumatologist and the President of the New York State Rheumatology Society. I have been a speaker for several of pharmaceutical companies mentioned today.

I polled New York rheumatologists, State rheumatology society leaders, and I

spoke to my patients, and we have remarkably consistent views. Events have reminded everyone of what rheumatologists and our patients already know. NSAIDs are important because of their role in the treatment of the pain of arthritis and because of the numbers of people who suffer from this pain.

We have seen recently far too many patients who have experienced the recurrence of their pain and their suffering because they stopped their medications out of fear or because of changes in managed care formularies.

None of us can emphasize enough the importance to these patients of reducing their pain and preserving their mobility. So, our consensus opinions are, number one, that access to anti-inflammatories needs to be preserved. Physicians and patients need to be provided with the important information about these medications in a more rational and timely fashion, and the process for disseminating this information should be improved.

The coxibs, we have learned today, and we have known, have less GI toxicity, but their own side effects. Everyone wants an NSAID free of toxicity, but no one can say today to any patient that this NSAID has been tested and found to have no CV, GI, or renal toxicity.

So, we need to maintain access while deciding the best next research.

Patients act on what they read and hear, and they believe the information that appears in the media. The evidence on NSAIDs presented to the public has focused on only a small number of published studies, and the public is

making its judgments without knowing all the information.

Juries in this country do not deliberate and reach a verdict based on the last three pieces of evidence.

DR. WOOD: Thank you. The next speaker will be Dr. Qureshi, No. 17.

**DR. QURESHI (Given Imaging camera pill GI endoscopy):** Good afternoon. Before I start I should let you know that I am being paid by Given Imaging to be here, but not enough to influence my results.

I am going to talk about NSAIDs and the small intestine injury they cause. The occasional findings of intestinal blood loss or anemia in the setting of normal upper and lower endoscopy led to the realization that NSAIDs cause significant disease in the small intestine.

We performed the first controlled study to look at NSAIDs using new technology that is a camera pill that takes a video wirelessly of the small bowel. We looked at 41 patients, half of them on NSAIDs for at least three months and half that took Tylenol or nothing.

This is a camera that you swallow.

Much to our surprise, we found small ulcers in the small bowel, large ulcers, and bleeding in the small intestine.

We found that 71 percent of NSAIDs takers had some form of injury in their small intestine, 20 percent had severe injury compared to none in the controls.

So, symptoms and signs of ill health among chronic NSAIDs users is often

attributed to the underlying disease, but we think that dyspepsia and not responding to acid suppression, vague abdominal symptoms, iron deficiency anemia, or hypoalbuminemia may result from small intestinal injury.

We have a new technology now that enables us to look at the small intestine. Video capsule endoscopy is very useful for diagnosing and for comparing the damage that different NSAIDs might cause on the small bowel, and in a subset of patients where we suspect small bowel injury, this technology is useful and shows promise. Thank you.

DR. WOOD: Thank you. We will go on to No. 18, Mr. Matthews.

**MR. DAVID MATTHEWS (litigation lawyer):** Thank you. My name is David Matthews. I am a lawyer and I represent individuals who have been harmed by the drugs being discussed here today.

The fact that these hearings have become necessary to address the safety of COX-2 drugs is yet another tragic example of the continuing failure of the pharmaceutical industry to disclose the truth, the whole truth, and nothing but the truth to the FDA, prescribing physicians, and the citizens of this country.

Why is the whole truth not forthcoming? Simple. Billions and billions of profit dollars and absolutely zero individual accountability by company officers who submit drug safety data both before and after a drug is approved.

With the coxibs, the FDA has had to negotiate with the drug sponsors to

change labels, conduct patient and physician education, limit advertising, modify approved indications, and to even complete studies.

The time for these negotiations should end. In response to a rash of corporate scandals involving the likes of Tyco, WorldCom, Enron, and others, Congress passed the Sarbanes-Oxley Act of 2002. It provides criminal penalties of up to \$5 million and 20 years in prison for knowingly submitting false finance information to the SEC.

These penalties are for lying about a company's financial status, not for causing injury or death to an individual. Because everyone deserves nothing less than the whole truth from pharmaceutical companies and complete disclosure about clinical trial data, there must be personal accountability for any individual who fails to do so.

I urge Congress, and I hope these hearings can be a springboard, to enact legislation which follows the Sarbanes-Oxley Act, but with more severe penalties for any drug company, officer, or employee who submits false, misleading, or deceptively modified drug safety data to the FDA, a physician, or to the public.

If someone who submits false financial information to the SEC can be fined \$5 million and sentenced to 20 years in prison, there is no compelling reason that the penalties for submitting false, misleading, or deceptively modified data to the FDA.

DR. WOOD: Next speaker will be No. 19, Dr. Wilson, and as you start, Dr. Wilson--we are not counting your time

yet--try and step back a little bit from the microphone. Apparently, there is a lot of distortion from people being too close to the microphone, and that goes to the other speakers, as well. Thanks.

**DR. WILSON (practicing rheumatologist):** First of all, I have no sponsorship, I am here on my own recognizance. I am a practicing rheumatologist in Atlanta, Georgia, and my life is dedicated to alleviating the pain of arthritis.

Almost 2 million Georgians suffer from arthritis. In fact, the latest figures from the CDC are that 1 in every 4 Georgians has a chronic joint symptom, and arthritis is the number one cause of disability in America.

Pain matters. It may not kill you, but you may wish that you were dead.

My patients are not concerned about living forever, they want to live well without arthritis pain. It is not surprise that the more experience we gain using medications, the more we learn when to use it and when not to use it. Patients do not take medications if they don't work, and millions of patients taking COX-2 selective medications evidence that they are effective. Indeed, this has been my experience.

I am concerned about safety. We should try to figure out what is unique about the 1 to 2 percent of patients with very serious side effects rather than depriving the 98 to 99 percent of patients with significant relief from their arthritis pain who have not experienced a serious side effect.

In a perfect world, I would have endless choices because all patients are not created equal. I believe that the choice to choose COX-2 selective medications is too important to answer for the patient. To limit choices based on evolving knowledge is unfair to tens of millions of Americans with arthritis pain.

On average, 29 people a week die in a car in Georgia. I suspect that all of us came in a motor vehicle today and accepted a risk.

We must consider both sides of the equation when we decide how to treat patients and what to treat them with. Ideally, it should be a patient's decision to decide based on the information provided by their personal physician.

Most of my patients would take some significant risk for a better quality of life with relief from arthritis pain. Please thoughtfully consider our patients' pain when you make your decision. Thank you for your time.

DR. WOOD: Thank you. The next speaker is No. 20. Dr. Williams.

**DR. GARY WILLIAMS:** I am Dr. Gary Williams. I am here on my own time and at my own expense.

It is generally accepted that COX-2 inhibitors are a safer alternative to patients with arthritis. Cost containment has been a competing force. Those among us who feel these drugs are expensive or overused may be pleased with the recent changes in the market share of COX-2 specific drugs.

This shift has been caused largely by prolonged concerns regarding Vioxx,

culminating in the decision by its manufacturer to withdraw the drug from the market.

Our current attention is directed to possible cardiovascular risks for two currently marketed drugs, celecoxib and valdecoxib. The data that concerns us is to date in non-arthritis trials designed to explore possible additional uses of these drugs beyond their current indications.

The largest effort to date to assess the impact of these drugs on cardiovascular risk in patients using them for their current indications is the FDA-sponsored Kaiser trial. This trial reinforces the cardiovascular risk for users of Vioxx and raises additional concerns for possible increases in cardiovascular risk in users of nonsteroidal anti-inflammatory drugs including Naprosyn.

In this trial, Celebrex was not associated with increased risk compared to any other treatment option or even when compared to non-users or remote users of any of the treatment options.

On this background, we should be cautious in recommending that thousands, or even millions, of current users of COX-2 specific inhibitors move to other, older non-selective NSAID options.

We should be realistic and assume that they will continue to use anti-inflammatory drugs obtained either over the counter or by prescription. Since they would be moving away from the GI safety advantage demonstrated with the COX-2 selective drugs toward the options included in the Kaiser trial, they would be moving toward increasing GI risk.

Unfortunately, as it relates to the decisions facing this Advisory Committee, the same FDA Kaiser data suggests that the recommended movement--

DR. WOOD: Thank you. The next speaker is Rebecca Burkholder, No. 21.

**MS. REBECCA BURKHOLDER (National Consumers League):** I am Rebecca Burkholder from the National Consumers League. In the interest of full disclosure, NCL occasionally receives unrestricted financial support from pharmaceutical companies for consumer education and research projects. The research cited below is one of those projects. My expenses for this meeting were not paid by an external organization and my statement reflects the interests of those NCL represents, consumers.

NCL urges the FDA to carefully weigh the risk and benefits of COX-2 inhibitors as it decides how best to protect the public. Whatever action this committee takes, NCL believes it is important to anticipate consumer response in the wake of the publicity surrounding COX-2 drugs.

Although COX-2 drugs were originally intended for use by those patients who had GI side effects with traditional NSAIDs, a much broader population actually took the medications. Given recent events, some patients taking COX-2 drugs for arthritis for other pain will now likely turn back to traditional over-the-counter NSAIDs for relief, but consumers likely do not understand how to safely use these OTC NSAIDs.

A 2003 survey of over 4,000 adults commissioned by NCL on consumer use and attitudes towards OTC pain relievers found that 47 percent of those who take OTC NSAIDs take more than the recommended dose. Nearly half would not consult a doctor when taking for more than 10 days. Nearly half thought it was more important to control pain regardless of risk, and the survey revealed the following about arthritis sufferers - 85 percent take OTC for pain relief with 60 percent choosing OTC NSAIDs, 30 percent take pain relievers on a daily basis, and 70 percent do not discuss the risks.

Based on these findings, we believe consumers must be educated about the relative risks and benefits of all medications, OTC or prescription. We call upon the FDA to engage with relevant partners in a broad-based educational campaign that would cover relative risks and benefits of various pain medications, appropriate pain management strategies, the importance of talking with a health care professional, and the role--.

DR. WOOD: Thank you. The next speaker is No. 22. Amy Leong.

**MS. AMY LEONG (President of Healthy Motivation):** My name is Amy Leong. Before I begin, I would like to say that while my funding here was as a result of the Foundation for Better Health Care, a nonprofit health education firm, I have had a role as a motivational speaker in previous years with several of the pharmaceutical companies mentioned today. However, my presence here today is as a concerned patient and a citizen.

As President and CEO of Healthy Motivation, a consulting firm in health education, and as spokesperson of the United Nation's endorsed Bone and Joint Decade, I am very concerned about the issues that you all are addressing today. I am very pleased that you are addressing them, but I think that we need to look at the benefit-risk that you are all so diligently doing today.

I am that patient that you are addressing. I have got rheumatoid arthritis, I have had it for over 25 years. Within 8 years of diagnosis I ended up in a wheelchair, unable to feed myself. As a teenager, not being able to walk or feed herself, it is one of those frightening scenarios that we know should not ever happen.

Because of arthritis medications that did not work in my years, I ended up going through 16 surgeries, 12 of those were joint replacements. I have been hospitalized for over 312 days, and have indeed taken over 35 arthritis medications including every single nonsteroidal anti-inflammatory and the coxibs.

So, I am here today to just tell you and to share with you that while we look at risk, we really do have to consider the benefit. I am a standing benefit in front of you. It is my choice to work with my physician to determine what is at higher risk for me and what is not.

Every single arthritis medication I have taken has come with some serious adverse effect - abdominal pain, fluid retention, gastric ulcers, upset stomach, nausea, vomiting, heartburn, indigestion, ringing in the ears, reduction in kidney function, increasing liver enzymes, rash, weakness, unusual tiredness,

sleeplessness, sleepiness, respiratory infections, infections, sepsis, and it goes on and on.

This is what I deal with.

DR. WOOD: Thank you. No. 23. Donna Fox-Keidel.

**MS. DIANE ZUCKERMAN (friend's son has Juvenile RA):**

My name is Diane Zuckerman. I am here on my own to read for Donna. She was unable to attend because her son is a juvenile RA patient, and he had a serious flare.

She writes:

"I am 39 years old and have lived with scleroderma and juvenile rheumatoid arthritis for 35 of those years. I began taking Celebrex in 2001 as part of my treatment plan. Prior to 2001, I had been on almost every medication known to treat juvenile arthritis. I had endured many corrective and replacement surgeries. I have suffered setbacks and side effects too many to mention.

When my doctor spoke of this new medication called Celebrex, I was indeed skeptical, what would the side effects of this new medication bring to me, headaches, fatigue, and the dreaded gastrointestinal problems I had learned to despise, would it alter organ function, or, better yet, would it really even work, because so many medications I had experience had not shown any benefit, and my drug cocktails were never less than two medications and that is not counting the injections I received.

With my skepticism aside, I tried the new drug and within weeks saw a

remarkable difference. I was able to attend school full time versus part time, I was able to manage my home better, and, most importantly, I was able to be a mom I wanted to be.

I was able to spend quality time with my boys, maintain my home, and continue my work with a volunteer group I started for children with arthritis. My life was full for once and I was able to enjoy every moment of it.

For once, taking medication didn't mean chasing the pills with a bottle antacid. I could eat without fear of feeling nauseated. My then 90-pound frame was able to gain 15 pounds. For a brief period of time, I was taken off Celebrex due to insurance issues. I was borderline depressed because I was afraid my new-found life would disappear. Fortunately, this did not happen because my rheumatologist and I fought for my--."

DR. WOOD: Thank you. The next speaker, Erika Umberger, is she here? No? All right. Let's go to No. 25, Theresa Ray.

**MS. JUDY SARAFIN (friend has osteoarthritis):** Hi. I am Judy Sarafin. I am here on my own and speaking for Theresa, who was unable to attend due to a last-minute emergency and she asked me to read her story.

"I am 35 with a history of osteoarthritis starting in college. After the birth of my second child, my arthritis worsened. Advil wasn't working, my GP gave me Celebrex, which worked for about four months. When that was no longer sufficient, he sent me to Dr. Fleishman. Together, we worked through Mobic and Bextra before settling on Vioxx.

With the combination of Vioxx, multivitamins, glucosamine, and avoidance of caffeine, I became stable. For the first time in about five years, I could honestly say that I had periods of time where something didn't hurt. I could always feel pain somewhere prior to this point.

I reached stability with the Vioxx combination in August of 2004. When the FDA pulled Vioxx, I had no choice but to go back to the Bextra at least temporarily. Once again, Bextra failed to give me a sufficient quality of life. I hurt so badly I could feel it in my toes. We are now trying to find something that will return me to my Vioxx quality of life. My family has no history of heart disease or stroke, my blood pressure is perfect, and my cholesterol is ideal. I understand and do not wish to dispute that Vioxx can cause some serious complications in a certain portion of the population, however, what about someone with my medical history?

I completely agree that all new information, whether good or bad, should be disseminated to patients and physicians, but I believe the withdrawal of Vioxx was premature. Each patient and physician should be allowed to perform the risk-benefit assessment and further studies should be performed to fully understand the interaction before removing this drug from the marketplace."

DR. WOOD: Thank you. The next speaker is No. 26, Judith Whitmire.

**MS. JUDITH WHITMIRE (Celebrex osteoarthritis patients):** Pfizer has paid my travel

expenses. I came from Reno, Nevada. I contacted Pfizer, though, because I wanted to try to keep my drug of choice, Celebrex, on the market, so that is why I am here today.

When I was a young teenager, I helped my grandfather in his home printing business. It was difficult for him to set type since his hands were even worse than mine are now. Certainly, I never did think that my hands would resemble his one day.

Now I face a similar challenge. When I retired at the end of 2002 from a 40-year career in public health microbiology, which was a problem with my hands, my husband introduced me to the wonderful world of woodturning. It seems I have a natural talent and my wooden bowls are in much demand if I can only keep my osteoarthritis under control, and this is what I do and love.

I will be 65 years old next week. Subsequent to a severe whiplash when I was 16, I developed osteoarthritis in my neck at the age of 30. It was then that I embarked on the search for an effective anti-inflammatory.

I started with Clinoril and have spent the next 30 years trying all of the new drugs as they became available. They either provided limited relief or caused me gastritis, or both. I had a three-day run on Naprosyn before my stomach said no.

My new rheumatologist prescribed Celebrex last fall for the osteoarthritis in my hands, neck, and right knee. It gives me far better relief than all of the other anti-inflammatories, and no gastritis.

I do not have any risk factors for cardiovascular disease. Interestingly enough, most of my family has died of cancer. My rheumatologist is comfortable with my low dose regime of 200 mg per day. I urge you to keep this drug available for the clinicians to judge if it is appropriate for their patients like me. Thank you.

DR. WOOD: Thank you. The next is No. 27, Judy Fogel.

**MS. JUDY FOGEL (Celebrex osteoarthritis patient):** My name is Judy Fogel. I drove myself here from my home in Ithaca, New York, to talk to you today. I found out about this hearing from inputting in Google the word Celebrex, a drug I have been taking with great success for three years.

I feel like Celebrex was created for me. My OA started when I was in my early 20s. It started with pain and stiffness in my fingers. The symptoms continued to worsen. In the early '70s, a rheumatologist had me take increasing doses of aspirin, which led to gastric upset and ringing in my ears. Since there was no other drug available, I would sometimes take an aspirin and just pay the consequences.

We raised three children and being a soccer, football, and ice hockey mom, cold weather environments was especially difficult. In the '80s and early '90s, I tried about 10 of the NSAID drugs. As each new one came on the market saying it was better than the preceding one, I would take one pill and have gastric upset, bruising, and ringing in my ears.

Three years ago I went to my rheumatologist with an inflamed right arm and hand. He prescribed a new drug that would be easier on my stomach, he said. It was called Celebrex. He gave me samples and a prescription form.

After taking the samples with no adverse aftereffects, I had the prescription filled and have taken 200 mg of Celebrex each day ever since.

It took several months to have the pain and swelling in my right hand and arm subside, so I could use them again, and gradually, the morning stiffness and pain in the rest of my body was remarkably better.

Most days I feel better than I did 30 years ago. I downhill ski, play golf, shuffle cards at bridge, sit through days of lectures and take notes, dig and clip in my gardens. I have regained the manual dexterity--.

DR. WOOD: Thank you very much. The next one is Dr. Preston Mason, No. 28.

**DR. PRESTON MASON (pro-oxidant effects of Vioxx and etoricoxib):** Thank you. I would also like to acknowledge the contribution of my colleague, Professor Corey, Nobel laureate in Chemistry.

Both the studies I will discuss were conducted without interference from the pharmaceutical industry. We both purchased the drugs used in our studies. I have received unrestricted grants from the manufacturers of these drugs.

Dr. John Vane, also a Nobel laureate, suggested as early as 2002 that differences in CV risk observed among

COX-2 inhibitors may be attributed to their physico-chemical properties.

Confirmation of this hypothesis was provided by Professor Corey. He reported that rofecoxib readily formed potentially cardiotoxic metabolites under physiologic conditions. One of these metabolites would promote LDL oxidation, a well-known contributor to inflammation. Such toxic metabolites were not observed in the other agents he tested.

The findings of Professor Corey corroborate our own findings submitted before Vioxx was removed from the market. We showed that this drug dramatically damaged LDL and membrane lipids through oxidative modification. We saw this at pharmacologic levels.

In this figure, we also show an increase in isoprostanes, a mediator of inflammation, and we again report that this change in LDL oxidation was not seen among other agents tested.

In the next slide, we contrast the pro-oxidant effects of Vioxx against a potent antioxidant. Remarkably, the combination only partially attenuated the effects of the rofecoxib.

We also saw that rofecoxib reduced the capacity of human plasma to defend against free radicals. We have seen, and others have reported, similar changes in patients with diabetes and a recent MI.

The next slide is a further explanation for the cardiotoxicity. We evaluated its molecular effects on lipid structure. Vioxx indeed altered lipid structure in a manner that we have seen consistent

with increasing rates of oxidative damage.

We also saw adverse effects on lipid structure and oxidative damage with etoricoxib, another sulfone-type agent.

So, in summary, the last slide, we have seen increased reactive oxygen species with rofecoxib that contribute to mechanisms that lead to cardiotoxicity. Thank you.

DR. WOOD: Thank you. Is No. 29, Dr. Ross, here? No. All right. Let's move on to No. 30, Dr. Singh.

**DR. GURKIEPAL SINGH (epidemiologist collaborator with David Graham):** I am Gurkiepal Singh and I am here on my own. This morning you heard data from the collaborative study that David Graham and I did. I am also the lead author of the Estimate of NSAID GI Bleeds in the Country that Dr. Cryer referred to, and as a handout, I provided you our latest study on the hospitalizations because of complicated gastric and duodenal ulcers in the United States from 1988 to 2001 that I presented in a plenary session last year.

In the next 30 seconds, reviewing it very, very quickly, if you go on to page 3, the top slide on the right side shows you what we found, that there were a total of 493 million hospitalizations in the U.S. and 3.6 billion patient years, and over the years, there has been a decline in the amount of gastric and duodenal ulcer complication hospitalizations in the country with two periods of remarkable decline, the first one '94 to '95, perhaps coinciding with the introduction of H. pylori guidelines

by the NIH, and the second one in 1999, coinciding with, not necessarily caused by, the introduction of COX-2 inhibitors.

The last slide also shows you the same rate expressed for 100,000 NSAID prescriptions, and you would see that the 1999 decline was of 22 percent. We do not know what causes it, but here are the numbers.

One last point I would like to make on our Medi-Cal study, is that we did look at the recent exposures and current exposures and remote exposures. I know that issue came up, and the study was internally consistent and that the current exposure was always the highest followed by the recent exposure and then the remote exposure. So, internally, we were consistent in defining that exposure.

Thank you very much, ladies and gentlemen, and I will be here to answer any questions that you want.

DR. WOOD: Thank you very much. The next speaker is No. 39, Dr. Allan Fields.

**DR. ALLAN FIELDS (medical spokesperson for Swiss Medica):** Good afternoon. My name is Dr. Allan Fields. I have been a physician practicing general and pelvic surgery and sports medicine for over 30 years. Presently, I am also the medical spokesperson for Swiss Medica, the maker of 024, Essential Oil Pain Neutralizer.

This is a potent, safe, and effective topical analgesic. It contains only natural ingredients that have been clinically studied and tested in the U.S. and around

the world including double-blind studies. It carries a U.S. process patent.

As physicians, we have taken an oath to provide the most effective care while not knowingly harming the patient. To that end, I would like to share some of my experiences with you.

I personally am asked on a daily basis what can patients do or take to control pain for a variety of medical conditions. I have been advising my patients to minimize the use of oral prescription OTC medications and instead to use the 024, which due to its purity, does no harm to the human body.

We also recommend that 024 be applied with massage therapies. This has provided pain relief that has often lasted 6 to 8 hours. These results have been very exciting. The patients have been using less of the aforementioned drugs and saving money in the process.

No serious adverse effects, such as GI bleed, hypertension, or cardiovascular problems have ever been reported. There is no interference with other medications that are necessary to maintain the patient's health because 024 is all natural.

It contains no binders, preservatives, or additives. Diet, exercise and work control are also stressed, but in the future, we must strive to enhance our body's natural responses to pain and healing by safe and effective methods.

I am also a patient with diabetic neuropathy. I use it on a twice daily basis. I have had no pain since. Thank you very much.

DR. WOOD: Thank you. The next speaker is No. 32, Grant Johnson.

**MR. GRANT JOHNSON (Chief Operations Officer at Swiss Medica):** Thank you. I would like to start off by saying there is a little bit of a logistical mistake. The presentation packages will be circulated at the end of the public presentations.

My name is Grant Johnson. I am the present Chief Operations Officer at Swiss Medica, the manufacturer of 024. It's a topical pain relief medication that competes against the NSAIDs and the COX-2 inhibitor class of drugs.

We are all very aware of the huge potential negative side effects when certain high-risk patients take NSAIDs and COX-2 medicine for any length of time. At Swiss Medica, we have compiled scientific evidence that powerful topical pain relievers, such as the 024, are as effective as many oral medications, but without the side effects, such as the bleeding ulcers, high blood pressure, or increased risks to the heart.

These claims are supported by three European medical studies, one American-based open trial, and a recently completed Canadian randomized, double-blind clinical study over an extended period of time.

Every one of these studies demonstrates that there was a 60 percent or greater quantifiable reduction in pain for those who suffer from chronic pain conditions.

The first study was conducted five years ago, the latest was concluded last month. In your presentation packet folders I have included the appropriate summaries

and the five pages of professional endorsements, and you will also find anecdotal feedback from pain sufferers who switched to the O24 after failing to find relief from a wide variety of pain medicine and magic solutions, particularly the NSAIDs and COX-2 inhibitors.

Consumers need to be better advised by the FDA, healthier eating choices, regular exercise. These are things that have worked for centuries on this planet. Does it make sense to allow multibillion dollar companies to spend tens of millions of dollars to persuade consumers to pop a pill instead of making a healthy lifestyle decision?

I propose the FDA consider a moratorium on all direct-to-consumer advertising until these drugs have been properly studied, and as of today, no one has a straight and honest answer to the question how many have really died from using these pain pills. Thank you.

DR. WOOD: Thank you. The next speaker is No. 33, Necole Kelly.

**MS. NECOLE KELLY (American Chronic Pain Association):** Hi. I am here speaking for the American Chronic Pain Association. We want to make sure that everyone here understands that chronic pain also destroys lives.

People who have chronic pain fight to get their pain validated, to keep their jobs, to keep their health insurance, to maintain their homes and their families.

For 25 years, the ACPA has offered support and taught pain management skills to people with pain, to help them

live more normal lives. Yet, in spite of their best efforts, many of these people still need medications including COX-2 inhibitors that come with both benefits and risks.

Imagine learning that one of the tools you need to live a normal life is no longer available. In recent weeks, we have received hundreds of letters and e-mails from people who have told us they have stopped taking their medications because they are afraid of heart attacks.

Others also have told us that they would rather live 10 years with manageable pain than live 20 in agony. Some people are getting their medications from Canada because they can't function without it.

The ACPA is not a research facility. We can't speak to the science behind these studies. We can speak for people with pain. What these people want and need is to share with their doctors the medical decisions that affect their lives. They need to know the risks of taking any medications and weigh them against the benefits, to make intelligent personal treatment decisions. They need to retain the right to make these decisions for themselves.

People with pain need the FDA to continue helping the public to get the accurate science-based information they need to make good decisions, but we ask you to look beyond the science and see the human face of pain.

Imagine just one person who woke up today, as every day, with intractable pain, unable to function, and ask yourself what is best for that individual.

We hope your decision will make a positive difference for that person.

DR. WOOD: Thank you. The next speaker is No. 34, Karen Kaiser. Is she here? No. All right. Then, let's go on to No. 35, Robert Thibadeau.

**DR. ROBERT THIBADEAU (ankylosing spondylitis patient):** I am an experimental research scientist in a non-medical field with no financial interests in the medical industry whatsoever.

I have had rheumatoid arthritis and ankylosing spondylitis since 1973, diagnosed by blood tests in 1983. Vioxx saved my life. It acts in an hour with no high or other perceptual side effects. It is like aspirin for headaches, it just makes the arthritis pain and stiffness go away.

I am here solely to reinforce the probability of an experimental confounding and ask for public analysis and full disclosure.

The confounding: You don't exercise for 25 years and now you have no pain and stiffness. You run upstairs because you are amazed you can. Risk of heart attack or stroke goes through the roof, not for bad reasons, but for good reasons.

Control: Since these are brief, unpredictable episodes, electronic monitor all waking hours to see if patients show brief, spontaneous increases in aerobic physical activity over placebo controls. I have not seen this done or even mentioned for control by any study available to be read by the public.

I predict mentally incompetent people, Alzheimer's, much more likely to show this exertion side effect. People physically debilitated by joint damage should show less effect due to physically restricted mobility. Other predictions are in my longer paper.

I ask the advisory group to review for this confounding and ask the FDA to report the findings and justifications out publicly. Thank you.

DR. WOOD: Thank you. The next speaker will be Lois Humphrey, No. 53. No? Not here. I beg your pardon, Glenn Eisen, No. 36, was 52.

**MR. GLENN EISEN (small bowel mucosal injury with naproxen but not Celebrex):** Close enough. I would like in the interests of full disclosure to acknowledge that I have done research and consulted with Pfizer, AstraZeneca, and Given, and like Dr. Qureshi, they are barely covering my expenses today.

Next slide, please.

I would like to discuss the fact that there has been accumulating data over the last decade as far as gastrointestinal toxicity that has gone beyond the ligament of trique (ph) to both the small and large bowel.

This is an autopsy study from the New England Journal approximately 10 years ago, which showed a greater than 10-fold incidence of nonspecific ulcers in an autopsy study.

Next slide.

A case-control study of hospitalized patients who presented with upper and lower GI bleeding found that patients within a week of admission had equal use of NSAIDs whether it was an upper GI bleed or a lower GI bleed, and this was twice of the control population.

Next.

As a secondary analysis in the VIGOR trial, you can see from these bars that there was twice the risk of lower gastrointestinal bleeding for naproxen as compared to rofecoxib.

Next slide.

In another analysis from the CLASS study, showed that in an FDA-mandated outcome, having a greater than 10 percent drop or a drop in hemoglobin of greater than 2 grams per deciliter, there was double the risk of dropping the blood count in both diclofenac and ibuprofen as compared to celecoxib.

If we remove patients who have had overt bleeding, the trend continues.

Next slide.

So, because of this, we developed a study to show proof of principle for small bowel damage, and the combination of a nonspecific NSAID with a proton pump inhibitor should be associated with a rate of small bowel mucosal break that is significantly higher than the rate for placebo or COX-2 selective agent.

Next slide, please.

We have already shown this.

Next slide.

Dr. Qureshi showed some nice pictures.

Next slide.

This was a double-blind, randomized trial where healthy volunteers had a two-week run-in period, were randomized after a baseline capsule, which was normal, and then were given 1 of 3 treatment arms.

Next slide.

The primary endpoint was the mean number of small bowel mucosal breaks, and as you can see, naproxen with a PPI had 10 times the number of mucosal breaks as compared to celecoxib.

Next slide.

The secondary endpoint showed that there was 55 percent incidence of small bowel mucosal breaks for combination therapy as compared to 16 percent for celecoxib.

Next slide.

So, in conclusion, as in the upper GI tract, inhibition of COX-1 by naproxen, and not celecoxib, translated into significantly different rates of mucosal injury in the small bowel, and these findings extend the original COX-1-sparing hypothesis beyond the upper GI tract and into the small bowel. Next slide. You can read it because I am out of time. Thank you.

DR. WOOD: Thanks. The next speaker is Susan Winckler. Is she here? Yes, No. 37.

**MS. SUSAN WINCKLER (American Pharmacist Association):** I am here representing the American Pharmacist Association, and we did not receive funding to participate in today's meeting. The views I am presenting are solely those of the Association and its membership.

We are here because the safety profile of COX-2 selective NSAIDs has recently come into question. Some have suggested that these drugs are too risky to be marketed, but a consideration often lost in comments and debates, such as this, is the reality that no drug has zero risk.

Every medication has benefits and risks, and those risks increase exponentially when the products are used inappropriately.

Unfortunately, patients have lost access to several medications because the health care system failed to appropriately manage risk. Patients should not lose access to these products because of the health care system's failure to reduce risk.

If the agency determines that the benefit-risk profile is insufficient for these products to remain on the market, that assessment must consider the responsibility of health care professionals and patients in making medications work.

By collaborating, pharmacists, physicians, and patients can mitigate some level of risk if we focus on identifying potential risks and determining systematically how best to manage those risks.

There are a few things that can help us with that risk management. First, is to increase the reporting of adverse events by pharmacists and other health care professionals and to continue to encourage that reporting.

Providing pharmacists with complete information about the patients would also improve our ability to manage potential risks.

When products are identified as having a risk or requiring more attention, access to a more complete medical history would allow pharmacists to help assure that at-risk patients do not take medications that could exacerbate such a condition.

If the agency determines that there is a need for special oversight of COX-2 inhibitors or other NSAIDs, we urge the FDA and product sponsors to involve pharmacists in both the development and implementation of any risk management program.

Please avoid the misperception that only these products present a risk to patients when, in reality, every medication has benefits and risks. Thank you.

DR. WOOD: Thank you. The next speaker is No. 38, Virginia Ladd.

**MS. VIRGINIA LADD (President of the American Autoimmune Related Diseases Association):** My association is paying for my travel. Good afternoon. My name is Virginia Ladd. I am President of the American Autoimmune Related Diseases Association. We are a nonprofit health organization representing patients living with autoimmune diseases, which

include rheumatoid arthritis, lupus, scleroderma, and over 80 other disorders sharing similar complications as the result of the body's attack on itself.

Autoimmune disorders are serious chronic and disabling conditions that often present with constitutional symptoms of joint and muscle pain, widespread inflammation, and fatigue.

We ask that the agency and its advisory committee respectfully consider the critical role of patient and physician dialogue in conducting risk-benefit analysis of any therapy at the level where it belongs - with the individual patient rather than a diverse clinical population as a whole.

We believe that patients should have access to as broad an array of essentially safe and effective therapies as possible, with informed labeling, providing the means by which the provider and the patient can consider treatment options.

For many patients, the remote and even more common risk of a serious acute adverse event is, and would be, outweighed by the benefit of maintaining or regaining freedom from pain, mobility, and independence.

Since there has not been a new drug approved specifically for the use of most autoimmune disorders in the last 40 years, it is necessary that clinical reliance on off-label use of existing anti-inflammatories and immune-modulating drugs.

In particular, the COX-2 inhibitors have contributed to the improved life quality of many autoimmune patients to which I have personally spoken. Without COX-2

inhibitors, many autoimmune patients with sensitivities to other NSAIDs would be relegated to the use of low-dose corticosteroids with therapy for the treatment of their debilitating symptoms, and as you are aware, such therapies carry--.

DR. WOOD: Thank you very much. The next speaker is No. 39, Paola Patrignani.

**DR. PAOLA PATRIGNANI (whole blood assay of COX-1 and COX-2 inhibition):** I am Paola Patrignani, University of Chieti G. D'Annunzio Italy. I am Professor of Pharmacology. I am in the field for 20 years.

This slide compares the therapeutic plasma concentrations of cyclooxygenase inhibitors, reported in pink, with the concentrations of the different drugs inhibiting by 80 percent the activity of platelet COX-1, a biomarker of gastrointestinal toxicity, shown in panel A, and monocyte COX-2, a biomarker of efficacy, shown in panel B, as determined in the whole blood assay that I developed. This is in vitro, reported in blue.

It should be pointed out that 80 percent inhibition of COX-2 is associated with clinical efficacy.

Ibuprofen and naproxen therapeutic concentrations are proper to inhibit more than 80 percent platelet COX-1 and monocyte COX-2. Thus, these two drugs have similar pharmacodynamic traits and they should be placed in the same box.

Differently, therapeutic concentrations of COX-2 inhibitors are from 4 to 200-fold lower than those inhibiting platelet

COX-1 by 80 percent, thus demonstrating a variable impact on COX-1 depending on the dose and selectivity.

The impact of COX-2 inhibitors on monocyte COX-2 is shown in panel B.

The therapeutic plasma concentrations of nimesulide, rofecoxib and etoricoxib are proper to inhibit more than 80 percent COX-2.

Diclofenac and lumiracoxib plasma concentrations are several-fold higher than those inhibiting by 80 percent COX-2 while celecoxib and valdecoxib plasma concentrations are 2- to 4-fold lower.

In summary, ibuprofen and naproxen have similar pharmacodynamic features towards COX isoforms, so they have to be in the same class.

Diclofenac and celecoxib have superimposable pharmacodynamic traits, but they are given at not comparable doses.

Lumiracoxib 440 mg is an overshooting dose.

Next slide, please.

This slide is very interesting because I compared, I gave different drugs, lumiracoxib, rofecoxib, celecoxib, ibuprofen, naproxen to healthy subjects or patients, and I compared the inhibitory effect on COX-1 and COX-2 and the synthesis of prostacyclin.

The most interesting part of the slide is that all the other coxibs gave a similar

inhibitory effect of prostacyclin. Also, the other important--.

DR. WOOD: Thank you very much. The next speaker will be No. 40, Betsy Chaney.

**MS. BETSY CHANEY (Celebrex patient):** Good afternoon. I am Betsy Chaney. I am a Celebrex user. I took Vioxx before.

I am here to say would you all pick up your elbow and whack your funny bone and feel that pain that stops you in your tracks from doing what you are doing. All you want to do is say a bad word.

Well, I have cracked vertebrae in my neck, and without Celebrex, I start to lose the feeling in my hand, and I can't grasp a paper, I can't hold onto something, I can't do things around my house.

I am concerned that you all will take my ability away to make a decision with my physician, my family, and my friends, to make an advised decision to take COX-2 inhibitors.

There is a lot of people here for profit, for many things, whether it be the drug companies or the lawyers, or whoever, but my issue is please don't take this medication that works so well for me.

I can't take other medication because I am taking two Nexium and a Xantac today. That is maxed out on the stomach medication. They looked inside and said it looks like Barrett's esophagus. I have GERD and you all know I have NSAID, NSAID, NSAID. I could name 100 of them, but those names don't matter.

What matters is that I retain the right to make a decision, with my doctors and my family, to continue taking this medication even if there are risks.

I am willing for my quality of life to take those risks, and I thank you all very much for watching over us. Thank you.

DR. WOOD: Thank you very much. The next speaker is No. 41, David Peterson. Is he here? No. Then, let's go on to No. 42, Jack Klippel.

**DR. JACK KLIPPEL (Arthritis Foundation):** Thank you, Mr. Chairman.

The Arthritis Foundation represents and is the voice of millions of Americans with arthritis. Our constituency is keenly interested and is a major stakeholder in the discussions being held today.

They seek clear answers from us, you, their doctors, industry leaders, and regulatory authorities about the role of COX-2 inhibitors and other NSAIDs in the treatment of their arthritis.

The Arthritis Foundation believes there are two main factors that must be considered in these discussions of these drugs and similar discussions about other medications in the future.

First, there must be a more balanced discussion about the benefits, as well as the risks for these medications. Recent attention of COX-2 inhibitors and NSAIDs have focused almost exclusively on one particular risk, cardiovascular disease, with little mention of other risks associated with these drugs, or more importantly, the benefits of this class of drugs.

Numerous studies have documented that COX-2 inhibitors and other NSAIDs relieve pain and inflammation which has benefited millions of people with arthritis. Many have found COX-2 inhibitors to provide greater pain relief than other medications. For some, COX-2 inhibitors have controlled pain when nothing else has worked.

They would ask you the question, whether their public health was made better or worse by the decision to withdraw Vioxx. Their greatest concern and risk is not about side effects of drugs, but that they live with arthritis.

Second, is the central role of informed patient choice in allowing patients with arthritis to make their own decisions about treatment. We believe that patients should be able to choose for themselves whether or not the benefits of a particular medication or treatment outweigh the risks.

Full disclosure of these benefits, side effects, and risks, and discussion with the patient's doctor--

DR. WOOD: Thank you. The next speaker is labeled as No. 43. Kathy Pinkert. Is she here? No. Then, No. 44, Carol Spitz.

**MS. CAROL SPITZ (Bextra osteoarthritis patient):** Hi. My name is Carol Spitz and my travel expenses have been paid for.

I have severe osteoarthritis. I have had a knee replacement, shoulder replacement, and three back surgeries.

Bextra has allowed me to be able to function, some of the normal things that people take for granted like walking and dressing. I couldn't even do that before.

I am unable to take Motrin and Naprosyn and aspirin due to anaphylactic reactions. Other NSAIDs have given me adverse reaction of my stomach, and that's it. Thank you.

DR. WOOD: Thank you. The next speaker is No. 45, Eileen Lacijan.

**MS. EILEEN LACIJAN (osteoarthritis patient):** Good afternoon. My name is Eileen Lacijan. I am grateful for the opportunity to be here today to speak to you about my experience with COX-2 inhibitors.

I would like to advise the committee that I do not have any financial relationship with the sponsor, product, or competitors. I am here today representing myself on the advice of my cardiologist.

I am 57 years old and reside in Arnold, Maryland. I am a registered nurse and the Executive Director of a Hospice Program in Maryland.

I have osteoarthritis of the basal thumb joints of my hands. I was first prescribed Vioxx in March of 2000. My rheumatologist changed my prescription to Celebrex in June of the same year. I then took Celebrex for the next four years until July of 2004. Following a flare-up, the Celebrex was no longer effective and I was prescribed Bextra in July of 2004.

I have never smoked. I don't drink alcohol. I don't have diabetes or any

family history of heart disease. I have never had high blood pressure. I exercise regularly. I am not overweight, and I have always maintained a health diet.

On the evening of August 12, 2004, I survived a myocardial infarction. A cardiac catheterization, which was performed the following day at GW Hospital, revealed no blockages. My heart attack was thought to be caused by a coronary vasospasm, which affected the left anterior descending coronary artery and initially resulted in a moderately large amount of heart damage.

I received excellent cardiac care and was able to return to work full time a month after my heart attack. I continue to work out at cardiac rehab several mornings a week before work. I thank God every day that I am alive and have the love and support of my family and friends. However, I still have many unanswered questions about the cause of my heart attack as does my cardiologist.

DR. WOOD: Thank you very much. The next speaker is No. 46, Gloria Barthelnes.

**MS. GLORIA BARTHELNES (Vioxx and Bextra arthritis patient):** I am Gloria Barthelnes and I am from South Grafton, Massachusetts.

When I was in my 30s, I was having problems with my legs and my neck – didn't figure what it was. I figured it would go away. Finally, in 1984, I was living on a second floor apartment and I was carrying my grandson who was 10 months old up the stairs, got halfway up the stairs and couldn't finish, I had to sit down the pain was so bad.

I had contacted the doctor and he had me go through several tests. Finally, he recommended a rheumatologist. They tried several medications on me, it didn't work. Then, finally, he had given me Vioxx. It was such a relief that I was able to go to work without any pain, without any problems.

To go to work, I had to travel like 37 miles one way, and sometimes there was a lot of traffic, and just to sit in the traffic was the hardest thing to do.

I have the arthritis in my neck, lower back, and in my legs. When they took the Vioxx away, I panicked and I tried using just the over-the-counter medication. It didn't work. So, finally, I had called the rheumatologist and I said, "Can you help me?"

So, he put me on Bextra. I am hoping that you people can help me, and not take these medications away. Thank you for your time.

DR. WOOD: Thank you very much. The next scheduled speaker is No. 47, Rebecca Dachman. Is she here?

**DR. REBECCA DACHMAN (occupational medicine physician):** Hello. My name is Dr. Rebecca Dachman. I am an occupational medical physician, and I also have significant experience in clinical trial design.

There were a number of thoughts that came to my mind as I read in the papers about what was going on with the COX-2 inhibitors. One of them, as an occupational medicine physician, there are many people who only respond to

COX-2 inhibitors, and that makes a difference between working and not working for them, which has significant effects both on disability and ultimately on their health, because nonworking, sedentary people are a setup for cardiovascular disease, as well.

As a clinical trialist, looking at the data, I know I was surprised that I didn't get more subgroup analysis of those who ended up having the cardiovascular events, whether there were more diabetics in that group or whether there were any other ancillary factors that one could tell that would identify them, and I think that is important.

I also think that vis-a-vis drugs, we have to put it all in context, all drugs do have ADRs. Birth control pills are as extensively used as non-steroidals and anti-arthritis drugs, and they all do cause increase in thrombotic events, yet, we haven't taken them off the market either.

I think we have to remind ourselves of that and what it means is not that they won't have events, but knowing about them and knowing how to subgroup the people in who those events occur.

I think from the FDA stance, they have to develop registries post licensure, so that for the first two years, you get all the adverse events that occur, and that is what is being done in Britain.

DR. WOOD: Thank you very much. The next speaker is No. 48, Barrett Collins. Not here. No. 49, Cynthia Lee. Not here. No. 50, Robert Humphrey. No. 51, Michael Paranzino.

**MR. MICHAEL PARANZINO (Psoriasis Cure Now):** I am Mike

Paranzino. I am here on behalf of Psoriasis Cure Now, a patient advocacy group. We have no financial conflict. We receive no pharmaceutical industry funding or funding from their trial lawyer opponents.

I am here to represent the 6 1/2 million Americans with psoriasis, more than a million of those who have psoriatic arthritis, and many of those psoriatic arthritis patients take NSAIDs and/or the COX-2s.

Our written statement is on the FDA website. It is available at psoriasiscurenow.org, and there are some copies in the press room. Our central point there was that absent a scientific consensus against these drugs, that they continue to be available so that patients can decide, with their physicians, if in their own particular set of circumstances, the benefits outweigh the possible risks.

But in the remaining time, I want to make a different point and I am amazed that in the last 50 years no one has made, and that is, that in some of the rhetoric surrounding some of the critics of FDA, some of the critics of the pharmaceutical industry, we are hearing even some buzz in Congress, that somehow the drug approval process is broken, and we think that is false.

Patients need expeditious approval of medications, and there are many still in clinical trials that need to get approved, and we are concerned that the FDA may become timid or gun-shy and flinch about approving those drugs that are coming down the pipeline that millions of Americans with disease desperately need.

Where it does appear--and I am just a lay guy, I am lay person, liberal arts guy--but where it does appear we need work is in postmarketing monitoring, post-FDA approval, that is where we need long-term monitoring.

We can't wait 20 years to get long-term studies before drugs are approved, but when that data does become available, it does appear that the ball is being dropped on a lot of sides in adding that information to the mix.

So, please, keep approving the drugs. We need new treatment options, and I thank you.

DR. WOOD: Thank you. The next speaker is Dr. Lawrence Goldkind.

**DR. LAWRENCE GOLDKIND (former Deputy Division Director, FDA Anti-Inflammatory and Analgesic Drug Products Section):** I would ask that I go over 20 or 30 seconds, I could use some of the time that some others didn't use. <DR. WOOD: No, you get two minutes. Good try.>

DR. GOLDKIND: That's the Chair's prerogative, I understand. <DR. WOOD: Good try.>

DR. GOLDKIND: From 2001 to 2003, I was the Deputy Division Director of the Anti-Inflammatory and Analgesic Drug Products Section at the FDA.

Over the past decade, there has been an evolution of what is considered feasible in the realm of clinical trials. Drugs, such as the statins, beta blockers, ACE inhibitors have been developed to reduce

mortality from cardiovascular disease. Demonstration of these benefits requires large and multi-year study.

Risk-benefit analyses are not so hard when there is superiority in an outcome of death, and placebo control, which is really add-on to standard care, is ethical and feasible.

What is unique about the COX-2 story is that the indication is pain relief, chronic in the case of arthritis, but the perceived value was a safety advantage compared to NSAIDs, which were known to have substantial risks that were reflected in the labeling.

In fact, everybody here knows that NSAIDs have been the poster child for problem drugs for over a decade. So, it seemed obvious that large outcome studies would adequately test the hypothesis of superiority of safety.

The concept of a large simple trial sounds simple, but, in fact, is not. We are now learning the limits of outcome studies. At the time that VIGOR and CLASS were done, they were the longest and largest trials by an order of magnitude of NSAIDs.

We can now say they were imperfect and lessons can be learned. One, therapeutic, super-therapeutic doses are not the best choice. They promote off-label usage, and you cannot extrapolate well back to the therapeutic dose levels.

Single comparator trials, when there are many standards of care available, likewise is hard to interpret and put into a context of therapies.

Allowing the duration and size to be driven by a single prespecified safety endpoint does not provide robust evidence necessarily of overall superiority, and yet it is impossible to power a study for unexpected or as yet uncharacterized safety problems. Even today, the term "cardiovascular outcome study" is bantered about as if it were cookbook simple. Well-known cardiologists have stated that the obvious population for study is the high risk patient--

DR. WOOD: Thank you very much. The next speaker is Louis Humphrey, No. 53. Is she here? No. Then, we will go through the ones that didn't respond to our call earlier. Rakesh Wahi, No. 2. Erika Umberger, No. 24. Gilbert Ross, No. 29. David Peterson, No. 41. Barrett Collins, No. 48. Cynthia Lee, No. 49. Robert Humphrey, No. 50. Lois Humphrey, No. 53. In the absence of them, we will take somebody off the wait list, who is Yvonne Shira. Is she here? Yes.

**DR. YVONNE SHIRA (practicing rheumatologist):** Hi. My name is Yvonne Shira. I am a practicing rheumatologist, and while I have worked with all of the companies mentioned here, and many others, doing clinical trials and as a consultant, I am here today representing myself. I paid for this trip myself.

I am representing my patients and I hope most of the rheumatologists who are seeing patients day by day.

I ask the committee to consider that quality of life issues are as important as length of issues to many of our patients. When Vioxx was removed from the

market, a number of my patients refused to discontinue the drug despite its risk, because they deemed the quality of life benefit to be greater than the risk.

One patient said to me regarding its removal, "Dr. Shira, they just don't understand how much we suffer."

So, I ask that you do not take away choices unless there is compelling evidence that the coxibs are substantially less safe than the available alternative NSAIDs.

The data you have presented so far does not suggest this, but that rather the traditional NSAIDs have not been sufficiently scrutinized in long-term trials.

Remember that real life data is more consequential than theories no matter how good they sound. Rheumatologists have always been aware of the cardiovascular effects of all NSAIDs. That is why most of us monitor patients at high risk by having them come back within a week or so for blood pressure monitoring.

The problem has been that we have accepted blood pressure increases that we thought were insufficient, that in light of new cardiovascular information, may actually have hit long-term consequences.

It is likely, I believe, that all NSAIDs have cardiovascular risk, but they have

not all been studied equally. Please don't away our patients' choices without compelling evidence that the alternatives are truly safer. Thank you.

DR. WOOD: Thanks very much. That was the last speaker in the public hearing. I am grateful to all of you for sharing your views with us. I am sure they will be helpful to the committee. We are going to go straight back to the program, and Dr. Villalba.

MS. MALONE: Excuse me, Dr. Wood.

DR. WOOD: Sure, yes.

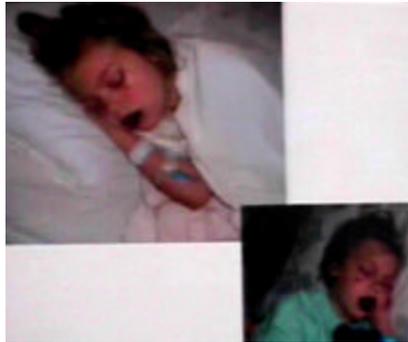
**MS. LEONA MALONE (committee patient representative):** I am Leona Malone.

I am the patient representative on the program. I just wanted to tell the people who did give testimony that--and this is not facetious at all--that I literally do feel your pain, and I think that everyone here is here because we are aware of the pain and the situation that you are in, and no one here is taking it lightly. I know how much trouble especially for the patients it was to get here, to sit here, to listen, and to get up to speak, and I applaud you for that. I just want you to be assured and to be confident that all of us here will take it seriously and give a voice to everything that you have said. Thank you.

DR. WOOD: Thank you, Leona. That was helpful.

# Presentation Slides

Note: Some of the slides presented may not be included below.



**COX-2 Inhibitors and iHAD™ Test**  
**BioJENC, LLC**  
 Presenter – Jennifer Lo, Ph.D.  
 CEO & President

Other Contributors: LA & Company Team  
 Fred Ehrlich, DVM, Ph.D.  
 Gene Luther, DVM, Ph.D.  
 Donald Luther

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 Fax: 225-675-3375  
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**iHAD™ Test Risk Assessment**

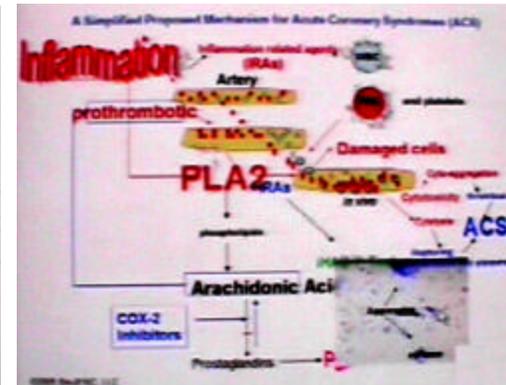
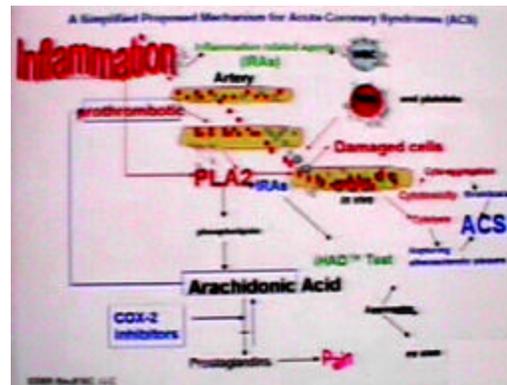
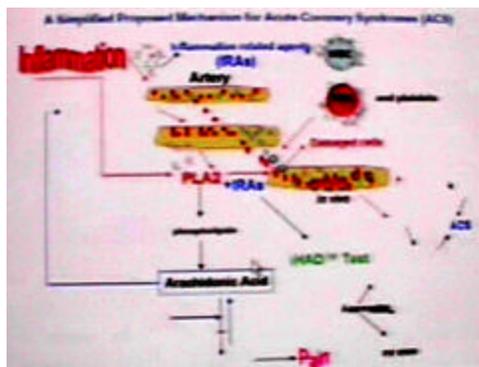
- Pathobiological effects in the form of cytotoxicity by inflammatory mediators/ inflammation related agents (IRAs).
- Cytotoxicity: 2 general categories- cytolysis and cyto-aggregation.
- The level of risk is determined by the severity of cytotoxicity.

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**Cytotoxicity: Cytolysis**

**Cytotoxicity: Cyto-Aggregation**

**Cytotoxicity: Cyto-Aggregation**





**8. Elizabeth Tindall, M.D.**  
President  
American College of Rheumatology



**12. Janet Arrowsmith-Lowe, M.D.**  
President  
Arrowsmith-Lowe Consulting, Inc.



**The Bigger Problem**  
We will never solve this problem without eliminating misleading and harmful animal testing of drug safety and efficacy



**The Wrong Scientific Evidence:  
Why Did Doctors Prescribe So Much Vioxx?**  
**John Abramson MD**  
Clinical Instructor Harvard Medical School  
Author "Overboard America"

**15. Herbert S. B. Baraf, M.D.**  
Clinical Professor of Medicine  
George Washington University  
Arthritis and Rheumatism Associates  
Wheaton, Rockville, Laurel and Chevy Chase, MD  
Washington, DC



**16. Max Hamburger, M.D.**



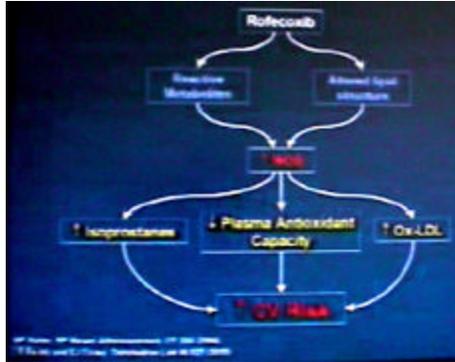
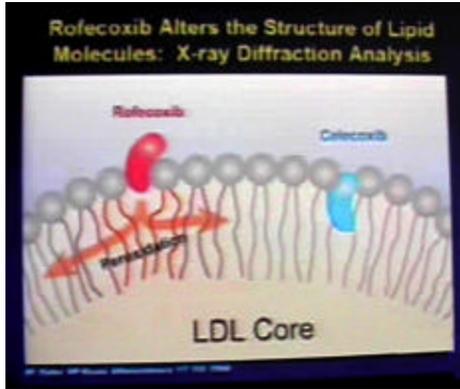
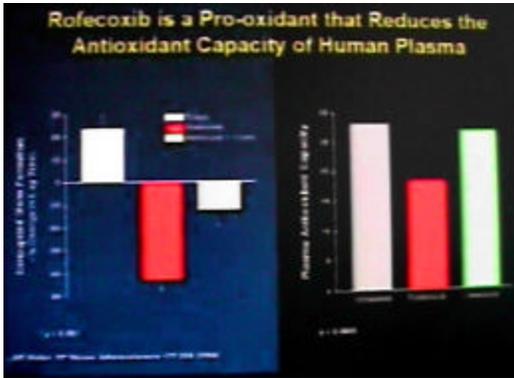
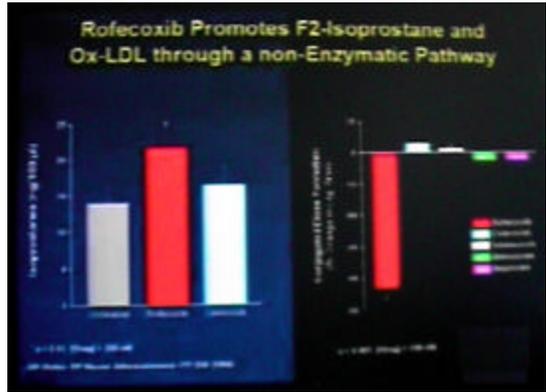
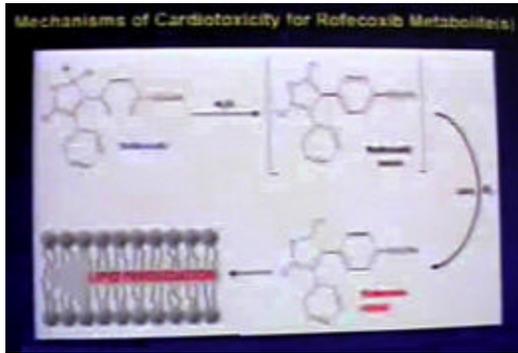
**Chronic NSAID Use: Small Bowel Injury**  
Wagdy Gurett, MD, FACP, FACC  
Associate Professor of Medicine  
Chief of Endoscopy  
Baylor College of Medicine/VAMC



**NSAIDs and the Small Intestine**  
The occasional finding of intestinal blood loss or anemia in the setting of normal upper and lower endoscopy led to the realization that:  
• NSAID-induced small intestinal ulceration and bleeding were clinically important

**A Controlled Study of NSAID-induced Small Bowel Injury Using VCE**  
**Methods:**  
• 41 ambulatory subjects (mean age = 49.5 y) with various types of arthritides (OA/RA/gout/non-specific) were enrolled  
• 21 subjects took NSAIDs daily (>3 mo duration)  
• 20 took acetaminophen alone or not





**30. Gurkirpal Singh, M.D.**  
 Adjunct Clinical Professor of Medicine  
 Division of Gastroenterology and Hepatology  
 Stanford University School of Medicine



**33. Necole Kelly**  
 President  
 American Chronic Pain Association

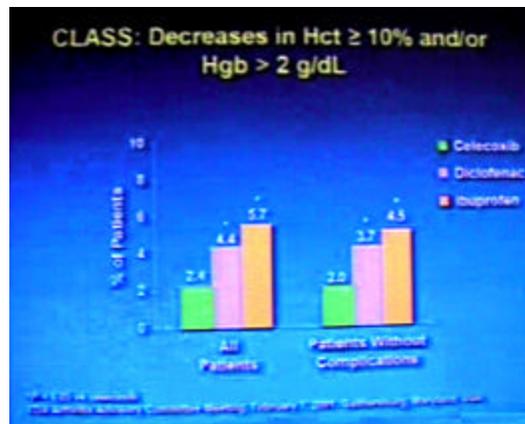
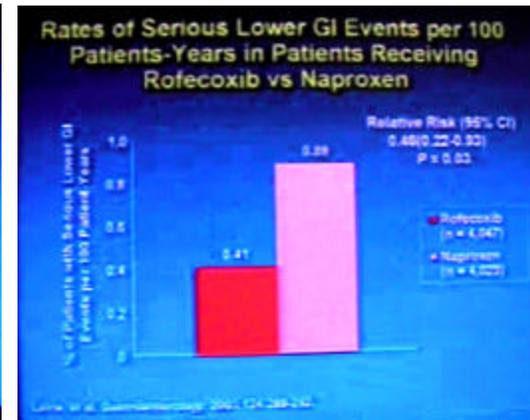
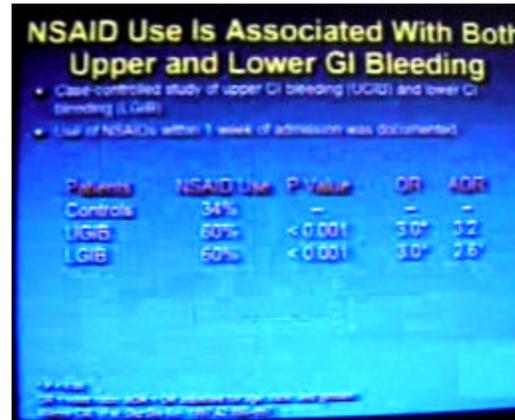


35. Robert Thibadeau, Ph.D.



### Small Bowel Toxicity of Nonselective NSAIDs Revealed by Capsule Endoscopy: Results From a Pivotal Clinical Trial

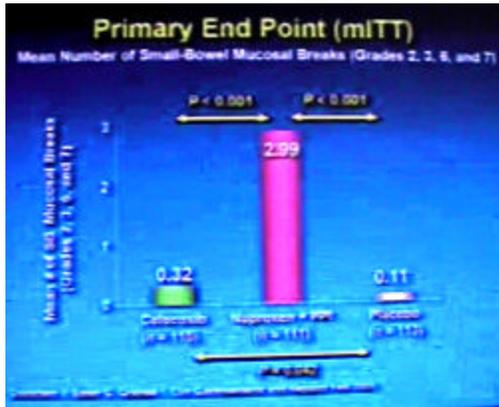
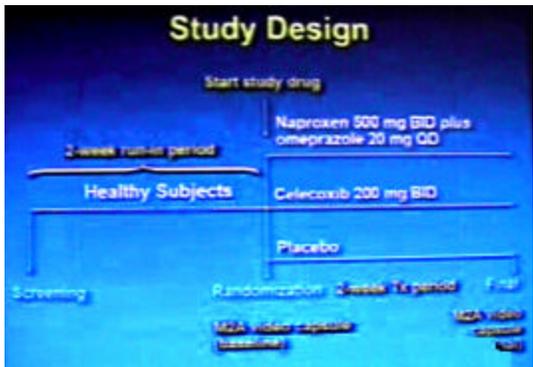
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#### Hypothesis

The combination of a non-specific NSAID + PPI will be associated with a rate of small bowel mucosal breaks that is significantly higher than the rate for placebo or for a COX-2 specific inhibitor





### Capsule Endoscopy Study

Secondary End Point (mITT)

Incidence of Small Bowel Mucosal Breaks

	Celecoxib (n=112)	Naproxen + omeprazole (n=111)	Placebo (n=112)	P value*
Incidence of mucosal breaks (n/10)	13 (16%)	41 (58%)	4 (7%)	< 0.001

\*Two-sided, two-tailed comparison to general population of the Crohn's Inflammation Study, unpublished data.

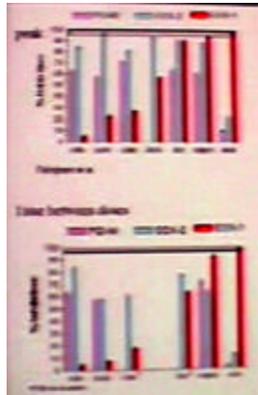
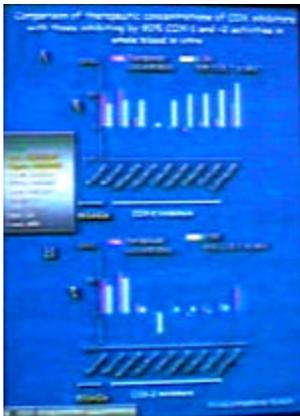
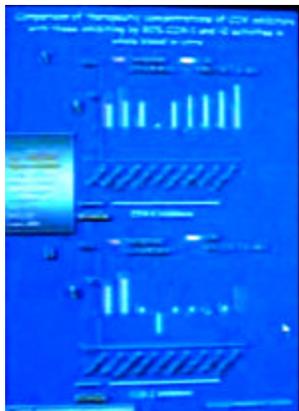
### Conclusions

- As in the upper GI tract, inhibition of COX-1 by naproxen and not celecoxib translates into significantly different rates of mucosal injury in the small bowel
- These findings extend the original COX-1 sparing hypothesis beyond the upper GI tract and into the small bowel

### Conclusions (2)

- Use of NS-NSAIDs can potentially lead to mucosal lesions, gastrointestinal bleeding beyond the ligament of Treitz
- PPI use does not protect against NSAID induced damage to the small/large intestine
- Capsule endoscopy provides a noninvasive assessment of the small bowel, which may be clinically useful in patients at risk for small bowel injury

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APHA's Vice President of Policy and Communications and Staff Counsel



40. Betsy Chaney



**42. Dr. John Klippel**  
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**44. Carol Spitz**



**45. Eileen Lacijan**

