

These summary minutes for the February 16, 17 and 18, 2005, Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on 3/7/05.

I certify that I attended the February 16, 17 and 18, 2005, Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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LCDR Dornette Spell-LeSane, MHA, NP-C  
Supervisory Health Science Administrator

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Alastair Wood, M.D.  
Chair

For, Kimberly Topper, M.S., Executive Secretary

Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee  
**February 16, 17, and 18, 2005**

The following is an internal report, which has not been reviewed. It is not meant to be a comprehensive review of the meeting. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cder05.html#ArthritisDrugs>. Slides shown at the meeting will be available at the same website.

All external requests for the meeting minutes and transcripts should be submitted to the CDER Freedom of Information office.

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Joint Meeting of The Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on February 16, 17 & 18, 2005, at the Hilton, located at 620 Perry Parkway, Gaithersburg, Maryland to discuss the overall benefit to risk considerations (including cardiovascular and gastrointestinal safety concerns) for COX-2 selective nonsteroidal anti-inflammatory drugs and related agents. The meeting was chaired by Alastair J.J. Wood, M.D.

**Arthritis Advisory Committee Members Present (voting):**

Joan Bathon, M.D., Dennis Boulware, M.D., John J. Cush, M.D., Michael Finley, D.O., Allan Gibofsky, M.D., Gary Hoffman, M.D., Norman Ilowite, M.D., Susan Manzi, M. M.D., M.P.H.

**Drug Safety and Risk Management Advisory Committee Members Present (voting):**

Stephanie Y. Crawford, Ph.D., Ruth S. Day, Ph.D., Curt D. Furberg, M.D., Ph.D., Jacqueline S. Gardner, Ph.D., MPH, Peter A. Gross, M.D., Eric S. Holmboe, M.D., Arthur A. Levin, M.P.H., Louis A. Morris, Ph.D., Richard Platt, M.D., M.Sc., Robyn S. Shapiro, J.D., Annette Stemhagen, Dr.Ph

**SGE Consultants (voting):**

Alastair J.J. Wood, M.D., Steve Abramson, M.D., Steven L. Shafer, M.D., Robert H. Dworkin, Ph.D., Steven Nissen, M.D., Charles H. Hennekens, M.D., Emile Paganini, M.D., Leona Malone, L.C.S.W., (Patient Rep) , Thomas Fleming, Ph.D., John T. Farrar, M.D., Janet Elashoff, Ph.D., Ralph D'Agostino, Ph.D.

**SGE Consultants (non voting):**

Cryer, Byron, M.D., (Speaker and Discussant) Packer, Milton M.D., (Speaker only)

**National Institute of Health Participants (voting):**

Richard O. Cannon III, M.D., Michael J. Domanski, M.D., Lawrence Friedman, M.D.

**FDA Invited Guest Speakers (non-voting):**

Garret A. FitzGerald, M.D., Ernest Hawk, M.D., M.P.H., Constantine Lyketsos, M.D., M.H.S., Bernard Levin, M.D.

**FDA Participants at the Table:**

Jonca Bull, M.D., Brian Harvey, M.D., John Jenkins, M.D., Sandra Kweder, M.D., Robert O'Neil, Ph.D., Paul Seligman, M.D., Steve Galson, M.D., Robert Temple, M.D., Anne Trontell, M.D., M.P.H.

**FDA Presentors:**

David Graham, M.D., M.P.H., Sharon Hertz, M.D., Joel Schiffenbauer, M.D., Lourdes Villalba, M.D., James Witter, M.D.

**Open Public Hearing Speakers:**

**Joan Brierton Johnson and Sabrina**

**Sidney M. Wolfe, MD**

Director, Public Citizen's Health Research Group

**Linda Suydam**

Vice President, Regulatory and Scientific Affairs, Consumer Healthcare Products Association - CHPA

**Jennifer Lo, Ph.D. and**

CEO & President, BioJENC, LLC, Louisiana Business & Technology Center

**Gene Luther, D.V.M., Ph.D.**

**Jim Tozzi**

Member, Board of Advisors, Center for Regulatory Effectiveness

**Diana Zuckerman, Ph.D.**

President, National Research Center for Women & Families

**Elizabeth Tindall, MD**

President, American College of Rheumatology

**Dimitra Poulos**

**John Pippin, M.D.**

Physicians Committee for Responsible Medicine

**MAJ Christopher Grubb, M.D.**

Womack Army Medical Center, Department of Anesthesiology and Pain Management

**Janet Arrowsmith-Lowe, MD**

President, Arrowsmith-Lowe Consulting, Inc.

**Mark H. Einstein, M.D.**

Assistant Professor, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health Montefiore Medical Center

**John Abramson M.D.**

Harvard Medical School

**Herbert S. B. Baraf, MD, FACP, FACR**

Clinical Professor of Medicine, George Washington University

**Max Hamburger MD**

**Waqar Qureshi, MD, FACP, FACG**

Associate Professor of Medicine, Chief of Endoscopy, Baylor College of Medicine

**David P. Matthews**

**W. Hayes Wilson, MD**

Chief of Rheumatology, Piedmont Hospital  
President, Piedmont Rheumatology Consultants, PC

**Gary W. Williams, M.D., Ph.D.**

Chairman, Department of Medicine and Vice President of Medicine Services, at Scripps Clinic and Research Foundation

**Rebecca Burkholder**

Director of Health Policy, National Consumers League

**Amye L. Leong, MBA**

President & CEO, Healthy Motivation, Spokesperson, UN-endorsed Bone and Joint decade 2000-2010

**Donna Marie Fox- Keidel**

**Theresa Ray**

**Judith Whitmire**

**Judy Fogel**

Brigham & Women's Hospital, Harvard Medical School

**R. Preston Mason, Ph.D.**

Brigham & Women's Hospital, Harvard Medical School

**Gurkirpal Singh, MD**

Adjunct Clinical Professor of Medicine  
Division of Gastroenterology and Hepatology  
Stanford University School of Medicine

**Dr. Allan N. Fields**

**Grant Johnson**

**Necole Kelly**

President, American Chronic Pain Association

**Robert Thibadeau, Ph.D.**

**Lawrence Goldkind MD**

Assistant Professor of Medicine, Department of  
Gastroenterology, Uniformed Services University of Health  
Sciences

**Susan Winckler, RPh, Esq.,**

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

**Virginia Ladd**

President American Autoimmune Related Diseases Association  
(AARDA)

**Paola Patrignani, Ph.D.**

Professor of Pharmacology, Department of Medicine and Center  
of Excellence on Aging, "G. d'Annunzio" University

**Betsy Chaney**

**Dr. John Klippel**

President and CEO of the Arthritis Foundation

**Carol Spitz**

**Eileen Lacijan**

**Gloria Barthelmes**

**Rebecca Dachman**

**Michael D. Paranzino**

President, *Psoriasis Cure Now!*

**Dr. Glenn Eisen**

Oregon Health Sciences University

**Yvonne Sherrer, M.D.**

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**The members and the invited consultants were provided with the background material from the FDA, Merck, Pfizer, Novartis, Hoffmann-La Roche Inc., and Bayer Healthcare LLC, Consumer Care Division prior to the meeting.**

**The meeting was called to order at 8:00 a.m. each day by Alastair Wood, M.D. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record each day by the Executive Secretary, Kimberly Littleton Topper, M.S. There were approximately 600 people in attendance. The agenda proceeded as follows:**

**Wednesday, February 16, 2005**

Call to Order	Alastair J. J. Wood, M.D., Chair
Conflict of Interest Statement	Kimberly Littleton Topper, M.S. Executive Secretary
Welcome	Steven Galson, M.D., M.P.H. Acting Director, Center for Drug Evaluation and Research (CDER)
Regulatory History	Jonca Bull, M.D. Director, Office of Drug Evaluation V, CDER
Gastrointestinal Effects of NSAIDs and COX-2 Specific Inhibitors	Byron Cryer, M.D. University of Texas Southwestern Medical School
Mechanism Based Adverse Cardiovascular Events and Specific Inhibitors of COX-2	Garret A. FitzGerald, M.D. University of Pennsylvania School of Medicine
Committee Questions to Speakers	
Break	
<b><u>Vioxx (rofecoxib)</u></b> <b><u>Sponsor Presentation:</u></b> Rofecoxib	Ned S. Braunstein, M.D. Senior Director Merck Research Laboratories
<b><u>FDA Presentation:</u></b> Vioxx Cardiovascular Safety	Lourdes Villalba, M.D. Medical Officer, CDER
Committee Questions to Speakers	
Lunch	

**Celebrex (celecoxib)**

**Sponsor Presentation:**

Introduction

Joseph M. Feczko, M.D.  
Senior Vice President,  
Pfizer Global Research and Development,  
and President, Worldwide Development

**Wednesday, February 16, 2005 (cont.)**

Cardiovascular Safety and  
Risk/Benefit Assessment of Celecoxib

Kenneth M. Verburg, Ph.D.  
Vice President, Inflammation and  
Immunology, Clinical Research and  
Development, Pfizer Global Research and  
Development

**FDA Presentation:**

COX-2 CV Safety: celecoxib

James Witter, M.D., Ph.D.  
Lead Medical Officer, CDER

**NIH and Investigator Presentation:**

Celecoxib in Adenoma Prevention Trials:  
The APC Trial  
(Prevention of Sporadic Colorectal  
Adenomas with Celecoxib)

Ernest Hawk, M.D., MPH  
Director, Office of Centers,  
Training, & Resources  
NCI/OD/NIH

The PreSAP Trial  
(Prevention of Colorectal Sporadic  
Adenomatous Polyps)

Bernard Levin, M.D.  
M.D. Anderson Cancer Center  
The University of Texas

Committee Questions to Speakers

Break

**Bextra (valdecoxib) and parecoxib**

**Sponsor Presentation:**

Cardiovascular Safety and Risk/Benefit  
Assessment of Valdecoxib and Parecoxib

Kenneth M. Verburg, Ph.D.

Closing

Joseph M. Feczko, M.D.

**FDA Presentation:**

COX-2 CV Safety: valdecoxib – parecoxib

James Witter, M.D., Ph.D.

**Naproxen**

**Sponsor Presentation:**

Bayer and Roche Joint Presentation on Naproxen

Leonard M. Baum, R.Ph.  
Vice President, Regulatory Affairs  
Bayer HealthCare  
Consumer Care Division

Martin H. Huber, M.D.  
Vice President, Global Head  
Drug Safety Risk Management,  
Hoffmann-La Roche, Inc.

Committee Questions to Speakers

**Thursday, February 17, 2005**

Call to Order  
Conflict of Interest Statement

Alastair J. J. Wood, M.D., Chair  
Kimberly Littleton Topper, M.S.

Interpretation of Observational Studies of  
Cardiovascular Risk of Non-steroidal Drugs

Richard Platt, M.D., M.S.  
Harvard Medical School

Review of Epidemiologic Studies on  
Cardiovascular Risk with Selected NSAIDs

David Graham, M.D., M.P.H.  
Medical Officer, CDER

Committee Questions to Speakers

**Arcoxia (etoricoxib)**  
**Sponsor Presentation:**  
Etoricoxib

Sean P. Curtis, M.D.  
Senior Director, Clinical Research  
Merck Research Laboratories

**FDA Presentation:**  
Analysis of Cardiovascular Thromboembolic  
Events With Etoricoxib

Joel Schiffenbauer, M.D.  
Medical Officer, CDER

Break

**Lumiracoxib**  
**Sponsor Presentation:**  
Lumiracoxib: Introduction

Mathias Hukkelhoven, Ph.D.  
Senior Vice President and Global Head,  
Drug Regulatory Affairs  
Novartis Pharmaceuticals Corporation

Gastrointestinal and Cardiovascular Safety  
of Lumiracoxib, Ibuprofen, and Naproxen

Patrice Matchaba, M.D.  
Global Medical Director  
Lumiracoxib Program, Novartis  
Pharmaceuticals Corporation

**FDA Presentation:**  
Lumiracoxib

Lourdes Villalba, M.D.  
Medical Officer, CDER

Committee Questions to Speakers

Lunch

Open Public Hearing

Break

Committee Discussion

**Friday, February 18, 2005**

Call to Order  
Conflict of Interest Statement

Alastair J. J. Wood, M.D., Chair  
Kimberly Littleton Topper, M.S.

**Naproxen**

**Investigator Presentation:**

Alzheimer's Prevention Study: ADAPT  
(Alzheimer's Disease Anti-Inflammatory  
Prevention Trial)

Constantine Lyketsos, M.D.  
The John Hopkins Hospital

**Additional Background Presentations**

Interpretation of Observed Differences  
in the Frequency of Events When the  
Number of Events is Small

Milton Packer, M.D.  
University of Texas  
Southwestern Medical School

Committee Questions to Speakers

Clinical Trial Design and Patient Safety:  
Future Directions for COX-2 selective NSAIDs

Robert Temple, M.D.  
Director, Office of Medical  
Policy, CDER

Issues in Projecting Increased Risk of  
Cardiovascular Events to the Exposed Population

Robert O'Neill, Ph.D.  
Director, Office of Biostatistics, CDER

Committee Questions to Speakers

Break

Risk Management Options for Action  
*(added to agenda on 2/18/05)*

Anne Trontell, M.D., M.P.H.  
Deputy Director, Office of Drug Safety

Summary of Meeting Presentations

Sharon Hertz, M.D.  
Deputy Director, Division of  
Anti-Inflammatory, Analgesic and  
Ophthalmologic Drug Products, CDER

Advisory Committee Discussion of Questions

Lunch

Advisory Committee Discussion of Questions

Break

Advisory Committee Discussion of Questions

Meeting Wrap-up

Alastair J. J. Wood, M.D.

Adjourn



**Thursday, February 17, 2005:**

Discussion Points:

1. Please discuss the available data regarding the potential cardiovascular (CV) risk for the non-selective and COX-2 selective NSAIDs. Please discuss whether the available data support a conclusion that increased CV risk is a class effect for all NSAIDs, the COX-2 selective NSAIDs only, or only for certain agents within the class. Also, please discuss the possible mechanism(s) of action for an increased cardiovascular risk with these agents.

***The Committee shared various opinions with the members agreeing, in general, that there was inadequate data to draw a definite conclusion regarding whether a class effect exists. However, that being said, they agreed that it did appear likely that for at least the three approved COX-2 products, a class effect appears to be present. They further indicated that they believed that if sufficient drug was given in high enough doses to high risk patients an increase incidence of cardiovascular events would be yielded. There is a dearth of data on the other NSAIDs and the consensus of the Committee was that each drug should be individually evaluated for CV risk. It is unknown whether a CV signal is present across all the products, with possible different mechanisms of action, but each is suspect when used chronically and until proven otherwise, patients/physicians should be warned.***

2. Please discuss the contributions and limitations of the currently available observational studies to the assessment of CV risk for the non-selective and COX-2 selective NSAIDs. In particular, please discuss the role of such observational studies in informing regulatory decisions about post-marketing safety issues.

***While the Committee stated various opinions, most agreed that observational studies do provide useful, although limited, information. In general, observational studies are supplementary to randomized, controlled, clinical trials (RCT) since selection bias is likely present. Additional comments provided by the committee were:***

- **Observational studies are supplementary to Randomized Control Trials (RCT)**
- **With COX-2 products, there is good correlation between observational and RCT trials**
- **Long term follow up after drop out from RCT is necessary**
- **More observational studies on older drugs are needed**
- **FDA review of observational studies does not follow the same process standards used by FDA in reviewing RCTs**
- **Observational studies are most helpful if they find a strong and consistent association across studies, with a hazard ratio greater than 2 or 3; Observational studies with hazard ratios under 2, even if statistically significant, are difficult to interpret since low but precise estimates of risk may be due to residual confounding or biases**
- **Observational studies can be classified as “hypothesis generating”; they provide clues as to whether and if to conduct RCTs but observational studies do not establish causality**

3. Please discuss the available data regarding the potential benefits of COX-2 selective NSAIDs versus non-selective NSAIDs and how any such benefits should be weighed in assessing the potential benefits versus the potential risks of COX-2 selective agents from a regulatory perspective.

***Overall the committee felt that the GI benefits should not be minimized, however, the GI benefits of the COX-2s appear to be less than first reported. Vioxx is the only product with GI benefit in labeling; no clear data that show GI benefit for Celebrex and Bextra. Although not a benign event, a GI event is in most cases not as permanently disabling as a myocardial infarction or a stroke. The Committee members offered the following additional considerations for weighing benefit versus risk:***

- ***Benefit versus risk in patients who do not tolerate nonselective NSAIDs should be considered***
- ***Pain relief should be considered***
- ***If no clear benefit, there should be an extremely low threshold for increased CV risk***
- ***Pediatric issues should be considered; there are fewer choices in this population and only 3 NSAIDs are approved for use in pediatric population, only 2 liquid formulations***
- ***Tolerability - fewer serious GI events, but a lot of symptoms should be considered***

**Friday, February 18, 2005**

Questions to the Committee

**Approved products**

Three COX-2 selective NSAIDs are currently approved for marketing in the United States; celecoxib (Celebrex), rofecoxib (Vioxx) and valdecoxib (Bextra). The original approvals and subsequent supplemental approvals were based on a determination by FDA that the potential benefits of each product outweighed the potential risks when used for the approved indications according to the directions included in the product labeling. Since approval, additional data regarding the safety and effectiveness of these products have accumulated, in particular new information regarding the potential cardiovascular risks of these products. FDA must consider the impact of these new data on the benefit versus risk profile for each product in making decisions about appropriate regulatory actions.

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

Based on the data presented in the background package and during the committee meeting, please address the following questions regarding the approved COX-2 selective NSAIDs.

1. Celecoxib
  - a. Do the available data support a conclusion that celecoxib significantly increases the risk of cardiovascular events?

**Yes- 32**

**No- 0**

**Abstain - 0**

b. Does the overall risk versus benefit profile for celecoxib support marketing in the US?

**Yes - 31**

**No - 1**

**Abstain - 0**

c. If yes, please describe the patient population(s) in which the potential benefits of celecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use of celecoxib.

- ***The Committee agreed that osteoarthritis and rheumatoid arthritis patients, in addition to patients being treated for pain were populations where the benefits of celecoxib could outweigh potential risks. They agreed that there appeared to be no evidence of CV risk at the 200 mg dose and marginally positive evidence at the 400 mg dose. No signal was seen in the epidemiologic studies. With regard to the colon polyp study, 400 and 800 mg doses were studied. An excess CV risk would likely be seen with the 800 mg dose, probable at the 400 mg dose and possibly no evidence with the 200 mg dose.***

***The following were suggested as potential actions for the FDA to take:***

- ***Black Box Warning (BBW) (24)***
- ***Remove BBW if clinical trial results demonstrate safety (4)***
- ***Restrict Direct to Consumer Advertising (22)***
- ***Provide both known and unknown information to patients and health practitioners (22)***
- ***Develop Patient Guide or Med-guides (25)***
- ***Provide Dear Health Care Provider Letter (2)***
- ***Restrict patient population (7)***
- ***Restrict dose (5)***

2. Valdecoxib

a. Do the available data support a conclusion that valdecoxib significantly increases the risk of cardiovascular events?

**Yes - 32**

**No – 0**

**Abstain - 0**

b. Does the overall risk versus benefit profile for valdecoxib support marketing in the US?

**Yes - 17**

**No - 13**

**Abstain - 2**

c. If yes, please describe the patient population(s) in which the potential benefits of valdecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use of valdecoxib.

***In general, the Committee felt that the evidence was very limited and it is difficult to extrapolate to a real life setting.***

***The following were suggested as potential actions for the FDA to take.***

- ***Black Box Warning (22)***
- ***Remove BBW if clinical trial results demonstrate safety (2)***
- ***Restrict Direct to Consumer Advertising (19)***
- ***Provide known and unknown information to patients and health practitioners (19)***
- ***Develop Patient Guide or Medguide (17)***
- ***Dear Health Care Provider Letter (2)***
- ***Restrict population (6)***
- ***Restrict dose (3)***
- ***Restrict duration (6)***
- ***Contraindications in the post CABG setting***

3. Rofecoxib

- a. Do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events?

**Yes - 32**

**No - 0**

**Abstain - 0**

- b. Does the overall risk versus benefit profile for rofecoxib support marketing in the US?

**Yes - 17**

**No - 15**

**Abstain - 0**

***The Committee had the following comments:***

- ***The blood pressure effects seen with the product are clearly outside the norm and are undesirable; a mechanism other than a prostacyclin mechanism could be at play since the other COX-2s do not appear to have such a large blood pressure effect***
- ***A signal for heart failure is present and the other NSAIDs have not exhibited this same signal***
- ***The blood pressure and the heart failure data is compelling indicating it is substantially worse than other COX-2s***
- ***A strong dose relationship is very apparent***
- ***Rofecoxib is the only COX-2 selective product approved for pediatric patients however, there are minimal data to support safe long-term use in pediatrics***

- c. If yes, please describe the patient population(s) in which the potential benefits of rofecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use of rofecoxib.

***The following were suggested as potential actions for the FDA to take:***

- ***Black Box Warning***
- ***Remove BBW only if future clinical trial results demonstrate safety***
- ***Restrict Direct to Consumer Advertising (DTC)***
- ***Provide known and unknown information to patients and health practitioners***
- ***Patient Guide or Med-Guides Development***
- ***Dear Health Care Provider Letter***

- **Require strong Post Marketing follow-up**
- **Restrict dose to 12.5 mg, 25 mg and remove 50 mg from the market**
- **Require informed consent**
- **Provide patient reminders about risk 1 year after starting the drug**
- **Require clinical trial using 12.5 mg. dose**
- **Consider restricted access to the drug**
- **Be aware that the pediatric patient could increase their risk of CV events earlier - but keep for use in pediatric patients because pain is not always adequately controlled**
- **Institute a patient registry**
- **Restrict patient population**

4. If the available data support a conclusion that one or more COX-2 selective agents increase the risk of cardiovascular events, please comment on the role, if any, of concomitant use of low-dose aspirin in reducing cardiovascular risk in patients treated with COX-2 selective NSAIDs.

**No vote was offered for this question; some of the Committee comments were as follows:**

- **There is insufficient evidence to make a conclusion**
- **There is no compelling evidence that concomitant low dose aspirin is effective in preventing CV disease when used in “normals”**
- **Must be careful - ASA is not a panacea for CV disease**
- **There is no compelling evidence that ASA will reverse CV toxicity based on available studies, but data is limited**
- **Aspirin appears to “undo” any possible GI benefit of the COX-2s**
- **If ASA is needed for CV prophylaxis, then patients should not be on a COX-2 inhibitor**

5. What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential cardiovascular risk of celecoxib, rofecoxib, and valdecoxib? What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential benefits (e.g., reduced gastrointestinal risk) of celecoxib, rofecoxib, and valdecoxib? Please be specific with regard to which COX-2 selective agent to study, trial design, patient populations, control groups, endpoints, duration, sample size, etc.

**No vote was offered for this question; some of the Committee comments were as follows:**

- **Across all products and to rule out the risk of excess cardiovascular events, additional randomized clinical trials (RCT) should be conducted at doses to be marketed; blood pressure measurements should be included in these trials**
- **Comparator drug used in the trials should not be limited to naproxen; placebo as the comparator should be used in trials designed to determine the absolute risk of CV events**
- **Choice of comparator would also depend on the population/indication being studied; for example, arthritis trials would not utilize placebo, however pain trials might**
- **Follow-up of all patients is critical - especially the RCT drop out patients**
- **It is important that we not ignore the need for additional safety trials with the nonselective NSAIDs**

There are more than 20 non-selective NSAIDs currently approved for marketing in the United States. Unlike the situation with the COX-2 selective agents, large, long-term, placebo-controlled clinical trials have not been conducted to evaluate long-term risks, including cardiovascular risks. Based on the data presented in the background package and during the committee meeting, please address the following questions regarding the approved non-selective NSAIDs:

6. Do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical trial data to assess the potential cardiovascular effects of these drugs? If so, please describe how you recommend that information be conveyed (e.g., warning, precaution).

**Yes - 28**

**No – 0**

**Abstain - 0**

***(The following members were not present and therefore did not offer a vote for question 6: Paganini, Shapiro, Gibofsky, Hoffman)***

***Committee comments included:***

- ***Taking a blanket approach with these drugs is not recommended***
  - ***Providing observational data is important with the absence of clinical trial data***
  - ***Provide all data so both patients and prescribers are informed on our knowledge level on these drugs***
  - ***Although it appears that the CV risk applies to the class as a whole, any BBW should be modified to reflect what we know about each individual product***
  - ***Rather than a BBW, some suggest that text be added to the warning section of the label while additional data is collected***
  - ***Concern was raised that a BBW may shift patients to meloxicam or other products with even less available risk data; there is no assurance that these products don't have the same risks***
  - ***Some indicated that they felt that the available data on naproxen would justify a decreased warning requirement***
  - ***It was stated that based on the committee discussions at the AC meeting, a shift in prescribing practice could occur. It is important to send the message that the current state of information is insufficient to state that any of the products are absolutely safe.***
  - ***It is important to require that sponsor marketing materials provide the information that is known about their products while at the same time providing adequate information as to what is as of yet unknown about product risk (describe the absence of data)***
  - ***The committee advised that caution be used such that revisions regarding long-term use risks to the OTC product labeling does not cause "hysteria"***
7. What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential cardiovascular risk of the non-selective NSAIDs? Please be specific with regard to which non-selective NSAIDs (i.e., all or only selected agents), trial design, patient populations, control groups, endpoints, duration, sample size, study drug etc.

**The Committee comments included:**

- **Randomized Clinical Trials (RCTs) are likely impossible for these products; as an alternative, it was suggested that sponsors conduct large scale, cluster, randomized trials; Randomization to drug would be an important feature to include**
- **The committee suggested that sponsor incentives could be proposed; These might include deletion of a BBW or warning text should a sponsor design and complete adequate trials.**
- **The committee agreed that in the absence of “good” safety data, no additional NSAIDs be switched to OTC status**

**Standards for approval of new NSAIDs (non-selective and COX-2 selective agents)**

The information that has accumulated about the safety and effectiveness of COX-2 selective NSAIDs since their approval, including the potential for increased cardiovascular risk, must be considered as FDA determines the standards for data to be submitted in support of approval of new non-selective and COX-2 selective NSAIDs. In addition, the experience with the approved COX-2 selective agents will help inform benefit versus risk assessments that will need to be made by FDA in evaluating pending and future applications for new NSAIDs.

Based on the data presented in the background package and during the committee meeting, please address the following questions regarding the approval of new non-selective and COX-2 selective NSAIDs.

8. With regard to evaluation of cardiovascular risk, what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? With regard to the evaluation of the potential benefits (e.g., reduced gastrointestinal risk), what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? Please be specific with regard to trial design, patient population, control groups, endpoints, duration, sample size, safety monitoring and patient protections, etc.
  - **It is important to be practical for new drugs to enter the market and they must undertake an APPROVE type of trial in low risk populations and in the active control group - trials must be 1-2 years in length**
  - **The Committee recommended that future studies include primarily naproxen as a comparator. Ibuprofen and diclofenac should also be studied as comparators for different purposes, ibuprofen as a typical NSAID while diclofenac may be a model of a relatively selective traditional NSAID.**
  - **Need a neutral or better than neutral, upper confidence boundary against naproxen; the standard/bar needs to be high enough in order to protect the public**
  - **Suggested populations likely to use the products include those that are older and with a mild CV risk**
  - **Regarding GI benefit, it would be appropriate to compare new products versus naproxen or another NSAID combined with a PPI**
  - **The Committee cautioned that recommendations must be practical; trials such as the APPROVe and CABG 2 studies should be conducted in indications sought for marketing, i.e., OA, RA, and low risk individuals (not high risk individuals). The duration of the trials should preferably run two years and include an active control.**

9. If the pre-approval studies recommended as essential in question 8 do not demonstrate an increased risk of cardiovascular events for a new NSAID, please comment on how FDA should handle the issue of cardiovascular risk in labeling. For example, would the absence of a cardiovascular risk signal in the pre-approval database preclude the need for any warnings or precautions in the labeling for the new product? Alternatively, should all future NSAIDs carry a “class” warning or precaution about cardiovascular risk even in the absence of a signal of increased risk in the pre-approval database? If yes, please describe your recommendations for the “class” labeling regarding cardiovascular risk with particular attention to whether you recommend it apply to all NSAIDs or only COX-2 selective NSAIDs.

***No vote was offered for this question; The Committee made the following comments:***

- ***The absence of establishing an increase risk is not the same as no increase; evidence sufficiently powered and controlled to rule out an increase in incidence is needed***
- ***The Committee consensus was that for new products, the standard for demonstrating safety should be higher***

The meeting was adjourned at 5:15 p.m.