Summary Minutes of the Arthritis Drugs Advisory Committee
November 29, 2006:

The summary minutes for the November 29, 2006 meeting of the Arthritis Drugs Advisory Committee were approved on January 5, 2006.

I certify that I attended the November 29, 2006 meeting of the Arthritis Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/	/s/
Johanna Clifford, M.Sc., RN Executive Secretary, ODAC	Joan Bathon, M.D., Acting Chair, AAC

The meeting of the Arthritis Advisory Committee was held on November 29, 2006 in the Ballrooms of the Gaithersuburg Hilton, 620 Perry Parkway, Gaithersburg, MD. Approximately 150 people were in attendance. The meeting was chaired by Joan Bathon, M.D.

The committee met to discuss new drug application (NDA) 20-998/S021, CELEBREX (celecoxib), Pfizer, Inc., for the proposed indication of the relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older.

Attendance:
Arthritis Advisory Committee Members Present (voting):
Joan Bathon, M.D. (Chair), Dennis Boulware, M.D., John Davis, M.D. , Dennis Turk, Ph.D. (by phone).

Arthritis Advisory Committee Consultants (voting):
Joan Chesney, M.D., Robert Daum, M.D., Deborah Dokken (patient representative), Richard Gorman, Eric Holmboe, M.D., Thomas Lehman, M.D., Arthur Levin, MPH, Louis Morris, Ph.D., Kathleen O'Neil, Michael Proschan, Ph.D., Kathy Weise, M.D.

Industry Representative (non-voting):
Charles McLeskey, M.D.

Arthritis Advisory Committee Members Absent:
Allen Gibofksy, M.D., J.D., Kenneth Saag, M.D., Sherine Gabriel, M.D., M.Sc., Steven Geis, Ph.D. (Industry Representative)

FDA Participants:
Robert Myers, M.D., Bob Rappaport, M.D., Sharon Hertz, M.D., Jeffrey Siegel, M.D., Carolyn Yancey, M.D.

Open Public Hearing Participants:
Vincent Del Gaizo
Kathy and Lacey Whatley
Earl Brewer, M.D.
Balu Athreya, M.D., American Academy of Pediatrics and American College of Rheumatology
Gloria Higgins, M.D., Columbus Children's Hospital
Patience White, M.D., M.A., Arthritis Foundation
Brandt Groh, M.D., Penn State Children's Hospital
Kathleen Haines, M.D., Joseph M. Sanzari Children's Hospital
Harry Gewanter, M.D. on behalf of the American Academy of Pediatrics

The agenda proceeded as follows:

Opening Comments	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia and Rheumatology Drug Products, CDER, FDA
<u>FDA Presentation</u>	
Introduction of Juvenile Rhematoid Arthritis & State of the Art Treatment Armamentarium	Carolyn Yancey, M.D., Medical Officer DAARP, CDER, FDA

Overview: Non-Steroidal Anti-Inflammatory Drugs and COX-2 Selective Inhibitors	Sharon Hertz, M.D., Deputy Director DAARP, CDER, FDA
Sponsor Presentation Juvenile Rheumatoid Arthritis: Clinical Overview	**Pfizer, Inc.** Daniel J. Lovell, M.D., MPH Cincinnati Children's Hospital Medical Center
Celecoxib in the Treatment of Juvenile Rheumatoid Arthritis	Simon Lowery, M.D. Pfizer, Inc.
Risk/Benefit Profile of Celbrex for Use in JRA	Jeffrey Siegel, M.D., Medical Team Leader DAARP, CDER, FDA

Questions from the Committee

Open Public Hearing

Questions to the Committee

Discussion Points:

1. Discuss the need for new therapies in children with juvenile rheumatoid arthritis (JRA), including therapies such as celecoxib.

The commmittee agreed that there is a need for new drugs in thi s patient popuulation related to new therapies related to JRA to include:

- *That having additional options for children with JRA would be beneficial and that variability for children who don't respond to other therapies is a priority.*
- *There are cetain defined settings in which COX-2's would be of benefit, such as a perioperative setting.*
- *The Pediatric Rheumatology experts were impressed with the dosing flexibility that celebrex offers. Proposing a twice daily dosing could potentially enhancing compliance with medications.*
- *The dosing formulation is attractive and patient friendly as a sprinkle formulation, but recommended that a suspension be offered if possible.*
- *Providing an alternative to patients that decreases bleeding, GI Toxicity and bruisingis an attractive options to prescribers as well as patients.*
- *By increasing the alternatives in the treatment armamentarium for JRA, there is a potential of postponing the use of other therapies, such as DMARDS.*

2. Discuss the safety of celecoxib when used in children with JRA based on the data derived from the pediatric studies, the known risks, including cardiovascular risks, in adults and the risks of alternative therapies.

In reviewing the toxicity profile associated with this class of drugs, the committee voiced concerns with Celebrex and it's potential for adverse cardiovascular and thromboembolic events. The committee suggested that further studies be conducted to evaluate potential risks with cardiac and GI toxicities going beyond the 3 month period using tests to determine effects on cardiovascular and renal function as well as conducting imaging studies and BP monitoring to examine surrogate markers for cardiovascular disease in the JRA population.

The committee discussed labelling restrictions noting the safety of the product, suggesting language to include that the product is safe and effective for short durations, but that the study conducted did not show data to support use beyond a certain point.

In the absence of long term safety data, the committee was very supportive of a registry to fully evaluate the risks and benefits of the product and its proposed indication for an extended length of time like 10 or 20 years. They further supported that a mechanism be proposed in which a government institution, such as the NIH, be financially responsible the registry.

MEETING QUESTIONS

1. Do the available data demonstrate that Celebrex® is effective in the treatment of JRA?

    - If not, what additional studies would you recommend to further assess efficacy?

    Yes = 16 ***No = 0***

    The committee agreed that the data presented has potential durability and showed a response in the JRA patient population, given the short time period of the non-inferiority trial. The committee noted concerns with the 25% non-inferiority margin being too large, but that the data did show a 13% confidence interval for patients in all subtypes. There committee also noted concerns that the placebo rate may have been underestimated given the recent remicade trial, showing a placebo rate of 48%. However, given their concerns, the committee voted overwhelmingly that the evidence presented by Pfizer, Inc. suggests that celebrex is effective over placebo in the JRA population.

2. Do the available data demonstrate that Celebrex® is safe in the treatment of JRA?
    - If not, what additional studies should be undertaken to further assess safety?
    - If yes, do you recommend any phase 4 studies to further characterize the safety of Celebrex® in JRA?

    Yes = 7 ***No = 8*** ***Abstain = 1***

    The committee reinforced the use of a registry to potentially track outcome data and provide a more accurate standardization of care for the product and its use. The committee noted that with the increase of obesity and the complications surrounding this issue such as diabetes and hypertension, a registry would be helpful in determining the effect of the drug for chronic use.

3. Is the risk/benefit ratio of celecoxib in the treatment of JRA adequate to support the approval of the product for this indication?

    Yes = 15 ***No = 1***

    Given the burden of disease and the number of treatment options available and the short term safety data shown, the committee voted overwhelmingly that the data is adequate enough to support full approval of celebrex for treatment of sign and smptoms of JRA in children 2 years and older.

The meeting adjourned at approximately 5:00 p.m.