# Joint Meeting of the
# Arthritis Advisory Committee
# and the Drug Safety and Risk Management Advisory Committee
# Hilton, 620 Perry Parkway, Gaithersburg, MD
# February 16, 17, and 18, 2005

## Discussion Points

**Thursday, February 17, 2005:**

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.

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.

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.

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## Questions

**Friday, February 18, 2005:**

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

2. Valdecoxib
   a. Do the available data support a conclusion that valdecoxib significantly increases the risk of cardiovascular events?
   b. Does the overall risk versus benefit profile for valdecoxib support marketing in the US?
   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.

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## Questions (cont.)

3. Rofecoxib
   a. Do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events?
   b. Does the overall risk versus benefit profile for rofecoxib support marketing in the US?
   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.

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.

5. What additional clinical trials or observational studies, if any, do you recommend as <u>essential</u> 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 <u>essential</u> 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.

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).

7. What additional clinical trials or observational studies, if any, do you recommend as <u>essential</u> 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.

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## Questions (cont.)

**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.

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.