

# Regulatory History (FDA): Jonca Bull, MD

## 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.

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### Highlights

- **1986:** Public Advisory Committee Meeting: Discussed GI Paragraph & databases.
- **1994:** Celebrex IND.
- **1995:** Revisions to NSAID class label.
- **1998:** Advisory Committee Meeting to discuss “new science of the COX-2s”.
- **DECEMBER 1998:** Celebrex NDA approval.
- **MAY 1999:** Vioxx NDA approval.
- **2001:** Advisory Committee Meeting to discuss relevance of endoscopic studies.
- **NOTHING IS RISK FREE:** No improvements in drug development can completely eliminate the risk of unexpected events”.
- **QUESTIONS ON COX-2S:**
  - In what ways are they different from traditional NSAIDs in GI, CV, renal, hepatic, allergy risk?
  - What additional science is needed?
  - What risk management options are appropriate?
  - What is the impact of “aggressive marketing”?
- **PRESENTATION SCHEDULE:** Dr. Cryer and Fitzgerald; Vioxx; Celebrex; NIH polyp; Bextra/parecoxib; naproxen; observational studies; ADAPT trial; Dr. Packer, Dr. Temple, Dr O’Neill and Dr. Hertz; Questions to Committee members.

### Presentation Text

Good morning. Again, I would like to extend a warm welcome to the members of the committee and to extend and acknowledge a particular thanks to our staff at FDA, specifically Dr. Villalba, Dr. Witter, Dr. Schiftenbauer from our team, our statistical staff, and colleagues

in the Office of Drug Safety who have put in countless hours in preparation for this meeting.

The NSAID class is one that probably everybody in this room has a product in their medicine cabinet that is a member.

It is a large class of marketed products for both OTC and prescription indication use. It is a wide range of products with varying risk/benefit profiles. Their approved indications are for short-term use such as dysmenorrhea and acute pain; chronic use for osteoarthritis, rheumatoid arthritis, familial adenomatous polyposis in the example of Celebrex.

So, clearly, we have drugs that for everyone, from the young female with cramps to the senior citizen with arthritic pain, have importance and clearly there is a need for them in the marketplace. There are other proposed uses that are known to be under investigation, and you will hear about studies in the setting of Alzheimer's disease, as well as sporadic polyp prevention.

I would like to briefly review some of the regulatory history for these products, going back to December of 1986 when there was a public advisory committee meeting that discussed the GI paragraph and databases were discussed at that time.

This was followed in 1995 where revisions for the NSAID class label were discussed, as well as a subsequent advisory committee in 1998 when the new science of the COX-2s were discussed and their potential enhanced safety for GI benefit.

In December of 1998 an advisory committee was held to discuss the data for Celebrex, followed in December of 1998 when that drug was approved first in this new class of products. In April of 1999 an advisory committee was held for Vioxx, followed by its approval in May of 1999. We held another advisory

committee meeting in 2001 which discussed the large outcome studies which sponsors had undertaken to further evaluate how clinically meaningful the data from endoscopic studies was in order to further evaluate the enhanced GI safety claim.

This time line has several points I would like to bring to your attention. The first IND for these products came in 1994 so we are dealing with a relatively short time line, given that this is year 2005, in drug development, marketing and an evolving picture for safety.

The products below the time line are the ones that have been approved, and I would like to bring your attention to those above the line, Arcoxia, Prexige, the IV formulation of Bextra which have not been approved in the United States due to insufficient safety data.

- The COX-2 agents--are they different? In what way?
- When we look at risk to benefit, how do these agents differ from the traditional NSAIDs?
- Can a clinically meaningful benefit for GI safety and less risk, that is for CV risk, renal risk, hepatic risk, allergy--can that be characterized?
- What additional study is needed to better understand the science of COX-2 inhibition?
- When we think in terms of labeling risk management, what risk management options are appropriate in this setting, ranging from potential withdrawal of the product to labeling changes?

Certainly there are lessons learned for drug development. I cite a quote at the end of an article by Dr. Temple and Marty Himmel, in JAMA in May, 2002, and I think the statement is quite a relevant one to our deliberation, that no improvements in drug development can completely eliminate the risk of unexpected events.

Looking at large NDA databases is helpful but continued monitoring is essential to assess evolving risk profiles for new products. Certainly, the impact of aggressive marketing must be taken into account for these unknowns of drug safety.

Dr. Galson has already gone through the schedule for the meeting. I will just briefly allude to our framework for this deliberation. Following me, Dr. Byron Cryer will be discussing the gastrointestinal effects of the NSAIDs and COX-2 specific inhibitors; followed by Dr. Garret FitzGerald on mechanisms for cardiovascular risk from inhibition of COX-2s. This will be followed by a presentation by Merck and the FDA presentation by Dr. Lourdes Villalba.

This afternoon you will hear from Pfizer and their review of cardiovascular safety and risk/benefit assessment of celecoxib, followed by the FDA presentation by Dr. James Witter. There will be a presentation then on the NIH-sponsored colon polyp prevention trials, with subsequent presentations by Pfizer on valdecoxib and parecoxib, and an FDA presentation on valdecoxib. This will be followed by Bayer and Roche discussing naproxen.

Tomorrow you will hear about the epidemiologic studies, followed in the

afternoon by the open public hearing and committee discussion.

Day three in the morning will focus on the Alzheimer's prevention trials. The ADAPT trial will be discussed that morning by Dr. Constantine Lyketsos; followed by a presentation by Dr. Milton Packer on interpretation of cardiovascular events; a presentation by Dr. Robert Temple on clinical trial design and patient safety, future directions for COX-2 selective agents; and a presentation by Dr. Robert O'Neill on issues in projecting increased risk of cardiovascular events to the exposed population. Dr. Sharon Hertz will then present a summary of the meeting presentations prior to the afternoon discussion of our questions.

Again, our thanks to the committee members for taking time from their extraordinarily busy schedules for this important meeting as we reach another milestone in the regulatory history of these products.