



JUL 26 2005

Food and Drug Administration  
Rockville MD 20857

Sidney M. Wolfe, M.D.  
Dawn Jennings-Peterson  
Public Citizen Health Research Group  
1600 20<sup>th</sup> Street, NW  
Washington, DC 20009-1001

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Re: Docket No. 2005P-0034/CP1 and SUP1

Dear Dr. Wolfe and Ms. Jennings-Peterson:

This letter responds to your citizen petition dated January 24, 2005 (petition), and supplement dated January 31, 2005, asking the Food and Drug Administration (FDA) to immediately remove celecoxib (Celebrex) and valdecoxib (Bextra) from the market, based on what you term "mounting evidence of cardiac toxicity" associated with the entire class of COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs). Your petition asserts that neither Celebrex nor Bextra has demonstrated sufficient safety or efficacy benefits to outweigh the cardiovascular (CV) risks that they present, particularly when compared to older "non-selective" NSAIDs. In support, you contend that most of the clinical studies on the five drugs in the COX-2 selective class "demonstrate a rise in [CV] toxicity due to a COX-2 class effect."<sup>1</sup> As discussed below, your petition is granted in part and denied in part.

After your petition was submitted, on April 7, 2005, FDA announced several actions relating to the entire NSAID class. These actions were based on an extensive and detailed review and analysis by FDA of all of the available clinical data on the NSAID drugs, including the five COX-2 selective drugs and the older, non-selective NSAIDs. We also reviewed data from extensive observational studies on these agents. The Agency's review and analysis is detailed in the attached memorandum entitled "Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk" (NSAID Memo).<sup>2</sup>

The NSAID Memo comprehensively analyzes the issues and data discussed in your petition. With regard to the class effect issue that you raise, the FDA concluded that the three approved COX-2 selective NSAIDs are associated with an increased risk of serious adverse CV events compared to placebo.<sup>3</sup> However, we were unable to find based on the

<sup>1</sup> As described in your petition, the five COX-2 selective drugs are the three FDA-approved drugs, celecoxib (Celebrex), rofecoxib (Bextra), and valdecoxib (Vioxx), and two investigational agents, etoricoxib and lumiracoxib.

<sup>2</sup> In keeping with the FDA's efforts to make our regulatory decisions as transparent as possible, this memo was recently posted on FDA's public internet website at:  
<http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf>.

<sup>3</sup> As noted in your petition, rofecoxib (Vioxx) was voluntarily withdrawn from the U.S. market by its sponsor on September 30, 2004.

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available long-term, placebo-controlled clinical trial data on the non-selective NSAIDs, that the COX-2 selective agents confer a greater risk of serious adverse CV events than the older, non-selective NSAIDs. We therefore concluded that, until additional long-term controlled clinical trial data become available, the current data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for *both* COX-2 selective and non-selective NSAIDs.

As explained in the NSAID Memo, given our finding of a “class effect” of increased CV risk for all NSAIDs as a baseline, it was necessary for us to consider other factors in determining the overall risk versus benefit profile for individual drugs within the class and what, if any, regulatory actions were appropriate. Among the factors we considered were any demonstrated benefits or unique toxicities of a given drug compared with other drugs in the class. After conducting this analysis, FDA concluded that the risks of continued marketing of Bextra outweigh the benefits, and we asked the sponsor to voluntarily withdraw Bextra from the market. Your petition is, therefore, granted in part. In the case of Celebrex, we concluded that its benefits outweigh its risks in properly selected and informed patients, and we declined to seek its removal from the market, as you had requested. Accordingly, your petition is also denied in part.

The NSAID Memo also describes a series of further steps, such as changes to the professional labeling and development of a patient medication guide, that FDA is taking to ensure continued safe and effective use of NSAIDs. In addition, we will continue to monitor new information on these drugs as it becomes available.

Sincerely,

*DC [Signature] to S. Galson 7.26.05*

Steven Galson, M.D., M.P.H.  
Acting Director  
Center for Drug Evaluation and Research

Attachment