DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. 2005P-0072/CP1

Dear Dr. Salisbury:

This letter responds to your citizen petition dated February 15, 2005, submitted on behalf of seven petitioners. You request that the Food and Drug Administration (FDA) take the following actions:

1. conduct a risk assessment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with the use of ibuprofen products;

2. conduct an investigation into manufacturers' withholding of critical safety information regarding the risks of SJS and TEN associated with ibuprofen products; and

3. require manufacturers of ibuprofen to amplify their prescription and over-the-counter (OTC) labeling to adequately warn prescribers, healthcare professionals, and consumers of the risks of SJS and TEN.

For the reasons that follow, your petition is granted in part and denied in part.

I. BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) is a class of drugs that includes ibuprofen products. Ibuprofen products are available by prescription and OTC. Prescription and OTC ibuprofen are indicated for temporary relief of minor aches and pains and reduction of fever. In addition, prescription ibuprofen is indicated for relief of mild to moderate pain; relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis; and treatment of primary dysmenorrhea.

NSAIDs, including ibuprofen, are known to cause SJS and TEN, as reflected in the labeling of NSAIDs, including ibuprofen prescription labeling. While adverse skin reactions to drugs are frequent, serious adverse cutaneous reactions are not. SJS and TEN are within a spectrum of the same disease and are severe drug eruptions. Prompt recognition of the onset of symptoms, such as the appearance of rash or blisters on the

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skin, and withdrawal of the suspected drug can minimize the effects of SJS/TEN and improve prognosis.[1]

In 2005, FDA engaged in a comprehensive review of the risks and benefits, including the risks of SJS and TEN, of all approved NSAID products, including ibuprofen. This comprehensive risk-benefit assessment focused primarily on potential cardiovascular and gastrointestinal safety concerns associated with COX-2 selective and non-selective NSAIDs. On April 6, 2005, FDA issued a press release and public health advisory announcing a series of actions to alert consumers and healthcare practitioners about the risks associated with the use of COX-2 and NSAID products. FDA also posted a Decision Memo entitled "Analysis and Recommendations for Agency Action- COX-2 Selective and Non-selective NSAIDs" (www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf) (Decision Memo). In its Decision Memo, FDA emphasized the public health importance of maintaining a range of options in the NSAID class from which physicians and patients may choose (Decision Memo at 11-13).

The Agency's actions included issuing supplemental request letters to manufacturers of all NSAIDs asking that they make labeling changes to their products. In addition, FDA posted labeling templates for both the prescription and OTC NSAIDs and a template for a medication guide to be distributed with the entire class of prescription products. The labeling changes resulting from this comprehensive analysis include additional warnings regarding the risks of SJS and TEN (discussion in section II.C of this response). For a comprehensive posting of FDA's actions regarding NSAIDs, see our Web site at www.fda.gov/cder/drug/infopage/COX2.

II. DISCUSSION

A. Review of Adverse Event Reporting System (AERS) Data

You have requested that FDA conduct a thorough assessment of the risks of developing SJS or TEN associated with the use of prescription and OTC ibuprofen drug products (Petition at 1). FDA uses a number of methods to monitor the safety of marketed drugs, including review of clinical trials submitted to FDA for marketing approvals, review of other clinical studies available in the scientific literature, and review of the Adverse Event Reporting System (AERS) surveillance database implemented in 1997. As you recognize in your petition (based on the thorough citation of the clinical studies from publicly available literature (Petition at 10-17)), clinical trials provide strong evidence of the potential for adverse reactions associated with a particular drug.

[1] Fritsch, P.O., and A. Sidoroff, "Drug-Induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis," *American Journal of Clinical Dermatology*, 1(6):349-360, Nov-Dec 2000; Wolkenstein P., and J. Revuz, "Drug-Induced Severe Skin Reactions. Incidence, Management and Prevention," *Drug Safety*, 13(1):56-68, July 1995; and Mockenhaupt, M., et al., "The Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Nonsteroidal Anti-Inflammatory Drugs: A Multinational Perspective," *Journal of Rheumatology*, 30:2234-2240, 2003.