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Lester Crawford, D.V.M., Ph.D.
FDA Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5600 Fishers Lane, Rm. 1061
Rockville, MD 20857

Dear Dr. Crawford:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 19,000 Board certified orthopaedic surgeons, welcomes the opportunity to comment on the draft guidance, "FDA's 'Drug Watch' for Emerging Drug Safety Information" [Docket No. 2005D-0062]. While the intention behind the creation of this early drug safety warning Web page is noble, the Academy has concerns about the functionality, usability, and attendant consequences of such a Web page.

In the May 10, 2005 *Federal Register* notice, the FDA stated that the development of the proposed Web page is in response to the recent handling of drug safety issues. The withdrawal of Vioxx from the market generated tremendous controversy from medical professionals, patients, and members of Congress. While the AAOS is supportive of the distribution of drug safety information as soon as it is available, we suggest that the FDA reconsider the drug safety Web page as outlined in the guidance document. Furthermore, the Academy maintains that the reason the FDA is not more responsive to the immediate needs of drug safety issues is due to resource allocation. Substantial resources are devoted to new drug application reviews while fewer resources are devoted to drug safety in the Center for Drug Evaluation and Research (CDER). While the AAOS supports allocating significantly more resources toward drug safety

efforts, we are uncertain that the creation of this proposed Web page will serve the public as the FDA intends.

In order to better serve the public needs, the Academy has several recommendations. The Academy recommends the following considerations with respect to the FDA proposed 'Drug Watch' Web page:

- The FDA should clarify ambiguous terminology prior to the launch of the 'Drug Watch' Web page;
- The FDA must consider the medical-legal consequences of this Web page;
- Information on patient genetic composition, and interactions with food, drugs, and supplements will be important considerations for safety data;
- The FDA Drug Safety and Risk Management Advisory Committee should provide input and scrutiny into the contents posted on the 'Drug Watch' Web page;
- The FDA should proceed rapidly with definitive actions when a safety signal is known;
- The Center for Drug Evaluation and Research should continue to pursue active surveillance programs;
- The Center for Drug Evaluation and Research should concentrate post-market surveillance issues on newly approved drugs, in addition to maintaining efforts to provide guidance on labeling issues.

The FDA should clarify ambiguous terminology prior to the launch of the 'Drug Watch' Web page

The Academy recommends the clarification of subjective terminology in the draft guidance prior to the implementation of the Web page. The AAOS suggests that the FDA define "sufficiently credible" when referring to new safety information. Additionally, as part of this guidance, it would be useful for the FDA to elaborate on how it will determine that public notification is warranted. It is imperative that the Agency work with the public to define ambiguous terms prior to the launch of the 'Drug Watch' Web page.

The FDA must consider the medical-legal consequences of this Web page

The Academy is concerned about the prospect of physicians facing increased liability for having prescribed, or continuing to prescribe a drug posted on the Web page. The physician-patient relationship may become more strained as a

result of patients second guessing their medication prescribers. Medical-legal consequences must be considered prior to the implementation of this Web page.

Information on patient genetic composition and interactions with food, drugs, and supplements will be important considerations for safety data

The practice of medicine will change markedly as research findings on genetic predisposition for diseases and drug assimilation accumulate. As prescription medication becomes more personalized, the information generated on the 'Drug Watch' Web page will be increasingly confusing for patients who have not undergone genetic screening. For instance, the recent findings on the variance of haplotypes for assimilation of the drug warfarin will be unknown to patients who have not previously undergone genetic testing.

Prior to posting on 'Drug Watch,' the FDA must be able to assess patient information on comorbid conditions and interactions with food, drugs, and supplements. Additionally, recent studies conclude that gender differences may have a profound effect on the human body's assimilation of some medical products, including pharmaceutical drugs and devices. Furthermore, BiDil was approved as the first medication targeted to a specific racial population. In the clinical trial, race was a self-identified component and may in fact not reflect the racial composition of the patient. All of these factors must be assessed prior to posting information on the 'Drug Watch' Web page.

The FDA Drug Safety and Risk Management Advisory Committee should provide input and scrutiny into the contents posted on the 'Drug Watch' Web page

The AAOS suggests changes to the composition of the Drug Safety Board as it is comprised solely of FDA/Department of Health and Human Services (HHS) personnel. Given that the Drug Safety Board will meet prior to Web page postings to determine the content and the timing of information posted on the Web page, the Academy strongly believes that the 'Drug Watch' Web page should have scrutiny and input from the FDA Drug Safety and Risk Management Advisory committee. While recent conflict of interest issues were widely publicized from the Arthritis and Drug Safety and Risk Management Advisory committees, the level of conflict is an immensely important component. Advisory committees must be comprised of experts in their particular field and for some members perceived or actual conflicts will be inevitable. Committee members may have a small research funding conflict with all manufacturers of a

particular product, whereas other panel members may have a large material conflict with one manufacturer of a particular medical product under review. These two types of conflict of interest should be assessed differently by the FDA. Advisory committees should be utilized to gain the breadth of perspective from practicing clinicians and scientists.

The FDA should proceed rapidly with definitive actions when a safety signal is known

From a patient safety standpoint, it is important for the FDA to move definitively and rapidly on emerging safety information. However, posting information on the 'Drug Watch' Web page will be considered a de facto interim step to regulatory action by the public, regardless of the outcome. The AAOS is supportive of the efforts of the FDA to provide timely information about drug safety through the usual FDA communication vehicles. Manufacturers must share relevant safety information as soon as it is known and must work with the FDA to distribute safety alerts and market withdrawal information to physicians and the public. When the FDA has determined a definitive safety signal, they should proceed rapidly with disseminating the information to the public. The Academy is particularly pleased with the swift and definitive action taken by the FDA on Palladone (hydromorphone hydrochloride), recently.

The Center for Drug Evaluation and Research should continue to pursue active surveillance programs

The AAOS realizes that the FDA must determine the risk vs. benefit ratio for each pharmaceutical drug prior to its approval. Furthermore, considerably more information is known about a pharmaceutical after it is consumed by a large population in the drug's post market surveillance period. While the adverse event reporting system (AERS) is particularly adept at identifying rare adverse events, commonly occurring adverse events such as heart attacks are more difficult to determine causation. The Academy is pleased with the FDA's recent pursuit of active surveillance programs. These data should lead the FDA to a database comprised of more meaningful information. We encourage the pursuit of cooperative agreements with large healthcare providers like Kaiser Permanente. Demonstration projects with other HHS agencies, such as the Centers for Disease Control and Prevention (CDC) in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event (NEISS-CADES) project, will provide much needed information on adverse drug events diagnosed and treated in the emergency room setting. We encourage

collaboration with the National Institutes of Health (NIH) institutes, centers, and offices, as well as projects with the Agency for Healthcare Research and Quality (AHRQ) to acquire meaningful post-market information on pharmaceutical drugs.

The Center for Drug Evaluation and Research should concentrate post-market surveillance issues on newly approved drugs, in addition to maintaining efforts to provide guidance on labeling issues

The CDER should concentrate surveillance efforts on newly approved drugs as many new drugs have been removed from the market, whereas only one generic drug has been recalled in the last twenty years. The AAOS supports more funding for post-market surveillance on newly approved drugs.

The FDA should ensure that efforts continue to be focused on providing guidance on confusion with product names, packaging, and labeling. According to some estimates, twenty-five percent of adverse drug events are due to labeling problems.

The Academy shares the concerns of the FDA in providing timely drug safety information to physicians and their patients. We support the meaningful collection and assessment of post-market surveillance information for all critical medical products. The Academy looks forward to working with the FDA in any manner possible to ensure patient safety.

Sincerely,

Stuart L. Weinstein, MD
AAOS President