DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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STATEMENT

OF

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U.S. FOOD AND DRUG ADMINISTRATION

BEFORE THE

COMMITTEE ON FINANCE

UNITED STATES SENATE

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Sandra Kweder, Deputy Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to participate in this hearing regarding drug safety and the worldwide withdrawal by Merck & Co., Inc. of Vioxx.

I. BACKGROUND ON DRUG SAFETY

Modern drugs provide unmistakable and significant health benefits. It is well recognized that FDA's drug review is a gold standard. Indeed, we believe that FDA maintains the highest worldwide standards for drug approval. FDA grants approval to drugs after a sponsor demonstrates that they are safe and effective. Experience has shown that the full magnitude of some potential risks do not always emerge during the mandatory clinical trials conducted before approval to evaluate these products for safety and effectiveness. Occasionally, serious adverse effects are identified after approval either in post-marketing clinical trials or through spontaneous reporting of adverse events. That is why Congress has supported and FDA has created a strong post-market drug safety program designed to assess adverse events identified after approval for all of the medical products it regulates as a complement to the pre-market safety reviews required for approval of prescription drugs in the United States. Monitoring the drug safety of marketed products requires close collaboration between our clinical reviewers and drug safety staff to evaluate and respond to adverse events identified in ongoing clinical trials or reported to us by physicians and their patients. The most recent actions concerning the drug Vioxx (rofecoxib) illustrates the vital importance of the ongoing assessment of the safety of a product once it is in widespread use.

It is important to understand that all approved drugs pose some level of risk, such as the risks that are identified in clinical trials and listed on the labeling of the product. Unless a new drug's demonstrated benefit outweighs its known risk for an intended population, FDA will not approve the drug. However, we cannot anticipate all possible effects of a drug during the clinical trials that precede approval. An adverse drug reaction can range from a minor, unpleasant response to a drug product, to a response that is sometimes life-threatening or deadly. Such adverse drug reactions may be expected (because clinical trial results indicate such possibilities) or unexpected (because the reaction was not evident in clinical trials). It may also result from errors in drug prescribing, dispensing or use. The issue of how to detect and limit adverse reactions can be challenging; how to weigh the impact of these adverse drug reactions against the benefits of these products on individual patients and the public health is multifaceted and complex, involving scientific as well as public policy issues.

II. VIOXX

The Vioxx Approval

FDA approved Vioxx in May 1999 for the reduction of signs and symptoms of osteoarthritis, as well as for acute pain in adults and for the treatment of primary dysmenorrhea. Vioxx received a six-month priority review because the drug potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects, including bleeding. A product undergoing a priority review is held to the same rigorous standards for safety, efficacy, and quality that FDA expects from all drugs submitted for approval.

As with many other new molecular entities, this product was taken before the Arthritis Advisory Committee, April 20, 1999, prior to its approval. It was the second of a new class (COX-2 selective) of non-steroidal anti-inflammatory drugs (NSAIDs) approved by FDA. The original safety database for this product included approximately 5,000 patients on Vioxx and did not show an increased risk of heart attack or stroke.

In the clinical trials conducted before approval, the risk of gastrointenstinal (GI) side effects was determined through the use of endoscopy. At the time that FDA approved Vioxx , the available evidence from these endoscopy studies showed a significantly lower risk of gastrointestinal ulcers, a significant source of serious side effects such as bleeding and death, in comparison to ibuprofen.

The VIGOR Study

After Vioxx was approved in 1999, Merck continued studies of Vioxx designed to look at clinically meaningful GI effects, such as stomach ulcers and bleeding (VIOXX Gastrointestinal Outcomes Research, or VIGOR study). This study was designed to provide longer term clinical outcome data to confirm the shorter term endoscopy findings and to evaluate overall safety. The VIGOR study was a large (8,000-patient) study designed to evaluate the GI safety of Vioxx as compared to naproxen. This study was done in a rheumatoid arthritis population who typically require a higher dose (50 mg was used) of anti-inflammatory medication.

VIGOR did not have a placebo group because to do so would have meant patients with rheumatoid arthritis would have been randomized to receive no pain relief. Use of a placebo would have been intolerable, because untreated patients would have suffered and left the study. The study also excluded subjects taking low dose aspirin for cardiovascular (CV) prevention because use of aspirin might have contributed to increased rates of GI bleeding in the study and confound the results. However, the exclusion of patients on low dose aspirin may have influenced CV events in the study, since low dose aspirin has been shown to reduce CV risk.

In April 2002, FDA approved extensive labeling changes to reflect the findings from the VIGOR study. FDA also approved a rheumatoid arthritis indication at the 25 mg dose based on separate efficacy trials. The new label provided additional information to the Clinical Studies, Precautions, Drug Interactions and Dosage and Administration sections to reflect all that was known at the time about the potential risk of cardiovascular effects with Vioxx. These labeling changes included detailed information about the increase in risk of cardiovascular events relative to naproxen, including heart attack. It also included data from the ongoing placebo controlled Alzheimer's study at the 14 month time point which did not show an increase in CV risk. The new labeling change also noted that Vioxx 50 mg was not recommended for chronic use.

Other Vioxx Studies

In the years following the 1999 FDA approval of Vioxx, Merck began conducting a series of clinical trials exploring other potential indications of this product. All trials for chronic use were designed to monitor carefully for CV safety and included data safety monitoring committees as well as blinded experts to assess all CV events in the trials. Some of these studies included placebo-controlled studies of Vioxx in Alzheimer's disease, prostate cancer, and colon polyps. Following the 2001 Advisory Committee meeting and the 2002 labeling changes, FDA focused on ensuring that all clinical trials conducted with Vioxx were designed to include careful monitoring of CV risk, and required that Merck submit all available CV data in ongoing trials.

In the period following the 2002 Vioxx labeling changes, FDA also continued to monitor the scientific literature reviewing several retrospective epidemiologic studies. Some of these studies suggested an increased risk for CV events with Vioxx, primarily with the 50 mg dose, while others did not. Epidemiologic studies in real world populations of conditions such as heart attack or stroke are difficult to conduct and interpret because of the need to carefully and adequately account for the many known powerful risk factors for these diseases. Merck, or Pfizer, the manufacturer of Celebrex (another COX-2 inhibitor), sponsored, directly or indirectly, many of these epidemiology studies.

Given the need for data to distinguish the impact of the use of these drugs on cardiovascular risk from factors such as smoking, hypertension, diabetes, low dose aspirin use, high cholesterol and others, the long-term, placebo-controlled trials that were being conducted offered the best opportunity to carefully assess both the existence of and the magnitude of these cardiovascular effects.

III. MERCK'S WORLDWIDE WITHDRAWAL OF VIOXX

Merck contacted FDA on September 27, 2004, to request a meeting to discuss with the Agency the Data Safety Monitoring Board's decision to halt Merck's long-term study of Vioxx in patients at increased risk of colon polyps. Merck and FDA officials met the next day, September 28, and during that meeting the company informed FDA of its decision to remove Vioxx from the market voluntarily. The data presented demonstrated an increase in

risk in cardiovascular risk and stroke starting at the eighteen month time point compared to placebo. This was the first demonstration of a difference in comparison to a placebo group and supported the previous signal seen in the VIGOR trial and some of the epidemiologic studies.

IV. THE KAISER STUDY ON VIOXX

In follow up to the VIGOR findings, FDA worked with Kaiser Permanente California HMO as part of a collaborative agreement to provide an alternative means of evaluating the CV safety signal using a managed care database. In 2001, the forerunner of the Office of Drug Safety (ODS) and Dr. David Graham began informal discussions with Kaiser Permanente about projects of mutual interest. At the same time, FDA's Arthritis Advisory Committee was reviewing the cardiovascular risk observed in clinical trials for Vioxx and recommended the need to collect additional information regarding this risk. Dr. Graham indicated that Kaiser was interested in the CV safety of the COX-2 agents in general and in pursuing a scientific collaboration with ODS on this topic even if Agency funding were not available for the full study. FDA provided funding to partially support this pilot scientific collaboration in August 2001 and again in August 2002. A protocol for the study was developed to study the risk of myocardial infarction among users of selective (COX-2) and non-selective non-steroidal anti-inflammatory agents (NSAIDs). Dr. Graham was designated the ODS project officer for this study to work with his counterparts at Kaiser Permanente. Dr. Wayne Ray, an epidemiologist at Vanderbilt University and a cooperative agreement grantee of FDA, was added to the study team during the course of the study. Dr. Graham periodically discussed his work with his supervisors to provide updates on the progress of the study.

In February 2004, Dr. Graham and his coauthors submitted an abstract to the International Society for Pharmacoepidemiology (ISPE) for possible presentation at the August 2004 meeting in Bordeaux, France. No study results were included in this abstract, which was accepted for a poster presentation in August 2004. In May 2004, Dr. Graham and his coauthors submitted an abstract of their study findings to the American College of Rheumatology (ACR) for possible presentation at their October 2004 meeting in San Antonio. The deadline for submitting abstracts for the San Antonio meeting was May 13, 2004. Dr. Graham informed his supervisor about his authorship role in the ACR abstract in early September 2004.

On August 11, 2004, David Graham first shared a draft of his ISPE poster presentation with his supervisors to obtain their review and clearance, as is required of any FDA author or presenter. At that time, Dr. Graham's supervisors in ODS informed him of the importance of this work and the need to promptly complete a study report for circulation within the Agency and for broader dissemination in a scientific journal. In reviewing the poster presentation, scientists within ODS and within the Office of New Drugs with specific expertise in COX-2s provided comments and raised questions regarding the study design and statistical modeling, which were not detailed in the poster. The conclusion that high dose Vioxx should never be used was questioned, as the label for the drug already recommended limiting high dose use to no more the five days based on the cardiovascular risks identified in clinical trials. A concern

was expressed that the data presented in the poster and in the medical literature did not support the recommendation of never using high dose Vioxx. These comments and concerns were shared with Dr. Graham who chose to revise his conclusions voluntarily. A disclaimer was placed on the poster to reflect that some of the conclusions and statements in the poster were those of the authors and did not necessarily reflect Agency policy.

Dr. Graham presented his poster in Bordeaux, France, on August 23-24, 2004, and participated in press coverage that discussed the findings. (Graham et al. at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 2004 reporting an elevated cardiovascular risk for the 50 mg dose of Vioxx).

Upon Dr. Graham's return from Bordeaux in late August, given the data's potential application to regulatory actions, Dr. Graham was asked to submit a draft report for Agency review within two weeks. He asked for a September 30, 2004, deadline and on that date, Dr. Graham provided a first draft of his report to his supervisors. Discussions concerning the report are ongoing between Dr. Graham and his supervisors. Dr. Graham has meanwhile submitted a manuscript version of the report to Lancet for publication.

V. FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

At FDA, we are constantly searching for ways to improve our processes and methods, and thereby better serve the public health. On November 5, 2004, FDA announced a five-step plan to strengthen its drug safety program. First, CDER will sponsor an Institute of Medicine (IOM) study on FDA's drug safety system. An IOM committee will study the effectiveness of the United States' drug safety system, with an emphasis on the post-market phase, and assess what additional steps could be taken to learn more about the side effects of drugs as they are actually used. We will ask IOM to examine FDA's role within the health care delivery system and recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs.

Second, CDER will implement a program for addressing differences of professional opinion. Currently, in most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisors, leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel that his or her opinion was not adequately considered. Such disagreements can have a potentially significant public health impact.

In an effort to improve the current process, CDER will formalize a program to help ensure that the opinions of dissenting scientific reviewers are formally addressed and transparent in its decision-making process. An ad hoc panel, including FDA staff and outside experts not directly involved in disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

Third, CDER will conduct a national search to fill the currently vacant position of Director of the Office of Drug Safety, which is responsible for overseeing the post-marketing safety program for all drugs. The Center is seeking a candidate who is a nationally recognized drug safety expert with knowledge of the basic science of drug development and surveillance, and has a strong commitment to the protection of public health.

Fourth, in the coming year, CDER will conduct workshops and Advisory Committee meetings to discuss complex drug safety and risk management issues. These consultations may include emerging concerns for products that are investigational or already marketed. Examples of areas where FDA may seek input include:

* Whether a particular safety concern alters the risk-to-benefit balance of a drug;
* Whether FDA should request a sponsor to conduct a particular type of study to further address an issue;
* What types of studies would best answer safety questions;
* Whether a finding is unique to one product or seems to be a drug class effect;
* Whether a labeling change is warranted and, if so, what type; and
* How to otherwise facilitate careful and informed use of a drug.

These consultations will include experts from FDA, other federal agencies, academia, the pharmaceutical industry, and the healthcare community.

Finally, by the end of this year, FDA intends to publish final versions of three guidances that the agency developed to help pharmaceutical firms manage risks involving drugs and biological products. These guidances should assist pharmaceutical firms in identifying and assessing potential safety risks not only before a drug reaches the market and but also after a drug is already on the market. These guidances will rely on the use of good pharmacovigilance practices and pharmacoepidemiologic assessment. These documents are:

* "Premarketing Guidance," which covers risk assessment of pharmaceuticals prior to their marketing;
* "RiskMAP Guidance," which deals with the development and use of risk-minimization action plans; and
* "Pharmacovigilance Guidance," which discusses post-marketing risk assessment, good pharmacovigilance practices and pharmacoepidemiologic assessment.

VI. CONCLUSION

In summary, FDA worked actively and vigorously with Merck to inform public health professionals of what was known regarding CV risk with Vioxx, and to pursue further definitive investigations to better define and quantify this risk. FDA also reviewed and remained current on new epidemiologic studies that appeared in the literature. Indeed, the recent study findings disclosed by Merck, leading to its decision to voluntarily withdraw Vioxx from the marketplace, resulted from FDA's vigilance in requiring these long-term outcome trials to address our concerns.

Detecting, assessing, managing and communicating the risks and benefits of prescription and over-the-counter drugs is a highly complex and demanding task. FDA is determined to meet this challenge by employing cutting-edge science, transparent policy, and sound decisions based on the advice of the best experts in and out of the agency. We are confident that the additional activities discussed above will strengthen the agency's program to greater ensure the safety of medical products that make a major contribution to the health and quality of life of millions of Americans. Medicines that receive FDA approval are among the safest in the world, and the measures we are taking are designed to strengthen this quality, as well as consumer confidence that FDA's processes ensure the highest protection of the public health.