

## FDA Officer Suggests Strict Curbs on 5 Drugs

Makers Dispute Claims About Health Risks

*By Marc Kaufman*

Washington Post Staff Writer

Friday, November 19, 2004; Page A01

A veteran Food and Drug Administration safety officer said yesterday at a Senate hearing on the abrupt recall of the arthritis drug Vioxx that five other widely used drugs should either be withdrawn or more sharply restricted because they have dangerous side effects.

Describing the agency he works for as incapable of stopping dangerous drugs from entering and staying on the market, David J. Graham, associate director of the Office of Drug Safety, told the senators that the FDA's role in reviewing and approving new drugs sometimes conflicts with its duty to address safety issues.

Asked by Sen. Jeff Bingaman (D-N.M.) to identify the five drugs, Graham hesitated and then named them to the startled listeners: the popular cholesterol-lowering drug Crestor, the weight-loss drug Meridia, the painkiller Bextra, the acne medication Accutane and the asthma medication Serevent.

Each poses different issues, Graham said in response to senators' questions, but all require more aggressive FDA action.

AstraZeneca's Crestor, he said, poses risks of kidney failure and a rare muscle disease; Abbott Laboratories' Meridia is of little use and has cardiovascular side effects; Roche's Accutane can cause birth defects if used by pregnant women; Pfizer's Bextra carries cardiovascular risks similar to those linked to Vioxx; and GlaxoSmithKline's Serevent increases the risk of dying of asthma. The makers of all five drugs later defended their products vigorously.

A 20-year veteran of the FDA, Graham has played a significant role in the withdrawal of nine drugs over the past decade, and his highly unusual attack on his own agency astonished many in the hearing room. He called the FDA's handling of Merck & Co.'s Vioxx -- which he said should have been pulled from the market years ago -- the most distressing episode of all and a "profound regulatory failure."

"I would argue that the FDA as currently configured is incapable of protecting America against another Vioxx," Graham said in his scathing assessment. "The scientific standards [the FDA] applies to drug safety guarantee that unsafe and deadly drugs will remain on the U.S. market."

Citing estimates he said were based on the results of Merck's own clinical trials, Graham said that between 88,000 and 139,000 Americans probably have had heart attacks or strokes as a result of taking Vioxx, and that 30 to 40 percent probably died.

Graham's sentiments were endorsed at the hearing by two other drug safety experts, but they were disputed by a ranking FDA official as "not the FDA that I know."

Sandra L. Kweder, deputy director of the Office of New Drugs, said that the agency is dedicated to protecting consumers and that drug safety is at the heart of its activities. She acknowledged, however, that "clearly, there's concern by the public and this committee that the system isn't working as well as it should, and we need to address that."

Asked about the five drugs that Graham identified as needing immediate action, Kweder said, "I don't have reason to believe that set of five drugs gives more reason for concern than any other set."

Graham's revelations and criticisms were the centerpiece of the hearing called by Sen. Charles E. Grassley (R-Iowa), chairman of the Senate Finance Committee and an increasingly sharp critic of the FDA. After Graham's comments, Grassley pointedly warned agency officials against disciplining Graham in any way.

Merck chief executive Raymond V. Gilmartin came to the defense of the FDA and his company's actions in dealing with the issues around Vioxx, a heavily advertised and hugely profitable drug until it was abruptly recalled in September. He said the company had no scientific reason to withdraw the drug until it heard clear negative results reported by the safety monitoring committee of an ongoing clinical trial. At the time, Gilmartin said, his wife was taking the drug regularly.

"Throughout Merck's history, it has been our rigorous adherence to scientific investigation, openness and integrity that has enabled us to bring new medicines to people who need them," Gilmartin said. "I am proud that we followed that same rigorous scientific process at every step of the way with Vioxx."

The drug, which was introduced in 1999, is among a class of painkillers known COX-2 inhibitors that are widely used by people with arthritis. It was withdrawn after researchers stopped a clinical trial because patients taking Vioxx were experiencing twice as many heart attacks and strokes as patients taking a placebo, but witnesses testified there had been suggestions of possible cardiovascular risks dating to the mid-1990s.

Graham, Stanford University COX-2 expert Gurkirpal Singh and University of Washington drug safety expert Bruce M. Psaty all said Merck and the FDA should have been more attentive to the "signals" of trouble in Vioxx studies as far back as the 1990s.

This has been a difficult week for the FDA, which was sharply criticized Wednesday in a congressional hearing into the shortage of flu vaccine. The agency has been without a permanent commissioner for more than two of the past four years, and three important

divisions -- the Center for Drug Evaluation and Research, the Office of New Drugs and the Office of Drug Safety -- are all being headed by acting or deputy directors.

Officials of the companies whose drugs were cited by Graham said they were surprised by his testimony. Carolyn Glynn, a spokeswoman for Roche, said the firm has long recognized that Accutane -- used to treat serious acne that does not respond to other medications -- requires special handling because of its known connection to birth defects. Female users must first have a pregnancy test and may get only one month's supply at a time.

AstraZeneca said in a statement that "to date, the FDA has not given the company any indication of a major concern regarding Crestor, and the comments today are inconsistent with past public statements from the FDA." More than 12 million prescriptions for the drug have been written worldwide.

Abbott Laboratories issued a statement defending Meridia, which 15 million patients worldwide have used since 1997. "Obesity remains one of the leading health epidemics in the U.S., and Meridia is one of the few effective drugs that are currently available," it said.

GlaxoSmithKline stood by its asthma drug Serevent, which Graham said can make the condition worse and even be deadly. Serevent, used by 23 million patients worldwide since 1990, "is safe and effective when used appropriately," the company said. A black box warning was placed on the drug's label in August 2003.

Pfizer spokeswoman Susan Bro said its COX-2 inhibitor, Bextra, "has been found safe and effective when used as indicated." She noted that the company has "committed to conducting further studies to confirm the longer-term cardiovascular safety profile." More than 7 million Americans have taken it.

*Staff writer Brooke A. Masters and researcher Richard S. Drezzen contributed to this report.*

[Home](#)