HARVARD MEDICAL SCHOOL **BRIGHAM AND WOMEN'S HOSPITAL**

Jerry Avorn, M.D.
Professor of Medicine

Chief, Division of Pharmacoepidemiology and Pharmacoeconomics

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Representative Henry Waxman
House Committee on Government Reform
2157 Rayburn House Office Building
Washington, D.C. 20515-6143

Dear Congressman Waxman,

I am writing to respond to your request for my views on the enforcement record of the Food and Drug Administration over the last five years in relation to drug products that are mis-labeled or inappropriately promoted. As a professor of medicine at Harvard Medical School, I have spent over 20 years performing research on the determinants and outcomes of physician and patient medication use. In this role, I have also become a close observer of the FDA and its regulatory activities.

I have grave concerns about the recent decline in FDA enforcement. We have seen a reduction in the agency's vigilance and effectiveness on a variety of fronts, including drug promotion and advertising. At the same time, there have been – as all Americans are aware – a series of major problems in the agency's capacity to detect and act on major drug safety problems. Vioxx was the most publicized example, but far from the only one. In all of FDA's once-proud recent history, I cannot recall a time of greater concern about its work on the part of doctors, patients, and policy researchers.

At your request, I have reviewed these files carefully and I find the picture they present a disturbing one. Many of us in the medical community have been concerned about a growing laxity in FDA's surveillance and enforcement procedures in several domains related to the safety of pharmaceuticals; the evidence the agency provided to your committee provides further substantiation of this problem.

In overview, there appears to have been a sharp drop-off in the number of warning letters FDA has issued in recent years, from an average well over 1,000 for the period 1992 – 2001 to an average of only about 700 for the years 2002 – 2004. It is unlikely that the behavior of the regulated industries improved so much during these years to account for a reduction of 300 warning letters per year. There was a striking downward trend in CDER, which oversees drugs, and CDRH, which handles devices. In the former Center, the number of warning letters for the period 2000 – 2004 was 1,154, 1,032, 755, 545, and 725 respectively. For CDRH, the downward annual trend was 528, 498, 285, 205, and 198. The latter reduction in oversight occurred during a period, we

1620 Tremont Street, Suite 3030, Boston, Massachusetts 02120 Tel: (617) 278-0930 Fax: (617) 232-8602
e-mail: javorn@partners.org www.DrugEpi.org

now know, of growing problems in the safety of devices such as implantable pacemakers and defibrillators.

The origin of this dangerous decline in regulatory vigilance becomes clearer with inspection of the correspondence that the agency provided to your committee. These letters seem to reveal a pattern of regulatory neglect in FDA's central office, despite ongoing attempts by field officers to draw attention to problems. Here are two striking examples:

- FDA's Denver district office asked FDA's central compliance branch to issue a warning letter to one company when agency staffers became aware that its "Hangover Formula" product contained toxic levels of caffeine – 40 times greater than would be found in a typical caffeine-containing beverage.

  FDA's Division of Enforcement took a year and a half to respond to the report it received from the Denver district. It agreed that the remedy contained unsafe levels of caffeine that were close to "the dose range at which risk of death may occur," but then determined that the product was a "food," and noted that "a hazard analysis has not been conducted." The agency refused to issue a warning letter.

- The Los Angeles district office recommended that a warning letter be issued to a California firm selling products containing estrogen-related hormones over-the-counter for the relief of menopausal symptoms. In response, the FDA Office of Compliance indicated that the district office should rescind its recommendation, and refused to issue a warning letter.

- The New England district office requested that FDA's office of compliance issue a warning letter to another firm marketing over-the-counter drugs because it made unsubstantiated claims for its products' capacity to prevent heart attacks and treat migraine headaches. The agency's Office of Compliance took a year and a half to respond. It noted that the district had done commendable work on the case, and acknowledged that the central office had even encouraged the submission of such a recommendation. But it went on to disapprove of a warning letter, arguing in part that by then the case was too old.

- The Minnesota district office requested that a warning letter be issued to a Wisconsin dietary supplement company. The company made a product that was 50% alcohol (100 proof), which it promoted for oral ingestion and also as a gargle, inhalant, and topical preparation for a wide variety of medical problems. FDA acknowledged that there were legitimate safety questions about the ingredients, that the product made unsubstantiated claims, and that there were problems in the quality of the company's manufacturing processes. However, it noted that the district office's report was written two weeks after the expiration of the four-month deadline established by the agency's Office of General Counsel, and disapproved the warning letter.

Many similar instances occur in the materials provided by FDA, illustrating an apparent reluctance of the agency's central offices to act on problems of drug safety or false promotion that had been identified by its own district offices. As in the examples above, these complaints dealt with dangerous substances, false claims, mislabeled products, and faulty manufacturing processes. I was struck by the delays on the part of the FDA Office of Compliance (often exceeding one year), and its obvious unwillingness to move forward even on claims from its own field offices which it acknowledged were worrisome. The reduction in the number of total warning letters issued and the detailed responses of FDA officials to specific compelling requests add to the growing picture of an agency unwilling to exert its regulatory authority in defense of the public's health. Coupled with the continuing evidence of problems in the agency's Office of Drug Safety, one is left with the image of an organization unable or unwilling to do its job effectively.

These reports should be brought to the attention of a wider audience, including other members of Congress and the public, to stimulate further debate on what might be done to restore the effectiveness and credibility of what was once the most vigilant drug regulatory body in the world.

Sincerely,

Jerry Avorn, M.D.
Professor of Medicine
Harvard Medical School