United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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Grassley suggests FDA is abdicating its responsibilities with off-label prescribing

WASHINGTON - Senator Chuck Grassley has asked the FDA Commissioner to explain agency actions that appear to cede its authority to the drug and medical device industry when it comes to off-label use of industry products.

Grassley said draft guidance from the Food and Drug Administration would expand industry's ability to promote off-label use of drugs and devices through the distribution of scientific literature that supports off-label use, even while there's growing evidence of industry efforts to manipulate scientific literature to industry advantage.

"The Food and Drug Administration needs to stay focused on its mission of overseeing pharmaceutical products and devices and assessing their safety," Grassley said. "The agency's new guidance tells drug and device makers that they are 'home alone' and free to promote off-label prescribing as long as they do it under the umbrella of peer-reviewed scientific articles."

The text of Grassley's letter to the FDA Commissioner is below.

April 21, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Off-Label Promotion of Drugs

Dear Commissioner von Eschenbach:

As a senior member of the United States Senate and as Ranking Member of the Committee on Finance (Committee), it is my duty under the Constitution to conduct oversight

into the actions of the executive branch, including the activities of the Food and Drug Administration (FDA or Agency). In this capacity, I must ensure that FDA upholds its responsibility to the public's safety by properly regulating the nation's drug supply and ensuring that the drugs Americans use are safe and effective.

Physicians can prescribe any drug or device approved for marketing by the FDA as they see fit. Pharmaceutical and device manufacturers, however, are not allowed to promote products for "off-label" uses, or those that have not been cleared by the FDA as safe and effective. Off-label prescribing can raise significant safety concerns because there may be limited, if any, evidence that the benefits of the off-label use outweigh the risks.

I have repeatedly insisted that the FDA make more information available to the public about the safety and efficacy of drugs and devices so that physicians and in turn, their patients can make informed medical decisions. It would therefore seem reasonable for the FDA to encourage the distribution of available scientific literature as a way to ensure that physicians have additional information about the products they prescribe to their patients. However, I have serious concerns about FDA's current proposal to expand direct distribution of scientific articles to physicians by pharmaceutical and device sales representatives in light of recent studies and editorials regarding "ghostwriting" and manipulation of scientific data by the drug industry, as well as, my own findings about the integrity of the peer review process.

In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA), which included a provision, Section 401, allowing drug manufacturers to distribute scientific literature and reference publications on new or off-label uses under certain conditions. The drug manufacturer was required to submit a supplemental new drug application (NDA) for the off-label use or obtain an exemption from the requirement from the Secretary of the Department of Health and Human Services. Section 401, however, expired in September 2006, and in February 2008, the FDA proposed draft guidance on the dissemination of scientific literature to physicians by drug and device manufacturers at the prompting of, among others, the drug industry.

FDA's draft guidance is similar to Section 401, but it lacks an important requirement: that drug manufacturers submit a supplemental NDA or obtain an exemption from the requirement. As a result of this decision FDA is essentially ensuring that there would be no review by the FDA of data that would have earlier been made available to the Agency through the supplemental application process.

FDA's proposal expands not only the pharmaceutical industry's ability to promote off-label drug use, but also the medical device industry's ability to distribute scientific literature to physicians regarding unapproved uses of their products. What the FDA once considered evidence of unlawful marketing/misbranding/adulteration of a drug or device, the Agency would now consider an appropriate dissemination of information. In effect, the FDA is ceding some of its oversight of off-label promotion. In fact, the FDA states in its draft guidance that "if a manufacturer follows the recommendations of…this guidance and there is no unlawful promotion of the product, FDA does not intend to use the distribution of such medical and scientific information as evidence of an intent by the manufacturer that the product be used for

an unapproved use." But, Dr. von Eschenbach, the intent of the manufacturers in distributing such scientific literature is to "promote" an unapproved use, and now it appears manufacturers would be permitted to do so with FDA's blessing.

Last week, a study in the Journal of the American Medical Association (JAMA) showed how the manufacturer of the painkiller Vioxx sought out academic "ghost writers" to put their names on journal articles about the drug, which were drafted by the manufacturer or a medical communications firm hired by the manufacturer. Manufacturers have academic doctors and scientists headline their medical articles because they know practitioners read and rely on articles authored by the experts in their field. What is troubling is that some of these doctors and scientists may agree to be the primary authors of the articles even though they may not be intimately familiar with the underlying study data. Such attempts to meddle in scientific literature can mislead doctors to prescribe treatments that may not work or even be harmful, which in turn would be costly to the health care system. In addition, such activities may make medical literature nothing more than an extension of drug or device marketing.

FDA's proposed guidance would require that the articles be published in peer reviewed journals, but as quoted by the New York Times, the author of one of the JAMA articles asked, "What does it mean to be peer-reviewed,…if the company has essentially conceived the article, composed the draft and written the paper?" In addition, earlier this year, I reported that a peer reviewer for the New England Journal of Medicine leaked a copy of a confidential draft article on the diabetes drug Avandia to the manufacturer of the drug. This is not the first time a breach of this kind has occurred, and it also calls into question the integrity of the peer review process as a whole.

Some critics of FDA's draft guidance also point out that the guidance will enable manufacturers to circumvent the FDA approval process because there would be limited incentive for a company to conduct rigorous clinical trials and seek FDA approval for off-label uses when the company can go directly to physicians about those uses.

Under the current environment, I believe that there are some very important questions that the FDA must answer prior to proceeding on its current path with regard to off-label promotion. For example, how will the FDA ensure that companies follow the recommendations of the guidance? In particular, how will the FDA ensure that companies are not using journal articles selectively to market off-label uses of their products? How will the FDA ensure that companies are not manipulating the science to support off-label uses? Indeed, since the FDA would no longer be provided a copy of the literature that a manufacturer is distributing directly to physicians, how will the FDA identify cases of noncompliance? What enforcement actions would be taken if a company fails to follow the guidance?

I look forward to your cooperation and assistance on this important matter.

Sincerely,

Charles E. Grassley

United States Senator
Ranking Member of the Committee on Finance