U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
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For Immediate Release
Wednesday, September 20, 2006

Grassley outlines problems at FDA, urges reforms

WASHINGTON — Sen. Chuck Grassley is continuing his effort to improve the work of the Food and Drug Administration by seeking reforms that would make the agency more transparent and its leadership better guided by the scientific process and public interest.

Grassley's oversight of the drug-safety agency has exposed a too-cozy relationship with the pharmaceutical drug industry and an agency culture that has sought to suppress concerns of agency scientists about drug safety risks. In response, Grassley has sought both administrative and legislative reforms. He has introduced bipartisan legislation with Sen. Christopher Dodd to create a mandatory clinical trials public registry and to improve the FDA's post-market surveillance of drugs on the market.

In a letter sent today, Grassley urged the acting commissioner of the Food and Drug Administration to take action. The text of that letter follows here.

September 20, 2006

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

Dear Dr. von Eschenbach:

As a senior member of the United States Senate and as the Chairman of the Committee on Finance (Committee), it is my constitutional duty to conduct oversight into the actions of executive branch agencies. For nearly three years, I have been investigating matters related to, among other things, the safety and efficacy of products regulated by the Food and Drug Administration (FDA or agency).

I have reviewed and questioned how the FDA handles the pre-market review and postmarket surveillance of drugs, biologics, devices and veterinary medicines to assess whether or not the agency is fulfilling its mission to protect the public health. Additionally, I have worked to give voice to the concerns of a number of rank-and-file scientists and FDA managers who share a common complaint: a deep-seated cultural divide exists within the FDA, and it has

led to systemic problems that plague the agency. Together we have shed sunlight on how frequently differences of scientific opinion are quashed, the nature of the cozy relationship between the FDA and the industries it is supposed to regulate, and the failure of the agency to be adequately transparent and accountable to the public.

Others also have identified serious leadership problems at the FDA. Editorial pages of publications across the nation, including a number of the most esteemed scientific journals, have recognized and expressed outrage at the FDA's failures in recent years. The Government Accountability Office (GAO), the independent and non-partisan agency that works on behalf of Congress and the American people, has also identified serious and systemic problems at the FDA. Still, the most powerful messages come from the increasing numbers of current and former FDA personnel, who often come forward at great personal and professional expense to express their disenchantment that the FDA has lost its way and "sold out" to the industries it is charged to regulate.

In the face of such criticism, the FDA appears to be focused on damage control rather than addressing its core problems. As a science-based agency, the FDA is remarkable for its lack of introspection, second-guessing, and failure to assess its own performance and capabilities in a systematic way. Despite all the recent criticism, the agency does not have a comprehensive plan of action in place to address its weaknesses. Instead, the FDA comes off as an agency in denial that chooses to keep its head in the sand in the hope its problems will go away. I am writing this letter to encourage you to establish and implement a resuscitation plan to restore the FDA's credibility in the mind of its own employees and the American public. An agency that hemorrhages whistleblowers is an agency needing critical care. The following concerns are by no means comprehensive, but they illustrate several common themes of my oversight of the FDA.

Suppression of Scientific Dissent

I am very troubled by FDA's attempts to suppress scientific dissent by muzzling its own scientists. Such actions by the FDA show a lack of respect for the dedicated scientists working at the agency and a lack of respect for the scientific process.

In February 2004, the FDA held an advisory committee meeting to discuss whether or not there was a link between some antidepressant drugs and suicidal behavior in children. Dr. Andrew Mosholder, the FDA's expert on this matter, concluded that there was a link. However, his FDA supervisors disagreed and canceled Dr. Mosholder's presentation to the advisory committee. Instead, Dr. Mosholder was given a script by his supervisors to read if he were asked why he was no longer presenting before the advisory committee.

Similarly, in February 2005, Dr. David Graham was finishing a study on Medicaid patients taking COX-2 inhibitors and was told by his supervisors that he could not present his findings regarding these drugs at an upcoming advisory committee meeting. The scientific process ultimately prevailed, but only after then-Acting Commissioner Lester Crawford overruled Dr. Graham's supervisors to allow him to present his findings. This was not the FDA's first attempt, however, to muzzle Dr. Graham. Several months prior to the advisory committee meeting, Dr Graham went public with allegations about the FDA's mishandling of the COX-2 inhibitor Vioxx, which was manufactured by Merck & Co, Inc. (Merck). According to Dr.

Graham himself, as well as information and documents obtained by the Committee, senior FDA officials attempted to intimidate him so he would not testify about the adverse cardiac effects of Vioxx before Congress. The FDA also tried to prevent the publication of Dr. Graham's findings in Lancet.

In July 2005, the FDA approved the Vagus Nerve Stimulation (VNS) Therapy System, a medical device for treatment-resistant depression (TRD), even when FDA scientists could not determine if the device worked. Rather than allow the scientific process to dictate FDA's decision, a senior FDA official overruled a team of more than 20 FDA scientists, medical officers, and management staff who recommended against approval of the device based on their comprehensive scientific evaluation of the sponsor's application. In addition, while the FDA has publicized differences of scientific opinion within the agency regarding controversial regulatory decisions in the past, in this case, the FDA did not publicize scientific dissent regarding the effectiveness of the VNS Therapy System for TRD.

More recently, my office was approached by yet another FDA scientist who is being prohibited from submitting an article to a major scientific journal despite the fact that an appropriate disclosure statement would be made.

Cozy Relationship with Industry

I have frequently criticized the FDA for its relationship with the industry, which I believe is far too cozy. The FDA needs to distance itself from the industry and return to its role as regulator, not a facilitator. Despite findings from a Merck study that heart attacks were five times higher for Vioxx patients than for patients on another drug, nearly two years passed before label changes were made. The overriding concern of the FDA should have been the health and safety of the American people. However, while the FDA was negotiating label changes with the company, patients and doctors remained largely unaware of the cardiovascular risks. In addition, Merck was aggressively marketing Vioxx during that time.

Another troubling example of FDA's coziness with industry is the removal of Dr. Victoria Hampshire, a drug safety reviewer, from the review of ProHeart 6, a heartworm prevention drug for dogs. Dr. Hampshire was reassigned following the drug company's presentation of findings from its private investigation of Dr. Hampshire after the company met with then-Commissioner. It appears the purpose of that investigation was retaliatory and an effort to discredit Dr. Hampshire. The company's investigation led to a criminal investigation by the FDA; however, the investigation resulted in no action taken against Dr. Hampshire. In fact, Dr. Hampshire subsequently received an award for her job performance related to ProHeart 6.

Unfortunately, it appears that Dr. Hampshire is not the only FDA employee who was the target of a company's campaign to discredit individuals who may present impediments to its agenda. Two months ago, I wrote to the Department of Health and Human Services Office of Inspector General (HHS OIG) to investigate whether or not one or more FDA employees conspired with Merck to discredit Dr. Graham and/or call into question Dr. Graham's allegations regarding the safety and efficacy of Vioxx. FDA's handling of the antibiotic Ketek is another example where the FDA appears to have accommodated a drug company despite the fact that the company submitted fraudulent data from a safety study to the FDA and repeatedly provided incomplete safety information. What baffles me even more is the fact that the FDA continued to

cite Study 3014 in publicly released safety information for Ketek even after its Division of Scientific Investigations concluded that Study 3014 involved "multiple instances of fraud" and that "the integrity of data from all sites involved in [the] study…cannot be assured with any degree of confidence."

Pressure to Alter or Exclude Information

Not only has the FDA disregarded and downplayed important concerns and warnings from its own scientists, but FDA supervisors have also pressured some of these scientists to change their findings or conclusions regarding the safety and/or efficacy of a product. Most notably Dr. Mosholder and Dr. Graham, among others, have been pressured by their supervisors to soften their safety findings or conclusions regarding antidepressants and Vioxx, respectively. In addition, a survey released by the Union of Concerned Scientists (UCS) and the Public Employees for Environmental Responsibility (PEER) on July 20, 2006, found that approximately one-fifth of the nearly 1,000 FDA scientists surveyed said that they had been asked, for nonscientific reasons, to inappropriately exclude or alter technical information or their conclusions. One-fifth said that they have been asked explicitly by FDA decision-makers to provide incomplete, inaccurate or misleading information to the public, industry, the media and government officials. My Committee staff are presently reviewing such allegations in ongoing investigations.

Pressure to Approve Products

Throughout numerous investigations by my Committee staff, FDA employees have also stated that they are under constant pressure to approve drugs within deadlines established by the Prescription Drug User Fee Act. For example, during the Committee's investigation into the delay in labeling changes regarding blindness risks for Viagra, the safety evaluator for that drug informed my staff that the Office of New Drugs is under such time pressure to approve new drugs that safety concerns were often "fit in" wherever they could. According to a survey by the HHS OIG in 2002, nearly one in five scientists polled said that they had been pressured to approve or recommend approval of a new drug despite concerns about its safety, effectiveness, or quality. This needs to be corrected immediately, and FDA needs to resume its science-based mission.

Atmosphere of Fear of Reprisal

According to the FDA, there are regulations and procedures in place to help resolve organizational and individual disagreements. However, my Committee staff continues to hear from FDA employees who experience intimidation and reassignments when they raise concerns about the integrity of FDA's work. In addition, the 2006 UCS and PEER survey found that over one-third of the FDA scientists who responded to the survey said they could not openly express any concerns about public health within FDA without fear of retaliation. Moreover, the GAO found that the dispute resolution processes for disagreements over postmarket drug safety decisions "have not been used and may not be viewed as sufficiently independent."

Your recent meeting with FDA staff involved in the review of Ketek is a disturbing example that FDA's internal dispute resolution processes are not working. Instead of reassuring

FDA employees that they can raise concerns without being subjected to retaliation or intimidation, the meeting itself appears to be an act of intimidation. Scientists who speak up about problems and concerns, whether internally or externally, help ensure that our government operates efficiently, effectively, and in the best interest of the American people. FDA employees need to hear from the leader of the agency that they can freely voice their concerns without fear of reprisal.

Organizational Challenges

The GAO report released on April 21, 2006, calls for long overdue reform at the FDA. Under the current FDA review system, patient safety takes a back seat to the fast approval of products. For example, the drug safety office, now known as the Office of Surveillance and Epidemiology, is under the thumb of the Office of New Drugs (OND), which is hampered by real and perceived conflicts of interest. According to the GAO report, the drug safety office is under-funded, lacks independence and lacks decision-making responsibility. OND—which is responsible for approving or disapproving drug applications in the first place—is the office responsible for taking regulatory actions related to the safety of drugs already on the market, not the drug safety office.

To improve the decision-making process for postmarket drug safety, the GAO has recommended that Congress expand the FDA's authority to require drug companies to conduct postmarket studies when additional data is needed. A number of us in Congress have repeatedly asked the FDA what additional authorities and/or resources are needed to enable the agency to achieve its mission. In a related matter, during private meetings with FDA management, the need to have pharmaceutical companies submit their applications for new drugs and other requests electronically comes up repeatedly as critical to improving the efficiency and effectiveness of the FDA. Yet, the FDA continuously denies the need for greater authority and resources. Why the FDA is resisting such offers from Congress is a mystery to me.

Lack of Leadership

The FDA has been without a permanent leader more often than not in recent years. The agency needs and deserves a strong, permanent Commissioner who is unequivocally committed to the scientific process and can make the administrative reforms necessary to ensure greater transparency and accountability. While you are not the permanent Commissioner of the agency, you are nevertheless in the position, as Acting Commissioner, to turn things around and restore public confidence in the FDA. I sincerely hope you seize the opportunity to do just that.

Sincerely,
Charles E. Grassley
Chairman
Committee on Finance