U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
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Grassley questions FDA about information on antidepressants, suicide

WASHINGTON — In a letter this week, Sen. Chuck Grassley spelled out what he has learned to date in his investigation of the Food and Drug Administration's handling of information about antidepressants and suicide among young people and asked new questions about possible efforts by the agency to withhold certain information from the public.

Grassley also described new concerns about the relationship between the Office of New Drugs and the Office of Drug Safety within the Food and Drug Administration.

The text of Grassley's letter to the Food and Drug Administration and the Department of Health and Human Services follows here. Grassley is chairman of the Senate Committee on Finance.

June 16, 2004

The Honorable Tommy G. Thompson
Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dr. Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Secretary Thompson and Dr. Crawford:

Last March, I instructed my staff to review whether or not Dr. Andrew Mosholder, who works in the Office of Drug Safety (ODS), was precluded from delivering his analysis of clinical data relating to children, anti-depressants, and suicidal events to a Food and Drug Administration

(FDA) Advisory Committee Meeting (ACM) on February 2, 2004. My concerns at the time centered around the public's right to know the possible effects of certain anti-depressants on children and reflected my deep and unbridled concern for the thousands of children across America who are faithfully taking potentially life-threatening medication, which have been found to be no better than placebo in the treatment of depression in children. In addition, I expressed concern to you regarding the investigation that was launched into the "leak" of Dr. Mosholder's analysis.

Let me begin by saying that Dr. Mosholder appears to be a man of great integrity, placing his findings and recommendations above all else, despite FDA efforts to limit and strategically manipulate information to be provided to the public. This country needs more civil servants with Dr. Mosholder's devotion to doing what is right in the face of adversity.

Interviews conducted during the course of this investigation have provided the Committee with a trove of information to consider. To begin with, it is necessary to address the ODS, both its function and mission. The ODS has a very specific mission: it "evaluates drug risks and promotes the safe use of drugs by the American people." In essence, ODS maintains a system of "postmarketing surveillance" to identify adverse effects that did not appear during the drug development process. This mission makes perfect sense. Clinical studies conducted, prior to a drug entering the U.S. market, involve a limited number of highly selected individuals and a similarly limited number of trials. In other words, the laboratory in which the drug is being tested for its usefulness is understandably small and controlled. As a result, the full range of possible adverse effects of a new drug does not always surface. Indeed, the real laboratory for new drugs occurs once the drug is dispensed across large numbers of people after marketing begins. The ODS learns about adverse events through reporting by companies and through voluntary reports submitted to FDA's MedWatch program; a program for health professionals and consumers to report adverse events to FDA. Staff in ODS, like Dr. Mosholder, use this information to identify drug safety concerns and recommend actions to improve product safety and protect public health. Unfortunately, interviews with FDA employees suggest that a disconnect exists within the ODS, between its mission and its current operations.

According to staff interviews, Dr. Mosholder is a child psychiatrist who, prior to joining ODS, served for almost 10 years in the Division of Neuropharmacologic and Psychiatric Drugs (Neuropharm) within the Center for Drug Evaluation and Research (CDER) of FDA. Neuropharm, located within CDER's Office of New Drugs (OND), is responsible for approving drugs for entry into the marketplace. During his decade in Neuropharm, Dr. Mosholder was responsible for reviewing safety and effectiveness studies on anti-depressants and children. As a result of his unique knowledge and experience, Dr. Mosholder is the de facto expert at FDA for the efficacy of anti-depressants in children, and accordingly was sought out by Dr. Katz, the Director of Neuropharm, to do a "rush consult" to evaluate the clinical studies involving children, anti-depressants and suicide. This "rush consult" was sparked by several factors, including the availability of new data analyses indicating an increase in suicidal thoughts and behaviors in children treated with some of these drug agents. As a result of this consult, Dr. Mosholder was protected from all other assignments so that he could complete this important analysis quickly (the Mosholder Analysis).

Dr. Mosholder conducted his review of the clinical data, prepared his analysis, and provided that analysis, without recommendations, to his peers and superiors including, Drs. Mary Willy, Mark Avigan, and Anne Trontell in September 2003. Overall, the Mosholder Analysis was widely disseminated. Moreover, Dr. Mosholder's findings were and remain that there is a link between anti-depressant use by children and suicidal and self-injurious thoughts and behaviors. His report was well received. In fact, his immediate supervisor Dr. Willy noted a job well done, while Drs. Avigan and Tronell, both of whom would later write dissenting opinions to Dr. Mosholder's analysis, advised Dr. Mosholder that he had done a "great job" and "good job," respectively.

Over the course of the next several months, Dr. Mosholder said that he continued to refine his analysis, but his findings never changed, i.e., the link between children, anti-depressants and suicide was unmistakable. As a result of these and other events, a decision was made by Neuropharm and OND that Dr. Mosholder would present his analysis and findings at the February 2, 2004 Psychopharmacologic Drugs Advisory Committee Meeting (ACM), as noted in the Federal Register on October 31, 2003.

On December 10, 2003, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) issued a statement regarding children, anti-depressants and suicide. The MHRA noted that only Prozac should be given to children with depression and that the use of all other selective serotonin reuptake inhibitors (SSRI anti-depressants) was contraindicated. The FDA was well aware of this determination.

In anticipation of the February 2, 2004 ACM, a planning meeting took place in December 2003. During the course of that planning meeting, Dr. Mosholder distributed to all the attendees an outline of his talking points, which noted that a child taking an anti-depressant, other than Prozac, was twice as likely to have a suicidal event as a child taking a placebo. This was a significant finding and was consistent with the MHRA findings and the Lancet study.

Dr. Laughren, the Deputy Director of Neuropharm and formerly Dr. Mosholder's team leader during his tenure in Neuropharm, objected unexpectedly to Dr. Mosholder's methods at a December meeting. This was the case despite the fact that he had received a copy of the analysis and had an opportunity to review it several months earlier. It is my understanding that Dr. Laughren wanted to get further analysis of the data done by Columbia University before reaching a conclusion.

On January 6, 2004, Dr. Mosholder was contacted by Dr Katz. During a 20 minute conversation, Dr Katz informed Dr. Mosholder that he would no longer be presenting at the ACM because Dr. Mosholder: 1) reached a different conclusion than OND; and 2) utilized incomplete data. This decision was neither embraced by Dr. Mosholder, nor by his superiors in the ODS, but it appears that little could be done to ameliorate the situation.

During the course of this investigation, it has become increasingly more apparent that the ODS and the OND exist in a relationship that is best described as "separate but unequal." According to staff interviews, the ODS serves a subservient role to the OND. Indeed, the ODS was described by one employee as the "unwanted stepchild" at FDA, rather than a watchdog for the public at large. This observation merits further in-depth review because of the seriousness of

the impact of any organizational weakness at the FDA upon public safety.

Subsequent to the decision to remove Mosholder from the agenda of the ACM, the FDA engaged in a series of other activities that are also very troubling. In anticipation of the fact that parties interested in the Mosholder analysis were expected to attend the ACM, including family members of children harmed by one or more anti-depressants, it appears the FDA: 1) prepared scripted answers for Dr. Mosholder to read if questioned at the ACM; 2) attempted to have Mosholder present data known to be unreliable and deceptively misleading; and 3) engaged in behavior that overall is unexpected from an organization charged with ensuring and protecting the safety of American consumers taking prescription medications.

To begin, Dr. Mosholder was advised at one point that if he were willing to modify his recommendations, perhaps he could present his analysis at the ACM. Indeed, new recommendations were drafted for his consideration. However, Dr. Mosholder refused to accept new, alternative language, stating that the alternative language misconstrued his recommendations.

In addition, Dr. Mosholder was told that he was not sitting at the meeting table during the ACM, despite the fact that he was providing information on another topic. This decision was made by the OND. Dr. Mosholder was advised that in the event he was asked any questions regarding his anti-depressant analysis, he was not allowed to speak about his analysis, he could only speak from the "prepared" answers. This seems like a peculiar way to treat the "established" expert in the area of SSRIs and children.

Perhaps most troubling, however, was the fact that OND attempted to have Dr. Mosholder present "reporting rates" of suicidal thoughts, rather than the available clinical trials data on anti-depressants and children, which formed the foundation of his analysis. This is bothersome for several reasons. "Reporting rates" are considered marginally reliable and clinical trials data have long been regarded by FDA as the most reliable type of data based upon the experts interviewed. As one interviewee stated, "clinical data trumps reporting data any time." These rates are derived from dividing the number of cases reported to the FDA by pharmacists, physicians and others and stored in the computerized Adverse Event Reporting System (AERS). AERS is a voluntary reporting system intended, among other things, to monitor the safety effects of drugs once they are approved by the FDA for marketing. In order to determine the reporting rate you simply take the AERS data for a particular drug and divide it by the number of prescriptions filled for that particular drug. This provides the "reporting rate" for that drug. In the instant situation, the OND wanted Dr. Mosholder to present "reporting rates" of suicidal thoughts and behavior for anti-depressants in children at the ACM. However, Dr. Mosholder refused to do so because most serious adverse drug effects are never reported to FDA.

Consequently, any "reporting rate" would be extremely low, not because the SSRI anti-depressants do not promote suicidal thoughts and behaviors in children, but because voluntary reporting is so poor and infrequent. The use of "reporting rates" at the ACM would be deceptively false and misleading and would provide a "false sense of security" to the public. Staff interviews suggest that had these reporting rates been presented at the ACM, the public, the

media and the Congress probably would have concluded that anti-depressants are all extremely safe for children.

On one hand, it can be said that the public should be grateful that Dr. Mosholder held his ground and refused to present "reporting rates" at the ACM; yet, on the other hand, the fact that a high-level official at the OND/FDA would consider such an alternative is alarming. In fact, it begs the question: in how many other instances were reporting rates provided when more reliable data was available? In how many other instances has the OND manipulated its advisory committee meetings to withhold from the public and misrepresent safety information about marketed drugs of critical importance to patient safety?

It appears from this investigation to date, the turning point for removing the Mosholder Analysis from the ACM was not the fact that Columbia University was going to further analyze the data or that Dr. Mosholder's superiors had not "cleared" the consult, as reported in the press. After all, it was repeatedly reported to us that consults/analyses that had not been "cleared" were regularly presented to the ACM. The lynchpin for removal of the Mosholder consult from the ACM was the insertion of "recommendations." Specifically, Dr. Mosholder recommended that "a risk management strategy directed at discouraging off-label pediatric use of anti-depressant drugs, particularly the use of drugs other than fluoxetine (Prozac), in the treatment of pediatric MDD (major depressive disorder)."

During the course of discussions regarding the removal of the Mosholder Analysis from the ACM agenda, another matter of interest came to light. Specifically, staff interviews suggest that inserting recommendations into drug consults are neither encouraged nor wanted by the OND. In fact, one employee at the ODS stated, that he was "hazy" on whether or not recommendations should ever be written. Another employee stated that consult recommendations are outright discouraged because they force the hand of the OND to "do something" and that the OND preferred that ODS consults remain "sterile."

The fact that ODS employees believe that they should not insert recommendations in their consults appears to be in direct contravention of ODS claims. Specifically, the ODS's website states that ODS is to "identify drug safety concerns and recommend actions to improve product safety and protect the public health." It would seem that OND's decision to discourage scientists at ODS from recommending action intended to serve the public interest is inconsistent with its stated mission. More importantly, it is contrary to the basic fundamental principle upon which our government is built: that is; having independent and objective reviewers of fact to protect the American public in a timely and effective manner, particularly when it comes to the issues of public health.

A review of the facts surrounding the removal of the Mosholder Analysis from the ACM, coupled with efforts to have "reporting data" presented as opposed to clinical data at the ACM and attempts to modify Mosholder's recommendations, in return for a seat at the ACM table, lend themselves to a number of concerns. First, the relationship between the ODS and the OND does not appear to be in the best interest of the consumer. Indeed, some staff interviews noted that ODS is simply there to "serve" OND. Still others stated that perhaps ODS should consider

re-naming itself to the "Office of Drug Safety Consultants" or the "Office of Dumb Simpletons." In addition, I continue to be extremely interested in the investigation that was launched into the "leak" of information to the press and to Congress regarding the findings of the Mosholder Analysis. Although I am continuing my review of that matter, there is one point that must be made. My letter, dated March 25, 2004, asked: "What was the purpose of this alleged investigation?" In response, I was advised that: "This investigation was initiated to determine if there was an inappropriate disclosure of sensitive information." This response appears to be 1) not true; 2) an insult to the process in which I am engaged; and 3) at best, a misleading response to my inquiries.

It was well-established among ODS employees that the "leak" investigation was intended to ferret out the name or names of the individuals who contacted the press with Dr. Mosholder's findings. The investigation was a catalyst for fear and was, according to those interviewed to date, intended to target the "leak." In fact, none of the individuals interviewed had any recollection of the "leak" investigation being driven by a concern about the disclosure of sensitive information; rather they believed that FDA was after the "leaker," and if found, that individual(s) would likely suffer severe negative consequences. Accordingly, in the future, I would greatly appreciate that my inquiries be taken with the seriousness in which they are asked; I expect no less.

Thank you for your continued cooperation.

Sincerely,

Charles E. Grassley
Chairman