U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
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For Immediate Release
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Grassley Questions FDA's Approach to Managing Attention Deficit Prescription Drugs

WASHINGTON – Sen. Chuck Grassley, chairman of the Committee on Finance, is expressing concern that the Food and Drug Administration is taking a disjointed, slow approach to regulating prescription drugs for Attention Deficit Hyperactivity Disorder.

As prescriptions for these drugs have dramatically increased over the past four years, so have the reports of serious cardiovascular and psychiatric adverse events related to the use of these drugs. Further, with more than 2.5 million children under the age of 17 using these drugs, Grassley expressed his concern in a letter to Dr. Andrew C. von Eschenbach, the acting commissioner of the agency.

"I remain concerned that while both psychiatric and cardiovascular risk signals have cropped up across this class of drugs this past year, it appears that FDA is just now beginning to 'discuss approaches' for studying these risks," Grassley wrote this week. "More specifically, I question why it has taken nearly an entire year for FDA to begin to address these concerns given the serious nature of the adverse events associated with these drugs."

Grassley sent his letter in advance of two FDA advisory panel meetings to examine adverse events related to Attention Deficit Hyperactivity Disorder prescription drugs. The first panel convenes this Thursday and Friday. The text of his letter follows.

February 6, 2006

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

Dear Dr. von Eschenbach:

The United States Senate Committee on Finance (Committee) has exclusive jurisdiction over the Medicare and Medicaid programs, and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage under these programs. Each year Medicare and

Medicaid pay hundreds of millions of dollars for prescription drugs, including reimbursement for prescription drugs used to treat Attention Deficit and Hyperactivity Disorder (ADHD). As Chairman of the Committee, I write out of concern regarding the Food and Drug Administration's (FDA) handling of the safety concerns associated with the class of drugs indicated for treatment of ADHD, including Adderall, Concerta, and Strattera, and whether or not the drugs' long-term risks have been adequately and promptly explored.

Sales of ADHD drugs have skyrocketed over the past few years. IMS Health reports that ADHD drugs sales increased over threefold between 2000 and 2004, from a total of $759 million to $3.1 billion. Whether or not ADHD drugs are overprescribed to children remains extremely controversial. Yet, in this context of increased ADHD drug treatment, it does not appear that FDA has taken a comprehensive approach toward addressing the potential cardiovascular and psychiatric risks associated with this class of drugs. Rather, FDA's actions appear ad hoc and disjointed leaving serious questions in the minds of the parents of 2.5 million (See Note 1) children and adolescents who use ADHD medications.

This past year, adverse event reports for these ADHD drugs have detailed cardiovascular episodes, such as hypertension, chest pain, arrhythmias and tachycardia (rapid heartbeat), among others. Additionally, concerns were raised regarding sudden unexplained deaths (SUD), strokes, and various psychiatric events—including reports of abnormal behavior, aggression, anxiety, depression, and suicidal thoughts. Each of these adverse events presents serious and possibly life threatening side effects for those using these prescription drugs to treat ADHD.

Adderall XR

In February 2005, cardiovascular concerns raised in adverse event reports ultimately led Health Canada (the Canadian equivalent of FDA) to suspend market authorization of Adderall XR for six months. Health Canada's temporary suspension of Adderall XR was based upon post-marketing reports compiled in the United States. According to Health Canada, the decision came as "a result of a thorough review of safety information provided by the manufacturer, which indicated there were 20 international reports of sudden death." (See Note 2)

At the same time that Canada decided to suspend use of Adderall XR, FDA "[did] not believe that any immediate changes [were] warranted in FDA's labeling or approved use of the drug." (See Note 3) However, FDA did note that it had required the modification of the labeling for Adderall XR in August of 2004 to include a warning to patients with an underlying heart defect that they might be at an increased risk for sudden death.

Concerta

Last summer, the safety of ADHD drugs was again called into question when FDA publicly stated that it had concerns about possible psychiatric side effects stemming from the use of Concerta for the treatment of ADHD. Specifically, FDA stated on its website that it had "identified two possible safety concerns with the methylphenidate drug products: psychiatric adverse events and cardiovascular adverse events." (See Note 4) These statements were made in conjunction with the June 29 and 30, 2005 meeting of FDA's Pediatric Advisory Committee.

Over the course of the two-day meeting, the Pediatric Advisory Committee discussed the cardiovascular and psychiatric adverse events reported to FDA. Through spirited discussion the

various members of the Pediatric Advisory Committee expressed concerns that label changes to methylphenidate products may be necessary for both cardiovascular and psychiatric side effects. Ultimately, the Pediatric Advisory Committee decided that moving too quickly with label changes could alarm the public and according to press accounts, would hold off making any recommendations regarding the Concerta label until an FDA review of the entire class of drugs could be completed in early 2006.

Strattera

In September of 2005, FDA issued an alert to Healthcare Professionals regarding the use of Strattera in children and adolescents. The public health advisory directed Eli Lilly, the manufacturer of Strattera to "revise the labeling…to include a boxed warning and additional warning statements regarding an increased risk of suicidal thinking in children and adolescents." (See Note 5) FDA cited data showing an increase in suicidal thoughts among those in 12 separate studies, including one individual who attempted suicide.

Upcoming Advisory Committee Meetings

FDA recently announced meetings of two different advisory committees to examine adverse events related to ADHD drugs. In early January 2006, the FDA announced a meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM), which is scheduled for February 9-10, 2006. According to the DSaRM agenda, "[c]ases of sudden death and serious adverse events including hypertension, myocardial infarction, and stroke have been reported to the [FDA] in association with therapeutic doses of drugs used to treat Attention Deficit Hyperactivity Disorder (ADHD) in both pediatric and adult populations."

On the first day of the DSaRM meeting, "the committee will be asked to discuss approaches that could be used to study whether these products increase the risk of adverse cardiovascular outcomes." On the second day of the DSaRM meeting, "the committee will be briefed on agency actions for the COX-2 selective Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)," among other issues. The juxtaposition of these two drug classes (ADHD and COX-2) on the agenda may be coincidentally ominous. Indeed, it was reported recently, with respect to the potential cardiovascular risk associated with ADHD drugs, that the chairman of the DSaRM Committee, Dr. Peter Gross, said, "it almost sounds like cox-2 inhibitor redux."

Two weeks ago, the FDA announced another meeting to examine adverse events of ADHD drugs before the Pediatric Advisory Committee. FDA stated that it would convene the Pediatric Advisory Committee on March 22, 2006, to discuss neuropsychiatric adverse events associated with ADHD medications for the pediatric population. In the announcement, FDA stated that this panel will also "receive an update on efforts to better understand cardiovascular adverse events."

While I am pleased that FDA has convened both the DSaRM advisory panel to discuss cardiovascular concerns and the Pediatric Advisory Committee to discuss neuropsychiatric adverse events, I remain concerned that lost between the two meetings is a comprehensive review of all adverse events for this entire class of medication for all populations served. It is understandable that FDA would use multiple panels to review some of the ADHD drugs individually, mainly because there are so many drugs used to treat ADHD. However, at some point a comprehensive review of the entire class of ADHD drugs would be beneficial to the millions of Americans taking ADHD medications and the parents of the 2.5 million children on

these drugs.

Further, I remain concerned that while both psychiatric and cardiovascular risk signals have cropped up across this class of drugs this past year, it appears that FDA is just now beginning to "discuss approaches" for studying these risks. More specifically, I question why it has taken nearly an entire year for FDA to begin to address these concerns given the serious nature of the adverse events associated with these drugs.

Thank you in advance for your assistance with this matter by having your staff coordinate with my staff no later than the close of business on February 8, 2006, to provide a briefing. Additionally, I request that you provide a complete list of participating panel members and a complete list of conflict disclosures for both the February 9-10 DSaRM advisory committee and the March 22 Pediatric Advisory Committee. I look forward to hearing from you regarding the issues and questions set forth in this letter and would appreciate a response no later than February 16, 2006.

Sincerely,

Charles E. Grassley
Chairman

(1) *See* National Center for Birth Defects & Developmental Disabilities, Centers for Disease Control and Prevention, *available at* http://www.cdc.gov/ncbddd/adhd/default.htm (last visited Feb. 3, 2006).
(2) Health Canada Health Advisory, February 9, 2005
(3) Letter from FDA to Senator Charles E. Grassley (March 15, 2005)
(4) FDA Statement on Concerta and Methylphenidate for the June 30 PAC, available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4152b1_00_05a_Statement%20for%20June%2030.pdf
(5) FDA Alert for Healthcare Professionals on Atomoxetine (marketed as Strattera), September 29, 2005.