United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

June 24, 2005

Via Facsimile: (301) 827-1960
Original via USPS Mail

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

Dear Dr. Crawford:

The Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs, and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage, including prescription drugs, under those programs. This coverage includes payments for phosphodiesterase type 5 (PDE-5) inhibitors, including Pfizer, Inc.'s (Pfizer) Viagra, Lilly ICOS LLC's Cialis and Bayer Pharmaceuticals Corporation's Levitra, to treat erectile dysfunction (ED). It is estimated that over the next ten years Medicare and Medicaid combined will pay $2 billion for these drugs.

By letter dated June 2, 2005, I requested that the Food and Drug Administration (FDA) make a safety evaluator in the Office of Drug Safety (ODS) available for an interview with my Committee staff and provide documents related to her assessment of adverse reactions associated with the use of Viagra. That safety evaluator is and was assigned the task of monitoring adverse events for, among other drugs, Viagra.

Last week, my Committee staff met with the safety evaluator and the FDA responded to the Committee's document request. Thank you for your cooperation in scheduling the interview and for providing the materials requested in a timely manner.

Based upon our interview and a review of the materials provided, I am troubled by the FDA's actions, or lack thereof, related to the updating of Viagra's product label to include safety information about an adverse reaction that may be associated with the use of Viagra, specifically, non-arteritic anterior ischemic optic neuropathy (NAION). NAION is a condition that can lead to permanent blindness, usually in one eye. In

essence, it is the equivalent of having a stroke in an eye that may then leave the patient blind in that eye. Based on my Committee staff's review of documents and information obtained to date, it appears that the Office of New Drugs (OND) did not initiate label change negotiations until a very short time ago. This is the case despite OND's knowledge of the blindness risks since January 2004 and general agreement among FDA staff last spring that the label should be updated.

The safety evaluator from ODS submitted her initial draft safety consult to her supervisors on March 1, 2004. That draft made recommendations for a Viagra label change. Specifically, the safety evaluator noted that:

> The labeling for sildenafil should be updated to include a precaution and warning about the potential increased risk of non-arteritic AION resulting in permanent visual loss with the use of sildenafil in patients with vascular risk factors (such as hypertension, diabetes, hypotension) or optic disks anatomically predisposed to non-arteritic AION. Ophthalmologists and optometrists should be encouraged to solicit information regarding sildenafil usage from male patients who have optic disks anatomically predisposed to non-arteritic AION. These patients should be made aware of the potential increased risk of non-arteritic AION and permanent visual loss with the use of sildenafil. This information should also be included in the patient package insert.

Further, the safety evaluator advised the Committee that ODS was very supportive of both her findings and her recommendation. Indeed, her direct supervisor noted that she prepared a "superb consult." In addition, when that safety evaluator consulted with the deputy director of OND's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, he reviewed the NAION cases reported to AERS and concluded in January 2004 that it was "plausible to add something to the labeling" for Viagra even though a link between Viagra use and the occurrence of NAION had not yet been established. On April 26, 2004, the ODS report was made final and provided to the OND. It was explained to my staff that OND had the last word on what actions the FDA would take based on the analyses, reviews, and consults conducted by ODS employees.

Over the course of the next 13 months, that safety evaluator continued to monitor FDA's adverse event reporting system (AERS) for reports of new NAION events. During this period, cases of NAION increased and were also identified in two other ED drugs, specifically Cialis and Levitra, suggesting a link between NAION events and the use of all three ED drugs. More interestingly, when the safety evaluator was asked by my staff why 13 months passed and no changes had been made to the Viagra label, she explained that because OND is under such time pressures to approve new drugs, often safety concerns needed to "fit in" wherever it could. What we appear to have here, Dr. Crawford, is yet another example of the "separate but unequal" relationship between OND and ODS that my bill is intended to correct once and for all.

During the interview with the safety evaluator, my Committee staff also explored the issue of underreporting of adverse events. The safety evaluator explained to my Committee staff that because ophthalmologists are not the usual prescribers of Viagra, their patients are not likely to volunteer information about Viagra use, although ophthalmology is the specialty that would address NAION. The evaluator went on to note that the physicians who are prescribing Viagra, such as urologists, may not be aware of the NAION risks associated with Viagra. The first cases suggesting a concern were reported in the medical literature in March 2002 by Dr. Howard Pomeranz, an associate professor and director of Neuro-Ophthalmology Service at the University of Minnesota; however, Dr. Pomeranz's findings and most other findings regarding ED drug use and the occurrence of NAION are published in medical journals that are targeted at the ophthalmology community, not the urology or other physician communities that may be prescribing ED drugs. In addition, NAION is known to be linked to the same illnesses, such as diabetes and heart disease, that can lead to ED. Therefore, conversations between physicians and their patients about NAION risks and ED drug use are not likely to take place before patients are prescribed the medication. In other words, we have the classic disconnect problem between two medical specialties, creating an environment for underreporting to the FDA of NAION that occurs in patients who have taken Viagra or another ED drug.

In light of the aforementioned, please provide the requested information and/or respond to the following questions related to NAION and ED drugs:

1. Provide a copy of the administrative file and related documents on labeling changes regarding NAION risks and Viagra.

2. Provide all documents related to internal communications regarding NAION risks and Viagra, including but not limited to e-mail communications, teleconference minutes, and meeting minutes, notes, and/or summaries (all drafts and final versions), from January 1, 2004 through June 17, 2005.

3. Provide all documents related to communications between the FDA and Pfizer's representatives and consultants regarding NAION risks and Viagra, including but not limited to e-mail communications, teleconference minutes, and meeting minutes, notes, and/or summaries (all drafts and final versions), from January 1, 2004 through June 17, 2005.

4. According to internal FDA documents, Pfizer resisted the FDA's initial request to update the Viagra label to include information about NAION risks. It appears that the company may have relented after it learned that CBS News would be doing a story on the possible link between NAION and Viagra. The FDA has stated repeatedly that it does not need additional regulatory authorities and enforcement powers to ensure the safety of drugs, but how can you make this statement when a pharmaceutical company can refuse to make label changes requested by the FDA?

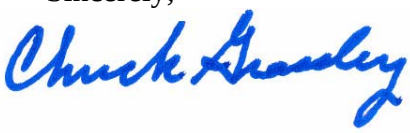
5. The safety evaluator from ODS informed my Committee staff that NAION may also be associated with the use of the two other PDE-5 inhibitors, Cialis and Levitra. Please state whether or not the FDA is considering label changes for the entire class of drugs to include safety information regarding NAION. If so, what is the time frame for implementation of the label changes?

6. Please describe, in detail, any actions the FDA plans to take to ensure that physicians and patients are informed of NAION and its association with ED drug use. For example, will the FDA consider issuing a "Dear Health Care Professional" letter, and if so when?

7. Because the physicians who are prescribing ED drugs are not likely to be the same physicians who diagnose and treat NAION in patients taking an ED drug, please describe, in detail, any actions the FDA plans to take to improve reporting of NAION cases to AERS and enable the FDA to determine if this serious side effect is more prevalent than previously reported.

Thank you in advance for your assistance. I would appreciate a response to my inquiries and document requests no later than July 15, 2005. Please provide the requested information and documents in accordance with the definitions attached to this letter.

Sincerely,



Charles E. Grassley
Chairman