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

February 1, 2008

**Via Electronic Transmission**

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

Dear Commissioner von Eschenbach:

The United States 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 under those programs to oversee their proper administration. As the senior Senator from Iowa and Ranking Member of the Committee, I have a duty to ensure that the Food and Drug Administration (FDA/Agency) 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. In carrying out this duty, I have been conducting an ongoing inquiry concerning foreign pharmaceutical manufacturers and the FDA's foreign drug inspection program.

This past October, I wrote to you concerning the FDA's program for inspecting foreign pharmaceutical manufacturing plants and ongoing questions regarding inspection funding, emerging exporters, weaknesses in the inspection process, over-the-counter drug importation, and other pressing issues. On Thursday, December 13, 2007, FDA representatives visited my office to discuss these topics, and I greatly appreciate the information they provided to my staff. That same week, I received FDA's written response to my August 7, 2007 letter. I am writing today to review what your agency officials told my Committee staff and follow up with a number of additional questions.

In the letter and briefing, your staff provided the number of FDA inspections of international pharmaceutical plants for fiscal years 2002 – 2007, some of which is reiterated below. I found these numbers very troubling. Since the beginning of FY 2002, the FDA conducted approximately 1,379 inspections of foreign pharmaceutical facilities, often focused in countries with few reported quality concerns. The table below contains the number of inspections conducted by the FDA in the 10 countries with the highest number of pharmaceutical facilities inspected.

**Top Ten Total Inspections by Country, FY 2002-2007**

| Country | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | Total |
|---|---|---|---|---|---|---|---|
| India | 10 | 19 | 36 | 33 | 34 | 61 | 193 |
| Germany | 23 | 14 | 35 | 25 | 20 | 18 | 135 |
| Italy | 16 | 31 | 25 | 21 | 17 | 12 | 122 |
| Canada | 27 | 12 | 17 | 22 | 24 | 16 | 118 |
| United Kingdom | 17 | 22 | 17 | 18 | 16 | 9 | 99 |
| France | 14 | 18 | 13 | 12 | 15 | 24 | 96 |
| Japan | 10 | 13 | 13 | 21 | 13 | 12 | 82 |
| China | 11 | 6 | 18 | 13 | 16 | 11 | 75 |
| Switzerland | 11 | 11 | 11 | 15 | 9 | 14 | 71 |
| Ireland | 11 | 5 | 12 | 14 | 2 | 7 | 51 |

In China, the world's largest producer of active pharmaceutical ingredients (API), and where export safety appears to be a growing problem, only 11 inspections were conducted during FY 2007, compared to 14 in Switzerland, 18 in Germany, and 24 in France, all countries with advanced regulatory infrastructures. Moreover, the table shows a drop in the number of inspections conducted in China from a peak of 18 in 2004, while inspections in countries with robust internal controls such as France appear to be on the rise. This seems to be a misplacement of limited FDA resources. Accordingly, I am interested in learning how the United States might utilize the advanced inspection capabilities of our industrialized trading partners to better focus the FDA's limited inspection resources in countries where export quality is of greater concern. On this topic, I would appreciate answers to the following questions:

(1) How many Chinese and Indian pharmaceutical plants that are currently exporting product directly or indirectly to the US market have never been inspected by the FDA?

(2) From the list of countries above, please provide the number of Official Actions that have been taken each year for fiscal years 2002 through 2007. In the case of Warning Letters, please provide a copy of the letter.

(3) For fiscal years 2002 through 2007, please provide the amount of exports from each of the countries listed above to the United States.

(4) Please detail FDA efforts to establish any additional bilateral and multilateral agreements that would allow the sharing of inspection information. Please also discuss the FDA's position on shifting its inspection resources away from highly developed nations and towards countries where export quality is less established.

Concerns over the quality of Chinese pharmaceutical exports were reinforced by the recent scandal involving the Shanghai Pharmaceutical (Group) Co. One of China's largest pharmaceutical companies, Shanghai Pharmaceutical is accused of producing and distributing a tainted leukemia drug. Recent news reports indicate that this contaminated drug has harmed nearly 200 patients in China, in some cases causing them to become paralyzed. Shanghai Pharmaceutical claims to be in partnership(s) with multinational drug companies and to actively export API around the globe. Please identify what products this company exports to the United States, and specify whether any of the API produced by this company is shipped to other plants which export to our market. If so, what is being done to ensure that these products are not also contaminated?

I was also disturbed by an event that occurred this past summer in Japan. When FDA inspectors visited the Tomita Pharmaceutical Company (Tomita) from July 31 through August 2, 2007, they discovered significant deviations from FDA standards. These deviations included incomplete analyst worksheets, insufficient computerized systems, a lack of written protocols, and other problems. Without these records, FDA inspectors are unable to confirm manufacturer tests. Furthermore, during the inspection Tomita officials refused to provide FDA inspectors with certain records, effectively preventing the FDA from completing its inspection. The January 14, 2008 FDA Warning Letter to Tomita asked that the company conduct an evaluation of its own facility, and threatens that the FDA will "recommend disapproval of any new applications or supplements" from the company.

I am troubled by this response, which seems woefully insufficient. Tomita officials have refused to allow FDA officials to complete inspection of their manufacturing facility, yet the company appears to still be allowed to export its product to consumers in the United States. Please confirm if this is the case. Also, I would be interested to know the full range of enforcement measures available to the FDA when a manufacturing plant refuses to give our inspectors full access, and how FDA officials decide what actions to take against uncooperative companies.

Another topic covered during the December briefing was the establishment of FDA facilities abroad. One important step to improving the FDA's ability to inspect foreign pharmaceutical plants would be the establishment of offices in Asia, where pharmaceutical manufacturing is rising dramatically. In the December briefing, your staff indicated that no firm plan was in place for such an office. However, recent comments by the Department of Health and Human Services Secretary Michael Leavitt indicate that the establishment of an office in India is under consideration. I would appreciate additional information regarding this effort and your input on the resources that would be required to make an FDA office in India a reality.

In addition to the inspection of foreign pharmaceutical plants, FDA representatives also commented during the December briefing on efforts to prevent tainted dosage forms and API from entering this country. A similar problem highlighted over the last few months by the Seattle Times is the importation of unproven medical devices. The Seattle Times published a series of articles over the last few months regarding its investigation into the sale and use of unproven medical devices that are manufactured overseas and claim to manipulate the body's energy fields to improve

health, including curing diseases like cancer and AIDS. According to the Seattle Times, the FDA recently took action against a network of foreign manufacturers of such devices in response to that investigation. In addition, FDA regulations do not require that a device manufacturer always obtain FDA's approval in order to initiate a study of its device. Under 21 C.F.R. 812, a device manufacturer can ship and use an investigational device in a clinical study that does not involve significant risk as long as it obtains an investigational device exemption from an institutional review board. Consequently, as reported by the Seattle Times, the FDA does not know how many and which unproven devices are being tested in clinical trials. This week, you also testified that the problem with manufacturers importing fraudulent devices into the U.S. need to be stopped at the source. On this topic, I would appreciate answers to the following questions:

(1) Please describe any efforts underway to improve FDA's ability to identify what devices are involved in clinical trials as well as to identify and track foreign manufacturers and/or distributors of non-FDA approved devices.

(2) Please elaborate on FDA's plans to stop importation of fraudulent and unproven devices at the source.

(3) How will the FDA work with state, local, and other federal authorities as well as foreign governments to investigate and prevent the importation of fraudulent and unproven devices into this country?

(4) What oversight and enforcement actions can be taken by the FDA to protect patients against fraudulent and unproven medical devices manufactured overseas?

Thank you in advance for your cooperation and assistance on this important matter. I look forward to hearing from you regarding the issues and questions set forth in this letter by no later than February 15, 2008. I would also appreciate a written response to my previous letter, dated October 30, 2007. Any questions or concerns should be directed to Christopher Armstrong at (202) 224-4515. All formal correspondence should be sent via electronic transmission in PDF format to Brian_Downey@finance-rep.senate.gov.

Sincerely,

Charles E. Grassley
Ranking Member