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United States Senate

WASHINGTON, DC 20510

June 27, 2011

Dr. Margaret Hamburg
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993

Dear Commissioner Hamburg:

I am writing in regards to the Food and Drug Administration's (FDA) recent special report, "Pathway to Global Product Safety and Quality." I would first like to commend you and your agency for compiling an in-depth report examining the serious problems facing the United States due to the importation of FDA-regulated products – in particular active pharmaceutical ingredients (APIs).

As stated in the report, a startling 80 percent of APIs were imported into the United States in 1998 alone. And it appears this trend has continued. During a Senate HELP Committee hearing in 2008, Pfizer testified that it outsourced 17 percent of the company's active ingredients and drug product manufacturing and hoped to double that number to 35 percent by 2010. Presumably, other leading pharmaceutical companies are following suit. With this dramatic increase in foreign manufacturing comes an increased public health concern, as evidenced by the 2008 heparin tragedy.

In 2008, tainted heparin killed over 100 people – including at least three people from Toledo, Ohio – and caused at least 785 severe allergic reactions. According to news reports, the contaminated heparin likely came from facilities in China, facilities that had not been inspected by the FDA, or by the drug's manufacturer, Baxter International.[1] At the time, Baxter produced approximately 50 percent of the heparin sold the United States.[2] According to a 2008 GAO report, the FDA was never able to determine with certainty the original source of the contamination.[3] This is alone is cause for concern. If the source of the contamination cannot be positively identified, how can the FDA ensure a similar tragedy will not occur again?

In the light of the heparin crisis and the potential for the its recurrence, the "Pathway to Global Product Safety and Quality" report has significantly more importance. In the report, the FDA cites a Government Accountability Office (GAO) recommendation to increase foreign inspections. However, the report also notes that given current staffing and funding levels, it

[1] Packer, Judy. "Toledoans Tell Congress of Tainted-heparin Grief." Toledo Blade, 30 Apr. 2008.
[2] Weise, Elizabeth and Julie Schmit. "Baxter Recalls Most Heparin Products After Allergic Reactions." USA Today, 29 Feb. 2008.
[3] GAO Report, *Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added*, October 2010.

would take the FDA nine years to perform one inspection at each foreign-based "high-priority" pharmaceutical facility and 13 years to inspect all foreign-based pharmaceutical manufacturing plants.

Recognizing these constraints, the report highlights the need for an alternative model for carrying out FDA oversight activities. The four core building blocks for this new model are: global coalitions of regulators; development of a global data information system for the exchange of real-time information and resources; expanded intelligence gathering and risk analytics capabilities; and allocation of agency resources based on risk.

While I applaud your agency for these efforts, I also have some additional question and concerns that are not addressed in the report. As you look to develop international coalitions and strengthen partnerships with foreign nations, it is imperative that high-export nations – such as China, India, and Mexico – be included in these efforts. China has the largest number of foreign FDA-registered drug manufactures, followed closely by India. And both countries are likely to increase their overall exports by 400% in the next ten years. Most worrisome, however, is that China and India have higher than average import refusal rates, and it has been widely reported that the Chinese government does not always cooperate with FDA investigations.[4] In that context, please provide the following information:

- What steps can your agency take to ensure that key exporters are not only included in the coalitions, but also abide by the resulting comparability and information sharing standards?
- How often are FDA inspectors denied access to a foreign pharmaceutical or API facilities either by the company or government officials?
- Does your agency have the authority to refuse entry into the United States of pharmaceutical products or APIs from foreign entities if the FDA has been denied access to manufacturing facilities? If it does not have such authority, is further legislation necessary?
- As discussed above, China accounts for a high number of pharmaceutical imports, as well as a high number of import refusals. What role do import refusals from China – and other countries – play in the in the drug shortage crisis in the United States? Specifically, what percentage of drug shortages result from import refusals as compared to consolidation of pharmaceutical companies, economic decisions of a company to cease production, and problems in manufacturing?
- The report also notes that some countries, including Mexico and Costa Rica, consider the FDA seal of approval equivalent to approval from their respective oversight agencies. What countries does the FDA believe have stringent enough regulations to be equivalent to FDA-approval?

In examining the other core building blocks for your new global model, I have some questions with regard to allocation of agency resources based on risk, expanded intelligence gathering, and the development of a global data-information system.

- Which APIs or pharmaceutical products are at the greatest risk for adulteration or counterfeiting?

[4] Harris, Gardiner. "FDA Confronts Challenge of Monitoring Imports." The New York Times, 20 June 2011.

- Are the pharmaceutical companies that manufacture these products or utilize these APIs aware of these risks and what oversight activities do these companies perform themselves at contracted facilities?
- Your efforts to create IT tools that will enable you to quickly identify potential risks is a necessary step in monitoring imports in an increasing globalized world. However, a recent New York Times article noted that a computerized alert system started by the FDA in 2001 has yet to be completed.[5] What is the FDA's timeframe for expanding its intelligence gathering capabilities?
- The report states that the FDA may be unable to fully and completely share data across the coalition due to legal restrictions. What restrictions are currently in place, and what sort of legislative change is necessary to facilitate the FDA's exchange of information with foreign counterparts?

From a budgetary perspective, the report asserts that the average cost to inspect a foreign facility is twice what it costs to inspect a domestic facility ($52,000 vs. $23,000). While the FDA has a responsibility to ensure food, drugs, and medical devices are safe for the American people, Congress has a responsibility to ensure government resources are used wisely. To that end, I would be interested in your views on the following:

- Assessing companies that chose to move their operations overseas a fee equal to the difference between the agency's cost to inspect a domestic versus foreign facility. It is inequitable for pharmaceutical companies to take advantage of cheaper labor and manufacturing costs overseas at the expense of your agency and the American taxpayer.
- Assessing fees on *all* pharmaceutical and API manufacturing facilities in order to offset the cost of more frequent inspections.
- Assessing fees on companies responsible for contaminated, counterfeit, or recalled pharmaceuticals or APIs.

I again commend the FDA for its frank and honest review. I look forward to continuing this discussion and working with you to improve the safety of our nation's pharmaceutical supply.

Sincerely,

Sherrod Brown

Sherrod Brown
United States Senator

[5] *Id.*