United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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For Immediate Release
Tuesday, October 30, 2007

Grassley delves further into FDA review of foreign-made pharmaceuticals

WASHINGTON — Sen. Chuck Grassley is following up on his initial inquiry of the Food and Drug Administration regarding its work to ensure the safety of foreign-made pharmaceutical ingredients and medicines with a series of questions about foreign inspection funding, FDA registration of foreign plants, newly emerging exporters of pharmaceuticals, and weaknesses in the foreign inspection process.

The text of the letter he sent today to the FDA Commissioner follows here, along with the text of his August letter. FDA officials briefed Grassley staff following the first letter.

October 30, 2007

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 the proper administration of the programs. As 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.

On August 7th of this year, I wrote to you concerning the FDA's program for inspecting foreign pharmaceutical manufacturing plants. This is because these plants produce a large amount of the active pharmaceutical ingredients (API) and dosage forms that make up America's pharmaceutical supply, and I wanted to know more about the problems confronting the FDA in

its efforts to ensure that the products coming out of these facilities are safe for Americans. On August 23, FDA representatives briefed my committee staff about the FDA's ongoing efforts and the challenges the Agency faces. This briefing was very informative, and I would now like to take this opportunity to review what your agency officials told my Committee staff and follow up with a number of additional questions.

The pharmaceutical industry, like many sectors, has experienced rapid globalization in recent years. Today, it is estimated that nearly 80% of the pharmaceuticals used in the United States are manufactured overseas, including both active pharmaceutical ingredients and dosage forms. The responsibility for ensuring the safety of these drugs is placed on the FDA, which inspects plants where API and dosage forms are manufactured both at home and abroad. I now understand that most foreign inspections occur in China and India, which are the largest exporters of pharmaceutical products to the United States, followed, in order, by leading exporters Italy, France, Germany, Israel, Spain, the United Kingdom, Ireland, and Japan. I understand many of these Western European countries, as well as Israel and Japan, have robust regulatory systems and dependable drug safety protocols, while other exporters are less dependable and demand more of the FDA's inspection resources. I also understand that the FDA conducts inspections of pharmaceutical manufacturing plants in these countries on the basis of free trade agreements, bilateral agency-to-agency memorandums of understanding, and informal letters.

The FDA is in an understandably difficult position, in that it is charged with ensuring the safety of America's pharmaceuticals, which are produced in nearly every corner of the globe. Understanding this challenge, I sought to learn more about how the FDA accomplishes this task. Through discussion with the director of the FDA's Division of Field Investigations and others, my staff learned that the FDA employs roughly 1,300 Consumer Safety Officers (CS Officers) to conduct the Agency's national and international inspection activities. Of these, there are approximately 600 CS Officers, usually senior investigators, qualified to conduct foreign inspections. On a voluntary basis, these inspectors travel abroad for about three weeks at a time, during which they aim to inspect three manufacturing facilities.

With an annual foreign inspection budget of about $3.5 million, and an estimated cost of $3,100 to $3,500 per inspector per inspection, the FDA aims to conduct approximately 1,000 foreign inspections annually. Because this budget includes inspections of foreign food producers, medical device manufacturers, and makers of veterinary medicine, pharmaceutical manufacturing plants only make up between a third and half of the inspections conducted in most years.

My staff learned further that inspections of foreign pharmaceutical plants are arranged in advance, and conducted by FDA teams of two CS Officers. I understand that once the FDA team arrives, inspections do not actually cover the API or dosage forms. Rather, the FDA teams inspect the plants for overall integrity and ask the manufacturing plants being inspected to send samples of their products to the United States for testing. These products are then tested by the FDA's Forensic Chemistry Center.

Once an inspection is completed, my staff was told that there are three possible

outcomes: 1) No Action, 2) Voluntary Action, and 3) Official Action. I understand that the "Official Action" can take two forms: an "untitled letter" if the plant is not yet shipping product to the United States, and a "warning letter" if it is and some concern has come to FDA's attention as a result of the onsite review or the testing of the samples provided. A "warning letter" serves to put the plant on official notice of a deficiency and requires corrective action in a timely fashion. FDA's briefing provided also revealed that, upon recommendation, the FDA can also detain the product from entering the United States until corrective action is taken.

I thank the FDA for briefing my staff on the Agency's inspection process, and would appreciate further discussion on this process. There are a number of other matters regarding the FDA's ability to monitor and ensure the safety of the API and dosage forms produced and manufactured abroad that are of interest to me. I will outline these matters below, and look forward to an additional briefing on these points.

Inspection Funding

Following the briefing, it is clear that fiscal constraints are a major reason behind the FDA's inability to inspect foreign pharmaceutical manufacturing plants as widely as is needed. My staff was told that other countries, including the United Kingdom and Australia, may charge host plants the cost of inspection, and that European Union members may charge host plants or host governments for their inspections. The August briefing did not cover this issue at great length, but I would like to revisit it and discuss ways to make certain that the FDA has the resources it needs to ensure the safety of API and dosage forms imported to the United States.

FDA Registration

One reason the FDA's task is so daunting is that the pool of registered foreign plants is ever expanding. Exacerbating this problem, many foreign plants register with the FDA while having no intention of exporting to the United States. This registration process has the effect of increasing the costs and inspection pool of the FDA while having no benefit at all to the American consumer. I am under the impression that many plants register simply to bolster their credentials internationally, as opposed to being interested in exporting their products to the United States. For example, in China there are approximately 578 companies registered with the FDA, but only 200 to 300 actually ship product to the United States. One possible explanation is that FDA registration is free to foreign companies and gives them the imprimatur of having an FDA "seal of approval," However, this seal of approval comes on the American taxpayer's dime, as it is their tax dollars that fund the foreign inspections. I am interested in learning what, if anything, the FDA may be considering to address this problem.

Emerging Exporters

The FDA's limited resources to conduct these inspections results in another problem. Some emerging exporters have never been inspected. According to your staff, most of the FDA's international inspection efforts focus, understandably, on China and India. Other emerging exporters, such as Bangladesh, sparked my interest because there appear to be few, if any, inspections of pharmaceutical plants in emerging exporter countries. I am interested in learning

more about efforts to inspect emerging pharmaceutical exporters.

Weaknesses in the Inspection Process

I am also concerned with the ease with which foreign manufacturers can get around FDA regulations. Due to the FDA's lack of extraterritorial authority, FDA teams must arrange inspections far in advance, and have no authority to conduct surprise inspections. Drug samples are not always collected on site, but are often sent to the United States for testing by the manufacturer. This system seems to allow room for foreign manufacturing plants to get around FDA's efforts to protect American consumers, and I look forward to hearing your ideas on how to better approach these issues. I would also like to know whether this policy of "mailed-in" samples is FDA's policy, or that of the foreign plants. In other words, are foreign manufacturing limiting our ability to obtain samples on site or in any way prohibiting samples from being taken on site by FDA's inspectors.

In addition to the issues presented above, I would like to continue our discussion from late August, focusing more on the following areas:

1) How does the FDA identify all of the foreign pharmaceutical manufacturing plants that exist in a given country?
   a. How does the Agency monitor which plants export to the United States and which do not?
   b. How does the Agency monitor keep this list up-to-date?

2) Beyond pre-approval inspections, how frequently do FDA teams inspect a typical foreign pharmaceutical manufacturing plant?
   a. Does FDA conduct follow-up inspections only after a specific complaint is received, or is there another system for conducting follow-up inspections?

3) How does the FDA select plants for inspection?
   a. Does it conduct a pre-approval inspection at every facility before the facility ships pharmaceutical products to the United States? If not, why not?
   b. What process does FDA use to decide whether and when to conduct follow-up inspections?

4) After the FDA takes "Official Action" by way of an untitled letter or warning letter, how does the FDA ensure that problems are corrected?
   a. Does an FDA team conduct a second inspection in every case? If not, how frequently does the FDA conduct second inspections?

5) If a particular foreign pharmaceutical manufacturing plant uses subcontractors or imports API or dosage forms from other plants, does the FDA inspect these subcontractors or other plants before the primary plant is approved to export to the United States? If not, why not?
   a. If so, does the same FDA team that inspects the primary plant also inspect the secondary?

6) My staff was told that FDA inspectors used to take drug samples during the course of an inspection, and that these samples would be kept in the custody of the FDA until tested. According to the briefing in August, I understand that this is no longer the practice. Instead, the FDA reportedly permits foreign pharmaceutical manufacturing plants to ship the samples to the Forensic Chemistry Center themselves, allowing for limited, if any, assurance that the samples are indeed from the plant that is the subject of inspection. Is my understanding of the current procedures correct?
   a. If so, why has the FDA changed its approach, and how does it ensure the integrity of its inspection process?

7) It has been reported that generic and over-the-counter drug importation is a major concern. I would like to receive more information about this issue, and to explore with you what additional tools the FDA needs to ensure that these pharmaceuticals are safe for Americans.

I look forward to your cooperation and assistance on this important matter. Please have your staff contact my Committee staff to schedule the requested briefing by November 16, 2007.

Sincerely,
Charles E. Grassley
Ranking Member

For Immediate Release
Thursday, Aug. 9, 2007

Grassley Seeks FDA Briefing on Steps to Ensure Safety of Foreign-made Medicine

WASHINGTON – Sen. Chuck Grassley, ranking member of the Committee on Finance, is asking the Food and Drug Administration for an explanation of its steps to ensure the safety of foreign-made medicine. In a letter to the agency commissioner, Grassley said he is disturbed by reports of the inadequacy of FDA inspections of foreign pharmaceutical manufacturing facilities, especially given the growing predominance of overseas manufacturing of such products.

The text of Grassley's letter follows here.

August 8, 2007

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 the proper administration of the programs, including the payment for prescription drugs regulated by the Food and Drug Administration (FDA). As Ranking Member of the Committee, I have the duty to ensure that the FDA 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.

I have been troubled by a number of recent articles discussing the FDA's failures in inspecting foreign pharmaceutical manufacturing plants. In fact, in a recent *Washington Post* article, William Hubbard, a former FDA associate commissioner, characterized the problem as "dire and deteriorating." Given the fact that nearly 80 percent of the active pharmaceutical ingredients used in the U.S. are manufactured abroad, this is a significant problem that needs to be addressed immediately.

Even more troubling is that this problem is not a new one. Congress has expressed concerns about the FDA's oversight of foreign drug manufacturing facilities in the past. In 1998, the Government Accountability Office prepared a report to the United States House Committee on Commerce responding to concerns about the FDA's "ability to ensure the safety and quality of the increasing volume of foreign-produced drugs imported daily into the United States." The fact that this problem persists nearly ten years after this report was published is unacceptable.

Accordingly, I am requesting that the FDA provide information about how it is handling this serious problem. I would like to know the measures the FDA has in place today to inspect foreign drug manufacturing facilities, as well as how it intends to improve these measures in the future. Specifically, I ask the FDA to brief my staff and provide formal responses to the following questions:

1) What protocols does the FDA currently have in place regarding inspection of foreign pharmaceutical manufacturing facilities? What specifically does the FDA do when it inspects a foreign pharmaceutical manufacturing facility? Please include copies of the protocols in your response.

2) How many on-site visits of foreign pharmaceutical manufacturing facilities has the FDA performed since 2002 and who performed them? In what countries were these inspections performed? How many inspections were performed in each country? What were the results? When an inspection results in negative findings, what kind of follow-up occurs? How much does the FDA spend on foreign inspections annually? How many of these inspections were for pre-approval purposes rather than ongoing inspections of existing sites? How many were for facilities producing generic drugs, and how many were for those producing brand name ones? In India, what number were for PEPFAR Aids programs?

3) What kinds of cooperative relationships does the FDA have with its foreign counterparts or other foreign regulatory bodies? How does the FDA measure the efficacy of the inspections performed by these foreign agencies? By those measures, how well are these agencies performing the function of thorough inspection of drug manufacturing facilities?

4) What strategies is the FDA developing to improve the inspection of foreign pharmaceutical

plants, and what is the timeline for the implementation of these strategies? What, if any, are the barriers to implementing these strategies?

5) How long do FDA inspectors typically remain abroad? How long do inspections of foreign facilities usually last?

6) Does the FDA currently have any plans to create an agency outpost in India? If so, what is the status of these plans?

7) A report by PriceWaterhouseCoopers recently stated that, in the near future, pharmaceutical manufacturers will make a large shift from domestic facilities to ones in Asia. How is the FDA preparing to respond to this possibility?

I look forward to your cooperation and assistance on this important matter, and would greatly appreciate a briefing for my staff. Please have your staff contact my Committee staff to schedule a meeting.

Sincerely,
Charles E. Grassley
Ranking Member

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