United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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For Immediate Release
Thursday, February 28, 2008

Grassley presses FDA for more information about foreign inspections, drug safety

WASHINGTON - Senator Chuck Grassley has sent another letter to the Food and Drug Administration about its program for inspecting overseas facilities that manufacture pharmaceutical drug components.

Grassley's new questions cover a range of issues, including the drug-safety agency's reliance on translators provided by the manufacturing plants during foreign inspections; responsibilities within foreign chains of production; the identity of the plant that had been confused with the Chinese manufacturing plant that made an ingredient in the blood thinner heparin; and other drugs on the market that may contain ingredients also manufactured by the Chinese plant in question.

Earlier this month, production of heparin was suspended by its manufacturer due to concerns that deficiencies at a Chinese manufacturing plant where the active ingredient in heparin was made may have contributed to the adverse reactions in hundreds of U.S. consumers using the drug.

Grassley previously has asked the Food and Drug Administration about its targeting of agency resources for inspections of pharmaceutical plants around the world, expressing concern about the majority of inspections taking place where a minority of drugs and drug ingredients are manufactured.

The text of all of his letters on the foreign inspection system for pharmaceutical drugs follows here.

February 28, 2008

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

Dear Commissioner von Eschenbach:

As Ranking Member of the Committee on Finance (Committee), I have a responsibility to the more than 80 million Americans who receive health care coverage under the Medicare and Medicaid programs to oversee the proper administration of these programs and ensure that taxpayer and beneficiary dollars are appropriately spent on safe and effective drugs and devices.

In December, officials from the Food and Drug Administration (FDA/Agency) briefed my staff regarding FDA's program for inspecting foreign pharmaceutical manufacturing plants and ongoing questions regarding inspection funding, emerging exporters, and weaknesses in the inspection process, among other things. During that briefing, FDA officials noted that although there are some employees who can speak a foreign language, they are not necessarily part of the inspection teams. Therefore, FDA sometimes relies on translators provided by the facility to be inspected. I find this problematic because, among other things, relying on translators provided by the facility under inspection creates an apparent conflict of interest, which in turn raises questions about the accuracy, independence, and thoroughness of FDA's inspection of that facility.

Accordingly, please respond to the following questions:

1. It is my understanding that the FDA does not have designated employees who act as translators during foreign inspections. Given our country's increasing reliance on foreign facilities to produce the active pharmaceutical ingredients (API) that are used in the drugs sold on the U.S. market, it is troubling that the FDA does not ensure that independent translators are part of its inspection teams when there is a need for a translator. Since the FDA does not always have access to its own translators, what systems, if any, does FDA have in place to ensure that the Agency is receiving truthful, accurate, and independent information from the translators provided by the inspected facilities? Has or would the FDA consider employing independent contractors to assist with translations during its foreign inspections?

2. In FDA's December 12, 2007 response, the Agency provided the Committee with the number of inspections conducted by country in fiscal years 2002-2007. Please identify all of the facilities that were inspected in China, India, Brazil, Saudi Arabia, and Thailand during that time period. For each inspection, please specify whether a translator was required for the inspection. Please also specify whether the translator was an FDA employee, an independent contractor, or an individual provided by the inspected facility.

In my letter dated February 14, 2008, I asked the FDA to respond to several questions regarding its failure to inspect a Chinese facility prior to approval of Baxter's application for heparin. Please also provide a response to the following questions:

1. Since my Feb. 14 letter, I have learned that Changzhou SPL Co. is the Chinese facility that was supposed to be inspected by the FDA prior to regulatory action on Baxter International Inc.'s (Baxter) application. Was Baxter informed that Changzhou SPL Co. had been previously inspected and therefore did not have to be inspected again? If so,

when and how was Baxter informed?

2. Was Scientific Protein Laboratories LLC, the Wisconsin company that supplied Baxter the active ingredient in heparin through Changzhou SPL Co., informed that the facility had been previously inspected? If not, why not? If so, what duty did Scientific Protein Laboratories LLC have to inform Baxter and/or the FDA that the Chinese facility had never been inspected? Whose responsibility is it to ensure the quality of the API imported into this country?

3. Does Changzhou SPL Co. produce API used in other drugs that are sold on the U.S. market? If so, please identify these API and the companies that are buying them either directly or indirectly from Changzhou SPL. Is the FDA also investigating the quality of these ingredients?

4. Please provide the name and location of the facility that was mistaken for Changzhou SPL Co. and specify when this facility was last inspected and what drugs and/or API are produced at this facility.

In addition, I request that the FDA brief my staff regarding its findings from the inspection of Changzhou SPL Co. as soon as possible after the inspection is completed.

Thank you for your cooperation and attention to this important matter. Please respond to the questions and requests set forth in this letter by no later than March 14, 2008.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

For Immediate Release
Thursday, February 14, 2008

Grassley says hold on imported blood thinner component underscores questions about FDA foreign inspections

WASHINGTON — Senator Chuck Grassley is asking questions about whether deficiencies at a Chinese manufacturing plant that's never been inspected by the Food and Drug Administration could be behind adverse reactions in hundreds of U.S. consumers to the blood thinner heparin, for which production was suspended this week by the drug maker. The active ingredient in heparin is produced at the plant in question.

Grassley's inquiry today follows on a letter he sent earlier this month to the Food and Drug Administration about where the agency has targeted its foreign inspections of pharmaceutical plants around the world.

"The heparin case illustrates perfectly the questions about how the Food and Drug Administration is conducting foreign inspections of pharmaceutical plants worldwide," Grassley said. "It doesn't make sense that the vast majority of inspections are happening in places that aren't where the vast majority of drug products coming into the United States are made. The Food and Drug Administration clearly has a demanding and high-stakes job in verifying the safety of prescription drugs that come from all over the world. Smart and appropriate use of its drug-safety resources is essential to public safety."

Grassley is Ranking Member of the Senate Committee on Finance, which has legislation and oversight responsibility for the Medicare and Medicaid programs. He has conducted extensive oversight of the U.S. drug safety system.

The text of the letters he sent today to the Food and Drug Administration and to Baxter International Inc., the maker of heparin, follows here, along with the text of three letters he previously sent to the Food and Drug Administration regarding foreign inspections of pharmaceutical drugs sold in the United States.

February 14, 2008

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 protect the public's health 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.

As you know, Baxter International Inc. (Baxter) has temporarily suspended production of its blood thinner heparin because of an increase in the reports of adverse events that may be associated with its drug. According to the FDA, about 350 adverse events associated with heparin have been reported since the end of last year. It has also been reported that four people died after receiving heparin, but whether those deaths are related to the drug has yet to be determined. According to Baxter, 40% of the adverse events were classified as "serious," mostly occurring in patients undergoing kidney dialysis and heart surgery.

Recent news reports indicate that the active ingredient in heparin was produced at a

facility in the People's Republic of China, and that "due to human error, and inadequate information-technology systems," this facility was never inspected by the FDA. This comes on the heels of my earlier inquiry, which raised serious concerns that the FDA inspected only 11 pharmaceutical plants in China during 2007, even though hundreds if not thousands of facilities are producing active pharmaceutical ingredients (API) used in drugs sold in this country.

Accordingly, I am requesting that FDA provide a timeline of events that led to the discovery that a pre-approval inspection had not been conducted at this Chinese facility as well as input on what can be done to prevent such situations from occurring in the future. Please keep me apprised of any developments and findings in FDA's investigation of this matter. In addition, I would appreciate responses to the following questions:

1. According to the FDA, the Agency normally conducts "pre-approval" inspections before approving a drug application to determine whether establishments participating in the manufacture, packaging or testing of a dosage form or API comply with current Good Manufacturing Practices. Please describe FDA's process for identifying all foreign facilities that must undergo pre-approval inspection and ensuring that such inspections take place.

2. According to the FDA, the Chinese facility producing the active ingredient in heparin was supposed to undergo a pre-approval inspection. When was that pre-approval inspection supposed to have been conducted?

3. Please describe in detail the "human error" that prevented a pre-approval inspection from taking place at this facility. What safeguards exist or need to be in place to protect against such errors? When, how, and by whom was the error first discovered?

4. FDA officials have previously briefed my staff on the information-technology hurdles facing the foreign inspection program. Please describe in detail the specific "inadequate information-technology systems" that contributed to this mistake.

5. Please identify the U.S. supplier and its Chinese facility that produced the API used in Baxter's heparin. How long has this facility been producing API? How long has this facility been exporting to the United States, and what other drugs and/or API is produced at this facility?

6. What is the status of FDA's investigation into the four patients who died after receiving heparin?

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 29, 2008.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

February 14, 2008

Robert L. Parkinson, Jr.
Chairman and Chief Executive Officer
Baxter International Inc.
One Baxter Parkway
Deerfield, IL 60015-4625

Dear Mr. Parkinson:

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 protect the public's health 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.

Recent press reports indicate that Baxter International Inc. (Baxter) has temporarily suspended production of its blood thinner heparin because of an increase in the reports of adverse events that may be associated with the drug. According to the FDA, about 350 adverse events associated with heparin have been reported since the end of last year. It has also been reported that four people died after receiving heparin, but whether those deaths are related to the drug has yet to be determined. According to Baxter, 40% of the adverse events were classified as "serious," mostly occurring in patients undergoing kidney dialysis and heart surgery.

I understand that Baxter imported the active ingredient in heparin from a facility in the People's Republic of China. While this facility "was supposed to be inspected," according to the FDA, the inspection was never conducted "due to human error, and inadequate information-technology systems." This comes on the heels of my earlier inquiry, which raised serious concerns that FDA inspected only 11 pharmaceutical plants in China in 2007, even though hundreds if not thousands of facilities are producing active pharmaceutical ingredients (API) used in drugs sold in this country.

However, I understand that your company inspected the Chinese facility in question less than six months ago, and plans to inspect it again soon, along with the U.S. facilities, as part of an investigation to determine the cause of the adverse events. Please keep me apprised of any developments and findings in your investigation of this matter. Please also describe in detail the steps Baxter has taken and/or plans to take to investigate the increase in adverse events. In addition, I would appreciate responses to the following questions and requests for information:

1. Please identify the U.S. supplier and its Chinese facility that produced the API used in heparin. Please also provide a description of Baxter's relationship with the supplier and the facility, including the length of the relationship with the facility and a description of

all goods and/or services this facility provides to your company.

2. Please describe the results of Baxter's inspection of this facility, which was conducted "less than six months ago," as well as any previous inspections. Please provide any documents and reports related to those inspections.

3. Please describe Baxter's protocols for establishing a relationship with a foreign manufacturing facility. Please also describe Baxter's process for ensuring that the products provided these facilities meet Good Manufacturing Practice standards.

4. When did Baxter first become aware of the adverse events related to heparin? Please provide a timeline of events that led to Baxter's investigation of the increase in adverse events associated with the drug.

5. What is the status of Baxter's investigation into the four patients who died after receiving heparin?

In cooperating with the Committee's review, no documents, records, data, or other information related to these matters, either directly or indirectly, shall be destroyed, modified, removed, or otherwise made inaccessible to the Committee.

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 29, 2008. I would also appreciate a briefing for my staff at the earliest convenience. Please provide the requested documents and information in accordance with the attached instructions and definitions.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

February 1, 2008

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
U.K.	17	22	17	18	16	9	99
France	14	18	13	12	15	24	96
Japan	10	13	13	21	13	12	92
China	11	6	18	13	16	11	76
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.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

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?
    1. How does the Agency monitor which plants export to the United States and which do not?
    2. 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?
    1. 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?
    1. Does it conduct a pre-approval inspection at every facility before the facility ships pharmaceutical products to the United States? If not, why not?
    2. 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?
    1. 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?
    1. 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?

1. 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
United States Senator
Ranking Member of the Committee on Finance

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
United States Senator
Ranking Member of the Committee on Finance

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

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United States Senator
Ranking Member of the Committee on Finance

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