ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

February 14, 2008

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

Dear Dr. von Eschenbach:

A recent disclosure in the Wall Street Journal alleges that a Chinese facility that has not been inspected by the Food and Drug Administration (FDA) produced the active ingredient in a widely used Baxter International, Inc. blood-thinning drug that has recently been associated with hundreds of adverse events, including four deaths.

While it is neither clear from the article nor from initial conversation with your staff if this plant is the source of the cause of the over 350 adverse reactions, we find it remarkable that the Wall Street Journal article reports that the FDA has publicly admitted they never inspected the Chinese facility that made the active ingredient in the Baxter drug due to "human error and inadequate information technology systems."

Throughout this past year, we have repeatedly raised concerns with you regarding the disastrous state of your agency's foreign inspection program related to pharmaceuticals manufactured abroad. These problems included a lack of resources and antiquated information technology (IT) systems that are used to track foreign firms making products destined for the United States. For example, in a recent hearing we heard testimony that the IT system used by FDA to specifically manage this program was found to be archaic and contained significant inaccuracies that directly affected the agency's ability to prioritize inspections.

As was reported by the U.S. Government Accountability Office (GAO) in that same hearing, FDA could not tell with certainty how many foreign firms were subject to inspection, or even where they were located. One database, for example, reported approximately 3,000 foreign establishments registered to market drugs in the United States in fiscal year 2007, while a

separate database reported almost 7,000 foreign establishments that appeared to have shipped drugs into the U.S. that same year. To date, FDA has not reconciled this difference. Given the FDA's antiquated computer monitoring system and their inability to easily access reliable data, we are not surprised that FDA cannot say with precision when or if this firm was inspected.[1]

The matter of resources to conduct inspections was a particularly troubling aspect of our investigation. Both the Committee's own investigation and the audit by GAO found that FDA's resources were completely inadequate for inspecting foreign firms with meaningful frequency. While current law requires that FDA inspect a U.S. domestic firm making a drug product for the U.S. market once every 2 years, GAO found that FDA had only enough resources to inspect foreign firms on average once every 13 years. For China alone—now one of the largest producers of drug product for the U.S. market and the partner in these recently-signed agreements—FDA has only been able to inspect between 10 and 20 firms each year against a backlogged inventory of more than 700 firms (which are only growing in number). At this rate, FDA can only inspect a Chinese firm exporting drug products to the U.S. once every 40 to 50 years.[2]

A lack of resources regarding foreign drug inspections and the problems with the agency's IT systems used to track manufactures and imports was also pointed out to you by your own Science Advisory Board review. Recall that in December 2006, you requested that this internal advisory group form a special subcommittee to assess whether "science and technology" at the agency was capable of supporting existing and future regulatory operations at FDA. A scathing report entitled *"FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology"* was produced and concluded that FDA was dangerously underfunded and was unable to pursue core regulatory missions, thus placing American lives at risk. This report was the main topic of a hearing just last month before the Subcommittee where you also appeared. Each of the witnesses who testified on behalf of this study noted that your agency was failing, and that your agency's ability to safeguard both the food and drug supply was a considerable and growing risk. Regarding drug inspections, the report's language was particularly stark:

> "Although approximately 80 percent of the active pharmaceutical ingredients used in our prescription drugs are imported from abroad, and foreign imports of drugs and active pharmaceutical ingredients were valued at more than $42 billion in 2006, FDA conducted only 361 foreign drug and biological product establishments in 2006. Only 32 Field inspections were made in India and 15 in China, the two largest sources of

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[1] U.S. Government Accountability Office, Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturer. Statement of Marcia Crosse, Director Health Care, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 1, 2007.

[2] Id.

> pharmaceutical exports to the United States. *Millions of shipments of FDA-regulated products are imported into the country each year from foreign facilities that have never been inspected by FDA and, with current appropriations, never will be* [emphasis added]."[3]

We have had countless conversations with you regarding your agency's inability to adequately inspect the Nation's drug supply, particularly those sources that are increasingly originating from abroad and from areas lacking robust regulatory regimes. Conversations and related hearings on this matter, the findings of the GAO, and those findings of your own Science Board, however, appear to go unheeded.

There is little material indication through the President's 2009 budget request or recent actions at the agency, which would lead us to believe you are making the needed changes to safeguard the public from these growing threats. GAO spoke to this matter directly in testimony heard by you at the November 1, 2007, hearing regarding FDA's foreign drug inspection program: "[U]ntil FDA responds to systemic weaknesses in the management of this important program, it cannot provide the needed assurance that the drug supply reaching our citizens is appropriately scrutinized, and safe."[4] Clearly to date, you have been unable to assure the public these products are safe because you have been unable to competently address the systemic weaknesses in this program identified by GAO, the Science Board, and this Subcommittee. Because of such inaction, American lives are unnecessarily being placed at risk.

Therefore, we request that you provide the Committee with the following information, specifically regarding the drug Heparin, and in general the foreign inspection program:

1. All inspection reports related to the Chinese company that Baxter International Inc. was apparently using to produce Heparin (e.g., all FDA form 483s);

2. A complete timeline of inspections for each of these facilities;

3. An explanation as to why this plant may have been allowed to ship drug products into the U.S. without a formal GMP preapproval or surveillance inspection;

4. A detailed explanation as to what steps FDA is currently taking regarding all active ingredients from this plant;

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[3] "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," Prepared for FDA Science Board, November 2007, B-22.

[4] U.S. Government Accountability Office, Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturer. Statement of Marcia Crosse, Director Health Care, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, November 1, 2007, p. 22

5. A detailed explanation about how the President's fiscal year 2009 budget will materially change the inspection frequency regarding foreign inspections now conducted, on average, once every 13 years;

6. For Baxter and every other manufacturer of the finished dosage form, please supply all pages of the NDA, ANDA, or related documents wherein FDA has been notified of the raw material suppliers, all documents wherein FDA has concurred with the choice of any supplier or a change in the choice of supplier;

7. All inspection reports of manufacturers of Heparin for the past five years;

8. All documents in the Data Master Files or elsewhere relating to FDA approval of raw material suppliers of the active ingredient in Heparin.

Thank you for your attention to this matter. We would ask that you provide this information on a rolling basis to the Subcommittee as soon as possible, but no later than February 22, 2008. If you have any questions on this matter, please have your staff contact Christopher Knauer or David Nelson with the Committee on Energy and Commerce staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations