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

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

March 19, 2008

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

Dear Dr. von Eschenbach:

The circumstances surrounding the outbreak of adverse reactions associated with heparin raise questions about the Food and Drug Administration's (FDA) current ability to assure the safety of foreign drugs or pharmaceutical ingredients imported for use in the U.S. drug supply. In particular, the Committee on Energy and Commerce's investigation into why FDA mistakenly identified the wrong Chinese facility as the supplier of bulk heparin for Baxter Laboratories has revealed questionable policies and practices concerning FDA's assessment and inspection of drug manufacturing risks among foreign firms, especially, in this instance, within China.

FDA stated in response to the February 21, 2008, letter from Chairman Dingell and Subcommittee Chairman Stupak that its policy has been, and continues to be, to approve drugs after verifying that a drug's manufacture, processing, and packing are adequate to preserve the drug's identity, strength, quality, and purity. Verification that these standards are met is based upon a recent inspection of the manufacturing facility or facilities named in a new drug or abbreviated new drug application. FDA noted further that, if it had a "recent, satisfactory inspection on record for a given facility named in the application, we generally will not conduct a new pre-approval inspection of that facility..." unless FDA determines "...the circumstances warrant it."

In the course of investigating the heparin case, we have learned that FDA essentially relies upon a vague and ad hoc policy when deciding whether "the circumstances warrant" a preapproval inspection. In interviews with Majority and Minority Committee staff, officials with the Center for Drug Evaluation and Research (CDER) initially maintained that the Chinese

supplier of the bulk heparin product was not inspected as a direct result of mistaken identity with a manufacturer of a similar name. When seeking to understand how this mistake was made, however, we discovered a larger and broader problem—FDA's decision to waive the inspection was not based solely on mistaken identity, but also on questionable judgment regarding when to conduct preapproval inspections.

According to FDA's approach in this heparin case, a Chinese plant previously inspected for making a diuretic and antibiotic for export to the United States would not need a new inspection for initiating a completely different line of product, a biological line, for export. Committee staff was provided no clear rationale or policy guidance for making this decision. It remains unclear whether FDA has any rational policy for deciding when the manufacturing process for one drug is sufficient to assure the quality of the process for an additional different drug to be made in that same facility.

Indeed, of the 10 criteria in the CDER preapproval policy regarding whether a plant could be determined to be in compliance without a new physical inspection, neither facility location, complexity of the manufacturing process, nor sensitivity of the final drug product make the list. While the formal policy document dealing with preapproval inspections does not say so explicitly, the CDER compliance official responsible for the decision not to inspect the plant in China told the Committee staff that neither the complexity of the heparin extraction process nor the location of the plant in China would compel him to order a preapproval inspection.

This policy—or lack thereof—is even more troubling because FDA has not been able to assure us that all Chinese facilities providing product to the U.S. drug market have ever received a single preapproval inspection, let alone follow-up surveillance inspections necessary to assure continued quality and safety. Both the Committee's own investigation and the U.S. Government Accountability Office's (GAO) audit have found that for China alone—now one of the largest producers of drug product for the U.S. market—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 inspection rate, FDA can only inspect a Chinese firm exporting drug products to the U.S. once every 40 to 50 years.

The policy for choosing follow-up surveillance inspections of foreign plants also generally appears ad hoc and based on vague criteria. For example, it is not clear why certain foreign firms are selected for a follow-up surveillance inspection or what drives the duration FDA allows between such inspections. While FDA has repeatedly told staff that these decisions are based on a sophisticated "risk-based model," a GAO audit of this program suggests FDA's model is limited in value because it is predicated on poor or incomplete data. As noted by GAO in November 1, 2007, testimony before the Subcommittee on Oversight and Investigations, "FDA lacks sufficient data to make an accurate assessment of the potential risk of [foreign drug-making] establishments." In other words, any model based on limited data necessarily has limited capability in predicting risk.

In light of this situation, we seek additional information to evaluate FDA's current practices and policies with regard to its risk assessment of drug product from China. Accordingly, pursuant to our ongoing investigation of the ability of FDA to ensure the safety of the Nation's drug supply, we formally repeat a long-standing request from the Committee for a listing of each of the more than 700 plants operating in China that are registered to export to the United States, what they manufacture, and their inspection histories. Alternatively, you may supply the most recent Form 483 report of inspection for each facility. Further, for each Chinese plant, please provide a list of each manufacturer of finished drug products that has been authorized by FDA to import active pharmaceutical ingredients (APIs) or other raw material ingredients from these Chinese suppliers. Please supply these records along with inspection histories for each of these firms since January 1, 2001, within two weeks of the receipt of this request.

In addition, FDA has previously requested and received from China reports of China's own inspections of Chinese pharmaceutical firms. Therefore, we request that, if not already done so, you obtain the most current report of pharmaceutical drug firms from China's State Food and Drug Administration that have been identified through China's own inspections as producing counterfeit products or products not meeting Chinese standards, and provide this information to us.

With regard to the heparin case, we are aware of the intense efforts of FDA to isolate the source of the contamination and determine how it reached American consumers. We have avoided any formal hearing pending FDA's determinations. Given FDA policies, however, leading to CDER's failure in the heparin matter and the continued inability of FDA to ensure the quality of drug imports, a public discussion of the policy and resource issues related to heparin is needed.

Accordingly, please note that the Subcommittee on Oversight and Investigations intends to hold a hearing on April 15, 2008, on this matter. We expect that you will provide the Committee staff with all documents requested that are related to the FDA approvals for the manufacture and sale of heparin and for the plant that was confused with the Scientific Protein Laboratories (SPL) application. Those records should be provided forthwith.

If you have any questions regarding these requests, please have your staff contact Chris Knauer or David Nelson of the Majority Committee staff at (202) 226-2424 or Peter Spencer of the Minority Committee staff at (202) 225-3641.

Sincerely,

John D. Dingell
Chairman

Joe Barton
Ranking Member

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

John Shimkus
Ranking Member
Subcommittee on Oversight and Investigations