DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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APR 24 2008

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of February 14, 2008, co-signed by Chairman Bart Stupak, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, requesting information and documents regarding the drug Heparin and the Food and Drug Administration's (FDA or the Agency) foreign inspection program. We have sent partial responses on February 27 and March 5, 2008. This is a further partial response.

Information contained in the enclosures may include information that is trade secret, commercial confidential or other information protected from disclosure to the public under the Freedom of Information Act (Title 5, *United States Code* [U.S.C.] 552), the Trade Secrets Act (18 U.S.C. 1905), the Privacy Act (5 U.S.C. 552a), and FDA regulations. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of any specific information.

We have repeated your question below in bold followed by our response.

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.

Changzhou Scientific Protein Laboratories (Changzhou SPL) was able to ship heparin sodium active pharmaceutical ingredient (API) into the United States because the API was the subject of a new drug application (NDA) from Baxter International, Inc. (Baxter) that FDA approved in 2004. The Center for Drug Evaluation and Research (CDER) approved Baxter's NDA for heparin API without a pre-approval inspection of Changzhou SPL as a result of human error. FDA staff entering data into a database mistakenly selected the name of another manufacturing facility instead of Changzhou SPL. The facility selected had a satisfactory inspectional history; FDA had inspected this facility three times prior to 2004 and had found the facility to be in compliance with current good manufacturing practices (cGMP). Therefore, in accordance with CDER policy, the CDER Office of Compliance (OC) determined that the NDA could be approved without a pre-approval inspection. Had the proper facility (Changzhou SPL) been identified in the system, FDA would have conducted an inspection of this site.

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

We are no longer importing heparin sodium API manufactured by Changzhou SPL. An Import Alert was issued on March 10, 2008, for "Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs." Further, Scientific Protein Laboratories (SPL) of Waunakee, Wisconsin, a partial owner of Changzhou SPL, initiated a voluntary recall of all of its heparin sodium API of Chinese derivation. This API was used primarily in drug products but also in some medical devices. SPL's recall covered all possible users of this API, primarily in drug products and also some medical devices, which have in turn conducted recalls of finished products using these ingredients. There were other recalls of finished pharmaceuticals, that were previously manufactured, that used these APIs. Further recalls were not of APIs but of finished dosage forms. FDA inspected the Changzhou and United States SPL facilities in Waunakee, Wisconsin; collected and analyzed numerous samples in conjunction with various academic institutions; and reviewed many of the results of analytical work done by SPL, Baxter, and other entities. This collaborative work led to the identification of the contaminant, over-sulfated chondroitin sulfate, and FDA's release of information about two tests that manufacturers and regulators can use to screen for the contaminant. Our investigation into the source of this contaminant is ongoing.

Further, on March 10, 2008, FDA added Changzhou SPL to the list of firms and pharmaceuticals that are subject to import detention without physical examination. This Import Alert covers all heparin from Changzhou SPL, including API intended for both possible use as a component in drug products or medical devices. Although FDA has no information that Changzhou SPL is manufacturing medical devices, medical device product codes are included in the Import Alert in the event of potential miscoding of import entries. Refer to the attachment of Import Alert 66-40, "Detention Without Physical Examination of Drugs from Firms Which Have Not Met Drug GMPs" which is available at *http://www.fda.gov/ora/fiars/ora_import_ia6640.html*.

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.

The fiscal year (FY) 2009 program level budget request for FDA's Human Drugs Program is $738.7 million. The program level budget includes budget authority and user fees. This amount represents a proposed Human Drugs Program increase of $58.5 million from the FY 2008 enacted appropriation.

Of the $738.7 million for the Human Drugs Program, the allocation for field activities conducted by the Office of Regulatory Affairs (ORA) in the Human Drugs Program is $99.5 million. This amount represents a proposed increase for field activities of $5.4 million compared to FY 2008. The $5.4 million includes budget authority increases, user fee increases, and administrative savings.

Of the $5.4 million, $1.256 million is targeted for ORA's Office of Criminal Investigations (OCI). This amount will increase the ability of OCI to investigate criminal import violations. The volume of drugs imported into the United States is estimated to increase by 12 percent during FY 2009. This increase in volume heightens the need for OCI investigators to investigate criminal import violations.

The budget also includes $1.9 million for the annual pay inflation adjustment for ORA employees assigned to the Human Drugs Program. The $5.4 million will not increase the frequency of foreign inspections.

In the FY 2007 Revised Continuing Resolution, Congress provided increased funds that allowed ORA to hire new investigators. In FY 2007, ORA hired 104 new investigators across all field program areas. These new investigators were quickly able to perform routine ORA inspections. As a result of the inspections conducted by the new investigators, more experienced investigators became available to conduct more complex inspections, such as foreign drug inspections. The table below displays the increases in foreign inspections that FDA anticipates as a result of our hiring new investigators. This table is a component of the table that appears on page 97 of our FY 2009 budget justification.

PROGRAM OUTPUTS-		
IMPORT/FOREIGN INSPECTIONS	**FY 2008**	**FY 2009**
	Estimate	**Estimate**
Foreign Pre-Approval Inspections (NDA) incl the President's Emergency Plan for AIDS Relief (PEPFAR)	192	192
Foreign Pre-Approval Inspections (ANDA) incl PEPFAR	92	187
Foreign Bioresearch Monitoring Program Inspections incl PEPFAR	46	57
Foreign Drug Processing (GMP) Program Inspections	221	281
Foreign Adverse Drug Events Project Inspections	16	16
Total Above Foreign FDA Inspections	567	733

6. **For Baxter and every other manufacturer of the finished dose 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.**

Documents responsive to this request are enclosed as TAB A.

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

Documents responsive to this request are enclosed as TAB B.

Thank you again for your interest in this matter. If you have any further questions, please let us know. A similar letter without the enclosures has been sent to Chairman Stupak.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosures

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

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