

**Staff Testimony**  
**Subcommittee on Oversight and Investigations**  
**Hearing on**  
**“The Heparin Disaster: Chinese Counterfeits and American Failures”**

**April 29, 2008**

This is the fourth in a series of Subcommittee hearings concerning the Food and Drug Administration’s (FDA) ability to adequately protect Americans from unsafe foreign manufactured pharmaceuticals. Today, the staff is prepared to summarize the results of its investigation of the events that led to at least 81 deaths and hundreds of severe allergic reactions associated with the manufacture of contaminated heparin, a blood thinner used widely in surgery and dialysis whose active ingredient was produced in China.

The heparin case illustrates both the best and the worst of FDA’s performance under this Administration. As with the melamine contamination of wheat gluten that resulted in an untold number of pet deaths last year—events that were highlighted by this Subcommittee in hearings held in July and October of 2007,<sup>1</sup> FDA acted swiftly once the pattern of adverse events from heparin was identified.

FDA moved with speed and efficiency to carry out the following: identify the source of the adverse events; remove the contaminated Baxter product; develop a methodology for identifying the contaminant; require all existing inventories of finished product and active pharmaceutical ingredients (API) to be tested; and issue an Import Alert requiring the testing of heparin drug intermediates entering this country.

As their investigation progressed, FDA received reports from and provided information to public health agencies around the world. These aggressive actions that led to international coordination and the collaboration with scientific experts in this country likely prevented many premature deaths and further adverse events. To date,

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<sup>1</sup> See, “Diminished Capacity: Can the FDA Assure the Safety and Security of the Nation’s Food Supply?” Part II, Tuesday, July 17, 2007, and Part III, Thursday, October 11, 2007.

FDA has helped to identify manufacturers in 11 countries that received contaminated heparin from some 12 Chinese sources.

FDA's inspection of the Chinese factories, albeit after the fact, was also done efficiently and professionally. After learning of the tainted heparin, FDA conducted a comprehensive inspection in February 2008, of the Chinese source of API to Baxter, Changzhou SPL, and both of the upstream suppliers of crude heparin to that plant. FDA inspectors issued a Form 483 noting significant deviations from current Good Manufacturing Practices (cGMPs). Subsequently, FDA analyzed the company's response to the 483, issued an Establishment Inspection Report (EIR), and ultimately a Warning Letter on April 21, 2008, the day before this Subcommittee's last hearing, which detailed a host of serious deficiencies at the facility.<sup>2</sup> The Warning Letter effectively blocks imports from Changzhou SPL until all outstanding issues regarding cGMPs have been resolved and the facility reinspected.

While FDA may respond quickly to a crisis when the danger to the public health is known, Committee staff found that its routinely poor performance as a regulatory agency, responsible for the safety of food, drugs, biologics, and medical devices, invites catastrophe and may have contributed to the tragic use of contaminated heparin on patients in the United States.

Our investigation uncovered a number of serious shortcomings with the operations and policies of FDA:<sup>3</sup>

1. FDA Has Abandoned Its Mandatory Pre-approval Inspection Policy

FDA acknowledges that they failed to inspect the Chinese facility, Changzhou SPL, prior to the approval of the Baxter supplemental application in 2004, which

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<sup>2</sup> Attached as Appendix A to this statement.

<sup>3</sup> The attached briefing memorandum for this hearing provides a time line of the events from January 17, 2008, to date regarding the serious adverse events and deaths associated with the use of Baxter's heparin. FDA, Baxter, and Scientific Protein Laboratories (SPL) witnesses will provide further detail regarding these events.

changed the source of the active pharmaceutical ingredient (API) for Baxter's heparin sodium products from the SPL Wisconsin plant to the newly constructed operation in China.

The Changzhou SPL facility is a joint venture by the U.S. firm Scientific Protein Laboratories (SPL), which also owns the heparin API plant in Wisconsin, and with Techpool, a Chinese firm that "consolidates" raw heparin from a number of workshops that extract crude heparin from the mucus linings of pig intestines. The SPL and Techpool facilities border one another in Changzhou.

While the Chinese Government disputes that counterfeit product was the cause of these adverse events, both FDA and the drug firms involved believe that to be the case. There is no dispute that raw material for the production of heparin sodium containing oversulfated, or hypersulfated, chondroitin sulfate was shipped to the U.S. market.

This form of chondroitin was apparently added to crude heparin in China at some stage in the production process by parties that have yet to be identified. This contaminant was not detected in the standard current United States Pharmacopoeia (USP) tests required of both the active pharmaceutical ingredient producer and the finished product manufacturer. Baxter and FDA have advised Committee staff that this counterfeit ingredient was most likely what caused the reported deaths and adverse health effects of patients receiving heparin.

Chondroitin sulfate is a very inexpensive product marketed as a dietary supplement here in the United States. The oversulfating process gives it anticoagulant properties that mimic heparin sodium, but at a much lower production cost. One FDA official stated that it costs approximately \$20/kilogram (kg) to produce oversulfated chondroitin sulfate versus \$2,000/kg to produce crude heparin. Accordingly, there is speculation that the contaminant was added deliberately to increase profits for the

workshops and/or consolidators that ship the crude material to Changzhou SPL, SPL Wisconsin, and other heparin API producers.

While an inspection conducted in 2004 would not have detected the counterfeit ingredient in the crude heparin supply in 2007, it is possible that an FDA inspection at that time would have uncovered other indicators of potentially serious problems, including the failure of the SPL plant to register with Chinese authorities. Furthermore, an FDA inspection in 2004 might have revealed many of the serious deficiencies highlighted in FDA's inspection report of February 2008—a report that ultimately resulted in the issuance of the Warning Letter that effectively blocked exportation to the United States.

## 2. FDA's Woefully Inadequate Information Technology Systems Resulted in Identification of the Wrong Plant

For years, this Committee has highlighted deficiencies in FDA's various computer systems. As recently as last week, the Government Accountability Office (GAO) and the FDA Science Board testified before this Subcommittee that FDA computer systems are viewed as problematic at best and at worst, dangerous.<sup>4</sup> The heparin case illustrates the consequences of this problem.

FDA attributed the lack of pre-approval inspection of the Chinese SPL production facility to a clerical mistake by an FDA chemist who misidentified the plant in his request for such an inspection. The staff interviewed a number of individuals involved in the review process of the 2004 application filed by Baxter to change its API supplier from the Wisconsin source to the newly constructed plant in Changzhou, China. We found that an FDA employee did in fact choose the wrong plant from the pull down menu on his computer. He erroneously picked "Changzhou Pharmaceutical" instead of the correct name of the facility—"Changzhou SPL Pharmaceutical." Despite this error, he

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<sup>4</sup> See "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," Prepared for FDA Science Board, November 2007, page 5.

entered the correct “unique” New Drug Application (NDA) number and NDA supplement number for the Baxter application and the correct “unique” Drug Master File (DMF) number for the Changzhou SPL plant.

The FDA computer system, however, is not programmed to recognize these errors and alert the operator of the mistake. It accepted three unique numbers for one plant and permitted the selection of the incorrect plant from a menu of facilities for inspection. Furthermore, since FDA determines which facilities to inspect using the often confusing and nearly identical names of Chinese facilities, rather than the unique identifying numbers assigned to them, it was unlikely that this error would have been detected. Thus, the Center for Drug Evaluation and Research’s (CDER) Office of Compliance processed the inspection request for the wrong Chinese facility.

### 3. FDA Inspection Policy Fails to Assess Relative Risks

Our investigation revealed that the wrongly identified facility, Changzhou Pharmaceutical, had been inspected in 2002, two years before the heparin request. That facility, however, has only been inspected for manufacturing two drugs: a simple, well-known, and well-characterized diuretic, hydrochlorothiazide, and a simple, semi-synthetic antibiotic, doxycycline. The manufacturing process for each of these drugs is very different from the extraction process required to produce crude heparin.

The FDA official who was in charge of determining which foreign plants must be inspected prior to approval to manufacture offered Committee staff two possible explanations for the error in his 2004 decision that Changzhou Pharmaceutical was “in compliance” and did not warrant an inspection. This official cited the relatively recent inspection conducted in 2002, and the misconception that the plant was a “crude heparin manufacturing facility,” rather than one that manufactured the active pharmaceutical ingredient. Neither explanation justifies the decision to allow a new heparin intermediate supplier, with no history of producing complex, biological-based

products, to export product to the United States without prior inspection of its manufacturing facilities.

Indeed, of the eight criteria employed by FDA during pre-approval inspections,<sup>5</sup> none involves geographic location, manufacturing complexity, or final product sensitivity. In fact, as far as Committee staff is aware, there is no systematic rationale for choosing which sites to inspect and which to ignore prior to approval by CDER of a foreign inspection application.

Intuitively, one would assume that among the most important criteria for prioritizing pre-approval inspections would be geography, complexity of the manufacturing process, and sensitivity of the final drug product. According to these common sense criteria, the supplemental request in 2004 from Baxter to change the manufacturing site of its heparin API from a plant in Wisconsin to one in Changzhou, China, should rank in the highest priority of risks. The plant is located in China, a country that FDA knows lacks a meaningful drug regulatory scheme and knows (or should have known) has manufacturers that to a large extent operate out-of-compliance. Such observations have been documented by FDA during inspections and observed by Committee staff during field investigations.

In addition, compared to most chemical syntheses, the process of extracting a drug from a biological source is a very different endeavor. While heparin sodium is an old drug, it is not a simple one to manufacture. Again, it would seem that FDA would prohibit any firm from providing to the U.S. market heparin sodium, its API, or crude heparin without first determining whether the firm could manufacture it properly. Manufacturing complexity should have triggered an inspection by FDA before the product was approved for export. Unfortunately, this was not the case.

In its final finished dosage form, heparin is a sterile drug administered to very sick patients, primarily those on dialysis for kidney failure and those undergoing open-

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<sup>5</sup> Food and Drug Administration Compliance Program Guidance Manual 7346.832, pp. 10-11.

heart surgery. Because patients who receive heparin are particularly vulnerable physically, the margin for error in production is virtually zero. Although the sensitivity of the final drug product should have guaranteed an FDA inspection, it did not because this is not a criterion for inspection.

#### 4. The Role of Corporate Due Diligence Cannot Be Relied Upon

Committee staff investigation raised a number of questions about the due diligence performed by the various companies involved in this disaster. As previously mentioned, on April 21, 2008, FDA issued a warning letter to Changzhou SPL, where the adulterated heparin allegedly originated. In that letter, FDA details a litany of significant deviations from cGMPs discovered in the manufacture of Heparin API at that plant. Those deviations were listed in summary form on FDA form 483 at the close of the team's initial inspection. According to the warning letter, the cGMP deviations observed by FDA at Changzhou SPL were sufficient to require its heparin API to be classified as adulterated under the Food, Drug, and Cosmetic Act.

According to FDA's inspection, the Changzhou SPL facility was unable to provide FDA with any assurance "that processing steps used to manufacture heparin sodium, USP are capable of effectively removing impurities." FDA also found that the facility failed "to have adequate systems for evaluating the suppliers of crude heparin materials, or the crude materials themselves, to ensure that these materials are acceptable for use." Moreover, the methods employed to test heparin sodium United States Pharmacopoeia (USP) had not been verified to ensure suitability under actual conditions of use, and the equipment used to manufacture the product was "unsuitable" for its intended use.

In layman's terms, FDA determined that this plant was unable to manufacture drug product consistent with the requirements under the Food, Drug, and Cosmetic Act. An obvious question that must be asked in relation to FDA's inspection findings is why Baxter obtained drug product from a facility that FDA found to be unsuitable? More

specifically, what due diligence did Baxter perform to determine that it could safely manufacture heparin API for the U.S. market before using this facility?

Committee staff found several facts that should have alerted Baxter to potential problems, but which appear to have been ignored. For example, Baxter's own records indicate that they were aware that the plant had never been inspected by FDA. It seems very odd that Baxter accepted the risks of using this facility to obtain the API used to manufacture a sterile biologic without an FDA inspection. Moreover, this plant was apparently not one that China's State Food and Drug Administration was aware of since Chinese authorities listed it as a chemical plant rather than a licensed pharmaceutical plant. This too should have been cause for enhanced attention to its manufacturing processes.

Finally, Committee staff questions the quality and nature of the inspection performed by Baxter on September 20, 2007, relating to the factory's condition to manufacture drugs. According to records provided by Baxter to the Subcommittee, the scope of that audit was "to ascertain the cGMP compliance status of Changzhou SPL Co. LTD. facility in China for cGMP Active Pharmaceutical Ingredient manufacturing as well as other potential future products." The audit "consisted of an in-depth review of Changzhou's quality systems and capabilities" and included documentation and procedures related to incoming materials, sampling procedures, stability operations, quality assurance processes, and stability operations. The results of Baxter's audit differ significantly from those reported by FDA, which inspected the facility only five months later.

The Baxter audit team satisfactorily closed out any problems they uncovered during their inspection in a February 26, 2008, letter to Baxter. This was done within days of the onsite inspection by FDA's own investigators, whose findings ultimately led to halting all imports from that facility. The radically different conclusions drawn from the inspections by Baxter and FDA, despite their close juxtaposition in time, suggest

that either Baxter's auditors were less than competent or the facility fell radically out-of-compliance in the few months that elapsed between the two inspections.

This case also raises troubling questions when viewed in the context of recent testimony by FDA Commissioner Von Eschenbach extolling greater reliance on third party or self-inspection as a substitute for FDA performing its mission.

Moreover, this case demonstrates the quality and value of an FDA inspection. Despite the time and translation constraints inherent in an inspection in China, a team of professional FDA inspectors readily determined that Changzhou SPL could not supply safe API for the U.S. market—a conclusion that neither the Chinese authorities nor the corporations involved were willing or able to determine before hundreds of patients were seriously hurt or killed. Although it is most regrettable that FDA did not inspect this plant sooner, when it finally acted, FDA lived up to what is expected from such an important government agency—ensuring that our citizens are protected from unsafe pharmaceutical products.