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**BEFORE THE**

**SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS**

**COMMITTEE ON ENERGY AND COMMERCE**

**UNITED STATES HOUSE OF REPRESENTATIVES**

**APRIL 29, 2008**

**Release Only Upon Delivery**

## **INTRODUCTION**

Mr. Chairman and Members of the Committee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to discuss the important issues related to FDA's ongoing heparin investigation, in particular, and more broadly, the safety of drugs and pharmaceutical ingredients imported from countries outside the United States.

FDA's mission is to ensure that safe and effective new drugs, devices and biologics are made available to American consumers and that drugs, devices and biologics on the market remain safe and effective, regardless of where they are produced. I want to reiterate today what FDA Commissioner von Eschenbach has stated previously before this Subcommittee: we at FDA are fully committed to strengthening the drug safety system as fast as available science and resources will allow.

In my testimony today, I will first provide background about and the status of the Agency's ongoing heparin investigation. I will then briefly discuss the challenges presented by the globalization of drug development and manufacturing and the steps the Agency is taking to address these challenges.

## **ONGOING FDA HEPARIN INVESTIGATION**

### **Brief Overview**

Beginning in January 2008, Baxter Healthcare Corporation (Baxter) recalled various lots of heparin, a blood thinning drug, following a spike in reports of adverse events, including deaths, associated with the product. On April 21, 2008, after many weeks of intensive investigation and laboratory analysis, we were able to establish a link between a contaminant found in heparin, oversulfated chondroitin sulfate, and the serious adverse events seen in patients given heparin. We have been able to trace the contaminant to 12 different Chinese companies and it has been found in heparin batches shipped to 11 countries. We have made substantial progress in this case and FDA investigators and scientists are continuing to work independently and in collaboration with the Centers for Disease Control and Prevention, Baxter, and many other private and public entities in this ongoing investigation. FDA continues to monitor its post-marketing safety database for additional cases and has contacted regulators around the world to determine whether similar events have been seen in other countries with similar products.

### **Agency Process**

Upon learning of the unusual spike in adverse events, FDA assembled an Agency-wide response team. Our goal has been to investigate and find the problem, to keep the public informed about the status of the safety of the heparin supply, to work with international partners in defining the scope and nature of the problem, and to make sure that an adequate supply of heparin is available to patients who need it.

This is a far-ranging investigation in the U.S. and abroad. FDA has inspected Baxter's domestic facilities, examined heparin product in the U.S., and sent a team of FDA experts to China to conduct a comprehensive inspection of Scientific Protein Labs (SPL) in Changzhou, China, the facility that makes the active pharmaceutical ingredient (API) for the heparin recalled by Baxter.

### **FDA Development of New Test Methods**

One of our first steps in the investigation was to analyze the product for any abnormalities. FDA worked closely with the manufacturer and experts in academia and private laboratories to carry out a thorough chemical analysis of the suspect products. Conventional laboratory testing did not initially identify the contaminant. FDA experts then developed new test methods using state-of-the-art technologies such as nuclear magnetic resonance, capillary electrophoresis, enzymatic kinetics, and bioassays. As a result of a disciplined systematic examination, FDA scientists identified the previously unknown contaminant in the heparin. Specifically, some of the heparin product and heparin API manufactured by Baxter's supplier, SPL, was contaminated by oversulfated chondroitin sulfate, a heparin-like product derived from animal cartilage.

Chondroitin sulfate is sold as a dietary supplement. The contaminant is a derivative of that chemical compound and is not approved or sold for any medical purpose. The derivative compound reacts like heparin in many tests, which is why the traditional release tests did not detect it.

The Agency then publicized information on the two FDA-developed tests, and recommended use of the tests to manufacturers and suppliers for screening heparin API. FDA posted these FDA-recommended test methods on its website.

### **Linking the Contamination to the Adverse Events**

After identifying the contaminant, FDA scientists then attempted to determine whether the contaminant in the product could be causing the adverse events. On April 21, 2008, FDA announced a link, based on animal testing and analysis, between the adverse events and the contaminant found in the drug. On April 23, 2008, FDA shared this scientific information in two journal articles published on-line in the New England Journal of Medicine and Nature Biotechnology, <http://content.nejm.org/cgi/content/full/NEJMoa0803200> and <http://www.nature.com/nbt/extra/nbt1407.pdf>.

### **Import Alert/Import Bulletin**

The Agency's first priority in the heparin situation is detecting any contaminated products and preventing such products from reaching U.S. consumers or to remove them from the U.S. market. On January 25, 2008, Baxter announced the voluntary recall of nine lots of heparin sodium injection 1000 units/mL 10mL and 30mL multi-dose vials. The company began recalling the lots on January 17, 2008, as a precautionary measure due to an increase in the number of reports of adverse patient reactions that may be associated with the product. On February 11, 2008, FDA issued a public health advisory to inform the public about reports of serious adverse events in patients who received bolus injections of heparin sodium for injection primarily from multiple-dose vials manufactured by Baxter, and to recommend

measures that may help to minimize these risks if this product must be used due to medical necessity, <http://www.fda.gov/cder/drug/advisory/heparin.htm>. On February 28, 2008, Baxter announced that the company was proceeding with the voluntary recall of all remaining lots and doses of its heparin sodium injection multi-dose, single-dose vials and HEP-LOCK heparin flush products. On February 28, 2008, FDA issued a public health update regarding the extension of the heparin recall, [http://www.fda.gov/cder/drug/infopage/heparin/public\\_health\\_update.htm](http://www.fda.gov/cder/drug/infopage/heparin/public_health_update.htm).

On March 10, 2008, FDA announced that all heparin coming into the U.S. from Changzhou, SPL in China was subject to an Import Alert (Import Alert 66-40). This means that, as with other products subject to this Import Alert, FDA can detain Changzhou SPL's heparin API and refuse its admission into the U.S. until it is demonstrated to FDA that appropriate corrections have been made. On March 14, 2008, FDA issued an assignment to its field staff requiring examination and sampling of all heparin sodium API coming into the U.S., except sodium heparin API being shipped to firms where FDA knows the recommended tests will be conducted. This sampling assignment means that all heparin sodium API shipments are being sampled and tested before being used or sold in the U.S. All other heparin products are also subject to sampling and testing at FDA's discretion. Testing imported heparin products will help ensure patients and healthcare professionals that heparin is safe for its indicated uses.

### **Early Communication**

FDA has communicated throughout this investigation with the press, Congress, healthcare professionals, and the public to keep these groups apprized of important findings and developments as we move forward in our investigation. Transcripts and recordings of media calls are posted on FDA's website to provide broad access to information about developments. These communications are consistent with our Early Communication commitment to provide the public with information on developing and ongoing public health issues at the Agency. In addition, FDA created a page on the FDA website that contains the latest up-to-date information on heparin. We are continually posting information on this site located at: [www.fda.gov/cder/drug/infopage/heparin/default.htm](http://www.fda.gov/cder/drug/infopage/heparin/default.htm).

### **International Collaboration**

Our investigation confirmed that the contamination is not limited to Baxter's heparin. Contamination of the heparin supply is a worldwide problem. At this point, because of FDA's sharing of its test methods, contamination has been detected in heparin in at least 11 different countries involving many different suppliers. FDA's working hypothesis is that this was intentional contamination, but this is not yet proven.

While the contaminant was first identified in the U.S., the recall of this product is international in scope. FDA has notified key regulatory international partners, and we are working closely with our Chinese and European counterparts in the investigation. The recently signed Memorandum of Agreement (MOA) (described later in this testimony) facilitated FDA investigators going to China to perform an investigation. In addition, five

individuals from the Chinese State Food and Drug Administration (SFDA) were present during the February 20, 2008, inspection of the Changzhou, SPL facility.

On April 17 and 18, 2008, FDA convened a meeting with international counterparts that have been working on the heparin issue to discuss laboratory analysis/data interpretation and good manufacturing practice (GMP) inspections. The meeting focused on: (a) the challenges of analytical approaches we are presently using and the challenges of interpreting the results; (b) leveraging and integrating the information we are amassing and resources we are spending on our respective GMP inspections/investigations related to this matter; (c) initiating discussions on developing appropriate international compendia standards for heparin that will help mitigate the chances of such contamination in the future; and (d) considering how we can work together to identify products that may be contaminated in the future and how we can prevent and rapidly detect such contaminations. Representatives from the regulatory authorities of Australia, Canada, China, Denmark, European Union, France, Germany, Italy, Japan, Singapore, and Switzerland attended, as well as representatives of the U.S. Pharmacopoeia, European Pharmacopoeia, and the Massachusetts Institute of Technology. FDA will continue its leadership on this issue through ongoing discussions with colleagues from around the world.

### **Medical Devices**

In an effort to remain vigilant in their efforts to assure that the safety and effectiveness of heparin-containing devices and *in vitro* diagnostic devices are not compromised, FDA's Center for Devices and Radiological Health (CDRH) has been proactive and collaborative by

forming an intercenter task force who have been in daily and weekly contact with CDER's heparin task force. The objective is to maintain consistency of Agency actions and communications with device industry, professional and public stakeholders.

Using a multipronged approach to identify suppliers and distributors for devices identified as either coated with heparin or which use heparin as part of the device or *in vitro* diagnostic device, CDRH's task force searched and analyzed the medical device adverse event database to determine the scope and extent of any reported events similar to those events reported for bulk heparin. CDRH has contacted manufacturers of medical devices that contain heparin or use heparin during the manufacturing process to alert them to the potential for their devices to be affected by contaminated heparin. To maintain continued vigilance, CDRH is also notifying manufacturers of these types of devices about recommended testing procedures and follow up actions to assure continued device safety and adequate adverse event reporting.

### **Assuring Availability of Heparin for Patients**

During this recall, FDA has been able to assure healthcare professionals and patients that there are no shortages of this critical drug. Another U.S.-based heparin API manufacturer, APP Pharmaceuticals, was able to supply the vast majority of the U.S. market, and continues to do so.

### **Could FDA Have Prevented the Situation?**

The circumstances surrounding the recent recall of heparin raised questions about FDA's ability to fully assure the safety of pharmaceuticals and pharmaceutical ingredients produced

outside the U.S. However, previous testing methods were not adequate to detect the potential contaminant. In investigating the most recent heparin situation, FDA learned in January 2008 that Baxter received FDA approval to use the API manufacturer, Changzhou SPL in Changzhou, China, although FDA did not conduct a pre-approval inspection of the plant. The plant subsequently shipped product to Baxter. As FDA has acknowledged, FDA's failure to inspect the plant was the result of human error. FDA staff entering data into a database confused the name of the Changzhou plant with another plant that had been previously inspected.

There is no justification for the theory that contamination of heparin would have been prevented if the inspection of Changzhou SPL had occurred in 2004. Intentional contamination is difficult to detect during an inspection and, in any case, the contamination appears to have begun long after the inspection would have been completed. Moreover, heparin contamination is not limited to product from Changzhou SPL, so timely inspection of that one firm would probably not have prevented the problem.

### **Process Improvements**

We believe that process improvements that are already underway will prevent future data entry errors like this. These improvements include additional training for those who do the data entry on which inspection assignments hinge, hiring new staff dedicated to this data entry, and putting procedures in place that will provide FDA with the necessary data from drug manufacturers in a user-friendly way.

Unfortunately, there are sometimes factors beyond our control that affect the integrity of a product, such as when someone intentionally contaminates a product. We hope that systems in place would discourage or detect such manipulation but it would be disingenuous for FDA to suggest that it would be feasible for the Agency to inspect every single production facility and every single product, and that such inspection would discover every single problem.

The imperfection of any system is a primary driver for FDA's life-cycle approach to product regulation. We must be able to identify a problem, aggressively and decisively investigate its root cause, and intervene to minimize the damage and to prevent future similar events.

Our goal is, of course, to minimize the risks associated with the use of drug products to the greatest possible extent. FDA recognizes that drug safety relies on a foundation of drug quality. Improperly manufactured drugs and drugs that are contaminated or illegally marketed can cause significant harm to patients. For this reason, FDA devotes considerable effort to reviewing and monitoring drug manufacturing activities. We know how important it is for FDA to determine that facilities named in drug applications will meet FDA standards for marketed drug safety, effectiveness, and quality, no matter where they are located.

## **GLOBALIZATION OF DRUG DEVELOPMENT AND MANUFACTURING**

FDA increasingly faces challenges due to globalization of drug development and manufacturing. Not long ago, most drugs were developed, studied, and manufactured in the U.S. Today we routinely review and monitor drugs – both innovator and generic – that are studied or manufactured, at least in part, outside the U.S. The supply chain for finished

drugs and active pharmaceutical ingredients now frequently links to manufacturing sites in China and India. With the globalization of the supply chain, FDA faces an ever-growing number of brokers, traders, distributors, repackagers, and other players involved in the import of pharmaceuticals. The changing world – including the fundamental challenges of many different languages and protocols – requires FDA to devise and evaluate more complex risk scenarios and apply more sophisticated technologies to screen and evaluate drugs entering the U.S. to ensure their quality.

Our generic drug program illustrates the dramatic changes during the last 10-15 years. Since 1992, we witnessed a 400 percent increase in the number of foreign establishments named in generic drug marketing applications. Today, in India alone, there are nearly 25 times as many drug establishments as there were eight years ago. Yet, FDA must be able to determine that facilities named in drug applications will meet FDA standards for marketed drug safety and effectiveness, no matter where they are located. FDA is taking many important steps to provide this assurance.

### **IT Enhancements**

One of the keys to protecting the American drug supply is for FDA to have up-to-date, complete, interoperable data systems. The Commissioner has stated before this Subcommittee that upgrading FDA's Information Technology (IT) systems is one of his top priorities. Last year, FDA hired a new Chief Information Officer (CIO) with experience in developing and managing innovative and cost effective multi-organizational scientific and

business programs, re-engineering governmental processes and managing the reduction of duplicative systems.

Efforts are underway to centralize all FDA's IT systems. This centralized approach provides the CIO the authority and oversight of available IT resources to meet the challenges of the FDA in the 21st century. Coupled with resource planning and development activities, FDA's Office of Information Management has undertaken detailed succession planning to ensure that the IT organization that FDA is building for the 21st century remains reliable in support of FDA's mission and sufficiently flexible to accommodate the science and technology advances of the future.

Logistically, foreign firms are more difficult to track and more challenging to inspect than domestic firms because we cannot always easily gain access to the firms. In addition, the data we have regarding foreign firms is not always easy to confirm or check for accuracy. Foreign firms must register with FDA before shipping to the U.S. Because for most firms there is no cost to register, some firms register, but do not actually produce a product or ship products to the U.S., or discontinue shipping without any notice to FDA. The practice of registering without producing or shipping can create uncertainty at any given moment about the precise number of FDA registered firms from which to target inspections, often requiring secondary data-source checking.

FDA monitors the importation of drug products and the manufacturer of those products through its Operational and Administrative System for Import Support (OASIS) system.

However, our systems do not yet have the capability to automatically verify the accuracy of all of the information submitted.

The formation of FDA's Bioinformatics Board (BiB) in 2006 provided an important means of ensuring that business needs and public safety endeavors are equally met by Agency IT services. Members of my office are actively involved in the work of BiB and the Business Review Boards created under it. BiB oversees the quality and performance of information systems, including business decisions on prioritization, planning, and execution of Agency cross-cutting business automation projects, positioning the Agency to meet external demands while, at the same time, satisfying the needs of FDA programs.

## **INTERNATIONAL EFFORTS**

### **International Agreements**

Good public health protection demands much more than a solid inspection program to manage imports. Faced with an unprecedented increase in products from abroad, FDA has relied on augmenting our foreign inspection program and entry admissibility reviews with the pursuit of two significant international strategies for helping to assure the quality of these products: harmonization of standards through multilateral fora, and two-party (bilateral) agreements with other countries.

In general, FDA and other countries enter into harmonization initiatives to assure product quality while at the same time conserving human and financial resources and improving the

efficiency of their operations. When nations can agree on scientific standards for establishing the safety, effectiveness, and manufacturing quality of pharmaceutical products, everyone wins. Sometimes, harmonization efforts among many nations do not address specific national needs. In such situations, FDA and its international counterparts find it mutually beneficial to enter into one-on-one agreements that allow them to share information and work closely together to solve specific problems.

On December 11, 2007, Secretary Leavitt announced the signing of a MOA between the United States and China, to improve the safety of drugs and medical devices. Some of the critical aspects of the agreement include: (1) all Chinese producers of items covered under the agreement for export to the U.S. must register with Chinese authorities; (2) the Chinese will adopt quality-assurance electronic tracking methods for certain products; (3) information sharing by providing timely notification to U.S. regulators regarding certain inspectional failures at drug manufacturing facilities and shipments of products that may be dangerous. In addition, the Chinese will facilitate and expedite inspections by FDA investigators of Chinese drug plants. The MOA covering drugs was instrumental in expediting FDA's entry into China to investigate the problems with heparin.

FDA has a variety of cooperative relationships with foreign regulators that support our efforts to manage the challenges presented by global production of drugs and biologics. A list of FDA's commitments appears on FDA's Office of International Programs, International Arrangements, <http://www.fda.gov/oia/agree.htm>.

### **Establishing an FDA Presence Abroad**

On March 14, 2008, FDA announced that it had received approval from the U.S. State Department to establish eight full-time FDA positions in China, pending authorization of the Chinese government. FDA regards this as an important step forward in our plans to hire and place FDA staff in China over the next 18 months. In addition, FDA will be hiring a total of five local Chinese nationals. These staff members will enhance FDA's capacity to inspect Agency-regulated industry in China as well as improve our understanding and oversight. This initiative facilitates the building of stronger cooperative relationships with FDA counterpart agencies around the world and enhanced technical cooperation with foreign regulators. The overseas presence in China will also allow greater access for inspections and greater interactions with manufacturers to help assure that products that are shipped to the U.S. meet U.S. standards for safety and manufacturing quality.

Building FDA's capacity outside of the U.S. is the primary driver of FDA's "Beyond Our Borders" initiative which was described more fully in the Commissioner's testimony to this Subcommittee on April 22, 2008.

### **Educational Workshops**

FDA also works around the world to help regulators and manufacturers understand modern drug standards. For example, my office conducted a series of educational workshops in China in December 2005 and April 2006 on current GMP (cGMP), in collaboration with the International Society for Pharmaceutical Engineering and Peking University. The workshops educated participants on current methods for compliance with cGMP to ensure

effective cGMP programs and to further the common goals of FDA and providers of quality pharmaceutical products. The workshops were open to any professionals involved in the manufacture, control, and regulation of pharmaceutical products, including process/production engineers, manufacturing personnel, quality assurance/quality control and regulatory affairs professionals, consultants, regulatory investigators and cGMP compliance officials. Just last month, I taught workshops on cGMP and on prevention of contamination and counterfeiting to members of China's SFDA.

## **CONCLUSION**

Ensuring the safety and efficacy of the drug products used by American consumers continues to be a top priority for FDA. Despite the challenges that face us, the American drug supply continues to be among the safest in the world. Thank you for the opportunity to testify. I look forward to responding to any questions you may have.