STATEMENT OF
THE HONORABLE BART STUPAK
SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS
"THE HEPARIN DISASTER: CHINESE COUNTERFEITS AND AMERICAN FAILURES

APRIL 29, 2008

Today, this Subcommittee is holding another in a series of hearings examining the adequacy of the efforts of the Food and Drug Administration to protect Americans from unsafe drugs. Today's hearing will focus on the circumstances surrounding the recent catastrophe caused by the contamination of the drug heparin. To date, contaminated heparin has been linked to at least 81 deaths and hundreds of severe allergic reactions in the United States. Today, we will hear from the two companies responsible for introducing the contaminated heparin into the United States. We will also hear from FDA regarding the circumstances that led to the introduction of the contaminated heparin and its actions after the outbreak was discovered. Finally, we will also hear from family members of victims who died after being treated with heparin.

To understand how and why this outbreak occurred, it is first necessary to understand what heparin is, how it is made, and where it is made. Heparin is an important anticoagulant, or blood thinner, that is widely used in surgery and dialysis. It is derived from pig intestines and has been marketed in the United States since the 1930s. Heparin is a natural product that exists in the lining of a pig's blood vessels. Membrane of the intestine are collected and processed to form a dry substance known as crude heparin. Crude heparin is then further refined and made into an active pharmaceutical ingredient (API) that is sold to drug companies that manufacture the final product.

It is now estimated that China produces over half of heparin's active pharmaceutical ingredient. Indeed, all of the tainted heparin in this case was manufactured from API produced in China. Baxter, the final manufacturer of the contaminated heparin has a complex, international supply chain shown on the slide we have up on the screens. Their supply chain starts in China where 10-12 Chinese workshops make crude heparin. This crude heparin is then either sold to middle men called brokers or is sold directly to two companies that consolidate the product. These consolidators then sell the crude heparin to an American company Scientific Protein Laboratories (SPL) which has a joint venture plant in Changzhou, China. SPL, also has a plant in Wisconsin, which produces heparin API from that crude heparin. This heparin API is then sold to another American company Baxter, which manufactures finished heparin drug products at its plant in Cherry Hill, New Jersey.

In November 2007, Children's Hospital in St. Louis, MO began noticing adverse reactions in their dialysis patients. On January 7, 2008 the Missouri Department of Health

and Senior Services notified the Centers for Disease Control and Prevention, who in turn notified the FDA and Baxter of the cluster of adverse events.

On January 17, 2008, Baxter, which produces about 50 percent of the heparin used in the United States, initiated an "urgent" nationwide recall of nine lots of heparin products after there was an increase in adverse reactions patients suffered after being given heparin products produced by Baxter. On February 11, FDA announced that Baxter had halted the manufacture of multi-dose vials of heparin because of serious allergic reactions and low blood pressure in patients. On that same day, FDA announced that approximately 350 adverse events associated with heparin had been reported since the end of 2007 and that FDA classified 40 percent of the events as "serious"—including four deaths. Days later, Baxter recalled all of its heparin injection and solution products remaining on the U.S. market. As of today, there have been 81 deaths and at least 785 severe allergic reactions associated with heparin since January 2007. 62 of these deaths occurred between November 2007 and February 2008.

FDA's investigation into the cause of the outbreak revealed that heparin API made by Changzhou SPL contained a contaminant called oversulfated chondroitin sulfate. Chondroitin sulfate is made from animal cartilage and is cheaper than raw heparin. By itself, chondroitin sulfate does not have blood-thinning properties; however, it can be chemically altered to form oversulfated chondroitin sulfate, which mimics real heparin and is less expensive. Because oversulfated chondroitin sulfate mimics heparin, it was not detected by standard tests. Oversulfated chondroitin sulfate is not an approved drug in the United States, and it should not be present in heparin. In samples collected from Changzhou SPL in China, FDA found that this contaminant was present in amounts ranging from 2 to 50 percent of the total content of the API. The contaminant was also found in some of the Baxter heparin lots associated with adverse reactions.

Today, it is not known whether this contaminant entered the supply chain accidentally or was introduced intentionally. Because oversulfated chondroitin sulfate is not normally found in nature and is produced through chemical modification, evidence would suggest that this contaminant was intentionally introduced at some stage in the supply chain.

While FDA must be applauded for its outstanding efforts in responding to this outbreak, it must also be held accountable for one glaring and fatal mistake. In 2004, a series of FDA blunders resulted in an FDA decision to approve Changzhou SPL to sell heparin API to Baxter without first conducting a pre-approval inspection of Changzhou SPL's production plant as is FDA's policy. It was not registered in China as a drug manufacturer and Chinese officials had never inspected the plant either.

If FDA had conducted such an inspection in 2004, would they have concluded that Changzhou SPL was not capable of meeting Current Good Manufacturing Practices (cGMP's) as was concluded in FDA's inspection after the heparin deaths? It was not until February 20, 2008, that the FDA began an inspection of the Changzhu plant. In that inspection FDA determined that Changzhou SPL was incapable of providing safe heparin

API to the United States. We may never know whether an FDA pre-approval inspection would have prevented this outbreak from occurring. However, it is regrettable that FDA did not inspect this plant sooner, as this may have positively impacted the events related to the heparin tragedy we are discussing today.

While much of this Subcommittee's ire regarding the safety of drugs in this country has been directed towards FDA, perhaps a greater responsibility to ensure the safety of drugs in this country lies with the drug companies themselves. Make no mistake about it; both Baxter and SPL have failed the American public.

One only needs to look at FDA's inspection report of Changzhou SPL which revealed "significant deviations" from U.S. Current Good Manufacturing Processes in the production of heparin API. FDA found that Changzhou SPL's processing steps provided no assurance that they were capable of removing impurities. It found that SPL failed to have adequate systems for evaluating both the crude heparin and the suppliers of crude heparin to ensure that the product was acceptable for use. FDA found that the test methods performed by SPL had not been verified to ensure suitability under actual conditions of use. Finally, FDA found that the equipment SPL used to manufacture heparin was unsuitable for its intended use.

These findings raise several questions. Why was Baxter obtaining drug product from a facility that FDA found to be unsuitable? What due diligence did Baxter or SPL perform before they began using this plant to confirm that it could safely make heparin API for the U.S. market? Why did Baxter sell ingredients from this plant when it knew it had never been inspected by FDA or China? Why did Baxter buy ingredients from a country that provided little oversight and had a history of producing contaminated products?

The questions in this case are endless. Hopefully, some of these questions will be answered today and that these answers will help this Committee to continue to move forward in its quest to fix our country's broken drug safety system. Today, we look forward to examining what steps must be taken to strengthen this broken system.

I would like to thank all witnesses for being here today, especially the family members that lost loved ones. I am deeply sorry for the losses you have suffered and I appreciate you having the courage to testify before us during these trying times.