

Testimony of Robert L. Parkinson  
Chief Executive Officer, Baxter International  
Before Subcommittee on Oversight and Investigations  
Committee on Energy and Commerce  
U.S. House of Representatives  
April 29, 2008

**SUMMARY OF MAJOR POINTS**

- More than any other company in the world, Baxter's products are involved in critical care settings. Because of this, we are greatly concerned that our heparin product appears to be the target of a deliberate adulteration scheme. Patient safety is our number one priority, and we deeply regret the impact this contamination in Baxter's heparin has had on patients and the clinicians who treat them.
- The developments of the last several weeks have demonstrated that this is both a global and industry-wide crisis, with a root cause – oversulfated chondroitin sulfate (“OSCS”) -- that was so novel and so insidious as to avoid the quality systems of a multitude of companies and the oversight of the world's most sophisticated drug regulatory agencies.
- Because of the swift identification of OSCS, and the development of advanced NMR and CE tests methods to detect it, FDA and regulatory authorities around the world have been able to respond proactively, averting a much broader crisis by detecting and screening out the contaminant in other manufacturers' heparin before it was more broadly distributed to patient populations.
- The complexity of the global drug supply chain creates new and emerging risks that call for new ways of thinking about, identifying and addressing vulnerabilities. Resting on old standards – even ones that have worked for decades – is no longer enough. These are the most critical lessons of this entire crisis, and Baxter embraces them.
- We support funding directed to enhancing FDA's ability to fulfill its mission of providing safe and effective products to the American people, and we welcome any opportunity to work with Congress and the Agency in support of this mission.

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Introduction

Good Morning Mr. Chairman and Members of the Committee. My name is Bob Parkinson, and I am Chairman, Chief Executive Officer and President of Baxter International (Baxter). I appreciate the opportunity to be here today to provide testimony and to respond to the Committee's questions on the crucial topic of medical product safety and the recent recall of heparin products that Baxter and many other companies have implemented.

Our mission at Baxter is to provide life saving and life sustaining medical therapies to patients across the world. We are not a traditional pharmaceutical company. Every one of the products we develop and manufacture is injected, infused or inhaled by patients who need them to stay alive. This is true across our three divisions: our Renal division provides dialysis therapies for patients with end-stage renal disease; our Bioscience division provides biologic therapies for patients with serious blood disorders like hemophilia or primary immune deficiency; and our Medication Delivery division provides a wide range of hospital products for use in acute and critical care settings. If you or a loved one has kidney failure; if your child was born without a functional immune system or with blood that doesn't clot; if you have the misfortune to find yourself in an intensive care unit, an emergency room or an operating room, Baxter products are the difference between life and death. In my four years at Baxter, I have been inspired by the extent to which this is a source of pride for Baxter employees, and it is the source of the profound commitment and responsibility we feel for each of our patients.

Baxter has been in business for over 75 years. More than any other company in the world, our products are involved in critical care settings. Because of this, we are greatly concerned that our heparin product appears to be the target of a deliberate adulteration scheme. Patient safety is our number one priority, and we deeply regret any harm this contamination in Baxter's heparin may have had on patients or impact on the clinicians who treat them.

Through Baxter collaboration with FDA, oversulfated chondroitin sulfate (“OSCS”) was identified as a contaminant in certain lots of our injectable vial heparin product. Baxter scientists did not stop there, and in laboratory animal tests have observed a causal relationship between OSCS and hypotensive effects, the results of which were recently confirmed in an article published in The New England Journal of Medicine. Given the knowledge that we have developed over a short period of time, we have made a significant contribution to helping regulatory bodies and manufacturing companies around the world protect the world’s heparin supply from this insidious contaminant.

#### Baxter’s Manufacturing of Heparin

Baxter, and its predecessor company ESI Lederle (Wyeth), has been manufacturing heparin in a vial form for over 30 years. Baxter purchases heparin active pharmaceutical ingredient (“API”) from Scientific Protein Laboratories (“SPL”), a company located in Waunakee, Wisconsin. Heparin API is derived from the mucosal lining of pig intestines. SPL initially sourced the crude material for its API from the United States. In the mid-1990s, SPL embarked on a program to find other raw material suppliers to assure a consistent quality supply of heparin. Because of supply constraints around the world, SPL, like virtually all heparin API manufacturers, began sourcing this product from raw material suppliers in China, the source of over half of the world’s pig supply. ESI and Baxter consistently manufactured heparin made from SPL’s API, sourced from China crude, since 1996.

In order to be closer to its Chinese supply chain and to increase its manufacturing capabilities, SPL built a heparin API manufacturing facility in Changzhou, China (SPL-CZ) in 2000. In December 2002, Wyeth Global Compliance performed a qualifying audit of this facility. The facility had run three consecutive validation lots before this inspection. Baxter acquired ESI shortly after this audit. Baxter undertook the process of having SPL-CZ qualified by the FDA as a supplier of heparin API. Baxter submitted a Prior Approval Supplement (PAS) to the FDA on February 6, 2004. The PAS requested that the FDA approve “Changzhou-SPL Co., Ltd. as an alternate supplier” for heparin.

On June 8, 2004 FDA sent a letter to Baxter approving SPL-CZ as an alternate supplier for heparin. Once we received that approval, the manufacture of the API from this facility was approved by the FDA. That approval was not subject to or conditioned on an FDA inspection.

Speaking for Baxter, however: we don't rely on FDA inspections to ensure the quality of our product – that's our job, independent of the FDA's role.

To fulfill this obligation, Baxter relied on Wyeth's December 2002 qualifying audit. In hindsight, we should have conducted our own qualification audit as well, before beginning to receive product in 2004. It bears noting, however, that plant audits were not the only thing we relied on to ensure the quality of our product – we also consistently monitored the quality of both the incoming product we received from SPL and the finished heparin product that we released. Although sample testing is regulatorily acceptable, we tested each and every lot. Our testing exceeded the standards of the U.S. Pharmacopoeia ("USP"), the official public authority that sets standards for all healthcare products sold in the United States. The USP standards for heparin have been successfully used for decades. Unfortunately, we now know that these standards were insufficient to detect this new heparin-like contaminant because OSCS could not be detected with established and validated test procedures. Going forward, Baxter is committed to working with USP and FDA in re-evaluating standard heparin test procedures.

Baxter's Quality team performed a cGMP audit of the SPL-CZ facility in September 2007. The audit consisted of an in-depth review of CZ SPL's quality systems and capabilities including, but not limited to, its supply chain quality systems, such as the documentation and procedures associated with incoming materials and sampling. Baxter was assured that SPL's QA department audits the workshops it uses on an annual basis. SPL also provided assurances that these workshops collect veterinary data for all porcine sources to assure the stock is disease-free prior to collection.

#### Baxter's Recall of Heparin

Heparin vials are used in a variety of critical care settings, including cardiac and dialysis procedures. Allergic-type reactions are indicated in the label for heparin, and every year Baxter receives approximately 30 reports of adverse events associated with its heparin vial products. At the very end of December 2007 and the beginning of January 2008, we noticed an increase in the rate of reported allergic-type reactions associated with our 1,000 unit/mL multi-dose heparin product, and we launched an investigation. The initial reports came from dialysis centers, so Baxter physicians and quality professionals traveled to reporting dialysis centers. We also began an investigation of our own manufacturing and quality procedures and records for heparin. We also ceased all production and distribution of this heparin product.

After additional adverse event reports came in from other facilities, Baxter (in consultation with FDA) recalled nine lots of its 1,000 unit/mL heparin product that were associated with these adverse events on January 17, 2008. After this recall was announced, we saw a slight increase in reactions in other lots and sizes of heparin. We contacted FDA about expanding the recall. Based on FDA's market data, both we and FDA were concerned about a shortage of heparin. On February 8, 2008 Baxter and FDA concluded that it was better for the public health to allow Baxter's product to remain in distribution so it could be used with caution in situations where the use of heparin was medically necessary and alternate sources of heparin were not available. Baxter sent an Important Safety Information Bulletin to thousands of health care providers on February 11, 2008, apprising them of this situation. When we read that another supplier of heparin said it had the ability to source the U.S. heparin market, we asked FDA for confirmation and, upon receiving it, we expanded our heparin recall on February 28, 2008.

During this recall, Baxter informed health care professionals, customers, renal home care patients, wholesalers, distributors and known customers of wholesalers and distributors by mailing thousands of letters via overnight mail about the recall. Baxter also called thousands of renal home patients directly to discuss the recall. Frequent press releases were issued, a press conference was held, a hotline was staffed and information about the recall was regularly posted on Baxter's website.

#### Baxter's Investigation of Root Cause

Baxter has been thoroughly investigating the potential cause of the increase in adverse event reports. After multiple variables were ruled out in the manufacturing process and the supply chain, we began to focus on possible issues in the heparin API. Baxter has devoted more than 30 scientists to this investigation and has employed distinguished outside scientists as consultants. Most of our scientists are based at the company's laboratories in Illinois, although we also took advantage of the expertise of Baxter scientists in Europe. We worked openly and diligently in collaboration with FDA on our analytical results. A wide variety of laboratory methodologies and hundreds of different tests were employed in these investigations, including state-of-the-art analytical instrumentation tests such as nuclear magnetic resonance spectroscopy (NMR) and capillary electrophoresis (CE). Using these tests, it was determined that extra signals and a peak were detected in the heparin associated with the recall (test) compared to heparin that

was not associated with the recall (control). The contaminant from the test lots was identified as OSCS.

NMR and CE tests have confirmed that the contaminant found in the API was also found in the crude heparin supply. According to early reports, similar peaks were found in Australia in AstraZeneca's heparin as well as in Germany in RotexMedica's heparin. Neither of these companies received their supply of heparin API from SPL. Since then, the FDA has reported that multiple companies in 11 countries have found this contaminant. Based on the appearance of OSCS in the crude heparin material coming into SPL, and on the fact that other companies with other suppliers have also had OSCS contamination, it is clear that OSCS was added farther up the supply chain, before the crude material reached SPL. Baxter is still trying to understand where exactly the contaminant was introduced.

The introduction of OSCS was difficult to detect because of how closely this contaminant mimicked heparin. Heparin is the most highly charged molecule found naturally in living systems. As such, it is an extremely polar molecule and requires an extremely polar solvent, like water, to stay in solution. In normal heparin production, the heparin is the most polar molecule among the normal constituents of crude heparin (including dermatan sulfate and chondroitin sulfate). OSCS contains more sulfate groups than does heparin, making it more polar than heparin, and making it the first material to lose solubility when ethanol is added to the aqueous solution of impure heparin. Thus, the OSCS is precipitated along with the heparin. In a process designed to collect the most polar material from solution, the OSCS is collected with the heparin.

Over the last few weeks, our investigation has focused on biologic tests aimed at determining whether there is any relationship between OSCS and the increased adverse events that were associated with this recall. The most common adverse event reported was hypotension. Baxter scientists were able to establish that OSCS can cause hypotensive reactions – that is, consistent, prolonged declines in blood pressure – in laboratory animals. They found the same results from exposure to heparin contaminated with OSCS. The hypotensive response was dose-dependent; increased amounts of the OSCS or the contaminated heparin led to greater decreases in blood pressure. Baxter scientists are still searching to understand the cause of a decrease in blood pressure in humans. This result is consistent with the New England Journal of Medicine study in which scientists found a scientific rationale for a potential biologic link between the presence of OSCS and observed clinical adverse events. That article, a copy of which is

attached, reached this conclusion: “Our results provide a scientific rationale for a potential biological link between the presence of OSCS in suspect lots of heparin and the observed clinical adverse events.”

#### Recall of Heparin Around the World

OSCS, the apparent cause of the increase in heparin adverse events, is a very effective imposter that mimics heparin. Not only did this substance avoid detection through long-established USP testing, it avoided detection through the quality systems of several major pharmaceutical companies around the globe, and through the oversight of regulatory authorities in countries around the world, including Australia, Canada, China, Denmark, France, Germany, Italy, Japan, The Netherlands and New Zealand. Because of the swift identification of OSCS and advanced NMR and CE tests methods to detect it, FDA and regulatory authorities around the world have been able to respond proactively, averting a much broader crisis by detecting and screening out the contaminant in other manufacturers’ heparin before it was more broadly distributed to patient populations. Baxter continues to cooperate with Ministries of Health around the world and share information we and they have learned about OSCS, including how to detect the presence of OSCS in heparin API and finished product.

#### Corrective Actions

The developments of the last several weeks have demonstrated that this is both a global and industry-wide crisis, with a root cause that was so novel and so insidious as to avoid the quality systems of a multitude of companies and the oversight of the world’s most sophisticated drug regulatory agencies. This extraordinary problem calls for extraordinary corrective actions. It is important to harness the resources and thinking of the entire industry and the global regulatory community to address those new and emerging risks, both deliberate and not, that threaten the safety of life-saving drugs and biologics. In particular:

- Baxter is methodically re-examining our global supply chain practices in light of the heparin mimic that surfaced here, to assess whether unexpected vulnerabilities exist in the supply chain *beyond* our direct suppliers. This review is necessarily going above and beyond current regulatory requirements and industry standards, which proved inadequate to detect this problem. Although less than 1% of all Baxter products sold in the U.S. include components sourced from China, we are beginning our evaluation with a

thorough review of our China-based suppliers and their sources. We have retained recognized experts in supply chain management strategy to assist us in this effort.

- Based on what this full-scale evaluation tells us, we will impose targeted prevention and detection methods on our suppliers to limit exposure to vulnerabilities that exist in their supply chains.
- We have convened a group of Baxter scientists whose mission will be to consider how would-be counterfeiters or saboteurs might threaten our supply chain, much the way that law enforcement or national security agencies have groups dedicated to thinking like potential enemies. By directing outstanding scientific minds at this kind of question, our aspiration is to imagine, address and prevent this kind of threat before it happens. Going forward, we will try to anticipate the unanticipated.
- We believe this type of supply chain threat evaluation is something the FDA and the global regulatory community ought to require more broadly of industry participants. Moreover, we would encourage these agencies to facilitate collaboration on and sharing of these efforts, since the positive changes that could result will be effective only if they are consistently applied and enforced across the industry. Just as the fruits of Baxter's and the FDA's efforts to identify and test for OSCS were immediately shared with the industry in *reaction* to a problem, the world's patients and the global drug and biologic supply would far better served if the fruits of these *proactive* analyses were a common asset for the public good.

### Conclusion

Baxter's quality systems for heparin have come under intense scrutiny as a result of this recall. We believe our quality systems are robust, but no quality system is bullet proof. We certainly acknowledge that we should have conducted our own qualification audit of the facility, rather than relying on our predecessor's audit. Importantly, it is not clear that such an additional inspection would have detected or prevented the OCSC contaminant. Therefore, it would be wrong for us to ascribe this problem to a missed inspection and move forward based on improved inspection frequency. Indeed, such a reaction would miss the real points: that the complexity of the global drug supply chain creates new and emerging risks that call for new ways of thinking about, identifying and addressing vulnerabilities, and that resting on old

standards – even ones that have worked for decades – is no longer enough. These are the most critical lessons of this entire crisis, and Baxter embraces them.

Baxter fully supports the allocation of increased resources for FDA. Baxter references the statements by Commissioner von Eschenbach (in testimony last week before this Subcommittee) that FDA lacks adequate resources to conduct effective overseas inspections and to keep a modern and effective database of foreign firms processing products for US patients. We support funding directed to enhancing FDA’s ability to fulfill its mission of providing safe and effective products to the American people, and we welcome any opportunity to work with Congress and the Agency in support of this mission.

We appreciate the Committee’s interest in medical product safety, and we fully support the Committee’s goals. Baxter is eager to continue collaborating with this Committee and others to ensure the safety of heparin. This has been a learning experience for Baxter, and I hope it can be a learning experience for the entire global industry and the global regulatory community so we can all work together to ensure that these types of incidents never happen again. Thank you for giving me the opportunity to be part of this important discussion.