



## BAXTER PROVIDES UPDATE ON HEPARIN INVESTIGATION

- I. **Baxter confirms that the contaminant identified in the company's U.S. heparin vial products is hypersulfated chondroitin sulfate.**
- II. **Baxter scientists have detected the contaminant in crude heparin, which indicates the contaminant is introduced in the supply chain before it reaches the API manufacturer (SPL).**
- III. **Baxter is working on establishing causality between the contaminant and adverse reactions; tests underway.**
- IV. **No fatalities have been confirmed by medical evidence to be caused by allergic reactions to Baxter heparin.**

DEERFIELD, Ill., March 19, 2008 – Baxter is providing an update on several advances related to the investigation into recent heparin adverse reactions associated with the company's U.S. vial-based heparin products, which have since been recalled.

**I. Baxter confirms that the contaminant identified in the company's U.S. heparin vial products is hypersulfated chondroitin sulfate.**

Baxter scientists have provided information to the U.S. Food and Drug Administration (FDA) that confirms the presence of hypersulfated chondroitin sulfate in the heparin Active Pharmaceutical Ingredient (API) that was used in Baxter's vial-based heparin products in the U.S., which the company fully recalled.

Chondroitin sulfate is a molecule that occurs naturally and is a major component of cartilage – the tough, connective tissue that cushions the joints. Chondroitin sulfate is a common, biologically derived material that is sold in oral form as a dietary supplement. The substance we found in the affected lots of heparin API is not a naturally occurring substance, but the hypersulfated version of chondroitin sulfate, which means that it has been chemically modified, resulting in a more heparin-like molecule.

This finding is consistent with last week's update stating that the unknown material appeared to be a highly sulfated glycosaminoglycan-like (GAG-like) material. While heparin-like, the material is structurally different from naturally-occurring heparin. The hypersulfated chondroitin sulfate has approximately the same molecular weight as heparin and is similar in other ways, which is why standard testing did not detect its presence.

**II. Baxter scientists have detected the contaminant in crude heparin, which indicates that the material is introduced in the supply chain before it reaches the API manufacturer (SPL).**

Baxter has collaborated with FDA in the development of sophisticated analytical procedures, using capillary electrophoresis and nuclear magnetic resonance spectroscopy technology. Baxter has also applied these sophisticated analytical procedures to test the crude heparin material, which comes from consolidators, and has detected the peak in some crude material lots. Consolidators and workshops handle the crude material used in the manufacture of the heparin API, and Baxter will continue to seek access to consolidators and workshops that supply SPL in an effort to understand how hypersulfated chondroitin sulfate was introduced.

“The hypersulfated chondroitin sulfate is not only found in the active pharmaceutical ingredient (API) we use to make our heparin, but in the crude material used to make the API,” said Norbert Riedel, Ph.D., Baxter’s corporate vice president and chief scientific officer. “That means that this contaminant was very likely introduced at the workshop or consolidator level, before it reached our API supplier and definitely before it reached Baxter.”

“We’re at a critical juncture in the investigation and further progress can be accelerated with the cooperation of the consolidators and workshops,” said Riedel.

**III. Baxter is working on establishing causality between the contaminant and adverse reactions; tests underway.**

While a causal link has not been established, the increase in adverse events has been associated with lots of the product containing this substance.

To confirm a causal link, the same allergic response must be reproduced in a test environment. Considering that a very narrow population of patients (approximately one per 10,000 doses) had an allergic reaction, developing a way to mimic the clinical environment is difficult.

Baxter has already conducted a number of biologic tests, trying to determine whether the contaminated API causes allergic reactions.

“So far we have not been able to trigger allergic responses in biologic tests,” said Riedel. “Given that the rate of reactions associated with the recalled heparin were reported in approximately one per 10,000 doses, recreating this reaction is statistically challenging,” he said.

Baxter is continuing its efforts to determine if there is a link between the contaminant and adverse reactions, using additional advanced tests.

“The remaining questions are how and why hypersulfated chondroitin sulfate was introduced into heparin crude materials, and whether or not causality can be established,” said Riedel.

**IV. No fatalities have been confirmed by medical evidence to be caused by allergic reactions to Baxter heparin.**

At this point in time, neither Baxter nor the U.S. Food and Drug Administration (FDA) has confirmed that allergic reactions to Baxter’s heparin have caused any fatalities. The company determined that there are four cases in which patients received Baxter heparin and suffered an allergic-type reaction to heparin that may have contributed to the adverse outcome, though there is not yet enough medical data available to draw a firm conclusion that the allergic reaction caused the death. In each of these cases, the patient had multiple, complex medical conditions. In three of these four cases, patients had either undergone, or were in the process of undergoing, invasive cardiac surgery. The company has received approximately 600 heparin-related adverse reaction reports to date.

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**Media Contacts:** Erin Gardiner, 847/948-4210  
Deborah Spak, 847/948-2349