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Heparin: A Wake-Up Call on Risks to the U.S. Drug Supply

Why is the Heparin Case Study Important?

The adulteration of heparin, a widely used blood thinner, is a tragic example of the risks resulting from an increasingly globalized and complex pharmaceutical manufacturing system. The U.S. Food and Drug Administration (FDA) estimates that 40 percent of the finished drugs used by U.S. patients, and 80 percent of their active ingredients, are manufactured abroad.[1–3] While the vast majority of drugs in American pharmacies and medicine cabinets are safe, globalization and reliance on outsourced manufacturing creates new risks, including deliberate tampering with ingredients and inadequate quality controls in plants that operate largely outside the scrutiny of the FDA.

As a result of the heparin adulteration, dozens of patients in the United States suffered adverse events,[4] and several lost their lives.[5] Investigations into this occurrence have revealed a number of systemic failures, including inadequate oversight and supply chain management. Ultimately, heparin's complex production chain was vulnerable to abuse by perpetrators who have yet to be identified or penalized.

> "In this day and age, companies must be able to effectively demonstrate that safety, quality and compliance with international and U.S. standards are built into every component of every product and every step of the production process."
>
> —FDA Commissioner Margaret Hamburg, 2010

What Happened?

In early 2008, the U.S. Centers for Disease Control and Prevention (CDC) began investigating an outbreak of unexpected allergic-type reactions dating from November 2007 in patients undergoing dialysis.[6] Most of these patients had received intravenous heparin manufactured by Baxter Healthcare.[7] Further investigation revealed that a synthetic adulterant with toxic effects, oversulfated chondroitin sulfate (OSCS),[8] had been introduced during heparin's manufacture in China.[9] OSCS costs nearly 100 times less to produce than heparin[10] and is so similar to the actual drug that it was undetected by standard tests.[11]

Dozens of Americans suffered adverse reactions, including death.[12] Baxter Healthcare, the major U.S. manufacturer of heparin, along with 14 other U.S. companies recalled at least 11 drug products and 72 medical devices containing heparin.[13] According to local health agencies and news reports, heparin products were also recalled in Australia, Denmark, France, Germany, Italy, Japan, Sweden, and Switzerland.[14–17]

In response to the adulteration, the U.S. Pharmacopeial Convention, a nongovernmental standards-setting authority for medicines in the United States, has updated its testing standards for heparin.[18] Baxter reports that it has instituted a number of initiatives to secure its supply chain against future adulteration—from reviewing relationships with high-risk suppliers to conducting more intensive audits.[19]

How is Heparin Made?

Heparin is derived from animal mucosal tissues, almost exclusively from pigs. China, due to its large swine herds, is essential to the market for heparin.[20] The supply chain for the drug begins at slaughterhouses, followed by small workshops that harvest basic heparin material (known as "heparin crude") by extracting the mucous membranes from pig intestines. Heparin crude is then sold, sometimes through consolidators, to other plants that then further refine the material into an active pharmaceutical ingredient (API).[21,22] Finally, this API is combined with inactive ingredients (often a sterile solution) to create a finished heparin product such as a vial of injectable medicine.

At What Point Was the Heparin Supply Chain Breached?

Both Baxter and the FDA remain unable to pinpoint the exact source or sources of the heparin adulteration, but evidence suggests OSCS was likely introduced by entities upstream of the Chinese API production site, Scientific Protein Laboratories–Changzhou (SPL-CZ). Baxter's heparin API had been manufactured using crude material from China since 1996;[23] SPL-CZ became part of Baxter's heparin supply chain in 2004.[24,25]

During investigations following the adulteration, OSCS was identified in both the finished heparin API made by SPL-CZ and in the crude material provided to the factory from Chinese consolidators.[26]

Why Was the Heparin Adulterated?

The FDA believes that the adulteration was an economically motivated act.[27,28] OSCS entered the supply chain at a time when a widespread swine virus outbreak had greatly diminished Chinese pig herds.[29] The price of pigs increased in 2007,[30] and the cost of heparin grew more than 100 percent between May and November 2007.[31]

One industry insider estimates that one to three tons of OSCS must have been produced and used to dilute the heparin, which would have generated $1 million to $3 million in profit for those who sold it.[32]

What Other Problems Were Exposed by the Tragedy?

The heparin incident revealed a number of supply chain management and oversight failures:

- Baxter began receiving heparin API made at SPL-CZ in 2004, but it did not conduct its own audit of the plant until 2007, relying instead on an earlier assessment by a different company.[33]
- The FDA approved SPL-CZ as a supplier for Baxter without conducting a pre-approval inspection, in part because the agency confused SPL-CZ with another site in the agency's database.[34]
- The inspection conducted after the adulteration by the FDA of SPL-CZ found a number of manufacturing quality issues, including insufficient quality control systems for incoming raw materials.[35]
- When Baxter sent investigators to retroactively evaluate its supply chain in 2008, they were denied access to upstream workshops and consolidators.[36] The FDA was also denied access to two upstream consolidators of heparin.[37]
- SPL-CZ was classified within China as a chemical plant and therefore was not registered with the Chinese State Food and Drug Administration.[38] As a result, it likely did not receive any oversight from the Chinese authorities.

What Can Be Done to Protect Patients?

To prevent another event like the heparin adulteration, Congress must enact legislative reforms to better safeguard the U.S. pharmaceutical supply. The legislation must:

- **Ensure meaningful control of globalized pharmaceutical manufacturing** by requiring modernized systems for supply chain management and quality.
- **Increase FDA oversight of high-risk plants overseas** through adequate resources and improving the agency's infrastructure and tracking systems.
- **Eliminate barriers to FDA's drug supply safety work** by providing it with the regulatory authority needed to fulfill its mission.

*The **DRUG SAFETY PROJECT** works to ensure a safe, reliable pharmaceutical manufacturing and distribution system.*

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