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Heparin's Deadly Side Effects

By Bill Powell/Shanghai

Leroy Hubley, 72, married for 48 years and a father of three, has lived through tragedy no one should endure once, and he did so twice in the span of a month. Bonnie Hubley, his wife, had polycystic kidney disease, in which cysts grow in the kidneys, often becoming so large that the kidneys fail and have to be replaced. All of the Hubley children inherited the genetic disease. In 1995, Bonnie had a kidney transplant, and in October of last year, her body began to reject the replacement kidney, requiring her to start dialysis.

A month earlier and half a world away, a team of quality-control specialists from Baxter International, the big multinational health-care company (2007 sales: \$11.26 billion) based in Deerfield, Ill., arrived in Zhejiang province, China, about two hours by car from Shanghai, to inspect a facility owned by one of its key suppliers. CZ-SPL is a joint venture controlled by Scientific Protein Laboratories LLC (SPL), a Waunakee, Wis., company started in 1976 by Oscar Meyer, of hot-dog fame. (The connection: pigs naturally produce proteins used in pharmaceuticals.) CZ-SPL makes a key ingredient, what in the pharmaceutical business is called an active pharmaceutical ingredient, or API, for a drug called heparin, a blood thinner that is widely used by kidney-dialysis and postsurgical patients to prevent blood clots. The team found little unusual and gave the facility a clean bill of health.

On Dec. 17, after two months of dialysis using heparin produced by Baxter, Bonnie Hubley was rushed into intensive care. She had developed diarrhea, vomiting and eventually severe pain in her chest and abdomen. She deteriorated rapidly and by Dec. 19 was unconscious and on a breathing tube. Stunned doctors at the Toledo, Ohio, hospital told Leroy there was no hope. "She was gone," he says. So with "Christmas carols playing in the background," he says, "we said our goodbyes, and my wife of 48 years drifted away."

Three weeks later, his 47-year-old son Randy, also a dialysis patient and a heparin user, suddenly had symptoms similar to those that had killed his mother. Shockingly, he died on Jan. 15, as his wife Colleen, a dialysis nurse (they had met at the clinic years earlier), frantically and futilely tried to revive

him. An uncomprehending family buried Randy Hubley next to his mother in Toledo.

Now add tainted baby milk to a seemingly unending stream of foods, drugs, pet foods and toys that over the past two years have killed or injured thousands worldwide. These products all have three words in common: MADE IN CHINA. A large state-owned Chinese company, Sanlu Group, based in Hebei province in central China, as well as several smaller companies, apparently diluted milk products with an additive called melamine. Industrial-grade melamine is a masking agent used to hide the dilution of protein, in this case in milk products, including an infant formula widely popular in China. Nearly 53,000 small children in China have developed kidney stones, four have died, and product recalls have spread to 11 countries, including the U.S. The recall list includes seven instant-coffee and milk-tea products made in Taiwan using Chinese milk. (Melamine also tainted the pet food that harmed so many animals in the U.S. last year.)

As China rapidly becomes the world's workshop, supplying everything from Thomas the Tank Engine toys to computer chips to blood thinners, the world is coming to understand what Chinese citizens have known for quite a while. The country's growth--and intense competition among manufacturers in industry after industry--has gone far beyond the government's ability to regulate the economy effectively. In an ostensibly communist country, unfettered competition combined with nonexistent or, in many cases, corrupt government oversight has often produced a race to the bottom among businesses. Competition based on cost, in which manufacturers eke out slim profits by underpricing rivals, is by far the dominant industrial strategy. China, in short, is where the U.S. was in the early 20th century when Upton Sinclair wrote *The Jungle*, his seminal work about the horrifying conditions in the meatpacking industry.

The milk scandal is simply the latest and not by any means the most lethal example of the dark side of Chinese capitalism. The heparin case, in fact, has been far deadlier. Last summer the Food and Drug Administration updated the estimated death toll worldwide associated with tainted heparin to 149. As more and more pharmaceuticals are sourced in developing countries--an estimated \$1.5 billion from China and India alone in 2007, according to a study by Credit Suisse--the heparin case has raised a fundamental question in the U.S. and the rest of the developed world: How safe are our drugs?

The answer is, Not nearly safe enough. What happened from September 2007, when the Baxter safety inspectors arrived and left, to the end of the year, when deaths and illnesses apparently related to use of the drug began to occur, is a tale of the risks global companies take in engaging the cutthroat ethos that is the underside of China's economy.

It is jarring to see where a drug like heparin begins. Liu Jing, a cheerful 36-year-old, is stomping around in pig poop and mud in knee-high boots. He is a farmer in Jiangsu province, north of Shanghai, where providing the raw ingredients for heparin is a big business. Liu's farm produces a key source of heparin: pig intestines. (Heparin is derived from the mucous membranes in the intestines.) Nearly half the world's pigs are in China, so companies like SPL have set up shop. In SPL's case, it first began buying

raw heparin in 1996, established its own production facility to make the API in 2000 and began selling to Baxter, among others, in 2004. More than half the heparin sold--for Baxter alone it was a \$30 million business last year--is made from pig guts bought in China.

Farmers like Liu sell to small-scale companies--often family-run businesses--that process the intestines into crude heparin, which in turn becomes the key ingredient for the heparin that Baxter and other major drug firms sell worldwide. SPL's CEO, David Strunce, told Congress last spring that the raw material comes from "government-regulated slaughterhouses." But that regulation, farmers in Jiangsu told TIME, is haphazard at best. And if the slaughterhouses are haphazardly regulated, the small heparin-processing businesses--hundreds of them across the country--are virtually unregulated. "We haven't ever had the government come and inspect our operation," said a processor in Jiangsu whose given name is Chang and who didn't offer his family name.

SPL in Changzhou says it relies on two companies--its joint-venture partner, Changzhou Techpool, as well as a Hangzhou-based firm, Ruihua Biomedical Products Co.--to buy its crude heparin. Strunce has described them as meticulous in ensuring the quality of the crude heparin they buy for SPL. But several small suppliers told TIME they have sold directly to SPL or have been approached by the company, looking for product. And when FDA inspectors showed up in Hangzhou this year, after reports of a spike in deaths and illness, Ruihua Biomedical stiff-armed the investigators. It refused to let them inspect its processing lab and declined to provide a list of crude-heparin suppliers. Before last summer, SPL's China facility had never been inspected by Beijing's drug-safety agency because, says a spokesman, the agency thought "it was a chemical plant." A source close to the FDA's heparin investigation puts it bluntly: "China simply has no regulatory regime to speak of."

That judgment gains credence from a simple fact: the heparin disaster goes beyond Baxter, SPL and their suppliers--none of whom have been charged with wrongdoing and all of whom say they are cooperating with regulators to find out where problems arose in the supply chain and why. French pharmaceutical giant Sanofi Aventis told French regulators and the FDA that it too had found and recalled tainted heparin last spring. (Baxter pulled all its heparin from the market last January.) In April, deputy FDA commissioner Janet Woodcock said the agency had traced the contaminated heparin api, which ultimately found its way to companies like Baxter in 11 countries, to 12 separate Chinese companies. To date, those 12 firms have not been identified by the FDA, Baxter or SPL. But the "working hypothesis," as Woodcock put it, is that the contamination was intentional. In other words, it was not the result of the filth from which crude heparin emerges. "It was economic fraud," said a senior U.S. official.

Why intentional? To cut costs. Heparin suppliers substituted a chemical--oversulfated chondroitin sulfate, or OSCS--that is derived from animal cartilage and used only in dietary supplements, not in medicines. The compound's key advantages: it is, as a Baxter spokeswoman puts it, a "virtual mimic of heparin" in most tests and, according to a congressional investigator, costs only \$20 per kg. vs. \$2,000 for crude heparin. The suppliers, investigators believe, colluded to substitute OSCS in the crude heparin

they passed along for the standard price and pocketed the \$1,980 difference for each kilogram they sold.

Working with Baxter, the FDA devised a test that now identifies OSCS in heparin. The FDA will deploy eight full-time staffers in China, including four inspectors and a senior technical expert in foods, medicines and medical devices. And working with its counterpart agency in Beijing--which FDA commissioner Andrew van Eschenbach acknowledges is primarily responsible for drug safety there--the FDA will now be able to do "more timely" inspections in China. In 2008 the FDA did all of 30 inspections in China.

But where agencies may lack muscle, the personal-injury bar doesn't. To date, plaintiff attorneys have filed 60 suits against Baxter and SPL in federal court. SPL CEO Strunce can claim his company's heparin met Chinese standards, but that's probably a meaningless defense in a U.S. trial. For American drug companies using sources in China, quality control is not just China's problem--it's also their problem.

In any event, it's too late for Johanna Staples, a kindergarten teacher whose husband Dennis, a popular disc jockey in Toledo, Ohio, died of a reaction to tainted heparin in January, a day shy of his 60th birthday. She says she's still afraid. "There are so many variables in how we receive our drugs that it's amazing there hasn't been a worse problem. Now look at all these kids sick in China because of tainted milk. Sometimes I get in a sheer panic thinking about it."

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