

# Flood of drugs, little oversight

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By the time St. Louis Children's Hospital called in its infectious-disease specialist Jan. 4 to diagnose a mysterious spike in allergic reactions to kidney dialysis, it was clear there was a major problem.

Three patients had become ill after taking the blood-thinning drug heparin. One had developed the same reaction during a dialysis treatment in November. Minutes after dialysis needles punctured their veins, the boys' lips and eyelids swelled. Their blood pressure dropped, and their heartbeats raced at dangerous levels.

When infectious-disease specialist Dr. Alexis Elward homed in on the problem -- putting high on her list the drug made by Baxter International Inc. of Deerfield -- she became the first doctor to alert the Centers for Disease Control and Prevention. It wasn't until late in February, though, that Elward and others learned that no U.S. or Chinese government inspectors had visited the Chinese plant that produced the drug now linked to more than 400 illnesses and as many as 21 deaths across the U.S.

The plant isn't being overlooked anymore.

Last week, a team of Food and Drug Administration inspectors visited the Chinese plant owned by Baxter supplier Scientific Protein Laboratories of Waunakee, Wis. There they found evidence of lax hygiene and safety standards. According to the inspection report, testing procedures at the plant were inadequate. In some cases, records of testing were missing. And for some batches of the product, there was no way to trace where the plant obtained its raw material, which is scraped from the mucous lining of pig intestines.

One of the more worrisome findings: When heparin produced at the plant did not pass its quality testing, plant workers failed to diagnose what caused the failures. On two lots that failed tests, plant workers simply -- but incorrectly -- dismissed the results as "outliers."

Now a congressional committee is asking whether the FDA's lapse in allowing a plant it never inspected to export to the U.S. is part of a larger problem of poor oversight and a shortage of resources at the agency. And Baxter itself is scurrying to learn what went wrong.

"My hope is, after this investigation, there will be additional checks and balances put in the system," Elward said. "My hope is that this investigation will lead to changes in the process to be sure that inspections and checks can happen."

## **A struggle to keep pace**

Indeed, a close look at the FDA's resources and inspection record paints a picture of an agency struggling to keep pace. Although its officials insist the agency inspects every foreign plant sending medical products to the U.S., the agency's own data make it appear unlikely.

An FDA-appointed commission that studied the agency's inspection record last fall found the FDA is short

of financial resources, has cut personnel, has rickety data management systems and is struggling to meet its oversight obligations.

"Millions of FDA-regulated products are imported into the country each year from foreign facilities that have never been inspected by FDA and, with current appropriations, never will be," according to a report in November by the FDA Science Board's subcommittee on science and technology.

The head of the FDA study group, in an interview, held out little hope the FDA is coming to grips with its challenges. The heparin case is a warning signal, said Gail Cassell, vice president of scientific affairs at drug giant Eli Lilly & Co.

"Unless the deficiencies can be addressed rather urgently, this is not the last such situation," said Cassell. "We will have more of them."

Where the FDA is not keeping up, private industry has become almost a de facto self-regulator. Struggling to protect both public health and their corporate reputations, companies often step in where FDA inspections have not.

Baxter attempted to do so. A Baxter team visited the plant in September. By that time, though, timelines produced by Baxter, the FDA and the CDC indicate the suspect heparin already was making its way through the Baxter supply chain. The production line stretches from Baxter's Deerfield headquarters, to Scientific Protein's offices in Waunakee, Wis., to Changzhou, China, and back to Cherry Hill, N.J., where the heparin produced by Scientific Protein is processed, poured into bottles and shipped to hospitals around the country.

A Baxter spokeswoman would not comment on the timing.

The lure of inexpensive and plentiful supplies prompted Baxter three years ago to give the go-ahead to longtime supplier Scientific Protein when the company said it was converting a Chinese pharmaceutical plant to U.S. standards. After the Baxter inspection team visited the plant in September and delivered a positive report, all seemed to be in order.

Then, in late December, the troubles started. Reports from hospitals showed a spike in allergic reactions to one dosage strength of multidose vials of the clear liquid drug. The reactions were particularly aggressive: More than 40 percent of the patients with ill effects were classified as serious -- meaning death was a possibility.

At first, the reports were confounding. Besides the on-site inspection, Baxter also routinely tested heparin that traveled from China to its Cherry Hill processing plant. Those tests showed no difference between vials connected to the allergic reactions and the rest of Baxter's production of some 100,000 injection vials a day -- roughly half of the country's supply of that dosage.

By the time the St. Louis Children's Hospital alerted the CDC in early January, though, investigators at Baxter and the FDA had zeroed in on nine suspect lots of the product. Adverse reactions to heparin injections were being reported at more than 20 times normal rates.

Ten more days passed, though, before Baxter recalled the lots in question and FDA inspectors descended on Baxter's U.S. manufacturing facilities. A Baxter spokeswoman declined to explain the 10-day delay.

### **Call to action at Baxter**

Inside Baxter's Deerfield headquarters, it was code red. Robert Parkinson, the company's chief executive, began holding early morning meetings with a team of key leaders: people responsible for Baxter's drug surveillance, drug quality, legal, manufacturing, research, and regulatory affairs.

After the morning meetings, Parkinson made a point of popping in on his key executives. This kept him up to speed on developments and gave people a chance to share what they had learned.

One surprise: Parkinson soon learned the FDA never had inspected the China manufacturing plant. Recalling the finding in a recent Tribune interview, Parkinson sought to minimize the oversight.

"It's not unusual for us not to know that the FDA has not inspected a supplier to a supplier," he said.

Dozens of Baxter scientists began searching for a cause of the outbreak. They deployed nuclear magnetic resonance imaging and atomic emission spectroscopy tests on the heparin itself. More mundane tests were conducted, too, on everything from water systems to processes for mixing drugs, to sterilization of equipment, to supplies such as rubber stoppers.

The FDA's study of Baxter's domestic operation was coming up empty. FDA tests at Scientific Protein's production plant outside Madison, Wis., also found no connection.

Baxter's scientific research kept pointing to one place: Scientific Protein's China production plant, and the nine suspect lots it produced.

By the time the FDA sent a team of inspectors to China Feb. 20, Parkinson was beginning to turn his attention to Baxter's next big challenge: getting Baxter's version of heparin back on the market. That effort ran aground last week, though, after the initial FDA inspection results forced Baxter to recall virtually all its heparin in the U.S.

Baxter's one major competitor in the heparin market, APP Pharmaceuticals of Schaumburg, announced in mid-February it was boosting production. APP's China supplier has passed inspections by both the FDA and China's State Food and Drug Administration.

Parkinson prefers not to emphasize the competitive dynamic, though. Instead, he focuses on the key role heparin plays as a blood thinner in kidney dialysis and heart operations.

"We have, as a company, an obligation to the medical and the patient communities to get this product available," Parkinson said. "It's not a matter of the financial significance of the product. It's a matter of the role that it plays in medicine."

While Baxter scrambles to find answers about heparin, a search for answers is under way on Capitol Hill, too. This search, though, is focused on assessing whether the FDA is applying strategies and resources capable of protecting American consumers in a day of a global supply chain.

The House Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee is scrutinizing the FDA's oversight of the drug industry, and imports from China in particular.

By law and as a matter of policy, the Food and Drug Administration is the first line of defense for drugs entering the U.S. But critics say the agency's financial resources and manpower have not kept up with the workload required to protect the public.

The Science Board report put the picture in stark relief. Even as the U.S. imported an estimated \$72 billion in drugs and active ingredients in 2006, the FDA that year spent \$12.75 million inspecting foreign production plants. Although drug imports have ballooned over the last five years, the amount spent on inspections fell slightly during that time.

While some 3,250 non-U.S. plants were subject to FDA inspection last year, the agency has conducted only 1,445 foreign inspections in the last five years, according to a recent Government Accountability Office study. That seems to leave the agency far short of a requirement that it inspect each plant every two years.

### **Acute shortfall in China**

The inspection shortfall is particularly acute in China. The FDA has averaged just 15 inspections in China in each of the last five years. Yet China's fast-growing industry now numbers 714 plants that ship drug products to the U.S.

At that rate, it would take the agency nearly 48 years to inspect each plant just once -- and well more than that, if China's booming 17 percent annual growth rate for drug exports is taken into account.

By 2010, China is expected to produce nearly 25 percent of the world's pharmaceutical ingredients, according to a recent study by the investment firm Credit Suisse.

"If you haven't been in a plant for the last two or three years, you don't have any clue what's going on in those places," said a congressional source familiar with investigative work into the FDA by the House Commerce Committee's subcommittee. "They could be running monster truck rallies on the plant floor, and we wouldn't know about it."

Baxter's heparin troubles have also brought to light problems with the FDA's data management systems.

"The computer infrastructure is outdated, it's not stable, there is insufficient security and capability," said Dale Nordenberg, a Science Board member who specialized on the computer systems. "The FDA is still relying on an amalgamation of paper-based records and poorly integrated electronic platforms."

The two main FDA databases cannot agree on how many foreign companies are subject to FDA inspection. One claims the number is 3,000, the other, 6,800.

Compounding the confusion, the FDA uses corporate names, rather than identification numbers, to track production plants and registration information. For an agency monitoring the operations of companies in dozens of countries worldwide, this creates confusion.

Indeed, Scientific Protein's China operation slipped through the FDA's inspection regimen primarily because of confusion over the company's name. But Nordenberg is hardly encouraged by the agency's admission this was at the root of the FDA's failure to inspect the plant.

"That's just another error that they're admitting to," Nordenberg said.

## **Heparin timeline**

September 2007: Baxter International Inc. inspects the Changzhou, China, plant that has supplied Baxter with heparin's active ingredient since 2004. The plant is owned by Scientific Protein Laboratories of Waunakee, Wis.

September-November: Lots of heparin containing the active ingredient from China are produced, filled and finished at Baxter's Cherry Hill, N.J., plant for shipment to hospitals and dialysis centers.

Nov. 19: Doctors at St. Louis Children's Hospital treat the first child to have allergic reactions from heparin, including swollen lips and eyelids and a drop in blood pressure within minutes after dialysis.

Jan. 7: Dialysis patients experiencing allergic reactions from heparin at St. Louis Children's are called the "initial cluster" by the Centers for Disease Control and Prevention.

Jan. 17: Baxter recalls nine lots of multidose vials of heparin. The CDC says eight of the lots were produced "September-November" at Baxter's Cherry Hill plant.

Feb. 11: Baxter says it will halt production of multidose heparin vials for concerns over the allergic reactions of high-dosage patients including pediatric and adult dialysis patients and heart surgery patients. The FDA urges doctors and hospitals to switch to another heparin-maker, APP Pharmaceuticals Inc. of Schaumburg, and braces U.S. health facilities for potential shortages since Baxter supplies half the U.S. market.

Feb. 20: FDA begins inspection of Scientific Protein's Chinese manufacturing plant.

Feb. 28: Baxter announces recall of its remaining heparin on the U.S. market. The FDA says its investigation of Scientific Protein's China plant turns up several potential "deficiencies" related to its manufacturing, but the agency had yet to determine its root causes. The FDA says it is looking at a number of Chinese firms "upstream from the manufacturing process," including village workshops also involved in making a drug derived from an enzyme in pig intestines.

SOURCES: The Centers for Disease Control and Prevention; The Missouri Department of Health and Senior Services; the U.S. Food and Drug Administration