MARKETPLACE

Heparin Probe Finds U.S. Tie to Chinese Plant

BAXTER INTERNATIONAL Inc.'s investigation into the cause of deaths and allergic reactions linked to its blood-thinner heparin is focusing on variations in batches of the active ingredient for the drug, most of which were supplied by a Chinese manufacturing facility co-owned by a Wisconsin company.

By Thomas M. Burton, Anna Wilde Mathews, Nicholas Zamiska and Gordon Fairclough

Baxter said the active ingredient for its heparin was supplied by **Scientific Protein Laboratories LLC**, a Waunakee, Wis., company with a manufacturing facility there and a joint-venture operation called Changzhou SPL in Changzhou, China. Baxter declined to elaborate on the nature of the variations, but heparin is a particularly tricky product to manufacture because it is derived from pig intestines.

David G. Strunce, president of Scientific Protein, said most of its active ingredient for heparin is made at the China plant, but some comes from the Wisconsin facility. "There's nothing that would explain these reactions, and we are very concerned about this," he said. "We have no idea if these reactions have anything to do with our product."

Though the cause of the reactions still isn't clear, the incident places Baxter and Scientific Protein, which is majority-owned by the Bethesda, Md., buyout firm **American Capital Strategies** Ltd., at the center of a broader debate about the oversight of overseas drug manufacturing. The U.S. Food and Drug Administration has said it didn't inspect the Chinese operation, which is also owned by **Changzhou Techpool Pharmaceutical** Co., of China.

On Monday, Baxter said it had temporarily stopped production of heparin because of about 350 bad reactions, including four fatalities, potentially tied to the drug, which is used primarily in kidney dialysis and heart surgery. An FDA official estimated that about 40% of the adverse reactions among patients taking the Baxter drug were classi-

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...ors of the basketball court while reducing ... Hannah Jones, who oversees the new de-...

MARKETPLACE

Heparin Probe Finds New U.S. Tie

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fied as serious. They ranged from stomach pain to vomiting and diarrhea, low blood pressure, speeding heartbeats and fainting.

China's rise to become the world's largest manufacturer of drug ingredients has helped drug companies elsewhere trim production costs, particularly for generic products like heparin, where margins are generally slim. Changzhou SPL, also known by its Chinese name, Kaipu Biochemical Co., is one of hundreds of Chinese manufacturers that have quietly become a linchpin of the global pharmaceutical industry. In 2005, China had $4.4 billion, or 14%, of the world's $31 billion market for active pharmaceutical ingredients, topping India and Italy, according to a report written last year by Jinsong Du, a health-care analyst in Hong Kong with Credit Suisse.

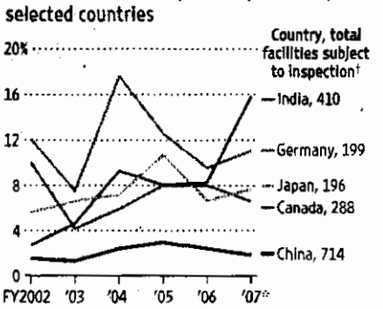
Yesterday, Sen. Charles Grassley, an Iowa Republican, wrote to the FDA and to Baxter, asking for more data about the heparin and its supplier. Michigan Democrats John Dingell and Bart Stupak, leaders of the House Energy and Commerce Committee, have been investigating import-safety issues with drugs and medical devices. In their own letter to the FDA, they said "American lives are unnecessarily being placed at risk" by the limited oversight over foreign manufacturing.

Baxter spokeswoman Erin Gardiner said the company is using "molecular separation" analysis to "look for chemically meaningful differences" between heparin batches linked to bad reactions and "control" batches known to be of high quality.

Heparin is a complex sugar molecule that normally exists on the lining of blood vessels in people and animals. It is now made from pig intestines, but processing them can lead to impurities. "Crushing tissue to get extracts means you can get contamination from other things in the tissue," says John R. Hess, a blood expert at the University of Maryland.

Lack of Oversight

Percentage of facilities involved in the manufacture of drugs for the U.S. market that were inspected by the FDA, selected countries



*Data supplied on Sept. 26, prior to the end of the fiscal year, Sept. 30 †Based on the number of facilities the FDA used to plan its 2007 prioritized surveillance inspections

Source: Government Accountability Office analysis of FDA data

In manufacturing, raw intestines are exposed to an enzyme and then to a resin that separates the heparin from the rest of the liquid. The end product is heat-treated to destroy microorganisms.

Scientific Protein Laboratories said that the cause of the patient reactions hasn't been identified. The company said that it has been making the heparin active ingredient at the Chinese facility since 2004, and that it "engages in the same testing and quality-control procedures as U.S. facilities that produce bulk heparin" and meet FDA standards. American Capital Strategies didn't return calls.

An FDA spokeswoman said the agency is "doing everything possible to discover the root cause of these reactions, but this information takes time to gather." Neither the Chinese State Food and Drug Administration nor the General Administration for Quality Supervision, Inspection and Quarantine, which polices quality issues, could be reached. Changzhou Techpool declined to comment.

Yesterday at Changzhou SPL's factory, about a two-hour drive northwest of Shanghai, the smell of chemical reagents and the whir of exhaust fans were detectable outside. Two workers in green uniforms, black rubber boots, face masks and surgical caps scrubbed equipment outside the plant. Guards blocked reporters from entering the compound.

U.S. regulators can provide only limited oversight for such operations. A woman in the administration office of Changzhou SPL said the company is expecting investigators from the U.S. FDA to arrive Monday for their first visit to the plant. "We'll fully cooperate with Baxter and FDA investigators," said a manager of the quality-control department.

The FDA isn't legally required to inspect every foreign drug facility, but it generally does examine them if they are named as a maker in a new application to market a drug in the U.S. If the holder of an existing, approved application switches manufacturers, the new facility would usually get inspected as well. However, a legal requirement for drug manufacturers to get inspected every two years applies only to domestic plants, not the growing list of overseas facilities.

The FDA's commissioner, Andrew von Eschenbach, has said he would like to base FDA inspectors and other experts overseas, including in China. Currently, they are all in the U.S. and must do overseas inspections during strenuous trips that typically allow the foreign drug makers to have advance notice. The agency said an FDA presence in China would require formal agreement from the host nation, and the State Department "is presently discussing this with the Foreign Ministry on behalf of the FDA and the U.S. government."

—Ellen Zhu and Sue Feng contributed to this article.

China Plant Played Role In Drug Tied To 4 Deaths

By Anna Wilde Mathews And Thomas M. Burton

A Chinese facility made the active ingredient in much of the widely used Baxter International Inc. blood-thinner that is under investigation after reports of hundreds of allergic reactions and four deaths among its users, the U.S. Food and Drug Administration said yesterday.

Both Baxter and the FDA said it isn't clear that the product from the Chinese supplier is tied to the bad reactions that occurred in some patients who took the anticlotting drug heparin. "We honestly don't know" the cause, an agency spokeswoman said.

The FDA said in a statement last night that the agency hadn't inspected the Chinese facility.

"While no FDA inspection of the facility has been conducted to date, preparations are being made to perform an inspection as soon as possible. We have already requested expedited access to the facility, facilitated through a recently signed agreement with the Chinese State Food and Drug Administration. FDA also has requested the facility's inspection data and adverse-event reports connected to the product," an FDA spokeswoman said in an emailed statement that she confirmed by phone.

Amid broader concern about the safety of products imported from China, including toys and food ingredients, the role of a Chinese manufacturing facility in making the suspect heparin is likely to immediately spark inquiries from Congress and consumer advocates.

Lawmakers have already been investigating the safety of drugs imported from overseas. Around 80% or more of active pharmaceutical ingredients used by U.S. manufacturers are imported, according to an estimate released by staff of the House Energy and Commerce Subcommittee for Oversight and Investigations, and the amount is rising, with a growing share expected to come from China and India.

Recent testimony from the Government Accountability Office said that the agency may be inspecting only around 7% of foreign drug-making facilities in a given year, and it would take the agency more than 13 years at that rate to inspect all the plants.

The testimony also said the FDA "cannot provide the exact number of foreign establishments that have never been inspected." The agency also had varying counts of how many overseas manufacturers import drug ingredients into the U.S.

On Monday, Baxter announced that it had temporarily suspended production of heparin because of about 350 reactions potentially tied to the drug, including four fatalities, primarily in patients undergoing kidney dialysis and heart surgery. An FDA official estimated that around 40% of the bad reactions potentially linked to the drug were classified as serious. Patients' reactions have ranged from stomach pain to vomiting and diarrhea, low blood pressure, speeding heartbeats and fainting.

Heparin, which is derived from pig intestines, has been sold in the U.S. since the 1930s. Baxter had been selling the product at a rate of about 100,000 vials a day. Given either intravenously or by injection, the drug is used in a wide range of medical procedures to treat or prevent clotting. In particular, it is essential during procedures like cardiac surgery, in which a patient's blood is removed from the body. It is also used in kidney dialysis and in apheresis, a procedure used for some patients with immune-system disorders in which blood is taken outside the patient's body and some components of it are removed.

A Baxter spokeswoman confirmed that the company gets the active pharmaceutical ingredient for its heparin from a U.S. supplier that operates a plant in China and another in the U.S., but she declined to identify the supplier. She said that Baxter, in cooperation with the FDA, plans to inspect the Chinese factory, but she declined to say when.

The spokeswoman said Baxter has been working with the U.S. supplier for 20 years, and the supplier has made the heparin ingredient for three decades.

Baxter has only sold heparin since late 2002, when it bought a unit of Wyeth, the company spokeswoman said. "There have not been changes" recently in the Chinese operation, the spokeswoman said. She added, It's not a foregone conclusion" that the Chinese facility is connected to the problem.

Because heparin is widely used in hospitals and dialysis centers, Baxter didn't suspend sales of existing supplies of the drug to avoid shortages. FDA officials made that decision along with executives of the Deerfield, Ill.-based company.

Baxter supplies about 50% of the heparin used in the U.S., so the possibility of a shortage arising is a real one. Although more than a week ago the company said it had concluded the reactions were confined to nine lots of heparin, it later found the bad reactions had spread beyond those lots and to a wider range of dosages.