The New York Times
nytimes.com

February 29, 2008

Blood Thinner Might Be Tied to More Deaths

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Amid indications that more people may have died or been harmed after being given a brand of the blood thinner heparin, federal drug regulators said Thursday that they had found "potential deficiencies" at a Chinese plant that supplied much of the active ingredient for the drug.

Baxter International, which makes the brand of heparin associated with the problems, and buys supplies from the Chinese plant, announced that it was expanding a recall to include virtually all its heparin products. Though Baxter produces much of the heparin used in the United States, regulators said the other major supplier would be able to meet the demand.

The Food and Drug Administration said the number of deaths possibly associated with the drug, made from pig intestines, had risen to 21 from 4. But it cautioned that many of those patients were already seriously ill and that the drug might not have caused their deaths.

The F.D.A. emphasized that it had yet to identify the root cause of the problem, and that it had not concluded that the Chinese plant was responsible. The agency also said it was investigating two Chinese wholesalers — also called consolidators — that supplied crude heparin to the Chinese plant, Changzhou SPL, as well as those that sold raw ingredients to the consolidators.

The New York Times reported Thursday that at least one of the consolidators received supplies from small, unregulated family workshops that scraped mucous membrane from pig intestines and cooked it, eventually producing a dry substance known as crude heparin.

The F.D.A. admitted this month that it had violated its own policy by failing to inspect SPL, located west of Shanghai, before the factory began shipping the heparin ingredient to Baxter in 2004. China's drug agency also did not inspect the plant.

Last week, the F.D.A. sent inspectors to the plant. Among the potential problems they found was a failure to properly follow the steps for identifying impurities and deficiencies related to manufacturing equipment. According to a redacted inspection report released by the agency, the SPL plant appeared to have made at least some heparin with "material from an unacceptable workshop vendor." The vendor was not identified.

Scientific Protein Laboratories, a Wisconsin company that is the majority owner of the Chinese plant, issued a statement Thursday saying the F.D.A.'s finding did not represent its final determination as to whether the plant complied with federal regulatory rules. S.P.L., the statement said, is committed to finding the root cause of the adverse reactions.

Erin Gardiner, a spokeswoman for Baxter, said the company was reviewing the F.D.A.'s report. "We expect S.P.L. to respond to those observations thoroughly and promptly," Ms. Gardiner said. "The observations are important and need to be addressed promptly but they are not necessarily indicative of the root cause."

The F.D.A.'s concern about heparin had previously centered on Baxter's multidose vials, but on Thursday Baxter agreed to voluntarily recall not only the multi-dose vials but also single-dose vials and a diluted solution of heparin used to keep blood clots from forming in intravenous lines. There have been no adverse reaction reports involving the latter product, called Hep-Lock heparin flush products.

"We have assurance from the U.S. Food and Drug Administration that there is an adequate supply in the market to meet the demand for these critical and lifesaving drugs," Peter J. Arduini, president of Baxter's Medication Delivery business, said in a statement released by the company.

The only heparin products made by Baxter that are still on the market are premixed bags of intravenous solutions, the Food and Drug Administration said.

"We at the F.D.A. understand how unsettling this whole situation with heparin is," said Dr. Sandra Kweder, the agency's deputy director, Office of New Drugs, Center for Drug Evaluation and Research. "We are determined to get to the root cause."

The F.D.A. estimates that more than one million multidose vials of heparin are sold per month in the United States, about half of which are manufactured and distributed by Baxter.

The problems with heparin, which is used to prevent blood clotting during dialysis and after some surgery, were first reported last month at a hospital in Missouri. Since then, the number of reported adverse reactions has risen to 448, the F.D.A. said. "Yes, we have gotten more and we are continuing to evaluate those reports," Dr. Kweder said.

At first, the agency said it believed that four people had died after allergic reactions to the drug. On Thursday, officials said as many as 17 more people may have died, but they described the links to heparin as more tenuous.

The adverse reactions have included decreased or low blood pressure and fast heart rate. Not all of them are known to involve Baxter products, but the drug agency did not issue warnings involving any other products.

The Chinese heparin market has been in turmoil over the last year, as pig disease has swept through the country, depleting stocks, leading some farmers to sell sick pigs into the market and forcing heparin producers to scramble for new sources of raw material.

As a result, even big companies have been turning increasingly to small village workshops, which are often unsanitary. In interviews this week at some of these workshops, employees told The Times that they had not been inspected by the government.

Scientific Protein Laboratories said it responded to the disease outbreak by buying less raw material in China. Its president, David Strunce, said in an interview this week that the Chinese plant bought supplies only from two reputable consolidators, and that its suppliers were audited.

The F.D.A has already finished inspecting one of the consolidators and is still looking at the second one, an agency spokeswoman said. The agency also plans, if necessary, to look at some of the small workshops that supply the consolidators.

"We will go where the investigation takes us," an agency official said.