

Heparin Recall: Another Crisis for China & the FDA

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Heparin is an anticoagulant drug, commonly called a “blood thinner,” that has been widely used by health care providers since the 1930s to prevent blood clots from forming in high risk patients. It is often used on patients following surgery, those on dialysis, or for those who may be bedridden for a period of time. The development of blood clots can lead to serious and even deadly complications, including heart failure or pulmonary emboli. Thus, the use of heparin is an integral part of patient treatment.

Heparin is injected into the patient’s blood stream intravenously, often with a large initial dose called a “bolus.” This bolus dose, manufactured in multiple dose vials, has been linked to at least 81 deaths and hundreds of serious adverse events in the United States since late 2007.¹ In December of 2007, the FDA posted a press release from AM2 PAT, Inc, a health care technology company, announcing a nation wide recall of one lot of pre-filled heparin lock flush solution because the syringes were contaminated with *Serratia macenscens*, which causes serious bacterial infections in patients.² AM2 PAT, Inc. distributed heparin under two brand names: Sierra Pre-Filled, Inc. and B. Braun Medical, Inc. On January 18, 2007, the FDA announced a nationwide recall of all AM2 PAT and B. Braun lots and sizes of pre-filled heparin syringes.³ On January 25, 2008, Baxter International, Inc. recalled nine lots of its heparin injection and multi-dose vials⁴ and on February 11, 2008, Baxter announced it had temporarily stopped manufacturing the vials because its product had been linked to severe allergic reactions in patients.⁵ By the end of February, Baxter recalled all remaining lots of heparin.⁶ Half of the U.S. supply of heparin comes from Baxter.⁷

During the flurry of recalls, the FDA conducted a frantic investigation into the source of the contamination. A link was finally established—the source of the “bad” heparin components was

¹ Gardner Harris, *U.S. Identified Tainted Heparin in 11 Countries*, N. Y. TIMES, April 22, 2008, available at: <http://www.nytimes.com/2008/04/22/health/policy/22fda.html?em&ex=1209096000&en=c53e1b39b9a17b69&ei=5087%0A> (last accessed April 23, 2008).

² *AM2 PAT, Inc. Issues Nationwide Recall of Pre-Filled Heparin Lock Flush Solution USP (5 mL in 12 mL Syringes)*, U.S. FOOD AND DRUG ADMINISTRATION, Dec. 20, 2007, available at: http://www.fda.gov/oc/po/firmrecalls/am2pat12_07.html (last accessed April 14, 2008).

³ *B. Braun’s Supplier Prompts Voluntary Recall of All Lots and All Sizes of Pre-Filled Heparin and Normal Saline Flush Syringes*, U.S. FOOD AND DRUG ADMINISTRATION, Jan. 18, 2008, available at: http://www.fda.gov/oc/po/firmrecalls/braun01_08.html (last accessed April 10, 2008); *AM2 PAT, Inc. Issues Nationwide Recall of All Lots and All Sizes of Pre-Filled Heparin and Normal Saline Flushes*, U.S. FOOD AND DRUG ADMINISTRATION, Jan. 18, 2008, available at: http://www.fda.gov/oc/po/firmrecalls/am2pat01_08.html (last accessed April 10, 2008).

⁴ *Baxter Issues Urgent Nationwide Voluntary Recall of Heparin 1,000 Units/ml 10 and 30ml Multi-Dose Vials*, U.S. FOOD AND DRUG ADMINISTRATION, Jan. 25, 2008, available at: http://www.fda.gov/oc/po/firmrecalls/baxter01_08.html (last accessed April 10, 2008).

⁵ *Baxter’s Multiple-dose Vial Heparin Linked to Severe Allergic Reactions*, U.S. FOOD AND DRUG ADMINISTRATION, Feb. 11, 2008, available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01797.html> (last accessed April 10, 2008).

⁶ *Baxter to Proceed with Recall of Remaining Heparin Sodium Vial Products*, U.S. FOOD AND DRUG ADMINISTRATION, Feb. 28, 2008, available at: http://www.fda.gov/oc/po/firmrecalls/baxter02_08.html (last accessed April 10, 2008).

⁷ Bruce Japsen, *Producers of Heparin Turn up Scrutiny of Supply Chain*, CHICAGO TRIBUNE, March 8, 2008, available at: http://www.chicagotribune.com/features/lifestyle/health/chi-sat_baxter-fdamar08,1,1143266,print (last accessed March 8, 2008).

China.⁸ The concern about Chinese manufacturing of heparin spread beyond the U.S. as European authorities announced similar allergic reactions occurring linked to heparin manufactured by a German company.⁹ Companies in Japan and Germany then recalled their heparin products.¹⁰ But still no one was sure what was causing the contamination or how it was occurring.

On March 6, 2008, the FDA announced the raw components of heparin that had been manufactured in China “contained a possibly counterfeit ingredient that mimicked the real drug.”¹¹ Most alarming, the FDA acknowledged it did not know if the introduction of this counterfeit ingredient was accidental or deliberate.¹² On March 14, 2008, the FDA said that all heparin imports would be stopped at the U.S. border and inspected for contaminants.¹³

On March 19, 2008, the FDA reported that the contaminant found was “likely made in China from animal cartilage, chemically altered to act like heparin, and added intentionally to batches of the drug’s active ingredient.”¹⁴ The implication was that the Chinese plant had intentionally used a man-made counterfeit ingredient in order to make heparin more cheaply. This ingredient was identified as over-sulfated chondroitin sulfate. Chondroitin sulfate, a naturally occurring substance, is made from animal cartilage and can be found in supplements that treat joint pain.¹⁵ But oversulfated chondroitin sulfate is a modified form of the mineral that mimics heparin’s active ingredient.¹⁶ This is why the counterfeit ingredient was not caught by routine tests.¹⁷

According to Baxter, China now provides the majority of the world’s heparin supply.¹⁸ The raw ingredient of heparin is made from pig intestines. Four years ago, an American company, Scientific Protein Laboratories, which processes heparin ingredients and supplies them to B. Braun and Baxter, opened a plant in China, where there was a larger supply of pigs than in the U.S. and Canada.¹⁹ It is this plant, in Changzhou, China, that has been linked to the heparin

⁸ See *Updated Questions and Answers on Heparin Sodium Injection (Baxter)*, U.S. FOOD AND DRUG ADMINISTRATION, March 7, 2008, available at: <http://www.fda.gov/oc/quanda/heparin.html> (last accessed April 10, 2008).

⁹ Japsen, *supra*, note 7.

¹⁰ Kirsty Barnes, *China-made Heparin Scare Spreads Beyond US*, OUTSOURCING-PHARMA.COM, March 3, 2008, available at: <http://www.outsourcing-pharma.com/news/ng.asp?n=83860-baxter-rotexmedica-fda-heparin-china> (last accessed April 14, 2008).

¹¹ Gardiner Harris & Walt Bogdanich, *Drug Tied to China Had Contaminant, F.D.A. Says*, N. Y. TIMES, March 6, 2008, available at: www.nytimes.com/2008/03/06/health/06heparin.html (last accessed April 10, 2008).

¹² *Id.*

¹³ Walt Bogdanich, *Tainted Blood Drug to Face Import Tests*, N. Y. TIMES, March 15, 2008, available at: <http://www.nytimes.com/2008/03/15/health/policy/15fda.html?scp=9&sq=&st=nyt> (last accessed April 15, 2008).

¹⁴ Jacob Goldstein, *Heparin Likely Cut With Cheap Counterfeit Ingredient*, THE WALL STREET JOURNAL HEALTH BLOG, March 19, 2008, available at: <http://blogs.wsj.com/health/2008/03/19/heparin-likely-cut-with-cheap-counterfeit-ingredient/?mod> (last accessed April 14, 2008).

¹⁵ *Id.* See also *FDA Identifies Contaminant in Blood-Thinning Drug*, MEDLINE PLUS, March 19, 2008, available at: http://www.nlm.nih.gov/medlineplus/news/fullstory_62400.html (last accessed April 14, 2008).

¹⁶ Goldstein, *supra* note 14.

¹⁷ Walt Bogdanich, *Heparin Is Now Suspected in 62 Fatalities Across U.S.*, N. Y. TIMES, April 10, 2008, available at: <http://www.nytimes.com/2008/04/10/health/policy/10heparin.html?scp=1&sq=&st=nyt> (last accessed April 15, 2008).

¹⁸ Harris & Bogdanich, *supra* note 11.

¹⁹ Bruce Japsen, *Synthetic Heparin Could Be Next Step, Recalls Lead To Pursuit Of Better Quality Control*, CHICAGO TRIBUNE, March 22, 2008, available at: <http://www.chicagotribune.com/business/chi-sat-baxter-heparin-bax-mar22.0.3420880.story> (last accessed April 14, 2008).

containing the counterfeit ingredient.²⁰ Chinese officials admitted that its drug agency had not inspected this plant, which is a chemical company, and had not certified it to make pharmaceutical products.²¹ Although the plant was supplying heparin components for years to American heparin manufacturers, the FDA did not inspect it until February 2008, after the problems began.²² Once the inspection took place, it was found that the plant was using materials from an “unacceptable vendor” and failing to “identify impurities and deficiencies”²³ and that the contaminant was found in more than half the lots.²⁴

The FDA admitted that the failure to inspect the Chinese plant was a violation of its own policies.²⁵ There are approximately 700 drug plants in China, and the FDA has only inspected 10-20 each year.²⁶ In fact, if the FDA continued to inspect foreign drug plants at its current rate, it would take 13 years to inspect them all.²⁷ The failure to inspect these types of plants in China has been called a “regulatory void” that has been difficult to fill because Chinese chemical companies do not fall under the jurisdiction of China’s drug agency.²⁸ In early April, China reversed itself and announced it had begun more closely regulating heparin producers.²⁹ A few weeks later, Chinese officials expressed doubt that the contaminant found in heparin manufactured in China actually caused any deaths, and insisted it be allowed to inspect the American facilities that finalized the product.³⁰ In the meantime, the FDA is scrambling to place permanent inspectors in China, although it has yet to get permission from the Chinese government, and there is an impending nationwide shortage of heparin.³¹ Most recently, the FDA has expanded the warning to manufacturers and distributors of heparin-coated devices, such as heart stents and grafts³² and has announced its discovery that 12 Chinese companies have supplied contaminated heparin to 10 other countries.³³

No matter the complications facing regulators, Americans are increasingly fed up hearing that another product manufactured or produced in China contains dangerous or deadly components.

²⁰ *Id.*

²¹ Walt Bogdanich & Jake Hooker, *China Didn’t Check Drug Supplier, Files Show*, N. Y. TIMES, Feb. 16, 2008, available at: <http://www.nytimes.com/2008/02/16/us/16baxter.html> (last accessed April 14, 2008).

²² Japsen, *supra* note 19.

²³ *Blood-Thinning Drug Under Suspicion*, CBSNEWS.COM, Mar. 1, 2008, available at: <http://www.cvsnews.com/stories/2008/03/01/eveningnews/printable3896578.shtml> (last accessed March 8, 2008).

²⁴ Walt Bogdanich, *Tainted Blood Drug to Face Import Tests*, N. Y. TIMES, March 15, 2008, available at: <http://www.nytimes.com/2008/03/15/health/policy/15fda.html?scp=9&sq=&st=nyt> (last accessed April 15, 2008).

²⁵ Gardiner Harris & Walt Bogdanich, *F.D.A. Broke Its Rules by Not Inspecting Chinese Plant with Problem Drug*, N.Y. TIMES, Feb. 15, 2008, available at: <http://www.nytimes.com/2008/02/15/washington/15fda.html> (last accessed April 14, 2008).

²⁶ Bogdanich and Hooker, *supra*, note 21.

²⁷ Harris, *supra* note 1.

²⁸ Bogdanich and Hooker, *supra*, note 21.

²⁹ David Barboza, *China Orders New Oversight of Heparin, With Tainted Batches Tied to U.S. Deaths*, N. Y. TIMES, March 22, 2008, available at: <http://www.nytimes.com/2008/03/22/world/asia/22heparin.html?scp=5&sq=&st=nyt> (last accessed April 15, 2008).

³⁰ Harris, *supra* note 1.

³¹ Gardiner Harris, *Problems in Blood Drug Lead to Halt By Factory*, N.Y. TIMES, Feb. 12, 2008, available at: http://www.nytimes.com/2008/02/12/health/12drug.html?_r=1&fta=y&oref=slogin (last accessed April 15, 2008); Jacob Goldstein, *FDA to Open China Office This Year*, THE WALL STREET JOURNAL HEALTH BLOG, April 15, 2008, available at: <http://blogs.wsj.com/health/2008/04/15/fda-to-open-china-office-this-year/?mod=WSJBlog> (last accessed April 15, 2008); Harris, *supra* note 1.

³² *Important Notice to Manufacturers and Initial Distributors of Medical Devices That May Contain Heparin Or Are Heparin-Coated*, U.S. FOOD AND DRUG ADMINISTRATION, April 8, 2008, available at: <http://www.fda.gov/cdrh/safety/heparin-notice.html> (last accessed April 16, 2008).

³³ Harris, *supra* note 1.

The deaths of hundreds of pets linked to a counterfeit Chinese ingredient in pet food and the recall of millions of toys made in China containing lead paint has led to vitriolic reactions among American consumers. China boycotts and bans are routinely discussed on blogs and TV call-in shows. Of course, talk of lawsuits has begun. But who can be held liable for this latest debacle? And who should be?

Numerous plaintiffs' firms have their heparin claims web pages up. Baxter, as the main manufacturer of the tainted heparin, will probably face a class action lawsuit not unlike that faced by Menu Foods, the manufacturer and distributor of the tainted pet food.³⁴ If the Menu Foods settlement is any indication, Baxter may well be held liable for the actions of its Chinese supplier and its failure to more closely monitor its production supply chain. Furthermore, Baxter may have violated federal law prohibiting the sale of counterfeit drugs.³⁵ For its part, Baxter has now conducted its own tests, and disputes the FDA's assertion that its product is linked to the 81 deaths.³⁶ An interesting question will be whether Baxter may be able to use a preemption argument similar to medical device makers who recently prevailed at the Supreme Court against patients attempting to sue them for product liability.³⁷ Baxter's drug development process was approved by the FDA; but is that enough to preempt a patient's cause of action in this situation? An important question will be whether the FDA will hold to the position that it is the pharmaceutical companies that are responsible for monitoring the development of the raw materials that go into their drugs.³⁸ The answer will probably require years of expensive litigation.

Physicians and hospitals who have been prescribing and administering heparin since the recalls first began may also have to worry about liability. The FDA, while warning health care providers of the tainted heparin, did not initially recall all Baxter heparin products for fear of a national shortage. Are health care providers liable for their decision to continue to use the Baxter products that were not initially recalled? Because they knew or should have known about the recall, could patients argue the physician's negligence in prescribing heparin was in fact willful and wanton? These questions will probably be answered in court at the expense of health care providers and their insurers.

And what of the FDA's own admission of failing to follow its own procedures? Can injured patients hold it accountable? Probably not. The FDA is one of many overburdened, underfunded, and liability immune government agencies that lets consumers fall through the cracks. This time, however, the result was the death of Americans. It is imperative that the FDA be better funded and managed so that inspections of production facilities outside of the U.S. can be done on a comprehensive level. The U.S. and Europe have been expanding their production of medical products globally for several years because it is cheaper to do so. Approximately 40% of drugs and 80% of their chemical ingredients are imported from countries like China and India that do not have ample inspection and safety procedures in place. According to Dr. Bryan Liang, an advisor to the Partnership for Safe Medicines, "the problem is only going to get worse as

³⁴ *Menu Foods Reaches Deal to Settle Pet Food Suits*, INSURANCE JOURNAL, April 1, 2008, available at: <http://www.insurancejournal.com/news/international/2008/04/01/88757.htm?print=1> (last accessed April 3, 2008).

³⁵ 21 U.S.C. 331, Federal Food, Drug and Cosmetic Act, Prohibited Acts and Penalties.

³⁶ Harris, *supra* note 1.

³⁷ *Riegel v. Medtronic, Inc.*, 128 S.Ct. 999 (Feb. 20, 2008).

³⁸ *See Heparin Deaths Reveal Troubles with FDA, Supply Chain*, available at: <http://www.serpefirm.com/library/heparin-deaths-reveal.cfm> (last accessed April 23, 2008).

more materials come from suspect sources.”³⁹ This is not news, however. The FDA knows it does not have the manpower or resources to inspect every overseas facility, as do Congress and the President, all of whom have been calling for more funding.⁴⁰ Perhaps holding the FDA liable for the damages experienced by the harmed patients is the only way to prod our government into properly funding this all-important agency and keeping American consumers safe.

Health Law Perspectives (April 2008), available at:
<http://www.law.uh.edu/healthlaw/perspectives/homepage.asp>

³⁹ Associated Press, *Heparin Probe Reveals Global Drug Market Perils*, MSNBC, April 13, 2008, available at: <http://www.msnbc.msn.com/id/24015019/> (last accessed April 16, 2008).

⁴⁰ For a thorough discussion of this issue, see U. S. GOVERNMENT ACCOUNTABILITY OFFICE, TESTIMONY BEFORE THE SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS, COMMITTEE ON ENERGY AND COMMERCE, HOUSE OF REPRESENTATIVES, *Drug Safety: Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program*, GAO-08-701T, April 22, 2008, available at: <http://www.gao.gov/new.items/d08701t.pdf> (last accessed on April 23, 2008).