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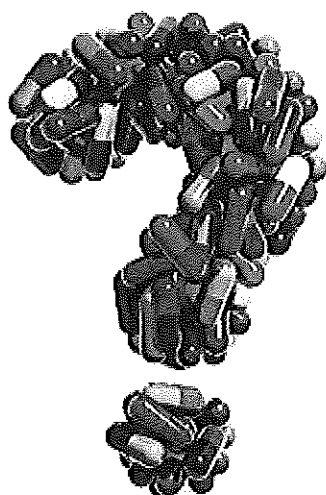
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Shock To The System

Big questions about drug safety arise in the wake of rampant supply-chain globalization

Rick Mullin



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In March 2008, the Food & Drug Administration announced a major recall of the injectable anticoagulant heparin, citing contamination of a raw material coming from China. The recall made front-page news when it was revealed that the contaminated drug likely caused 81 deaths in the U.S.

The drug's manufacturer, [Baxter Healthcare](#), was not able, using standard technology, to detect the contaminant: an oversulfated derivative of chondroitin sulfate. Authorities deemed the contamination to be a willful adulteration—the chondroitin derivative costs far less than heparin, a drug that is laboriously derived from pig intestines.

The story combined several shocking elements, not least of which was the failure of safeguards intended to prevent contaminants from entering a formulated drug. The crime itself, which is believed to have taken place

at a crude-heparin factory that supplied Baxter’s Chinese supplier, drew attention to a new risk from drugs: that of unsafe ingredients entering the supply chain as drugmakers increasingly outsource the production of active pharmaceutical ingredients (APIs) to third parties.

In the wake of the heparin scandal, FDA admitted that rampant globalization in drug manufacturing has outstripped the agency’s resources for inspecting foreign facilities. Regulators and manufacturers alike are concerned about the growing risk of substandard or criminally adulterated APIs, drug intermediates, and excipients entering the supply chain. The problem predates the 2008 heparin scandal, they say, and many predict further, perhaps more widespread, incidents of lethal drug contamination.

In 2007, for example, more than 300 people died in Panama after taking cough medicine manufactured with diethylene glycol that was believed to be glycerin. The adulterant was manufactured in China and is believed to have been relabeled as glycerin by a middleman in Spain.

Misrepresentation of a drug substance source, legally an adulteration, emerged in another case involving heparin. FDA discovered in 2008 that Shanghai No. 1 Biochemical & Pharmaceutical, an FDA-registered producer and exporter of heparin in Shanghai, never produced the product. Instead, two other Chinese producers supplied it, repackaged and labeled as having been produced by Shanghai No. 1. The agency found that since 2001, at least four lots of heparin were shipped by Shanghai No. 1 to International Medication Systems, a drugmaker in California. According to FDA, some of the heparin shipped from Shanghai No. 1 was contaminated.

Not all problems involve obscure companies. In 2008, FDA issued warning letters to India’s Ranbaxy Laboratories, one of the world’s largest suppliers of generic drugs, about deviations from current Good Manufacturing Practices at two plants in India involving 30 products. Nor do all problems occur in India and China. Last year, GlaxoSmithKline pleaded guilty and paid a record \$750 million to settle civil and criminal complaints that it knowingly marketed adulterated products made at a plant in Cidra, P.R., between 2001 and 2005.

FDA is trying to crack down with heavier fines and a string of warning letters. One it sent to China’s Xian Libang Pharmaceutical last year, for example, outlined significant deviations from cGMP involving quality assurance, manufacturing, and test data management. But the agency is inspecting only a fraction of the facilities on its fast-growing registry of API suppliers.

At a conference sponsored by the think tank the Council on Foreign Relations in February, FDA Commissioner Margaret Ann Hamburg acknowledged shortfalls in the agency’s oversight of food and pharmaceutical supply chains. “I think people have no idea in this country and around the world about the vulnerability of things that we count on every day,” she said, “and that we have a system that has big gaps in our protective mechanisms.”

The gaps Hamburg described are caused by an explosion in outsourced production of drug ingredients. According to FDA, imports now account for more than 80% of APIs in the U.S. and 40% of finished drugs. Yet the agency conducts far fewer foreign inspections than it does domestic inspections.

TALL ORDER
FDA inspects only a fraction of foreign drug plants

	INSPECTIONS BY FDA				ESTIMATED PLANTS IN FDA INVENTORY 2009
	2007	2008	2009	TOTAL	
India	64	64	59	187	502
China	19	36	52	107	970
Germany	26	34	36	96	228
Italy	28	28	30	86	169
Canada	20	19	35	74	310
UK	16	17	32	65	191
France	24	14	26	64	183
Japan	22	17	20	59	207
Switzerland	17	16	18	50	100
Ireland	14	11	19	44	63
All others	83	69	97	249	889
TOTAL	333	324	424	1,081	3,765

NOTE: Most frequently inspected foreign countries.
SOURCE: Government Accountability Office

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A recent report by the Government Accountability Office, the investigative arm of Congress, concluded that

FDA inspected just 11% of the foreign establishments that were on a list the agency used to prioritize inspections of sites supplying drug products sold in the U.S. in 2009. By contrast, FDA inspected 40% of domestic facilities on its list that year. Foreign sites have outnumbered domestic sites on the FDA registry since 2008.

Speaking in March at a conference sponsored by the Pew Charitable Trusts in Washington, D.C., John M. Taylor III, FDA acting principal deputy commissioner, outlined the agency's ambition to fundamentally change its approach to ensuring drug safety. "FDA's traditional model of manufacturing-site inspections and border examinations is simply not adequate in today's transformed world," he said.

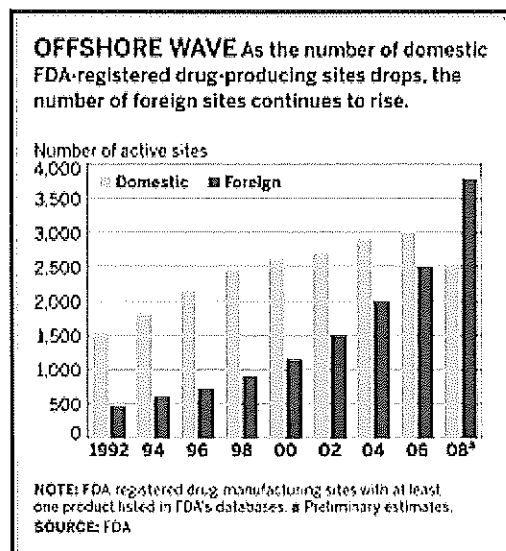
An effort to become more "prevention-focused and global," Taylor explained, has resulted in an information-sharing agreement with European, Japanese, and Australian regulators. The agency is investigating the use of third-party inspectors for the first time. FDA has opened regional offices in Asia and elsewhere and is working to build a global data system that it would share with its counterparts around the world.

Drug companies and their API suppliers are also beginning to share information through a two-year-old consortium called Rx-360. Its 56 members include 22 drug companies and 19 API suppliers. Rx-360 facilitates audits, publishes security alerts, and puts members to work on preventive strategies, including investigating what kinds of dangerous substitutes unscrupulous parties might use in place of chemicals in short supply, says Martin Van Trieste, vice president of quality operations at Amgen and chairman of Rx-360.

Guy Villax, chief executive officer of Hovione, an API supplier based in Portugal, tells C&EN that the severity of the threat to drug safety is hard to communicate to the public and to legislators because most of the criminal activity cannot be readily detected. "It is like an iceberg," he says. "The illegal supply that we see coming in on e-mails for Viagra, Lipitor, and Epogen is not the real problem. The problem is below the waterline, where we have heparin and diethylene glycol contamination."

Speaking at the Pew conference, Villax said a shift in health care toward generic drugs has made it difficult for regulators to inspect ingredient suppliers. Whereas patented drugs, made for the most part by large drug companies whose suppliers are monitored by FDA, dominated the market not long ago, 70% of prescriptions are now filled by generic drugs.

Villax said FDA's inability to inspect its growing list of foreign generic drug suppliers has created an environment in which it is possible to commit the perfect crime. "The victim swallows the murder weapon," he said, "though ideally the criminal wants return customers." He said the prominence of brokers, traders, and other middlemen further opens the door to economically motivated adulteration of drugs.



[View Enlarged Image](#)

"**Generic drugs** are important to controlling health care costs, and major generic companies do an excellent job," Villax said. But once a drug goes off patent, he pointed out, a world in which one manufacturer is answerable for quality becomes one in which any number of manufacturers are involved. "The arbiter of quality becomes the regulator, and it is a huge job for the regulator," he said.

Harry M. Lever, medical director of the hypertrophic cardiomyopathy clinic at Cleveland Clinic, says drug quality has become a serious concern for him. "One of the problems is that we don't know where a lot of the APIs are coming from," he says. "There have been a lot of problems with drugs coming in from overseas and also quality issues in this country. I worry about the drugs I give my patients."

Lever says he will no longer prescribe some generic drugs, but he notes that branded drugs have quality issues as well. He cites Johnson & Johnson's recent recall of 40 varieties of children's medicine—136 million products—in response to complaints from regulators and customers.

Drug shortages are another concern, he says, because any shortage opens the door to counterfeiters. The more immediate effect, however, is the lack of availability of drugs to treat patients. Cleveland Clinic, according to Lever, now has a full-time pharmacist in charge of dealing with drug shortages. "Why is this happening now?" Lever asks. "Everybody has to get their act together—the manufacturers and the regulators."

Manufacturers, for their part, claim they have their act together. Kendra A. Martello, assistant general counsel for trade group Pharmaceutical Research & Manufacturers of America, says she is surprised and alarmed by Lever's concerns. She says PhRMA's members, which include the top 10 pharmaceutical firms, operate according to cGMP standards. Martello notes that manufacturers filing New Drug Applications with FDA are required to identify the source of all ingredients in a finished drug, and all manufacturing sites have to operate in accordance with cGMP requirements.

Robert Billings, vice president for policy at the Generic Pharmaceutical Association, says his group's members—including large generics makers such as Teva Pharmaceutical Industries, Watson Pharmaceuticals, Mylan, and Ranbaxy—are held to the same FDA standards. "When you look at the approval process for a generic drug, it includes six of the seven steps involved in branded-drug approval," he says. "The only difference is that a generic isn't approved as a new molecular entity."

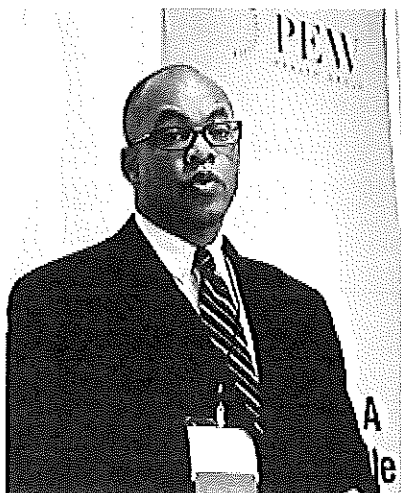
Indian companies take exception to the notion that generic drug ingredients from India present a particular risk. Yusuf Hamied, CEO of Cipla, a Mumbai-based manufacturer of generic APIs, says firms supplying U.S. drug companies have to be inspected by FDA on a regular basis.

Hamied contends that much of the finger-pointing at India and China comes from branded pharmaceutical producers hoping to undermine generic drug companies, which are the biggest customers of Asian API makers. Ironically, he says, the branded-drug companies get APIs from some of the same producers in India and China or are producing APIs in these countries themselves.

Kate Kuhrt, director of generics and API intelligence for Thomson Reuters, also questions the contention that the U.S. market is in danger of a massive infusion of substandard APIs. She says the requirement that FDA inspect all manufacturers of APIs before a drug can be sold gives some assurance of quality. Kuhrt adds that most API suppliers in China and India serve only their fast-growing domestic markets.

Amgen's Van Trieste posits that the risk posed by global supply chains is shared equally by makers of branded and generic drugs and that the key is auditing. "If you don't know your supplier, if you don't provide active monitoring and oversight of that supplier, if you are not doing the proper testing of your raw materials, if you don't know the supply chain that your raw material moves through, you are at risk regardless of whether you are a branded or a generics company."

The sharing of audit information among manufacturers has emerged as one way to enable comprehensive inspections of suppliers. Rx-360, Van Trieste says, completed its first joint audit last month at Avantor Performance Materials, a Phillipsburg, N.J.-based excipient manufacturer. The group has 10 shared audits scheduled for May and hopes to complete 17 by the end of June.



Pew Charitable Trusts

GLOBAL PERSPECTIVE FDA Deputy Commissioner Taylor calls for a network of regulatory information sharing.

Guarding the pharmaceutical supply chain has become a legislative goal in the U.S. as well. Two bills addressing drug safety are currently being considered by Congress. In the Senate, the Drug Safety & Accountability Act (S. 3690), sponsored by Michael F. Bennet (D-Colo.), would improve tracking of drugs manufactured at foreign sites, give FDA authority to recall unsafe drugs, and beef up the agency's enforcement powers. And in the House of Representatives, the Drug Safety Enhancement Act (H.R. 6543), sponsored by John D. Dingell (D-Mich.), would also give FDA more authority and resources to support a global regulatory framework.

Penalties for adulteration need to be stiffened, Van Trieste argues. Currently, sentences range from eight months to three years, which he considers an insufficient deterrent given the profit potential for criminals. Dingell's bill, he says, proposes more severe penalties.

Deborah M. Autor, director of the Office of Compliance at FDA's Center for Drug Evaluation & Research, argues that manufacturers have primary responsibility for ensuring drug safety. "They are responsible for ensuring the quality of what they sell," she tells C&EN. "They have the most control over suppliers." Ultimately, though, FDA is responsible for protecting consumers, she acknowledges.

Speaking at the Pew conference, Autor noted that the rallying of industry and regulators after the heparin tragedy is reminiscent of FDA's genesis in 1938 as part of the Food, Drug & Cosmetic Act, which Congress passed in the wake of a sulfanilamide contamination case that killed more than 100 people. She added, however, that the agency's regulatory authority needs to be significantly enhanced for the 21st century.

"People are shocked that we don't have mandatory recall authority," she said. "Nor do we have subpoena authority. And we don't have explicit authority to pursue crime outside the U.S."

Allan Coukell, director of medical safety for the Pew Health Group, which hosted the March conference, tells C&EN that a consensus is building behind policy change to support increased inspection of API production sites and increased resources for regulatory oversight.

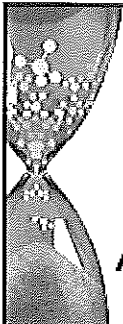

"We are a long way from where we need to be," he says. "But Deputy Commissioner Taylor saying FDA is increasingly looking to third-party sources of information to supplement its inspections is significant."

Sen. Bennet, who made a brief visit to the conference, applauded the effort to bring a broad range of stakeholders into one room and expressed his interest in a report that Pew plans to release in June. "We are in the business of stealing other people's good ideas," Bennet said.

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