

FDA Scrutiny Scant In India, China as Drugs Pour Into U.S.

Broad Overseas Checks Called Too Costly

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India and China, countries where the Food and Drug Administration rarely conducts quality-control inspections, have become major suppliers of low-cost drugs and drug ingredients to American consumers. Analysts say their products are becoming pervasive in the generic and over-the-counter marketplace.

Over the past seven years, amid explosive growth in imports from India and China, the FDA conducted only about 200 inspections of plants in those countries, and a few were the kind that U.S. firms face regularly to ensure that the drugs they make are of high quality.

The agency, which is responsible for ensuring the safety of drugs for Americans wherever they are manufactured, made 1,222 of these quality-assurance inspections in the United States last year. In India, which has more plants making drugs and drug ingredients for American consumers than any other foreign nation, it conducted a handful.

Companies based in India were bit players in the American drug market 10 years ago, selling just eight generic drugs here. Today, almost 350 varieties and strengths of antidepressants, heart medicines, antibiotics and other drugs purchased by American consumers are made by Indian manufacturers.

Five years ago, Chinese drugmakers exported about \$300 million worth of products to the United States. Eager to meet Americans' demand for lower-cost medicines, they, too, have expanded rapidly. Last year, they sold more than \$675 million in pharmaceutical ingredients and products in the U.S. market.

After the pet food scandal that triggered fears over the safety of human and animal foods imported from China, experts say medicines from that country and from India pose a similar risk of being contaminated, counterfeit or simply understrength and ineffective.

"As the manufacturing goes to China and India, the risk to human health is growing exponentially," said Brant Zell, past chairman of the Bulk Pharmaceuticals Task Force. The group represents American drug-ingredient makers that filed a citizen's petition with the FDA last year asking the agency to oversee foreign firms more aggressively.

"The low level there" of follow-up inspections, "combined with the huge amount of importing, greatly increases the potential that consumers will get products that have impurities or ineffective ingredients," he said.

FDA officials say that they are not aware of any health problems caused by drugs imported from India or China and that the American companies that import them usually do their own quality and safety testing. But the agency acknowledges that it is virtually impossible for it to know whether poor-quality or contaminated drugs from lightly regulated Asian plants have caused patients to get sicker or remain ill, especially because patients and doctors are unlikely to suspect poorly manufactured drugs as a problem.

What is clear is that the odds are growing rapidly that the contents of an American medicine cabinet will hold products from the two countries.

Analysts estimate that as much as 20 percent of finished generic and over-the-counter drugs, and more than 40 percent of the active ingredients for pills made here, come from India and China. Within 15 years, they predict, as much as 80 percent of the key ingredients will come from those countries -- which are quickly becoming attractive to brand-name drugmakers, too.

William Hubbard, a former FDA associate commissioner, called the situation dire and deteriorating.

"You have this confluence of events, with so much more product coming from abroad and fewer and fewer inspections," Hubbard said. "This is very serious stuff, because a contaminated drug hitting the market could cause lots of injuries or worse before it got tracked down."

He also said that the FDA inspection system is so weak that many foreign manufacturers believe they "can play games without consequences."

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents many Indian drugmakers, said he would like to see a more permanent FDA presence in his country because "it would help improve standards" and encourage more companies to seek FDA approval of their products.

He said, however, that when U.S. groups raise questions about the quality of India's products, "one must not forget that they may have some agenda," such as protecting their market share. All drugs imported from India, Shah said, come with "assurance of quality, safety and efficacy" from the FDA.

An executive for Shanghai Pharmaceutical, one of China's largest drugmakers, made a similar argument in a recent interview with the U.S. magazine *Chemical & Engineering News*. He said that all drug ingredients his company exports to the United States meet stringent FDA standards and that American trade groups sometimes "urge quality controls as a trade barrier to protect the interests of their members."

Hubbard and other experts agree that many Indian and Chinese drugmakers are high-quality firms that provide products at a fraction of the price charged by American and European manufacturers. But, they add, Indian and Chinese companies are not only new

to the FDA standards, but they also are in nations that have recent histories of widespread drug counterfeiting, lax quality control and very limited government regulation.

The former head of the Chinese drug and food safety agency, for instance, was recently sentenced to death for taking bribes from companies he regulated, and two major Indian companies received warning letters from the FDA in the past two years over serious infractions involving drug quality control.

Private inspectors hired by U.S. companies to check out foreign plants report finding very good ones but also some without walls and that are open to dust and pests, chemical equipment crowded in ways that could lead to cross-contamination, and one plant that had a hornet's nest atop a drugmaking vat.

One frequently cited case involves the intravenous antibiotic gentamicin, which was supplied by a company in China and linked to deaths in the United States in the late 1990s. Tests by German researchers found a wide range in quality and effectiveness in what were supposed to be uniform dosages of the drug, leading the scientists to write that "it was assumed" the deaths "were related to faulty manufacture."

FDA officials say they have recently begun a risk-based approach to manufacturing oversight -- one that seeks to ensure that drugmakers have proper quality-control systems and that requires fewer inspections. But they acknowledge that financial constraints keep them from making more of the expensive and often hard-to-organize visits to plants in India and China.

"The FDA does the best as it can to regulate overseas good manufacturing practices and do inspections, given the limited resources we have," said Joseph Famulare, deputy director for international inspections. "If we had more resources, we would get more inspections done."

Despite repeated requests for information about the FDA's budget for overseas drug inspections, the agency did not make it available.

India and China are hardly the only nations manufacturing drugs and active ingredients for the American market: The Commerce Department reported that more than \$42 billion in drugs and drug ingredients were imported last year.

Most of the other suppliers are in Europe, Japan and Singapore, however, and many have a long track record of working with U.S. drug companies and regulators. Other than Israel, which has a booming drug export industry, India and China are the fastest-growing suppliers of low-cost drugs and are poised, analysts said, to grow faster.

Their niche is primarily the quickly expanding market for generic drugs, which account for more than 60 percent of prescriptions filled in the United States. Analysts with Newport Strategies, a drug-information-gathering and consulting firm that works extensively in India and China, report that Indian firms won FDA approval to import

more than 100 generic drugs last year. Drug analyst Utkarsh Palnitkar of Ernst & Young in Hyderabad, India, said Indian firms accounted for more than 20 percent of FDA generic drug approvals last year, compared with less than 7 percent five years ago.

A similar dynamic can be seen in the drug "master files" reviewed by the FDA. These documents are submitted when a firm wants to sell "active pharmaceutical ingredients" to American companies.

In 1999, India did not appear on an FDA chart of master files. By 2004, almost half of the reviewed files for drug ingredients destined for U.S. patients came from Indian companies. More recently, Indian companies have moved more aggressively into making finished drugs, and Chinese companies -- which expect as many as 4,000 international buyers at a series of drug ingredient conferences in Shanghai this month -- have expanded their share of the market in active ingredients.

"The last two years were the tipping point when it comes to Indian finished drugs," said Michael Chace-Ortiz, senior director of Newport Strategies. "They still dominate here" with active pharmaceutical ingredients, "but finished generic drugs are their future," he said. "And as they move up the chain, the Indians themselves have begun to buy active ingredients from the Chinese."

China, for instance, specializes in making ingredients for antibiotics, which are often made into capsules in India and exported to the United States and elsewhere.

In addition to the United States' \$675 million in pharmaceutical imports from China last year, India sold \$800 million worth of finished drugs and ingredients here in 2006, according to Commerce Department records.

Yet on-the-ground inspections of Indian and Chinese plants remain rare and relatively brief and are always scheduled in advance, unlike the surprise visits that FDA inspectors pay to domestic manufacturers. FDA records show that 32 inspections were carried out last year in India, and most were for companies seeking approval to sell a drug or ingredients, not to check on the quality of manufacturing. Fifteen visits were made to Chinese plants.

Even these small numbers overstate the FDA's oversight. Some of the 32 India inspections -- the agency would not say how many -- involved drugs that, by law, cannot be sold to Americans. They were to review companies that wanted to take part in President Bush's program to supply cheap AIDS drugs to Africa.

FDA officials say U.S. drugmakers regularly test the drugs and active ingredients they buy from abroad, and industry officials say such testing -- which includes the all-important determination that the generic drugs are "bioequivalent" to brand-name products -- is essential to protect their reputations and often substantial capital investments.

But the generic-drug business is fiercely competitive, and the key to success often is providing the least expensive product -- a pressure on prices that has allowed Wal-Mart to sell almost 200 generic drugs for a flat \$4-per-prescription fee. Some experts worry that, to cut costs, expensive quality-control systems are being shortchanged.

That was the case at Able Laboratories, a once highflying New Jersey maker of generic drugs with close ties to India. It went bankrupt two years ago. FDA inspectors found that some of its quality-control data had been falsified, leading to one of largest drug recalls in FDA history. This year, four Able employees pleaded guilty to criminal charges of fraud.

Last year, two of India's largest and most respected drugmakers, Ranbaxy Laboratories and Wockhardt, received FDA warning letters about quality-control and documentation issues at their Indian plants. Both companies were told that if they did not improve, some of their Indian-made products would be barred from the United States.

In February, the FDA's Office of Criminal Investigations raided the New Jersey offices of Ranbaxy. The FDA would not comment on the raid, and the company has said it is cooperating with the agency. A company spokesman said that the FDA was conducting "a wide dragnet," and a source familiar with the investigation said that it involved an unusually large number of investigators.

Because of U.S. drugmakers' concerns over quality control, U.S. Pharmacopoeia -- a nonprofit organization that works with drugmakers and regulators to set drug-quality standards -- opened an office in Hyderabad, a center of the Indian drug industry. Executive Director Roger Williams said Dr. Reddy's Laboratories recently became the first Indian firm to agree to pay USP to check the quality of its products.

"The question is whether the perishingly low price of generics is making it impossible to get quality," Williams said. "It's the job of the FDA to make sure that doesn't happen, and I'm concerned that they just don't have the resources to get people over to places like India frequently enough."

Staff writer Mary Pat Flaherty and staff researcher Madonna Lebling contributed to this report.