Facing Cancer Drug Shortage, U.S. Relies on Banned Chinese Plant

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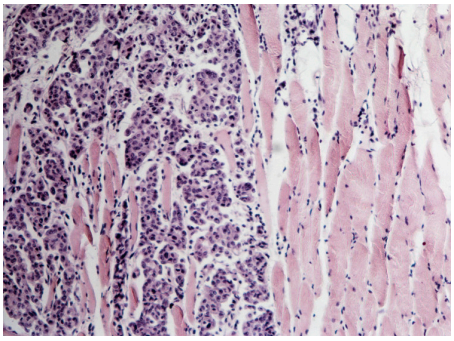

UNSPECIFIED - CIRCA 2003: Microphotograph of a section of carcinoma invading a human striated muscle.

Photographer: De Agostini Picture Library via Getty Images

Last September, U.S. regulators faced a dilemma: whether to allow importation of drug ingredients from a Chinese factory with a history of poor quality controls, or face shortages of treatments for American cancer patients.

Six months earlier, visiting Food and Drug Administration inspectors had uncovered what the agency later called "broad data manipulation" at the factory, located in Taizhou, about 200 miles south of Shanghai. Information about the potency and purity of some product batches had been deleted, making it difficult to investigate a significant increase in customer complaints, the FDA **said** in a warning letter to the plant's owner, Zhejiang Hisun Pharmaceutical Co.

The agency issued an indefinite ban on the factory in September, a first for Hisun, one of China's leading exporters of pharmaceuticals products. Yet to avoid possible shortages of drugs, the FDA allowed the plant continue exporting about 15 ingredients for use in finished drugs in the U.S., including nine key cancer medicine components. Hisun says that it takes quality seriously and has complied with requirements.

Daunting Challenge

How the FDA came to this compromise underscores the daunting challenge the agency faces in making sure that drugs are not only safe for U.S. patients, but also that they're available. More than 80 percent of drug ingredients are now produced **abroad**, mainly in China and India. The FDA has stepped up inspections and added 13 Chinese plants this year to its banned list, but it's up to the drugmakers buying components exempted from its bans to control their quality. The agency doesn't test imported ingredients itself, and relies on pharmaceutical companies to ensure they're up to American standards.

"There is no transparency," said Erin Fox, director of the **University of Utah's Drug Information Service,** which helps run a website listing shortages. "We just have to take FDA's word that they think it's OK."

Same Standards

Drugs sold in the U.S. are held to the same standards regardless of manufacturing location, the FDA said by e-mail. When products are exempted from its import bans because of shortage concerns, manufacturers are often asked to perform additional testing, hire independent auditors, or take other steps, the FDA said, declining to comment specifically on whether that was the case with Hisun. Drug manufacturers that import the components are **responsible** for testing, the agency said.

Companies aren't required to disclose to the public where they get their ingredients or where individual products are made, the agency said.

Hisun, in response to queries about its Taizhou plant, said by e-mail that it has always attached great importance to implementing good manufacturing practices, complied with regulatory requirements in China and abroad, and constantly improves its level of quality management.

While 15 products made at the plant have been barred from the U.S., about 15 others are still permitted because of the FDA's exemptions. Those include the chemotherapy ingredients doxorubicin and daunorubicin -- go-to treatments for leukemia, breast cancer and ovarian cancer. Other exempt products are ingredients of antibiotics and a treatment for irregular heartbeats.

Poor Marks

Before the March 2015 inspection that led to the ban, the FDA had conducted six human drug quality inspections at the Hisun factory in Taizhou between 2009 and 2013. Two led to so-called "voluntary action indicated" requests to fix problems, according to the agency's **database,** which doesn't specify the nature of the issues. While the database only goes back to 2008, Bloomberg was able to obtain some inspection reports from the early 1990s via the Freedom of Information Act.

The plant got poor marks during several inspections from 1992 to 1995, the documents show. Those inspections focused on daunorubicin, which Hisun had just started to sell to drugmakers in the U.S., and doxorubicin, which the company was awaiting FDA approval to sell.

The FDA said that until last year, Hisun had addressed any issue to the agency's satisfaction. It's not clear exactly how Hisun's inspections and citations compare to other companies', since the FDA doesn't make such records public. A handful of warning letters that are public as well as previous Freedom of Information Act requests by Bloomberg have revealed that other Chinese firms have had issues with data manipulation on quality tests.

Doxorubicin Shortage

Because of trade secret protections, it's difficult to obtain detailed information about the extent of shortages beyond an FDA **database** that lists drugs reported by pharmaceutical companies. Drugmakers aren't obligated to disclose whether they are currently buying Hisun's exempted ingredients.

A powder form of doxorubicin has been in short supply since December 2011, according to the database. While a separate shortage on the liquid form was resolved last month, Hisun's doxorubicin remains exempt from the ban to help increase availability, according to the FDA.

Companies that have listed a shortage of the component include Pfizer Inc. and Teva Pharmaceutical Industries Ltd.

Joint Venture

Pfizer said by e-mail that it makes sure its drugs meet standards before reaching the market and that the issues at Hisun had no impact on the quality of its therapies. The company declined to elaborate further on the steps it takes to guarantee its products are safe. The New York-based drugmaker formed a **joint venture** with Hisun in 2012 to make generic drugs for the Chinese and global markets. The import ban at Hisun doesn't apply to products covered by the joint venture, Pfizer said.

Teva said it doesn't use Hisun as a supplier in the U.S.

Drugmakers buying imported ingredients are supposed to check them for purity, strength and quality, as well as conduct on-site audits of components' manufacturers, said Robert Fish, a 33-year veteran of the FDA who served as its head of domestic and international investigations 20 years ago.

"Not all U.S. companies are doing that," said Fish, who left the FDA in 1995 and now advises drugmakers on compliance at EAS Consulting Group. "It costs money."

Missing Audits

The FDA relies on an honor system to ensure drug quality of imports. As an alternative to testing, agency rules allow drugmakers to get data from their component suppliers, "provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses." It means that in some cases, in lieu of doing the testing itself, a drugmaker can use its component supplier's test.

FDA inspectors who visited the Hisun plant in March 2015 uncovered failures including missing audits, altered test records, and even the case of an employee who ran away with what appeared to be a thumb drive. “FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm’s electronically stored data and paper records,” the **agency said in its warning letter** to Hisun. “Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.”

‘Objectionable Conditions’

Hisun declined to comment further on the FDA letter, other than to say it is committed to quality and complies with requirements.

During inspections from 1992 to 1995, FDA staff found hidden batches, missing records, as well as possible sanitation issues, such as a failure to fully test the water used to make the drug ingredients, according to documents obtained via the Freedom of Information Act. In 1995, inspectors listed 12 “objectionable conditions” and recommended that the FDA send Hisun a warning letter. The FDA never sent one.

The agency said it works with companies to help them correct their deficiencies, and until 2015 Hisun had addressed all of its issues.

With so much uncertainty about the origins of the vast majority of components, quality has become a source of worry for some doctors, especially oncologists. Cancer is a challenging disease, making drug potency more crucial than in other illnesses, said Roy Guharoy, chief pharmacy officer at Ascension Health, the largest non-profit health system in the U.S.

“The quality control is so critical,” Guharoy said. “It’s a major concern for providers.”