Other Voices

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Assessing the FDA's Safety Drive

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Tim Foley for *Barron's*

ON MARCH 2, 2015, INVESTIGATORS from the U.S. Food and Drug Administration walked into a factory at Zhejiang Hisun Pharmaceutical in China to conduct an inspection. According to the investigators, at one point a lab employee pulled a memory stick from a computer and put it in his pocket. When they asked what he had removed, the man ran away.

The FDA has never been able to piece together what, if any, drug-manufacturing data were on that memory stick. But its removal became one of a long list of significant deviations that FDA investigators observed on recent inspections of foreign drug-manufacturing facilities that would threaten the robustness of the U.S. pharmaceutical supply chain.

FDA officials say they could call into question the safety of the U.S. drug supply. The agency is now taking steps to improve its evaluation of drug-manufacturing facilities not just in the U.S. but abroad.

It is troubling, however, that the FDA has been so delinquent in developing a framework to more objectively assess the strength of quality systems throughout the industry, which could have identified such problems in their infancy, and done so more accurately.

The FDA dramatically increased its focus on foreign inspections after a scandal in 2008, when contaminated raw material for the anticoagulant heparin, sourced from China, was linked to at least 81 deaths and 785 serious injuries. Around the same time, there was a scandal in which human and animal food, mainly from China, was adulterated with the toxic substance melamine.

Many recent drug inspections have revealed egregious manufacturing practices, especially in India and China. The agency has followed up on these inspections by issuing a flurry of warning letters threatening enforcement action if the companies don't rectify the deficiencies in their quality systems.

These letters, which are in the public domain, paint a grim picture of the safety of the drug supply, as a disturbingly large percentage of the facilities in question are alleged to have "data integrity" violations, meaning that the FDA believes that the records kept as evidence of the safety of the manufactured products have been manipulated in some way. This is significant because approximately 40% of drugs sold in the U.S. are made outside the country, as are 80% of the active pharmaceutical ingredients used in these drugs. An increasing fraction of these are sourced from India and China.

Examples of data-integrity problems observed by the FDA at these facilities include the repeated testing of products until they are deemed to meet the threshold specifications (a practice known as "testing into compliance"); the destruction and falsification of laboratory data; the blending of out-of-specification batches of drug product with batches that met specifications; the backdating or predating of lab records; and the failure to implement measures preventing the manipulation, deletion, or overwriting of electronic data.

The FDA's letter warning Zhejiang Hisun included allegations involving several of these practices.

The depth of the quality-control problem over the past few years, particularly with drugs originating in the developing world, is stark. For instance, in 2012 only four warning letters were issued to Indian and Chinese pharmaceutical firms, versus 15 last year. The FDA has alleged data-integrity problems in 13 of those 15 letters. Those letters covered more than 70% of the facilities in the world where the FDA asserted data-integrity violations in 2015.

In addition to the public-health concerns associated with products deemed by the FDA to have been manufactured in serious violation of proper manufacturing practices, these problems threaten to worsen shortages of some drugs. The allegations are disrupting the supply chains of numerous U.S. drug manufacturers.

Case in point: Zhejiang Hisun Pharmaceutical is a linchpin manufacturer, supplying products to dozens of U.S. pharmaceutical companies, including Merck and Pfizer. After the FDA's inspection of Zhejiang Hisun, at least 15 of the company's active pharmaceutical ingredients, or API, were barred by the FDA from entering the U.S., forcing manufacturers in the U.S. to quickly identify alternative suppliers and get them approved by the FDA (which could take many months), or face a shutdown.

The FDA's favorite legal mechanism for barring such drugs from the U.S. is the Import Alert, and it doesn't take much for the FDA to be able to place a firm's products on that list of prohibited imports. A foreign facility's drug products can be refused admission into the U.S. simply if "it appears" that such articles are "adulterated or misbranded" as defined in the Federal Food, Drug and Cosmetic Act.

This threshold would be triggered as a result of virtually any of these problematic good-manufacturing-practice inspections. Furthermore, if the FDA alleges that a firm is in any way delaying, denying, or limiting an inspection, that too can cause the firm's pharmaceutical products to be barred from entering the U.S. Not surprisingly, the actions of Zhejiang Hisun's fleeing lab employee were deemed by the FDA to fall into this category.

Just since the beginning of 2015, 36 drug firms, which export hundreds of drugs to the U.S., have been added to the FDA's Import Alert list; 28 of those facilities were in India or China. Once a firm is on an Import Alert, it can be next to impossible to persuade the FDA to remove it, or its drug product, from that list. Indeed, firms have been known to languish on Import Alert for many years, well after they claim to have performed all of the facility remediation that the FDA has demanded.

While the FDA tries to exclude from Import Alert drugs that are on the shortage list or deemed medically necessary, it is likely that the agency's barring entry to so many of these drugs will eventually lead to more drug shortages, particularly for older generic drugs, which are often manufactured by only two or three FDA-approved facilities worldwide.

If one of those firms ends up on the receiving end of a bad "483," the term used for the FDA's inspectional observations, an Import Alert is likely to strain the U.S. supply of that API or drug product to the breaking point.

And if the FDA decided not to place that facility on Import Alert, it would be allowing products into the U.S. that it alleges were manufactured using falsified data, putting the agency and consumers in a no-win situation.

FDA representatives have long acknowledged publicly that the agency hasn't had an objective method for measuring quality in the drug industry. At which facilities are manufacturing procedures improving? By how much and in what way?

Last year, finally recognizing that one cannot effectively improve what one cannot measure, the agency released a public document on quality metrics. When finalized, it might allow for a comprehensive assessment of quality across the industry. It is based on data submitted to the FDA by drug firms.

The goal is to improve the FDA's evaluation of drug-manufacturing operations; predict scenarios where certain drugs might be at risk for supply disruptions; and better calibrate the agency's new risk-based inspection scheduling, where leading indicators for quality problems would prompt the FDA to inspect some facilities with greater frequency.

Also, the agency's New Inspection Protocol Project, for which no substantive documents have yet been issued, seeks to use semi-quantitative scoring on inspections to allow the FDA to make comparisons among facilities manufacturing similar products. It would also compare the results from within a facility over multiple inspections, with the goal of standardizing the inspection process.

These new FDA programs will take years to completely implement. Stakeholders should participate fully in the public consultation process to make sure that the intended objectives are achieved without imposing an undue burden on industry, and without foisting requirements on pharmaceuticals that exceed the agency's legal authority. Public health in the U.S. is at stake. ■

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