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Remote Methods Drove Most US FDA Enforcement Actions In FY 2021

by Shannon Brown

Product sampling and remote records requests accounted for most import alerts and drug GMP warning letters over the past year – and may play key role post-pandemic.

As remote records reviews conducted during the pandemic begin to account for a growing share of warning letters, experts advise industry to prepare for remote US Food and Drug Administration oversight to continue even after routine site inspections resume and the pandemic recedes.

The FDA, which historically relied solely on site inspections as a basis for drug adulteration warning letters, has only based 28% of warning letters issued in the first 11 months of fiscal year 2021 on site inspections, with 62% based on sample testing and 10% on remote records reviews.

Despite inspections falling by 60% in fiscal year 2020, the FDA issued a record number of import alerts for foreign drug manufacturers that year, using a combination of inspections and alternate tools. (Also see "*Chinese Firm Hit With Pandemic's First Remote-Records-Based FDA Drug GMP Warning Letter*" - Pink Sheet, 27 Jan, 2021.)

The stringent oversight was in part due to safety concerns regarding over-the-counter hand sanitizers, which were frequently found to contain poisonous methanol instead of ethanol. (Also see "*US FDA Adds Hand Sanitizer Import Alert Category After COVID-19 Production Surge Turned Deadly*" - HBW Insight, 18 Sep, 2020.)

A full 84% of hand sanitizer samples from Mexico were found to be adulterated, leading to the FDA's first use of a county/area import alert for drug products; the process is more commonly used in foods. (Also see "*US FDA's First-Ever Countrywide Import Alert For Drugs Bans Mexican Hand Sanitizers*" - Pink Sheet, 29 Jan, 2021.)

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FDA Ups Usage Of Records Requests, Sample Testing

Speaking at the recent Parenteral Drug Administration/FDA Joint Regulatory Conference, Frances Godwin, who heads the FDA Center for Drug Evaluation and Research's oversight of good manufacturing practice compliance, described the agency's shift in regulatory tactics.

In a change from previous years, in which all drug GMP warning letters were based on site inspections, fiscal year 2020 saw two of 79 warning letters based on sample testing and the other 77 based on inspections. The first 11 months of FY 2021 saw 43 of 69 warning letters based on sample testing, 19 from site inspections and seven due to remote records requests, Godwin said.

The FDA issued four more remote records review-based drug adulteration warning letters in September as well as two that were based on sample testing but none based on inspections.

"As the pandemic has caused a shift in international travel and domestic travel and the capability to do inspections, we have seen a resulting shift in the sources of our compliance actions," said Godwin, who is director of the Office of Manufacturing Quality in the CDER Office of Compliance.

The remote records request process was also used in several import alerts, increasing from zero in previous years to two (2%) in FY 2020 and 11 (26%) in the first 11 months of FY 2021. The use of sample testing additionally increased, to 45 (39%) in FY 2020 and 19 (45%) in the first 11 months of FY 2021.

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A Focus On OTC Products

Overall, the FDA issued 102 warning letters for hand sanitizers. Of these, six were based on remote records requests conducted under Section 704(a)(4) of the Food, Drug & Cosmetic Act, enacted as part of the July 2012 FDA Safety and Innovation Act. Eleven of the 12 704(a)(4)-based warning letters were for OTC products such as hand sanitizers, topical pain relievers and *facial serums*.

One warning letter based on a remote records request was issued to an active pharmaceutical ingredient manufacturer; it went to Proquimes S A Productos Quimicos Especializados S.A. in Colombia on 5 April. The organization manufactures "high purity APIs and basic mineral salts for pharmaceutical and food industry," according to its website.

One reason that the warning letters so far have focused on foreign over-the-counter products may be differences in what's being evaluated, Howard Sklamberg, a partner at Arnold and Porter, told the *Pink Sheet*.

For over-the-counter products, "a lot of the compliance work there relates to contaminants and what's in the products as opposed to the type of manufacturing issues FDA looks at for most application products." Good manufacturing practices apply to OTCs as well, but "the more complex products that are harder to manufacture have more complex manufacturing processes and in those situations, FDA is going to want to inspect in person more often," he said.

Concerns About Remote Evaluation

At the PDA/FDA conference, several questions were fielded by the FDA regarding records requests, including one on the risk of the agency misunderstanding the data provided or for a firm to misunderstand an agency request. (Also see "*Can We Talk? US FDA Remote Records Review Missteps Worry Industry*" - Pink Sheet, 19 Nov, 2020.)

In response, Godwin replied that "it's not just zero to 60 with the information provided" and that there are typically "multiple interactions" to clarify concerns before the FDA takes a final action.

Nick Lyons of the FDA's Office of Regulatory Affairs concurred. "We do actually have some follow-up correspondence of communications with the firms to ensure that the question or information we have requested wasn't misconstrued in terms of a language-specific issue," said Lyons, who is the director of compliance in ORA's Office of Pharmaceutical Quality Operations. (Also see "*US FDA To Share Remote Assessment Findings And Mull Replies Before Issuing Complete Responses*" - Pink Sheet, 1 Feb, 2021.)

Sklamberg believes that in some ways, remote records requests are not widely different from inspections.

"After an inspection where there's a warning letter, the warning letter is often based on records. And those records could have been obtained or looked at prior to the inspection," he told the *Pink Sheet*. In fact, if you go to a site as an investigator, wait for records to be compiled, and have to read them right there, that makes the inspection take longer and you're less prepared, he noted.

From a regulatory perspective, a limitation for these types of inspections is the area of

unannounced inspections, Sklamberg said. Many surveillance inspections and for-cause inspections are unannounced or on short notice, he pointed out.

However, for preapproval inspections where the company knows it's going to be inspected, "I think these are going to continue to play an important role," he said.

"And then if FDA finds a big problem through records, it can either issue a warning letter based on records alone, or it can then go and do an inspection, which I think you'll see more often in the future," Sklamberg added.

Remote Evaluations Could Continue For Foreseeable Future

Also speaking at the PDA/FDA conference, Douglas Throckmorton, deputy director for regulatory programs, said that the FDA would continue to use alternative evaluation methods, including 704(a)(4) records requests and information obtained from other regulatory authorities through mutual recognition agreements with the EU and the UK and confidentiality agreements with other regulatory authorities, as well as remote interactive evaluations.

Sklamberg thinks the use of remote methods will continue even as physical inspections resume, because "for one thing, though FDA has increased its domestic inspections, foreign inspections are still hard to do in person because of COVID-19. Second, even when foreign inspections become more possible, obtaining records for foreign inspections just makes the inspection more efficient," he said.

"I think the pandemic made FDA think about how to use tools like 704(a)(4) more often, and how to use and develop new tools. I think what's going to happen is even as inspections come online, they're going to continue to use some of the new tools they developed," Sklamberg said. "I think both the agency and industry have an incentive to make the 704(a)(4) records request process work, because both the agency and industry want inspections to be more efficient."