FDA Inspections Remain Stalled During the COVID-19 Pandemic

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FDA is relying on other global inspection reports and remote document review, yet does not consider them equivalent to on-site inspections. Manufacturers await more clarity.

Despite limitations posed by the COVID-19 pandemic, FDA has continued to oversee bio/pharma operations, issuing warning letters and, occasionally, 483s (**Sidebar**), and perform plant inspections prioritized based on risk. In March 2020, the agency had postponed routine site surveillance inspections, resuming them four months later for "mission-critical inspections" (e.g., those required to approve potential COVID-19 therapies or vaccines, critical drugs that are in short supply, and novel drugs developed for serious conditions on fast-track approval), and issued guidance (1) on the subject.

Between March and October 2020, the agency conducted more than 200 such inspections, Judith A. McMeekin, associate commissioner for regulatory affairs with FDA's Office of Regulatory Affairs, told attendees at the Food and Drug Law Institute's (FDLI's) annual conference on October 6, 2020 (2).

However, based on FDA 483 inspection data for the fiscal year, between Oct. 1, 2019 and Sept. 30, 2020, FDA conducted only 28 biologics plant inspections in 2020, compared with 116 the year before, and 349 drug facility inspections vs. 779 in 2019 (3,4). The lower inspection numbers in 2020 also reflect five months before COVID-19 travel restrictions prevented the agency from conducting inspections.

In lieu of onsite inspections, FDA is taking a number of different approaches, including document review (permitted under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act), before or in place of onsite inspections, McMeekin said. The agency is also leveraging inspection reports from other global regulatory authorities, under the Pharmaceutical Annex to the US/EU Mutual Recognition Agreement.

Data dump vs. communication

Well before the pandemic—in fact, for decades now—FDA has emphasized the importance of drug developers communicating with reviewers and inspectors at the agency. "Clearly, if one is a sponsor in need of a pre-approval or pre-license inspection, being in regular contact with the people at FDA who will be making decisions on your application is key, and should extend all the way up the chain of command if necessary," says Mark I. Schwartz, director at the Washington, D.C.-based law firm, Hyman, Phelps, & McNamara, P.C. Schwartz spent 13 years at FDA, and left five years ago as deputy director of the agency's Office of Compliance and Biologics Quality.

FDA's new remote document review process has underscored the need for sponsor outreach and communication with the agency. Recent examples have shown what can happen when FDA reviews documents remotely, without sufficient context. "The biggest mistake a company can make is throwing things over the wall to FDA. It's up to the owners of the documentation to put it into context for the regulators, requesting a meeting to discuss issues with them," says Peter Miller, President/CEO of Dynamic Compliance Solutions (DCS), which offers a platform designed to help pharma companies handle remote audits.

In October, for example, Alkermes received a complete response letter (CRL) from FDA due to tablet coating issues with its new schizophrenia treatment ALKS 3831. Only after the company received the CRL did it discover that FDA was concerned about the tablet coating process that had been used to make development batches. The firm had reportedly resolved these issues for manufacturing-scale batches (5).

"In instances where FDA requests documents, it is very important to suggest a call with FDA prior to sending the documents, to at least give an overview of

any nuances within the documents that exist," says Schwartz. Recalling working on the "other side" on inspections while at FDA, he says, "One is constantly seeking input from subject matter experts at the facility regarding arcane issues in the company's records. That connection is completely lacking if the firm just dumps the documents on FDA, and it can lead to misunderstandings with tragic consequences for the firm," he says.

So far, FDA has been reluctant to approve use of technologies such as 360-degree video (6) to perform remote site tours and inspections. However, regulators—including the European Medicines Agency (EMA), the UK's Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada, the Therapeutic Goods Administration (TGA) of Australia, Japan's Pharmaceutical and Medical Devices Agency, and the Russian Ministry of Health—are all using some forms of remote technology for remote inspections (7).

FDA piloting use of video

McMeekin reported in October 2020 (2) that the agency had begun to pilot the use of new technologies such as live or recorded video in food-related investigations. "As we learn more from the pilot and decide how and when we might use these and other technologies, we commit to having transparent dialogues with regulated industry as to how this may affect our procedures in the future," she said (2). However, FDA remains cautious about their use in pharmaceutical inspections. "The agency is exploring all options for evaluating facilities when a physical inspection is not feasible, [and] is assessing the potential use of other tools to serve as supplements to FDA inspections, including remotely evaluating pharmaceutical manufacturing operations, using remote live-streamed video and other remote and live interactions with facility operators and records," Charles Kohler, press officer with FDA's Center for Drug Evaluation and Research (CDER) stated in a written response to *Pharmaceutical Technology* in December 2020.

Some question whether the agency is moving quickly enough to approve the use of supplemental technology for drug and biologics inspections. In the title of an op-ed that was published in December 2020 (8), Schwartz accused FDA of 'fiddling while pharma burns.' "It's difficult to understand the agency's position, but it's certainly not helpful," he says. Schwartz argues that FDA's stance against using new technologies for remote inspections has left patients without access to potentially life-saving therapies in 2020. As an example, he cites the agency's failure to approve Bristol Myers Squibb's (BMS) lymphoma treatment, the chimeric antigen receptor T cell (CAR-T) therapy, liso-cel. This approval delay, the second so far for the drug, happened in November 2020, when a local flare-up of COVID-19 in Texas prevented FDA investigators from traveling safely to BMS's contract manufacturing partner's (Lonza's) facility for an on-site inspection. The postponement occurred, even though liso-cel met FDA's criteria of a 'mission critical' inspection, in that the therapy had been granted breakthrough therapy and regenerative medicine advanced therapy designations, he says.

Observers see a real need for timely pre-approval and pre-licensing inspections (PAIs and PLIs).

Schwartz also notes that there is a "real need" for timely pre-approval and pre-license inspections (PAIs and PLIs). "Companies' livelihoods—and in some cases, their very survival—depend on it," he says. It's also crucial that FDA find a solution for non-mission-critical inspections, he says, since only a tiny fraction of the inspections that need to be performed have been deemed mission critical by FDA. "While the agency has been performing some record reviews, FDA is unwilling to overturn a facility's Official Action Indicated (OAI) status based on a record review, so even if a firm's records demonstrate full CGMP [current good manufacturing practice] compliance, it won't overturn a previous problematic finding. FDA has also been ambiguous as to whether foreign regulatory reports can overturn a previous problematic FDA finding," he says, leaving pharmaceutical firms with few good options.

The vast majority of facilities are still waiting for FDA to explain how the agency will determine their CGMP compliance status, Schwartz says. The situation is bad enough for companies submitting new drug applications (NDAs) and biologics license applications (BLAs), but it's horrific for companies with OAI status. "FDA is basically telling them that they cannot improve their regulatory status until the pandemic ends. This essentially means that OAI facilities cannot be listed as API or finished dosage form manufacturers in new NDAs, ANDAs [abbreviated new drug applications], or BLAs," he says, "so they cannot get these applications approved for the foreseeable future."

The perfect as the enemy of the good

Schwartz has asked FDA for a breakdown of how the agency is performing inspections but hasn't received a response so far. He senses that the agency's leaders are concerned that the technology won't offer a complete view of what's going on in a facility. As a result, he says,"They have failed to heed the truism of not letting the perfect be the enemy of the good, or the good enough, as the case may be."

No inspection, even when it's onsite, can really offer a complete view of what's going on, Schwartz explains. "All inspections, whether remote or on-site, are only a snapshot into the firms' CGMP compliance status. In a one-week onsite inspection, investigators can only really see certain portions of the facility, certain activities and manufacturing practices, and review a finite number of records. In practice, you're limited to a set amount of time which limits what you can discover about the CGMP practices at the facil-

ity," Schwartz says. It's crucial for both regulators and companies to know that using technology in remote inspections can work, but won't be perfectly equivalent to an on-site visit, Anne Miller, senior counsel for Medtronic said during a panel discussion on remote inspections at FDLI's December meeting (7). "Regardless of the purpose of the remote audit, as an inspection by a regulator or a proactive site visit as a part of a sponsor's compliance program, it's not just about accepting the latest technology, but how effective the audits are in the end, which is based on completeness and consistency," says Miller of DCS. His company is working with the Parenteral Drug Association (PDA) to help establish best practices for auditors and auditees during remote audits.

A question of semantics

The fact that US legislation has often been interpreted as requiring that agency inspectors be physically present on site may be slowing FDA's use of remote technologies for inspections. A simple solution is broadening or redefining what "on site" means, says Miller. Coming up with the best definition will likely require working with industry partners, through groups such as PDA and the International Society of Pharmaceutical Engineering (ISPE). "Guidance from FDA on the use of these technologies isn't likely to come any time soon. It would likely be more productive to have industry stakeholders identify requirements," he says, noting that PDA is hosting a virtual conference in January 2021 to define some of these issues.

There are also some pre-requisites for any kind of remote inspection process to be considered effective. First, the facility tour must be interactive in real time and the auditor needs to be in control of what he or she is looking at, says Miller. In addition, no modifications or augmentations to the environment can be allowed, he says, and most companies don't want anything to be recorded in video or photos.

At a special panel on remote inspections at FDLI's December 2020 conference, Stephanie Haggerty, senior counsel at Pfizer, discussed the company's experience with remote inspections during the COVID-19 pandemic (7). "There are growing pains on both sides," she acknowledged, although she expects new technology to play a greater role in the future. The company had anticipated more than 20 FDA GMP inspections in 2020, she said, but did not have any onsite inspections from February through December, and all good clinical practice (GCP) inspections were in person in the US in 2020, she said.

Haggerty discussed FDA's requirements for documentation using FDA's Inspection Records Request Form 4003, which requires that inspected companies provide extensive lists of deviations, recalls, and lab events. "Pfizer sites have had to make over 30 submissions in order to complete each request," she said, and translations can double the volume of submissions.

In addition, there are size limits to what FDA can receive, requiring that responses be broken down into as many as 30 to 50 pieces, she said. Pfizer has not received requests from FDA for virtual inspections, but has had a number of them with other global agencies, Haggerty said, emphasizing that pre-inspection discussions must carefully consider such details as time zone differences when coordinating the timing of reviews and interviews.

For audits of suppliers and contract partners, smaller companies are becoming more comfortable with the remote approach, although many professionals recognize that it may not be the best way long term and its use will depend on the situation involved. "A big part of any audit, whether remote or onsite, is document reviews, and as long as there is a way to share document securely, remote audits work well for now" says Joelle Yang, head of HBT Labs' quality group. "When the pandemic is over, I am still planning to focus on onsite audits, because it is not clear how FDA will respond to remote audits for critical suppliers (e.g., for contract development and manufacturing organizations and API suppliers). But, for non-critical suppliers, remote audits work well," she says.

References

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Warning Letters Cite Inadequate Validation and OOS Event Analysis

Between Oct. 1, 2019 and Sept. 30, 2020, FDA issued 28 warning letters to biologics manufacturers and 349 to drug manufacturers (1). Echoing past years, the top four problem areas, according to FDA, included inadequacy in: defining quality unit responsibilities; reviewing batch failures; implementing and following lab and sampling procedures and written procedures; determining the root cause of out-of-specification (OOS) events; and establishing process and cleaning validation practices.

Water system and other maintenance problems figured in a number of inspection reports. One Canadian manufacturer of over-the-counter medications was cited for many of these problems, including lack of process validation or cleaning validation procedures; lack of stability data; failure to test incoming raw materials; inadequately outlined quality unit responsibilities; and water systems issues.

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