FDA Touts Wider Use of Remote Inspection Tools, But Questions Linger

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As the FDA tries to navigate the COVID-19 pandemic and keep up with pharma inspections, the agency touts its expanding use of remote tools such as teleconferences and livestreaming video of operations. The FDA says it is making records requests ahead of inspections to limit the amount of time spent on-site at manufacturing facilities and awaiting input from its new council that was launched in July on how to prioritize the implementation of new technologies for inspections.

The FDA is “doing as much as we can…in as many places as we can,” agency spokesperson Jeremy Kahn said in an Oct. 4 phone interview. He says the agency “is exploring all options for evaluating facilities when a physical inspection is not feasible.” In situations where the FDA determines that an inspection is necessary, he says, so-called remote regulatory assessment tools “create a bridge” until an on-site inspection can be conducted.

Overall, Kahn asserts that the FDA, after a lull at the pandemic's start in early 2020, has maintained timely reviews of "mission critical" applications for drugs and biological products by prioritizing inspections amid pandemic-related travel restrictions, quarantines and other challenges.

Industry lawyer Mark Schwartz, a former high-ranking FDA official, begs to differ. He tells AIS Health, a division of MMIT, that there remains a heavy inspection "backlog" (a term that Kahn says the FDA dislikes using) that is causing some pharma companies to feel left in the lurch at times. He says there seems to be far less use of remote tools than the FDA is touting and scant transparency on how the agency is managing its inspection workload. And long after the U.S. Government Accountability Office (GAO) blasted the FDA in a June 2020 report on how the pandemic has added a layer of complexity to an "already challenged" FDA foreign inspection program, Schwartz says some of his clients continue to report delays both overseas and in the U.S.

Moreover, Schwartz asserts that the council set up by the FDA to manage inspection issues is unlikely to create meaningful reforms without a new mandate. Nor does he see various pieces of recent FDA guidance on inspections "as doing much to change dynamics on the ground, catching up and remediating the backlog."

"It's unfortunate. The agency started going full bore in the springtime, certainly domestically and in some countries overseas. But with the delta variant, [the FDA] started pulling back again," says Schwartz, a director in the Washington, D.C., office of Hyman, Phelps & McNamara, which is the largest dedicated FDA law firm in the U.S.

Schwartz, former deputy director for the Office of Compliance and Biologics Quality in the FDA's Center for Biologics Evaluation and Research (CBER), says he has several clients requiring pre-approval inspections by the FDA on their products, "and these are stalled again — not completely, but it depends on the region."

As Kahn explains it, the FDA conducts a risk-based determination for each regulatory submission on whether an inspection is needed to support the submission. The agency is "utilizing alternative oversight approaches, where possible, to mitigate the need for inspections during the COVID-19 pandemic." The alternative tools described in FDA's guidance for industry, "Manufacturing, Supply Chain, and Drug and Biological Inspections During COVID-19 Public Health Emergency Questions and Answers," first released in August 2020 and updated in May 2021, are being used to facilitate remote

assessments of facilities if an inspection cannot be conducted.

The agency is using so-called "remote interactive evaluations" as one of these alternative tools, as described in guidance issued in April 2021, "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency."

"A remote interactive evaluation is not the same as an inspection as described in section 704(a)(1) of the FD&C Act," Kahn explains. "As discussed in this guidance, FDA will use existing risk management methods and related tools to determine when to request a facility's participation in a remote evaluation."

Schwartz notes that the FDA's April guidance, outlining its intent to use voluntary remote interactive evaluations at drug manufacturing facilities, says that when such an evaluation is completed, the agency will meet with the facility's management and typically present a written list of observations and discuss them. But this written list of observations "will not be a final Agency action or decision. FDA will not issue a Form FDA 483," the document concludes.

The agency "doesn't issue a typical form 483," Schwartz says, "so it's not exactly in place of an on-site inspection." As a practical matter, Schwartz adds: "I haven't heard much about remote evaluations." In fact, he says, one client company was told by CBER only a few weeks ago, in August 2021, that it would be involved in the center's first remote interactive evaluation.

Schwartz says the FDA views its "remote interactive evaluations" as being "virtual inspections," which the European Medicines Agency (EMA), along with other foreign regulatory entities such as Health Canada, approved as far back as the spring of 2020 in response to the first throes of the pandemic.

But Andrew Powaleny, a spokesperson for the Pharmaceutical Research and Manufacturers of America (PhRMA), draws a distinction. He says that PhRMA applauds the FDA for adapting to pandemic challenges and describing alternative tools, such as remote interactive evaluations, in its guidance that "the agency may utilize to assess manufacturing facilities."

However, PhRMA wants the FDA to "expand its use of alternative tools" to ensure timely assessments of manufacturing facilities and the delivery of new, innovative treatments. "In particular, we recommend that FDA establish a framework for (i.e., issue interim

“In particular, we recommend that FDA establish a framework for (i.e., issue interim guidance) and begin conducting virtual inspections with the consent of the inspected manufacturer,” he says.

As things now stand, “the backlog appears to remain huge,” Schwartz asserts, noting there were virtually no foreign inspections by the FDA for the first 12 months of COVID-19 despite “a rolling, continuous need” as facilities continue to operate, and new ones are cropping up. “It’s hard to know with certainty, but my sense is that they’re not being totally transparent with the numbers of applications not being approved because of inability to visit the site,” he says. “Anecdotally, I know over the past year-and-a-half, there have been applications deferred, and the only outstanding issue was the inability to go to the facility and inspect.”

Schwartz further explains that the FDA typically spends 10 to 12 months reviewing a pharma company’s entire application, and if regulators find clinical problems, “failing to go to the facility is moot because regardless there were other (non-manufacturing) deficiencies — and they’ve issued plenty of those.”

“And with many of my clients,” he continues, “the agency has not issued a CRL [i.e., complete response letter], but says, ‘We are deferring action on the application because we were unable to visit the facility and determine GMP [i.e., good manufacturing practices] compliance.’”

“They seem to deny that there are delays,” he says. “I have several clients who have been told there is nothing left in their application to review, but they haven’t been inspected yet, [so the FDA says] ‘We can’t give an answer on the application.’”

“In spring [2021], one of my clients had a delay of their inspection in California, and action was deferred,” Schwartz says. He adds that he has “found it exceedingly frustrating” to get information from the FDA.

Inability to Inspect Spurs Delays

For his part, Kahn stresses that the FDA has not been issuing CRLs for some drugs solely because regulators cannot physically inspect manufacturing facilities during the pandemic due to travel restrictions. (CRLs note that the agency’s initial review of an application is complete, but the agency cannot approve the application in its present form.)

Instead, the FDA is taking complete response actions "when there are deficiencies identified during the application assessment," says Kahn. "A pending inspection is not considered a deficiency and therefore would not be the sole reason for a complete response. In this case, an application goal date may be extended."

"However, to date," he says, "we have not denied, and do not intend to deny, approval of a product application solely because we have been unable to complete a domestic pre-approval inspection of a manufacturing facility due to the COVID-19 pandemic."

Yet Kahn acknowledges the agency has been deferring action on certain applications due to unfeasible on-site inspections. "In the event an inspection of a manufacturing facility is needed but cannot be completed by the goal date," he says, "the agency's current practice is to miss the goal date until the inspection can be completed, unless there are other application review issues that need to be addressed by the application sponsor." He notes that this policy has been in place since June 2020.

FDA Points to User Fee Metrics

Kahn provided a statement to AIS Health to clarify the agency's overarching goals.

"The FDA is not falling behind on taking action on drug applications," he said in the statement. "The agency recently performed an analysis of user fee metrics across our prescription drug and generic drug programs that demonstrate the FDA has been able to take on-time actions to evaluate and close out these drug applications more than 90% of the time, meeting our review program performance levels."

"We continue to prioritize meeting our user fee commitments while maintaining our high standards and responsibility to the public health and the safety of our staff," he says.

When the pandemic first hit, the FDA said it was temporarily postponing all domestic and foreign routine surveillance facility inspections, as outlined in its guidance on manufacturing inspections issued in August 2020 and updated in May 2021.

In late July 2020, the FDA began using its own COVID-19 advisory rating system to determine what regulatory activities could occur in a given geographic region. The agency said it would continue to conduct "mission critical" inspections, and resume prioritized domestic inspections — including preapproval, pre-license, surveillance and for-cause inspections — in safe regions.

In May the FDA also unveiled its "roadmap on inspections" that outlines how the agency plans to inspect and assess companies during the pandemic. The report provided data on its inspections during COVID-19 and its plan to move toward "a more consistent state of operations."

Amid ongoing pandemic restrictions, the FDA intends to continue using alternative tools, when appropriate, to evaluate facilities, the guidance says. FDA spokesperson Kahn says that with respect to evaluating facilities for product applications pending marketing approval, the agency intends to continue using other tools and approaches where possible, "including requesting existing inspection reports from other trusted foreign regulatory partners through mutual recognition and confidentiality agreements, requesting information from applicants, and requesting records and other information directly from facilities and other inspected entities."

From March 2020 through March 2021, the FDA said a total of 821 mission-critical inspections were done on a case-by-case basis to ensure the compliance of regulated pharma products, including 29 urgent inspections in foreign countries. At that time the FDA had conducted 777 prioritized domestic inspections since resumption of that work in July 2020.

Domestic travel is now open, but foreign travel remains problematic in places with high levels of virus, Kahn says, which is requiring the FDA to continue focusing on "mission critical" surveillance inspections or product approvals.

Of 13,500-plus applications for medical product approval or authorization received since March 2020, roughly 68 applications were delayed due to the inability to conduct inspections — and a majority of those were not deemed mission critical, the FDA said.

In July, the FDA Inspectional Affairs Council (FIAC) was officially launched. Currently, Kahn says, the council, though "very early on" in its work, is "reviewing and prioritizing inspectional initiatives to create action plans for future implementation."

"The council will provide insight and strategies on types of new technologies that can be implemented and how the FDA can optimize our inspection processes," he says.

FDA Cites Use of Remote Tools

Kahn points out the difference between routine surveillance inspections — in which

Kahn points out the difference between routine surveillance inspections — in which "not every facility is inspected every year," depending on level of risk — and product approvals. Historically, only about 20% of product approvals warrant in-person pre-approval inspection (PAI) by the FDA in order to begin manufacturing, he notes. "For the subset where a pre-approval inspection is normally required, we've used alternative tools to act on the majority of these applications on time," he explains.

Sometimes remote tools are all that is needed to get surveillance or PAIs done, he explains, but sometimes more information is needed.

"As a result of utilizing alternative tools, CDER [i.e., FDA's Center for Drug Evaluation and Research] completed facility assessments to meet user fee agreement dates by reducing the need to conduct [on-site] PAIs [roughly] 50% of the time since the start of the pandemic," Kahn tells AIS Health. He adds that the FDA has also "enhanced the sampling and testing of drugs being marketed."

Clear Presentation is Crucial

Industry consultant Alan Greathouse stresses that in such a regulatory environment without as much face-to-face interaction, it is incumbent upon pharma manufacturers to excel in their presentation. "It's much more imperative that the information provided [from the company to the FDA] is extremely thorough and well put-together," he says.

Greathouse, senior director of quality and service assurance with The FDA Group, a consulting group that assists organizations in filing various regulatory pathway applications and handling remediation efforts, notes that the FDA's own data dashboard shows a definite drop-off in inspections: 392 domestic and 29 foreign drug inspections thus far in 2021, compared with 760 domestic and 472 foreign inspections in 2020, the pandemic's first year. That's down from roughly 1,500 domestic inspections annually since 2009.

Citing the decline, Greathouse says, "but I haven't had folks calling me, really concerned that their application has taken significantly more time." Yet he acknowledges that when the pandemic first hit, initial inspection postponements "pushed things back months." Since then, though, "they've done a fairly good job of establishing remote inspections."

Greathouse says his firm is changing its own model as the FDA is changing its model. "Pre-pandemic, a lot of our audits were done on-site," he says, but now more audits are

being done remotely at less cost for travel and less need to adhere to standard business hours, "so it's been fairly smooth from my perspective."

"We probably do work with 50 to 60-plus organizations currently, and none have raised concerns that FDA practices are holding them up," Greathouse says.

Yet executives at Revance, Inc., have a different take, telling AIS Health that the "FDA delay has placed Revance in a holding pattern."

Mark Foley, Revance's president and CEO, told Politico in March that the biotech company had anticipated the FDA's approval in November 2020 for the use of its lead investigational drug candidate, daxibotulinumtoxinA, an injectable neuromodulator product, in treating frown lines. But pandemic restrictions led to a delay in the FDA's inspection of the biotech company's manufacturing facility in California.

According to Revance's second-quarter earnings report on Aug. 5, the FDA initiated its pre-approval inspection of the company's manufacturing facility in June. A Revance executive gave an update in an Oct. 4 email, saying the company continues to anticipate the approval of its lead product by the end of 2021, "as the FDA has not indicated there are any other review issues at this time." In the meantime, Revance has been "actively building inventory, advancing our commercial launch plans and refining educational and training materials," the executive said.

"As this is Revance's first drug approval, remote inspection was not a possibility," the company executive added, noting the biotech company is also evaluating its product for two therapeutic indications: cervical dystonia and adult upper limb spasticity. Revance plans to file a supplemental biologics license application for its product's use in treating cervical dystonia, which causes painful muscle contractions in the neck, in 2022.

Does FDA Suggest 'Lasting' Shift?

In late August, the FDA published its Prescription Drug User Fee Act (PDUFA) VII goals letter for fiscal years 2023 to 2027, concerning the seventh reauthorization of the prescription drug user fee program. It mentions advancing the use of alternative tools for manufacturing and product quality reviews. A Sept. 21 blog on the document written by two of Schwartz's colleagues at Hyman, Phelps & McNamara cites a potentially "lasting impact" of the COVID-19 pandemic on inspections.

"When travel restrictions and public health precautions halt facilities inspections, many

sponsors are left wondering how FDA will complete pre-approval inspections and meet their products' respective PDUFA dates," authors Charles Raver and James E. Valentine say. "In response, FDA memorialized its intention to use some of the new tools explored during the pandemic and potentially make them more permanent fixtures of facility inspections (e.g., requesting records in lieu of an inspection, use of information shared by trusted foreign regulatory partners)."

However, the blog continues, the FDA's plan to use new tools in facilities' inspections may be "welcome news" to companies whose PDUFA dates were extended due to a pending inspection during the pandemic, but "a far more disappointing consequence of the pandemic" is also apparent in the agency's goals letter.

"FDA appears to be more readily equating in-person with virtual (videoconference) face-to-face meetings," the authors say. "Several small textual changes as well as a footnote buried amidst the meetings goals show FDA using 'face-to-face' meetings to mean both in-person and virtual platforms." But in-person meetings create important opportunities for building rapport, and lead to more robust dialogue and collegial relationships between the FDA and regulated companies, the bloggers say, expressing the hope that such a broad interpretation of face-to-face meetings "will merely be an artifact when the pandemic risks subside," hopefully before the reauthorization ends in 2027.

In the end, Schwartz notes that he has had "some measure of success" on timely review for certain clients during the pandemic, possibly because "those applications for those biologics or drugs met FDA's amorphous definition of 'mission critical' products — though several other clients with analogous products are waiting endlessly for pre-approval inspections months after their PDUFA dates have passed."

Contact Schwartz at mschwartz@hpm.com, Greathouse at agreathouse@thefdagroup.com and PhRMA's Powaleny at apowaleny@phrma.org. The FDA's Kahn says product sponsors and manufacturers with questions may contact CDER-OPQ-Inquiries@fda.hhs.gov.

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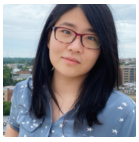

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