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Remote Site Visits Will Help US FDA Keep Reviews On Track During Remainder Of Pandemic

by Bowman Cox

Video facility tours expected to help clear way for timely drug and biologic approvals while COVID-19 still prevents inspections.

As the pandemic continues, the US Food and Drug Administration will rely selectively on virtual site visits to help it make timely approval and licensing decisions, though usually not to confirm post-warning letter corrective actions, the agency said 14 April in eagerly awaited *guidance* on what are generically called virtual inspections, but which it terms "remote interactive evaluations."

The ability to make decisions based on remote interactive evaluations is an important tool that counterparts like the European Medicines Agency and the UK Medicines and Healthcare products Regulatory Agency have been using since early in the pandemic. (Also see "*UK MHRA Relies On Remote Drug GMP Inspections As COVID-19 Pandemic Grounds Inspectors*" - Pink Sheet, 16 Jul, 2020.)

The US agency has been missing user fee goal dates in cases where it has no information about manufacturing facilities referenced in applications – and it has been issuing complete response letters in cases where it has negative information about facilities it cannot inspect due to COVID-19-related travel

KEY POINTS

Don't call us, we'll call you. Facilities must be prepared to host remote interactive

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restrictions. (Also see "*Complete Response Letters In Lieu Of Inspections: What To Expect During COVID-19*" - Pink Sheet, 19 Aug, 2020.)

Site inspections continue to be constrained by the pandemic; the agency is only conducting mission-critical inspections and high-priority domestic inspections.

The remote interactive evaluations "should help FDA operate within normal timeframes," the guidance document says, adding that the agency intends to rely on information from these evaluations to meet user fee commitments.

The FDA will consider responses to observations from remote pre-approval and pre-license evaluations during the current review cycle if received within 15 days. Otherwise if there is a complete response, it will consider them in the next review cycle.

evaluations if the FDA requests them, and that includes being ready to interact with the agency's technology platforms and having a strong wi-fi signal throughout the facility, even in those trouble spots they might wish investigators would pass by.

A commitment to new products. The FDA will use remote evaluations to help meet user fee commitments for regulatory reviews.

Data integrity caveat. You may not get the call if your plant has demonstrated poor data integrity.

Post-warning letter remediation. Unfortunately, the remote evaluations may not help much when it comes to checking whether companies have fixed problems raised in warning letters – that will usually require site visits.

The Process Starts With Agency Requests

The FDA says it may issue requests to conduct remote interactive evaluations in any of its drug inspection programs, including for pre-approval inspections, pre-license inspections, post-approval inspections (for post-approval changes), surveillance inspections of API and drug product manufacturing facilities and outsourcing facilities, and follow-up and compliance inspections to look into concerns raised by defect reports, informants, and violative activities discovered during inspections of other facilities, and inspections to assess corrective actions taken in response to warning letters or regulatory meetings.

Although industry has been clamoring to host virtual FDA visits, the agency made clear that it will not accept sponsor requests for remote interactive evaluations. The reason: a request-based program would be too burdensome on everyone involved, given the factors involved in the decision process, some of which the applicant or facility would not know.

For example, the FDA is unlikely to offer such evaluations in cases where the facility has demonstrated poor data integrity.

If it wants to conduct a remote interactive evaluation, the agency will contact the facility or its US agent by phone or email. If the facility agrees to it, planning interactions would follow.

The guidance warns that if facilities do not agree to remote interactive evaluations of relevant clinical trials or manufacturing facilities, the FDA may not be able to make timely decisions on pending applications.

Required Preparations

The guidance document provides a list of topics around logistics, responsibilities and expectations that the agency may want to discuss in a brief virtual meeting with site officials once they have confirmed their willingness and ability to host a remote visit.

They would go over objectives, scope, meet personnel, schedule interactions, set expectations, address time zone differences, any translation services needed and document sharing processes as well as verification of signal strength throughout the facility sufficient to support livestreaming video and audio.

The Evaluation Process

The FDA expects the same type of cooperation during evaluations as during site inspections in terms of, for example, staff availability and operating status of the facility.

For security reasons, the agency will use its own IT platforms and equipment to host virtual interactions, which currently are Microsoft Teams, Zoom for Government and Adobe Connect.

By the same token, the facilities will have to use their own equipment.

The agency aims to request and review most documents prior to the remote visits but will ask to see some during the remote evaluations. Facilities would need to be able to provide those electronically or screenshare them. If they are paper documents, the company would need to be ready to share them as scanned, searchable pdf files.

Footnotes point out that FD&C Act Section 704(a)(4) provides that remote records assessment information requests are mandatory, while requests made during remote interactive evaluations are voluntary.

Bioresearch Monitoring From Afar

The guidance also applies to bioresearch monitoring, or BIMO, inspections – even though FDA

remote records assessments do not.

The BIMO program monitors FDA-regulated research to ensure the rights, safety and welfare of research subjects, and to verify the accuracy, reliability and integrity of clinical and non-clinical trial data.

Sponsors have run into difficulties during the pandemic due to the FDA's inability to inspect many research sites.

Much Like An Inspection

For remote interactive evaluations, the FDA will not use the Form 482 that investigators present at the beginning of site inspections or the Form 483 they present at the end when there are observations to report.

However, the evaluation process will in many ways mirror the inspection process.

There will be closeout meetings with facility management upon completion of the remote interactive evaluations during which the FDA will generally present a written list of observations, if any. The agency will also provide a remote interactive evaluation report to the facility. The list and the evaluation report may be subject to disclosure under the Freedom of Information Act.

Although there will be no Form 483 report and the list will not be a final agency action or decision, the agency will encourage facilities to respond during the closeout discussion and in writing within 15 days, just as for Form 483 observations.

The FDA says it may use these evaluations to support application approvals and enforcement actions like warning letters – and to justify follow-up inspections.

Additionally, if the remote evaluation is meant to supplement a scheduled inspection, the agency would generally combine observations from both into a Form 483 report.

Guidance Was Joint Effort

The agency's Center for Drug Evaluation and Research prepared the guidance document with input from the agency's biologics and veterinary medicine centers as well as from its Office of Regulatory Affairs.

The guidance reflects what the FDA has learned in recent months by pilot testing video site tours, screensharing and other interactive technologies for oversight of manufacturing quality.

The guidance document remains in force during the COVID-19 public health emergency. The agency encourages industry to *file comments* any time at *docket number FDA-2020-D-1136*.