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03 May 2021 | **Analysis**

World's Pharmaceutical Inspectorates Prepare For Post-Pandemic Remote Site Assessments

by Bowman Cox

US, EU, global authorities share experiences, insights, advice for industry on remote alternatives even after inspectors can resume travels.

Regulatory authorities say they are likely to keep using remote alternatives to site inspections even after post-pandemic travel resumes, but for different reasons and probably to different degrees.

Importantly, they are working to align their approaches to remote inspection alternatives like video tours and screensharing, which became popular after suspension of most travel in March 2020.

These developments suggest that drug makers will continue to benefit from investments they have made in facilities, equipment and procedures for hosting live remote interactions with regulatory authorities, but that they may need to refine their hosting capabilities as they gain experience and as global regulators' approaches evolve.

There are two main international collaboration efforts to watch. The International Coalition of Medicines Regulatory Authorities, or ICMRA, has established a working group on digitalization of inspections and the Pharmaceutical Inspection Cooperation Scheme, or PIC/S, will establish one soon.

US and European authorities shared their latest thinking on the topic during a virtual 28 April International Society for Pharmaceutical Engineering regulatory summit.

US FDA Preparing Evaluation Template

Alonza Cruse, director of the Office of Pharmaceutical Quality Operations in the US Food and

Drug Administration's Office of Regulatory Affairs, said the FDA is working quickly to develop a template for remote interactive evaluations and hopes to harmonize its approach with those of other regulatory authorities to make for "seamless" interactions for the international pharmaceutical manufacturing community.

The agency issued guidance on 14 April spelling out its approach to what it calls remote interactive evaluations and European authorities call distant assessments. (Also see "*Remote Site Visits Will Help US FDA Keep Reviews On Track During Remainder Of Pandemic*" - Pink Sheet, 14 Apr, 2021.)

Will the FDA return to an onsite inspections-only approach after the public health emergency is over? "Looking into my crystal ball, I would say no," Cruse said.

There is no going back now that the agency has expanded its toolkit, he said. Rather, the question will be how the agency incorporates the new tools into its oversight process.

He explained that the agency may use alternative tools like remote evaluations to decide whether a facility named in a pending application is acceptable, or decide on the scope and timing of a surveillance inspection, or to determine whether a for-cause inspection is needed because of a defect report.

Not The First Tool In EMA's Toolbox

Brendan Cuddy, lead scientific officer for the European Medicines Agency's Clinical Studies and Manufacturing Taskforce, said EMA views distant assessments as a type of inspection that can be used as a basis for granting GMP certificates, but cannot replace on-site inspections.

Cuddy chairs the EMA's GMP/GDP Inspectors Working Group, which provided some initial *guidance* on use of distant assessments during the pandemic on 10 April 2020 and more detailed *guidance* on 15 October 2020. (Also see "*EU Allows Pharma To Temporarily Prioritize Reporting For COVID-19 Adverse Events*" - Pink Sheet, 21 Apr, 2020.)

"The distant assessment ... has advantages, it has disadvantages, so the way I see it is it's a useful tool and it's complementary, but it won't replace an onsite inspection," he said, adding that management support is key to hosting distant assessments successfully.

So far during the pandemic, the EMA has requested 34 distant assessments, including one at a *Thermo Fisher Scientific* plant in Florida, and they all had positive outcomes. (Also see "*How The European Medicines Agency Inspected Thermo Fisher's Florida Plant Without Leaving Europe*" - Pink Sheet, 20 Jul, 2020.)

Additionally, regulatory authorities in the European Economic Area had conducted 202

distant assessments by 31 March 2021, Cuddy said, including 37 of sites in non-EEA countries.

Cuddy noted that for the pandemic, the EU expanded upon its concept of distant assessments by adding live and recorded information, online and offline documents and the possibility of interviews to a concept that originated long ago as desk-based alternatives for areas where it would not be safe for inspectors to travel.

As for the prospects for them post-pandemic, he said, "I think there's a future for distant assessments in the toolbox. I mean, it may not be the first tool you'll reach for, but I think it's worth developing the concept, we put a lot of effort into developing it, technology is evolving and improving all the time."

Part Of A Societal Digitization Trend

David Churchward, deputy unit manager, Inspectorate Strategy & Innovation, UK Medicines and Healthcare products Regulatory Agency, put the recent rise of distant assessments in the context of broader changes afoot that were accelerated by the pandemic.

Remote working, digitalization, Pharma 4.0 and artificial intelligence has provided more opportunity "to make better use of specialist personnel and skills and sharing them across facilities in a virtual setting."

There's no reason why inspections cannot benefit from the digitalization that has accelerated regulatory, clinical trial, and chemistry, manufacturing and controls reviews, he said.

However, he added, authorities will need to revise guidance and regulations to accommodate digital environments while staying focused on international risk management and quality systems principles.

Eventually, today's pandemic challenges of travel restrictions, global supply pressures and backlogged work will give way to new challenges in the emerging digital environment – competition for digital skills, development of new regulatory approaches and harmonization of remote assessments among regulators to enable increased mutual reliance.

Churchward explained that considerations driving distant assessments will evolve. So, for example, during the pandemic, a distant assessment might be conducted to reduce the time spent onsite for a mission-critical inspection to reduce COVID-19 transmission risk.

Post-pandemic, agencies might respond to incidents at foreign sites by scheduling remote assessments because they could do it in a matter of days instead of the months required to schedule onsite inspections.

Inspectorates Support Harmonized Use

Anne Hayes, an inspection manager with Ireland's Health Products Regulatory Authority, shared survey findings from 53 pharmaceutical inspectorates that took part in an 8-10 December 2020 PIC/S seminar on distant assessments.

Hayes, who also is PIC/S chair, said 28% of the inspectorates said they planned to continue using distant assessments after the pandemic, while 49% had not decided, and that there was strong support for developing harmonized guidelines and tools for them.

Survey respondents said their ability to conduct on-site inspections had been reduced, particularly for foreign inspections, with 69% reporting the ability to conduct domestic onsite inspections but only 14% saying they could do them abroad.

Domestically, 57% were using distant inspections with virtual components, while only 38% were using them for foreign sites. Additionally, 57% of the inspectorates were using hybrid approaches to domestic inspections.

The most popular platforms for the assessments were Microsoft Teams and Webex. In two-thirds of the cases, authorities arranged videoconferences rather than the companies they were inspecting. To verify site location, 29% of the survey respondents used their global positioning system capabilities.

An Emphasis On Mutual Reliance

Panelists agreed the pandemic showed how important it is for inspectorates to share information, particularly through reliance initiatives rather than mutual recognition agreements.

MRAs like the recent one between the US and the EU create obligations as part of trade agreements, whereas mutual reliance initiatives like the one advanced by PIC/S enable harmonization of standards that in turn help countries use each other's information, Churchward said. (Also see "*EU, US Finally Agree On Mutual Recognition Of GMP Inspections*" - Pink Sheet, 2 Mar, 2017.)

EMA's Cuddy agreed, saying "focusing on reliance is the way to go."

Speaking with the assistance of a translator, Vladislav Shestakov, deputy head of the GMP inspectorate in the Russia State Institute of Drugs and Good Practices, suggested that as part of the mutual reliance effort, it would "be a good idea to have certain arrangements in place between the regulatory agencies to share the reports of distant inspections." It would help agencies share knowledge and experiences, he said.

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Distant Assessment Experiences Vary

There was widespread agreement among the regulatory authorities that remote assessments take more time and are less effective than onsite inspections.

Despite the challenges, however, the UK MHRA found that remote inspections trended similarly in terms of trends in deficiencies found, particularly with respect to quality systems, Churchward said. The agency compared 2020 findings with earlier findings and checked remote against onsite findings in hybrid inspections to come to that conclusion.

Klaus Eichmueller, Darmstadt Regional Council, Germany, who expressed perhaps the strongest preference for onsite inspections, said that Germany has identified fewer deficiencies when conducting distant assessments compared to onsite inspections, particularly in plant operations.

Italy has found distant assessments to have utility in limited situations during the pandemic, said Marisa Delbo, head of the Risk Management Office in AIFA, the Italian Medicines Agency.

Delbo said her agency only uses distant assessments for active pharmaceutical ingredient facilities, COVID-19 products such as cyclosporins or drugs used for intubations, and in non-critical, low-risk situations.

She said Italy has conducted 25 distant assessments for finished drug products and 15 for APIs. So far, there has been one negative outcome, but not all the assessments have been finalized.

“We consider the distant assessment only an emergency tool for the current pandemic circumstances.” However, she added, there may be a role for them going forward to handle easy, low-risk inspections, particularly as the agency works through its backlog of onsite inspections. There could be complementary roles to decrease site inspection time and clarify aspects of minor changes, check if certain types of deficiencies have been resolved and ascertain whether certain regular inspections can be safely postponed.

More Challenges Seen

Carmelo Rosa, a drug quality division director in the FDA Center for Drug Evaluation and Research’s compliance office, said transparency and assurance of data integrity have been especially challenging with remote assessments. For example, it is often not enough to ask for out-of-specification results. Only by submitting additional requests will the agency find that many such product test results are classified as unexpected, out-of-trend, atypical or some other unconventional or inappropriate category. He said the problem is that it is harder to be sure information is complete, whole and accurate.

“There’s a lot of information that is not being easily captured through these means,” said Manuel Ibarra Lorente, head of pharmaceutical inspection and enforcement at the Spanish Agency of

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Medicines and Healthcare Products. “When it comes to the amount of work invested and the amount of information received, it's not an advantageous exercise."

Jacques Morenas, technical advisor of the inspection division director at France’s agency for medicines and health products safety, ANSM, said “we also strongly believing that we will not replace onsite inspection by virtual or distant assessment. As soon as pandemic will be under control, we will be back to onsite inspection.”

Morenas went on to emphasize the importance of securing the data that flows between sites and regulatory authorities during remote assessments, given that the EMA and drug manufacturers have fallen prey to cyberattacks.

Preparation Is Key To Success

Hayes said Ireland’s HPRA normally must reschedule 10% of inspections because of conflicts with other regulatory inspections or client audits. But during the pandemic, there have been few such requests.

It is important for companies to prepare for remote assessments by ensuring the capacity to support the digital tools used, including making sure there is enough network bandwidth to livestream tours throughout their facilities, she said.

Russia’s Shestakov echoed Hayes’ recommendation on preparation.

He said his agency has conducted more than 300 distant inspections during the pandemic, but that in many cases could not access “deep areas” of manufacturing facilities where wi-fi signals failed.

Manufacturing sites should anticipate such issues by, for example, placing cameras in such areas, and more broadly to prepare rigorously for remote visits, he said.

‘War Room’ Preparation Advised

Joey Gouws, inspection services team lead for the World Health Organization’s prequalification team, encouraged inspectorates to share information about inspection plans so the WHO can do joint inspections with them.

Gouws encouraged companies to have virtual “war rooms” of translators and subject matter experts at the ready to help answer questions and keep inspections moving forward.

US FDA Stresses Communications

Rosa encouraged manufacturers to collect data for quality metrics and annual quality reports

concurrently so they could be shared easily during remote assessments.

Cruse stressed the importance of good communications. It would be good, for example, to test their technology "to see what a walkthrough would look like, the resolution and so forth."

There should be a good point of contact and a translator available if needed.

Cruse noted that the FDA has conducted more than 900 remote records reviews during the pandemic, half foreign, half domestic, in support of surveillance, pre-approval and pre-license inspections. "We have a lot of experience in that space and I'm really looking for that to roll over into our remote evaluations." (Also see "*US FDA Explains Why Remote Interactive Evaluations Guidance Took So Long*" - Pink Sheet, 26 Apr, 2021.)