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FDA Issues New Guidance on Remote Interactive Evaluations for Oversight of Drug Facilities

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On April 14, 2021, in response to continued requests from industry for remote inspections and concerns raised by members of Congress, the U.S. Food and Drug Administration (FDA) issued Guidance for Industry: Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency. The guidance establishes a framework for the FDA's use of remote interactive evaluations (RIEs) during the COVID-19 public health emergency, which has required the postponement of most establishment inspections. The FDA defines an RIE as the "use of any combination of [remote] interactive tools" (e.g., remote livestreaming video of operations, teleconferences, and screen sharing) to support regulatory decisions and oversight of facilities.

Background

As we have previously reported, in response to the COVID-19 outbreak, the FDA announced in March 2020 that it was temporarily postponing all domestic and foreign routine surveillance facility inspections except for those that were deemed "mission-critical." In July 2020, the FDA announced its plan to resume "prioritized" domestic inspections during the week of July 20.

According to a January 28, 2021 Government Accountability Office (GAO) report, as a result of these inspection postponements, the FDA conducted only three foreign mission-critical inspections and 52 domestic inspections from March 10 to October 1, 2020. By contrast, in each of the prior two years, the FDA conducted more than 600 foreign inspections and approximately 400 domestic inspections. In testimony prepared for the March 9, 2021 House Committee on Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies hearing "FDA's Foreign Drug Inspections Program," the GAO expressed concerns about the FDA's continued postponement of foreign drug inspections and the resulting inspection backlog and recommended that the agency fully assess alternative inspection tools to support future drug oversight. During the hearing, these concerns were shared by members of the subcommittee.

The postponements have affected the FDA's oversight of current operations and new product applications and have delayed resolution of outstanding compliance issues. Throughout the past year, the FDA has indicated that it will use "all available tools and sources of information" in reviewing product applications. Yet the inspection postponements

since March 2020 have put product applications at risk. In Guidance for Industry: Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers (issued August 2020 and updated January 29, 2021), the FDA stated that if it had determined the need for a pre-approval inspection (PAI) but could not conduct the inspection during the review cycle, it would issue a complete response letter. Meanwhile, for the past year, sites that have been classified as "official action indicated" (OAI) have remained in a holding pattern, with no ability to resolve open inspection issues because the FDA has stated that it must conduct on-site inspections to reclassify site inspection status.

In all cases, these postponements have hampered the agency's ability to ensure the continuous supply and quality of drug products. In private meetings, at industry conferences, and in the press, the pharmaceutical industry has urged the agency to use alternative tools to review applications and evaluate current good manufacturing practices (CGMPs). For most of the past year, industry has offered to host remote inspections and has pointed out to the FDA that other regulatory authorities, such as the MHRA (UK) and TGA (Australia), quickly began conducting remote inspections in response to COVID-19-related travel restrictions.

RIEs represent the FDA's response to industry and Congress. The guidance makes clear that RIEs are not inspections but are another tool that the FDA intends to use while inspections remain on hold.

Guidance Highlights

The guidance establishes a framework for the use of RIEs, which are voluntary, for all drug inspection programs. It provides details for planning, conducting, and concluding RIEs. It also provides the FDA's current thinking on the impact of RIEs on user fee commitments and timeframes for responding to RIE observations.

The guidance states that RIEs are not inspections under Sections 704(a)(1) and 510(h)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) or record reviews under Section 704(a)(4) of the FDCA. It asserts no specific legal authority for them. The agency does have statutory authority under Section 702(a)(1)(A) to conduct examinations and investigations.

The FDA will not accept requests from applicants or facilities for RIEs. Instead, the agency will initiate the contact. The guidance provides a detailed process for RIEs:

- The FDA will notify the target facility of its RIE request by email or phone call.
- If the facility agrees to participate, the FDA will contact the facility to determine the facility's technological capability for the RIE.
- Once the facility confirms its capability for the RIE, the FDA will schedule a brief virtual meeting to plan the RIE.
- The FDA will conduct the RIE as planned. It may terminate the RIE at any time, if needed.
- Upon completion of the RIE, the FDA will have a closing meeting to present observations.
- The facility will have 15 U.S. business days to respond to the observations.
- After the RIE concludes, the FDA will provide the final RIE report to the facility.

The FDA may use RIEs alone or in combination with other types of regulatory oversight activities (e.g., an inspection or a 704(a)(4) record review), and the FDA intends to use 704(a)(4) record reviews before conducting RIEs. The guidance states that RIEs can be used for all drug inspection programs, including pre-approval inspections (PAIs) and pre-license inspections (PLIs), post-approval inspections (PoAIs), surveillance inspections, follow-up and compliance inspections, and bioresearch monitoring (BIMO) inspections.

For all inspection programs, it appears that the FDA will use RIEs only in situations where there is a good compliance history and no data integrity issues or other concerns, such as a need for an in-person visual inspection. For follow-up or compliance inspections, the FDA will also consider "the nature of the facility and the reason for the assignment."

The FDA intends to follow a risk-based approach in its use of RIEs. To mitigate pandemic travel-related risks for its investigators, the agency will apply "risk management methods and tools" to determine when to request RIEs. In some cases, the FDA may use RIEs to reduce the workload of subsequent inspections to minimize the risk for its investigators.

Another factor that the FDA will consider is the risk of replacing in-person inspections with RIEs (e.g., the risk that an RIE will not detect CGMP violations and adulterated drugs will be distributed). In addition, the FDA intends to prioritize facilities for RIEs using the same risk-based approach that it employs for surveillance inspections, which are outlined in the FDA's MAPP 5014.1, Understanding CDER's Risk-Based Site Selection Model.

Our Initial Thoughts

While the use of RIEs may result in additional product approvals, it is unclear whether the FDA will utilize RIEs when the manufacturing process involves novel technology or is a new process for the manufacturing site. Also, it is unclear if the FDA will use RIEs to reclassify OAI facilities that have not received prior notice through a warning letter or regulatory meeting.

Historically, the FDA has required in-person inspections to close out warning letters and/or reclassify an OAI inspection status and has emphasized this point in public statements at industry conferences. The guidance does not change this policy; it reconfirms that after the issuance of a warning letter, a regulatory meeting, or an enforcement action (e.g., seizure or injunction), a follow-up inspection is needed. The purpose of these follow-up inspections is to verify that the firm has implemented thorough and effective corrective actions.

The guidance is less clear on the use of RIEs to reclassify an inspection status when there has been no warning letter or regulatory meeting. It states that the decision to use RIEs for follow-up inspections will depend on (1) "the nature of the facility," which we interpret to refer to the types of products manufactured (e.g., active pharmaceutical ingredient (API), solid dosage, sterile products); and (2) "the reason for the assignment, including, but not limited to, inspection history and any data integrity concerns." We interpret this to mean that the FDA will look carefully at the risk presented by the facility and determine whether an in-person inspection is necessary (e.g., to visually inspect equipment for which the FDA has observed cleaning deficiencies) to evaluate the facility's compliance.

The guidance states that RIEs are voluntary, and the FDA allows a facility to decline its request to perform an RIE. The guidance further states that "FDA requests, including requests for records, during [an RIE] are considered voluntary unless a section 704(a)(4) request is sent to the facility." The guidance also states that the FDA intends to use 704(a)(4) record reviews *before* conducting RIEs. This raises the question of whether the RIE is truly voluntary or if the FDA would rely on its authority under Section 704(a)(4) to require production of records if a facility denies an RIE request. The guidance recognizes that not all facilities have the technological capability to perform remote interactions with the agency's staff in real time. The quality of the interactions may be affected by factors such as connectivity and image quality. There are also potential security concerns associated with virtual interactions. During the initial contact, the FDA will request confirmation of the facility's willingness and ability to participate in an RIE. If the site is not prepared for an RIE or prefers to wait for an in-person inspection, it should ask the FDA to confirm that declining the request will not be treated as a refusal. Note that the FDA has cautioned that refusing RIEs could delay the agency's regulatory decisions (e.g., approval of drug applications).

Medical device and other FDA-regulated manufacturers

The guidance's scope is limited to RIEs at (1) drug manufacturing facilities; (2) facilities covered under the BIMO program; and (3) outsourcing facilities registered under Section 503B of the FDCA. Even though medical device and other FDA-regulated manufacturers, such as food establishments, have been affected by FDA inspection postponements due to the pandemic, this guidance does not apply to them.

It is notable, however, that the FDA's press announcement for the guidance states that RIEs are "part of a necessary strategy to evaluate medical product facilities." Medical device and other medical product manufacturers should seek clarification from the FDA regarding whether the Center for Devices and Radiological Health (CDRH) intends to take a similar approach to address its inspection backlog.

Our Recommendations

Preparing for RIEs

As a best practice, manufacturers routinely conduct self-evaluative activities to remain inspection ready. We recommend taking the same approach in anticipation of RIEs. Because the success of an RIE will depend, in large part, on the management of remote requests from the FDA, there are additional considerations.

Technological Capability: Manufacturers should first ensure that the target facilities can interact with FDA investigators through one of the FDA's IT platforms (Microsoft Teams, Zoom for Government, and Adobe Connect). They should also ensure that technologies at the facilities can support adequate quality of the remote connection (e.g., connectivity, image quality, cameras used) for FDA investigators to remotely review, observe, examine, and evaluate the records and information requested. To the extent practicable, the technologies should also enable FDA investigators to remotely view and evaluate operations at the facilities (e.g., aseptic practices, equipment cleaning and setup, material weighing and dispensing, instrument setup, sampling, testing).

Personnel Preparation: Manufacturers should prepare facility personnel (including facility leadership and subject-matter experts) for activities unique for RIEs, such as use of livestream and pre-recorded video to examine facilities, operations, and data and other information; use of videoconference for interviews; and screen sharing of documents.

Mock RIEs: Manufacturers should conduct mock RIEs to test the facilities' technologies and give facility personnel opportunities to practice virtual presentation skills and provide timely responses to FDA requests during the evaluations. For facilities located outside the United States, manufacturers should use their U.S. agents to further test cross-border connectivity.

Submitting comments to the FDA

The guidance is effective immediately, but "[c]omments may be submitted at any time for [the FDA's] consideration." Manufacturers should submit comments regarding circumstances or factors that the guidance has not considered. Examples of open issues that would be appropriate for comments include:

- Statutory authority for RIEs, which would give the FDA greater flexibility in relying on these evaluations for its regulatory decisions.
- Clarity regarding the link between a 704(a)(4) request and an RIE.
- Why the FDA does not consider RIEs to be inspections under Section 704(a)(1) of the FDCA.
- Whether RIEs will be used for combination products or other inspection programs (e.g., medical device, food).

Future legislative actions

Some members of Congress have expressed concerns about the FDA's foreign inspection backlog. It remains to be seen whether RIEs will help reduce the backlog. While the user-fee programs for prescription drugs, medical devices, generic drugs, and biosimilar biological products do not expire until September 2022, the Democratic-controlled 117th Congress and President Biden have indicated that addressing drug prices is a high priority. As Congress considers its upcoming legislative agenda, including an infrastructure bill and potentially a separate additional health-care-focused bill, Congress may include addressing the FDA inspection backlog among other drug-related priorities. If these issues are not addressed in 2021, Congress could look to reauthorizing the user-fee programs in 2022 as the legislative vehicle to address the inspection backlogs, assuming this still remains a mission-critical issue.

In addition, President Biden has yet to nominate an FDA commissioner, despite elevating Patrizia Cavazzoni as the head of the Center for Drug Evaluation and Research (CDER) just days before the release of the guidance. Political leadership is critical to advancing administrative priorities, and Cavazzoni's past experience as CDER's deputy director for operations may help in further advancing priorities to address the inspection backlog. If the FDA is able to address the backlog administratively, Congress may not need to take legislative actions, but manufacturers should monitor the progress and proactively communicate their proposals and concerns about FDA inspections and RIEs to legislators. With CDER leadership in place, manufacturers should also consider engaging with the center to develop and implement alternative solutions for the FDA to address the inspection backlog.

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