Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities

Guidance for Industry

DRAFT GUIDANCE

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Center for Veterinary Medicine (CVM)

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities

Guidance for Industry

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Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA conducts inspections for many purposes and programs, ensuring necessary oversight of FDA-regulated products and assessing facilities' compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA may use alternative tools, such as Remote Regulatory Assessments (RRAs)[2], in advance or in lieu of an inspection or to support an inspection of a facility and assess compliance with applicable laws and regulations. For instance, if a program office determines that an inspection is not necessary, feasible, or practical, FDA may instead conduct an RRA. An RRA is an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs may consist of (or include) a request to conduct voluntary remote interactive evaluations.

FDA is issuing this guidance to describe how we request and conduct voluntary remote interactive evaluations at facilities[3] where drugs[4,5] are manufactured, processed, packed, compounded, or held, and at drug facilities covered under FDA's bioresearch monitoring (BIMO) program. FDA may consider the use of a remote interactive evaluation for any of the inspection program areas described in Section III of this guidance.

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[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] See the FDA draft guidance for industry *Conducting Remote Regulatory Assessments — Questions and Answers* (July 2022). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] In this guidance, the term *facility* covers persons, sites, entities, and establishments subject to FDA drug manufacturing and bioresearch monitoring regulations and statutory authority for drugs.

[4] A "drug" includes human and animal drugs (including drug products produced by facilities registered as human drug compounding outsourcing facilities under section 503B of the FD&C Act, and all compounded animal drugs), and biological drug products for humans.

[5] In this guidance, the term *drug* includes biologics.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

During the Coronavirus Disease 2019 (COVID-19) pandemic, FDA expanded our use of alternative tools for evaluating drug manufacturing facilities to support regulatory decision-making. When an inspection was not feasible or practical because of the public health emergency, FDA used other available tools and information to support regulatory decisions and oversight of facilities. Although inspections have largely resumed and the Secretary of Health and Human Services has announced that the COVID-19 public health emergency declaration has ended,[6] FDA has determined that continued use of alternative tools, including remote interactive evaluations, based on risk and program needs, will enhance our ability to assess facilities.

This guidance describes the various remote interactive tools we may request to use to conduct an evaluation. In this guidance, we refer to our use of any combination of these interactive tools as a *remote interactive evaluation.* FDA may request to conduct a remote interactive evaluation prior to or following other types of regulatory oversight activities (e.g., an inspection or a request for records or other information).[7]

III. PLANNING A REMOTE INTERACTIVE EVALUATION

FDA may request to conduct a remote interactive evaluation whenever a program office determines it is appropriate based on mission needs and any travel limitations. FDA conducts inspections for many purposes and programs, and we will consider each of those inspection program areas as possible candidates for a remote interactive evaluation. This policy applies to all drug inspection programs including, but not limited to:

- *Preapproval Inspections (PAIs) and Prelicense Inspections (PLIs)*: FDA may perform a PAI or PLI to assess a marketing application. FDA uses these inspections to ensure that any facility named or referenced in support of an application can perform the proposed manufacturing operations in conformance with current good manufacturing practice (CGMP) requirements, to verify conformance with the application, and to confirm that data submitted in the application are accurate and complete.
- *Postapproval Inspections (PoAIs)*: PoAIs focus on a specific drug and changes to its

[6] https://www.hhs.gov/coronavirus/covid-19-public-health-emergency/index.html

[7] A remote interactive evaluation is not an inspection as described in sections 704(a)(1) or 704(a)(5) of the FD&C Act (21 U.S.C. 374(a)(1), 374(a)(5)) or a request for records or other information in advance of or in lieu of an inspection, as described in section 704(a)(4) of the FD&C Act (21 U.S.C. 374(a)(4)). Similarly, a remote interactive evaluation or a request under section 704(a)(4) does not constitute an inspection for purposes of sections 503B(b)(4) (21 U.S.C. 353b(b)(4)) and 510(h)(3) (21 U.S.C. 360(h)(3)) of the FD&C Act.

manufacturing operations, the evaluation of process validation, any changes submitted to the application, and the execution of supporting activities according to application commitments and CGMP requirements.

- *Surveillance Inspections*: Surveillance drug quality inspections examine overall operations, including controls that ensure manufacturing processes produce quality drugs, thereby reducing the risk of adulterated or misbranded drugs reaching consumers and patients. FDA uses surveillance inspections to evaluate the CGMP compliance of manufacturing operations. Surveillance inspections are performed at active pharmaceutical ingredient and drug product manufacturing facilities, as well as outsourcing facilities that have registered with FDA under section 503B of the FD&C Act (21 U.S.C. 353b).
- *Follow-Up and Compliance Inspections*: When a specific drug quality problem or facility issue comes to FDA's attention, we may initiate a follow-up or compliance drug quality inspection. For example, FDA may conduct an inspection to investigate: (1) product safety, effectiveness, or quality concerns arising from defect reports; (2) information provided by an informant about a facility; (3) violative activities involving a facility that were discovered during the inspection of another facility; or (4) corrective actions undertaken by a facility in response to, for example, a warning letter or regulatory meeting.
- *Bioresearch Monitoring (BIMO) Inspections*: The BIMO program is a comprehensive, Agency-wide program of inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research. The goals of the BIMO program are to protect the rights, safety, and welfare of research subjects; to verify the accuracy, reliability, and integrity of clinical and nonclinical trial data submitted to FDA; and to assess compliance with FDA's regulations governing the conduct of clinical and nonclinical trials, including regulations for informed consent and ethical review, and certain postmarketing requirements.

A. Selecting and Notifying the Facility

FDA intends to apply risk management methods and tools to determine when to request a facility's participation in a remote interactive evaluation. In some cases, FDA may request records or request that a facility participate in a remote interactive evaluation prior to an inspection. We do not intend to accept requests from applicants or facilities for FDA to perform a remote interactive evaluation. Such decisions depend on many factors and information not always known to applicants or facilities, and it would be unduly burdensome on all parties to establish a request-based program.

Once FDA determines that a remote interactive evaluation is appropriate for a particular facility or drug, we intend to notify the facility and applicant (when appropriate) by electronic correspondence or phone call. We will use the facility's registration or application information to identify the facility point of contact or U.S. agent. Correspondence or phone contact will include a request for confirmation of the facility's willingness and ability to participate in a remote interactive evaluation, including the use of teleconference, livestream video, and screen sharing of data and documents. The request would indicate the name and address of the facility to be

evaluated, the reason for the use of a remote interactive evaluation, and the names of FDA participants, if known in advance. Where practicable, FDA generally intends to seek to obtain such facility consent in writing.

Following a facility's agreement to be evaluated remotely, FDA will contact the facility to confirm the point of contact for the remote interactive evaluation, facilitate planning, and determine a facility's ability to transfer records and perform remote interactions with FDA staff. FDA will identify the FDA lead for the remote interactive evaluation. FDA will also work with facilities to procure information necessary to plan and coordinate the activities for a remote interactive evaluation. The facility should meet these requests or inform FDA of any challenges in meeting these requests as soon as possible.

Declining FDA's request to perform a remote interactive evaluation could impede our ability to make a timely regulatory decision (e.g., regarding adequacy of a clinical trial used in support of a pending application or adequacy of a drug manufacturing operation described in the application).

1. Specific Considerations for Preapproval and Prelicense Inspections

When FDA cannot perform a PAI or PLI, when we determine it would be useful to supplement a planned inspection, or when we determine that facility risks can be assessed and application assessment can be completed without inspection, we will consider using tools other than inspection, selecting the most appropriate method to address the specific risks at issue. FDA may request a remote interactive evaluation to support an application action if we determine that: (1) remote interaction with the facility will help us assess risks identified during application review, and (2) there are no data integrity or other issues that FDA determines require an inspection.[8]

FDA may request records and other information under section 704(a)(4) of the FD&C Act (21 U.S.C. 374(a)(4)) before initiating a remote interactive evaluation.

2. Specific Considerations for Postapproval Inspections

When FDA cannot perform a PoAI, or when we determine it would be useful to supplement a planned inspection, we will consider using tools other than inspection to address the specific risks that justify the need for the PoAI; we may determine that requesting a remote interactive evaluation is an appropriate alternative to conducting an inspection. FDA may request a remote interactive evaluation for PoAIs when: (1) a facility has an acceptable inspection history with no data integrity or other concerns that FDA determines require an inspection; and (2) specific application considerations and CGMP manufacturing risks that warrant a PoAI can be sufficiently assessed through a remote interactive evaluation.

[8] For criteria used to determine whether FDA will consider the use of a remote regulatory assessment or other alternative tools, see the FDA draft guidances for industry *Conducting Remote Regulatory Assessments — Questions and Answers* (July 2022) and *Use of Alternative Tools to Assess Manufacturing Facilities Named in Pending Applications* (September 2023), respectively. When final, these guidances will represent FDA's current thinking on these topics. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

3. Specific Considerations for Surveillance Inspections

In prioritizing facilities, domestic and foreign, for remote interactive evaluations, we intend to follow the same risk-based approach currently used by FDA for surveillance inspections.[9]

A remote interactive evaluation does not constitute an inspection for purposes of sections 503B(b)(4), 510(h)(3) (21 U.S.C. 360(h)(3)), 704(a)(1), or 704(a)(5) of the FD&C Act. However, FDA may use information gathered via a remote interactive evaluation to determine the scope, depth, and timing of a future inspection.

4. Specific Considerations for Follow-Up and Compliance Inspections

A follow-up or compliance inspection examines operations, records, and other information that relate to the specific issue being addressed (e.g., drug quality control, facility, or manufacturing problem). FDA will determine whether a remote interactive evaluation is appropriate, such as when an inspection cannot be performed due to travel restrictions or to supplement a planned inspection. The use of a remote interactive evaluation will depend on the nature of the facility and the reason for the assignment, including, but not limited to, inspection history and any data integrity concerns.

After pursuing an advisory action (e.g., warning letter or regulatory meeting), FDA generally will conduct an inspection to confirm that corrective actions have been implemented.

To evaluate defect reports (e.g., Field Alert Reports or Biological Product Deviation Reports), FDA may request a remote interactive evaluation and/or make a records request under section 704(a)(4) of the FD&C Act.

5. Specific Considerations for Bioresearch Monitoring Inspections

Selection of facilities for BIMO inspections is risk based. While some facility selection factors such as inspection history and time since last inspection may be common across BIMO programs, other factors are unique to each BIMO program.

FDA intends to consider BIMO facilities for remote interactive evaluation according to existing risk-based facility selection methodologies when there are no data integrity or other concerns that FDA determines require an inspection, and information to be evaluated can be accessed remotely. Generally, FDA intends to use information obtained from a remote interactive evaluation to assess the facility's conduct, including data reliability and human subject protections, to determine the acceptability of BIMO studies for FDA's application decision-making.

[9] See, for example, the risk-based approach described in MAPP 5014.1 *Understanding CDER's Risk-Based Site Selection Model*, available at https://www.fda.gov/media/118214/download.

B. Preparing for a Remote Interactive Evaluation

Once the facility confirms its willingness and ability to participate in a remote interactive evaluation, FDA will schedule a brief virtual meeting to discuss logistics, responsibilities, and expectations. Discussion topics may include, but are not limited to, the following:

- Objectives and scope of the remote interactive evaluation.
- Introduction of the FDA remote interactive evaluation team and the remote interactive evaluation lead.
- Identification of the facility point of contact and all other participants (e.g., sponsor or contract research organization, monitor, remote ancillary operations).
- Schedule of virtual interactions and the anticipated duration of the remote interactive evaluation.
- FDA's expectations during livestreaming walkthroughs of the facility.
- Time zone differences and translation services (i.e., spoken and written translation), if applicable. Virtual interactions, including remote observation of manufacturing operations or livestream assessment of data, usually will occur during the facility's normal business hours.
- Methods for sharing requested information, including sharing documents and the use of video-streaming technology.
- Technological limitations that could impair or prevent FDA's remote interactive evaluation of the facility.
- Check of the internet connection throughout the facility to verify that the signal strength is adequate to support livestreaming video and audio during the actual remote interactive evaluation.

IV. CONDUCTING A REMOTE INTERACTIVE EVALUATION

When facilities agree to participate in a remote interactive evaluation, FDA expects them to cooperate with the same level of transparency as they would during an FDA inspection. We expect appropriate staff to be available at scheduled times for interviews and other virtual interactions, and we expect the facility to be operational to the extent possible for FDA to evaluate areas and operations of interest (e.g., manufacturing, laboratory, packaging). If a facility is unable to support video or other virtual interactions, or if FDA determines that the video or any other virtual interaction during the remote interactive evaluation does not permit a sufficient examination of the facility or of a corrective action, FDA may terminate the remote interactive evaluation and instead perform an inspection or use other available tools.

As part of a remote interactive evaluation, FDA may:

- Request and review documents, records, and other information (electronic systems).[10]
- Use livestream and/or prerecorded video to examine facilities, operations, and data and other information.[11]
- Through the facility's point of contact, schedule interviews and meetings to address any questions or concerns.
- Evaluate a facility's corrective actions (e.g., in response to a previous inspection or evaluation, or to the current remote interactive evaluation). An inspection instead of a remote interactive evaluation may be necessary to verify the adequacy of some corrective actions, or if evaluating the corrective actions remotely would unreasonably extend the duration of the remote interactive evaluation.
- Provide verbal updates to the facility on observations and outstanding issues, whenever feasible.

FDA will not issue a Form FDA 482, Notice of Inspection, to announce or open a remote interactive evaluation.

A. Technological Requirements

The quality of the remote connection (e.g., connectivity, image quality, cameras used) should be adequate for FDA to remotely review, observe, examine, and evaluate the information requested. To the extent practicable, technologies employed also should allow access for clear and stable remote viewing and evaluation of operations at the facility, as necessary (e.g., aseptic practices, equipment cleaning and set up, material weighing and dispensing, instrument set up, sampling, testing). FDA understands that there may be temporary connection issues during the virtual interaction, and we expect either party to resolve the issue in a timely manner.

For security reasons, FDA will use its own IT platforms and equipment[12] to host virtual interactions during remote interactive evaluations (e.g., videoconferences, livestreaming video of the facility and operations in the facility). FDA currently uses the following conferencing platforms:

- FDA Microsoft Teams
- FDA Zoom for Government
- FDA Adobe Connect

[10] FDA requests, including requests for records, during a remote interactive evaluation are considered voluntary unless a section 704(a)(4) request is sent to the facility.

[11] For example, for a remote interactive evaluation supporting a pending biologics license application, FDA usually will expect a facility to provide for livestream video of the manufacturing operations described in the application.

[12] FDA is not able to supply equipment to a facility to enable FDA's remote interactive evaluation. Additionally, FDA is not able to accept equipment or devices from a facility for our use in conducting a remote interactive evaluation.

B. Remote Interactive Evaluation of Documents and Records

FDA will usually request and review documents and other information in advance of a remote interactive evaluation[13] to ensure the livestream interactions are as efficient as possible. However, we may request additional documents and other information, including video recordings, at any time during the remote interactive evaluation to address questions and to explain observations. Documents and other information requested during a remote interactive evaluation should be provided within a reasonable timeframe.

FDA expects all documents provided during the remote interactive evaluation in response to FDA's request to be provided in electronic format or accessible by screen sharing during a live interaction so that the documents can be assessed efficiently. FDA will provide a secure means to send requested information during a remote interactive evaluation. For electronic documents and other information, facilities should identify any limitations and ensure that encrypted and password-protected files can be accessed by FDA. Documents submitted during a remote interactive evaluation should be in English. However, if translation is needed during a livestream interaction, the facility may need to provide a translator.

FDA recognizes that some facilities maintain documents in paper format and not all electronic systems will be accessible for direct viewing. Thus, when such a facility agrees to participate in a remote interactive evaluation, they should consider taking steps to enable FDA's remote viewing and verification of the facility's documents, procedures, and electronic systems. Requested documents maintained in paper format should be scanned as searchable Portable Document Format (PDF) files when possible.

V. CONCLUDING A REMOTE INTERACTIVE EVALUATION

Upon completion of a remote interactive evaluation, FDA will have a closeout meeting with the facility's management. During this meeting, FDA will usually present a written list of observations, if any, and describe and discuss any observations in sufficient detail to enable understanding and foster an appropriate response.[14,15] This written list of observations will not be a final Agency action or decision. FDA will not issue a Form FDA 483, Inspectional Observations. As with an inspection, FDA encourages facilities to respond during the discussion and/or provide responses in writing to the observations within 15 U.S. business days.

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[13] Generally, such requests for records or other information prior to the remote interactive evaluation will be made under section 704(a)(4) of the FD&C Act.

[14] If the remote interactive evaluation, including the review of any records before or during the evaluation, is intended to supplement a scheduled inspection, then FDA usually will combine any observations from the remote interactive evaluation(s) into a single written list of observations issued at the close of the inspection, which would be issued on a Form FDA 483, Inspectional Observations.

[15] See the FDA draft guidance for industry *Conducting Remote Regulatory Assessments — Questions and Answers* (July 2022) for further information on processes related to the completion of a remote regulatory assessment. When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Depending on the purpose and outcome of the remote interactive evaluation, the information and documentation collected may be used to, among other regulatory purposes:

- Support FDA's assessment of pending applications, including whether to approve an application
- Preclude the need for an inspection in follow-up to a reported concern or defect
- Support a regulatory meeting, warning letter, import alert, recall activities, or enforcement action
- Rank or prioritize a facility for an inspection, particularly a surveillance CGMP inspection
- Justify a follow-up or compliance inspection or any other surveillance activity

After the remote interactive evaluation concludes, FDA will generally provide a copy of the final remote interactive evaluation report to the facility. A remote interactive evaluation report and any written list of observations may be subject to a disclosure request under the Freedom of Information Act.

If FDA determines that an inspection will be necessary based on the outcome of the remote interactive evaluation, we intend to use the information obtained from the remote interactive evaluation to prepare for and conduct the inspection.

VI. TIMEFRAMES FOLLOWING COMPLETION OF A REMOTE INTERACTIVE EVALUATION

In general, the use of remote interactive evaluations should not affect FDA's ability to operate within normal timeframes (i.e., in a manner similar to an inspection). FDA may use information gained from remote interactive evaluations to meet user fee commitments and to update relevant internal databases.

A. Response Timeframes for Remote Interactive Evaluations Generally

FDA encourages establishments to provide responses in writing to the observations made during the RIE within fifteen (15) U.S. business days. Any responses or corrective actions submitted to FDA during that timeframe in response to the issues identified during the RIE generally will be considered before further Agency action or decision.

B. Response Timeframes for Remote Interactive Evaluations in Support of Preapproval and Prelicense Inspection Programs

FDA encourages establishments to provide responses in writing to the observations made during the RIE within fifteen (15) U.S. business days. Any responses or corrective actions submitted to FDA during that timeframe in response to the issues identified during the RIE generally will be considered before further Agency action or decision.

FDA may defer consideration of responses or corrective actions in the current application review cycle if received after 15 U.S. business days. Deferred responses or corrective actions will be considered in the next application user fee cycle if the application receives a complete response action and the facility requires reevaluation.