Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023
Pharmaceutical Quality/Manufacturing Standards (CGMP)

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Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to provide information to applicants on how FDA intends to use alternative tools[2] to assess manufacturing facilities[3] identified in a marketing application (i.e., a new drug application (NDA), an abbreviated new drug application (ANDA), a biologics license application (BLA), or a supplement to any of these types of applications). As part of the negotiations relating to the reauthorization of the Prescription Drug User Fee Act (PDUFA) and the Biosimilar User Fee Act (BsUFA), as described in "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027" (PDUFA VII commitment letter)[4] and "Biosimilar Biological Product Reauthorization Performance Goals and Procedures for Fiscal Years 2023 Through 2027" (BsUFA III commitment letter),[5] FDA agreed to issue guidance on the use of alternative tools to assess manufacturing facilities named in pending applications and to incorporate best practices from the use of such tools during the Coronavirus Disease 2019 (COVID-19) pandemic.

This guidance, within the context of approval and licensure decisions by FDA, describes the use of alternative tools to assess manufacturing facilities identified in an NDA, an ANDA, or a BLA[6] to establish that these facilities meet the applicable requirements, including under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B))

[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 and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] In this guidance, the term *alternative tools*, as described further within, refers to methods used by FDA in advance or in lieu of an inspection or to support an inspection of a drug manufacturing facility and assess compliance with applicable laws and regulations.

[3] In this guidance, the terms *facility* and *establishment* are synonymous (see the definitions for establishment in 21 CFR 207.1 and 600.3(w)).

[4] See Section II.N.3 of the PDUFA VII commitment letter available at https://www.fda.gov/media/151712/download.

[5] See Section II.B.2. of the BsUFA III commitment letter available at https://www.fda.gov/media/152279/download.

[6] This guidance fulfills PDUFA VII and BsUFA III commitments applicable to NDAs and BLAs. However, FDA also continues to use alternative tools to support the assessment of all drug application types, including ANDAs.

and either 505 of the FD&C Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

This guidance does not apply to other drug[7] inspection programs including:

- Postapproval inspections
- Surveillance inspections
- Follow-up and compliance inspections (e.g., for-cause inspections)
- Bioresearch monitoring inspections[8]

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

The Prescription Drug User Fee Act of 1992 (PDUFA)[9] amended the FD&C Act to authorize FDA to assess and collect user fees[10] from companies who produce certain human drugs. Since the passage of PDUFA, user fees have played an important role in supporting the drug approval process, and user fee programs have been established by Congress to support certain FDA activities related to several other types of medical products, including medical devices, generic drugs, and biosimilar biological products.[11] These fees have helped FDA fulfill its mission of protecting the public health and promoting timely market availability of FDA-regulated products without compromising the Agency's commitment to scientific integrity, public health, regulatory standards, and patient safety. Reauthorization of FDA's medical product user fee programs continues FDA's authority to assess and collect these user fees. Most recently, the FDA User Fee Reauthorization Act of 2022 reauthorized FDA's human drug and device user fee programs.[12] The PDUFA VII and BsUFA III commitment letters applicable to this latest reauthorization build upon previous FDA performance goals and program enhancements to facilitate timely access to safe, effective, high quality, and innovative new medicines for patients.

[7] In this guidance, the term *drug* includes biological products.

[8] Section 3612 of the Food and Drug Omnibus Reform Act of 2022 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add section 704(a)(5)(C) clarifying FDA's authority to conduct bioresearch monitoring inspections; however, in this guidance, bioresearch monitoring inspections are considered out of scope.

[9] Title I, the Prescription Drug User Fee Act of 1992, of Public Law 102-571.

[10] User fees are available for obligation in accordance with appropriations acts.

[11] See sections 738, 744B, and 744H of the FD&C Act (21 U.S.C. 379j, 21 U.S.C. 379j–42, and 21 U.S.C. 379j–52), respectively.

[12] See titles I through IV of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023.

During the COVID-19 pandemic, FDA expanded its use of alternative tools to evaluate drug manufacturing facilities to support regulatory decision-making when facility inspections were not feasible. In the PDUFA VII and BsUFA III commitment letters, FDA agreed to issue guidance on the use of alternative tools, incorporating best practices from the use of such tools during the COVID-19 pandemic, to assess manufacturing facilities named in pending applications as part of FDA's normal operations beyond the COVID-19 public health emergency.[13,14]

The following alternative tools were used during the public health emergency:

- Requesting records and other information, pursuant to section 704(a)(4) of the FD&C Act (21 U.S.C. 374(a)(4)), directly from facilities and other entities subject to inspection [15]

- Performing remote interactive evaluations (RIEs) (e.g., remote livestreaming video of operations, teleconferences, screen sharing)

- Requesting existing inspection reports and other information from trusted foreign regulatory partners through mutual recognition agreements and other agreements

FDA has strategically used these tools within the context of decisions related to preapproval inspections (PAIs) or prelicense inspections (PLIs) to maximize facility evaluation efficiency as part of appropriate, risk-based assessments. Given the success of these innovative approaches, the Agency intends to continue risk-based use of these alternative tools and to apply certain virtual technological capabilities within a specific inspectional context defined within this guidance. When used in advance or in lieu of PAIs and PLIs or to support PAIs and PLIs, the appropriate use of these approaches will help FDA maintain operational flexibility to support timely facility evaluations and application decisions.

III. RISK-BASED USE OF ALTERNATIVE TOOLS

FDA generally conducts a PAI or a PLI to ensure that any facility named or referenced in an application can perform the proposed manufacturing operations in conformance to the current good manufacturing practice (CGMP) requirements,[16] to confirm that data submitted in the

[13] In this guidance, FDA refers to *normal operations* as the circumstances in which the COVID-19 public health emergency under section 319 of the Public Health Service Act (PHS Act) (42 U.S.C. 347d) has expired. The tools and discretion available to FDA in response to a public health emergency are beyond the scope of this guidance.
[14] See Section II.B.2. of the BsUFA III commitment letter and Section I.N.3. of the PDUFA VII commitment letter.
[15] Section 704(a)(4) of the FD&C Act gives FDA the authority to request from a drug or device establishment or a site or facility subject to bioresearch monitoring inspections—and requires a person who owns or operates such an establishment, site, or facility to provide—any records or other information that FDA may inspect under section 704 in advance of or in lieu of an inspection.
[16] In this guidance, *current good manufacturing practice* (*CGMP)* refers to the requirements in section 501(a)(2)(B) of the FD&C Act and in 21 CFR parts 4, 210, 211, and 600 through 680, as applicable.

application are accurate and complete,[17] to verify conformance to the application, and to assess a facility's ability to develop and manufacture drugs of consistent quality.[18] In some instances, FDA may determine that a PAI or a PLI may not be needed if sufficient information is otherwise available to FDA demonstrating the facility's ability, with respect to a drug's manufacturing, to ensure and preserve the drug's identity, strength, quality, and purity[19] (for an application subject to section 505 of the FD&C Act) or to ensure product safety, purity, and potency[20] (for an application subject to section 351 of the PHS Act).

During an application assessment, FDA conducts a product quality assessment to identify potential risks to product quality, including any product-specific risks; manufacturing process and control risks; or facility risks, that would be cause for an inspection. Potential sources of product quality or facility-related risks can include the following: (1) gaps in the current scientific knowledge or manufacturing process understanding, (2) new technologies or dosage forms, (3) manufacturing process complexities, (4) limited commercial manufacturing experience, and (5) issues identified from previous FDA inspections or from information provided by trusted foreign regulatory partners. FDA uses a risk-based approach to determine when an inspection in support of an application is necessary.

FDA intends to evaluate all risks or urgencies on a case-by-case basis and consider factors, including any or a combination of the following, to discern when the use of alternative tools may be appropriate in advance or in lieu of an inspection or to support a PAI or a PLI:

- The facility has a drug inspection history (FDA and/or a trusted foreign regulatory partner under a mutual recognition agreement or other agreement), and the proposed operations in the application are the same as or sufficiently related to existing operations covered in previous inspections.

- The application-specific risks or applicable facility operations can be adequately assessed through alternative tools.

- The product addresses an urgent need (e.g., a critical public health need, a pervasive drug shortage, or other unforeseen situations).

[17] See the guidance for industry *Data Integrity and Compliance With Drug CGMP Questions and Answers* (December 2018). 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.

[18] FDA uses drug and biologics compliance programs to guide the conduct of preapproval and prelicense inspections. Drug compliance programs are available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs. Biologics compliance programs are available at https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/compliance-programs-cber.

[19] See sections 505(d)(3) and 505(j)(4)(A) of the FD&C Act.

[20] See section 351(a)(2)(C)(i) of the PHS Act.

- An inspection is not feasible as a result of travel limitations (e.g., pandemics, natural disasters, other unstable situations preventing travel).

This is not a comprehensive list, given the constantly evolving unique considerations that may arise during a particular application assessment.

IV. CONSIDERATIONS FOR ALTERNATIVE TOOLS

FDA will consider using alternative tools for an application's facility evaluation, as appropriate and on a case-by-case basis, in advance or in lieu of an inspection or to support a PAI or a PLI. Because FDA may choose to inspect and/or to use an alternative tool at any point in the application assessment cycle,[21] FDA expects all manufacturing, packaging, and control sites for drug substance and drug product facilities to be ready for inspection at the time of application submission.[22] FDA does not intend to grant requests from applicants or facilities for FDA to use alternative tools. Such decisions depend on many factors and may include information bearing on internal Agency practices, and it would not be feasible to establish a request-based program.

Based on any or a combination of specific risks or urgencies described above, FDA may choose to use one or more alternative tools to aid in its application facility evaluation of whether the methods used in and the facilities and controls used for the manufacturing, processing, packing, and testing of a drug are adequate to ensure and preserve the drug's identity, strength, quality, and purity[23] or to ensure and preserve the drug's safety, purity, and potency.[24] FDA may use alternative tools to assess whether facilities named in the application can perform the proposed manufacturing operations in conformance to the application and in compliance with applicable requirements, including the CGMP requirements for drug manufacturing.

A. Remote Regulatory Assessments

To examine an application product, a facility, or a manufacturing process and its controls, FDA may choose to initiate a remote regulatory assessment (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. An RRA complements FDA's authority to conduct inspections under section 704(a)(1) of the FD&C;[25] however, in certain circumstances, records or other information obtained through an RRA (for example, under section 704(a)(4) of

[21] FDA does not intend to simultaneously conduct a remote regulatory assessment (RRA) and an inspection of a facility. See Section III.A.6. of the draft guidance for industry *Conducting Remote Regulatory Assessments Questions and Answers* (July 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[22] For more information regarding which facilities should be listed in Field 28 of the "Establishment Information" section of Form FDA 356h, titled *Application to Market a New or Abbreviated New Drug or Biologic for Human Use* (available at https://www.fda.gov/media/72649/download), see the guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers* (October 2019).

[23] See sections 505(d)(3) and 505(j)(4)(A) of the FD&C Act. See also 21 CFR 314.105.

[24] See section 351(a)(2)(C)(i) of the PHS Act and 21 CFR 601.2(d).

[25] FDA generally considers an inspection, such as described in section 704(a)(1) of the FD&C Act, to involve duly designated officers or employees of FDA physically entering (at reasonable times and in a reasonable manner) an establishment subject to regulation under the FD&C Act.

the FD&C Act)[26] may provide information similar to what would generally be evaluated on a PAI or a PLI or used to resolve application-specific deficiencies identified during a PAI or a PLI, as further described below. For example, FDA may use an RRA to assess an application-specific risk or to gather information sought relative to a facility evaluation.

An RRA may be conducted by employing the following alternative tools individually or in combination, as appropriate, to meet the needs of the assessment:

- Pursuant to section 704(a)(4) of the FD&C Act, requesting from the owner or operator of a drug facility, records or other information that are subject to inspection under section 704[27]

- Conducting an RIE during application assessment[28]

For an RRA conducted under section 704(a)(4) of the FD&C Act, a response from the facility is mandatory.[29] Upon receipt of a section 704(a)(4) request from FDA, each facility should carefully consider FDA's specific request and provide a response in the specified time frame with sufficient information to adequately satisfy the request. The types of records and information requested can vary based on the product, the facility, and manufacturing process and its controls, but may include, as applicable, equipment records, process validation records and reports, test results, deviations and associated reports, complaints, or other information related to compliance with the CGMP requirements and other applicable FDA requirements. The Agency may seek a teleconference or a virtual meeting for clarification of the records and other information sought by the Agency pursuant to section 704(a)(4) if the response does not sufficiently address FDA's request. Refusing to permit access to records as required by section 704(a), including section 704(a)(4), is a prohibited act,[30] and supplying insufficient information may: (1) delay application action if FDA does not have enough information to make a regulatory determination; (2) result in FDA sending a complete response letter[31] to the applicant if FDA

[26] As indicated in footnote 15, section 704(a)(4) of the FD&C Act gives FDA the authority to request from a drug or device establishment or a site or facility subject to bioresearch monitoring inspections—and requires a person who owns or operates such an establishment, site, or facility to provide—any records or other information that FDA may inspect under section 704 in advance of or in lieu of an inspection. Section 704(a)(4), as amended by the Food and Drug Omnibus Reform Act of 2022, clarifies that FDA "may rely on any records or other information that [FDA] may inspect under [that] section to satisfy requirements that may pertain to a preapproval or risk-based surveillance inspection, or to resolve deficiencies identified during such inspections, if applicable and appropriate" (section 704(a)(4)(C)).

[27] FDA uses Form FDA 4003, titled *FDA Inspection Records Request*, to request records or other information from drug establishments pursuant to section 704(a)(4) of the FD&C Act. A request under section 704(a)(4) may be used to support products named in multiple applications manufactured at one establishment. In this situation, one Form FDA 4003 will generally be issued to the establishment to cover requests for records or other information for all the products in the applications being assessed.

[28] FDA will not issue a Form FDA 482, titled *Notice of Inspection*, to announce or open a remote interactive evaluation.

[29] See section 704(a)(4)(A) of the FD&C Act.

[30] See section 301(e) of the FD&C Act (21 U.S.C. 331(e)).

[31] See the definition for *complete response letter* in 21 CFR 314.3(b) and 21 CFR 600.3(ll). See also 21 CFR 314.110 and 21 CFR 601.3.

cannot confirm that application deficiencies have been satisfactorily addressed; or (3) carry other potential regulatory or legal consequences.[32]

In contrast, a facility's participation in an RIE is voluntary. FDA generally may seek to conduct an RIE when visual observation (e.g., product, facility, manufacturing operations, records, and other documents) and virtual engagement with facility staff may help the Agency make an application decision. Each facility should assess its capability to interact with FDA using technologies such as remote livestreaming, teleconferences, and screen sharing and determine whether the facility can meet FDA's request. If a facility is unable to support a virtual interaction or if FDA determines that virtual interaction during an RIE does not permit a sufficient examination of the facility or of a corrective action, FDA may terminate the RIE and instead conduct an inspection or use other available tools.[33] A facility may decline participation in an RIE (or a particular RIE request) before or during the RIE; however, FDA may not be able to complete its facility evaluation until it uses other oversight tools. An RIE may be the quickest means for FDA to assess a facility's activities, especially when factors prevent FDA from conducting a timely facility inspection. As such, declining to participate in an RIE may prolong a decision on an application.

For additional recommendations on how to prepare for an RRA and for communication expectations after FDA requests, initiates, or conducts an RRA, applicants and facilities should refer to the draft guidance for industry *Conducting Remote Regulatory Assessments Questions and Answers* (July 2022) or any successor guidance.

B. Inspections Conducted by Trusted Foreign Regulatory Partners

Section 809 of the FD&C Act (21 U.S.C. 384e) authorizes FDA to enter into arrangements and agreements with a foreign government or an agency of a foreign government to recognize the inspection of foreign establishments registered under section 510(i) of the FD&C Act (21 U.S.C. 360(i)) if FDA determines that those authorities are capable of conducting inspections that meet U.S. requirements.[34] Although FDA has not to date recognized PAIs or PLIs conducted by a foreign regulatory authority in the context of a section 809 mutual recognition agreement, FDA does collaborate with regulatory authorities and assesses shared inspection information to support application decisions.

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[32] See section 501(j) of the FD&C Act, relating to adulterated drugs, and section 801(a) of the FD&C Act (21 U.S.C. 381(a)), relating to imports. Imported drugs from an establishment may be subject to refusal (for example, if they appear to be adulterated).

[33] The guidance for industry *Remote Interactive Evaluations of Drug and Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (April 2021) includes additional information on how to plan and prepare for an RIE. As described in the *Federal Register* of March 13, 2023 (88 FR 15417), FDA issued this guidance to address the circumstances of the public health emergency and revised it to continue in effect for 180 days after the COVID-19 public health emergency declaration expired on May 11, 2023. As further described in the document, FDA intends to revise this guidance with any appropriate changes based on comments received and the Agency's experience with implementation.

[34] FDA's mutual recognition agreements with the European Union, Switzerland, and the United Kingdom provide for the acceptance of official inspection reports issued by a regulatory partner for manufacturing facilities located inside and outside of the partner's territory. For more information, see https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra and https://www.fda.gov/media/103391/download.

1. Information Sharing by Trusted Foreign Regulatory Partners

FDA may request an existing drug inspection report and other information from a foreign partner through mutual recognition and other arrangements or agreements to assess a facility's previous inspection history, to describe a facility's current state of CGMP control, and to determine whether the inspection covered the proposed manufacturing operations described in an application.[35] When a facility does not have an FDA inspection history or if prior FDA inspection coverage was limited, these reports help inform the Agency's determination of: (1) whether a PAI or a PLI may not be needed in certain circumstances, or (2) if additional information is needed to adequately assess the facility through an inspection or an RRA. FDA may request additional records and information through a section 704(a)(4) records request if the inspection report does not adequately address the application product, facility, or process-related risks.

2. Foreign Regulatory Inspections With FDA Remote Participants

The widespread use of innovative regulatory approaches and virtual interactive tools by foreign regulators may provide an opportunity for increased inspection collaboration between regulatory authorities and for harmonized marketing authorization decisions for drug products. FDA is evaluating the utility of collaborative assessments with regulatory partners for PAIs and PLIs when regulatory agencies have a mutual interest in a facility and/or a drug(s). A collaborative assessment may include a combination of an on-site lead inspectorate and one or more participating remote regulatory authorities connecting through virtual interactive technologies.

Implementation of these collaborative assessments may help FDA streamline operations and overcome logistical travel challenges by leveraging local inspection teams and virtual interactive technologies to obtain information to support regulatory decisions. In addition, regulator collaboration may facilitate timely availability of critical drugs in multiple markets globally and reduce inspection redundancy for the same product and facility. At the time of issuance of this guidance, FDA is conducting a pilot project[36] in this area and intends to use information and experience gained from ongoing collaborative assessment activities to inform FDA's future decision-making on this topic.

C. PAIs and PLIs With FDA Remote Subject Matter Experts

As the Agency has gained experience with virtual interactive technologies, FDA sees the potential benefit of using these technologies to meet technical and logistical needs in certain circumstances by supplementing an inspection with remote resources. As a result, FDA intends to make the expertise of remote personnel available to on-site FDA inspection teams to support

[35] Section 809 of the FD&C Act authorizes FDA to rely on inspections performed by capable foreign regulatory partners. In the absence of FDA's capability determination, FDA intends to use inspection reports of other foreign regulatory partners as a source of information in evaluating an application.

[36] FDA is a participating member of the International Coalition of Medicines Regulatory Authorities that is piloting a program for collaborative hybrid inspections by multiple regulatory authorities. For more information, see https://icmra.info/drupal/en/strategicinitatives/pqkms.

PAIs and PLIs and to facilitate regulatory decision-making and timely application decisions.[37] This enhancement will help FDA maintain operational flexibility through enhanced efficiency and transparency.

For the purpose of the Agency's application decision, FDA may consider supplementing a PAI or a PLI with remote resources when: (1) the expertise and input of a subject matter expert (SME) is determined by the on-site inspection team lead to be necessary to adequately assess an application product, a manufacturing process and its controls, or a facility, and to verify conformance to the application and compliance with the CGMP requirements; and (2) the physical, on-site participation of such an individual is not feasible. To support a PAI or a PLI with remote resources, FDA will request confirmation of a facility's willingness to accept involvement of remote Agency personnel as well as confirmation of the facility's willingness and ability to adequately employ virtual interactive technologies to remotely connect an SME to an FDA inspection, when appropriate. FDA does not intend to grant requests from facilities for the use of remote personnel to support any PAI or PLI. Although facility agreement to the involvement of remote Agency personnel is voluntary, FDA's use of remote resources would provide for real-time, virtual engagement of an off-site expert directly with the on-site inspection team and facility staff, as the inspection team lead determines necessary, to address specific issues bearing on the inspection (e.g., aspects of product manufacturing, facility conditions).

When FDA anticipates using remote resources during an inspection, the Agency intends to notify the facility by electronic correspondence or by telephone call and include a written request for the facility to confirm its willingness and ability to interact with remote FDA personnel using virtual technology (to be provided by the facility or by the FDA on-site inspection team using FDA technology), including the use of a livestreaming video, screen sharing, and teleconference. The request would indicate: (1) the name, address, and FDA Establishment Identifier or unique identifier of the facility to be inspected; (2) the application or supplement number; (3) the reasoning for FDA's use of remote resources; and (4) the names and positions of the remote personnel, if known in advance.

Upon the facility's agreement to Agency use of remote resources, FDA will facilitate the planning and coordination of the inspection and involvement of a remote SME. The on-site inspection team lead will schedule a virtual meeting with the facility to discuss logistics and expectations. When a facility agrees to the involvement of a remote SME during an inspection, FDA expects the same level of cooperation and transparency with remote FDA personnel as expected with the on-site inspection team.

When the facility provides equipment enabling the involvement of a remote SME, the quality of the virtual 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 remotely viewing and evaluating operations at the facility, as appropriate (e.g., aseptic practices, equipment cleaning and setup, material weighing and dispensing, instrument setup, sampling, testing). Any

[37] FDA considers the remote subject matter expert to be a resource for use by FDA inspection teams and such use of a remote subject matter expert does not constitute an RRA.

challenges encountered by the facility in furnishing or operating such equipment or technologies should be communicated to the inspection team lead as soon as possible.

The FDA inspection team will initiate the inspection on-site before connecting the remote SME. Each virtual interaction with a remote SME will be made with the knowledge and agreement of the inspection team lead who is physically present on-site[38] and will include a participating inspection team member on-site and who is participating in that interaction at the time that interaction occurs. To ensure transparency, facilitate information collection, and provide for adequate on-site follow-up, any pertinent information or considerations noted by the remote SME will be communicated to the inspection team for confirmation while the team is physically on-site with facility staff. The on-site inspection team will maintain responsibility for verifying, documenting, and determining which observations are listed on Form FDA 483, titled *Inspectional Observations*. FDA will continually evaluate the utility of this alternative tool and the appropriate conditions for which a remote SME can best be used to support a PAI or PLI.

V. THE EFFECTS OF USING ALTERNATIVE TOOLS

In general, the use of alternative tools will help FDA fulfill its commitments to meet user fee goal dates and to make timely application decisions.

If observations are identified by FDA through the use of alternative tools, a written list of observations may be presented by FDA to the facility.[39] A facility should submit any responses or corrective actions to FDA within 15 U.S. business days for consideration in the application assessment. Responses received after 15 U.S. business days may be deferred for further assessment in the next application assessment cycle. If FDA determines that there is insufficient information available to make a determination on the acceptability of a facility and an inspection is needed to address concerns, FDA will communicate this determination in application milestone meetings, action letters, postaction letters, and/or communications regarding scheduling of the inspection, as appropriate.

[38] The on-site presence of the inspection team lead and other inspection team members is consistent with section 704(a)(1) of the FD&C Act, which authorizes inspections by physically present investigators. Use of remote SMEs can support inspections as described above.

[39] FDA issues a Form FDA 483, titled *Inspectional Observations,* at the conclusion of an inspection when FDA observes objectionable conditions or practices.