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Post COVID FDA Inspections

What ~~has~~ hasn't changed?

March 30, 2023

15:00- 15:45	FDA 2023 inspectional activity	Carl Accettura

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Facing Global Disruption...
Fully 3 Years to return to "New Normal"
And FDA post-Pandemic rules have really changed…

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Outline - FDA 2020-2022 Inspectional Crisis & Backlog

- Pre-COVID Routine – Foreign Inspection cadence, grouping & notice
- March '20 – Suspend Foreign Inspections; then Domestic Inspections
  - PAIs and NDA PDUFA Action Dates put at risk
    - Indeterminate Delays and Guidance came after the fact
    - Small, emergent companies - financial hits (Bankruptcy, Job cuts)
  - New Overseas Establishments "In limbo"
    - State of uncertainty or suspended animation
- 2021 Discussion – Priority Industry Proposals & Opportunities for Collaboration and Dialogue - FDA Reactions, Comments, and Questions for Industry

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SCORR Marketing
Tomita Pharmaceutical
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Veeva Systems
Waters Corp.
White Owl Global

PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION

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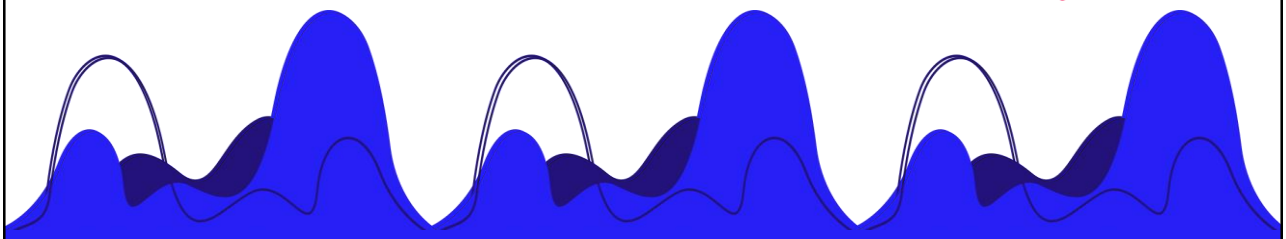
Still Facing Global Disruptions...

FDORA (2023) ALLOWED REMOTE RECORDS REQUESTS TO COUNT AS FDA INSPECTIONS.



What is the nature of those vulnerabilities, and how does FDA protect against future disruptions ?

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Outline - FDA 2021-2023 inspectional evolution

- **FDA Mutual Recognition Agreements with EU countries**
- **FDA stated "Mutual Reliance" on PIC/S members (October 2022)**
  - **FDA has requested PIC/S-based inspection reports by PMDA & Prefecture Authorities**
- **Remote Interactive Evaluations & Regulatory Assessments**
- **No "Boots-on-the Ground" Inspections in Countries for > 2 ½ yrs**
- **Still delays in scheduling & "rescheduling"**

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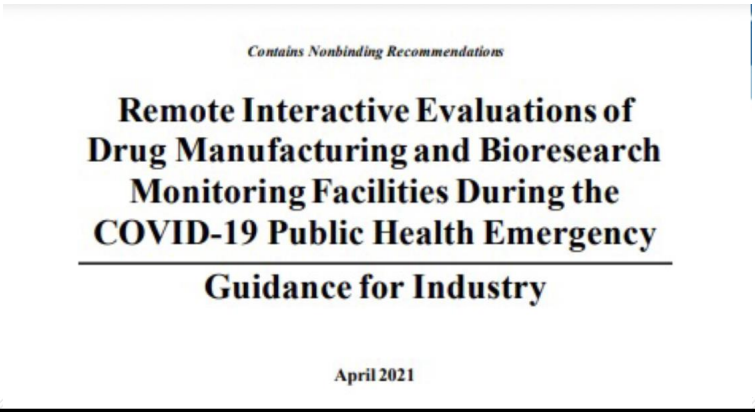
Outline - FDA 2021-2023 inspectional evolution

During the pandemic, the FDA made substantial efforts to rely on record reviews to reduce the number of applications for which a pre-approval inspection was deemed necessary. That in turn was critical in the FDA's ability to meet user fee goals for drug and biologic reviews throughout the pandemic.



Contains Nonbinding Recommendations

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency

Guidance for Industry

April 2021

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Alternative Tools

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- REMOTE INTERACTIVE EVALUATIONS
- RECORD REVIEW AUTHORIZED UNDER SECTION 704(A)(4) OF THE FD&C ACT
- PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S)
- BILATERAL INFORMATION SHARING

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Records Requests | Remote Facility Evaluations | Inspections

Industry seeks clarity on **(1)** the differences between Records Requests, Remote Facility Evaluations, and Inspections, as well as **(2)** when and how FDA will utilize each regulatory oversight tool/mechanism independently or in combination (if applicable).

- **Discussion Topics & Questions:**
  - Are remote facility evaluations different from 704(a)(4) records requests? If so, how?
  - What criteria will the Agency use to choose between a records request, remote facility evaluation, or inspection?
  - Will multiple tools be used to evaluate a given facility? For a PAI, for example, does FDA envision that the Agency would utilize more than one of these regulatory tools per regulatory application?
  - Industry recommends that FDA make public a document describing the differences between the tools as well as how the Agency intends to employ each tool.
  - Has FDA considered whether a records request or remote facility evaluation could be used to update a site's compliance status in the FDA Inspection Classification Database?

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Outline - FDA 2022-2023 inspectional evolution

- 2022 Guidance (May) – Benefit-Risk: Product Quality Assessment

Benefit-Risk Considerations for Product Quality Assessments

Guidance for Industry

DRAFT GUIDANCE

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Outline - FDA 2022-2023 inspectional evolution

- 2022 Guidance (May) – Benefit-Risk: Product Quality Assessment

B. Assessment of Risks Posed by a Product Quality Issue or Set of Issues

- **Inspectional findings.** FDA uses a risk-based approach to determine whether a preapproval or prelicensure inspection is needed using information provided in the application and information FDA may have regarding the facilities named in the application. The Agency may also use information from a previous surveillance inspection to inform a decision on the need for a preapproval or a prelicensure inspection or in lieu of such an inspection. A credible surveillance inspection may have been performed by FDA or by a national regulatory authority found capable under section 809 of the FD&C Act (21 U.S.C. 384e).

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Outline - FDA 2022-2023 inspectional evolution

- Next Steps 2023 – Backlog Challenges – Overseas Scheduling Investigator Shortages → Reschedule, Reschedule
- FDORA: Remote Records Requests = FDA Inspection
  - "Boots on Ground" no longer statutory constraint for FDA
- Fiscal 2024 (Oct. 2023) – New Inspection Workflow Platform

(Dr. Woodcock)

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FDA 2023-2024 inspectional evolution

Pink Sheet
Pharma Intelligence

03 Mar 2023 | **News**

US FDA's Woodcock Outlines Plans For Quicker Inspection Workflow Platform, Expected Next Year

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FDA 2023-2024 inspectional evolution

US FDA's Biggest Post-COVID Challenge Helped By Small Inspections Tweak In FDORA

31 Jan 2023 | **OPINION**

by Michael McCaughan | @RPMReportMike | michael.mccaughan@previsionpolicy.com

Executive Summary

The omnibus spending bill included dozens of reform provisions related to the US FDA. One seemingly minor change to FDA's inspection authorities could end up being a big help to the challenges ahead in catching up after the COVID-19 pandemic.

FDORA ALLOWED REMOTE RECORDS REQUESTS TO COUNT AS FDA INSPECTIONS.

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FDA 2023-2024 inspectional evolution

It is not just that the FDA hasn't visited nearly as many sites as it would have over the past three years. It is also that manufacturers have been under stress to try to maintain operations during that period as well. The FDA is bound to uncover some issues with quality where well-intentioned manufacturers just were not able to do things as well as they wished and, no doubt, some less well-intentioned operators who recognized a chance to cut corners under the circumstances.

The changes in the year end law make it a bit easier for the FDA to juggle all those challenges, even if they by no means make the challenge easy.

The new language amends the existing authority for the FDA to request and review records from firms to state that the agency "may rely on any records or other information that [it] may inspect under this section to satisfy requirements that may pertain to a preapproval or risk-based surveillance inspection, or to resolve deficiencies found in such inspections, if applicable and appropriate." The law also explicitly allows the FDA to rely on foreign regulatory partners in the context of pre-approval inspection, not just for surveillance inspections.

FDORA ALLOWED REMOTE RECORDS REQUESTS TO COUNT AS FDA INSPECTIONS.

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FDA 2023-2024 inspectional evolution

But there is one seemingly minor statutory change that could end up being quite important in helping the FDA address what may be its biggest looming challenge: how to catch up on inspections after the COVID-19 travel disruptions of the past three years.

My vote is that the most important statutory change enacted in FDORA is one that allows the FDA to use record reviews to satisfy the statutory requirement to "inspect" manufacturers. The change is found in Section 3613 of FDORA, which amounts to a codification of the FDA's policy of relying on alternatives to in-person inspections during the COVID pandemic. (Also see "Unannounced Foreign Drug Inspection Pilot, Other US Inspection Measures Enacted" - Pink Sheet, 10 Jan, 2023.)

The critical nuance, however, is that the new language explicitly states that the FDA may use record reviews to fulfill the statutory requirements for periodic inspections, not just to rule out the need for a pre-approval inspection.

FDORA ALLOWED REMOTE RECORDS REQUESTS TO COUNT AS FDA INSPECTIONS.

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FDA 2023-2024 inspectional evolution

Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection; Draft Guidance for Industry, Revision 1; Availability; Docket FDA-2013-D-0710-0018; https://www.regulations.gov/document/FDA-2013-D-0710-0018; no comment period.

Documents from Program 7356.002 Drug Quality Assurance and 7346.832 New Drug Evaluation are recommended. They describe changes to Q9, Q10, and Q12 and were implemented on 10/17/22

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM PROGRAM 7356.002

CHAPTER 56—DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE:
Drug Manufacturing Inspections REVISION: Revised to add elements of International Council for Harmonisation (ICH) guidances for industry *Q9 Quality Risk Management, Q10 Pharmaceutical Quality System,* and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management;*[1] control of nitrosamine impurities; and alternative tools for evaluating facilities.	10/17/2022

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM PROGRAM 7346.832

CHAPTER 46—NEW DRUG EVALUATION

SUBJECT:	IMPLEMENTATION DATE:
Preapproval Inspections Revision: Compliance program revised to add elements of International Council for Harmonisation (ICH) guidances for industry *Q10 Pharmaceutical Quality System* and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management,*[1] control of nitrosamine impurities, and alternative tools for evaluating facilities.	10/17/2022

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CMO/CDMOs: Challenges & Opportunities

PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION

Gil Roth • President • PBOA

US-Japan Healthcare Study Group

November 17, 2022

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Pharma & Biopharma Outsourcing Association

Founded in 2014, the **Pharma & Biopharma Outsourcing Association (PBOA)** is a nonprofit trade association dedicated to advancing the regulatory, legislative and general business interests of CMOs, CDMOs, and other contract service providers.

PBOA's 48 Member companies and 22 Affiliate members provide the technologies and services that help the pharma and biopharma industry develop, manufacture and package drugs, biologics, vaccines, OTC products and other treatments safely and cost effectively.

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PBOA CMO/CDMO Members

https://pharma-bio.org/

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Outline - FDA 2023-2024 Inspectional evolution

PBOA Annual Meeting & Conference **October 2022**

AGENDA

1:35-2:10	**FDA**: CDER CGMP Updates	Tara Gooen-Bizjak, CDR · **FDA**
3:45-4:20	**FDA**: Quality Metrics & Quality Management Maturity: Next Steps	Nandini Rakala · **FDA/CDER**
4:20-4:55	**FDA**: Inspectional Update	Alonza Cruse · **FDA/ORA**

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Mr. **Carl Accettura**

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ORA Inspectional Activity Updates

PBOA Annual Meeting & Conference - 2022

Alonza Cruse, Director

Office of Pharmaceutical Quality Operations

U.S. Food and Drug Administration

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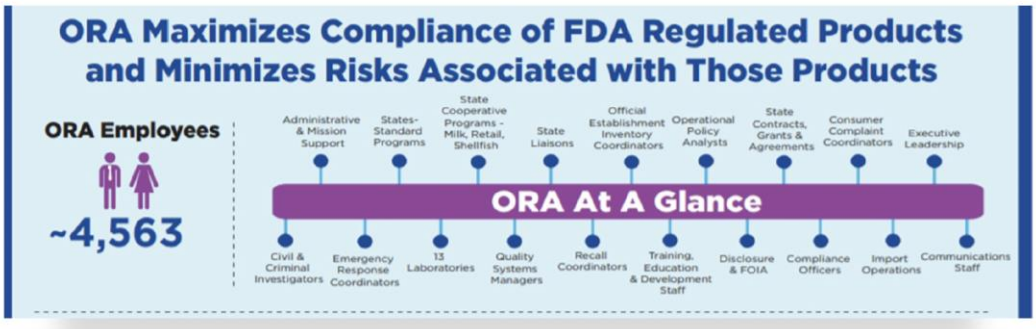
ORA Roles and Responsibilities



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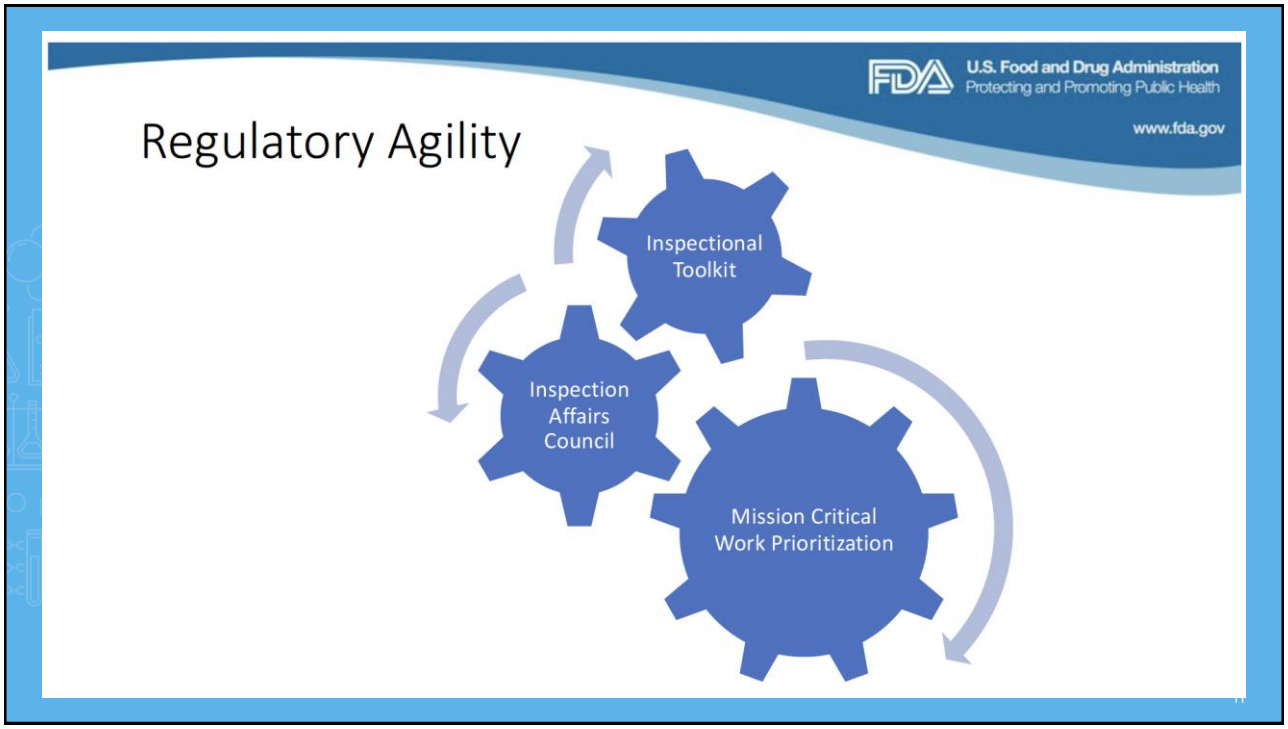

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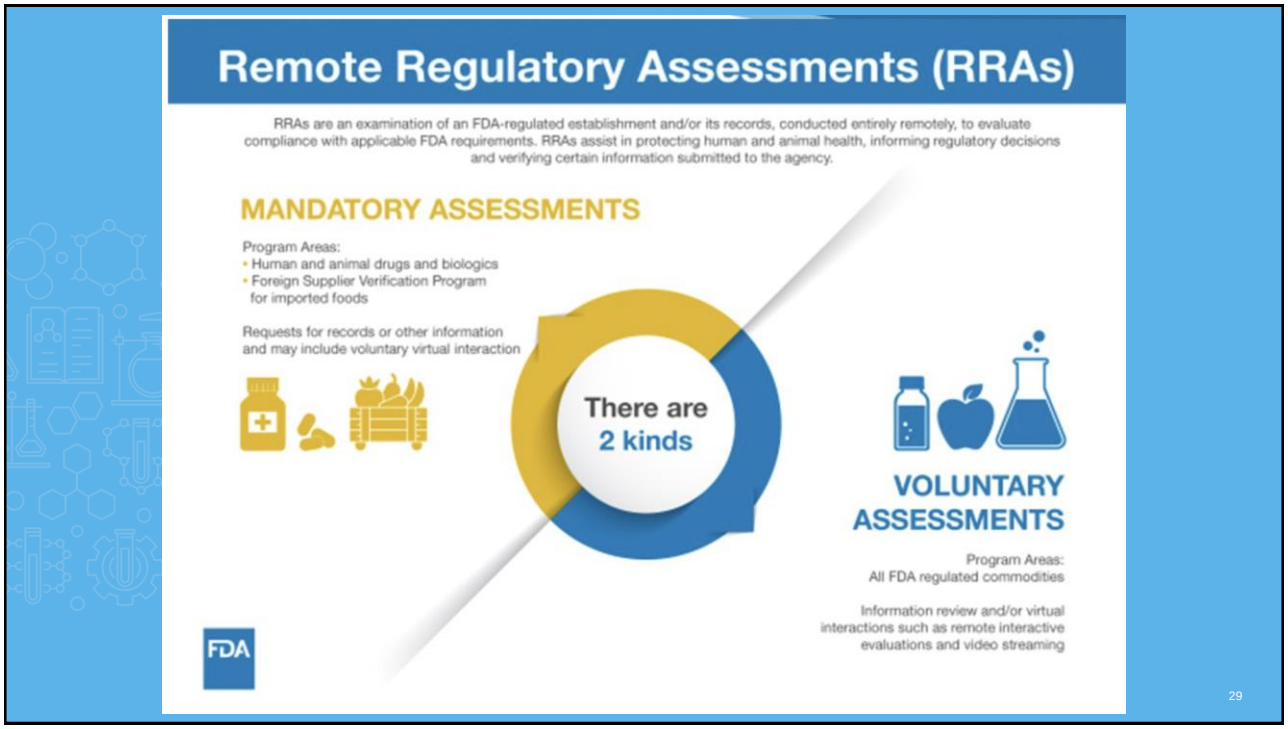
Remote Regulatory Assessments (RRAs)
RRAs are an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs assist in protecting human and animal health, informing regulatory decisions and verifying certain information submitted to the agency.
MANDATORY ASSESSMENTS
Program Areas:
• Human and animal drugs and biologics
• Foreign Supplier Verification Program for imported foods
Requests for records or other information and may include voluntary virtual interaction
There are 2 kinds
VOLUNTARY ASSESSMENTS
Program Areas:
All FDA regulated commodities
Information review and/or virtual interactions such as remote interactive evaluations and video streaming
FDA
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GUIDANCE DOCUMENT
Conducting Remote Regulatory Assessments Questions and Answers
Draft Guidance for Industry
JULY 2022
Download the Draft Guidance Document
Read the Federal Register Notice
Draft
Not for implementation. Contains non-binding recommendations.
Share
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https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-remote-regulatory-assessments-questions-and-answers

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Contains Nonbinding Recommendations

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency

Guidance for Industry

April 2021

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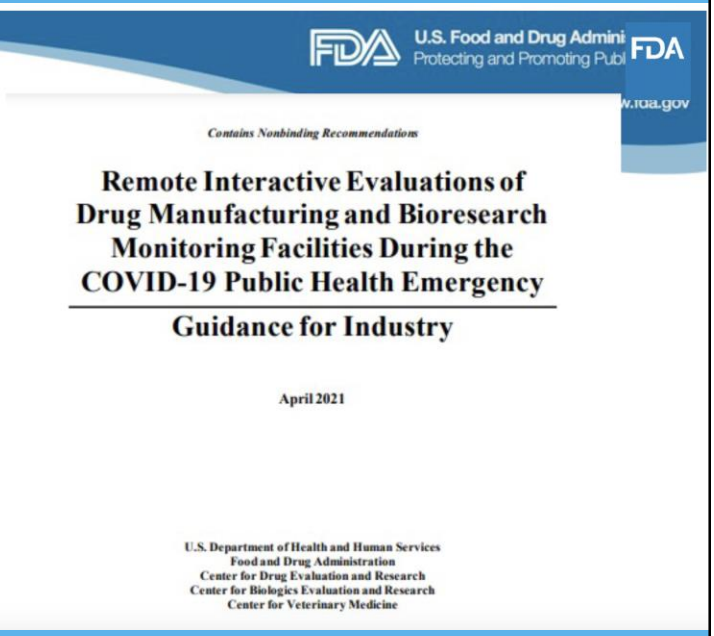
1. Drugs are manufactured, processed, packed, or held
2. Facilities covered under FDA's bioresearch monitoring (BIMO) program;
3. and outsourcing facilities registered under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)



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Compliance Activities…

For-Cause OAI Follow Up

Foreign Activities

CONOPS Commitments

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Questions and Answers: Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations

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Q1: What prompted development of the Concept of Operations (ConOps)?

A1: While working on Program Alignment, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) identified an opportunity to further enhance collaboration beyond the specialization of field staff in the district offices. The ConOps between ORA and CDER outlines responsibilities and workflows that help streamline human drug facility evaluations, inspections, and communication.

The ConOps enables CDER and ORA to more effectively manage the growing complexity of the pharmaceutical manufacturing and to meet new challenges by:

- Ensuring consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across FDA;
- Advancing strategic alignment across ORA and CDER functional units by creating clear roles and responsibilities;
- Improving FDA's operational capacity by enhancing collaboration between various CDER and ORA offices;
- Enhancing the quality of and increasing access to facility and regulatory decisional information across FDA; and
- Meeting user fee commitments and improving the timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.

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Inspections

- FDA Mutual Recognition Agreements with EU countries
- FDA's recently stated "Mutual Reliance" on PIC/S members **(Alonza)**
  - FDA has requested PIC/S-based inspection reports by PMDA & Prefecture Authorities
  - **This helped a Japanese Company receive NDA Approval, without on-site inspection**
  - **CMO shared GMP records over a year, some under FDA 704 (a) (4) Records Request**
    - **Extensive resources and time spent with large document translations (e.g. Methods Validation)**
    - **Voluntary submissions included PIC/S-based inspection reports by PMDA & Prefecture Authorities**
- Remote Interactive Evaluations
- Remote Regulatory Assessments
- No "Boots-on-the Ground" Inspections in Japan for > 2 ½ years
  - Continued delays in scheduling & "rescheduling"
  - **An early November trip scheduled in August was postponed in September; Yet to be rescheduled**

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Outline - FDA 2020-2023 inspectional evolution

- Pre-COVID Routine – Foreign Inspection cadence, groupings & notification
- March '20 – Suspension of Foreign Inspections; followed by Domestic Inspections
  - PAIs and NDA put at risk
  - New Establishments "In limbo" (state of uncertainty or suspended animation)
- Discussion – Priority Industry Proposals & Opportunities for Collaboration and Dialogue - FDA Reactions, Comments, and Questions for Industry
- Next Steps in 2023

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FDA-Industry Meeting to Discuss Risk-based Approaches to Inspections & Records Requests During and After the COVID-19 Public Health Emergency

January 26, 2021

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Meeting Objectives (Industry Perspective?)

- **Build shared understanding between the FDA and Industry through constructive discussion on (1) the challenges presented by the COVID-19 public health emergency (PHE), and (2) potential solutions to address the identified challenges**
- **Identify opportunities for Industry to support the FDA in its ongoing efforts as well as with any potential new initiatives the Agency is exploring**
- **Align on next steps and identify potential opportunities for future collaboration and dialogue between FDA and Industry**

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Industry Proposal Overview

- Industry supports FDA's efforts to enhance its risk-based approach to regulatory decision-making in the manufacturing space, including the Agency's utilization of "all available tools and sources of information to support regulatory decisions on applications that include sites impacted by FDA's ability to inspect due to COVID-19." [FDA Aug. 2020 Guidance]
- The Joint Industry Proposal titled, *Risk-based Approaches to Inspections and Records Requests During and After the COVID-19 Public Health Emergency*, offers 15 individual recommendations that build on FDA's ongoing efforts to ensure continuity of the global supply chain and timely patient access to quality medicines. Industry's 15 recommendations can be grouped under the following four topic areas:
  - Records Requests
  - Virtual Inspections
  - Pre-Inspection Dialogue
  - Pre-Approval and Pre-License Inspections
- Industry's recommendations describe the opportunities we see for the Agency to leverage the flexibility within the current legal and regulatory framework to create resource efficiencies and enhance the Agency's risk-based approach to regulatory oversight.

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Priority Topics for Today's Discussion

- A summary of each of the 15 Industry recommendations can be found in the "Back-up Slides." For today's meeting, Industry has prioritized the following topics for discussion:
  - Enhanced Communication, Challenges, and Process Optimization w/r/t Records Requests
  - Virtual Inspections
  - Remote Facility Evaluations
  - Differentiation between Records Requests, Remote Facility Evaluations, and Inspections & when and how each will be employed/utilized independently or in combination (if applicable)
  - FDA Approaches to Application Decisions During COVID-19

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Enhanced Communication, Challenges, and Process Optimization w/r/t Records Requests

Original Industry Proposal: Industry requests that FDA establish a formal process to provide a letter to firms indicating the conclusion of a 704(a)(4) records request, as well as whether the Agency intends to conduct an inspection in follow-up to the records request.

- **Discussion Topics & Questions:**
  - Industry understands that FDA may be working on a guidance or procedural document to address this topic. Can FDA provide more details?
  - In general, Industry member companies have run into resource challenges with the increased number of records requests during COVID-19.
    - What has been FDA's experience with the records request process throughout the COVID-19 PHE? Are there opportunities to work together to improve the process?
  - Industry member companies also feel that both the Agency and Industry would benefit from increased communication throughout the records request process in order to create efficiencies for both parties.
    - Does FDA have any preliminary thoughts on whether increased communication during the process would (1) be helpful to the Agency and (2) be feasible from a resource perspective?

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Virtual Inspections

Original Industry Proposal:

- Industry recommends that FDA establish a framework for (e.g., issue interim guidance), and begin conducting, "virtual inspections" (i.e., begin issuing virtual FDA Form 482s).
  - Industry envisioned that "virtual inspections" would incorporate the use of "virtual technologies" which Industry defined in our proposal as "interactive tools or platforms that can facilitate real-time discussion and document transfer as well as provide opportunities for investigators (and reviewers, when appropriate) to conduct a visual assessment of a manufacturing facility, including the remote observation of manufacturing processes."

Discussion Topics & Questions:

- Industry understands that FDA has interpreted the current statutory definition of an inspection to mean on-site inspections only. Can FDA confirm its definition of an inspection?
- Industry strongly supports FDA's increased reliance on the factual findings in inspection reports from "recognized" authorities under the MRA as well as other "capable" authorities with whom FDA has an established confidentiality agreement.
  - Given that many other health authorities are conducting virtual inspections, is FDA concerned that its inability to conduct virtual inspections will reduce the utility of current or future, formal or informal recognition agreements or practices?

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Remote Facility Evaluations

Industry understands that FDA is working to develop guidance and/or procedural documents to describe "remote facility evaluations."

- **Discussion Topics & Questions:**
  - Can FDA provide a description or definition of a "remote facility evaluation"?
  - Can FDA clarify whether virtual technologies will be incorporated in remote facility evaluations?
  - For what inspection types will remote facility evaluations be employed?
  - Can FDA describe how the Agency intends to utilize remote facility evaluations?
    - Will a remote facility evaluation be used to determine whether an inspection is needed? Or will this tool be employed after FDA has determined that a GMP/facility assessment of some description is needed, but the Agency has determined that an inspection is not necessary? Or will it be used for some other purpose?
  - Does the Agency have any concerns with the utilization and implementation of remote facility evaluations and/or the use of virtual technologies? Is there an opportunity for Industry to provide any assistance to the Agency on this effort?

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Records Requests | Remote Facility Evaluations | Inspections

Industry seeks clarity on **(1)** the differences between Records Requests, Remote Facility Evaluations, and Inspections, as well as **(2)** when and how FDA will utilize each regulatory oversight tool/mechanism independently or in combination (if applicable).

- **Discussion Topics & Questions:**
  - Are remote facility evaluations different from 704(a)(4) records requests? If so, how?
  - What criteria will the Agency use to choose between a records request, remote facility evaluation, or inspection?
  - Will multiple tools be used to evaluate a given facility? For a PAI, for example, does FDA envision that the Agency would utilize more than one of these regulatory tools per regulatory application?
  - Industry recommends that FDA make public a document describing the differences between the tools as well as how the Agency intends to employ each tool.
  - Has FDA considered whether a records request or remote facility evaluation could be used to update a site's compliance status in the FDA Inspection Classification Database?

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FDA Approaches to Application Decisions During COVID-19

Original Industry Proposal: Industry strongly recommends that FDA make every effort to [assess a facility via alternative means] before the Agency considers issuing a complete response to an applicant, if the only basis for the complete response is an inability to conduct an inspection due to travel restrictions.

- **Discussion Topics & Questions:**
  - Industry has significant concerns with FDA's intention to issue a CRL for applications where "FDA determines that an inspection is necessary for approval" but travel restrictions prevent the Agency from conducting an on-site inspection by the action date. [FDA Aug. 2020 Guidance]
  - Industry also has significant concerns with FDA's intention to "defer action on the application until an inspection can be completed" in cases where there is "inadequate information to make a determination on the acceptability of a facility." [FDA Aug. 2020 Guidance]
  - Can FDA help us understand its reasoning for issuing CRLs under these circumstances? Is FDA willing to reconsider this practice?
  - [Placeholder for any questions or concerns we want to highlight w/r/t the Dec. 2020 FDA guidance on review timelines for applicant responses to CRLs received due to COVID travel restrictions]
    - [I've heard from a few PhRMA members that they don't believe the guidance provides any info on the steps an applicant should take to retrigger the PAI/PLI and that there are a number of other unanswered questions, such as if and how these inspections will be prioritized once travel restrictions are lifted…]

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FDA Reactions, Comments, and Questions for Industry

Next Steps & Future Opportunities for Collaboration and Dialogue

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FDA-Industry Meeting to Discuss Risk-based Approaches to Inspections & Records Requests During and After the COVID-19 Public Health Emergency

January 26, 2021

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Back-Up Slides

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Industry Recommendations

Records Requests

- **(1)** Industry requests that FDA establish a formal process to provide a letter to firms indicating the conclusion of a records request (as described in FDCA 704(a)(4)), as well as whether the Agency intends to conduct an inspection in follow-up to the records request.
- Industry urges FDA to begin incorporating virtual technologies to supplement 704(a)(4) records requests and to issue interim guidance to allow for the use of virtual technologies in records requests in order to:
  - **(2)** Enhance Pre-Approval Facility Evaluations,
  - **(3)** Facilitate abbreviated on-site inspections, and
  - **(4)** Follow-up with Official Action Indicated (OAI) sites to verify that corrective actions have been implemented and to re-classify OAI sites, if applicable.

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Industry Recommendations, *cont.*

Virtual Inspections

- **(5)** Industry recommends that FDA establish a framework for (e.g., issue interim guidance), and begin conducting, "virtual inspections" (i.e., begin issuing "virtual FDA Form 482s").
- **(6)** Industry has significant concerns with FDA's intention to issue a CRL for applications where "FDA determines that an inspection is necessary for approval" but travel restrictions prevent the Agency from conducting an on-site inspection by the action date. Industry strongly recommends that FDA make every effort to conduct a virtual inspection before the Agency considers issuing a complete response to an applicant, if the only basis for the complete response is an inability to conduct an on-site inspection due to travel restrictions.
- **(7)** Industry encourages FDA to update its COVID-19 Q&A Guidance (or otherwise publicly disclose) that inspection reports generated for a virtual inspection are in scope of the Agency's current efforts as described in recently-published guidance for industry.

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Industry Recommendations, *cont.*

Pre-Inspection Dialogue

- **(8)** Industry recommends that FDA establish a structured process for pre-inspection dialogue with firms for all inspection types, including by issuing interim guidance (or otherwise publicly communicating guidelines) for pre-inspection dialogue that includes **considerations specific to the COVID-19 public health emergency** (e.g., discussion of a site's operational controls for visitors).
- **(9)** Industry recommends that FDA establish a structured process for pre-inspection dialogue with firms for all inspection types, including by issuing interim guidance (or otherwise publicly communicating guidelines) for pre-inspection dialogue that includes **specific considerations for virtual inspections**. (This recommended pre-inspection dialogue guide should also be included in the proposed interim guidance on virtual inspections.)

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Industry Recommendations, *cont.*

Pre-Approval and Pre-License Inspections

- **(10)** Industry proposes conditions under which the Pre-Approval Facility Evaluation defined in Compliance Program 7346.832 should be sufficient to waive a PAI/PLI *(see pg. 22 in the Joint Industry Proposal)* and recommends that FDA establish and communicate these criteria through guidance, MAPPs, SOPPs, or other guidelines/procedures, as appropriate.
- **(11)** Industry proposes that FDA establish a formal PAI/PLI waiver process to allow sponsors to request and justify a waiver for a PAI/PLI.
- **(12)** Industry requests that FDA establish timelines to inform sponsors whether or not a PAI/PLI will be required, such that sponsors and/or manufacturers (in cases where the sponsor and facility owner differ) can adequately prepare for the PAI/PLI and/or explore alternate methods (e.g., virtual inspections or records requests) for FDA to obtain and evaluate the information needed to complete its product quality assessment.

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Industry Recommendations, *cont.*

Pre-Approval and Pre-License Inspections, *cont.*

- **(13)** Industry strongly supports and applauds FDA's increased use of inspection reports from recognized health authorities under the MRA and certain other "capable" authorities (e.g., Health Canada, TGA) with whom FDA has an established confidentiality agreement. We encourage FDA to extend this practice to inspections of sites located outside the U.S. and EU as allowed under Article 8 of the MRA. For authorities that are not party to the MRA, Industry encourages FDA to update its agreements (either formally or informally) with those authorities to include "third countries."
- **(14)** Industry recommends that FDA create a process step to ensure that as soon as the review team is formed, reviewers (or the project manager) are checking with sponsors (and/or manufacturers) regarding the availability of inspection reports from other health authorities. Industry is aware that the Center offices responsible for quality surveillance provide reviewers with a site dossier that includes "foreign regulator inspection outcomes," however, it is unclear how often the site dossiers are updated, and Industry is concerned that reviewers may not have access to the most up-to-date information. FDA contacting the sponsor (and/or manufacturer) to obtain the latest information will ensure that the review teams have all available information for a given site.

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Industry Recommendations, *cont.*

Pre-Approval and Pre-License Inspections, *cont.*

- **(15)** In situations where FDA determines that a PAI/PLI is needed, Industry encourages FDA to establish procedures to enhance the Agency's utilization of the Mutual Recognition Agreement for pre-approval inspections, especially where travel restrictions may prevent FDA from traveling to a country with a recognized authority under the MRA.
  - For applications (1) for which a PAI/PLI is required, (2) that list a manufacturing facility in a country whose Health Authority is a party to the MRA, and (3) whose sponsor has requested (in the cover letter) that the Agency consider utilizing Article 11 of the MRA for that particular application, Industry recommends that FDA submit a written request to the HA to conduct a PAI/PLI no later than 74 days after receiving the application. As required under Article 11 of the MRA, the request will include the reason for the request and identify the precise issues to be addressed in the inspection, as well as the requested timeline for completing the inspection and transmitting the official GMP documents to FDA.
  - If the requested authority is unable to complete the inspection, FDA should consider conducting a virtual inspection or deferring the inspection to post-approval when travel restrictions are lifted or when Agency resources can accommodate an on-site inspection.

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