FDA's Facility Oversight

A Collaborative Effort between OPQ & ORA to Inspections during the COVID-19 Public Health Emergency (PHE)

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Office of Pharmaceutical Manufacturing Assessment - OPMA

Mission: **Ensure that Quality is built into commercial manufacturing processes and facilities over the product lifecycle**

[Report on the State of Pharmaceutical Quality FY2020 (Aug 2021)]

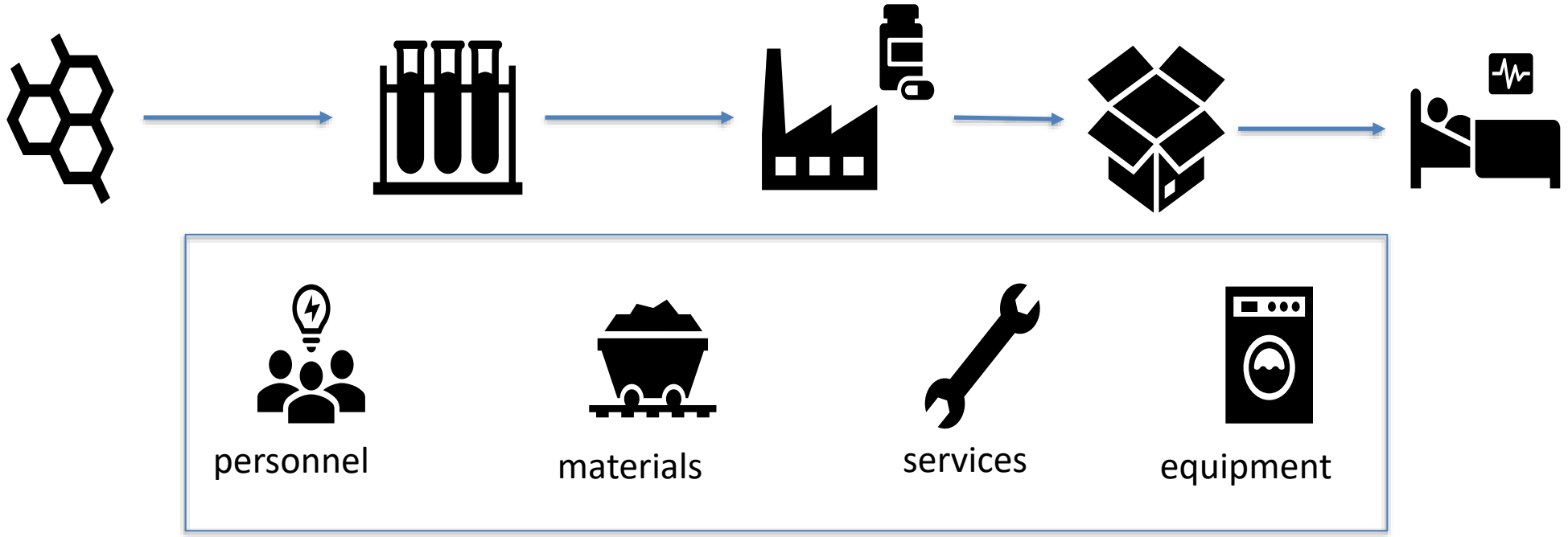
[Office of Pharmaceutical Quality (OPQ) Annual Report (Feb 2021)]:

Outline

- **Landscape of manufacturing & supply chains during the Covid-19 Pandemic**
- **FDA/CDER's Response**
- **Approach to Facility Assessments/Inspections**
  - Pre-Approval (PAIs) & Pre-License (PLIs) inspections
  - Remote Interactive Evaluations (RIEs)
- **Concluding Remarks**

Supply Constraints

- The supply chain supporting the manufacture of FDA-regulated products has been impacted at multiple levels
  - 55% of Drug manufacturing sites supplying product to USA are Abroad
  - ~ 1/3 of API Sites are in China and India



CDER COVID-19 Manufacturing & Supply Chain Initiatives

- Expedited assessment for drugs in shortage or drugs needed for COVID-19
- Provided direct feedback to inquiries on CMC changes related to COVID-19
  - Contact: CDER-OPQ-Inquires@fda.hhs.gov
- Implemented Alternative Tools to assess facilities in lieu of Inspections
- Issued Guidance & Regulatory Information
  - Manufacturing, Supply Chain, and Drug & Biological Product Inspections | COVID-19
  - Remote Interactive Evaluations of Drug Manufacturing and BIMO Facilities | COVID-19
  - Resiliency Roadmap for FDA Inspectional Oversight
- Engaged International Regulators and Industry
  - ICMRA Workshop – July 7-8, 2021

Actions to Enable COVID-19 Manufacturing Capacity

- Engaged with Sponsors on strategies to increase capacity for COVID-19 therapeutics

- Applied a risk-based approach for post-approval submissions
  - Flexibility with data requirements
  - Risk based submission approaches (e.g., filing category, Comparability Protocol)

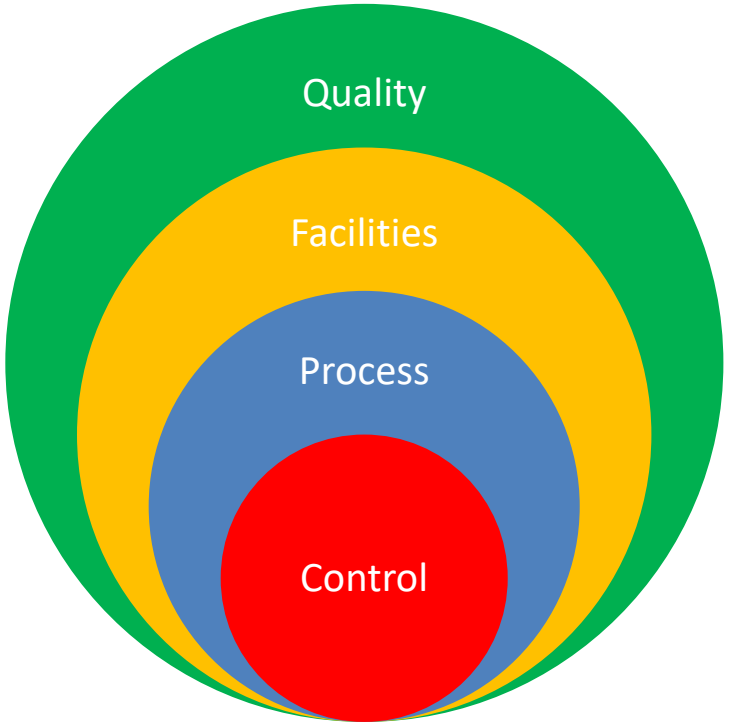
- Regular meetings with Sponsors to address Information Requests

- Regulatory Discretion
  - to release products for COVID-19 treatment
  - to mitigate drug shortage

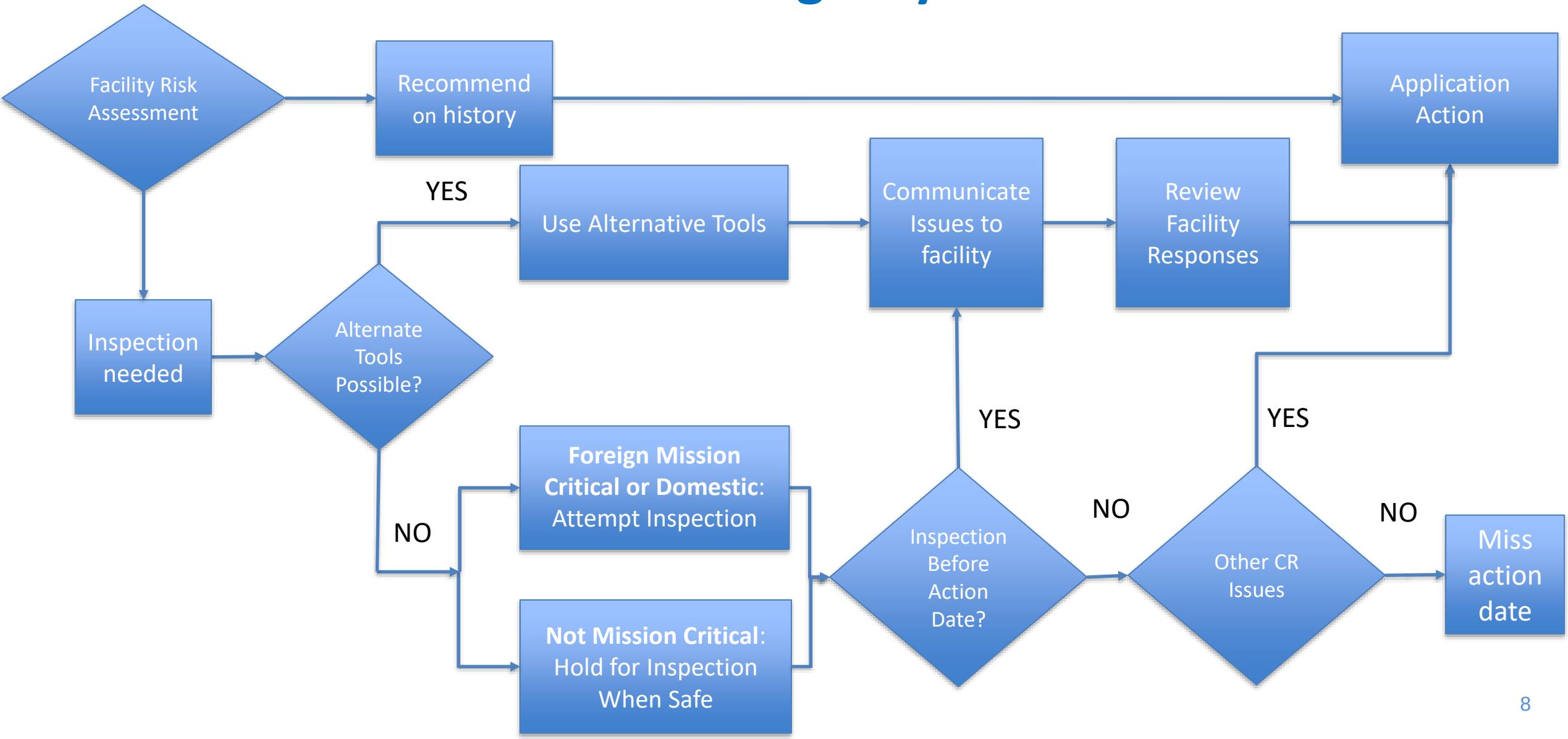
OPMA Facility Assessment during COVID-19

- **Same Quality Standards** using **risk-based** assessment of product, process and facility risks to determine inspection need

- **Alternative Tools to Inspections where possible**
  - Relying on Mutual Recognition Agreement (MRA) (EU and UK)
  - Information from other Regulatory Authorities through confidentiality agreements
  - Information using 704(a)(4) of the FD&C Act in lieu of inspection
  - Remote Interactive Evaluations (RIEs)



OPMA Facility Assessment during COVID-19 Public Health Emergency



Impact of Using Alternative Tools

- **Reduced need to conduct pre-approval inspections by 55%**
  - Not all applications warrant pre-approval inspections (historically ~20%)
- **Enabled approval of drugs and biologics used in the treatment of patients with COVID-19**
  - Over 60 Original Applications
  - Over 1,100 Supplements
- **Maintained on-time action >90% overall**
  - Across all User Fee goal dates

*All numbers through Q3 FY21: https://www.fda.gov/industry/fda-user-fee-programs/cders-work-meet-user-fee-goals-during-pandemic

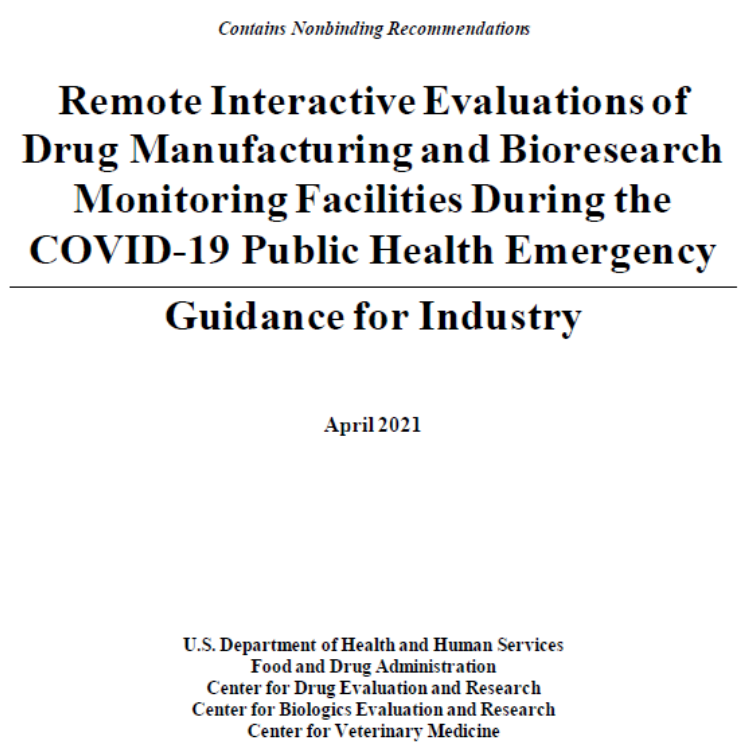
Remote Interactive Evaluations (RIEs)

- Guidance issued April 14, 2021 describing what to expect when FDA performs a "remote interactive evaluation"

- RIE means any interaction with a facility other than inspection or a record request (704(a)(4) of the FD&C Act)
  - t-cons, livestreaming video of facility/ops, screen-sharing of records/info, disclosing records, etc.

- **Voluntary**: a facility is not obligated to participate

- **Not considered an FDA inspection** under section 510(h)(3) of the FD&C Act



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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine

Remote Interactive Evaluations

- FDA uses risk management methods and tools to determine when to request a facility's participation in a remote interactive evaluation.

- For use to support an application action, considerations include:
  - Remote interaction with facility will help assess risks identified during application review
  - No data integrity or other concerns that FDA determines require an inspection

- Generally, FDA intends to request records and other information under section 704(a)(4) of the FD&C Act, before initiating a remote interactive evaluation

- **FDA will not accept requests from applicants or facilities for FDA to perform a remote interactive evaluation**

Takeaways from RIE Experience

- Livestreaming quality critical to observing facility operations
- Ensuring maximum coverage of facility with adequate WiFi signals to support video streaming
  - Some areas did not have access to WiFi signal
  - Multiple portable tablets for visits to facility and labs
  - Difficult to do close-up observations or observe production of the actual product
- RIE valuable to enhance (704(a)(4) of the FD&C Act) records request assessment
  - Difficult to do in-depth assessment of data, equipment cGMP use/maintenance
- Timing of RIE to compliment the application assessment

Concluding Remarks

- OPMA & ORA have utilized Alternate Tools (AT) to inspection wherever possible
  - ~55% reduction in PAIs/PLIs needed
  - Maintained on-time action >90% overall across all User Fee goal dates

- Applications will **not** automatically receive a Complete Response because of the need for an inspection that cannot be conducted due to travel restrictions

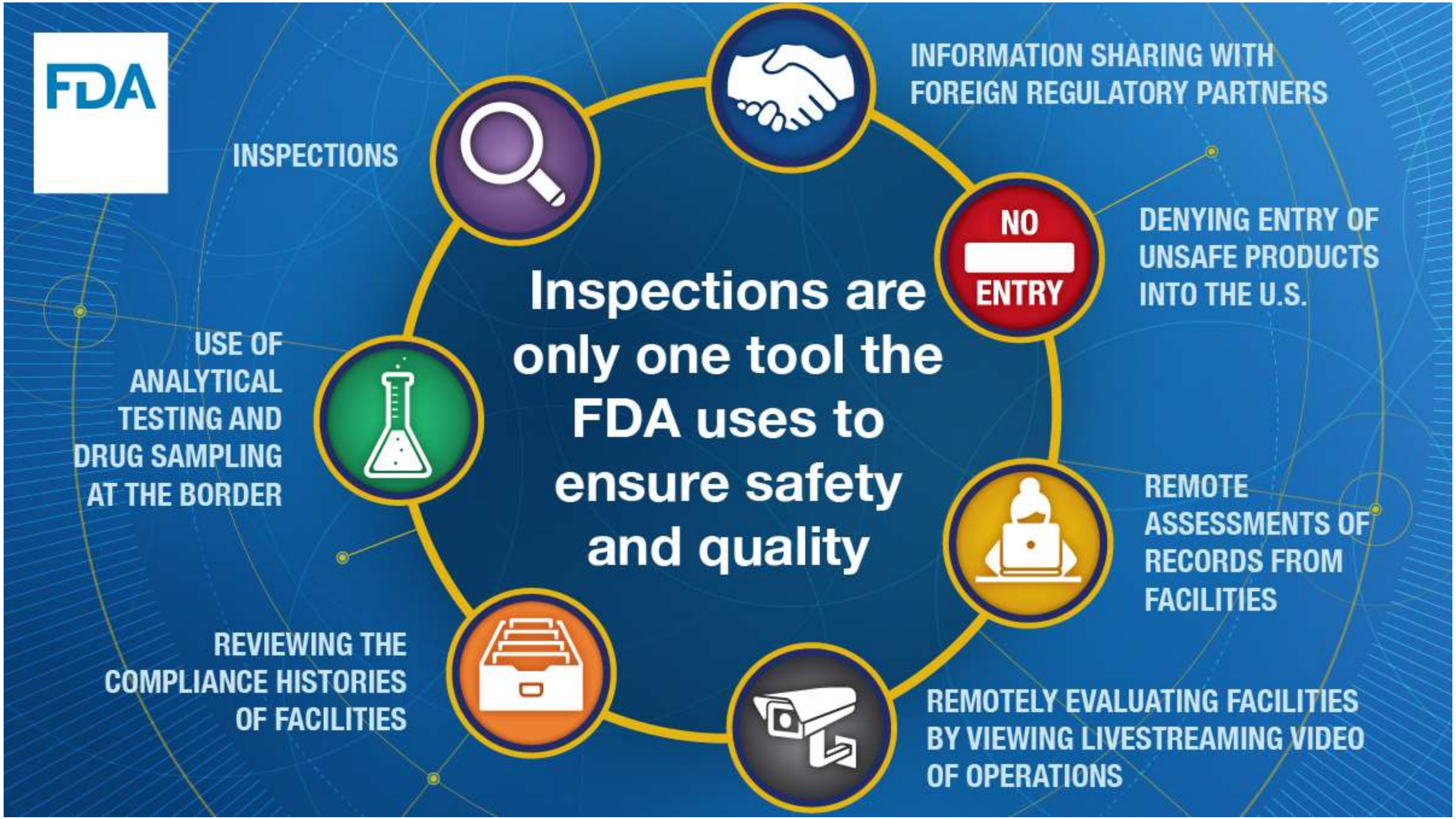
- Records Requests and RIEs may be used in lieu of inspections to make application decisions.
  - they are not considered inspections nor do they preclude a follow-up inspection

- Process Knowledge, Strong Pharmaceutical Quality Systems & Quality Maturity Management will greatly facilitate use of AT in application reviews

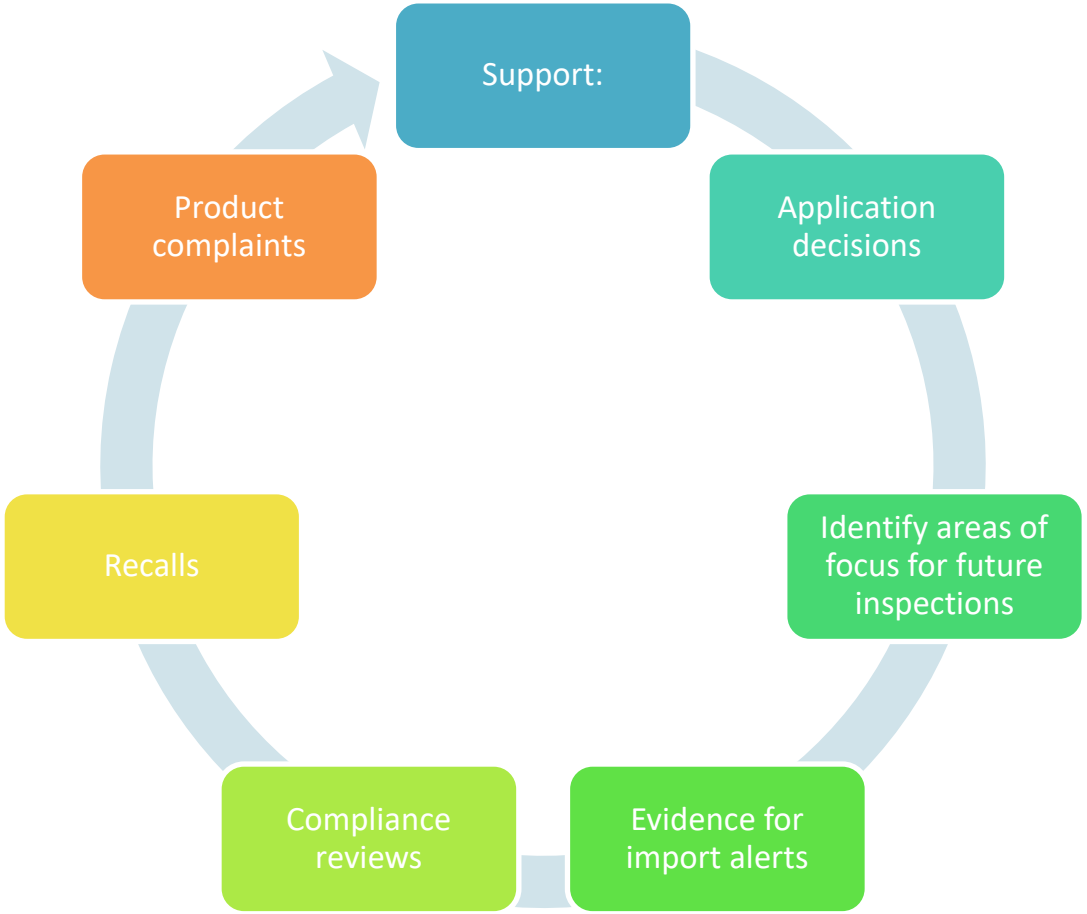
Your Questions Later

Let's Work Together to Assure Quality Medicines

We owe it to our Patients!


FDA
INSPECTIONS
INFORMATION SHARING WITH FOREIGN REGULATORY PARTNERS
NO ENTRY
DENYING ENTRY OF UNSAFE PRODUCTS INTO THE U.S.
Inspections are only one tool the FDA uses to ensure safety and quality
USE OF ANALYTICAL TESTING AND DRUG SAMPLING AT THE BORDER
REMOTE ASSESSMENTS OF RECORDS FROM FACILITIES
REVIEWING THE COMPLIANCE HISTORIES OF FACILITIES
REMOTELY EVALUATING FACILITIES BY VIEWING LIVESTREAMING VIDEO OF OPERATIONS

How are outcomes of Alternative Tools Used:

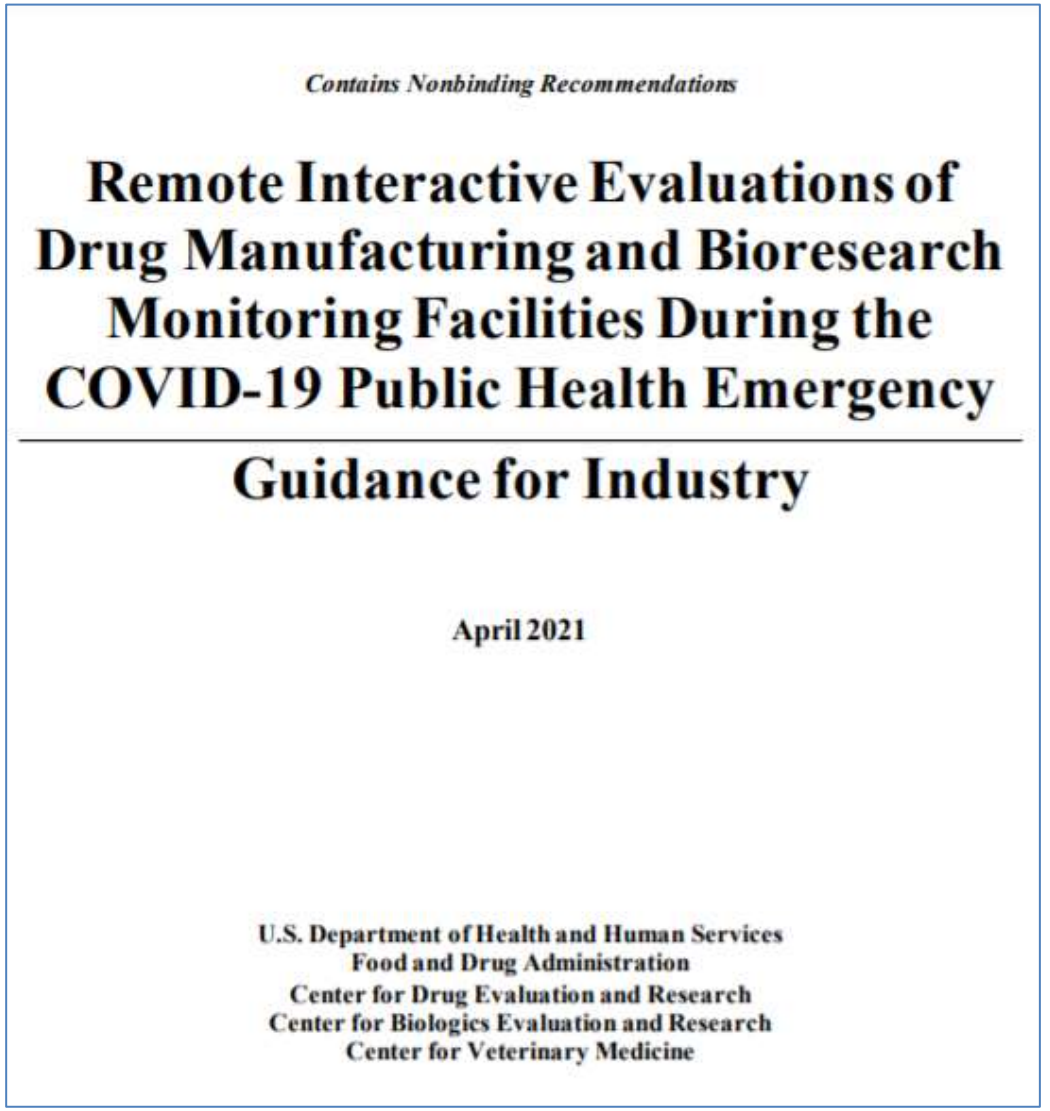


ORA/CDER Communication

- Weekly meetings with CDER to discuss upcoming user fee inspections and status of applications and prioritized inspections.
- Evaluation of applications and facilities by CDER and ORA
  - Integrated Quality Assessment Team evaluates drug application and GMP history to determine if an on-site inspection is needed.
  - Reviews applications to determine if application drug products are deemed mission critical.
  - Work together to schedule and monitor inspections in effort to meet user fee commitments.
  - Discuss status of ongoing inspections and enforcement strategies.

Remote Assessment of Records 704(a)(4)

- Assessment of records and other information in advance of on-site inspections
- Being used to assess facilities where travel restrictions exist
- Not equivalent to an inspection
- Identifies potential issues for future inspections



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https://www.fda.gov/media/147582/download

Records Request under § 704(a)(4) of the FD&C Act

- In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) added a provision to the FD&C Act

- Section 706 of FDASIA amended section 704(a) of the FD&C Act
  - 704(a)(4) allows FDA to request, in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, records or information that FDA may inspect under section 704(a)

What to expect during 704(a)(4) Record Review

- Investigator will notify firm of request to review records in lieu of or in advance of Inspection.
- Firm will receive notification of intention to conduct review, which will outline the reason for the request and the documents requested (form 4003)
- If records requested are not in English they should be translated into English. Firm should certify translations are accurate.
- If document requested refers to another document you may want to also include that record.
- Response should be received by due date or an extension should be requested

What to expect during 704(a)(4) Record Review

- Once initial records are reviewed, there may be follow-up requests for additional documents.
- If any issues/objectionable conditions are found during the review the firm will be notified in writing and have an opportunity to respond.
- Results of review will be used to:
  - Prioritize Inspections
  - Inform application decisions
  - Take action on products for which there is a public health risk

704(a)(4) Evaluations completed since March 2020

- Application reviews have resulted in numerous application decisions
  - Approval recommendations: 256
  - Withhold recommendations: 58

- GMP Reviews Completed:
  - Foreign = 267
  - Domestic = 450

What to expect for Remote Interactive Evaluations

- Firm will be notified of request to conduct RIE, and must agree as RIEs are conducted on a voluntary basis
- Once agreement is obtained, planning starts
- Discussion of dates for RIE and platforms to be used for remote evaluation
- May start with a 704(a)(4) request in lieu of or in advance of an inspection under the FD&C Act, before initiating a remote interactive evaluation
- Time zone differences need to be considered, as it may limit the time of each interaction

Remote Interactive Evaluations

- FDA will contact facility to request interest in allowing remote evaluation
- If the firm agrees to the RIE, an initial meeting with the firm will occur to go over logistics (e.g., technology platform, dates/times, personnel needing to be present)

- FDA communications with facility about remote evaluation may include:
  - Discussion of what will be covered and expectations for evaluation
  - Scheduling for remote evaluation, once firm agrees to RIE
  - Requests for records or information may be requested in advance of RIE
  - Discussion of written list of “observations”
  - prepare final report of coverage/findings

  ORA and CDER will evaluate findings and determine if any action is needed based on outcome of remote interactive evaluation (application recommendation, firm follow-up for identified issues).

- FDA will not issue Forms FDA 482, *Notice of Inspection*, or FDA 483, *Inspectional Observations*

Takeaways from RIE Experience

- Inspection remains the ***gold*** standard
- Livestreaming quality critical to interacting with employees and observing facility operations
- Ensuring maximum coverage of facility with adequate WiFi signals to support audio and video streaming
- RIE valuable to enhance 704(a)(4) records request assessment

What to expect during an inspection

- With few exceptions, inspections are currently being pre-announced due to the pandemic
- Discussions should be held of any social distancing requirements that have been in place and any requirements for entry into facility such as testing requirements or temperature recording.
- Social distancing should be practiced whenever possible (e.g., separate rooms when more than 1 investigator and for eating lunch, use of microphones)
- Notify investigator if they came in close contact with a person who has tested positive for Covid during or shortly after the inspection.
- An inspection may begin with a 704(a)(4) request for records in advance of an inspection.

Inspection Numbers

Thank you!

Your Questions