Use of Alternate Tools for Inspections during the COVID-19 Pandemic

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Outline

- OPMA's approach to manufacturing assessments
- Implemented alternate tools to assess facilities during COVID 19
  - Records Requests under §704(a)(4) of the FD&C Act
  - Remote Interactive Evaluation (RIE)
- Concluding remarks

OPMA Manufacturing Assessment

- OPMA tools for mitigating drug product risk to ensure the safety, efficacy and availability of the drug product

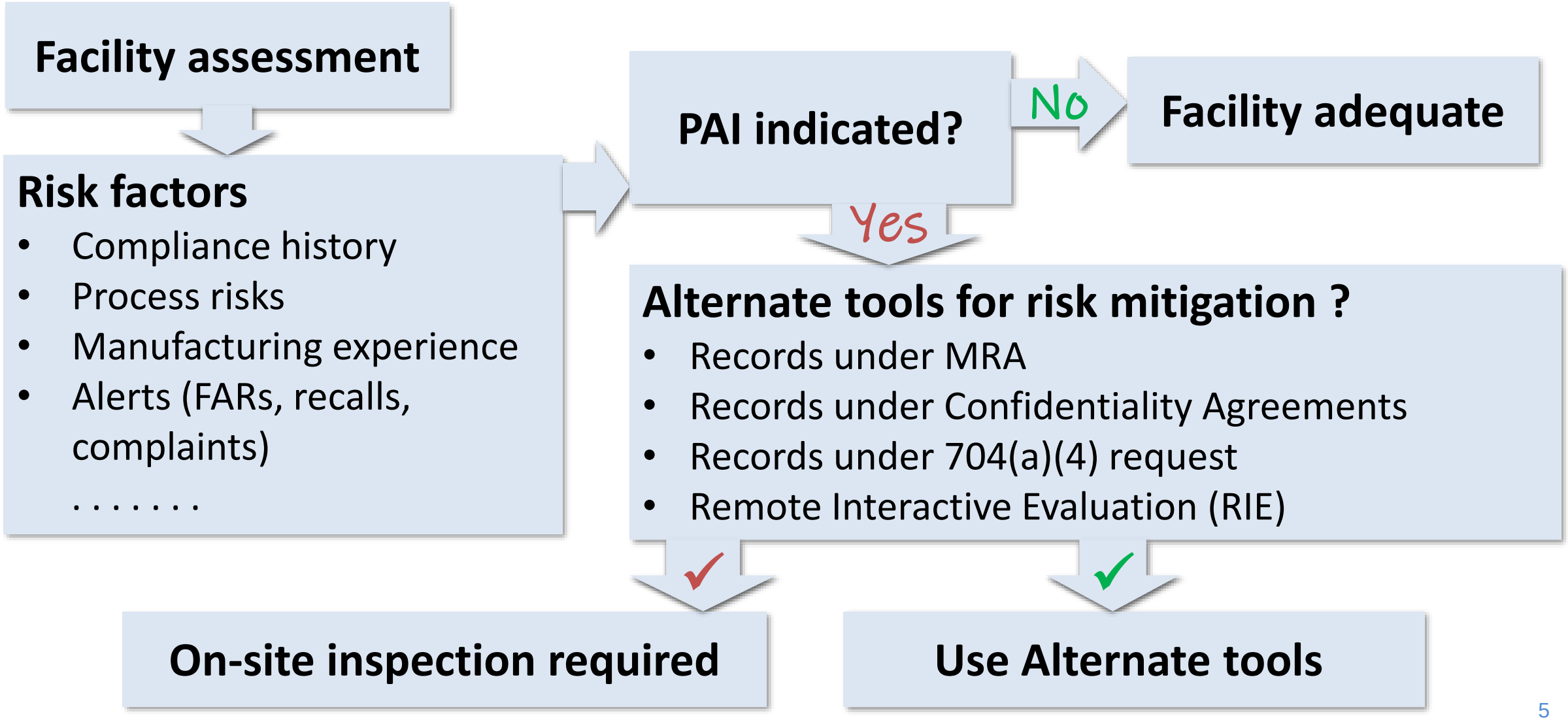
  - **Product and Process Risks**
  - **Facility Risks**
    - Pre-Approval Inspections (PAIs; CP 7346.832)
    - Post-Approval Inspections (PoAIs; CP 7356.843)

OPMA Facility Assessments During COVID-19 Public Health Emergency

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

- **Alternate Tools for facility assessments using:**
  - Record and other information request under FD&C 704(a)(4)
  - Relying on Mutual Recognition Agreement (MRA) (EU and UK)
  - Information from other regulatory authorities through confidentiality agreements
  - Remote Interactive Evaluations

OPMA Facility Assessment during COVID-19 Public Health Emergency



Hypothetical Example 704(a)(4) Records Request

- **Process risk**

  The product is an oral solution, particulate appeared, and pH of the solution was out-of-specification during stability studies of the registration batches

- **Facility risk**

  The firm has inspection history covering solid dosage forms manufacturing but not liquid oral solution compounding

- **Outcome**

  Adequate based on 704(a)(4) Record Request assessment

Remote Interactive Evaluations (RIEs)

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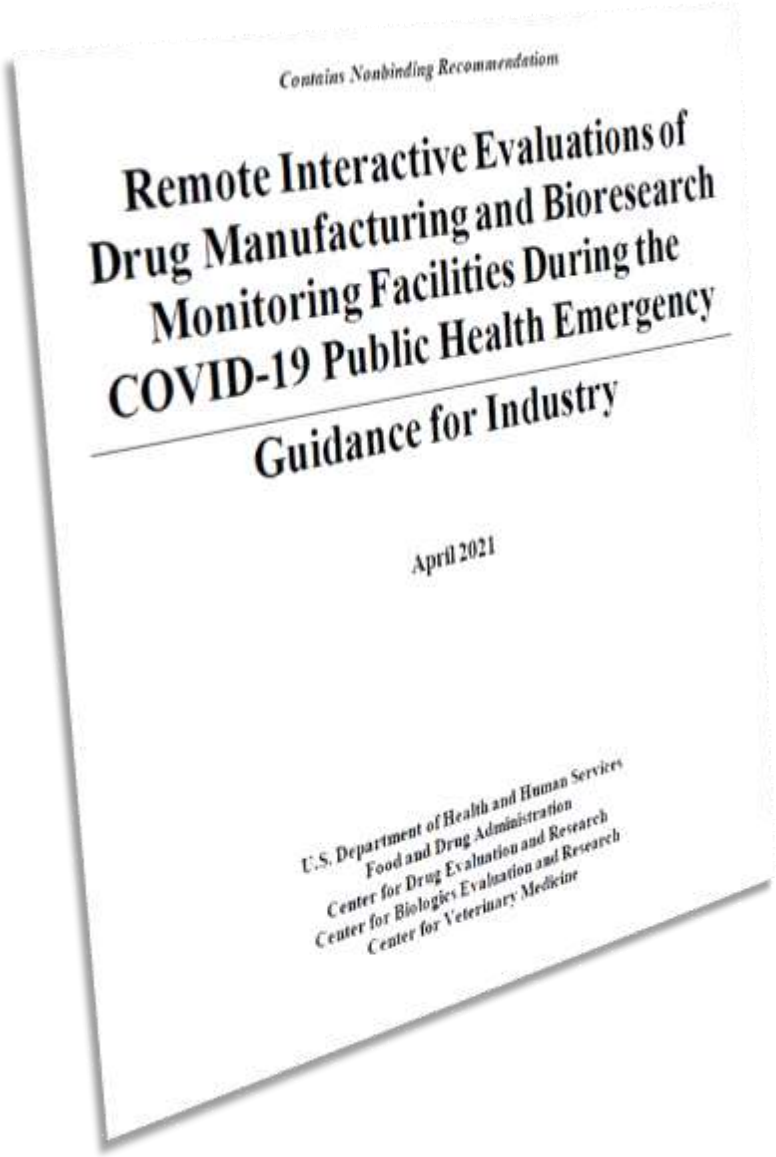
Contains Nonbinding Recommendation

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

- any interaction with a facility other than inspection or a record request.
- are **NOT** mandated under FD&C Act:
  - **NOT** inspections per 704(a)(1) or 510(h)(3);
  - **NOT** Record Requests as described in 704(a)(4);
- no credentials presented, no Forms 482 or 483 issued;
- are voluntary… **BUT** declining a request may delay a regulatory action;
- are used to assess CGMP compliance, collect information or prepare for future inspections.

Remote Interactive Evaluations (RIEs)

- Decision to request RIE is based on risk management methods
- For PAI purposes, considerations include:
  - will help assess risks identified in application review
  - no data integrity or other issues identified that require an on-site inspection
- Generally, records are requested under FD&C 704(a)(4) before RIE
- **FDA will not accept requests from applicants or facilities to perform an RIE**

Remote Interactive Evaluation: FDA Actions

Request Participation	Email or phone request seeking willingness for voluntary participation.
Schedule Virtual Meeting	Discuss logistics, objectives, scope, and expectations. Technology and platform. Translation needs.
Preparation	Request documents including production schedule; review submitted and uploaded documents and plan approach.
Opening	Start with an opening meeting. Schedule interviews/meetings to address initial questions or concerns.
Virtual Facility Tour	Dependent upon the scope of the RIE and the plan discussed by the team. Doesn't need to be all at once.
Discussions with Site	Address questions/concerns about the tour observations, requested data; interview SMEs; request additional documents, data and/or video.
Close Out	Close out meeting with the site. Issue observations, if any, at end of meeting (email). No Form FDA 483. Encouraged to respond within 15 US business days.

Challenge Question

Which statements regarding RIEs are true?

a) An automatic Complete Response will result if the firm declines RIE request;

b) A firm can request an RIE from FDA but only on resubmission;

c) The RIEs will sunset with expiration of Public Health Emergency;

d) Observations from RIE may lead to Withhold of Approval for a facility.

Examples of RIEs: Background

	Example #1	Example #2
→	DP manufacturing facility, foreign location	
→	PAI for 2 ANDAs both Delayed Release tablets	PAI for ANDA, aerosol foam (drug/device combination)
→	2018-2020 PAI for IR tablets and capsules	2018-2019 PAI for ointments and liquid products
→	new product profile; new unit operation (HME);	new product type; new unit operation (gas filling).
→	PAI deferred in the first review cycle due to travel restriction; 704(a)(4) record review was initiated prior to RIE.	

Logistics

- FDA team: ORA investigators, OPMA CMC reviewer as SME
- Timing:
  - Example 1: Four 3-hour sessions (5 – 8 AM).
  - Example 2: Three 4-hour sessions (11 PM – 3 AM).

- Zoom video-enabled meeting.
- Walk-through tech:
  - Firm #1: laptops on a cart, Wi-Fi connection, external USB cameras, blue-tooth microphones;
  - Firm #2: tablet PCs, Wi-Fi or phone connection depending on coverage

Coverage and Outcome

Complemented 704(a)(4) record review to cover PAI objectives

- Walk-through
  - Facility areas: warehouse, production, QC labs, stability chambers;
  - Equipment HMI: access control, recipes, process files, audit trails.
- Document control system

Coverage and Outcome

- Data integrity audit
  - QC lab computer systems: access control, data retention, audit trails.
  - Data audit: Evidence of reinjections, reprocessing, aborted sets, trial injections.
  - Record Authenticity: Raw data review, process user logs, analytical data sheets.

Outcome of the 704(a)(4) review and RIE were discussed at the conclusion of final RIE session. A No-Observation Memo was presented.

Concluding of 704(a)(4) or RIE

	Record Request	RIE
No observations	Form 4003 sent stating record request completed	No-observation memo at the close out meeting
	Facility Adequate	
Observations Made	Form 4003 sent with Observations letter attached, during review cycle	Observation letter sent, observations discussed at the close-out meeting.
	▪ Response within 15 days is requested. ▪ If unresolved, facility may be found inadequate. Post-Action Letter (PAL) sent after CRL. ▪ Responses to PAL evaluated in the next review cycle. Facility may require on-site inspection.	

Takeaways from RIE Experience

Live stream quality is critical to observing facility operations

- Wi-Fi coverage and bandwidth;
- Equipment compatible with production areas (contamination and exposure controls);
- Technical capabilities of video equipment

Tips for Enabling a Successful RIE

- Commit same level of importance and attention as you would for an inspection
- Clarify with the FDA lead any requests you don't fully understand or will require submission of a particularly high volume of records
- Organize requested documents in an easy-to-understand format
- Have subject matter experts available to explain operations and answer questions
- Identify whether there are any translation needs in advance of the RIE

Takeaways from RIE Experience

Benefits

- A significant complement to facility record review
- Flexibility in logistics

Limitations

- Not equivalent to an FDA inspection
- Reliant on what is being shown

Concluding Remarks

- An on-site inspection remains the gold standard
- Alternate Tools have been used when possible
  - Approximately 50% reduction in PAIs/PLIs needed
  - Maintained on-time action >90% overall across all User Fee goal dates
- FDA will communicate its thinking on use of alternative tools post-pandemic as FDA gains experience and evaluates lessons learned.


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