Best Practices for Remote Interactive Evaluations and other Alternative Inspection Approaches

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Outline

- FDA's Draft Remote Regulatory Assessment (RRA) Guidance
- Implementation of alternate tools to assess facilities during COVID 19
  - Records Requests under §704(a)(4) of the FD&C Act
  - Remote Interactive Evaluation (RIE)
- Other tools
- Lessons learned and directions forward. . .

Draft Guidance on RRAs

Status of the Draft Guidance

- Published in the Federal Register 7/25/2022
- If finalized, the draft guidance will represent the current thinking of FDA on this topic
- Comment period for the draft guidance closed on 9/23/2022
- FDA is currently reviewing stakeholder comments and will address them in the updated version of the GFI
- Recent changes in the law have added mandatory remote records request authority for devices and BIMO to §704(a)(4) of the FD&C Act

Draft Guidance on RRAs continued

What is an RRA?

- An examination of an FDA-regulated establishment and/or its records, conducted entirely remotely
- RRAs assist in informing regulatory decisions and verifying certain information submitted to the Agency.
- Examples include remote records requests under §704(a)(4) of the FD&C Act and remote interactive evaluations (RIE).

Draft Guidance on RRAs continued

Why did FDA Draft this Guidance?

- FDA concluded that they should be used for certain scenarios outside the current pandemic and for all types of FDA-regulated products.
- The draft guidance is intended to increase industry's understanding of RRAs and to provide answers to frequently asked questions surrounding RRAs.

Draft Guidance on RRAs continued

Decision to initiate or request an RRA is made by FDA when:

- Travel limitations brought on by pandemics, natural disasters, or other unstable situations
- Need to conduct elements of establishment oversight or support regulatory decisions.

Draft Guidance on RRAs continued

Under the Drug Program, is an RRA considered an Inspection?

- Because an RRA does not involve physical entry of a facility, we do not consider an RRA to be an inspection.
- FDA will not display credentials or issue an FDA Form 482 Notice of Inspection or FDA Form 483 Inspectional Observations.

Draft Guidance on RRAs continued

Benefits of RRAs:

- Reduce delays of approval or authorization of marketing submissions for FDA-regulated products
- Assist in gaining compliance insight when it was not practicable to inspect
- Provide information about deficient practices, which led FDA to take regulatory actions
- Informe future inspection planning

Challenge Question #1

What are some examples of a Remote Regulatory Assessment (RRA)? more than one answer can apply

a. Request for records and other information under §704(a)(4) for the FD&C Act
b. Onsite inspection
c. Remote Interactive Evaluation (RIE)
d. All of the above

Application Facility Assessment

Facility assessment

Risk factors

- Compliance history
- Process risks
- Manufacturing experience
- Alerts (FARs, recalls, complaints)

PAI indicated?

No

Facility adequate

Yes

Alternate tools for risk mitigation?

- Records under 704(a)(4) request
- Remote Interactive Evaluation (RIE)
- Records under MRA
- Records under Confidentiality Agreements

✓ **On-site inspection required**

✓ **Use Alternate tools**

Outcomes of Records Requests

704(a)(4) assessment activities (domestic and foreign)*

	Completed
Surveillance	~670
Pre-Approval	~330
Total	~1000

*Actions (as of Sept 2022):

- Application recommendations

  ~330 approval and ~75 withhold

- 35+ Import Alerts issued (IA 66-40, IA 99-32)

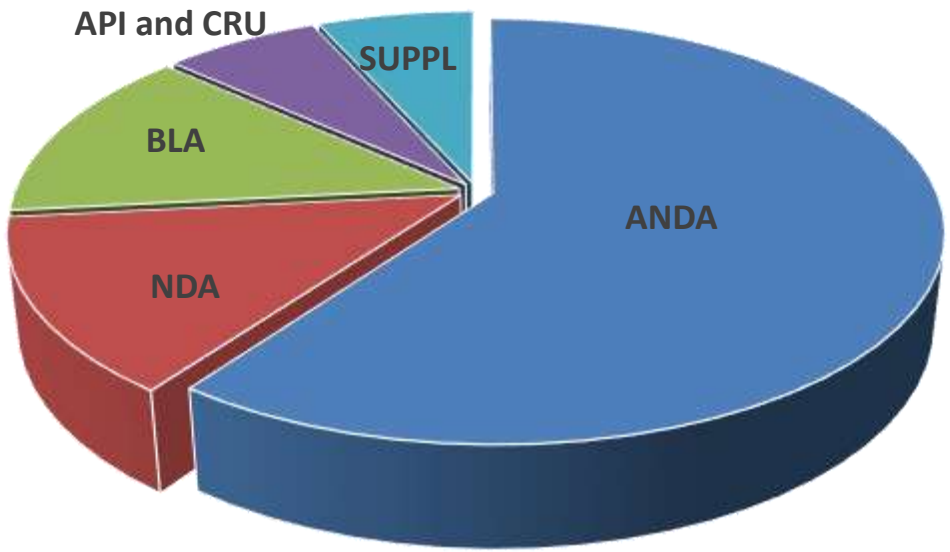
Approval/Withhold actions seen across application types (A/NDA, BLA) and dosage forms (sterile, nonsterile, API and critical intermediates) and locations (domestic, international)

Reference SBIA GDF 2021 Presentation: https://mail.sbiaevents.com/gdf2021/

Outcome of PAI Record Requests

Further look at withhold data from 2021:

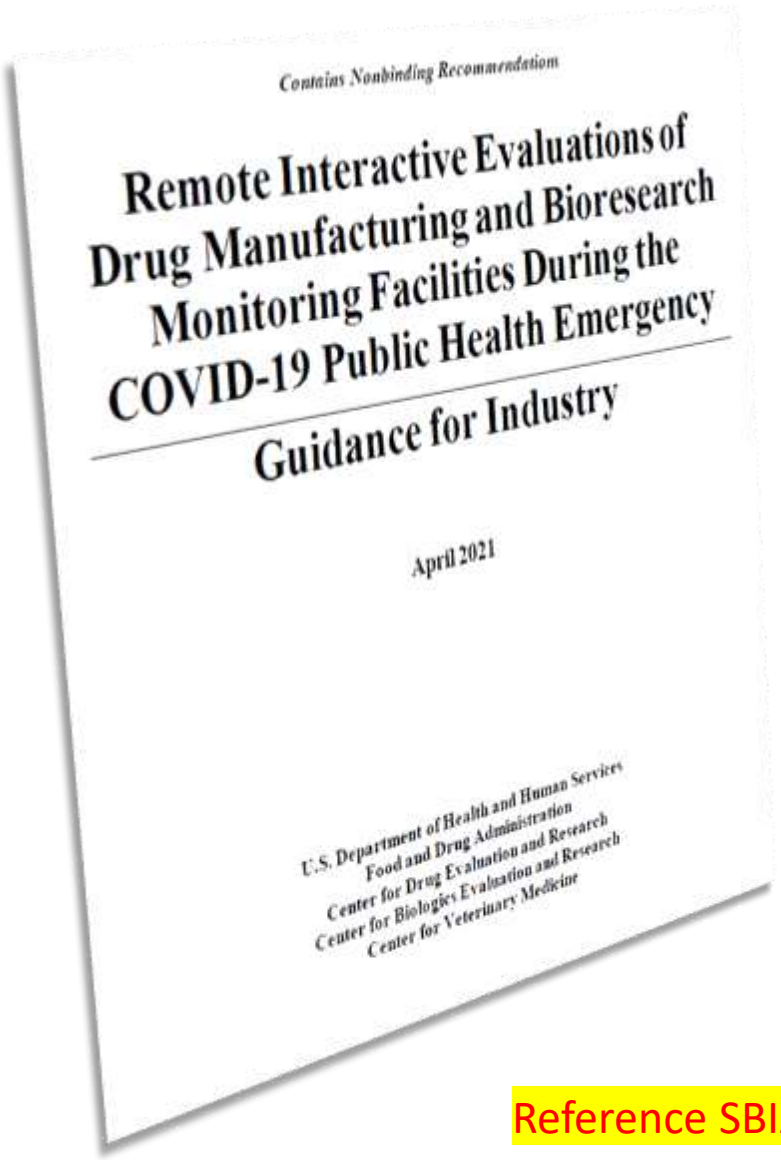
- Sites located in India, Germany, Italy, Canada, China, France, Croatia, Spain, Austria
- Responsibilities included manufacturers of API and critical intermediates; IR/DR tablets and capsules, device component of combo products, sterile solution/suspension injections, lyophilized powders; testing sites
- Original ANDA sites associated with multiple applications and ~60% of WH sites



What happened next:

- Approximately half were subsequently resolved through review process or on site inspection
- Approximately half remain pending CRL response . . . Overall application quality??

Remote Interactive Evaluations (RIEs)


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.
- For PAI purposes, considerations include:
  - will help assess risks during application review
  - no issues that require an on-site inspection
- FDA **will NOT** accept requests from applicants or facilities to perform an RIE
- Are voluntary… **BUT** declining a request may delay a regulatory action;
- Are used to assess CGMP compliance, collect information or prepare for future inspections.

Reference SBIA GDF 2022 presentation: https://sbiaevents.com/gdf2022/

Examples of RIEs

Example #1	Example #2
DP manufacturing facility, foreign locations	
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)
704(a)(4) record review was initiated prior to RIE. Outcome included **recommendations to approve sites**.	

Examples of RIEs continued

Example #3	Example #4
DP manufacturing facilities, foreign locations	
PAI for NDA, Sterile PFS	EUA for a biologic, solution for infusion
Site OAI after surveillance inspection in 2019 received WL	Previous inspection history with CMO, expedited nature
Sponsor asked about possibility of RIE due to travel restrictions	Records requested under 704(a)(4) leading to RIE – issues identified; sterility assurance, etc.
In both cases, outcome was an **on site inspection is recommended** and satisfactory outcome needed before agency can approve.	

Concluding an RRA

	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.	

Suggestions for Enabling a Successful RRA

- 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
- RIEs are technology and platform dependent

Challenge Question #2

The following statements about an RRA are true except:

more than one can apply

a. Virtual tour during an RIE doesn't need to be conducted all at once.
b. Records request are made in advance or *in lieu* of an inspection within a reasonable timeframe and in either electronic for physical form.
c. Since they are not considered an inspection, it is not necessary to respond to any observations made during an RRA.
d. Generally, records are requested under FD&C 704(a)(4) before an RIE.

Concluding Remarks

- What will inspections and our interactions with manufacturers look like in the future as we get more comfortable with these tools?
- We are leveraging lessons learned from across applications and inspection programs to inform how to improve.
- An RRA may be conducted in advance or in-lieu of an inspection.
- FDA may conduct an RRA following an inspection in order to conduct follow-up activities with the establishment or to assist in verifying corrective actions, if appropriate.

Concluding Remarks

- Story is not over. FDA continues to gather experience, seek feedback, work with stakeholders . . . Great time for hearing what industry has to say.
- FDA is currently reviewing stakeholder comments on the Draft RRA Guidance and will address them in the updated version.
- Recent changes in the law have added mandatory remote records request authority for devices and BIMO to §704(a)(4) of the FD&C Act.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