Remote Interactive Evaluations (RIEs) to Support FDA's Facility Oversight during the COVID-19 Pandemic and Beyond

December 3, 2021

Stelios C. Tsinontides, Ph.D., FAIChE
Director, Office of Pharmaceutical Manufacturing Assessment

Lane Christensen, Ph.D.
Branch Chief, Office of Pharmaceutical Manufacturing Assessment

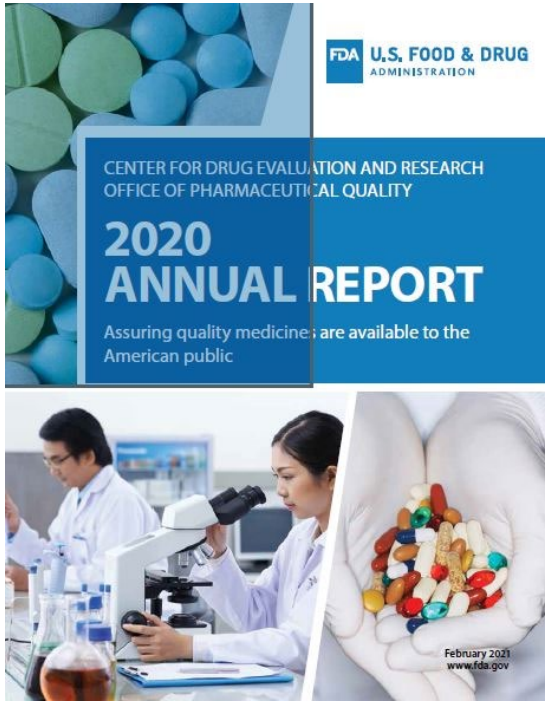
FDA

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)]:

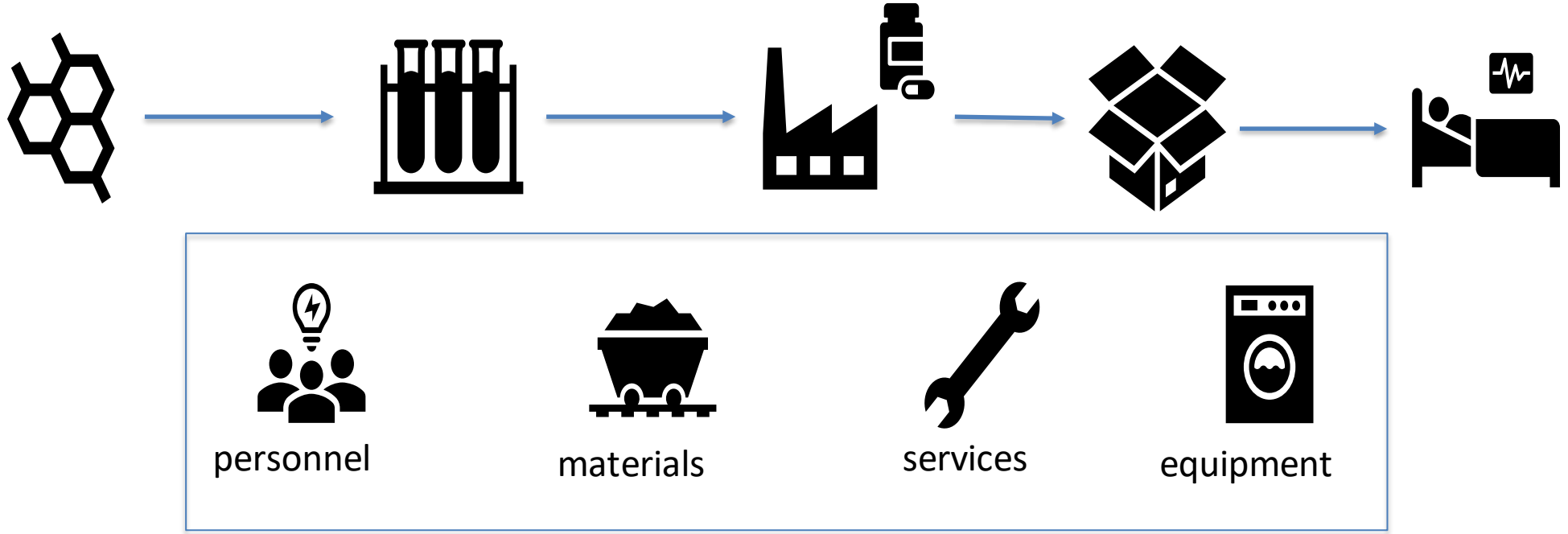


Outline

- **Landscape of manufacturing & supply chains during the Covid-19 Pandemic**
- **FDA/CDER's Response**
- **Approach to Facility Assessments/Inspections**
  - 704(a)(4) record requests
  - Remote Interactive Evaluations (RIEs)
- **Taking a further look at RIEs completed to date**
- **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



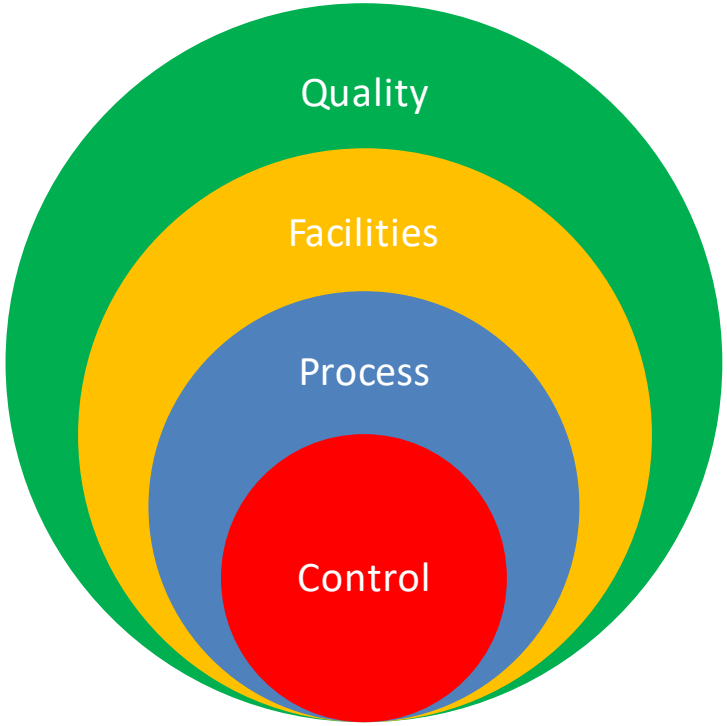
CDER COVID-19 Manufacturing & Supply Chain Initiatives

- 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

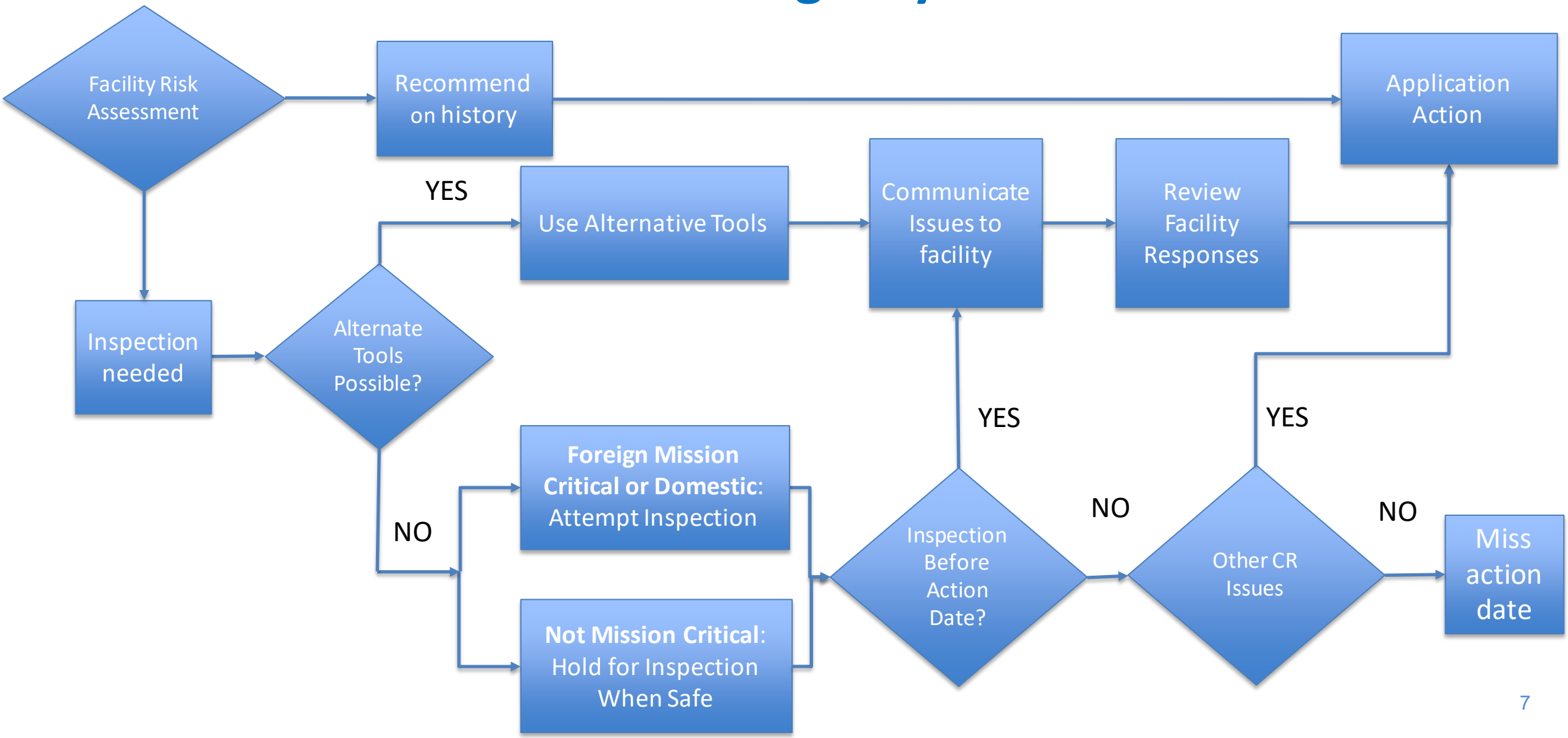
OPMA Facility Assessment during COVID-19

- **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 CDER/FDA Actions

- **Reduced need to conduct pre-approval inspections by 56%**
  - GDUFA Program: 54%; BLA Program: 48%
  - 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

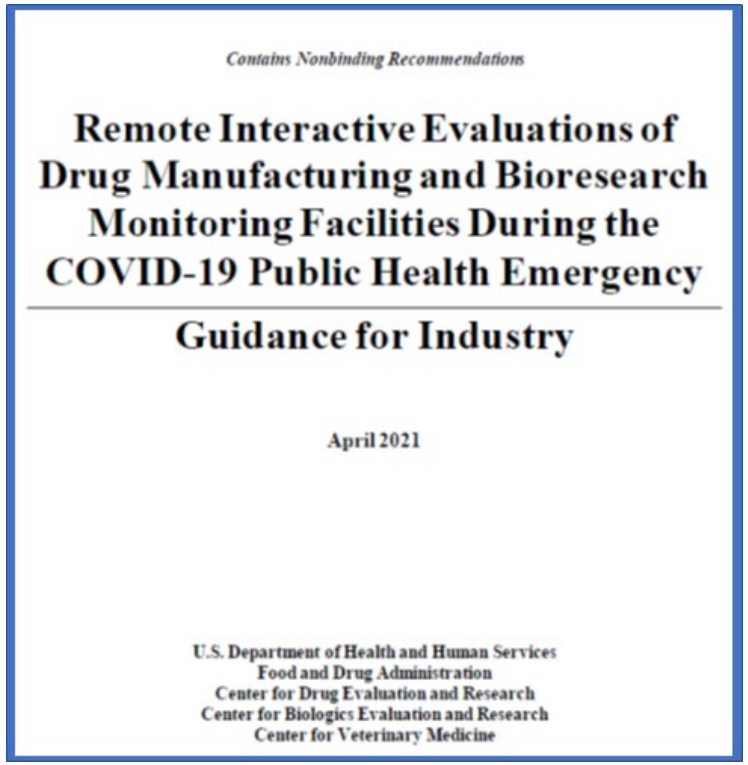
Remote Interactive Evaluations (RIEs)

- 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 (RIEs)

- 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

- **<u>FDA will not accept requests from applicants or facilities for FDA to perform an RIE</u>**

A Further Look at Completed Remote Interactive Evaluations (RIEs)

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

Guidance for Industry[1]

This guidance represents 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 or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to describe how we will request and conduct voluntary remote interactive evaluations at facilities[2] where drugs[3] are manufactured, processed, packed, or held; facilities covered under FDA's bioresearch monitoring (BIMO) program; and outsourcing facilities registered under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the duration of the COVID-19 public health emergency.

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

Manufacturing*:

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

BIMO:

- Not covered by 704(a)(4)

SEC. 704(a) (21 U.S.C. 374(a)) (FD&C Act) is amended by adding at the end the following:

(4)(A) Any records or other information that the Secretary may inspect under this section from a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug shall, upon the request of the Secretary, be provided to the Secretary by such person, in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form, at the expense of such person. The Secretary's request shall include a sufficient description of the records requested.

*Presented 10/26/2021, Pharmaceutical Quality Symposium, Tsinontides and Rolli

RIEs completed since June 2020

BIMO*:

- From June 2020 to August 2021
  - Remote Record Evaluation: 99
- Clinical and Analytical Reviews Completed:
  - Foreign: 67%
  - Domestic: 33%

Manufacturing:

- <10 completed or currently in process for preapproval applications (biotech and small molecule) and supplements

*Presented 11/08/2021, GrX-BioSims, Kassim

Remote Interactive Evaluation Process

Request Participation	Send email request seeking willingness for voluntary participation.
Schedule Virtual Meeting	Once confirmed, schedule a virtual meeting to discuss logistics, responsibilities, and expectations. Test connection, platform to use.
Preparation	Request documents including production schedule; review submitted and uploaded documents and plan approach.
Opening	Start with an opening meeting using one of FDA's platforms (MS Teams, Zoom for Government, Adobe Connect). 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. Break out groups?
Discussions with Site	Daily meetings to discuss any questions or concerns, if any, about the requested data; request additional documents, data and/or video.
Close Out	Conduct a close out meeting with the site. Issue observations, if any, at end of meeting via email prior to closing. No Form FDA 483. Encouraged to respond within 15 US business days.

Scope of the RIE

Varies by the issues identified and the assignment of the review team but could include one or all the following:

- Organization and Personnel
- Facilities & Site Operations
- SOPs, Protocols, Deviations, Change Controls, Failures, CAPAs, Recalls, Complaints…
- Manufacturing operations, established process controls
- New equipment since last inspection*
- Training Records/Technical expertise
- Storage, material handling & processing
- Laboratory, audit trails & data security
- Instrument installation, calibration & maintenance
- Equipment maintenance and cleaning program/records
- Stability samples, retain samples, sampling and testing procedures

How does an RIE compare to an in-person inspection?

- Very dependent on technology being used and effective communication.
- RIEs are not Inspections… **BUT** are used to assess a firm's overall cGxP compliance, collect information or prepare for future inspections → refusal can impede FDA's ability to take a timely regulatory action.
- FDA does not intend to replace traditional inspections with remote interactive evaluations.
- Time frames for conducting an evaluation are more flexible.

Hypothetical Example #1 – Eligible

Drug product is a sterile injection submitted as a BLA with COVID-19 review priority.

- Manufacturer is a contract manufacturer, site has acceptable inspection history, with similar unit operations
- Due to short review timelines and location, scheduling travel and conducting inspection within the review clock not possible

Outcome: Decision to reach out to application holder to initiate RIE

Hypothetical Example #2 – Eligible

Multiple ANDAs from same holder, 2 for DR tablets

- PAI deferred previous review cycle due to travel restrictions
- Manufacturer has acceptable inspection history for IR tablets but unit operations for DR tablets have not been previously inspected/approved
- 704(a)(4) records review currently ongoing, risks identified for further assessment that could be addressed through RIE

Outcome: Decision to reach to application holder to initiate RIE

Hypothetical Example #3 - Ineligible

Drug product is a sterile injectable submitted as an NDA

- Manufacturer is located in a foreign location associated with travel restrictions
- Site received a WL after completion of last surveillance inspection in 2019 resulting in an OAI alert

Outcome: application is put on hold until an onsite inspection can be scheduled and satisfactory inspection completed.

Takeaways from RIE Experience

- Livestreaming quality is critical to observing facility operations

- Ensuring maximum coverage of facility with adequate internet bandwidth/WiFi signals to support video streaming
  - Some areas did not have access to strong wifi
  - Multiple portable tablets for visits to facility and labs
  - Used portable laptops, tablets, smart phones and CCTV cameras
  - Able to do close-up or observe production of the actual product
  - Reliant on what is being shown, audio sometimes difficult to understand/ muffled

- 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

Takeaways from RIE Experience

- Useful approach when there is a large time difference
  - Flexibility of timing and duration
  - Records can be reviewed and document requests fulfilled during ‘off time’
- Use of breakout rooms enabled seamless interaction between inspection team and SMEs
  - Need for organization of documents requested, confirmation of receipt
- Timing of RIE to compliment the application assessment

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

Concluding Remarks

- An onsite inspection remains the ***gold*** standard
- OPMA & ORA have utilized Alternate Tools *in lieu* of inspection wherever possible
  - ~56% reduction in PAIs/PLIs needed
  - Maintained on-time action >90% overall across all User Fee goal dates
- RIE valuable to enhance 704(a)(4) records request assessment
- Records Requests and RIEs may be used in lieu of inspections to make application decisions as appropriate.
  - RIEs are not considered inspections, nor do they preclude a follow-up inspection
- FDA will continue to re-evaluate approaches to alternative tools and determine long term use post-pandemic

Thank you!

Let's Work Together to Provide Safe and High-Quality Medicines to our Patients!