Learnings and Insight from Records Requests under §704(a)(4) of the FD&C Act in lieu of Pre-Approval Inspections

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Presentation Outline

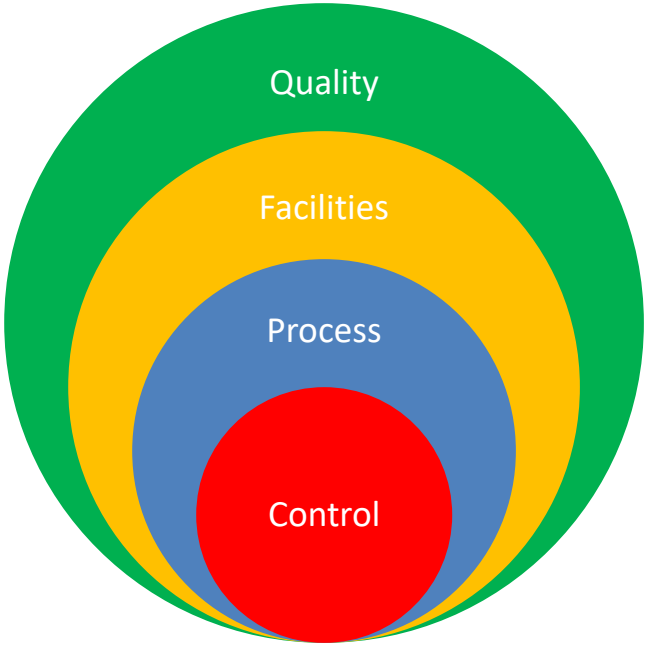
- Pre-COVID-19 OPMA evaluation of application manufacturing information
- OPMA quality risk assessment of sites requiring PAIs during travel restrictions due to COVID-19 pandemic
- OPMA's quality risk management in determining site eligibility for Records Request under §704(a)(4) of the FD&C
- Evolution of OPMA's 704(a)(4) process and Assessment Issues Letters (AILs)
- Two hypothetical scenarios for triaging a site for PAI or 704(a)(4)
- Conclusions

Learning Objectives

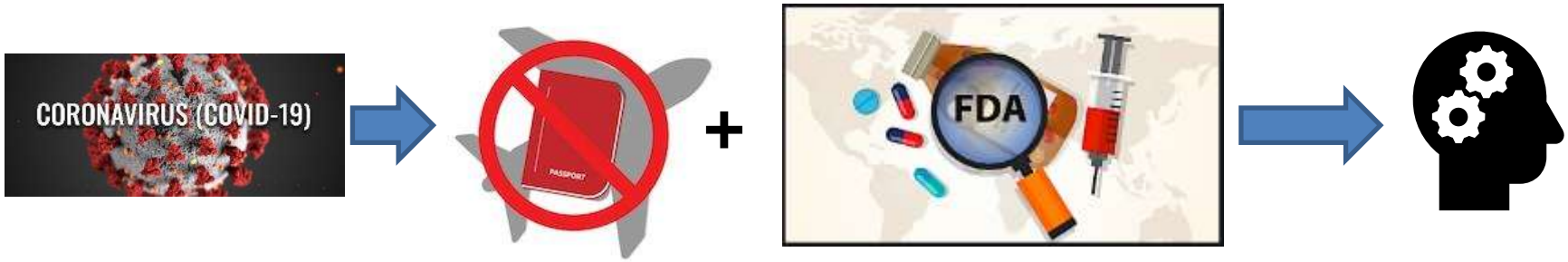
- Compare tools utilized by OPMA to mitigate drug product manufacturing risks prior to the COVID-19 Pandemic and during COVID-19 related travel-restrictions
- Discuss OPMA's risk assessment strategy to determine whether facilities risks can be mitigated via a 704(a)(4) records request or an onsite Pre-Approval Inspection is needed
- Identify when an Assessment Issue Letter (AIL) is sent following a 704(a)(4) records request

Pre-COVID-19 OPMA Manufacturing Assessment

- **Evaluate application's manufacturing and testing processes for the proposed commercial product**
- **Assess individual sites involved in the commercial drug product supply chain for their capabilities of performing the prescribed responsibilities per CGMP.**
- **OPMA tools for mitigating drug product risk to ensure patient safety, efficacy and availability**
  - **Design Risks:**
    - Information Requests (IRs)
    - Discipline Review Letters (DRLs)
    - Complete Response Letters (CRLs)
  - **Implementation Risks:**
    - Facility History (i.e., experience with operation(s) and compliance)
    - Pre-Approval Inspections (PAIs; CP 7346.832)
    - Post-Approval Inspections (PoAIs; CP 7346.843)



COVID-19, Travel Restrictions, Inspections and FDA



COVID-19 Travel Restriction and OPMA Manufacturing Assessment

- **Evaluate application's manufacturing and testing processes for the proposed commercial product**
- **Assess individual sites involved in the commercial drug product supply chain for their capabilities of performing the prescribed responsibilities per CGMP.**
- **OPMA tools for mitigating drug product risk to ensure patient safety, efficacy and availability**
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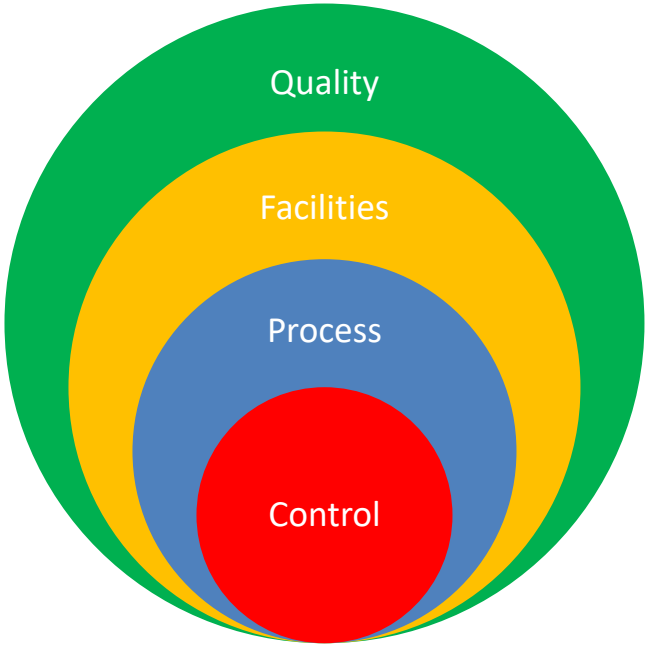
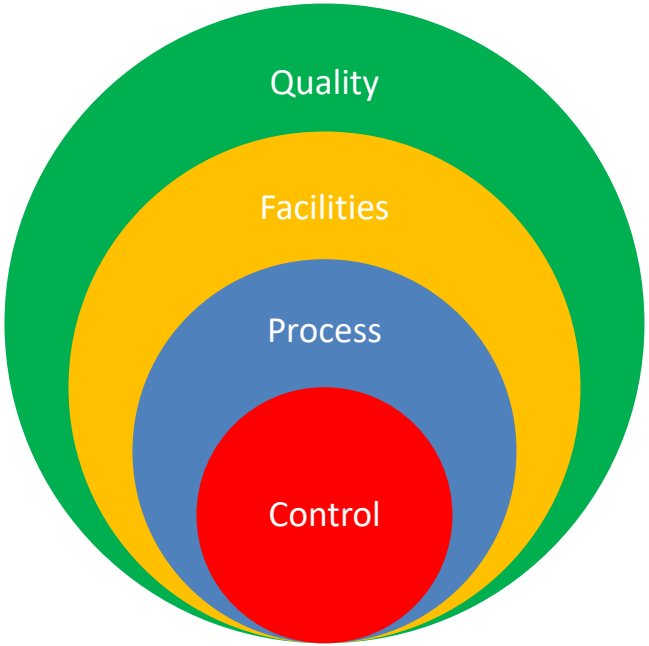


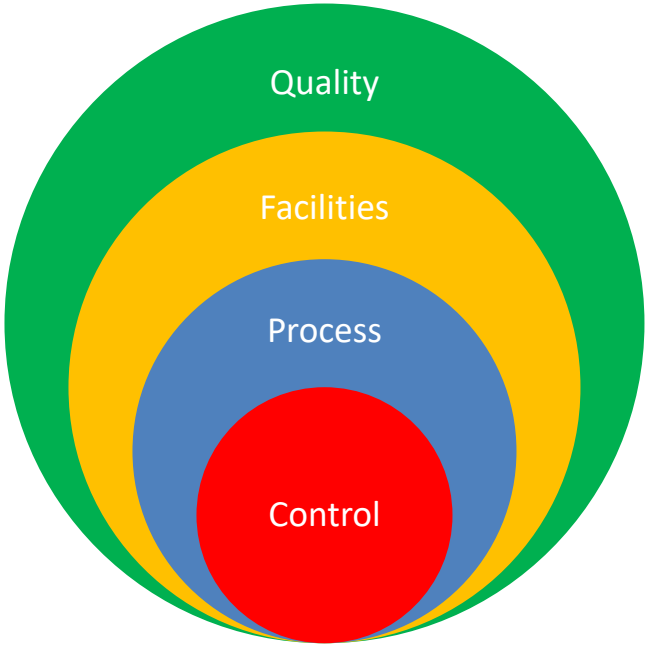
COVID-19 Travel Restriction and OPMA Manufacturing Assessment (cont.)

- **OPMA tools for mitigating drug product risk to ensure patient safety, efficacy and availability**
  - **Implementation Risks:**
    - Facility History (i.e., experience with operation(s) and compliance)
    - Pre-Approval Inspections (PAIs; CP 7346.832)
    - Post-Approval Inspections (PoAIs; CP 7352.843)



COVID-19 Travel Restriction and OPMA Manufacturing Assessment (cont.)

- **OPMA tools for mitigating drug product risk to ensure patient safety, efficacy and availability**
  - **Implementation Risks (Initial COVID-19 State):**
    - Facility History (i.e., experience with operations and compliance)
    - Mission Critical PAIs/PLIs
    - Use of Inspectional Information from other Regulatory Agencies
    - Records Request under § 704(a)(4) of the FD&C Act
    - Most recently, addition of Remote Interactive Evaluations (RIEs)



Mission Critical PAIs during COVID-19

- **FDA's assessment of whether an inspection is mission-critical considers many factors related to the public health benefit of U.S. patients having access to the product subject to inspection**

- **Factor(s) determining whether a product is mission critical include but are not limited to:**
  - Products having breakthrough therapy designation or regenerative medicine advanced therapy designation
  - products used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute

- **When determining whether to conduct a mission-critical inspection, FDA takes into account concerns about the safety of its investigators, employees at a site or facility, and where applicable, clinical trial participants and other patients at investigator sites**

Guidance for Industry: Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency, Questions and Answers (See Q2/A2)

Inspectional Information from Other Regulatory Authorities

- **Mutual Recognition Agreement (MRA) between FDA and EU:**
  - Rely upon information from inspections conducted within each other's borders
  - PAI capability determination is underway, but can rely on surveillance inspection information in evaluating compliance history

- **Use inspection reports done by capable MRA partner in a third country (i.e., countries other than US or their country)**

- **Confidentiality agreements allow FDA and other Regulatory Authorities to share information**

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

The Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law on July 9, 2012 amended the Food, Drug and Cosmetic Act:

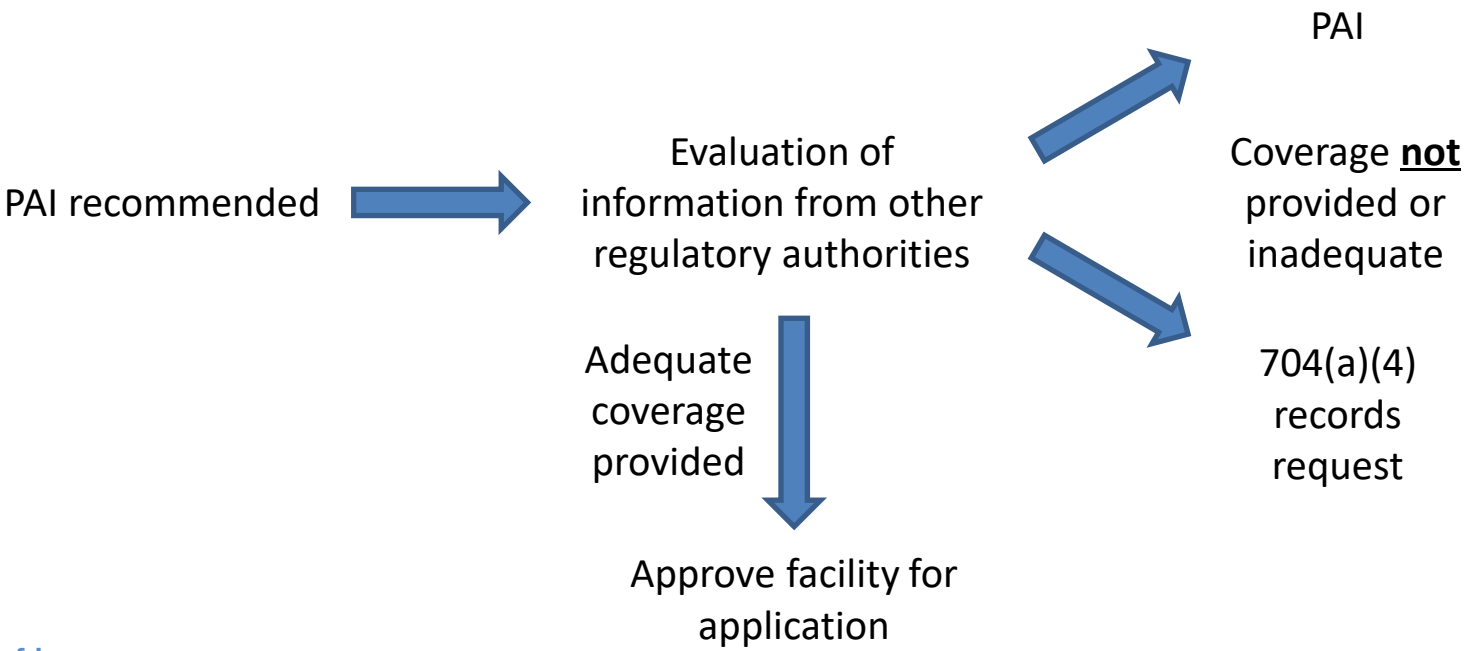
SEC. 704(a) (21 U.S.C. 374(a)) (FD&C Act) is amended by adding at the end the following:

(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.

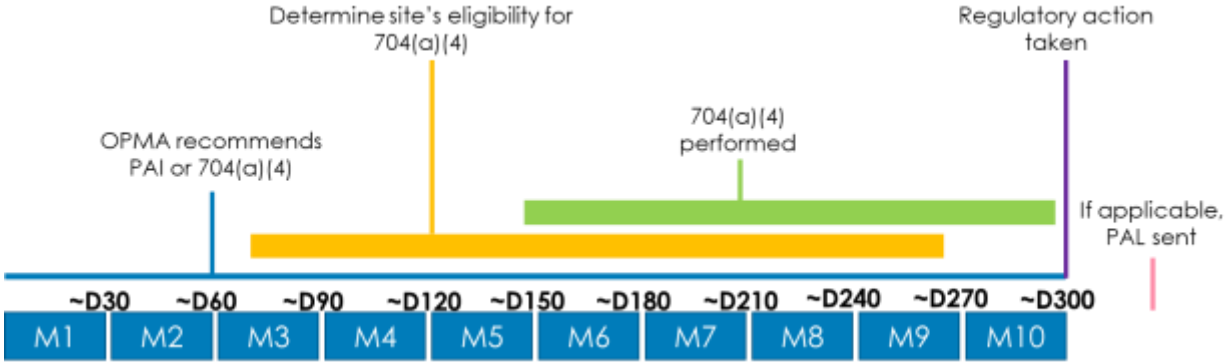
Records Request under §704(a)(4) of the FD&C Act

- FDA may request records from a facility upon completion of the application risk assessment
- Records requested will be used to assess capability of the facility and its quality systems to perform the manufacturing operations
- For PAIs, applicability will depend upon the risk factors (process, facility, micro, etc.) driving need for inspection
- If risks are not mitigated, FDA may determine that an on-site inspection is still warranted

Quality Risk Assessments for Sites Requiring Inspectional Activities during COVID-19 Travel Restrictions



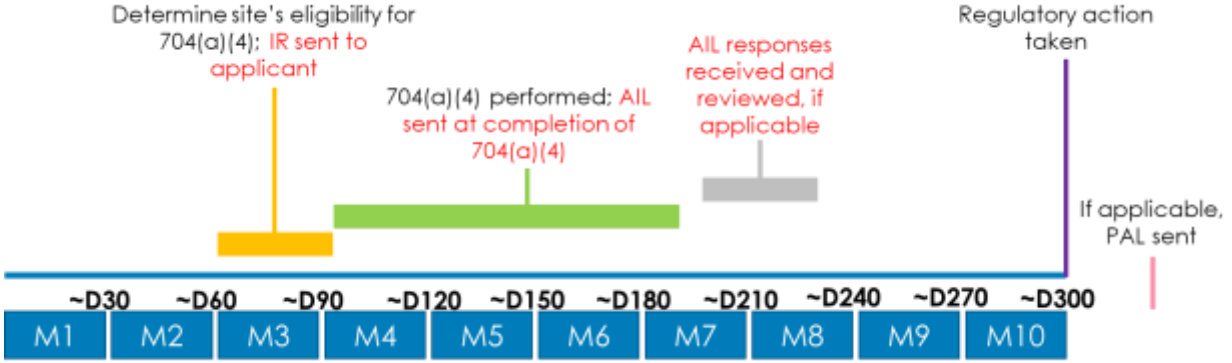
OPMA's Records Request under §704(a)(4) of the FD&C Act (Initial Public Health Emergency State)



- With COVID-19 travel restrictions, OPMA's use of 704(a)(4) Records Request in lieu of a PAIs started in March 2020
- Requests from the Agency were lengthy
- Required excessive time for facilities to gather requested information
- Utilized numerous rounds to reach a complete assessment
- Outcome of 704(a)(4) assessment was conveyed to the firm using Post-Action Application Letters (PALs), as applicable

Disclaimer: Schematic of typical GDUFA Original Application clock; timeline of 704(a)(4) assessment is for presentation purposes and not indicative of specific timeframes

OPMA's Records Request under §704(a)(4) of the FD&C Act (Current Public Health Emergency State)



- Improved timelines for making facility inspection decision (PAI vs. 704(a)(4))
- Focused records request on product and facility risks
- Enhanced communication with applicants regarding site inspection status
- Better transparency with firms indicating the end of the 704(a)(4) assessment via Assessment Issues Letters (AILs) outlining outstanding objectionable conditions (if any)

Disclaimer: Schematic of typical GDUFA Original Application clock; timeline of 704(a)(4) assessment is for presentation purposes and not indicative of specific timeframes

Conclusion of a 704(a)(4) evaluation and Assessment Issues Letter (AIL)

- The Agency is working directly with facilities to communicate any issues identified through a review of records or other information requested
- Following the conclusion of a 704(a)(4) record request assessment in lieu of a Pre-Approval Inspection (PAI)/Pre-License Inspection (PLI), the Agency issues an Assessment Issues Letter (AIL) to the firm.
  - FDA is evaluating expansion of AILs to other programs
- AILs indicate 704(a)(4) review is complete, outlines remaining issues and provides contact information for responses to such issues (if any).
- Responses to an AIL letter regarding these issues will, as feasible, be considered before taking an action on a pending application
- The Agency encourages applicants to be in communication with all their facilities and sites to ensure timely responses to any inquiries to support application assessment.

Guidance for Industry: Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency, Questions and Answers (See Q5/A5)

Hypothetical Scenario #1: 704(a)(4) Records Request Deemed Not Eligible; PAI Recommended

Drug Product (Solid Oral Dosage Form (SODF)) Manufacturing Facility

- **Product Risk:**
  - Multiple APIs, all low drug loading
  - Complex drug release profile
- **Process Risk:**
  - Insufficient In-Process Control data for bulk Blend Uniformity (BU) provided in the submission
- **Facility Risk:**
  - Site has acceptable inspectional history for manufacturing sterile parenterals via terminal sterilization
    - In other words, no experience with manufacturing SODFs
- **Outcome:**
  - Onsite PAI recommended

Hypothetical Scenario #2: 704(a)(4) Records Request Deemed Eligible

Sterile API Manufacturer

- **Product Risk:**
  - Sterile
- **Process Risk:**
  - Synthetic route potentially results in contamination of carcinogenic impurities
- **Facility Risk:**
  - Previous inspectional coverage includes sterile API manufacturing; however, Form FDA 483 Observations were noted regarding the Laboratory Control System
- **Outcome:**
  - 704(a)(4) recommended

Conclusion

- COVID-19 pandemic has altered the way OPMA performs manufacturing evaluations
- Since the pandemic started, OPMA used quality risk management strategies to reduce the need for Pre-Approval Inspections by approximately 55%
- Due to the revised quality risk management strategies:
  - The 704(a)(4) process is improving for efficiency, communication and transparency
  - The Agency maintains rigorous review standards, while ensuring the health, safety and well-being of our investigators.
  - The Agency continues to conduct mission-critical inspections of domestic and foreign manufacturing facilities to help assure compliance with our high standards for quality.

Challenge Question #1

Currently the Agency is performing onsite Pre-Approval Inspections (PAIs)

True

or

False

Challenge Question #1

Currently the Agency is performing onsite Pre-Approval Inspections (PAIs)

True

or

False

Challenge Question #2

When are Assessment Issues Letters (AILs) sent?

a. At the start of an onsite PAI
b. In the middle of a 704(a)(4) records request
c. Upon receipt of your application
d. Following the conclusion of a 704(a)(4) records request

Challenge Question #2

When are Assessment Issues Letters (AILs) sent?

a. At the start of an onsite PAI
b. In the middle of a 704(a)(4) records request
c. Upon receipt of your application
d. Following the conclusion of a 704(a)(4) records request

Challenge Question #3

A site listed in an original submission has no inspectional coverage for proposed operations. Which assessment option is most appropriate?

a. Onsite PAI

b. 704(a)(4) records request

c. Approval of site without further evaluation

d. None of the above

Challenge Question #3

A site listed in an original submission has no inspectional coverage for proposed operations. Which assessment options is most appropriate?

a. Onsite PAI

b. 704(a)(4) records request

c. Approval of site without further evaluation

d. None of the above

Acknowledgements

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Caryn McNab

Resources

1. COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders
2. CDER's Work to Meet User Fee Goals During the Pandemic
3. Manufacturing, Supply Chain, and Drug and Biological Product Inspections
4. Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency

Questions?

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