

# Pre-License and Pre-Approval Inspections during the COVID-19 Pandemic

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# Outline



- Alternative approaches utilized by FDA to mitigate Inspections
- Mission critical inspection criteria
- Impact on BLA CMC Review and application decisions

# Biologics Licenses: Issuance and Conditions

- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent (**PHS Act: Section 351(a)(2)(C)**)
- The applicant consents to the inspection of the facility that is the subject of the application(**PHS Act: Section 351(a)(2)(C)**)
- A biologics license application shall be approved only upon examination of the product and upon a determination that the product complies with the standards established in the biologics license application and the requirements prescribed in the regulations(**21CFR Sec. 601.20(a)**)
- A biologics license application shall be approved only after inspection of the establishment(s) listed in the biologics license application and upon a determination that the establishment(s) complies with the standards established in the biologics license application and the requirements prescribed in applicable regulations (**21 CFR Sec. 601.20(d)**)

# 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)

# Pre-License and Pre-Approval Inspection Objectives

- Readiness for Commercial Manufacturing
  - Verify that the applicant has demonstrated ability to operate with integrity and in compliance with CGMPs
- Conformance to Application
  - Assure adherence to application commitments
- Data Integrity Audit
  - Assure the authenticity and accuracy of data submitted in applications

# A Risk Based Decision for Biotech Inspection



- Prior inspection history
  - New facility/building/filling line without inspection history
  - Prior experience with similar manufacturing process
  - Information shared by other Regulatory Agencies
- CGMP issues relevant to application product
- Product and process specific risks
- Application specific concerns
- Significant process changes for supplements

# Alternative Tools

- Inspection reports from other trusted foreign regulatory partners
  - Mutual Recognition Agreement (MRA) between FDA and EU/UK. Though MRA has not been established for PAIs, information from MRA partner inspections may be used to understand site capabilities and CGMP compliance
  - Confidentiality agreements allow FDA and other Regulatory Authorities to share information
- Records requests under the Section 704(a)(4) of the FD&C Act
  - in advance of or in lieu of an inspection
- Information from applicants, directly from facilities, and other inspected entities

# Impact on the BLA Inspections during the COVID-19 Pandemic



- Travel restrictions and temporarily postponing all domestic and foreign routine surveillance facility inspections (March 2020)
- Resumption of domestic inspections with new risk assessment system per national guidelines (July 2020)
- Mission Critical inspections
  - Use other tools and approaches where possible to mitigate the need of inspections
  - Conduct mission-critical inspections on a case-by-case basis
- Foreign non mission-critical inspections remain temporarily postponed



# Mission Critical Inspections during COVID-19



- Mission Critical Applications
  - Breakthrough Therapy Designated (BTD) products
  - Drug Shortages
  - Products used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute
  - Products used in the treatment of patients with COVID-19
- Factors in Determining Mission Critical inspections
  - Safety of all those involved in inspections
  - public health benefits
- Conduct mission-critical inspections on a case-by-case basis

# Alternative Approaches to Inspections

- For BLA, applicability will depend upon the risk factors (product, process, facility, micro, etc.)
  - Initial assessment to determine if a PLI/PAI is required
    - No PLI/PAI
    - An inspection is required
    - Alternative approaches to mitigate an inspection if possible

# Alternative Approaches to BLA Inspections



- Records Request under § 704(a)(4) in advance of or in lieu of an inspection
  - Records requested will be used to assess capability of the facility and its quality systems to perform the manufacturing operations
- Information shared by other regulatory agencies (e.g. mutual recognition, confidentiality agreements)
  - Covered the same product, process and manufacturing areas
- Inspections not needed
  - Based on record review
  - Prior inspection history
  - Experience with similar manufacturing process
- PAI/PLI, alternative tools do not provide enough information to mitigate the need for an inspection.

# Impact on the BLA Review during the COVID-19 Pandemic



- Continue the quality assessment of all applications per normal assessment operations
- Evaluate manufacturing facilities using a risk-based approach consistent with existing guidelines
- Use alternative tools, where available, to mitigate the need for an inspection to support application assessment
- Conduct mission-critical inspections on a case-by-case basis
- Notify the applicant if a PLI/PAI is required before the application can be approved and the inspection may not be completed during the review cycle

# Application Decisions Impacted by Inspections



- Applications will not automatically receive a complete response letter if OPQ cannot conduct an inspection and no other deficiencies identified
  - Approval recommendation if:
    - an inspection can be mitigated using alternative tools
  - Withhold recommendation if:
    - past inspection history, or information gathered under 704(a)(4) raises concerns about the adequacy of the facility
  - Defer Action until an inspection can be completed if:
    - there is inadequate information to make a determination on the acceptability of a facility, and
    - the inspection of the facility cannot be completed by the action date

# What the Industry Can Do?



- Be in close communication with your manufacturing and testing facilities
- Ensure timely responses to Agency's Requests
- Treat the records request as you would an inspection
  - Provide complete, specific and accurate documents
- Be ready to provide information about other regulatory inspections at your facilities
- Consider alternate facilities where possible for increased flexibility

# Summary

- Continue application review and manufacturing facility assessment per normal operations and existing guidelines
- Use additional tools, where available, to mitigate the need of inspections during the COVID-19 pandemic, if possible.
- Conduct mission-critical inspections on a case-by-case basis
- Make application decisions based on all available information



# FDA Resources

- **Manufacturing, Supply Chain, and Drug Inspections | COVID-19 Website**
  - Inspections Q&A
  - Manufacturing and Supply Chain Change Requests Q&A
  - Regulatory Operations and Policy Q&A

<https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19>



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# Abstract

- This presentation is intended to provide updates on CDER pre-license and pre-approval inspections of biological products during the COVID-19 Pandemic. Due to the travel restrictions, FDA has temporarily postponed non-mission critical facility inspections and is only conducting mission critical inspections on a case-by-case basis. This presentation will discuss mission critical inspection criteria, alternative approaches utilized by FDA to mitigate Inspections, if possible, and impact on BLA CMC Review and application decisions if CDER cannot conduct an inspection during the review cycle.