The COVID-19 Public Health Emergency (PHE) and the Use of Alternate Tools for Facility Assessments

Presentation Outline

1. Site Inspections: background on inspection programs, framework for where and when inspections can happen during the PHE
2. Alternate tools: Defining and describing the use of alternate tools being used for site assessments during the PHE
3. Impact of travel restrictions on pending applications and supplements

Content of Presentation

Guidance for Industry

Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-supply-chain-and-drug-and-biological-product-inspections-during-covid-19-public-health

Guidance for Industry

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

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid

Resiliency Roadmap

Resiliency Roadmap for FDA Inspectional Oversight

https://www.fda.gov/media/148197/download

The Path Forward: A Federal Perspective on the COVID-19 Response

Testimony of

Janet Woodcock, M.D.

Acting FDA Commissioner Before the

Senate Committee on Health, Education, Labor, and Pensions

Inspection Programs

Inspection Programs

Pre-Approval Inspections (PAIs) and Pre-License Inspections (PLIs)

Used to ensure that any facility named or referenced in support of an application can perform the proposed manufacturing operations in conformance with current good manufacturing practice (CGMP) requirements, to verify conformance with the application, and to confirm that data submitted in the application are accurate and complete.

Inspection Programs

Post-Approval Inspections (PoAIs)

Focused on a specific drug and changes to its manufacturing operations, the evaluation of process validation, any changes submitted to the application, and the execution of supporting activities according to application commitments and CGMP requirements.

Inspection Programs

Surveillance Inspections

Examine overall operations, including controls that ensure manufacturing processes produce quality drugs, thereby reducing the risk of adulterated or misbranded drugs reaching consumers and patients. FDA uses surveillance inspections to evaluate the CGMP compliance of manufacturing operations.

Inspection Programs

Follow-Up and Compliance Inspections

When a specific drug quality problem or facility issue comes to FDA's attention, we may initiate a follow-up or compliance drug quality inspection.

Inspection Programs

Bioresearch Monitoring (BIMO) Inspections

- A comprehensive, Agency-wide program of inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research.

- The goals of the BIMO program are to protect the rights, safety, and welfare of research subjects; to verify the accuracy, reliability, and integrity of clinical and nonclinical trial data submitted to FDA; and to assess compliance with FDA's regulations governing the conduct of clinical and nonclinical trials.

COVID-19 and Drug Facility Evaluations Inspections

COVID-19 and Drug Facility Evaluations Inspections

- On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19
- On March 13, 2020, the President declared a national emergency in response to COVID-19.
- March 2020: FDA paused domestic and foreign surveillance inspections
  - Continued to conduct domestic and foreign mission-critical inspections

Mission Critical

Mission Critical includes drugs and biologics that:

- Have received breakthrough therapy, orphan-drug designation, or regenerative medicine advanced therapy designation;
- Are in the Drug Shortage or CBER-Regulated Products Shortage list;

Mission Critical

- Are used for critical care or as a medical countermeasure;
- Are used to diagnose, treat, mitigate, cure, or prevent a serious disease or medical condition, including COVID-19, for which there is no other appropriate and available treatment.

Mission Critical

- Both for-cause and preapproval inspections can be deemed mission-critical
- When determining whether to conduct a mission-critical inspection, FDA takes into account the safety of:
  - its investigators,
  - Employees at a site or facility, and
  - Where applicable, clinical trial participants and other patients at investigator sites.

Mission Critical

- From March 2020 through March 2021, FDA conducted a total of 821 mission-critical inspections, including 29 in foreign countries

COVID-19 and Drug Facility Evaluations Inspections

- July 2020: FDA resumed prioritized domestic inspections.
  - Rating system to assist in determining when and where it was safest to conduct prioritized domestic inspections.
  - Includes preapproval, pre-license, surveillance, and for-cause inspections
  - Currently being pre-announced

COVID-19 and Drug Facility Evaluations Inspections

- As of March 2021, the Agency conducted a total of 777 prioritized domestic inspections since resumption of that work in July 2020.

COVID-19 and Drug Facility Evaluations Inspections

- May 5, 2021: FDA issued a report titled, “Resiliency Roadmap for FDA Inspectional Oversight,” outlining the Agency’s inspectional activities during the COVID-19 pandemic and its detailed plan to move toward a more consistent state of operations, including FDA’s priorities related to this work going forward.

Alternative Tools to Assess Facilities

Alternative Tools
Pharmaceutical Quality/Manufacturing

- FDA assessment of inspection reports from trusted foreign regulatory partners
  - PIC/S Inspections
  - Confidentiality Agreements
  - Mutual Recognition Agreement (MRA)
- FD&C Act 704(a)(4) Requests
- Remote Interactive Evaluations
- Import Examinations
- Sampling and Testing

Trusted Foreign Regulatory Partners

- PIC/S Guidance on GMP Inspection Reliance
  - Nonbinding, high-level guidance

  https://picscheme.org/users_uploads/news_news_documents/PI_048_1_Guidance_on_GMP_Inspection_Reliance_1.pdf
- Confidentiality Agreements
  - Inter-agency agreements which allow specified confidential commercial information to be shared

Trusted Foreign Regulatory Partners: MRA

- Routinely used for surveillance inspections conducted in EU and UK
- Also used for surveillance inspections conducted by MRA partners in 3rd countries
- Considered an FDA manufacturing facility inspection under section 510(h)(3) of the FD&C Act
- Though MRA has not been established for PAIs/PLIs, information from MRA partner inspections may be used to assess facilities in pending applications

See https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra)

FD&C Act 704(a)(4) Requests

- Section 706 of FDASIA amended section 704(a) of the FD&C Act by adding 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)
  - Sites typically have 15 days to respond, or up to 30 days if translation is requested

FD&C Act 704(a)(4) Requests

- Not considered an FDA inspection under section 510(h)(3) of the FD&C Act
- Failure to Cooperate: may constitute a limiting of inspection. FDA may deem the relevant drugs manufactured at these establishments adulterated

See SMG 9004.1: POLICY AND PROCEDURES FOR REQUESTING RECORDS IN ADVANCE OF OR IN LIEU OF A DRUG INSPECTION (https://www.fda.gov/media/124338/download)

Remote Interactive Evaluations

- Includes teleconference, livestream video, and screen sharing of data and documents.
- Voluntary
- Not considered an FDA inspection under section 510(h)(3) of the FD&C Act

Remote Interactive Evaluations

- FDA uses risk management methods and tools to determine when to request a facility's participation in a remote interactive evaluation.
- FDA may request records or request that a facility participate in a remote interactive evaluation prior to an inspection
- FDA will not accept requests from applicants or facilities for FDA to perform a remote interactive evaluation.

Remote Interactive Evaluations

- See FDA Guidance *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*
  - Notification to the Facility
  - Specific considerations for different inspection programs
  - Preparing for a Remote Interactive Evaluation
  - Conducting a Remote Interactive Evaluation
  - Concluding a Remote Interactive Evaluation
  - Impacts of Remote Interactive Evaluations on Established Commitments and Timeframes

Import Examinations and Sampling

- Proven effective to help assure the quality of drug products in the US market
  - Physical examinations of products arriving at U.S. borders
  - Product sampling and testing before release into commerce
- Admission can be refused if standards for safety, effectiveness, or quality are not met

Import Examinations and Sampling

- Work with U.S. Customs and Border Protection (CBP) to target products that violate applicable legal requirements
- Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) import screening tool uses dynamic risk scores to focus on specific products with heightened concerns

Drug Quality Surveillance and Testing (DQST) Program

- Sample both APIs and FDFs that are manufactured domestically or internationally
- Samples can be collected in various ways
  - Directly from the manufacturer
  - From a distributor
  - At time of import
  - Via retail purchases
- Can do for-cause sampling or statistically-designed sampling plans

Import Examinations and Sampling

- Since March 2020, with the cooperation of and in coordination with CBP, FDA has received and destroyed almost 60,000 products, totaling over 11,093,868 capsules, pieces, and tablets of illegal or unapproved drugs.
- Since March 2020, FDA has refused approximately 94,725 lines of imported violative medical products.

BIMO Alternative Tools

- COVID-19 impacts BIMO inspections
  - Inspection history
  - Information sharing from trusted foreign regulatory partners
  - Information requests (applicants/sponsors)
  - Voluntary record requests and reviews
  - Remote interactive evaluations

Pending Applications and Supplements

Pending Applications and Supplements

- During the PHE, FDA continues to assess all applications, for all disciplines, where all manufacturing facilities will be evaluated using a risk-based approach consistent with existing guidelines.

- During the PHE, FDA is using all available tools and sources of information to support regulatory decisions on applications that include sites impacted by travel restrictions due to COVID-19.

Pending Applications and Supplements

- Strategically applying a holistic approach in the decision-making process to determine if an inspection is warranted or if an inspection is no longer needed due to information gained through the use of the alternative tools

Pending Applications and Supplements

- For pending applications and supplements, we work directly with facilities to communicate any issues identified through alternate tools (e.g., remote interactive evaluations, review of records, or other information requested).

- Responses from the facility regarding these issues will, as feasible, be considered before taking an action on a pending application.

Pending Applications and Supplements

- Decisions regarding applications will be based on the totality of the information available to FDA, including information obtained from use of the alternative tools

Application Approval

- Available information, including information obtained from the use of alternate tools, supports the adequacy of the facilities and sites named in a pending application, no other deficiencies have been identified, and the application otherwise satisfies the requirements for approval.

- In this case, the need for an inspection could be sufficiently mitigated by the FDA's use of alternate tools, including a firm's responses to outstanding issues identified from the use of alternate tools

Defer Action
(Missed Goal Date)

- If an inspection is necessary because there is insufficient information currently available to make a determination on the acceptability of a facility or site (e.g., no inspection history) and other deficiencies have not been identified.

Defer Action
(Missed Goal Date)

- FDA will inform the applicant of the situation as soon as possible during the review of the application.

- If FDA defers action on the application, the project manager will contact the applicant to explain the situation. In this case, therefore, there is no submission or communication needed by the applicant to ensure that an inspection will be scheduled to support application approval.

Complete Response With Facility Deficiency

- Available information from a prior FDA or mutual recognition agreement inspection or the use of alternate tools identifies concerns about the adequacy of a facility or site, and an inspection needed to address those concerns cannot be completed during the review cycle, or

Complete Response With Facility Deficiency

- Responses to outstanding issues identified from requested records and other alternate sources are not sufficient to address the issues identified for a facility or site.

Complete Response With Facility Deficiency

During the Review

- Where there is information that calls into question the adequacy of the facility or site, FDA intends to inform the applicant of the facility or site issues as soon as possible during the review cycle.

- Specifically, FDA intends to inform the applicant that an inspection will be needed before the application can be approved and that the inspection may not be conducted before the action date due to restrictions on travel.

Complete Response With Facility Deficiency

- If the inspection has not been conducted by the action date, FDA generally intends to issue a CR letter, including a deficiency related to the facility or site

Complete Response With Facility Comment

- An inspection is necessary because there is insufficient information currently available to make a determination on the acceptability of a facility or site and other deficiencies have been identified.

  - The same facility/site situation as when FDA defers action on the application, except, in this case, there are other deficiencies

Complete Response With Facility Comment

- During the review cycle, FDA intends to inform the applicant of the facility or site issues as soon as possible. Specifically, FDA intends to inform the applicant that the inspection may not be conducted before the action date due to restrictions on travel.

Complete Response With Facility Comment

- In this case, FDA will not include a facility or site deficiency in the CR letter if the needed inspection cannot be completed by the action date due to travel restrictions.

- Rather, in the CR letter FDA will list the other deficiencies and also include a non-deficiency facility or site comment stating that an inspection will be needed to support approval of the application because there is insufficient information available to make a determination on the acceptability of a facility or site.

Impact of COVID-19 on Pending Applications and Supplements

- Refer to the Agency's existing guidance documents on making changes to an approved abbreviated new drug application (ANDA), new drug application (NDA), or BLA, as well as scale-up and postapproval change guidance documents for specific dosage forms.
- Should circumstances resulting from the COVID-19 pandemic warrant atypical or flexible submission strategies for CMC changes, for CDER-regulated products, contact CDER-OPQ-Inquiries@fda.hhs.gov

Conclusions

- FDA is using all available tools to assess sites named in pending applications and supplements
- Inspections for mission critical products continue
- Applications will not automatically receive a Complete Response because of the need for an inspection that cannot be conducted due to travel restrictions
- Follow existing guidance for post-approval changes. For CMC supplements, if atypical or flexible strategies are being considered due to the COVID-19 pandemic, contact OPQ at CDER-OPQ-Inquiries@fda.hhs.gov