

In Vitro Diagnostic Devices Inspections

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Overview

- Examples of IVDs regulated by CBER
- Types of IVD Device Inspections
- IVD Device Inspection Process
- References

Examples of IVDs regulated by CBER

- Licensed IVDs
 - Donor screening tests (e.g., HIV, HTLV, Hepatitis B and C Viruses)
 - Reagent Red Blood Cells
 - Blood Grouping Reagents
 - Anti-Human Globulin
- Approved or Cleared IVDs
 - Diagnostic HIV test kits
 - Automated immunohematology analyzers
 - Plasmapheresis machines
 - Quality assurance reagents

Inspections of Licensed IVDs

Inspection	Description	Who: Lead Inspectors	When: Inspection Date
Pre-License Inspection (PLI) *	Submission of a Biologics License Application (BLA)	CBER – DMPQ	Midcycle
Pre-Approval Inspection (PAI) *	Significant changes to an approved application; Submission of a Prior Approval Supplement (PAS)	CBER – DMPQ	Midcycle
Surveillance	Routine and Compliance Follow-up CGMP Inspection	Team Biologics	Biennial
For Cause or Directed	Response to specific information that raises questions, concerns, or problems (e.g., recall, complaint, adverse reaction)	ORA Investigators	Anytime

* SOPP 8410: PLI and PAI may be waived

Inspections of Approved or Cleared IVDs

Inspection	Description	Who: Lead Inspectors	When: Inspection Date
PMA Preapproval Inspection	Submission of a Premarket Approval (PMA)	ORA	Midcycle
PMA Postmarket Inspection	CGMP Compliance; Confirm commitments made by firm (e.g., device design, manufacturing process, quality systems)	ORA	After PMA approval (generally 8 – 12 mo.)
Surveillance	Routine and Compliance Follow-up CGMP Inspection	ORA	Biennial (Class II or III); Risk-based
For Cause or Directed	Response to specific information that raises questions, concerns, or problems (e.g., recall, complaint, adverse reaction)	ORA Investigators	Anytime

Authority and Requirement to Inspect

- The regulatory authority to conduct inspections at any establishment where biological products are manufactured is provided at:
 - Section 351 of the Public Health Service Act
 - Section 704 of the Federal Food, Drug and Cosmetic Act
- Under 21 CFR 601.20, a biologics license shall not be issued except upon a determination that the product and establishment comply with the applicable regulations

IVD Device Inspection Preparation

- Coordination of Inspection Dates
 - Production Schedule (for PLI or PAI)
 - Projected shutdown / maintenance
- Inspection Logistics
 - Address confirmation and arrival instructions
 - Restrictions (e.g., wardrobe, jewelry, cosmetics, notebooks)
 - Vaccinations or other special requirements
 - Workspace, office support, and internet connectivity
- Pre-Inspection Document Request List
 - Production schedule
 - Procedures and documentation

IVD Device Inspection Process

- Introductions
 - Most Responsible Person (Name and Title)
 - Presentation of credentials
 - Presentation of the Form FDA 482, Notice of Inspection, if applicable
 - Opening meeting to state the objective of the inspection
- Facility Walk-through
- Observation of production per production schedule
- Review of documents
- Discussions with Subject Matter Experts (SMEs)

Inspection Plan

- CBER fulfills its regulatory obligation to inspect establishments where biological medical device products are manufactured in accordance with the following guides:
 - Compliance Program Guidance Manual Inspection of Licensed In-Vitro Diagnostic (IVD) Regulated by CBER (7342.008)
 - Guide to Inspections of Quality Systems (QSIT)
 - Investigations Operations Manual

<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references>

Subsystems of a Quality System



Requirements per device quality system regulations (21 CFR Part 820)



Compliance Program Guidance Manual

Inspection of Licensed In-Vitro Diagnostic (IVD) Devices Regulated by CBER (7342.008)

- Verify all relevant data were submitted to the BLA or supplement, and data are accurate and complete
- Verify device history record (DHR) is accurate and complete when compared to the submission
- Observe the processes, manufacturing and testing, and compare with the description and/or DHRs submitted in the CMC section and other sections of the submission
- Review process controls, analytical testing, and process validation for the finished device



Compliance Program Guidance Manual

Inspection of Licensed In-Vitro Diagnostic (IVD) Devices Regulated by CBER (7342.008)

- Review facility and process changes not covered in the submission that could affect the product or manufacturing
- Review design control documentation and compare data if submitted in the application
- Review batches or lots that did not meet and met specifications and verify out of specification investigations are completed
- Review data as needed, determined by submission review for qualification of new manufacturing areas, equipment, and utilities



Compliance Program Guidance Manual

Inspection of Licensed In-Vitro Diagnostic (IVD) Devices Regulated by CBER (7342.008)

- Verify raw materials and components testing have been performed
- Verify the new product has been incorporated into all aspects of the quality system
- Review shipping validation for the finished device
- Verify procedures have been established for reporting of Biological Product Deviation Reports (BPDRs) and Medical Device Reports (MDRs) per 21 CFR 600.14 and 21 CFR 803, respectively

Examples of 483 Observations

- The management and evaluation of unplanned maintenance activities of critical pieces of equipment used in the XX manufacturing are not adequate, specifically:
 - Quality is not involved in the oversight of unplanned equipment maintenance activities and impact on test results.
 - There have been no excursions, CAPAs, or change controls initiated from the unplanned equipment maintenance events.
 - There is no evaluation of the equipment repair(s) as performed by the service provider(s) to determine if the repair is adequate to prevent repeated equipment failure or that the repair has corrected the cause of the malfunction.

Examples of 483 Observations

- The design verification results, including identification of the design, methods, date, the individuals performing the verification were not documented in the Design History File (DHF).
- The facility design does not contain sufficient space to perform operations related to manufacturing activities as evidenced by:
 - In the sample receipt area, multiple delivery boxes were piled up partially blocking access to a work table and a refrigerator.
 - A chest freezer in the XX area was being used as a bench top for activities related to manufacturing.

Examples of 483 Observations

- Procedures to control labeling activities have not been adequately established. For example,
 - 320 labels were issued for manufacture of LOT AA with 305 labels applied to product vials and 2 labels within the DHR. There is no formal reconciliation process to account for the remaining 13 product labels.
 - The mislabeling of materials has led to two instances for mix-up potential as noted in exceptions A and B.

Examples of 483 Observations

- The control of documents and management of document changes is not adequate. Specifically, the removal of obsolete manufacturing procedures from the XX areas is not being performed in a timely manner as to prevent the use of an incorrect version being followed and has directly lead to three excursions, specifically Excursions AA, BB, and CC.

Inspection Tips

- Allow reasonable access to manufacturing areas, documents, and personnel
- Provide documents as requested
 - Exceptions: We will not review reports from management reviews, quality audits, and supplier audit reports but may review associated procedures and information in CAPA records
- If the inspector has a question or makes an observation you do not understand, please ask for clarification
- Provide thorough, accurate, and clear responses to questions
- If you disagree with the inspector, please state your position with supportive documentation, understand the inspector's comments, agree to disagree, and move on

IVD Device Inspection Closeout

- Mini-closeouts (daily) are recommended and Final Closeout
 - Discussion Items
 - Observations
- Issuance of a Form FDA 483 with objectionable issues (observations from the inspection team)
- (Voluntary) Annotation Program for the Form FDA 483
 - Reported corrected, not verified
 - Corrected and verified
 - Promised to correct
 - Under consideration

After an IVD Device Inspection

- Respond to the Form FDA 483
- Establishment Inspection Report (EIR)
 - Field Management Directive 145 (FMD-145), Procedure for Release of Establishment Inspection Report to the Inspected Establishment
- Inspection Classification (after review of the 483, EIR and response by the establishment to the observations, if any)
 - No Action Indicated (NAI)
 - Voluntary Action Indicated (VAI)
 - Official Action Indicated (OAI)

References

- Regulations in 21 CFR Parts 600, 601, 610, and 660, and in 21 CFR Parts 803, 806, 807, 809, and 820
- Compliance Program Guidance Manual Inspection of Licensed In-Vitro Diagnostic (IVD) Regulated by CBER (7342.008)
- Compliance Program Guidance Manual Inspection of Medical Device Manufacturers (7382.845)
- SOPP 8410: Determining when Pre-License/Pre-Approval Inspections are Necessary
- Investigations Operations Manual
- Guide to Inspections of Quality Systems (QSIT)
- Design Control Guidance for Medical Device Manufacturers
- Field Management Directive 145 (FMD-145), Procedure for Release of Establishment Inspection Report to the Inspected Establishment

