How to Survive an FDA Inspection

Greenlight Guru Webinar June 2, 2022

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Who Does FDA Inspect?

- Drug manufacturers
- Device manufacturers
- Blood banks
- Food processing facilities
- Dairy farms
- Animal feed processors
- Compounding pharmacies relevant to your FDA inspects
- Facilities that conduct studies in people
- Laboratories that conduct studies in animals (when used to support FDA approval of medical products)

Number of 483's issued from FDA's 483 database system*

Inspections ending between 10/1/2019 and 9/30/2020

Cite Program Area Name	483s Issued
Biologics	28
Bioresearch Monitoring	98
Devices	422
Drugs	349
Foods	1749
Human Tissue for Transplantation	47
Parts 1240 and 1250	9
Radiologic Health	9
Veterinary Medicine	100
Sum Product Area 483s from System*	**2811**
Actual Total in System 483s**	**2788**

**This table does not represent the complete set of 483's issued during the fiscal year as some 483's were manually prepared and not available in this format. The sum of 483's for all Product Areas will be greater than the actual Total 483's issued during the fiscal year since a 483 may include citations related to multiple product areas, and counted more than once, under each relevant product center.*

*** This is the Actual Total number of 483's issued from this system, and that are represented in this spreadsheet.*

Number of 483's issued from FDA's 483 database system*

Number of 483 issued from the System*

Inspections ending between 10/1/2020 and 9/30/2021

Cite Program Area Name	483s Issued
Biologics	17
Bioresearch Monitoring	133
Devices	191
Drugs	215
Foods	1751
Human Tissue for Transplantation	51
Parts 1240 and 1250	3
Radiologic Health	6
Veterinary Medicine	105
Sum Product Area 483s from System*	**2472**
Actual Total in System 483s**	**2430**

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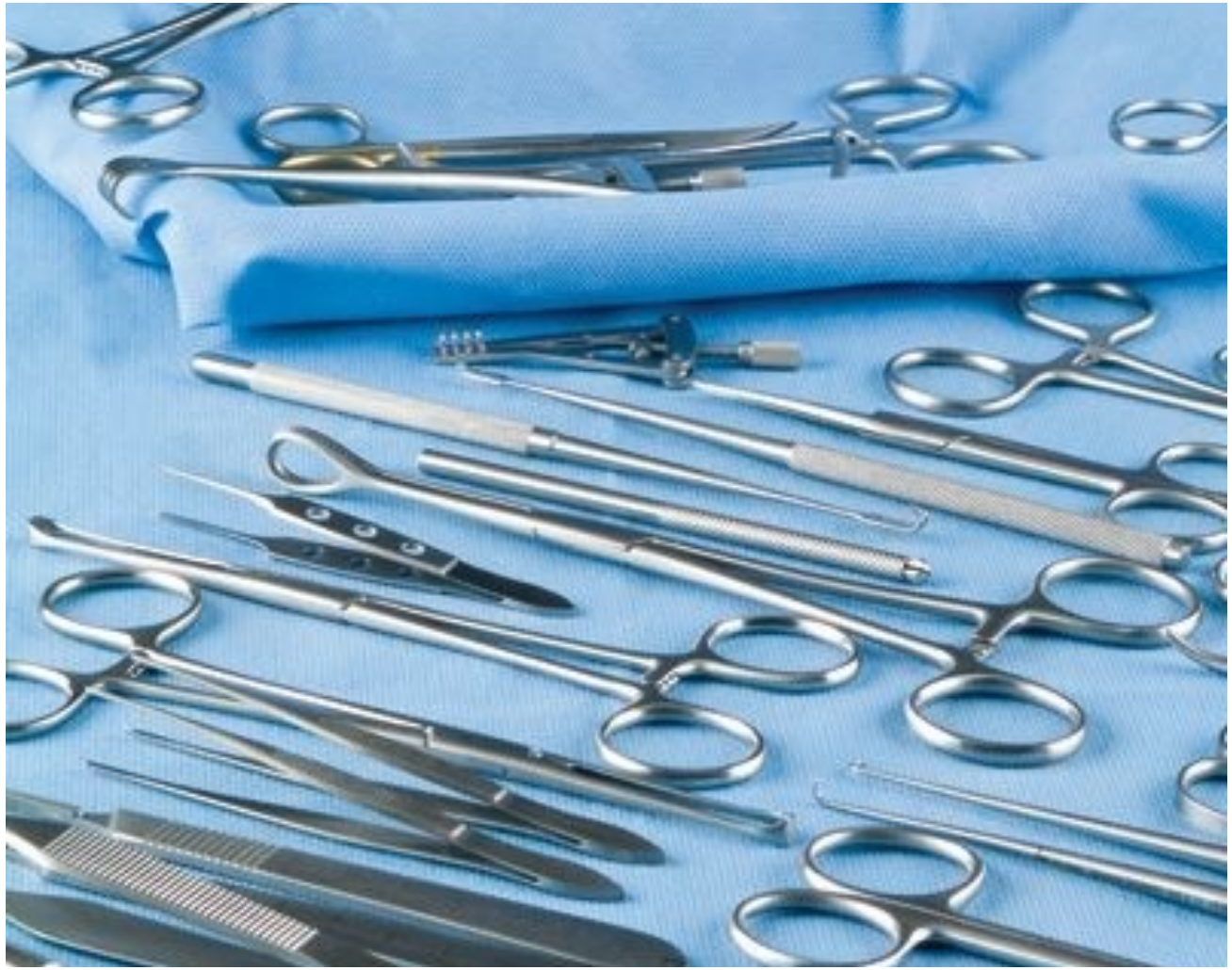
Definition of a Medical Device

The Food and Drug Administration (FDA) is the federal entity responsible for providing regulatory oversight of the manufacturing, sales, and distribution of medical devices in the United States. FDA's authority derives from the Federal Food, Drug and Cosmetic Act (the "Act"), as amended by the Medical Device Amendments of 1976. Within FDA, the Center for Devices and Radiological Health (CDRH) has primary responsibility for implementing these authorities. The Act defines medical device as follows:

- A medical device means … an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
  a) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
  b) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  c) intended to affect the structure or any function of the body of man or other animals, which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 360j(o) of this title.

Class I Devices

- Lowest Risk Devices
- Class I devices are “not intended for use in supporting or sustaining life or of substantial importance in preventing impairment to human health , and they may not present a potential unreasonable risk of illness or injury
- General Controls are adequate to provide a reasonable assurance of safety and effectiveness
- Prohibits adulteration (not meeting specification)
- Prohibits misbranding
- Generally, requires compliance with 21CFR §820 Quality System Regulation
- Must Register and List per 21 CFR Part 807
- Most Class I devices are exempt from premarket notification (510(k)) clearance requirements



Class II Devices

- Moderate risk device
- “General and “special controls” are adequate to provide a reasonable assurance of safety and effectiveness
- Generally subject to FDA review and clearance of a “premarket notification” known as a 510(k).
- Must submit a 510(k) prior to placing new device on the market
- Must submit a premarket notification if a device on the market that is significantly modified or changed to the extent that its safety or effectiveness could be affected

Class III

- Highest risk category of devices
- Generally, life supporting or life sustaining, are implanted, or present potential unreasonable risk of illness or injury
- Generally subject to FDA Premarket Approval (PMA) which requires demonstration of reasonable assurance of safety and effectiveness, based on valid scientific evidence.

FDA Inspections

Use of a risk-based approach for inspection preparation

How FDA Assesses Risk Level

- Type of Device: (Class III or Class II devices)
- Implantable devices, life supporting, and life sustaining devices
- Recently introduced a new device to the market
- Past compliance history
- What recalls a company has had in the past
- How often the facility has been inspected in the past
- Whether an inspection was carried out by a foreign government, or an agency related as per section 809 (In-vitro Diagnostics)
- Any other extenuating circumstances that warrant an increase in risk

Rationale for Risk-Based Approach

The risk-based inspection program aims to:

- Verify that manufacturers are maintaining compliance with current good manufacturing practices (cGMP) requirements. Where violations are detected, a company must provide proof that dangerous products are not entering the market.
- Assess a company's overall adherence to CGMP requirements.
- Provide valuable feedback during the inspection process.

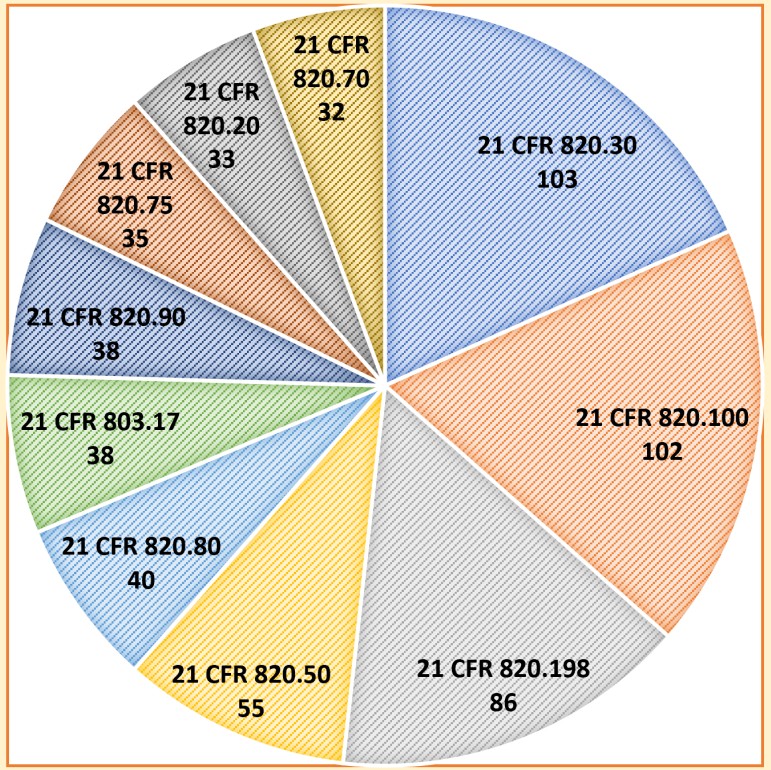
Quality System Inspection Technique (QSIT)

FDA’s most common pre-announced full quality system approach

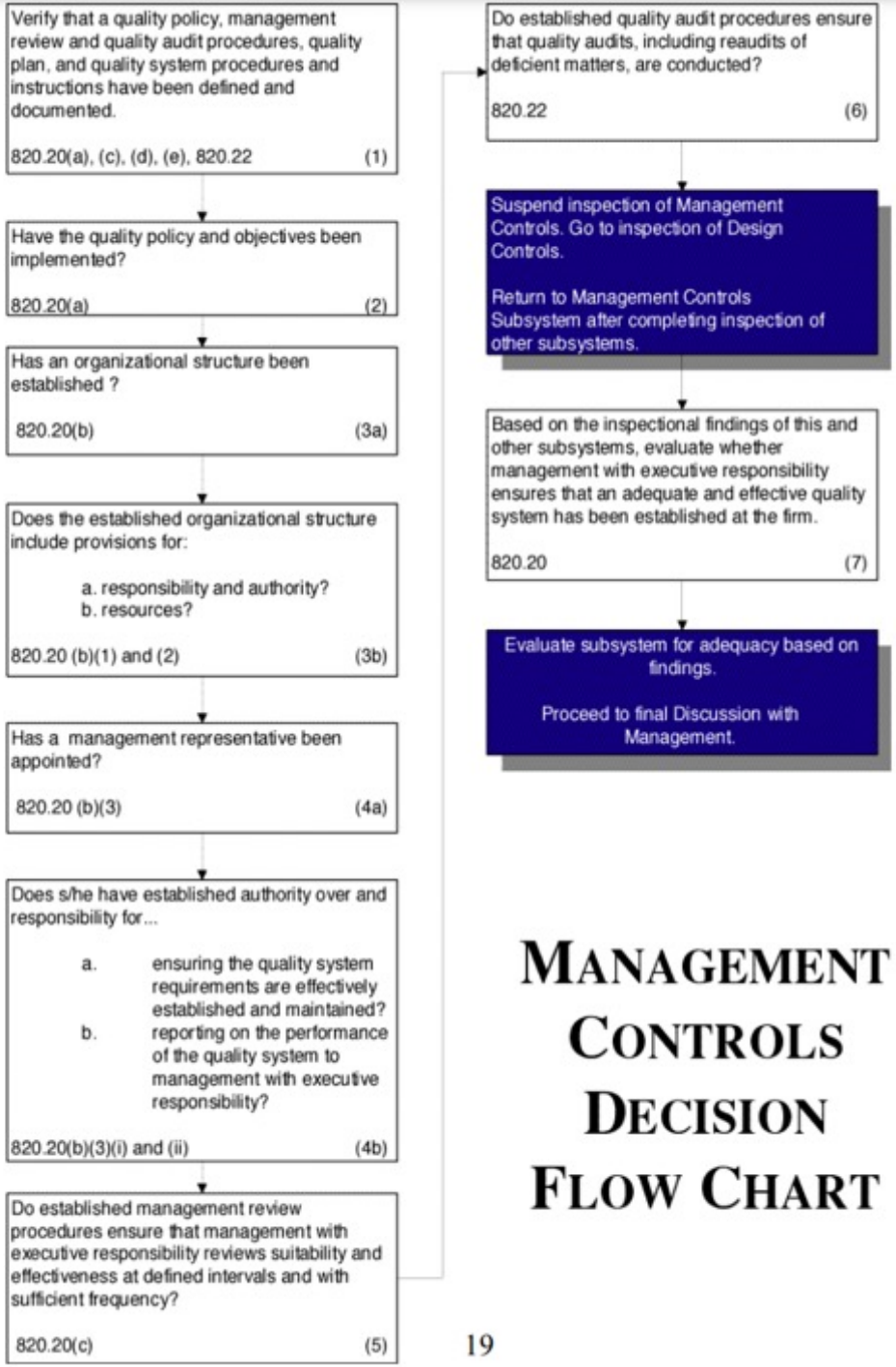
FREQUENCY

Reference Number	Frequency	Title
21 CFR 820.30	103	Design Controls
21 CFR 820.100	102	Corrective and Preventive Action
21 CFR 820.198	86	Complaint Files
21 CFR 820.50	55	Purchasing Controls
21 CFR 820.80	40	Receiving, In-Process, and Finished Device Acceptance
21 CFR 803.17	38	Medical Device Reporting
21 CFR 820.90	38	Nonconforming Product
21 CFR 820.75	35	Process Validation
21 CFR 820.20	33	Management Responsibility
21 CFR 820.70	32	Production and Process Controls

2021 483 Summary



fda.gov/Inspections-compliance-enforcement-and-criminal-investigations//inspection-references/inspection-observations



MANAGEMENT CONTROLS DECISION FLOW CHART

Inspection Methods

- Traditional On-site Inspection– an investigator is in the facility 100% of the time.
- A Virtual Inspection– uses video chat, teams or zoom for virtual interviews, walk throughs, and document reviews.
- Hybrid Inspection—A blend of onsite and virtual activities.

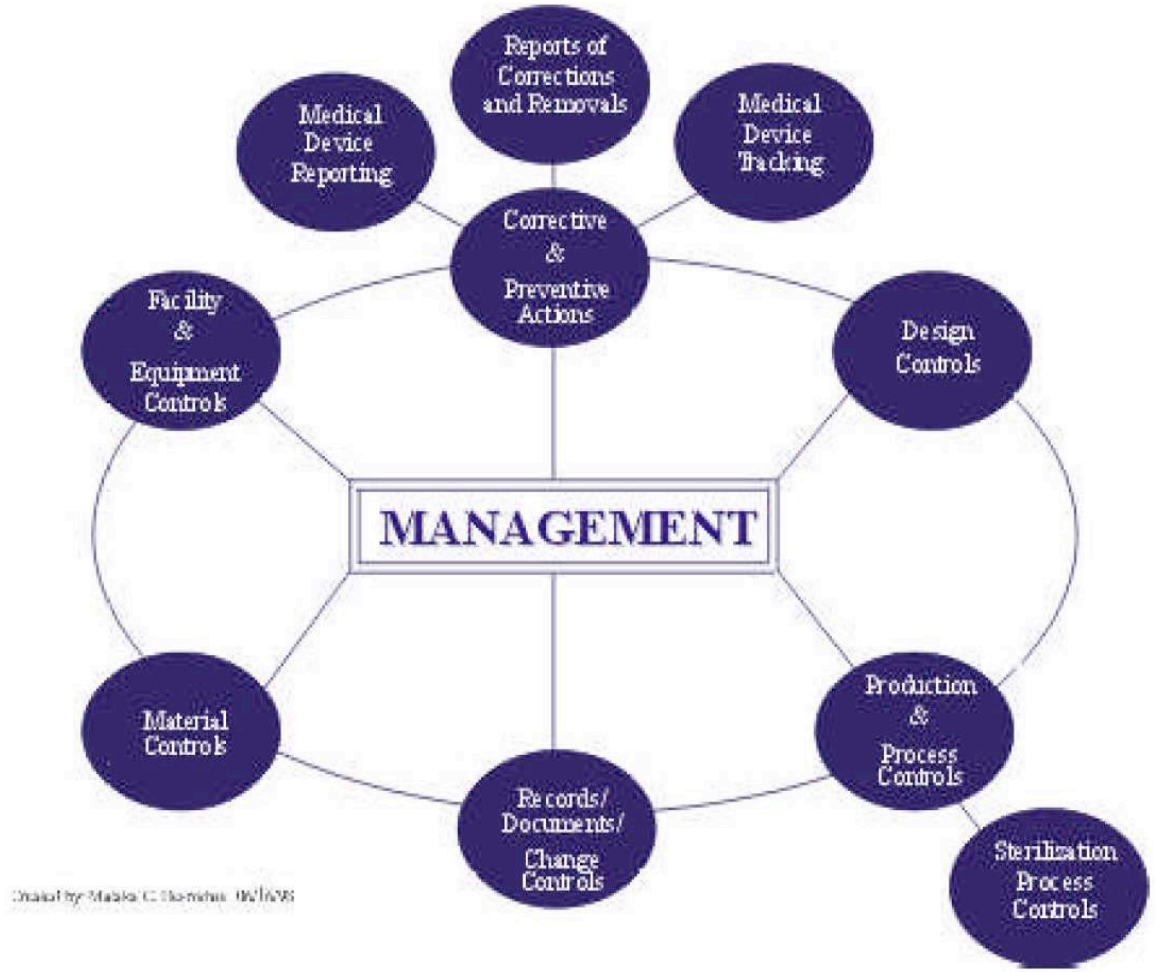
Types of Inspections

There are two types of QSIT inspections: Level I Abbreviated and Level II Baseline.

- A **Level II Baseline QSIT inspection** is a comprehensive inspection covering all four major subsystems. It is conducted when a firm has never had a Level 2 inspection, and every two years thereafter. It provides an overall evaluation of the quality system.
- A **Level I Abbreviated QSIT inspection** is conducted after a firm has had a Level 2 inspection, and the quality system was found to be in compliance with all requirements. A Level 1 inspection always includes the CAPA subsystem, plus one other major subsystem. A different subsystem will be chosen for each subsequent Level 1 inspection.

4 major subsystems reviewed during a Level II QSIT Baseline Inspection

1. Management Control
2. Corrective and Preventive Actions
   a. Medical Device Reporting
   b. Corrections and Removals
   c. Medical Device Tracking
3. Design Controls
4. Productions and Process Controls
   a. Sterilization Process Controls



Does FDA Notify Manufacturer of Inspections?

Generally, the Manufacturer ***is*** notified prior to the inspection.

- FDA contacts the company before the inspection.
- **Domestic manufacturers** are notified up to 5 calendar days before the inspection.
- **Foreign manufacturers** are notified 2-3 months in advance to schedule the inspection.
- The manufacturer may be requested to send their **Quality System Manual** or equivalent for pre-inspection review.

Types of Inspections (Continued)

- **Compliance follow-up**
  a. Conducted to verify adequate correction of previous violations or document continuing violations to support possible regulatory action.
  b. Is conducted to follow up on information indicating serious problems at firm.
  c. May include elements of QSIT.

- **“For Cause”**
  a. Initiated at the request of CDRH, ORA Headquarters, Regional or District Directive.
  b. Dictated by the source of information and may differ from typical QSIT approach.
  c. These inspections are generally more in depth in particular areas than typical QSIT inspections.
  d. Conducted as the need arises.

How to Prepare for FDA

Develop an SOP stating how to manage an inspection:

- Clearly state whom to contact first when the inspector shows up at the site.
- How will you notify the entire facility that an inspector is in the building.
- How will you document FDA requests for information.
- How will you handle the inspector's request for photographs or videos.
- How will you respond to an FDA request that is not in agreement with your quality procedures.
- Define team members and train all relevant personnel to the SOP including subject matter experts (SMEs).

Practice

- Each person should know their role.
- The FDA should always be escorted.
- Do NOT overexplain… just answer the question.
- Communication methods to use during inspection (teams, chat). The front room (present with inspector) needs to document what is being said and what will be needed next to the back room.
- *The back room can "make or break" the inspection. Example: the documents requested, reviewed and taken are not recorded.*
- Incorrect documents are provided to the FDA (the FDA should not be allowed access to internal audit reports, management review (21 CFR §820.20 Management Responsibility)

Do’s and Don’ts During Inspection

- If the question is vague, make sure to ask the Inspector to clarify.
- Be honest in answering questions.
- Let the SME’s discuss questions in their expertise.
- Be cool and calm.
- Be polite and show confidence.
- Know your strength areas and play to them.
- Know your soft spots and limit the damage.
- It’s OK to acknowledge you aren’t perfect but make sure to emphasize the positives.
- Answer only the questions asked by the Inspector.

- Do **not** sign affidavits.
- Argue with team members
- Volunteer to change or approve documentation during the inspection. Get management input.
- Speak outside your area of expertise or without reviewing the document
- Don’t do things known to be in poor taste- (talk politics, religion, sports) with the investigator.
- Review unofficial records.
- Volunteer access to your network or computer systems.
- Refuse to answer a lawful question. Instead let the Inspector know you need to confer with management/counsel.

During the Inspection

- Audit participants should follow the instruction/ requests of the Escort – let her/him lead.
- Do not leave the FDA inspector unescorted.
- Answer the specific questions asked concisely.
- Be silent when the FDA is not being asked questions.
- Use the well-trained SMEs.
- Explain requested information clearly using a flow chart from within the SOP.
- Provide truthful, accurate, and reliable information to FDA and its representatives.
- Prompt response requested information.

* My recent experiences

After the Inspection

- After the inspection, and dependent upon the firm's response to any 483 findings that are issued, the agency classifies the inspection with one of three statuses in the **establishment inspection report (EIR)**:

- ***No action indicated (NAI)*** means no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action).
- ***Voluntary action indicated (VAI)*** means objectionable conditions or practices were found, and the firm's response was satisfactory, so the agency is not prepared to take or recommend any administrative or regulatory action.
- ***Official action indicated (OAI)*** means objectionable conditions or practices were found, and/or the firm's response was not satisfactory, so regulatory and/or administrative actions will be recommended.

After the Inspection

Content of the Response- 15 working days

A response to a 483 should contain the following:

- ***Containment and correction(s)* –** immediate actions taken to resolve the issue. Examples include cease and desist of the objectionable conditions or practices, quarantine of suspected violative products, etc. The individual(s) responsible for containment and corrections and the expected date(s) of completion should be included.
- ***Completed actions* –** actions that were completed at the time the response was submitted. Examples of completed actions may include a corrective and preventive action was initiated (CAPA), suspected violative parts were re-inspected, etc. The individual(s) responsible for the completed actions and the date(s) of completion should be included.
- ***Planned actions* –** actions the firm will take to resolve the objectionable conditions or practices observed during the inspection. Examples of planned actions may include updating procedures and forms, validating/re-validating a process, additional training, remediation of previous records (CAPAs, NCRs, complaints), etc. The individual(s) responsible for the planned actions and the expected date(s) of completion should be included.
- ***Supporting documentation* –** objective evidence to support the response. The supporting documentation should be clearly labeled to facilitate the review by the agency. Supporting documents should be marked "CONFIDENTIAL" to indicate the organization's view that the documents are considered proprietary confidential information and not subject to the Freedom of Information Act (FOIA).

Question and Answers

Quiz Show Style

- Live poll

Question 1

What is the difference between an FDA full inspection and an abbreviated inspection?

1) The breadth of inspection of a manufacturer's cGMPs
2) Abbreviated is routine, full inspection is non-routine
3) Full inspection has 3-5 inspectors, abbreviated has 1-2

Question 2

Who should be the point person/people during an FDA inspection?

1) Director of QA & Director of RA
2) FDA Coordinator
3) CEO
4) Heads & managers from all departments

Question 3

What is the appropriate response when an inspector asks to take photographs?

1) FDA inspections are legally obligated to take photos
2) Photos are never allowed to be taken during an inspection
3) State your company's policy on taking photos

Need Help? Have Questions?

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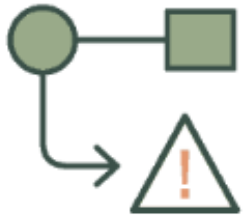

Microbiology

Need Help? Have Questions?

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