Clinical Investigator Site Inspections: What to Expect

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United States Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of Compliance (OC)
Office of Scientific Investigations (OSI)
Division of Enforcement and Postmarketing Safety (DEPS)
Compliance Enforcement Branch (CEB)

FDA Clinical Investigator Training Course
November 15, 2018

Learning Objectives

- Describe the types of clinical investigator site inspections
- Summarize the clinical investigator inspection process

Discussion Topics

- Inspection Types
- Inspection Process

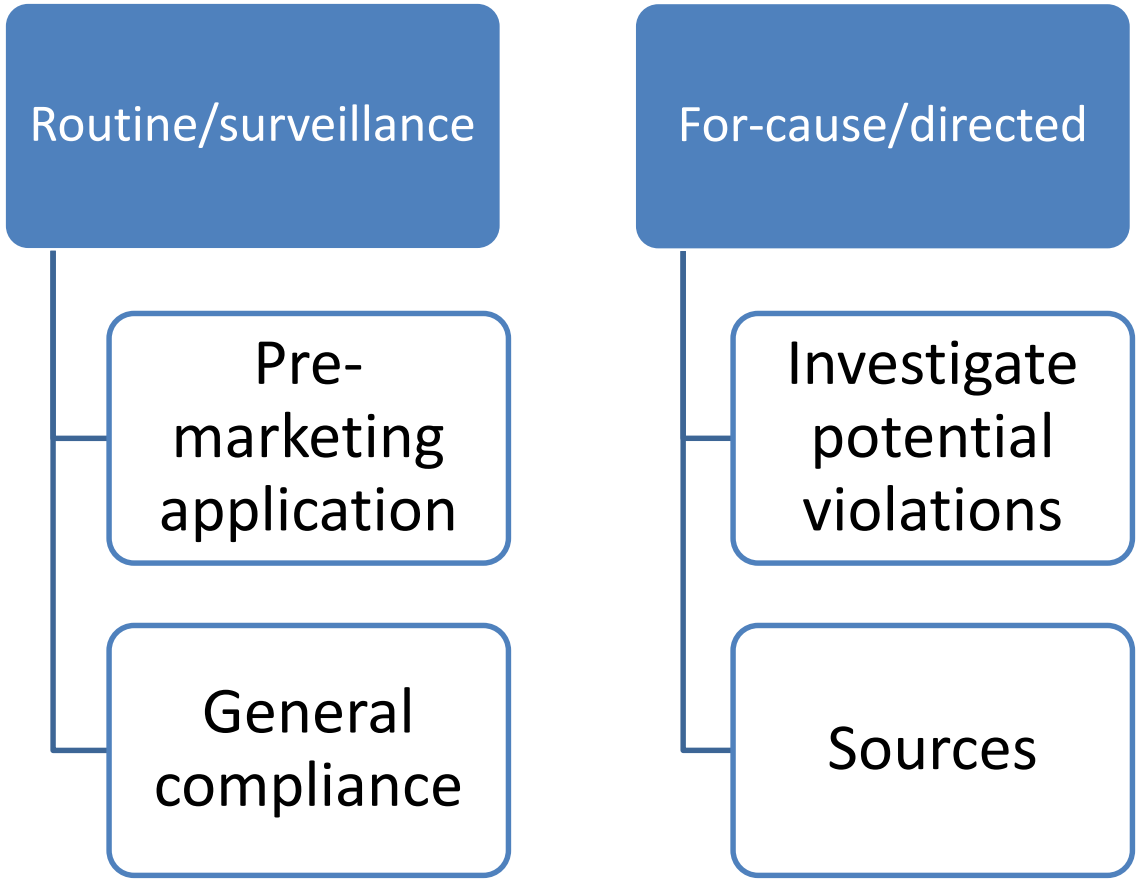
Opening Interview and Form FDA 482
(Notice of Inspection)

Inspection

Form FDA 483 (Inspectional Observations)
and Exit Interview

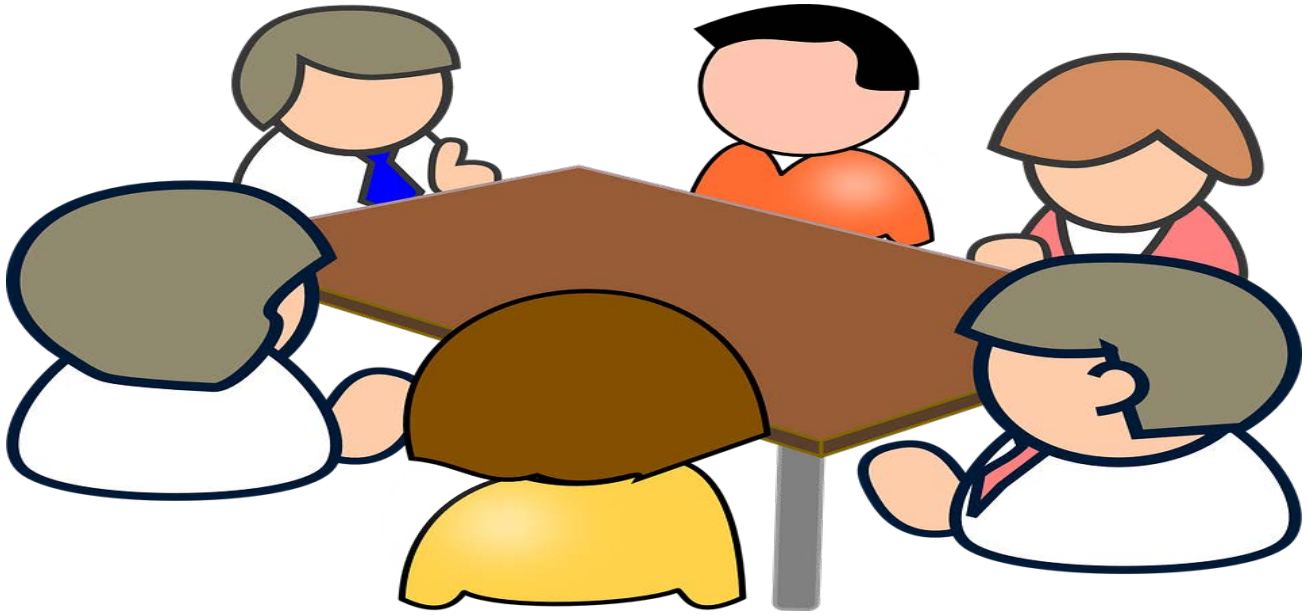
Post-Inspection

Inspection Types



Inspection Process

Opening Interview and Form FDA 482



Pre-Announced and Unannounced Inspections

- Clinical Investigator inspections generally pre-announced unless otherwise instructed in the inspection assignment
  - For-cause generally unannounced

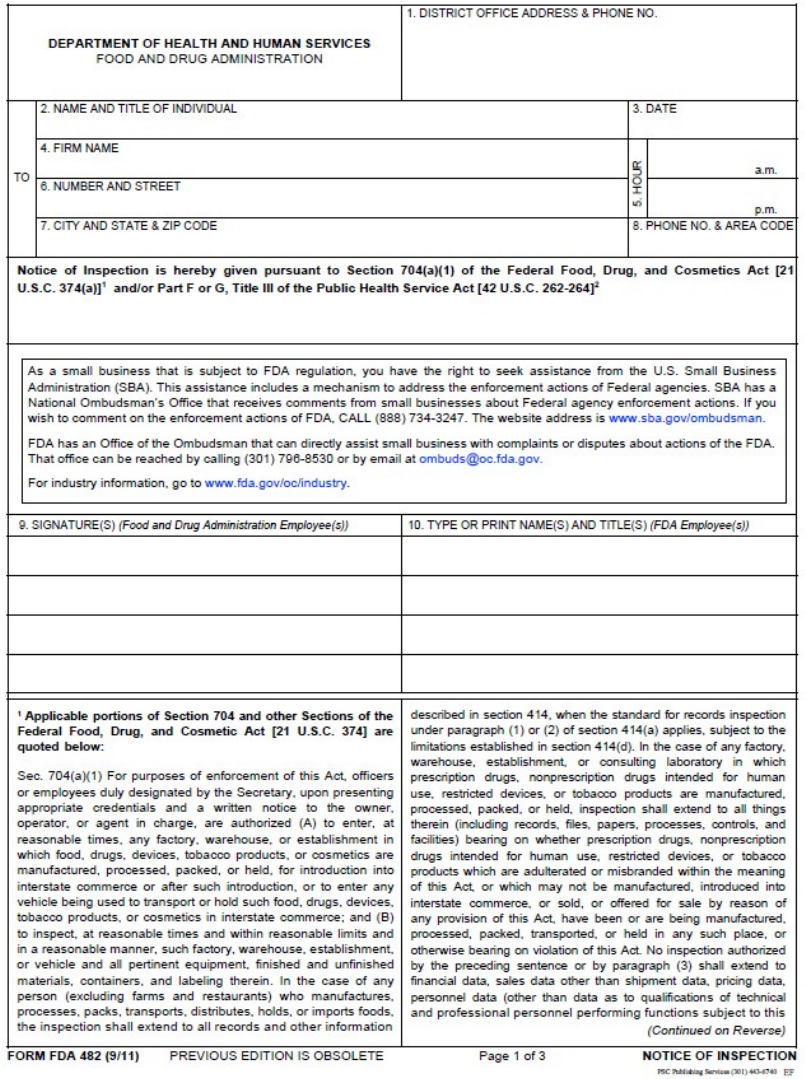
- All international inspections generally pre-announced

The best way to survive an FDA inspection is to always be prepared for one!

Opening Interview

- Performed by field investigator with or without Center subject matter expert
- Present credentials
- Issue Form FDA 482
- Describe the basis and scope for inspection

Form FDA 482 (Notice of Inspection)



DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1. DISTRICT OFFICE ADDRESS & PHONE NO.

TO	2. NAME AND TITLE OF INDIVIDUAL	3. DATE
	4. FIRM NAME	5. HOUR a.m. / p.m.
	6. NUMBER AND STREET	
	7. CITY AND STATE & ZIP CODE	8. PHONE NO. & AREA CODE

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8530 or by email at ombuds@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME(S) AND TITLE(S) *(FDA Employee(s))*

[1] Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)

PSC Publishing Services (301) 443-6740 EF

Inspection Process

Inspection

Inspection Logistics

- Time frame
- Work area
- Photocopier

- Daily discussions regarding inspection progress

Inspection Scope

- Inspection assignment

- Clinical Investigator Compliance Program (CP) – Program 7348.811

https://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm

- Investigations Operations Manual (IOM) – Section 5.10 Bioresearch Monitoring (BIMO)

https://www.fda.gov/ICECI/Inspections/IOM/default.htm

Inspection Scope

- Examples of records reviewed
  - Protocol and amendments
  - Informed consent documents
  - Drug accountability records
  - Institutional review board approvals
  - Source documents
  - Case report forms

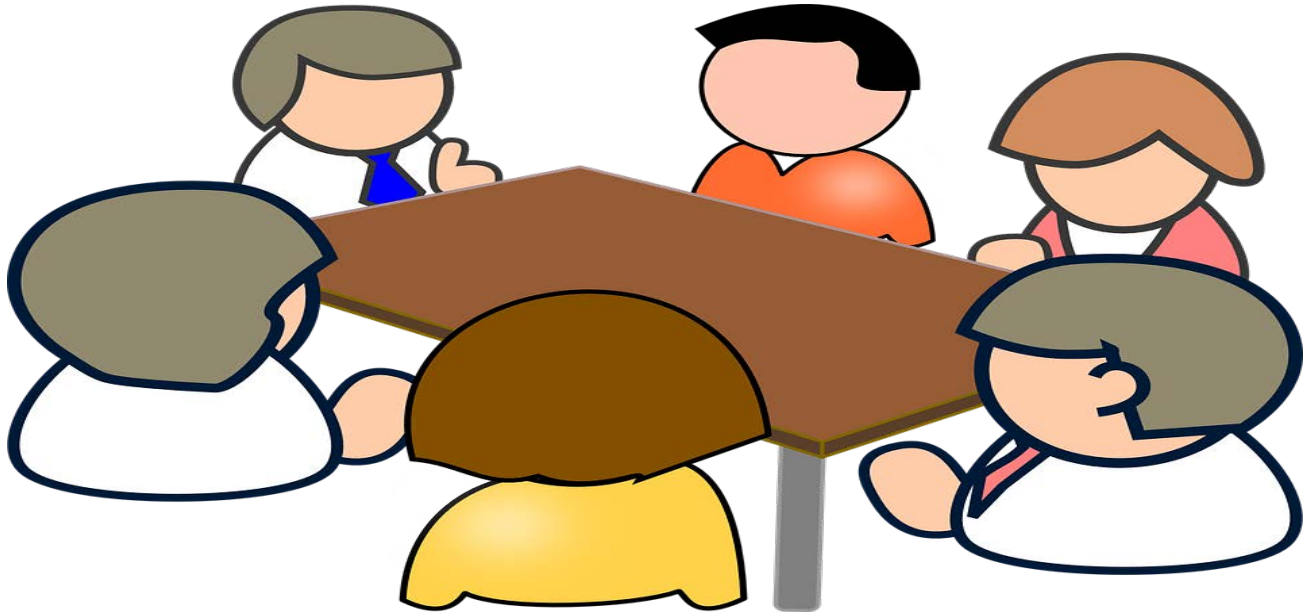
- A word about access to electronic systems

- Interviews

- Site walk-through

Inspection Process

Exit Interview and Form FDA 483



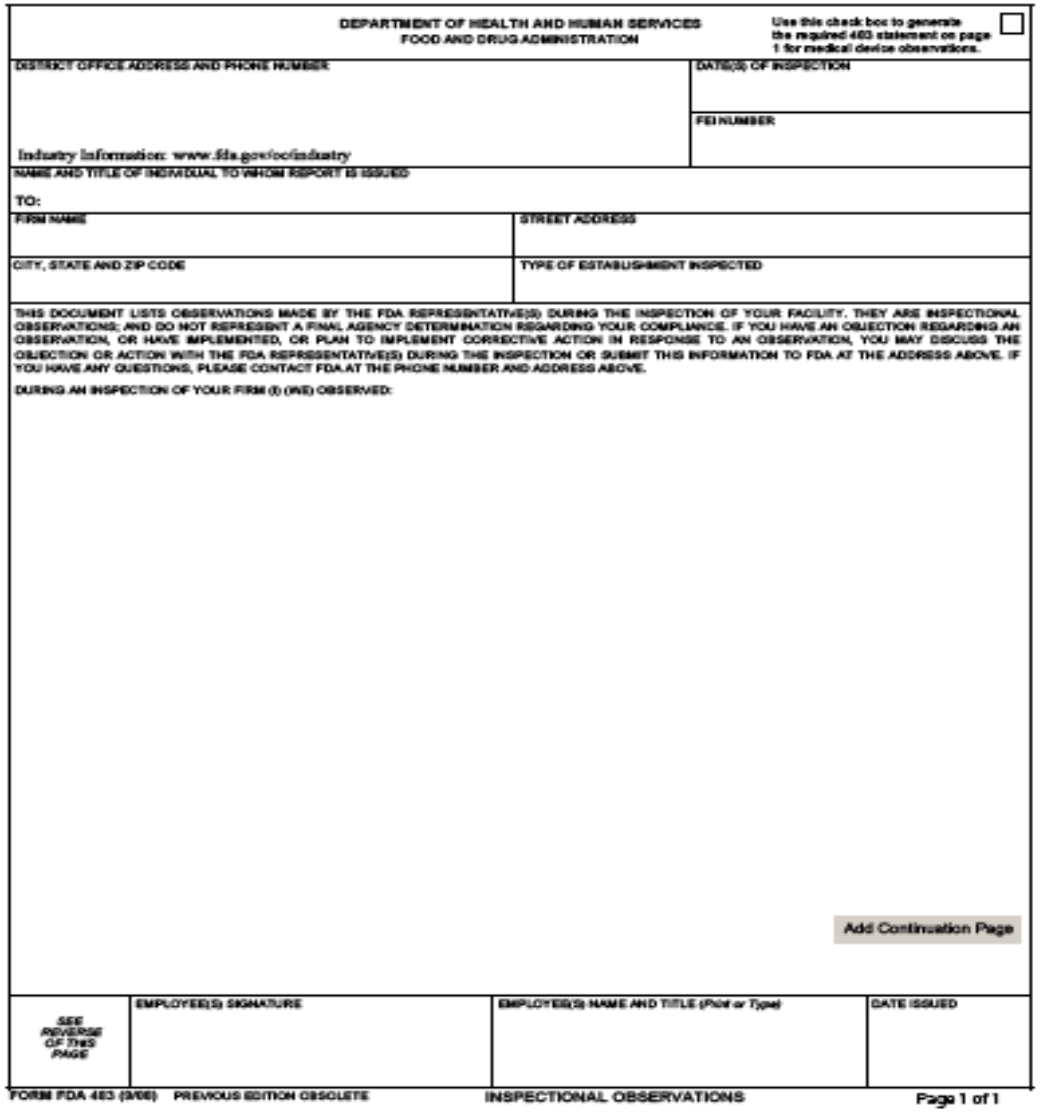
Form FDA 483

- Issued to highest management official available at end of inspection

- *Form FDA 483 items are field investigator's observations of possible deviations from federal regulations, and not necessarily regulatory violations*
  - Center determines whether each observation is a regulatory violation, and if a regulatory violation, will determine violation's impact on data integrity and subject safety

  - Verbal response to Form FDA 483

Form FDA 483 (Inspectional Observations)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Use this check box to generate the required 483 statement on page 1 for medical device observations. ☐

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

FIRM NAME

STREET ADDRESS

CITY, STATE AND ZIP CODE

TYPE OF ESTABLISHMENT INSPECTED

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM I (WE) OBSERVED:

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED

FORM FDA 483 (3/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS Page 1 of 1

Inspection Process

Post-Inspection

Let’s take a look at post-inspectional steps from your end….

Form FDA 483 Written Response

- Received within 15 business days after the close of the inspection to the field investigator's office

- What if you miss the 15-business day time frame?

Four Reasons to Submit a Well-Reasoned, Timely, and Complete Written Response to Form FDA 483

1. May be considered in an FDA compliance decision
2. Demonstrates your acknowledgment and understanding of the observations to the FDA
3. Demonstrates your commitment to correct the observations to the FDA (i.e., intent to voluntarily comply)
4. Establishes credibility with the FDA

How to Respond to Form FDA 483

- You should ensure that the communication provides an adequate response to FDA's observations, is easy to follow, and there are corrective actions in place to fix the issues
- Each response should address the central issues raised in the observations and provide factual objective evidence that permits evaluation and aids in understanding of the response

How to Respond to Form FDA 483

- Include a commitment from senior leadership
- Address each observation separately
- Note whether you agree or disagree with the observations
- Provide both corrective and preventive actions
- Provide both completed and planned actions
- Provide timelines for completion of the actions
- Provide a method of verification or monitoring of the effectiveness of the actions
- Submit documentation (training, standard operating procedures, records)

Now let’s take a look at post-inspectional steps from FDA’s end….


EIR and exhibits
Center review and classification
Post-inspectional correspondence

Inspection Classification

No Action Indicated (NAI)

No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further FDA action).

Voluntary Action Indicated (VAI)

Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any regulatory action since the objectionable conditions do not meet the threshold for regulatory action.

Official Action Indicated (OAI)

Objectionable conditions were found and regulatory action should be recommended.

If the inspection is classified OAI by the Center, the Center may issue one of the following types of letters….

OAI Letter Types

- Untitled Letter
- Warning Letter
  https://www.fda.gov/iceci/enforcementactions/warningletters/default.htm
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letter
  - Notice of Opportunity for Hearing (NOOH) Letter

  https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=clinicalinvestigatorsdisqualificationproceedings&displayAll=false&page=3

Additional Resources

BIMO Program

https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm160670.htm

Regulatory Procedures Manual (RPM)

- Chapter 4 - Advisory Actions (Warning and Untitled Letters)
- Chapter 5 - Administration Actions (Chapter 5-9: Disqualification of Clinical Investigators)

https://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

- Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

Challenge Question #1

Fill in the blank regarding the flow of the inspection process:

_____ → Inspection → Form FDA 483 and Exit Interview → Post-Inspection

Challenge Question #2

True or False:

All observations listed on Form FDA 483 are automatically regulatory violations.

Challenge Question #3

Which of the following should be included in your written response to Form FDA 483?

A) Corrective and preventive actions
B) Addressing each observation separately
C) Timelines for completion of corrective and preventive actions
D) Documentation (training, standard operating procedures, records)
E) All of the above

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