Research Professionals Network Workshop Series

FDA INSPECTION WORKSHOP

Presenters: Eric Stratton, MPH and Thomas Cheng, MS

BU Clinical & Translational Science Institute

Boston Medical Center — Exceptional Care. Without Exception.

The University of Vermont Larner College of Medicine

The University of Vermont Medical Center

Aims of this presentation

- Understand the purpose of audits
- Identify types of audits/inspections
- Examine best practices for audit preparation
- Describe the audit process and expectations
- Outline common audit findings
- Discuss resources for preparation

Purpose for audits

- To ensure patient rights are protected
- To confirm data reliability
- To analyze study compliance

How do you get audited

- Routine – “random”

- For cause – specific purpose

Site factors

- Amount of adverse events
- Number of protocol deviation / protocol compliance
- Enrollment (relative to overall study or site)
- Complaints
- Other site/sponsor audited

Activity – From: *Surprise! You're having an FDA Inspection*

Your site has 15 subjects over a period of 2 years which is half of the overall study-wide enrollment. Your site has 18 deviations and 13 SAEs in total which is also above the overall study-wide average. You get a notification for an FDA inspection.

Why?

What is an Audit? Inspection? Monitoring?

The ICH E6 Guidelines defines each as:

- *Audit - A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).*
- *Inspection - The act by a **regulatory authority(ies)** of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).*
- *Monitoring - The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)*

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

Types of audits/inspections/monitor

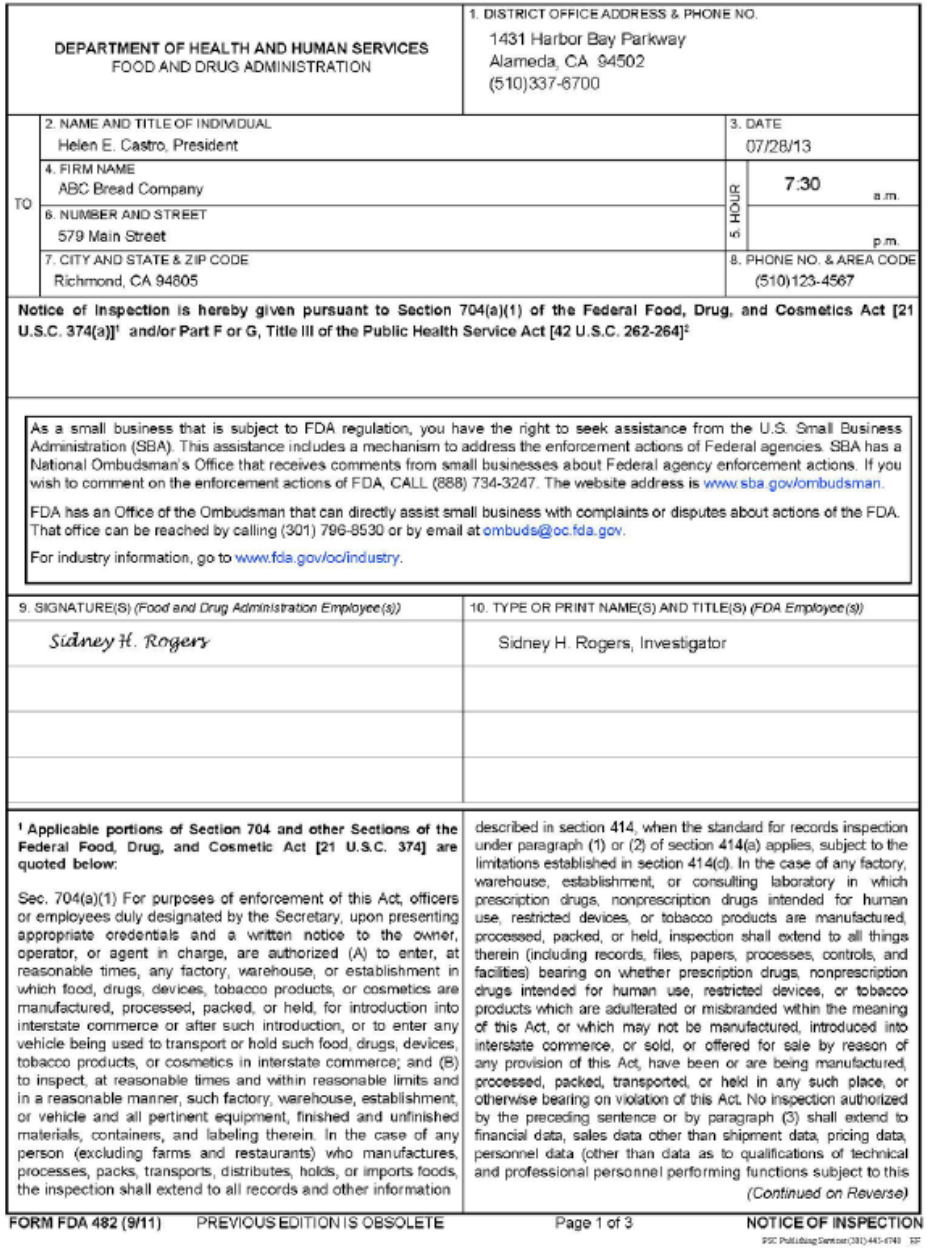
- Sponsor
- FDA/Other regulatory
- Internal

FDA Inspection Process

- Announcement (not required)
- Notify parties
  - Sponsor, IRB, lab, clinic, department, pharmacy, research unit
- Prepare/review documents
- Train staff on audit process
- Inspection
  - Notice of inspection issued (Form 482) – ask for credentials
  - You will be asked to state your role
  - Inspection (photography may be used)
  - Exit interview
- Respond to Form 483 (if applicable) within 15 business days
- Final report issued to inspected site and applicable parties
- FDA Establishment Inspection Report issued to inspected site
- Outcomes: No action indicated (NAI), Voluntary action indicated (VAI), Official action indicated (OAI)
- Warning letter

Form 482 Sample

Form 482



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1. DISTRICT OFFICE ADDRESS & PHONE NO.
1431 Harbor Bay Parkway
Alameda, CA 94502
(510)337-6700

TO

2. NAME AND TITLE OF INDIVIDUAL
Helen E. Castro, President

3. DATE
07/28/13

4. FIRM NAME
ABC Bread Company

5. HOUR
7:30 a.m.
p.m.

6. NUMBER AND STREET
579 Main Street

7. CITY AND STATE & ZIP CODE
Richmond, CA 94805

8. PHONE NO. & AREA CODE
(510)123-4567

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))*
Sidney H. Rogers	Sidney H. Rogers, Investigator

[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)

FORM FDA 482 (9/11) PREVIOUS EDITION IS OBSOLETE Page 1 of 3 NOTICE OF INSPECTION

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exhibits

Form 482

Act), and research data (other than data relating to new drugs, antibiotic drugs, devices, and tobacco products and subject to reporting and inspection under regulations lawfully issued pursuant to section 505 (i) or (k), section 519, section 520(g), or chapter IX and data relating to other drugs, devices, or tobacco products, which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j)). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704. (a)(2) The provisions of the third sentence of paragraph (1) shall not apply to (A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail; (B) practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in the course of their professional practice; (C) persons who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in research, teaching, or chemical analysis and not for sale; (D) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

Sec. 704. (a)(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 412 applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records (A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 412, or (B) required to be maintained under section 412.

Sec. 704(b) Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, tobacco product, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

Sec. 704. (c) If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

Sec. 704. (d) Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) An accredited person described in paragraph (3) shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.

Section 512 (l)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

[2] Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F – Licensing – Biological Products and Clinical Laboratories and* * * * * *

Sec. 351(c) "Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation

(Continued on Page 3)

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exhibits

Form 482

of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F – * * * * * "Control of Radiation.

Sec. 360 A (a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, 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 thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

* * * * * *

(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be necessary to identify and locate, for purposes of section 359, the first purchasers of such products for purposes other than resale, and (2) require manufacturers to preserve such information. Any regulation establishing a requirement pursuant to clause (1) of the preceding sentence shall (A) authorize such dealers and distributors to elect, in lieu of immediately furnishing such information to the manufacturer to hold and preserve such information until advised by the manufacturer or Secretary that such information is needed by the manufacturer for purposes of section 359, and (B) provide that the dealer or distributor shall, upon making such election, give prompt notice of such election (together with information identifying the notifier and the product) to the manufacturer and shall, when advised by the manufacturer or Secretary, of the need therefore for the purposes of Section 359, immediately furnish the manufacturer with the required information. If a dealer or distributor discontinues the dealing in or distribution of electronic products, he shall turn the information over to the manufacturer. Any manufacturer receiving information pursuant to this subsection concerning first purchasers of products for purposes other than resale shall treat it as confidential and may use it only if necessary for the purpose of notifying persons pursuant to section 359(a)."

* * * * * *

Sec. 360 B.(a) It shall be unlawful–

(1) * * *

(2) * * *

(3) "for any person to fail or to refuse to establish or maintain records required by this subpart or to permit access by the Secretary or any of his duly authorized representatives to, or the copying of, such records, or to permit entry or inspection, as required or pursuant to section 360A."

* * * * * *

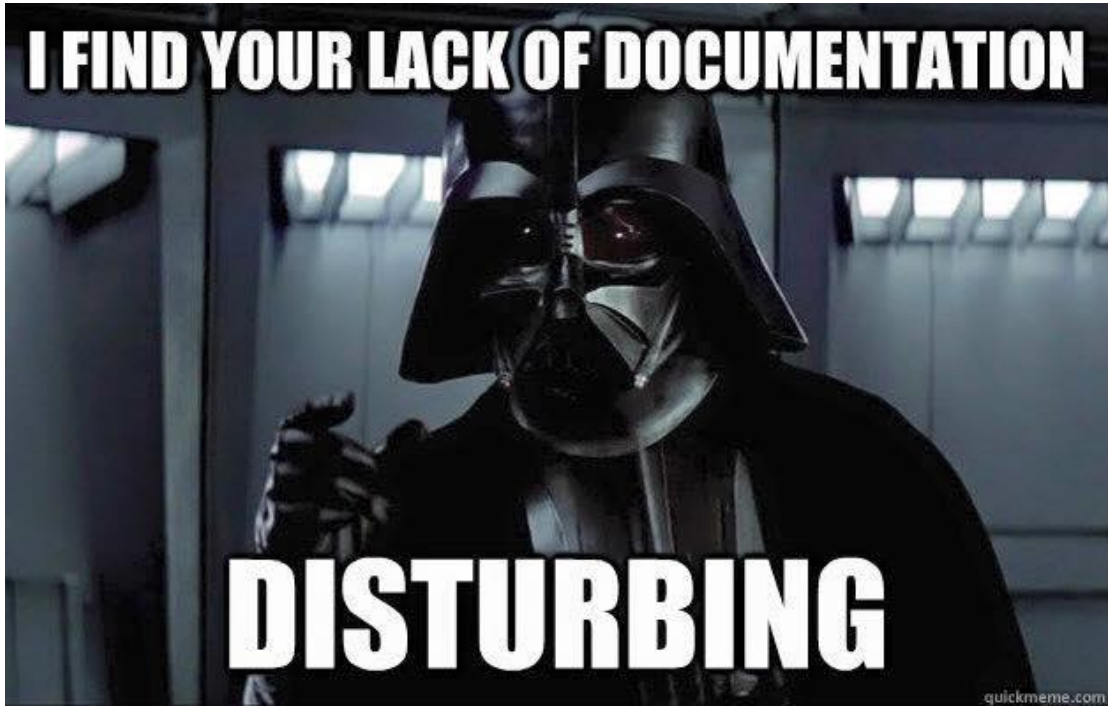
Part G - Quarantine and Inspection

Sec. 361(a) "The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exhibits

Best practices for audit preparation

- Think like an auditor/inspector/monitor
- Organize your documents in a consistent manner
- Be prepared for an audit since day 1 of study initiation
- Ensure all CITI, lab safety, CVs, medical licenses, and other training/study certificates are up to date
- Ensure all logs are up to date and any necessary signatures captured.
- Have a source for every data point – DOCUMENTATION!



Activity – From: *Surprise! You're having an FDA Inspection*

During your inspection, who do you think the FDA inspectors would want to meet with?

What follow-up items/actions can you expect at the end of the day?

Why?

FDA Audit Expectations

- Access to EMR, EDC, IRB, other study records
- Ability to operate study systems (ex: EDC)
- Assess understanding of study protocol(s)
- Site-specific study details
  - Enrollment
  - Deviations
  - AEs / SAEs

Working with the FDA

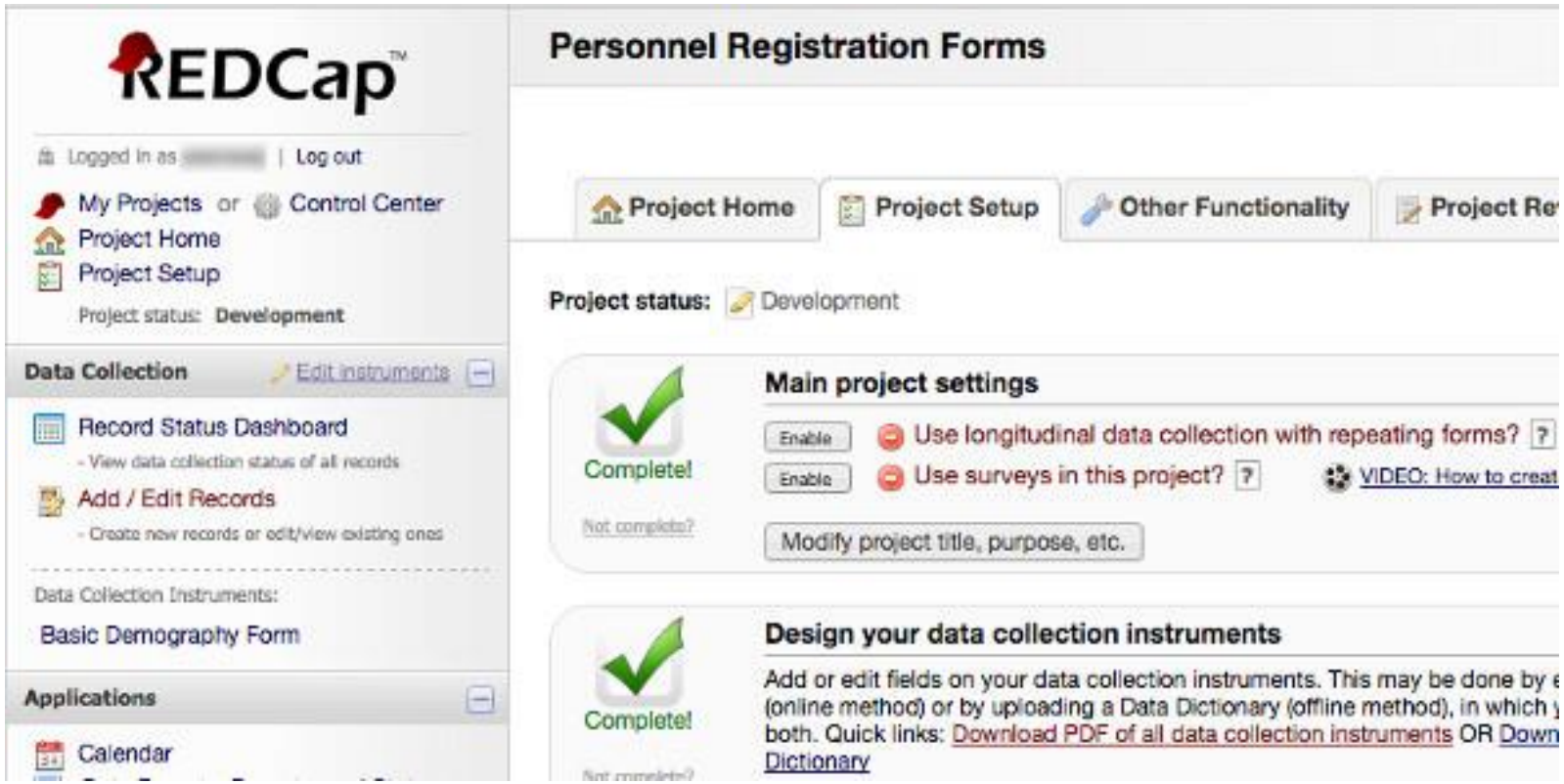
- Reserve a *quiet*, *private* conference room for the inspectors (9am to 5pm)
- Inspection days may not be the entire day as inspectors may need to report back to their office before end of business day (10am-3pm)
- Ask for credentials
- Record what happens throughout each day and what documents were given to inspectors (make copies of each document and file in a binder)
- Only involve necessary parties
- Ask if there are any outstanding questions before end of the day
- Escort the inspectors wherever they go
- Promptly answering questions or retrieving documents is important
- Be confident when answering questions
- Stay truthful


DREAD IT, RUN FROM IT
FDA STILL ARRIVES

Activity – From: *Surprise! You're having an FDA Inspection*

- During your audit, the FDA inspector asks you to show them the EDC system. Why might they want to see this?

Activity – From: *Surprise! You're having an FDA Inspection*



- Once you login, what is your next step?

Source: https://www.project-redcap.org/

Activity – From: *Surprise! You're having an FDA Inspection*

- Assuming the sponsor refuses to give the FDA inspector access to the EDC (citing that it is too high risk given that the study is still active), how do you proceed in responding to this request?
  What alternative(s) can you provide?

Activity – From: ***Surprise! You're having an FDA Inspection***

- You're asked during the inspection why a specific subject qualified for the study. What should you do?

- The inspector wants your response to the previous question, rather than reaching out to the investigator. Why might the inspector want to know this?

- The FDA inspector states that you seem tired during the interview. How do you respond and how is this relevant to their inspection?

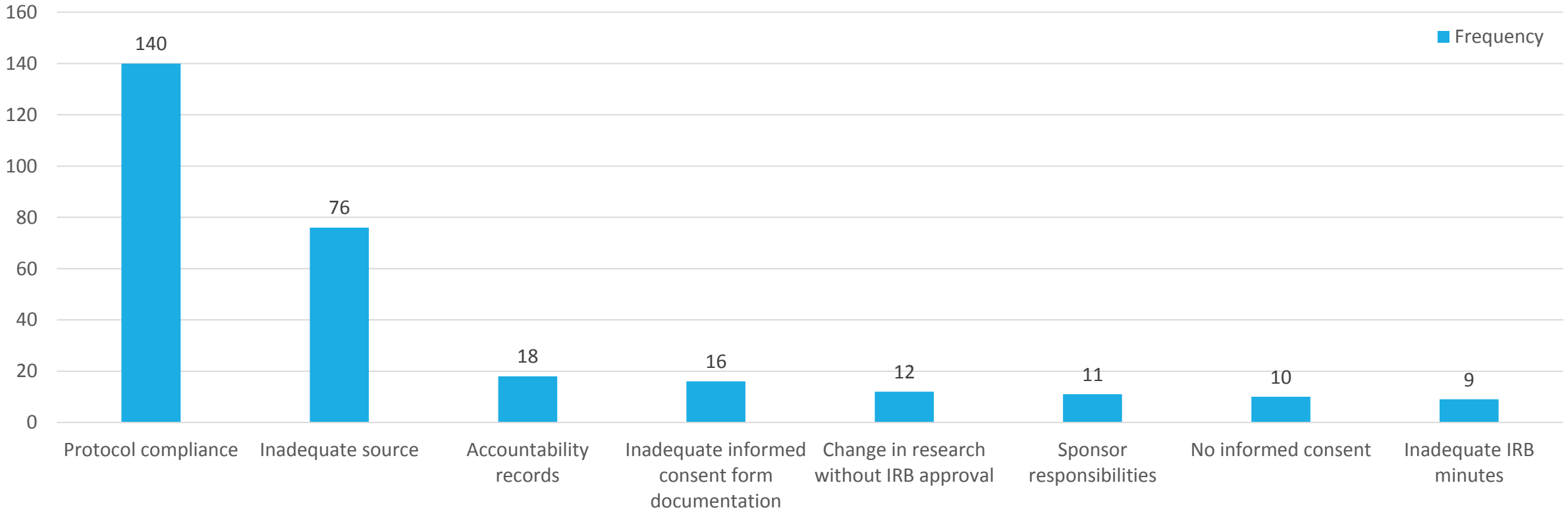
Activity – From: ***Surprise! You're having an FDA Inspection***

- During the inspection, you state that there are currently 15 subjects enrolled in the study, but the FDA inspector states that they were only informed of 7 subjects. What can possibly happen?

What is happening in the cartoon below?

Common findings in biomonitoring research

In 2017



Source: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fy-2017-inspectional-observation-summaries#Bioresearch%20Monitoring

Resources for preparation

- Yourself
- Investigators
- Other study personnel
- Other sites that underwent audits
- Sponsor
- FDA website
- Institutional
  - BU/BMC: CRRO, pharmacy
  - UVM: OCTR

FDA 483 Breakout

FDA 483 Breakout Questions

- How do you prevent observation 1? How do you rectify observation 1? If you came onto the study in September 2015, does this affect you?

- How do you prevent observation 2? How do you rectify observation 2? If you had retrained the investigators and documented it, could you still get cited? Does this stop you from performing retraining?