Regulatory Education for Industry (REdI): Focus on CGMPs & FDA Inspections

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What To Expect When Being Inspected

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Division of Inspectional Assessment
Office of Process and Facilities

Quality • Production • Laboratory • Materials • Facilities and Equipment • Packaging and Labeling

Overview

- Types of inspections
- How investigators prepare for the inspection
- The FDA inspection begins…
- The FDA inspection ends…
- Questions

Poll Question

What are your biggest concerns about a FDA Inspection? (select top 3)

Four Major CGMP Inspections

1. **Pre-approval***
2. **Post-approval***
3. **Surveillance (CGMP, routine)***
4. **For-cause or directed****

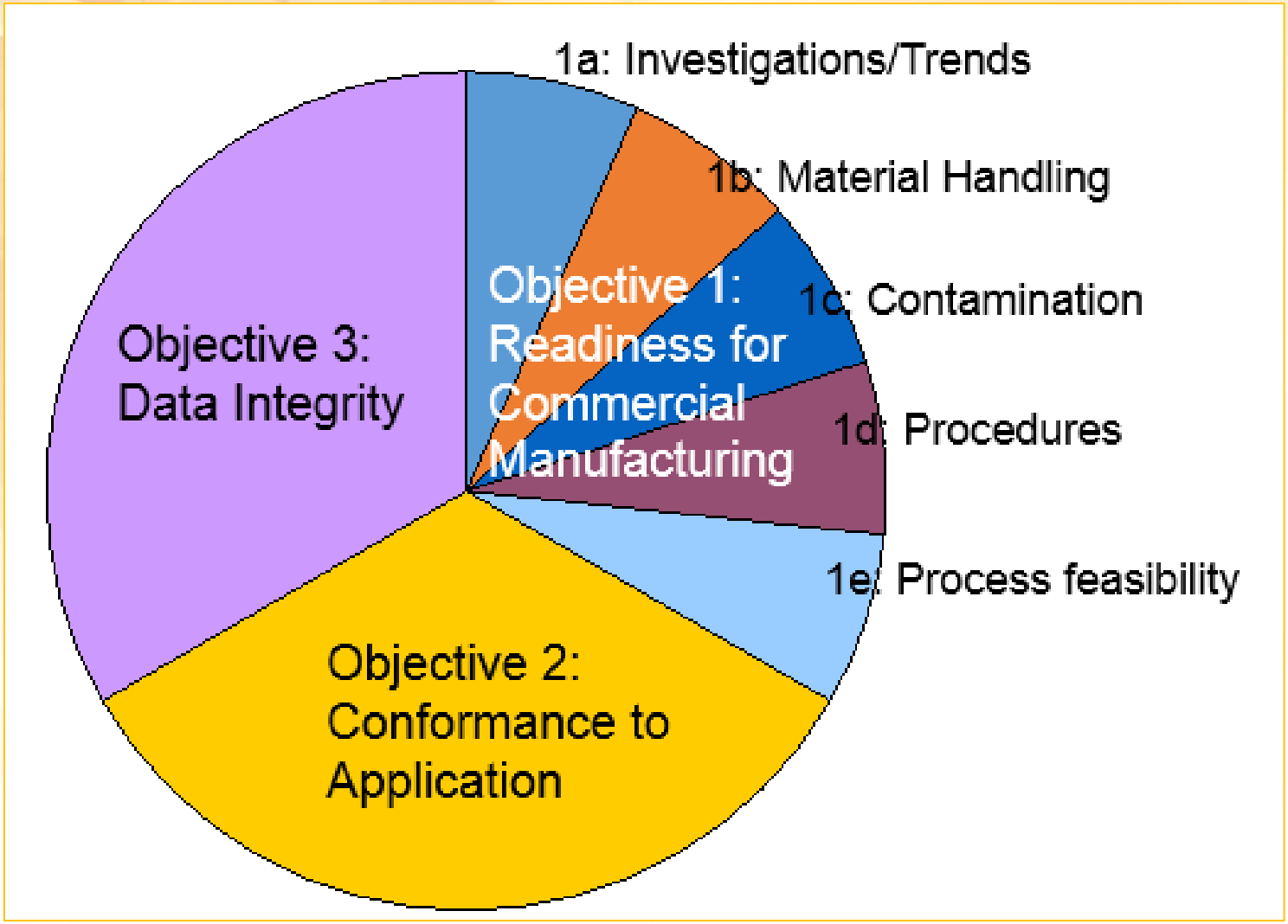
***1-3 have compliance programs and FDA's procedures are available on the web**

****For cause/directed are the most unscripted …is harder to prepare for and the investigator may have a specific assignment that is not publicly available**

Pre-Approval Inspection Program (7346.832)

A pre-approval inspection (PAI) is performed to contribute to FDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete.

Pre-Approval Inspection Program (7346.832)



Post-Approval Inspection Program (7346.843)

- **Inspection of products marketed under a recently approved application**
- **Monitor for changes in the production and control practices that occur after approval (6-24 months)**
- **Assignments issued by CDER based on recommendations and risk**
- **Coverage is based on reason for inspection (pre-approval inspection, past history…)**

Surveillance Inspections (7356.002)

CP7356.002 "Drug Manufacturing Inspections"

Covers both domestic and international inspections

Increased use of question-based inspection programs to focus and ensure consistent coverage regardless of location

FOOD AND DRUG ADMINISTRATION

COMPLIANCE PROGRAM GUIDANCE MANUAL PROGRAM 7356.002

SUBJECT: DRUG MANUFACTURING INSPECTIONS	IMPLEMENTATION DATE 2/1/2002
	COMPLETION DATE Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
All Human Drugs Industry codes: 50, 54-56, 59, 60-66	Domestic / Foreign Inspections: 56002 56002A Sterile products manufacture 56002B Repackers and relabelers 56002C Radioactive drugs 56002E Compressed medical gases 56002F Bulk pharmaceutical chemicals

FIELD REPORTING REQUIREMENTS

Forward a copy of each Establishment Inspection Report (EIR) for inspections classified as OAI due to CGMP deficiencies as part of any regulatory action recommendation submitted to HFD-300. For all inspections that result in the issuance of a Warning Letter, forward an electronic copy of each letter to the Division of Manufacturing and Product Quality, Case Management and Guidance Branch (HFD-325). An e-mail account has been established to receive copies of Warning Letters. The account e-mail address is CDERCGMPWL.

This program provides guidance in evaluating compliance with CGMP requirements. As soon as the District becomes aware of any significant inspectional, analytical, or other information developed under this program that may affect the agency's new drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS procedures. This includes filing OAI notifications and removing the notifications.

DATE OF ISSUANCE: 2/1/2002 PAGE: 1

FORM FDA 2438 (7/93)

New Inspection Protocol Project (NIPP)

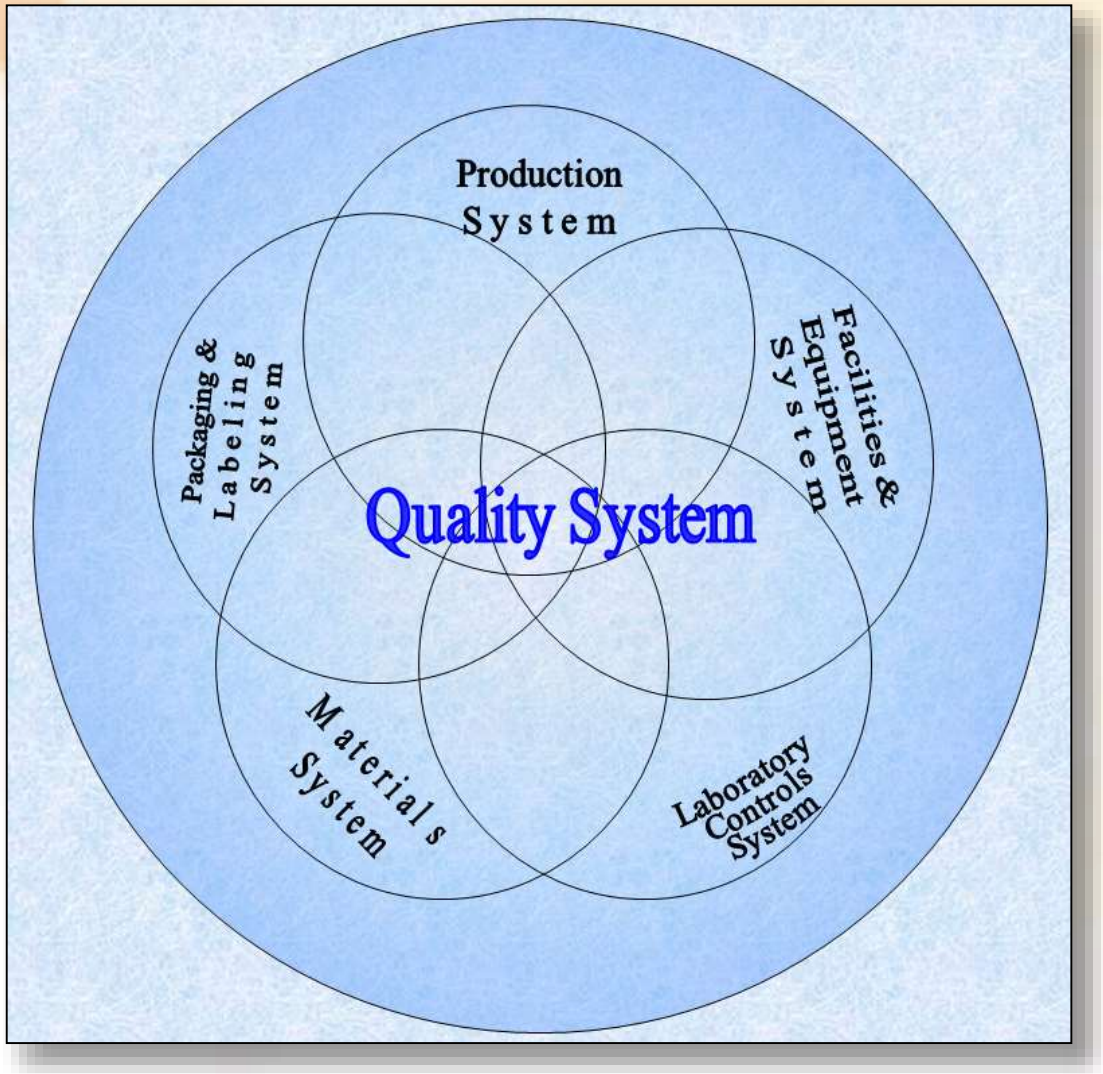
- New paradigm for inspections and reports that will advance pharmaceutical quality
- Standardized approach to inspection
- Data gathering to inform “quality intelligence” of sites and products: both positive and negative behaviors
- Risk-based and rule-based process using expert questions
- Semi-quantitative scoring to allow for comparisons within and between sites
- More common inspection report structure

Surveillance Inspections: Strategy

- **Activities in drug firms can be organized into systems that are sets of operations and related activities**
- **Control of all systems helps to ensure production of drugs that meet intended safety, identity, strength, quality and purity characteristics**

What are the systems?

- Quality
- Production
- Laboratory
- Materials
- Facilities & Equipment
- Packaging & Labeling



What are the Systems?

Six systems:

- **Quality**
- **Facilities and Equipment**
- **Materials**
- **Production**
- **Packaging and Labeling**
- **Laboratory Controls**

21 CFR 211:

- **Subpart B - Organization and Personnel**
- **Subpart C - Buildings and Facilities**
- **Subpart D - Equipment**
- **Subpart E - Components and Container/Closures**
- **Subpart F – Production and Process Controls**
- **Subpart G - Packaging and Labeling**
- **Subpart I - Laboratory**

Inspection of Systems

- **The inspection is defined as audit coverage of 2 or more systems, with *mandatory* coverage of the Quality System**
- **Different numbers of systems may be covered depending on the purpose of the inspection**

Inspection Options

- **Full inspection**
  - **Quality system plus three other systems**
- **Abbreviated inspection**
  - **Quality system plus one other system**

Full versus Abbreviated

Full:

- Initial inspection
- History of noncompliance
- Significant changes
  - New technologies, equipment, facilities
- Follow-up to a W/L
- Revert to an Abbreviated Option with District Concurrence

Abbreviated:

- When not using the Full Inspection Option
- Surveillance inspections
- Adequate for routine coverage
- Rotate systems with the Abbreviated Option – District will monitor

Abbreviated Inspection Option

Abbreviated Inspection Option is meant to provide an efficient update evaluation of a firm's CGMP compliance.

Generally done when:

- **a firm has a record of satisfactory CGMP compliance**
- **with no significant recalls or product defects or field alert incidents**
- **with little shift in the manufacturing profiles of the firm within the previous two years**

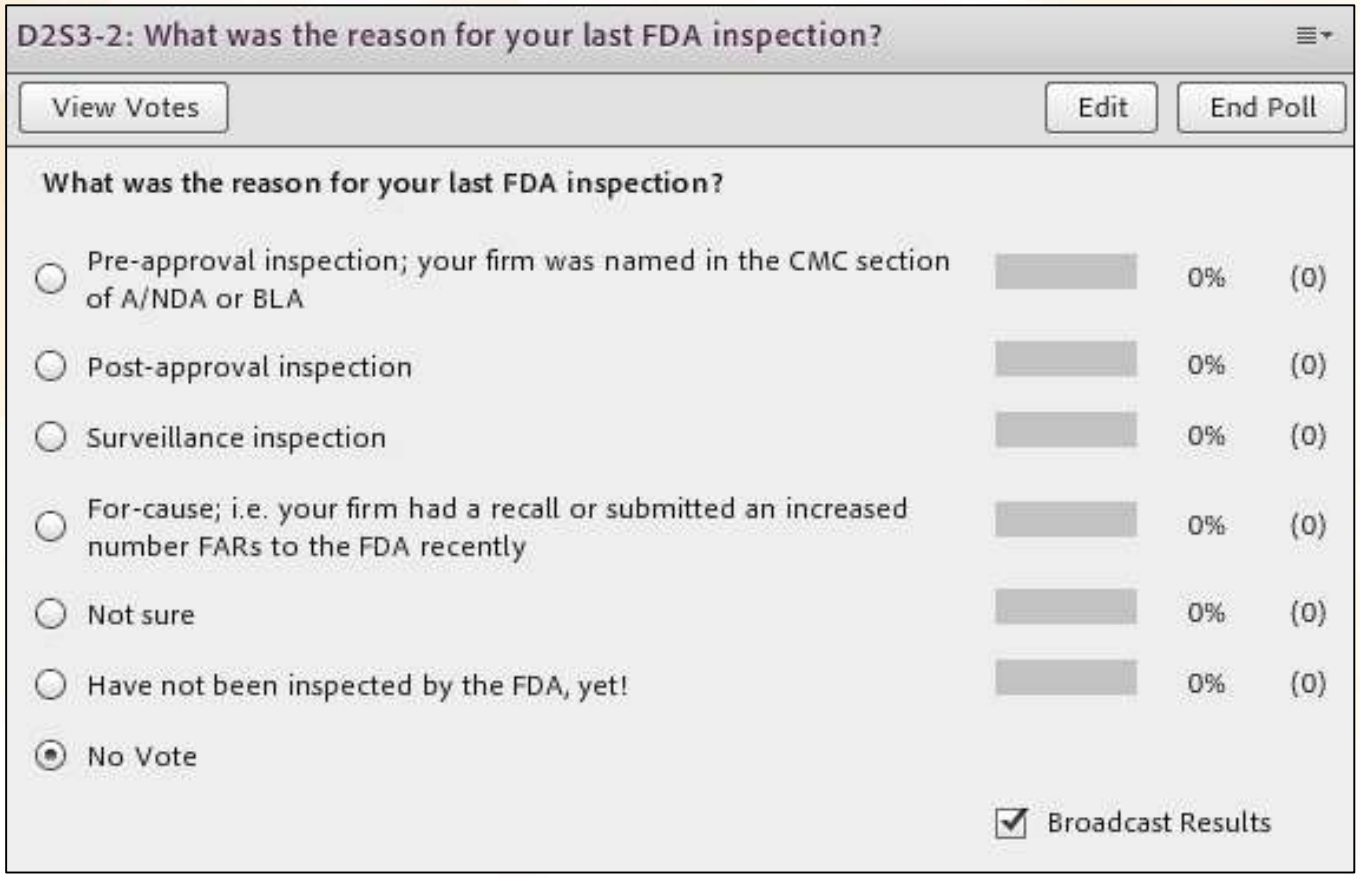
For-cause and Directed inspections

- **Anything other than a routine inspection***
- **Investigate a specific problem that has come to FDA's attention:**
  - **NDA Field Alert report**
  - **Recall**
  - **Adverse event cluster (i.e. heparin)**
  - **or other "event"**
- **Generally the focus is on the specific event and the company response**
- **Determine state of control in a specific area of processing (i.e. verify correction of previous deficiencies)**

***Routine inspections are PAIs, post approval and surveillance**

Poll Question #2

What was the reason for your last FDA inspection?



But what really happens ….

FDA Inspections

- **An official examination of a facility to determine its compliance with laws and regulations administered by the FDA**
- **Are FACT finding**
- **Obtain EVIDENCE**
- **Are REGULATORY**

Authority to Enter and Inspect

- **Section 704(a) of the FD&C Act provides authority for FDA to conduct inspections.**

  “upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge.”

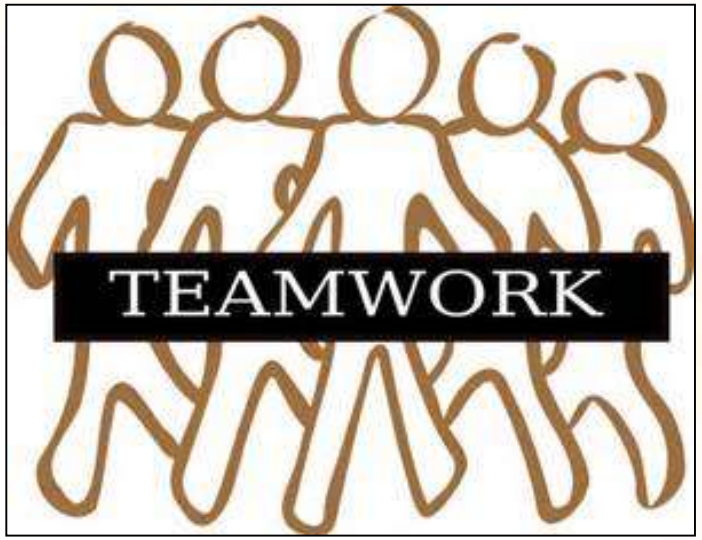
Be reasonable (Time, Limits, Manner) in order to achieve the objective of the inspection

Common FDA Inspection Forms

- **FDA-482 Notice of Inspection**
- **FDA-484 Receipt for Samples**
- **FDA-483 Inspectional Observations**

The inspection team

- **Investigators**
- **Other Specialists**
  - **Chemistry Expert**
  - **Microbiology Expert**
  - **Process/Facility Expert**
  - **Formulation Expert**



Preparing for an Inspection

Investigator(s) create an inspection plan based on the following information:

- **Previous establishment inspection reports (EIRs)**
- **Previous FDA Form 483 observations**
- **Responses to FDA-483s and/or Warning Letters and related firm commitments**
- **Firm's website (including product literature, products manufactured, recent press releases, etc.)**
- **Consumer complaints, ADE's, Recalls, FARs since the last inspection**

Preparing for an Inspection

- **Review application or Drug Master File (DMF)**
- **Review guidance documents**
- **CGMPs and the FFDCA**
- **FDA compliance programs**
- **Investigations Operations Manual (IOM) Chapter 5 ESTABLISHMENT INSPECTIONS**

(http://intranet.ora.fda.gov/directives/cpgm/master_list.htm)

Compliance Program Guidance Manuals

Pre-approval:

- 7346.832/7352.832, Pre-Approval Inspections/Investigations

Post-Approval/Surveillance:

- 7346.843, Post-Approval Audit Inspections

- 7356.002, Drug Process Inspections (sub-programs follow…)
  - 7356.002A, Sterile Drug Process Inspections
  - 7356.002B, Drug Repackers and Relabelers
  - 7356.002C, Radioactive Drugs
  - 7356.002E, Compressed Medical Gases
  - 7356.002F, Active Pharmaceutical Ingredients Process Inspections
  - 7356.002M, Inspections of Licensed Biological Therapeutic Drug Products
  - 7356.002P, Positron Emission Tomography

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm

“FDA Guide to Inspections of…”

- Topical Drug Products
- Pharmaceutical Quality Control Laboratories
- Validation of Cleaning Processes
- High Purity Water Systems
- Lyophilization of Parenterals
- Microbiological Pharmaceutical Quality Control Labs
- Dosage Form Drug Manufacturers – CGMPs
- Solid Oral Dosage Forms Pre/Post Approval Issues
- Oral Solutions and Suspensions

http://www.fda.gov/ICECI/Inspections/default.htm

“FDA Guidance for Industry”

- International Conference on Harmonization (ICH) Guidance
  - ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
  - ICH Q8, Pharmaceutical Development
  - ICH Q9, Quality Risk Management
  - ICH Q10, Pharmaceutical Quality System
  - ICH Q11, Development and Manufacture of Drug Substances
- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (September 2004)
- Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (October 2006)
- Process Validation: General Principles and Practices (Jan 2011)

Investigations Operations Manual

- **Primary source of information regarding Agency administrative and general procedural rules for FDA employees who perform field investigational activities**
- **Assures quality, consistency, and efficiency in field operations**
- **Extends to *all individuals* who perform field investigational activities**
- **Available on-line at**

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

Investigations Operations Manual

Contents

- Administration
- Regulatory
- Sampling
- Establishment Inspections
- Imports
- Recall Activities
- ORA Directory
  - incl. field program monitors

INVESTIGATIONS OPERATIONS MANUAL 2015 CONTENTS

CONTENTS 2015

Credentials

- **Required by law to be shown upon starting an inspection**
- **Investigator displays credentials to the top management official (“owner, operator, or agent in charge”)**
- **Management may examine the investigator’s credentials and record the number and name**
- **Credentials are <u>not</u> to be photocopied**

Delegated Authority

When investigators are issued *Credentials*, certain parts of the Commissioner's enforcement authority, as specified in Staff Manual Guide 1410.32, is re-delegated to them. (i.e. conduct examinations, inspections, and investigations; to collect and obtain samples; to have access to and to copy and verify records as authorized by law)

http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049578.htm

Notice of Inspection

- **Must be issued to start the inspection***
- **All team members must sign**
- **Original given to firm and copy included in EIR**
- **Also known as the FDA-482**

***A notice of inspection is not required to be issued during foreign inspections; however credentials should be presented to the top management official.**

Notice of Inspection

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: 07/26/13
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) 796-8030 or by email at ombuds@oc.fda.gov.

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

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

FDA-482 Notice of Inspection

The FDA Inspection Begins…

- Issue Notice of Inspection
- Display Credentials
- Lead investigator states purpose of inspection
- Lead investigator provides general agenda
- Tour facility
- Get into details
- Daily wrap up meetings

What are Investigators Looking For?

Verification that a manufacturer is operating in a sufficient state of control by reference to the GMP regulations and policies; if not, the investigator must document accordingly to support necessary action

CGMP violations include:

- **Poorly trained employees**
- **Poorly maintained or contaminated equipment and facilities**
- **Lack of process control**
- **Failure to conduct investigations and resolve discrepancies/failures/deviations/complaints**

Investigators look at facility and operations

- **Equipment and Facility**
- **Production**
- **Packaging and Labeling**
- **Laboratory**
- **Warehouse…reject cage**

Investigators watch the manufacturing process and employee practices

Investigators look at documentation

- **Can the firm produce documented evidence of past events?**
- **Is there scientific evidence to support conclusions made in reports?**
- **Do investigations or trending reports demonstrate issues that could effect the quality or safety of marketed product?**

Key Post Market Information

- **Recall [21CFR 7]**
- **Complaints → FDA, firm, MedWatch**
- **Field Alert Reports and Biological Product Deviation Reports**
  - **NDA and ANDA holders are responsible for filing FARs [21CFR314.81(b)(1)]**
  - **BLA holders are responsible for filing BPDRs [21CFR601.12]**
- **Rejects**

Investigators look for data integrity issues

- Not recording activities contemporaneously
- Fabricating data to create acceptable test results or copying existing data as new data
- Discarding data or re-running samples without appropriate documentation
- Data looks to good to be true
- Failing stability studies not submitted in the filing
- No raw data (i.e. sample weights, standard prep, sample solution prep)

Documentation of inspectional findings

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative and/or judicial actions.

Examples of Evidence:

- **Direct observation of CGMP deviations**
- **Procedures**
  - **Observe not following or lack of a written procedure**
- **Verbal communications**
  - **Admission that a violation occurred**
- **Written records and documents**
- **Investigator's regulatory notes**
  - **Written record created during inspection**

Regulatory Notes

- Are the contemporaneous, sequential record of daily investigatory efforts
- They record observations relevant to violations
- They document positive findings and corrective actions
- Should be accurate, objective, factual and free of personal feelings or conclusions
- Are the property of the government and are releasable under the Freedom Of Information Act
- Are used to refresh the investigator's memory when reporting certain important details of the inspection and serves as the basis for reports

The FDA inspection ends…

- **Formal Close Out**
- **May include:**
  - **Sample Collections**
  - **Affidavits (domestic)**
  - **Issuance of FDA 483, Inspectional Observations**

The FDA inspection ends…

- **Inspections are generally classified into one of three categories**
  - **NAI-No Action Indicated**
  - **VAI-Voluntary Action Indicated**
  - **OAI-Official Action Indicated**
- **Initial outcome:**
  - **PAI: Investigator informs firm management at the conclusion of the inspection of his/her initial recommendation**
  - **Post-Approval: Investigator will not provide recommendation at the conclusion of inspection**
- **Expect a copy of FDA inspection report**

Back at the FDA office investigators…

- **Write the Establishment Inspection Report**
  - **Must be done in a timely manner**
  - **Incorporate all inspectional findings from each team member**
- **Communicate with District personnel**
  - **Investigations Branch**
  - **Compliance Branch**
- **Communicate with laboratory**
  - **Prepare sample collection reports**
- **Submit District recommendation**

GMP Findings

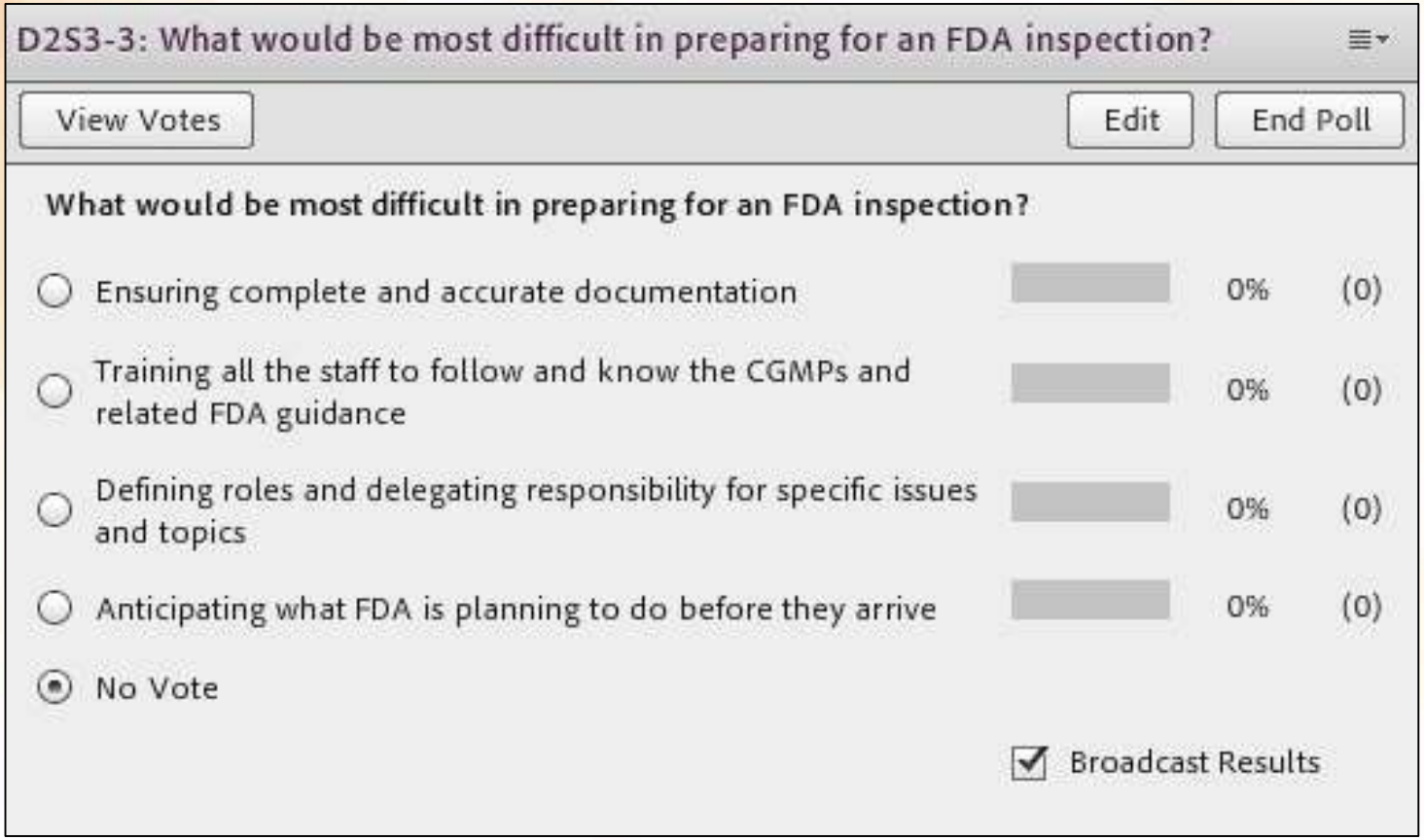
- **FMD-86 Establishment Inspection Report Conclusions and Decisions**
  - **Voluntary Action**
  - **Advisory Action (i.e. Warning Letter, Untitled Letter)**
  - **Legal Sanctions (i.e. seizure, injunction, prosecution**

http://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM382035.pdf

- **Positive behaviors recognized**

Poll Question #3

What would be most difficult in preparing for an FDA inspection?



Summary

To ensure a successful FDA inspection:

- Know and comply with FDA regulations and policies
- Ensure an effective quality system.
- Say what you do, and do what you say… have written SOPs and train your staff to follow them
- Ask the investigator for clarification if you don't understand or agree with an observation
- Be proactive and have a good attitude
- Display a willingness to correct problems…but don't promise to make a correction if you don't agree or are not positive you will be able to follow through

…and be prepared for the FDA inspection!!!

Take Home Message

Be Prepared For the FDA Inspection

- **Assure you and your staff are following and know the cGMP regulations and related FDA guidance**
- **Assure management is aware of significant issues before inspection**
- **Define roles and have responsible person for issues identified and accountable**
- **Constantly improve systems and processes**

If you are committed to making a high quality drug you will not have a problem!!!

Questions?

Evaluation: surveymonkey.com/r/CGMP-D2S3