Preparing for the Pre-Approval Inspection
What to do Before the FDA Arrives

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FDA Overview

FDA is a consumer protection agency within the Department of Health & Human Services.

FDA oversees:

- Most food products (excluding meat & poultry)
- Drugs (human & animal)
- Therapeutic agents of biological origin (blood, vaccines, etc.)
- Medical devices
- Radiation emitting products (x-ray, microwave)
- Cosmetics
- Animal feed

Organization of the FDA

Center for Devices and Radiological Health (CDRH)

Center for Biologics Evaluation and Research (CBER)

Center for Drug Evaluation and Research (CDER)

Center for Food Safety and Applied Nutrition (CFSAN)

Center for Veterinary Medicine (CVM)

National Center for Toxicological Research (NCTR)

Office of the Commissioner (OC)

Office of Regulatory Affairs (ORA)

In the Past

- The FDA placed major emphasis on basic procedures and record keeping
- Pre-approval inspections were focused on systems rather than science

- With the *Pharmaceutical cGMPs for the 21st Century*, there is a major shift towards innovation and continuous improvement

What are cGMPs?

- Current minimum standards for methods to be used in, and facilities or controls to be used for the manufacture, processing, packing or holding of a drug to assure that it meets its required quality characteristics.
- Failure to comply shall render the drug to be considered adulterated and the drug and the persons responsible shall be subject to regulatory action.

Short Course in GMP

- Think
- Write It Down
- Do What It Says
- Train
- Investigate, Fix and Learn
- Be Careful
- Perform Good Science

Purpose of cGMPs

To assure that all pharmaceutical, biologic, diagnostic and medical device products meet all the requirements of the Federal Food, Drug and Cosmetic Act as to safety and efficacy and have the identity and strength to meet the quality and purity characteristics which they purport to have

- *Safety*
- *Efficacy*
- *Identity*
- *Strength*
- *Quality*
- *Purity*

TITLE 21 OF U.S. CODE OF FEDERAL REGULATIONS - "21 CFR"

What do cGMPs Cover?

- Organization
- Personnel
- Facility
- Equipment
- Components, Containers and Closures
- Production and Process Control
- Packaging and Labeling
- Product Holding and Distribution
- Laboratory Control
- Records

Legal Basis
Code of Federal Regulations (CFR)

- 21 CFR Regulations are applied based on product classes:
- Biologics Products:
  - 210-211's
  - 600's
  - 820's for test kits
- Drug Products:
  - 210-211's
- Devices:
  - 820's

Paper Review vs. Inspection

- There is limited facility/cGMP information in biologics/drug product submissions
- Issues not in CMC or supporting guides become inspection issues
- Many of the issues can only be determined during the inspection (SOPs, Environmental Monitoring, deviations, investigations and records)

Timing for Biologics (PLI)

- “Ready for Inspection” at time of BLA/BLS submission; indicate on 356h form
- Always pre-announced, based on manufacturing schedule
- Generally, halfway through the review cycle, i.e., 5 months for BLA, 2 months for BLS

Timing for Drugs, Devices (PAI)

- For both types of products: The PAI is scheduled during the NDA, ANDA, NADA, PMA or PMA review cycle
- Firms should be ready for the inspection

Who Does What for Biologics GMP Inspection?

- Biologics Products
  - Team organization
    - Lead Team Biologics investigator
    - Member – Product specialist
  - Direct inspections that are joint among CBER, Office of Regulatory Affairs (ORA) and Team Biologics
  - Product specialist may participate off-site (available for consult)

What is Team Biologics?

- Organization that optimizes the FDA's ability to obtain compliance of Regulated Biologics Industries
- Originated as a joint effort of CBER and ORA
- Focuses on compliance and inspectional issues
- Inspections will include
  - Team Biologics Lead Investigator
  - CBER staff (trained biological inspectors)
  - Field personnel

PLI/PAI

- To assure cGMP compliance and to verify the authenticity and accuracy of the data in the application
- Focus on subject product
  - Process validation verified
  - Manufacturing of product

PLI/PAI and cGMP Inspections Similarities

- Quality System based inspections for both
  - Quality System
  - Facilities and Equipment
  - Materials System
  - Production System
  - Packaging and Labeling System
  - Laboratory Control System

PLI/PAI and cGMP Inspections Differences

- PLI/PAI may be more focused on the particular product, but all systems relating to the product will be evaluated during the inspection
- PLI/PAI will focus on qualification/validation of equipment and utilities as well as process validation with comparison to data in the application
- Routine GMP will focus on the ability to maintain manufacturing within your approved, validated and qualified parameters since the last inspection

PLI/PAI and cGMP Inspections Differences

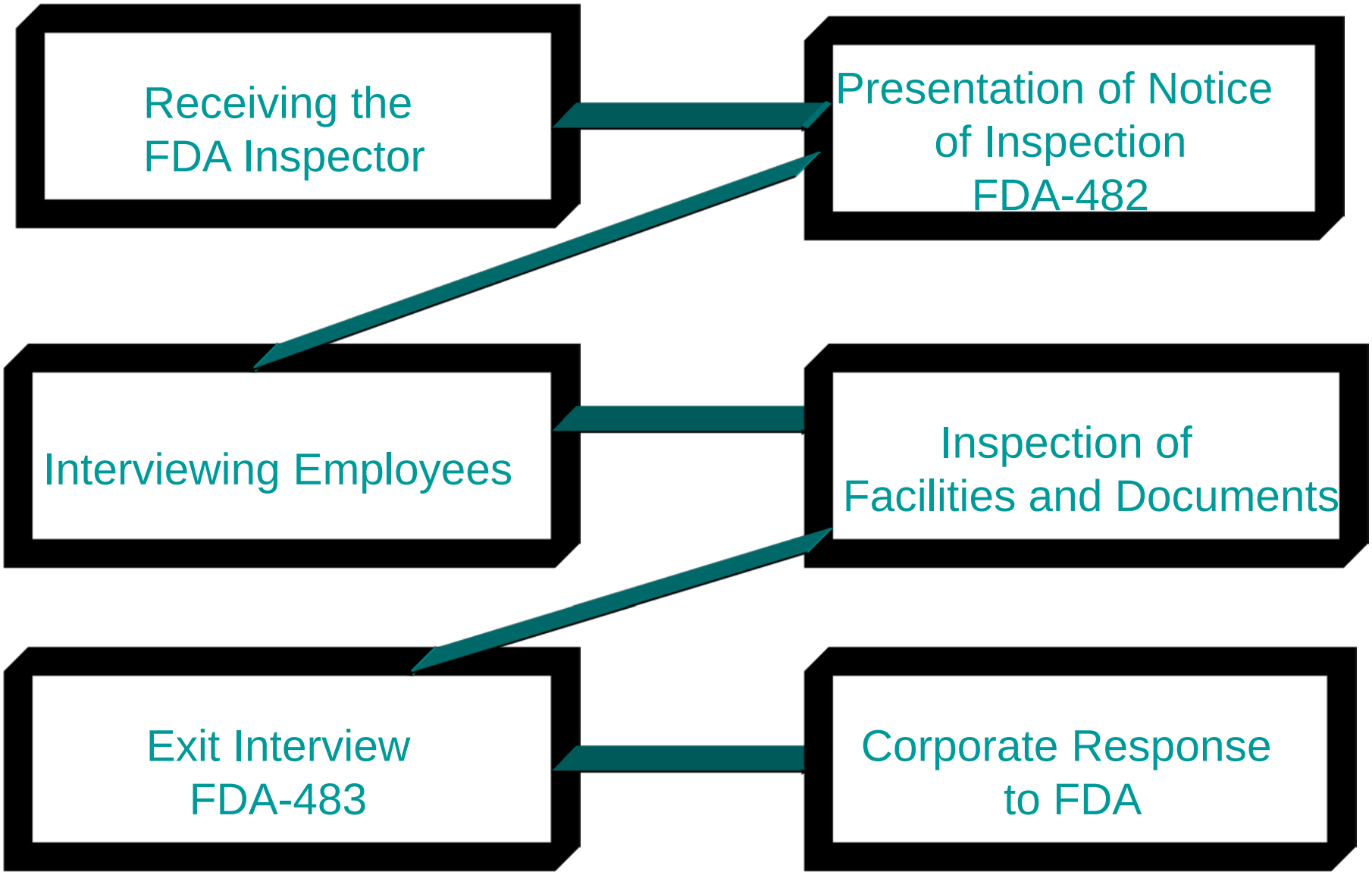
- Inspection resulting in non-compliance to the cGMPS
  - PLI/PAI
    - Product is not approved until non-compliance corrected
    - Could result in compliance action taken
  - Routine cGMP – some form of compliance action taken

Focus of the Inspection

- Post approval inspections
  - Routine GMP inspections – quality systems, adherence to cGMPs, follow-up from previous inspections (may be full, i.e., all six systems or abbreviated)
- PLI/PAIs cover cGMPs, but also
  - Verify information submitted for review
  - Determine if the firm has adequate controls in place to manufacture the new product consistently

Representative Outline of an FDA Inspection

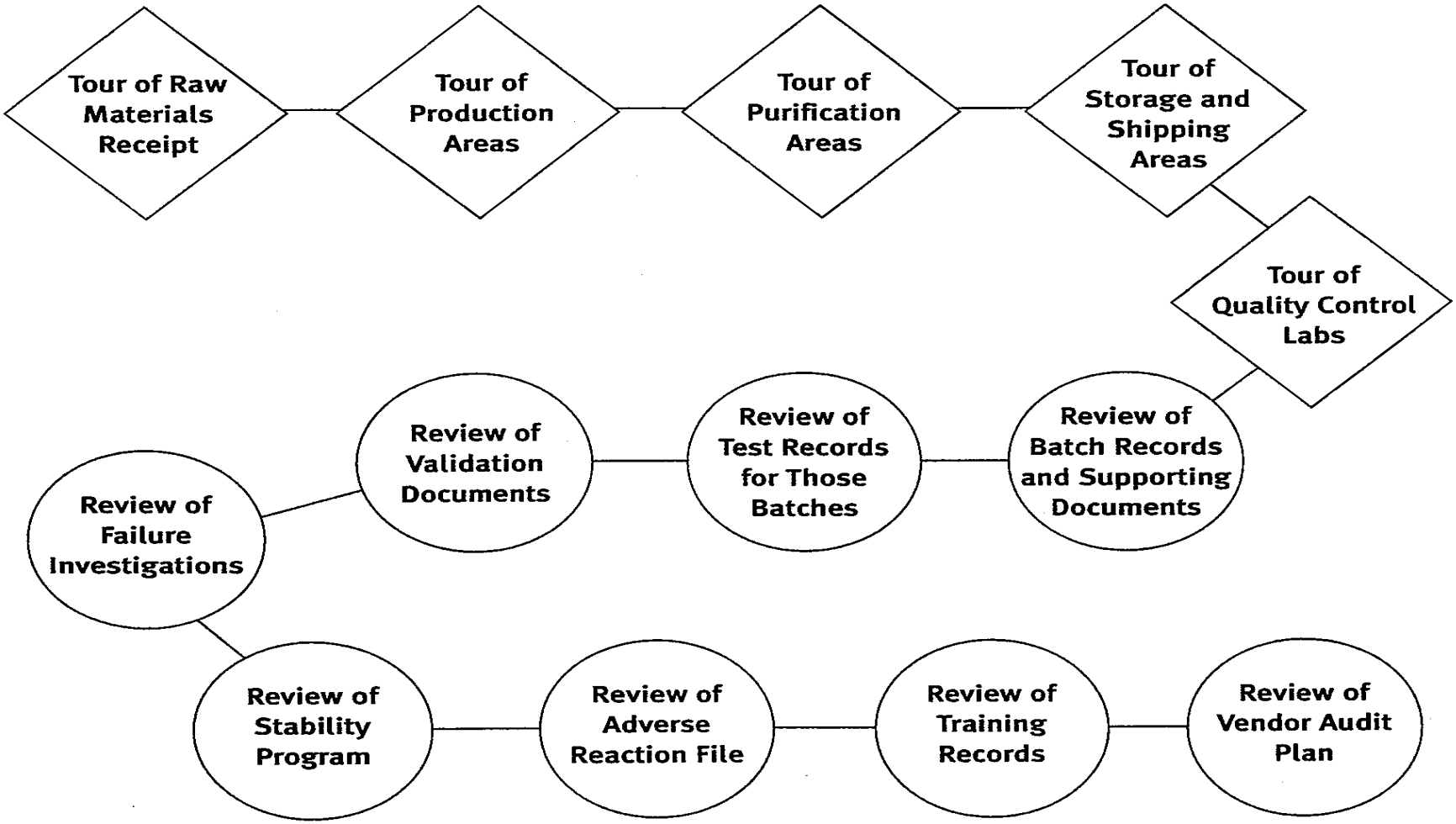
Figure 1



Items to be Available for Review and Inspection

CMC, History Section	Production Related Qualifications	Equipment	Quality Related
• Development Reports • SOPs • Change Control • Investigations (i.e., nonconformances, failures, deviations) • Field Alerts	• Process validation protocols & reports where done • System validations (e.g., water, gas, steam computer) •Critical Process Parameters (CPP)	• Batch production records • Raw material usage • Cleaning validation • Environmental Monitoring	• Complaints • Investigations • Failures •Reworks/reprocess laboratory • Raw data • Methods validation • Stability • Bioequivalence

Figure 2
Representative Information Examined
During an FDA Inspection



Preparing for an Inspection

- Paint and clean up inside; spruce up outside areas
- Review SOPs on receiving inspectors and handling inspections
- Establish as much as possible a tour route
- Walk the tour route
- Dispose of as much Hold and Reject material as possible
- Review status labeling in all storage areas

Preparing for an Inspection

- Review past inspections, responses and outstanding items, if any
- Conduct a walk-through examining instruments for calibration status, log books
- Prepare lists of commonly requested items
  - Rework/reprocessing events
  - Recalls
  - Product failures
  - Complaints
  - Media fills
  - Deviations, OOS investigations, CAPAs

Preparing for an Inspection

- Determine the roles of individual members of the inspection team
- Pre-determine the “Go To” lead person within each area of the tour
- Reserve conference rooms
- Review production schedules
  - Schedule routine products and activities
  - Best to avoid rework or other challenging activities

What you don’t Want to Happen During the Inspection

Who is Responsible???

Applicant

Contractor

FDA

Biotechnology Topics Covered During an Inspection

Cell Banking

- How is organism characterized?
- How is the culture stored?
- How was the cell bank characterized?
- How many aliquots are in the master and working cell banks?
- How was the DNA obtained for cloning?
- What is the method for growing the seed culture?
- What is the stability of the cell bank?
- What are the strategies for cell bank regeneration?

Fermentation

- How is the medium sterilized?
- How is the culture inoculated?
- How are the microbes killed/inactivated?
- What are the Critical Process Parameters (CPP)?
- What is the quality of the steam and other utilities used?
- How are entry lines sterilized? Validated process?
- How is the equipment cleaned?

Separation/Purification

- What steps are used in the process?
- Are the process steps validated?
- Have specifications been set for the process?
- Has stability been determined for each buffer?
- Have specifications been set for each buffer?
- What are the CPP?
- How often is maintenance conducted on the systems?

Chromatography

- How often are the beds cleaned?
- Are the cleaning agents non-toxic?
- Are specific resins/manufacturers specified for the process?
- Are the resins checked against specifications before use?
- What are the in-process controls?
- What is the environmental monitoring program that is in place?

Filtration

- Is the system validated?
- How is temperature controlled during the process?
- What types of filters are used?
- What provisions have been made to dilute/concentrate the API?
- What assays are in place to measure the API?

Testing

- What methods have been used to prevent contamination?
- What test methods are used during the manufacturing process?
- Have all of the methods been validated?
- What are the specifications for the final product?
- How are samples handled?
- How is stability analyzed?

Company's Actions Following Inspection

- Maintain your level of GMP
  - Start fixing problems the day you learn about them
  - Start documenting everything you learn about your products and processes
  - Implement a consistent CAPA system
  - Perform regular, professional self-inspections
  - Maintain senior management's involvement in quality issues
  - Regularly hire outside experts to challenge your operation

Thank You for Your Interest