PAUL HASTINGS

Regulation of Drug Manufacturing

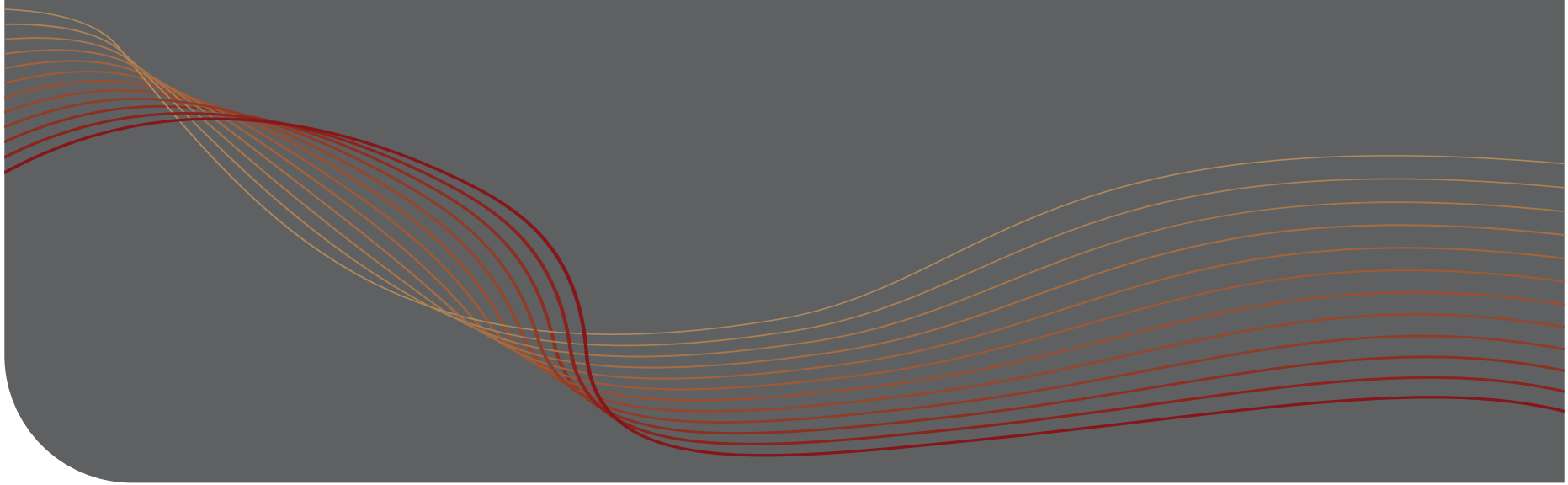
Introduction to Drug Law and Regulation

November 10, 2021

Regulation of Drug Manufacturing – Overview

- Establishment Registration and Drug Listing
- Adulteration
- FDA Inspections
- Current Good Manufacturing Practice (cGMP)
- Responding to 483 Observations

Establishment Registration and Drug Listing



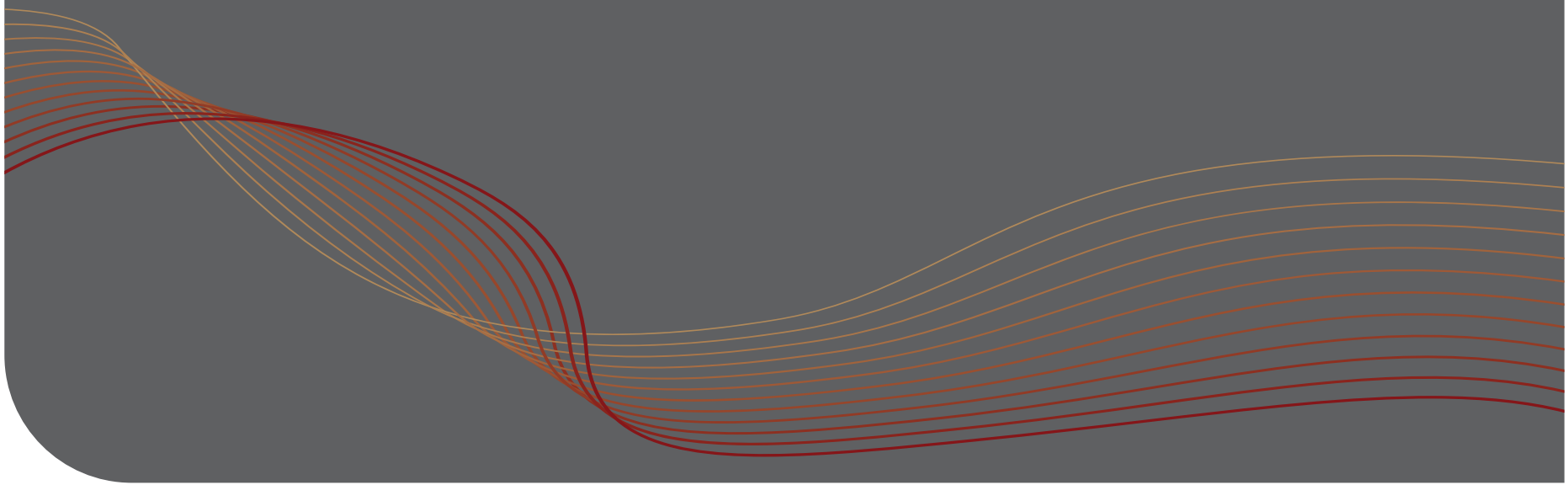
Establishment Registration and Drug Listing

- Establishment Registration
  - Register domestic establishments that manufacture, repack, relabel, or salvage drugs
  - Register foreign establishments that conduct these activities for drugs imported or offered for import into the U.S.
  - Exemptions
- Drug Listing
  - List each drug that registrant manufactures, repacks, relabels, or salvages

Establishment Registration and Drug Listing (cont.)

- Electronic submission of registration and listing information
- Annual reporting of the amount of each listed drug manufactured
- Failure to comply “misbrands” a drug, which is a “prohibited act”
    - Failure to register an establishment
    - Failure to list a drug

Adulteration



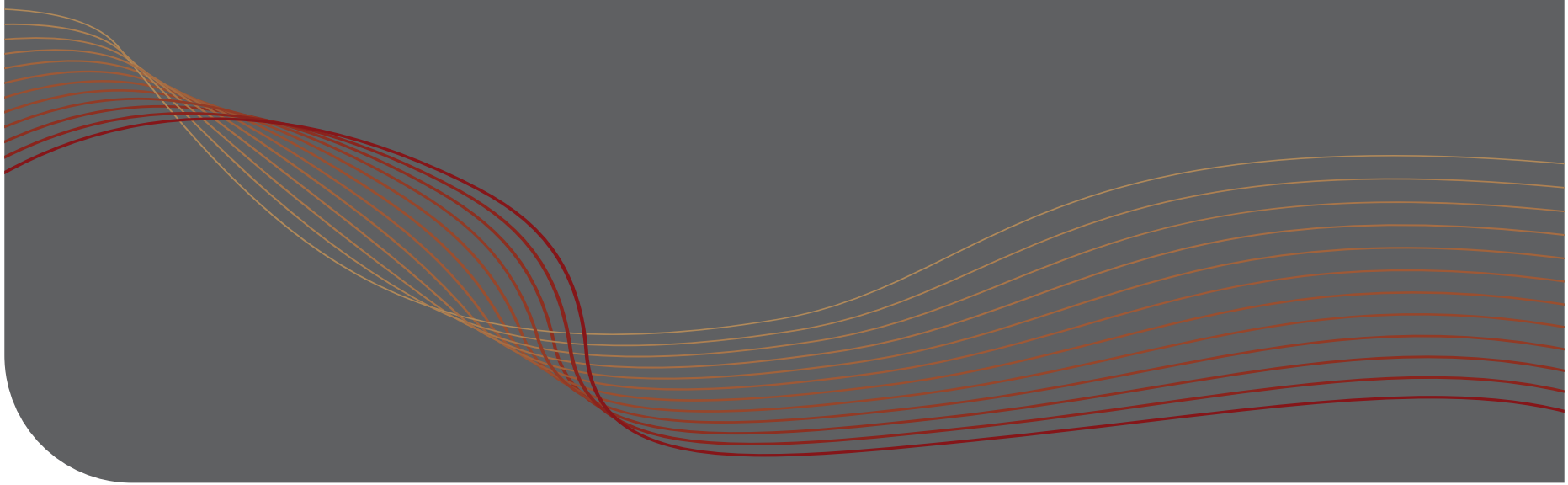
Adulteration

- Drug that “purports to be or is represented as a drug the name of which is recognized in an official compendium and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium”
  - U.S. Pharmacopoeia
  - Exception if difference plainly stated on the label
- Drug “has been prepared, packed or held under insanitary conditions whereby it may have been contaminated with filth”

Adulteration (cont.)

- The methods, facilities, or controls used in manufacturing, processing, packing, or holding “do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug”:
  - Meets the minimum requirements … as to safety
  - Has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess
- The term “current good manufacturing practice” includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs and finished drug products”

FDA Inspections



Audience Question

- **How much experience do you have with FDA inspections and cGMP issues?**
  - **Never worked with these issues**
  - **Occasional involvement**
  - **Frequent involvement**

FDA Inspections

- **FDA does not have general civil subpoena authority**
  - Agency cannot independently compel firms to provide documents
- **FDA has a broad right of inspection**
  - Does not need warrant to enter premises
  - Industry “long subject to close supervision and inspection”

FDA Inspections (cont.)

- **FDA broadly authorized to inspect**
  - Any factory, warehouse, or establishment in which drugs are manufactured, processed, packed or held, for introduction into interstate commerce or after such introduction
  - Any vehicle being used to transport drugs in interstate commerce
  - Records of common carriers that move the drug in interstate commerce
- **General Exclusions**
  - Properly licensed pharmacies
  - Properly licensed physicians
  - Researchers, teachers, and chemical analysts not making drugs for sale

FDA Inspections (cont.)

- **Inspection Limitations**
  - Reasonable times
  - Within reasonable limits
  - Reasonable manner
  - Commenced and completed with reasonable promptness
  - No financial, sales, pricing, or personnel data
- **Record Requests**
  - FDA can also request any records or other information subject to inspection “in advance of or in lieu of an inspection,” and in either electronic or physical form, at the expense of person providing the records

FDA Inspections (cont.)

- **Refusal to submit to inspection is a “prohibited act”**
    - Delaying, denying, or limiting inspection, or refusing to permit entry or inspection may cause a drug to be “adulterated”
- **Administrative inspection warrant to enter establishment**
- **Criminal search warrants also available, as appropriate**

FDA Inspections (cont.)

- **Types of inspections**
  - Pre-approval
  - Routine (surveillance)
  - “For Cause” (compliance)
    - Warning Letter
    - Recall
  - Follow-Up
  - Special surveys or initiatives

FDA Inspections (cont.)

- **Typical Investigator Process**
  - Presentation of credentials and Notice of Inspection (Form 482)
  - Generally introduction of purpose / goals for inspection
- **Typical Company Process**
  - Opening presentation
  - Plant tour
  - Escorts / subject matter experts / scribes (record requests and responses)
  - Backroom / document preparation
  - Duplicate samples / photos

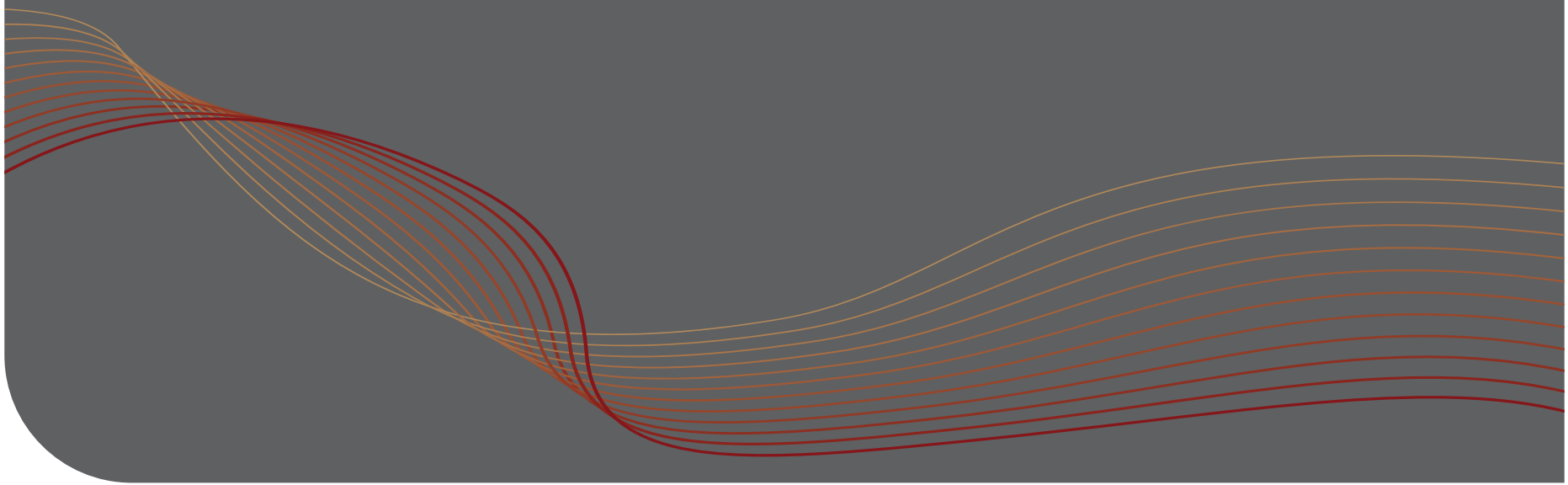
FDA Inspections (cont.)

- **Photographs**
  - Common company position historically
  - FDA position
- **Recordings**
  - Not used under normal circumstances
  - May be made to replicate company recordings
- **Affidavits**
- **COVID-19 Considerations**

Audience Question

- **On balance, do you believe that FDA should conduct more remote "inspections" or reviews?**
  - **Yes**
  - **No**
  - **Depends heavily on the facts of situation**

Current Good Manufacturing Practice (cGMP)



cGMP Requirements

- **Statutory requirements**
- **Regulatory requirements**
    - 21 C.F.R. Parts 210 and 211 (additional requirements, *e.g.*, biological products)
- **Guidance documents**
    - ICH guidance documents
    - Guidance documents related to quality systems, processes, and products
- **Enforcement precedents**

Quality Unit and Personnel: Example Requirements

- **Quality unit responsibility and authority to approve or reject:**
  - Components
  - In-process materials
  - Finished drug products
  - Packaging and labeling
- **Adequate education, training, and experience for all personnel**
- **cGMP training on continuing basis**
- **Adequate number of qualified personnel**
- **21 C.F.R. 211.22-34**

Buildings and Facilities / Holding and Distribution: Examples

- **Suitable size and separate or defined areas to prevent contamination or mixups**
- **Air filtration systems (HVAC) in production areas, where appropriate**
- **Sanitation**
- **21 C.F.R. 211.42-.58; 211.142-.150**

Components: Examples

- **Written procedures**
- **Receipt and testing of incoming components**
    - Active ingredients
    - Excipients (coating, binder, flavor, preservatives)
    - Containers and closures
- **Containers cannot alter safety, identity, or quality of drug**
- **21 C.F.R. 211.42-.58; 211.142-.150**

Production and Process Controls: Examples

- **Establish and follow written procedures for production and process controls to assure that drug products have the identity, strength, quality, and purity they are represented to possess**
    - Procedures to be reviewed and approved by Quality control unit
    - Procedures to address in-process controls, tests, and examinations to assure batch uniformity and drug product integrity
    - Control procedures to monitor the output and validate the performance of manufacturing processes, including causes for variability in in-process material characteristics
- **21 C.F.R. 211.100-.115**

Packaging and Labeling: Examples

- **Controls for labeling issuance**
- **Written procedures to assure that correct labels, labeling, and packaging materials are used for drug products**
- **Each drug product must have a lot or control number**
- **Expiration dating**
- **21 C.F.R. 211.122-.137**

Laboratory Controls: Examples

- **Establishment of specifications, standards, sampling plans, test procedures**
    - Reviewed and approved by Quality control unit
- **Determination of conformity to written specifications**
- **Test method validation**
- **Stability testing**
- **Equipment testing**
- **Reserve samples**
- **21 C.F.R. 211.160-.176**

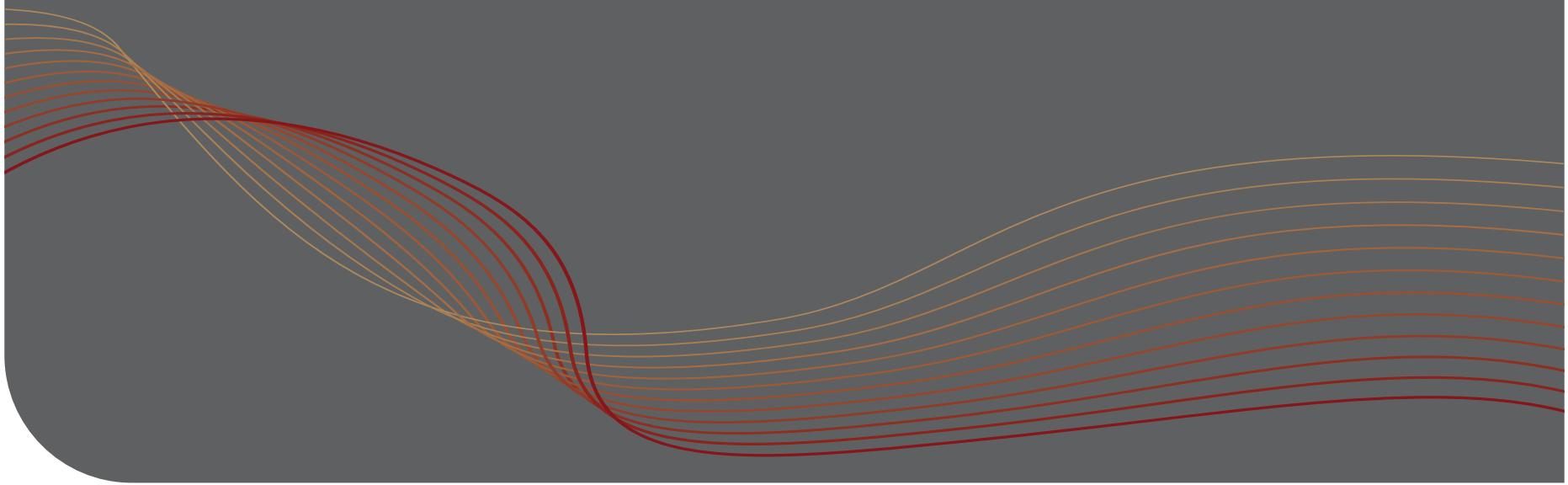
Records and Reports: Examples

- **Record retention**
- **Equipment cleaning records**
- **Master production and control records to assure uniformity from batch to batch**
- **Batch production and control records**
- **Production record review**
  - Review and approval by Quality control unit
  - Thorough investigation into unexplained discrepancy or failure of any batch / component to meet specifications
  - Investigation shall extend to other batches that may have been associated with the specific failure or discrepancy
- **Complaint files**
- **21 C.F.R. 211.160-.176**

Current FDA Focus Areas and Other Developments

- **Examples of FDA Inspection Focus Areas**
  - Laboratory data management controls
  - Laboratory investigations for Out of Specification (OOS) results
  - Sampling plans
  - Process validation / controls
  - Discrepancy / complaint investigations
- **COVID guidance**
- **Office of Regulatory Affairs (ORA) realignment**

Responding to 483 Observations



FDA Inspection Procedure

- **If alleged violations found, inspector presents a list of observations (Form 483)**
  - 483 available to public through FOIA
- **Wrap-up or exit meeting**
  - Verify observations are accurate and valid
  - Obtain clarification regarding observations
  - Possible annotation

FDA Inspection Procedure (cont.)

- **After the inspection**
  - Response to 483 observations expected
    - 15 business days to respond
    - Address specific issues and consider corrections to Quality systems, as needed
    - Develop corrective and preventive actions with timelines
    - Provide evidence of completion
  - Provide additional written updates, as appropriate
  - Investigator(s) prepare Establishment Inspection Report (EIR)
  - Agency makes determination regarding establishment’s compliance status

Audience Question

- **Do you believe that the current amount of dialogue between establishments and FDA is appropriate regarding the output of a regulatory inspection?**
  - **Yes**
  - **No, there should be more**
  - **No, there should be less**
  - **It should vary depending upon the facts of the situation**

FDA Inspection Procedure (cont.)

- **After the inspection (cont.)**
  - Inspections generally classified: “No Action Indicated” (NAI), Voluntary Action Indicated (VAI), or Official Action Indicated (OAI)
  - Inspections with “OAI” classification may result, for example, in a Warning Letter or Import Alert
  - Drug supply considerations

Questions?