

INSPECTION TRENDS



Janet Bowen
Vice President Compliance and Regulatory Services
May 8th, 2013
PDA NE Chapter



TOPICS TO BE DISCUSSED

- **Inspection Types**
- **Inspection Techniques**
- **Recent Observations**

WHAT DOES FDA REGULATE?

- Food
- Human Drugs
- Vaccines, Blood, Tissues
- Dietary Supplements
- Animal Drugs & Feed
- Toxicological Research
- Biotechnology
- Medical Devices
- Radiation-Emitting Products
- Cosmetics
- Tobacco



*FDA regulates products that are valued at **\$2 trillion** annually, which represents about 20 cents of every dollar consumers spend.*

MODEL FOR QUALITY SYSTEMS





TYPES OF INSPECTIONS DRUGS AND BIOLOGICS

- **Surveillance Inspections (Systems)**
 - **The Full Inspection** - At least four Systems are evaluated – one must be Quality (CAPA, recalls, annual product reviews)
 - **The Abbreviated Inspection** – At least two Systems – One must be Quality
- **Compliance**
 - Includes for cause



TYPES OF INSPECTIONS MEDICAL DEVICE

- **Quality System**

- Level 1 - two subsystems CAPA and Production and Process Controls
- Level 2 - The four major subsystems; Management Controls, Design Controls, CAPA and Production and Process Controls
- Level 3 - Compliance Follow-up and **Depends**



MEDICAL DEVICE

- **For Cause Inspections**
- **Foreign Inspections**



INSPECTION PRIORITIES

- **Target Class II and III Devices**
- **Aseptically filled products - Drugs and Biologics**
- **Compliance Follow up/for Cause**
- **Manufactures of high risk**
- **Special assignment from FDA**
 - Products with a higher frequency of recalls
 - Devices that are driven by software and those that the technology evolves quickly
- **Single Use Device Reprocessors**



DEMONSTRATION OF STATE OF CONTROL

- **A firm is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act and portions of the CGMP regulations that pertain to their systems.**

INSPECTION TEAM

- **Experts from the District Office**
- **Seek expertise from other Districts or Division of Field Investigations**
- **Encouraged to have participation from an analyst (microbiologist or chemist)**
- **Plan on having multiple inspectors!**





483 OBSERVATIONS

- **Only “significant items” should be recorded on the 483.**
- **It is acceptable to state your case in defending a process or action.**
- **Is considered unfavorable to argue and continue to argue. There are other means and paths if you disagree**




INSPECTION ACTIONS

- **Document the state of control**
- **Are there to protect the patient**
- **Are progressive as the offence is a higher risk**
- **Warning letters – are just that a warning to a company**
- **Consent Decree – Most unfavorable!**



QUALITY SYSTEM COMPONENTS

- ❑ **Q10 Pharmaceutical Quality System**
- ❑ **FDA Quality Systems based Inspection Approach**
- ❑ **CFR 820 – Quality System**
 - Quality
 - Facility and Equipment
 - Production
 - Laboratory
 - Materials
 - Packaging and Labeling/Printed materials
 - Management Reviews
 - These include the following and how they relate and interrelate to the systems listed above:
Deviation, Change Control, OOS, CAPA



FDA LOOKS FOR QUALITY SYSTEM PATTERNS

- **1) Pattern of failure to review/approve procedures.**
- **2) Pattern of failure to document execution of operations as required.**
- **3) Pattern of failure to review documentation.**
- **4) Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints.**
- **5) Pattern of failure to assess other systems to assure compliance with GMP and SOPs.**



FACILITIES AND EQUIPMENT

- **1) Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination, with demonstrated avenues of contamination, such as airborne or through unclean equipment**
- **2) Pattern of failure to validate cleaning procedures for non-dedicated equipment. Lack of demonstration of effectiveness of cleaning for dedicated equipment.**
- **3) Pattern of failure to document investigation of discrepancies.**
- **4) Pattern of failure to establish/follow a control system for implementing changes in the equipment.**
- **5) Pattern of failure to qualify equipment, including computers**



MATERIALS SYSTEM

- **1) Release of materials for use or distribution that do not conform to established specifications.**
- **2) Pattern of failure to conduct one specific identity test for components.**
- **3) Pattern of failure to document investigation of discrepancies.**
- **4) Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations.**
- **5) Lack of validation of water systems as required depending upon the intended use of the water.**
- **6) Lack of validation of computerized processes.**



PRODUCTION SYSTEM

- **1) Pattern of failure to establish/follow a control system for implementing changes in the production system operations.**
- **2) Pattern of failure to document investigation of discrepancies**
- **3) Lack of process validation.**
- **4) Lack of validation of computerized processes.**
- **5) Pattern of incomplete or missing batch production records.**
- **6) Pattern of nonconformance to established in-process controls, tests, and/or specifications.**



PACKAGING AND LABELING

- **1) Pattern of failure to establish/follow a control system for implementing changes in the packaging and/or labeling operations.**
- **2) Pattern of failure to document investigation of discrepancies.**
- **3) Lack of validation of computerized processes.**
- **4) Lack of control of packaging and labeling operations that may introduce a potential for mislabeling.**
- **5) Lack of packaging validation.**



LABORATORY CONTROL SYSTEM

- **1) Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations.**
- **2) Pattern of failure to document investigation of discrepancies.**
- **3) Lack of validation of computerized and/or automated processes.**
- **4) Pattern of inadequate sampling practices.**
- **5) Lack of validated analytical methods.**



LABORATORY CONTROL SYSTEM

- **6) Pattern of failure to follow approved analytical procedures.**
- **7) Pattern of failure to follow an adequate OOS procedure**
- **8) Pattern of failure to retain raw data.**
- **9) Lack of stability indicating methods.**
- **10) Pattern of failure to follow stability programs.**



INSPECTION OF PHARMACIES

- **Sterile products / high risk**
- **29 identified firms for priority inspections**
- **Identified 2 additional, which it then inspected, for a total of 31 firms.**
- **28 of the 31 are complete (covered 18 states)**



INSPECTION RESULTS

- **28 of the 29 firms received a list of inspectional observations**
- **One required the FDA to obtain a warrant to gain access**
 - US Marshalls escorted the FDA
- **4 out of the 31 initially refused FDA access to records or to observe**

This is not just another day at the office....





WHERE TO FIND MORE INFORMATION

- [2013 Pharmacy Inspections](#)²
- [Pharmacy Compounding](#)³
- [FDA Voice Blog: Proactive Inspections Further Highlight Need for New Authorities for Pharmacy Compounding](#)⁴

UNDERSTANDING AND READINESS

“Failure to Plan is a Plan for Failure”



PREPARATION REVIEW

- **Readiness helps avoid rushing**
- **Makes a positive impression**
- **Avoids confusion**
- **Never hand a document or package to the agency unless you have gone through it with a fine tooth comb.**
- **Cleanliness, cleanliness, cleanliness**



PREPARING YOUR STAFF





483 AND OTHER CORRESPONDENCE TO AN AGENCY

- **Clear**
- **Concise**
- **Usually has a lot of “legal ease”**
- **Do not make commitments that cannot be kept**
- **Do not make commitments that will impact other sites**

STRICT LIABILITY: WHEN GOOD INTENTIONS AREN'T ENOUGH

The Food Drug and Cosmetic Act is a strict Liability statute. This means that to charge a company or individual with a violation FDA **does not** have to show that the person intended to violate the act.



Example: Have you ever gotten a speeding ticket? This is also an example of “strict liability.”



***The harder you look,
the more you'll find***



REAL WORLD EXAMPLES





2012

- **1105 483 observations for**
- **Procedures not in writing, fully followed and the responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].**



2012

- **2027 for Investigations of discrepancies, failures**
- **1361 Absence of Written Procedures**
- **3603 Scientifically sound laboratory controls**



2012

- **3585 Control procedures to monitor and validate performance**
- **4352 Calibration - at intervals, written program, remedial action**
- **9001 Lack of quality control unit**



2012

- **4340 Written warehousing procedures established/followed**
- **3565 Buildings not maintained in good state of repair**
- **3572 Procedure Deviations are not Recorded and Justified**

INVESTIGATIONS



- **Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).**



FIELD ALERT REPORTS

- **Your firm failed to submit NDA/ANDA Field Alert Reports (FARs) within three working days of receipt of information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application (21 CFR 314.81(b)(1)(ii)).**



SPECIFICATIONS

- **Your quality control unit failed to approve procedures and specifications impacting the identity, strength, quality and purity of the drug product. Secondly, your quality control unit failed to exercise its authority to approve or reject drug product components, containers, closures, in-process materials, packaging material, labeling and finished products.**



SPECIFICATIONS

- **The establishment of specifications, standards, sampling plans, test procedures, laboratory control mechanisms including any changes thereto, are not drafted by the appropriate organizational unit, reviewed and approved by your quality control unit. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures...**



LABORATORY

- **Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release. [21 C.F.R. § 211.165(a)]**



LABORATORY

- **Your firm does not have an adequate written testing program designed to assess the stability characteristics of drug products in order to determine appropriate storage conditions and expiration dates. [21 C.F.R. § 211.166(a)]**



REPORTS AND RECORDS

- **Written procedures are lacking that describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, approval, rejection of components, drug product containers, and closures. Bagged or boxed components of drug product containers and closures are not stored off the floor and are not suitably spaced to allow cleaning and inspection. [21 C.F.R. § 211.80 (a) and (c)]**



TRAINING

- **Your firm failed to ensure that employees received training in current good manufacturing practices, as well as in particular operations assigned to the employees [21 C.F.R. § 211.25(a)].**



QUALITY

- **Failure of the Quality Unit to perform quality-related activities in accordance to established written procedures.**
- **Failure to perform process validation for critical manufacturing parameters of all manufactured API products.**



FACILITIES AND EQUIPMENT

- **Failure to maintain and clean manufacturing equipment and facilities.**



WRITTEN PROCEDURES RECORDS AND REPORTS

- **Failure to establish written procedures pertaining to handling of raw materials used in API production, and failure to establish specifications for finished API release.**
- **Failure to prepare adequate batch production records and failure to identify produced batches with a unique batch identification number**



STERILIZATION

- **Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).**

QUESTIONS?



Thank you!