FDA Compliance Activities

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PDA Metro Chapter Conference
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Agenda

- Program Alignment – brief overview
- ConOps – CDER and ORA
- Warning Letters and Aseptic Operations

What was Program Alignment?

- Implemented on 5/15/2017
- Only occurred in Office of Regulatory Affairs (ORA).
- Program-based management structure that aligns staff by FDA-Regulated product.

Program Alignment Structure

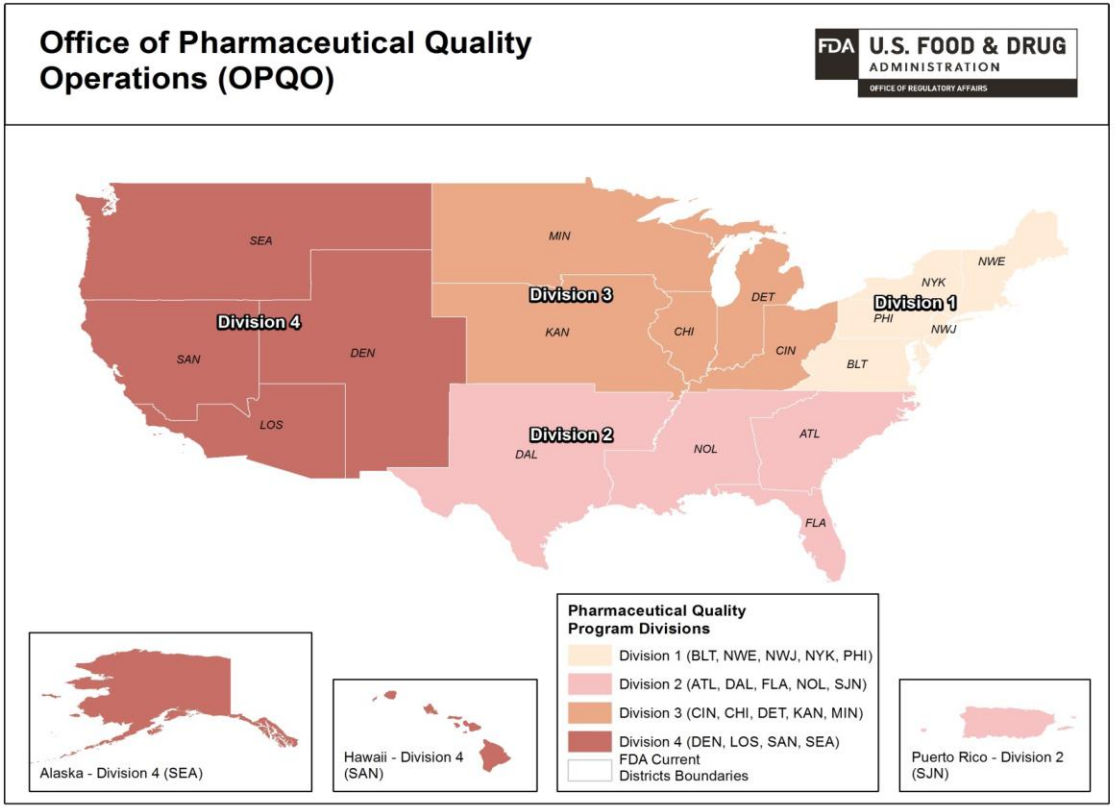
- Seven Program Divisions
  - Office of Bioresearch Monitoring Operations (OBIMO)
  - Office of Biological Products Operations (OBPO)
  - Office of Medical Device and Radiological Health Operations (OMDRHO)
  - **Office of Pharmaceutical Quality Operations (OPQO)**
  - Office of Human and Animal Food Operations (OHAFO)
  - Office of Enforcement and Import Operations (OEIO)
  - Tobacco Operations Program

About the Office of Pharmaceutical Quality Operations

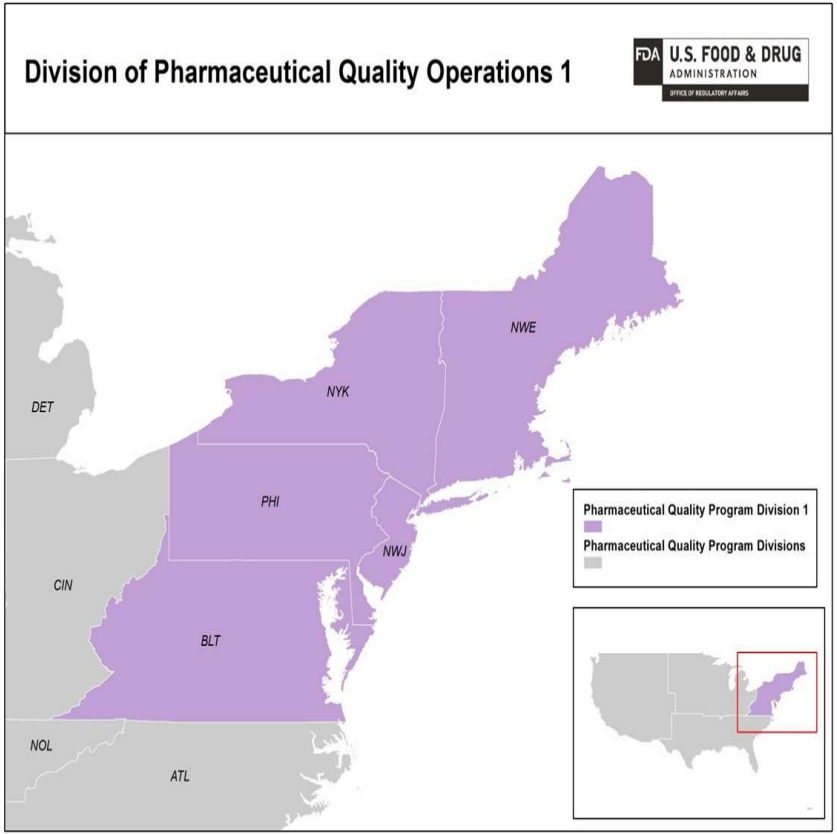
A specialized office to help protect and promote the safety and quality of human and animal drug products.

- A program within ORA's Office of Medical Products and Tobacco Operations (OMPTO)
- Investigators conduct foreign and domestic inspections of drug products for humans and animals
- Compliance officers and a mission support staff are assigned to the OPQO
- 7 Pharma Labs: DET, NRL, PHI, PSW, SJN, FCC, WEAC
- Advise and counsel agency leaders on pharmaceutical product field operations and emergency response activities
- Collaborates with CDER and CVM on all FDA-regulated pharmaceutical and biopharmaceutical products, and implementation of legislative mandates
- Provides technical assistance on investigational operations

Office of Pharmaceutical Quality Operations (OPQO)



OPQO Division I



The Program Division Director (PDD) and District Director (DD) oversee all inspections, compliance and other related program activities.

Diana Amador-Toro: Division I - PDD & NWJ DD

Division I – Points of Contact

Division I	Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia NWE* = Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont	**PDD, Diana Amador Toro & Deputy Division Director (DDD), Craig Swanson** Mailing Address: 10 Waterview Blvd. 3rd Floor, Room 300 Parsippany, NJ Office: 973-331-4901 Email: Diana.Amador-Toro@fda.hhs.gov	**DIB, Karyn Campbell** Mailing Address: US Custom House - 200 Chestnut St, Suite 901, Philadelphia, PA Office: 215-717-3731 Email: Karyn.Campbell@fda.hhs.gov **DIB, Nerizza Guerin** Mailing Address: 10 Waterview Blvd 3rd Floor Parsippany, NJ 07054 Office: 856-290-4040 Email: Nerizza.Guerin@fda.hhs.gov **Preapproval Managers:** **Alice Tsao** (NWE* and NY) Mailing Address: 158-15 Liberty Avenue, Room 4046 Jamaica, NY 11433 Office: 718-662-5657 Email: Alice.Tsao@fda.hhs.gov **Maria Estrella** (NJ) Mailing Address: 629 Cranbury Road East Brunswick, NJ 08816 Office: 732-390-3820 Email: Maria.Estrella@fda.hhs.gov **Gayle Lawson** (PA, DE, MD, DC, VA, WV) Mailing Address: US Custom House - 200 Chestnut St, Room 1003, Philadelphia, PA 19106 Office: 215-717-3737 Email: Gayle.Lawson@fda.hhs.gov	**DCB, Stephanie Durso** Mailing Address: 10 Waterview Blvd. 3rd Floor, Room 300 Parsippany, NJ 07054 Office: 973-331-4911 Email: Stephanie.Durso@fda.hhs.gov **Recall Coordinators:** **Lisa Mathew** (NY and NJ) Mailing Address: 10 Waterview Blvd 3rd Floor Parsippany, NJ 07054 Office: 973-331-4917 Email: lisa.mathew@fda.hhs.gov **Dellarese Priester** (NWE*, PA, DE, MD, DC, VA, WV) Mailing Address: Annex I - 60 Eighth St NE, Room 103, Atlanta, GA 30309 Office: 215-717-3747 Email: dellarese.priester@fda.hhs.gov **Email address for all correspondence, i.e. FDA 483, WL Response, etc.** ORAPHARM1_RESPONSES@fda.hhs.gov

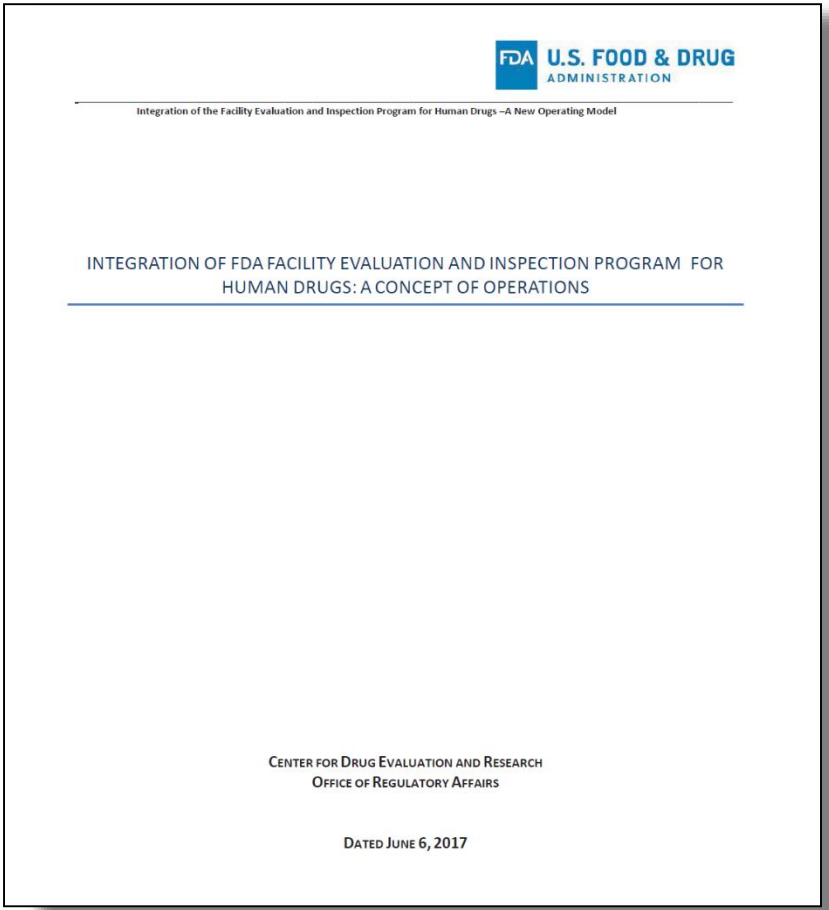
ORA Workflow

- The Division is comprised of
  - Investigations Branch
  - Compliance Branch
  - Administrative Branch
- The Investigations Branch is responsible for performing at minimum: inspections, investigations, and sample collections.

ORA Workflow

- Compliance Branch reviews Establishment Inspection Reports (EIRs), FDA 483, and FDA 483 responses of inspections that the Investigations Branch Management has classified as Official Action Indicated (OAI) for both domestic and foreign inspections.
- If the Compliance Officer concurs with the classification, they decide on the regulatory recommendation.
- The Compliance Officer submits a recommendation in accordance with the ConOps Agreement.

ConOps Agreement



U.S. FOOD & DRUG ADMINISTRATION

Integration of the Facility Evaluation and Inspection Program for Human Drugs –A New Operating Model

INTEGRATION OF FDA FACILITY EVALUATION AND INSPECTION PROGRAM FOR HUMAN DRUGS: A CONCEPT OF OPERATIONS

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF REGULATORY AFFAIRS

DATED JUNE 6, 2017

Why Concept of Operations?

Needs

- Better oversight of increasingly complex and global manufacturing of drugs
- Improved efficiency in line with the ORA Program Alignment into vertically integrated, program aligned areas
- Enhanced IQA approach – alignment/integration between field professionals and review staff
- New commitments and improved coordination and efficiency of work performed under generic drug program as per GDUFA II

Regulatory Tools

Compliance Actions:

- Recalls
- Warning Letters
- Untitled Letters
- Regulatory Meetings
- Administrative Detention
- Civil/Criminal enforcement actions

FDA Issued Letters:

- Request for Additional Information (RAI)
- Request for Regulatory Meeting (domestic firms)
- Warning Letter Acknowledgment Letters
- Nonadherence to Consent Decree Orders

Foreign Versus Domestic

Domestic Inspections

- Typically, Regulatory Meetings held within the Division
- Warning Letters and Untitled Letters signed by the Program Division Director

Foreign Inspections

- Regulatory Meetings will be held at CDER or on a teleconference with CDER, ORA will be in attendance
- Warning Letters, Untitled Letters, and FMD 145 will be signed and issued by CDER

Decisional Letters

- No Action Indicated: Acceptable State of Compliance

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM606022.pdf

- Voluntary Action Indicated: Minimally Acceptable State of Compliance

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM606027.pdf

- Official Action Indicated: Unacceptable State of Compliance

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM606026.pdf

FMD 145

Field Management Directive # 145

Release of Establishment Inspection Reports

- Inspections where no agency action is considered or pursued (i.e., inspections classified as No Action Indicated [NAI] or Voluntary Action Indicated [VAI] as classified by the District Inspection Branch)
- Inspections deemed closed in accordance with 21 C.F.R. § 20.64 (d)(3)
  - Inspections resulting in agency action (i.e., Warning Letter, Untitled Letter, Seizure, etc.) are not releasable until the agency deems the "matter" to be closed in accordance with 21 C.F.R. § 20.64 (d)(3).
- Under ConOps
  - Domestic Inspection – Issued by ORA Division
  - Foreign Inspection – Issued by CDER

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/field-management-directives

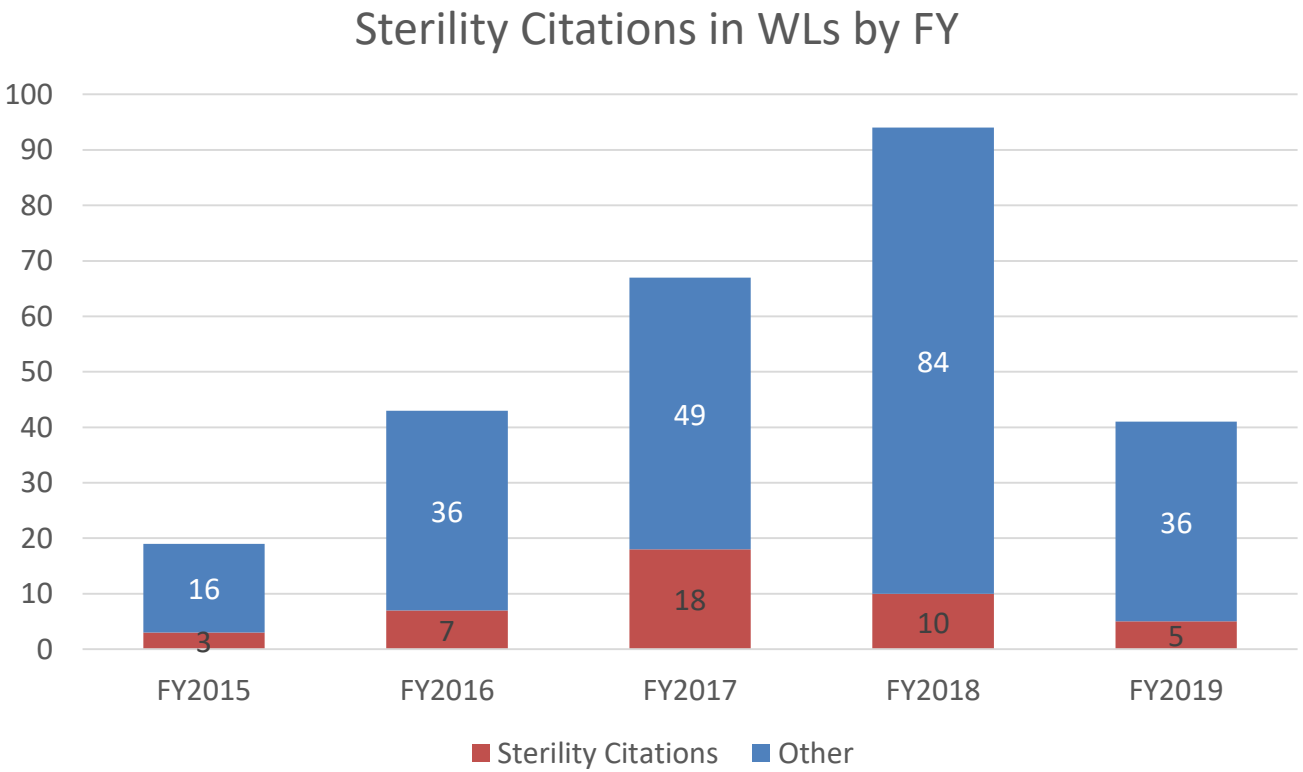
What happens if a Warning Letter is Issued??

- After the Warning Letter is issued, a redacted version, if necessary, is posted to the FDA website.
- Response to the Warning Letter is reviewed and evaluated, as per the Regulatory Procedures Manual, an Acknowledgement Letter is sent.
  - It will tell you if the response is adequate, inadequate or if we cannot determine adequacy.
- There will be a follow up inspection to verify corrective actions.
- If all corrective actions have been verified and they are adequate, a Warning Letter Close Out Letter is issued and posted to the FDA website. The status of the firm is no longer Official Action Indicated.

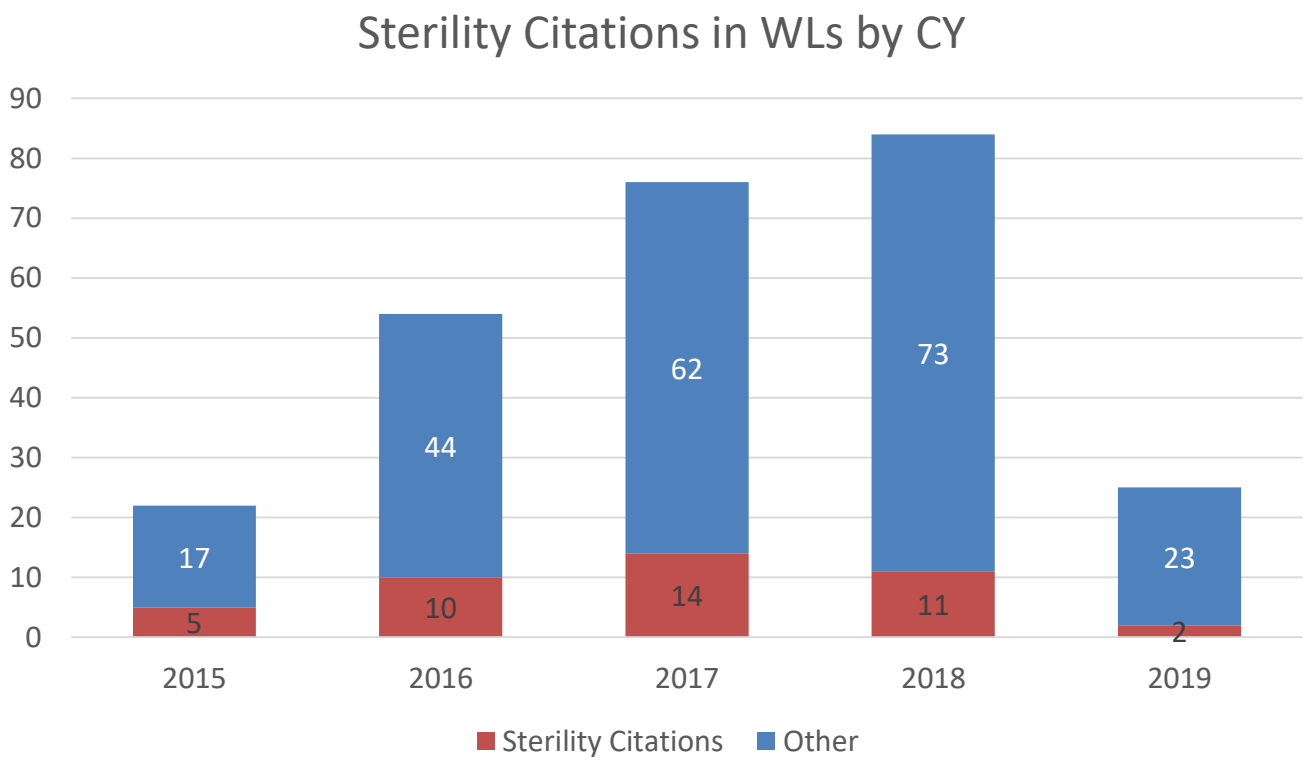
FDA U.S. FOOD & DRUG ADMINISTRATION

Warning Letters Issued for Sterile Operations

Warning Letters For Sterile Products



Warning Letters For Sterile Products



Compliance Program Guidance Manual

CPGM 7356.002A

Sterile Drug Process Inspections

- "A recommendation for regulatory action should be submitted by the District Office when a judgment is made that the firm is not operating in a state of control and management of the firm is unwilling or unable to make adequate corrective actions in an appropriate time frame."
- Provides 16 examples of what could warrant regulatory action.

https://www.fda.gov/media/75174/download

Compliance Program Guidance Manual

1. Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals; or a reasonable potential for product contamination, with demonstrated avenues of contamination such as poor aseptic methods, contact with unclean equipment, or airborne contamination.

2. Failure to assure that each batch conforms to label claims or established specifications, such as NDA, ANDA, USP monographs, and the firm's finished product specifications.

3. Distribution of product which does not conform to established specifications.

4. Lack of adequate validation of critical steps in sterilization processes, including sterilization by filtration; sterilization cycles used for drug products; and, for aseptically processed products, sterilization processes used to sterilize components (formulation and/or its ingredients, as well as containers and closures), or to sterilize equipment surfaces that contact sterile product or any elements of the product.

5. Lack of adequate validation of aseptic processing operations (media fills).

Compliance Program Guidance Manual

6. Failure to appropriately conduct and document investigations of discrepancies and failures of drug products or any of their components to meet specifications, especially inadequate investigations of sterility test failures, media fill failures and repeated or significant environmental or personnel monitoring results that meet or exceed action levels.

7. Facilities and equipment which do not provide adequate protection for aseptically processed product while the sterile product or sterile components are exposed to the environment. This includes both lack of robustness due to poor design, as well as failure to maintain equipment as sterile (e.g., by providing proper barriers as well as assuring adequate sterilization frequency).

8. Failure to assure a robust cleanroom disinfection program. This may include the failure to assure sufficiently detailed cleaning procedures to assure repeatability in cleaning, or failure to demonstrate the suitability and efficacy of the disinfecting agents used for the critical controlled areas and production equipment.

9. Failure of a WFI system to deliver water that consistently meets chemical, microbiological and endotoxin specifications.

Compliance Program Guidance Manual

10. For aseptic processing, poor employee practices that increase the risk of product contamination.

11. Failure to provide adequate training to employees who work in critical operations, such as operators on aseptic processing lines, operators responsible for initiating and checking sterilization cycles and those who perform the 100% inspection of filled injectable products.

12. Failure to perform adequate 100% inspections of injectable products for particulate matter and other defects.

13. Failure of batch records to include complete information related to the production and control of each batch, including documentation that assures environmental and personnel monitoring data and data related to the support systems, and assure quality unit review of these records prior to approval of a lot for distribution and release. For aseptically processed product, batch documentation includes records of purposeful operator interventions into critical (Class 100 / ISO 5) areas of the line. Operator intervention should be minimized as much as possible to preclude and control contamination.

14. Use of test methodology (sterility test, endotoxin test) that is not adequate or validated.

Compliance Program Guidance Manual

15. Lack of an adequate environmental monitoring program, that is, one that does not include dynamic monitoring during all production shifts or has not established appropriate alert and action levels and, in the case of aseptic processing, does not includ representative critical surfaces that come in contact with sterile product, containers and closures.

16. Lack of an adequate personnel monitoring program for aseptic processing operations. For example, the program does not include daily monitoring of operators' gloves and periodic monitoring of gowns; has not established appropriate limits or does not require investigations and corrective actions when limits are exceeded.

Examples of Violations listed on WL

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).

Deficiencies

- Lack of supporting documentation
- Failure to extend investigation to other batches
- Failure to extend the investigation to all departments, too narrow in focus
- Timeliness
- Lack of a risk assessment

Examples of Violations listed on WL

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)).

Deficiencies

- Poor Aseptic practices
- Smoke studies deficiencies
- Media Fills deficiencies

Examples of Violations listed on WL

Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Deficiencies

- Lack of active monitoring
- Inappropriate locations
- Inappropriate frequency

Examples of Violations listed on WL

Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

Deficiencies

- Failure to document results
- Incorrect results reported

Acknowledgements

- DCB Stephanie Durso
- CSO Sydney Rosebraugh, CDER/OMQ

THANK YOU