FDA 483 TRENDING TOPICS & SOLUTIONS

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DISCLAIMER

Today's presentation is only based on FDA public information. Anecdotes are based on the presenter's own interpretation of FDA Law and policies and her 30 years of work experience at FDA. No endorsement from or representation of FDA should be assumed during this presentation.

WHAT TOPICS WE WILL DISCUSS TODAY

- Data Integrity
- Documentation Practices
- Visual Inspection Execution and Documentation of Defects
- Container/Closure Integrity

HOW FDA DEFINES THESE CONCEPTS?

- Data Integrity
- Documentation Practices
- Visual Inspection Execution and Documentation of Defects
- Container/Closure Integrity

DATA INTEGRITY

- For the purposes of FDA's guidance, *data integrity* refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

- (Source: Data Integrity and Compliance With Current Good Manufacturing Practice Guidance for Industry – Draft)

DOCUMENTATION PRACTICES

"Under Title VII of the Food and Drug Administration Safety and Innovation Act (FDASIA) Public Law No. 112-144, FDA may require the submission of any records or other information that FDA may inspect under section 704 of the FD&C Act, in advance or in lieu of an inspection…"

(Source: Request for Quality Metrics Guidance for Industry (July 2015) DRAFT GUIDANCE)

VISUAL INSPECTION EXECUTION AND DOCUMENTATION OF DEFECTS

DRUGS

Post fill Visual Inspection/Automated Inspection Equipment. The 100% inspection of the final filled and sealed product may occur via a manual, automated, or semi-automated inspection process. Manual and semi-automated inspection processes involve specified viewing fields and calibrated light sources. Semi-automated processes may use conveyor belts and rotational units that present the filled product to an operator for visual inspection. All conveyor and rotational speed set points should be verified against established parameters. Automated inspection systems may inspect for one or all types of defects in a given filled product. Defect categories with relevant action levels should be defined. The qualification of the equipment and the challenges performed to verify equipment functionality prior to routine use should be evaluated as well as the training program for operators performing manual visual inspections.

(Source: Chapter 56 – Drug Quality Assurance Compliance Guidance 7356.002 A – Sterile Drug Process Inspections)

VISUAL INSPECTION EXECUTION AND DOCUMENTATION OF DEFECTS

Biologics

Visual inspection should be performed in appropriate areas, and operators should be trained and certified in visual inspection procedures.

(Source: Compliance Program Guidance Manual
Chapter – 45 Biological Drug Products Inspection of Biological Drug Products (CBER) 7345.848)

VISUAL INSPECTION EXECUTION AND DOCUMENTATION OF DEFECTS

Devices

All routine cleaning instructions should include instructions for visual inspection, which may include use of magnification and adequate lighting. The instructions should advise the user that if the device is determined not to be visually clean at the end of the cleaning step, the user should either repeat the relevant previous cleaning steps or safely dispose of the device.

Additionally, the visual inspection instructions should identify acceptance or failure criteria related to device performance (e.g., unacceptable deterioration such as corrosion, discoloration, pitting, cracked seals), as well as instructions to properly dispose of devices that fail.

(Source: Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff (March 17, 2015))

CONTAINER/CLOSURE INTEGRITY

A container and closure system refers to the entirety of packaging components that together contain and protect the product.

(Source: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products (February 2008))

WHY ARE DATA INTEGRITY, DOCUMENTATION, VISUAL INSPECTION, AND CONTAINER INTEGRITY IMPORTANT?

- Public Health Safety Hazard
- Tax payers' money
- We rely on accurate information to ensure drug quality
- Data integrity problems break trust
- We rely largely on trusting the firm to do the right thing when we are not there

MOST CURRENT OBSERVATIONS

483's or FDA Inspectional Citations from FY 2014 - 2016 for :

- Biologics
- Medical Devices
- Drugs

(Source: http://www.fda.gov/ICECI/Inspections/ucm250720.htm)

BIOLOGICS

For **2014**, **2015** and **2016**:

- 21 CFR 606.100(b)
- 21 CFR 606.100(c)
- 21 CFR 606.160(a)(1)
- 21 CFR 606.171
- 21 CFR 606.60(a)

MEDICAL DEVICES

2014

- 21 CFR 820.30(i)
- 21 CFR 820.75(a)
- 21 CFR 820.50
- 21 CFR 820.80(a)
- 21 CFR 820.90(a)

2015

- 21 CFR 803.17
- 21 CFR 820.100(a)
- 21 CFR 820.198(a)
- 21 CFR 820.184

2016

21 CFR 803.17(a)(1)

DRUGS

2014

21 CFR 211.160(b)
21 CFR 211.192
21 CFR 211.180(e)
21 CFR 211.25(a)
21 CFR 211.100(a)

2015

21 CFR 211.160(a)
21 CFR 211.165(a)
21 CFR 211.188
21 CFR 211.192
21 CFR 211.22(d)

2016

21 CFR 211.100(a)
21 CFR 211.198(a)

MOST CURRENT OBSERVATIONS

Citations given by FDA for **Data Integrity**:

Biologics - 21 CFR 606.60(a) Equipment used in the processing of blood and blood components is not standardized and calibrated on a regularly scheduled basis as prescribed in the SOP Manual.

Devices – 21 CFR 820.184 DHR - device history record has not been adequately maintained.

Drugs - 21 CFR 211.188 Batch production and control records do not include complete information relating to the production and control of each batch.

MOST CURRENT OBSERVATIONS

Citations given by FDA for **Documentation Practices**:

Biologics - 21 CFR 606.160(a)(1) Records are not concurrently maintained with the performance of each significant step in the storage and distribution of each unit of blood and blood components.

Devices - 21 CFR 820.50 Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been established.

Drugs -CFR 211.192 There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

MOST CURRENT OBSERVATIONS

Citations given by FDA for factors contributing to **Visual Inspection Execution and Documentation of Defects**:

Biologics - 21 CFR 606.40 Failure to maintain facilities in a clean and orderly manner.

21 CFR 606.160(a)(1) Records are illegible.

21 CFR 600.10(b) Failure to assure that personnel have a thorough understanding of the operations which they perform.

MOST CURRENT OBSERVATIONS

Citations given by FDA for **Container/Closure Integrity**:

Drugs – 21 CFR 211.87 Approved components are not retested or reexamined as appropriate for identity, strength, quality and purity after storage for long periods with subsequent approval or rejection by the quality control unit.

21 CFR 211.84(d)(3)Containers and closures are not tested for conformance with all appropriate written procedures.

21 CFR 211.166(a)(4)The written stability program does not assure testing of the drug product in the same container-closure system as that in which the drug product is marketed.

CONT'

Devices - 21 CFR 820.130 Device packaging and/or shipping containers are not designed and constructed to protect the device from alteration or damage during processing, storage, handling, and distribution.

FACTORS TO BE CONSIDERED…

- Regulatory maturity (regulators and inspected firms)
- Timely Communication & Transparency
- Investigator background and expertise
- Company culture and management oversight
- Geographical location of inspected firms
- Availability of required expertise

FOR VISUAL AND AUDITORIAL LEARNERS …

https://www.youtube.com/watch?v=wKsdMenonLw