U.S. FOOD & DRUG ADMINISTRATION

ORA Inspection and Enforcement Update

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OVERVIEW

- Most commonly used Drug FDA-483 citations for FY17
- Drug Inspection Classifications FY17 and FY18
- FY17 Enforcement Actions and Recalls overseen (CDER and CBER products)
- Recent Warning Letters
- Data Integrity
- Pharmacy Compounding and Outsourcing Facility Inspections

Most Common Drug Citations for FY17

Among approximately 694 Drug 483s
issued 10/1/2016 to 9/30/2017

21 CFR 211.22(d)

The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].

Appears 185 times…

Most Common Drug Citations for FY17

21 CFR 211.160(b)

Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.

Appears 124 times…

Most Common Drug Citations for FY17

21 CFR 211.192

There is a failure to thoroughly review [any unexplained discrepancy] [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.

Appears 100 times…

Most Common Drug Citations for FY17

21 CFR 211.100(a)

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Appears 91 times…

Most Common Drug Citations for FY17

21 CFR 211.67(b)

Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Appears 68 times…

Most Common Drug Citations for FY17

21 CFR 211.165(a)

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release.

Appears 64 times…

Most Common Drug Citations for FY17

21 CFR 211.68(b)

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Appears 62 times…

Most Common Drug Citations for FY17

21 CFR 211.113(b)

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed].

Appears 62 times…

Most Common Drug Citations for FY17

21 CFR 211.68(a)

Routine [calibration] [inspection] [checking] of [automatic] [mechanical] [electronic] equipment is not performed according to a written program designed to assure proper performance.

Appears 61 times…

Most Common Drug Citations for FY17

21 CFR 211.166(a)

There is no written testing program designed to assess the stability characteristics of drug products.

Appears 61 times…

Drug Inspection Final Classifications

FY17 Inspections
- 145 OAI
- 865 VAI
- 565 NAI

FY18 Inspections
(those finalized, to date)
- 57 OAI
- 649 VAI
- 347 NAI

CDER Enforcement Actions FY17
(Domestic and International)

Warning Letters	Seizures	Injunctions
161	0	6

CBER Enforcement Actions FY17

(Domestic and International)

Warning Letters	Seizures	Injunctions
6	1	0

Recalls Overseen for CDER Products

(Domestic and International)

Total events: 348 (1176 products)

- 46 Class I Recall events (75 products)
- 181 Class II Recall events (908 products)
- 121 Class III Recall events (193 products)

Recalls Overseen for CBER Products

(Domestic and International)

Total events: 669 (900 products)

- 484 Class II Recall events (607 products)
- 185 Class III Recall events (293 products)

"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))."

January 26, 2018 Warning Letter cited poor aseptic behavior, such as reaching over open vials and disrupting unidirectional airflow, without removing affected units; failure to include set-up and routine aseptic manipulations and interventions in smoke studies; rejection of integral vials during a media fill that would not have otherwise been removed during production; not all personnel authorized to enter aseptic processing were required to participate in a media fill at least once a year; no procedures for training and qualification of personnel performing examination of media fill units; and lack of active air monitoring in ISO 5 areas.

Also described failure to thoroughly investigate 140 complaints of a particular defect.

Various GMP Deficiencies

April 24, 2018 Warning Letter cited failure to test incoming components; the release of batches without reviewing all production and control records (microbiological testing); equipment design deficiencies (dead legs); lack of air handling systems and control/monitoring of temperature and humidity in production and warehouse.

"Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a))."

October 30, 2017 Warning Letter describes that, due to a reported translation error, a topical OTC drug product labeled as containing hydrocortisone actually contained dexamethasone acetate—a different API. Affected products were recalled, but firm did not fully assess impact and implement appropriate preventive measures.

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

May 31, 2018 Warning Letter cited several environmental monitoring plates from ISO 5 and ISO 8 areas which exceeded action limits, and for which no investigations were initiated (and "your firm had reported no results outside limits for over a year prior to the inspection date"); inadequate collection of surface samples, which "had been occurring for approximately 1–2 years"; late and missed stability pulls, for which no investigation was raised; failure to include 15 investigations of product yield failure in annual product reviews.

Data Integrity Remediation

In that same Warning Letter:

"Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. In response to this letter provide the following."

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

Data Integrity Remediation, continued

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA."

Pharmacy Compounding

In September 2012, contaminated medications distributed by a state-licensed compounding pharmacy, the New England Compounding Center, caused a fungal meningitis outbreak that killed more than 70 people and injured 750 in 20 states.

Our inspections of this and other facilities have found insanitary conditions and other deficiencies posing serious risks to patients. The **Drug Quality and Security Act** of 2013 strengthened the Agency's role in this critical area, and created the Outsourcing Facility Type.

Pharmacy Compounding and Outsourcing Facility Inspections in FY17

- 141 inspections total, 39 of which were self-registered 503B Outsourcing Facilities
- 62 Warning Letters issued
- Oversaw 41 recall activities
- 45 State Referral Letters

"Visible particles in some of the drug vials for injection"

April 13, 2018, FDA alerted health care professionals of a voluntary recall of all non-expired products marketed as sterile made by a particular firm, after a recent inspection found visible particulates in vials and poor sterile production practices.

The **483 issued April 6, 2018** describes inadequate environmental and personnel monitoring samples, pressure differential data not reviewed, inadequate gowning, inadequate conditions for visual inspection of finished vials, incomplete media fill records missing the number of vials filled, and rust observed on HEPA return grates in ISO 7.

"Lack of sterility assurance"

July 10, 2018, FDA alerted health care professionals, patients, veterinarians, and animal owners of a voluntary recall following our observation of insanitary conditions and poor sterile production practices at a particular firm.

Our **follow-up inspection** to a **March, 2017 Warning Letter** found personnel touching non-sterile surfaces without sanitizing their hands or changing gloves prior to returning to the ISO 5 hood; handling components with bare hands while disinfecting those items, prior to placement in the pass through; failure to use a sporicidal disinfectant at the appropriate concentration and contact time; use of non-sterile cleaning wipes in ISO 5; and white residue on the face panel of the HEPA filter supplying air to the ISO 5 area, as well as dirt and residue on the floor of the ISO 7 area. On **June 7, 2018, the firm informed FDA it was ceasing sterile operations**.

www.fda.gov https://www.fda.gov/Drugs/DrugSafety/ucm612911.htm 27

"Continued to produce and distribute…even after identifying instances of microbial contamination in your ISO-5 and ISO-7 areas"

April 4, 2018 Warning Letter also describes use of non-sterile wipes to clean the ISO 5 work surface, failing to disinfect gloves frequently between operations, failing to adequately clean after handling hazardous drugs, and the presence of cardboard boxes and a paper note pad in the ISO 7 room.

www.fda.gov https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm604269.htm 28

"Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed."

This **483 issued September 26, 2017** describes repeated media fill failures, after which product continued to be distributed. Discrepancies were observed in the media fill records, and the failures were inadequately investigated.

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM580869.pdf

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