FDA Compounding Quality Center of Excellence *What to Expect After an Inspection*

September 15, 2021

Jennifer DelValle Ortiz, Lead Consumer Safety Officer, CDER/OC/OCQC/CB2

Rebecca Asente, Compliance Officer, ORA/OPQO/Division II

Why are we here?

To take a look into:

- Form FDA 483s
- Inspection Closeout Meetings
- Responses to the Form FDA 483
- Post Inspection Expectations
- FDA 483 Examples and Regulatory Responses

Why is This Important?

- Ensure Safe Drug Products
- Ensure Availability of High-Quality Drug Products
- Ensure We are Building Quality into Systems
- Achieve Better Understanding of Your Operations
- Meet Regulations and Other Requirements (and beyond!)

First -

What is a Form FDA 483?

Sec. 704(b) [21 U.S.C 374] of the FD&C Act states: “Upon completion of any such inspection…and prior to leaving the premises, the officer…making the inspection shall give to the owner…a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate any…drug…(1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed or held under insanitary conditions….”

Scenario

- FDA Investigators conducted an inspection of your 503B facility and operations
- Your firm is meeting with the FDA Investigator to discuss the issued FORM FDA 483 and additional deficiencies not documented on the FORM FDA 483

How best to prepare and respond during the close-out meeting?

Post FDA 483 – How to Respond?

- Respond to Guidance Provided by the FDA Investigators
- Provide Adequate Corrective Actions that Address Deficiencies
- Provide Preventive Actions to Ensure Future Compliance
- Responses Should be Comprehensive and Well Organized
- Responses Should be Timely: Respond within 15 Business Days

Scenario

You submitted your response to the FDA 483 and inspection weeks ago…

What's Happening?!

What is FDA Doing?

Why am I not hearing anything from FDA?

LET’S DISCUSS A FEW EXAMPLES

What Should Your Response Include?

- Immediate Action: Correction and Resolution of Deviations
- Documentation/Evidence
- Actions Completed
- Actions Planned

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)).

- Quality Control Unit (QCU) failed to investigate to prevent the distribution to patients of the following drug product lots which did not pass sterility testing.
- QCU did not review and approve production records such as: sterility test results, analytical method validation, aseptic processing simulation, and cleaning logs.

Your firm failed to have buildings used in the manufacture, processing, packing, or holding of drug products with adequate space for the orderly placement of equipment and materials to prevent mix -ups and contamination (21 CFR 211.42(b)).

- The facility design allowed the influx of poor-quality air into a higher classified area.
- The facility was designed in a way that permits poor flow of personnel or materials.
- Products within expiry are not stored under controlled conditions.
  - Products requiring temperature-controlled conditions (i.e., 2º-8℃) are not controlled by the firm.
    - i.e stored on the floor of the warehouse or bathroom

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)).

- Failure to conduct Smoke Studies, or:
  - Inadequate smoke studies (Dynamic)
  - Failure to demonstrate unidirectional airflow
- Operators' movements blocked first pass air
- The media fills were not performed under the most challenging or stressful conditions
- Failure to conduct viable/no viable air sampling during aseptic operations

No evaluation has been performed to show the adequacy and efficacy of the cleaning and disinfection process used to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

- A sporicidal agent is applied to surfaces with a 15-minute contact time. Manufacturer's labeling requires a 30-minute contact time.
- Transfer carts are not wiped completely (tops, bottoms, legs, and wheels) prior to transferring them between ISO classified areas.
  - Carts are touched with bare hands while being cleaned.

Failure to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b))

- Insufficient control over data and software used during production
- Data, which per SOP are required to be protected and verified, were not protected from manipulation; SOP did not contain audit trail provisions
- Document control was not maintained as multiple versions of spreadsheets were found on computers used by the quality staff
- Software used to run equipment was not qualified at the time of installation
- Software was not password protected
- Technicians stated that they are able to override the software to make setting adjustments during production and changes are not documented or saved

There is no written program designed to assess the stability characteristics of drug products (21 CFR 211.166).

- Data to support the assignment of beyond-use-dates are captured in technical reports. However, these studies lacked data regarding:
  - Potency testing over the desired storage period
  - Sterility testing was not performed per USP <71> or by any validated test method
  - Accelerated studies were not used to assess potential impurities
  - Some products lacked data to support the established beyond use dates
- Program lacked adequate stability indicating methods for some products.

Possible Regulatory or Enforcement Pathways

- Immediate Actions
  - Recommend Recall and/or Request to Cease Operations
  - Press Release
  - ACRA Letter
- Untitled Letter
- Warning Letter
- Regulatory Meeting
- Injunction

Summary:
Your Response Should Include…

- Immediate Action: Correction and Resolution of Deviations
- Documentation/Evidence
- Actions Completed
- Actions Planned


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