U.S. FOOD & DRUG ADMINISTRATION

Here and Now: Inspectional Processes and COVID-19 Updates

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FDA Inspections During COVID-19 Pandemic

- The World Health Organization declared the global coronavirus crisis a pandemic on March 11, 2020

FDA Inspections During COVID-19 Pandemic

- Prior to traveling to the firm, the Investigator will check local and state requirements for Personal Protective Equipment (PPE) in jurisdictions they will travel through.
- In addition, the Investigator will contact the firm and pre-announce their arrival.

FDA Inspections During COVID-19 Pandemic

- The investigator will be self-screened each day of the assignment to assure they have:
  - No cough or shortness of breath
  - No symptoms similar to influenza or pneumonia
  - No temperature above 100.4 degrees Fahrenheit
  - Not traveled in areas covered by the current CDC travel advisory including travel out of the country in the last 14 days.
  - No known contact with anyone who has had lab-confirmed or symptoms consistent with COVID-19 in the last 14 days.

FDA Inspections During COVID-19 Pandemic

- The inspectional team should be limited to the least number of persons necessary.
  - If the team consists of multiple persons, each person should consider driving in separate vehicles.
    - Sanitization practices include, wiping car handle, steering wheels, and other hand contact areas prior to and after driving.

FDA Inspections During COVID-19 Pandemic

- Safe social distancing will be practiced during the entire inspection in accordance with CDC guidelines
  - PPE, including face masks, gloves, and hand and surface sanitizer, disposable lab coats and booties, thermometer or thermometer strips, or other equipment, as needed for the inspection.

FDA Inspections During COVID-19 Pandemic

- The Investigator will:
  - Refrain from:
    - All physical contact, including hand shaking.
    - Touching one's own face, especially the mouth, eyes, and nose at all times.
  - Visually display credentials.
  - FDA-482, Notice of Inspection, will be signed and placed on a surface for the firm's representative.
  - Will review and discuss safe social distancing practices during the inspection.
  - Agree to an area in the firm to practice social distancing of at least 6 feet.

FDA Inspections During COVID-19 Pandemic

- The Investigator will wash or sanitize their hands upon entry, periodically throughout the day, and when leaving the facility for at least 20 seconds, as suggested by the CDC, *When and How to Wash Your Hands*.
- During the inspection, hand washing or hand sanitizing (with at least 60% alcohol) should occur at frequent intervals including at a minimum:
  - Before, during, and after preparing or eating food;
  - After going to the restroom;
  - After blowing your nose, coughing, or sneezing;
  - After putting on, touching, or removing face coverings;
  - Before and after work and work breaks;
  - After touching surfaces such as desks, door handles, clipboards, pens, cameras, cell phones, laptops, keyboards, or electronic tablets;
  - After review of records, and observations of areas with employees.

FDA Inspections During COVID-19 Pandemic

- Limit the back and forth sharing of documents, pens, and other office supplies
- If possible use cleaning agents to wipe down hard surfaces prior to placing and reviewing inspectional items
- Electronic records are preferred when possible.
  - Flash/thumb drives should be carefully sanitized prior to exchanges

FDA Inspections During COVID-19 Pandemic

- Records may be obtained via email
  - Firm may contact SecureEmail@fda.hhs.gov to obtain a license to send encrypted messages to FDA via electronic mail.
- Records may also be collected for review offsite to comply with safe social distancing practices.

FDA Inspections During COVID-19 Pandemic

- In some instances, an FDA-483 issuance may be conducted via FDA WebEx meeting to close out the FDA inspection.
  - If a close out is conducted via FDA WebEx, the investigator will obtain confirmation from the firm this is acceptable.
  - Upon completion of the meeting, the Investigator will issue the FDA- 483 by email and confirm the receipt. Followed by sending the hardcopy of the FDA- 483 by UPS, registered, or certified mail, with a delivery signature.

U.S. FOOD & DRUG ADMINISTRATION

FDA Inspections of Outsourcing Facilities (503B)

CGMP for Outsourcing Facilities

- Unless a specific exemption applies, any drug that is not made in compliance with Current Good Manufacturing Practice (CGMP) requirements is considered "adulterated" under the law (FD&C Act Section 501(a)(2)(B)).
- Outsourcing facilities are not exempt, and must comply with CGMP requirements.

  – See draft guidance, "Current Good Manufacturing Practice —Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act" (January 2020)

  – CGMP regulations specific to outsourcing facilities are under development.

CGMP for Outsourcing Facilities

- FDA recognizes the differences between compounding outsourcing facilities and conventional drug manufacturers, and intends to tailor CGMP requirements to the nature of the specific compounding operations of outsourcing facilities, while maintaining the minimum standards necessary to protect patients.
- FDA evaluation of compliance with CGMP requirements by outsourcing facilities includes:
  - Assessing conformance with minimum CGMP standards
  - Identifying conditions that may represent a significant risk to patient safety

Insanitary Conditions

- FDA may also cite outsourcing facilities for insanitary conditions.
- FD&C Act 501(a)(2)(A) – “A drug is deemed to be adulterated if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.”
- The insanitary conditions prohibition applies to outsourcing facilities, in addition to CGMP requirements.

Initial Facility Walk-Through

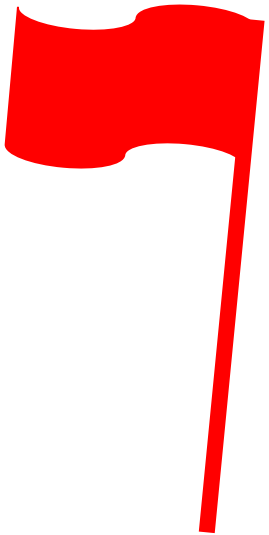
WHY?

Opportunity to see conditions as they actually are, and identify obvious issues that may inform inspection approach.

Initial Facility Walk-Through

Red flags

- Visible signs of filth, dirt, mold, insects, trash
- Aseptic manipulations outside of ISO-5 controlled air space
- Minimal or no recordkeeping system



Aseptic Operators and Operations

WHY?

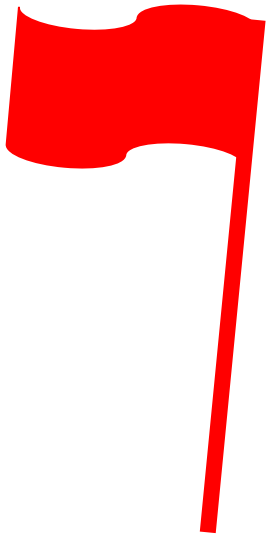
In our experience, the dirtiest items in the room are personnel.

Unqualified personnel and their actions can introduce contamination into the best designed and otherwise maintained facility.

Aseptic Operators and Operations

Red flags

- Improper aseptic gowning techniques
- Items in cleanroom that have not been cleaned and disinfected
- Filters used are not pharmaceutical grade



Process and Facility Design

WHY?

Normal environmental conditions are not

suitable for aseptic processing.

Process and Facility Design

21 CFR 211.42(b) states, in part: “The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.”

Cross Contamination

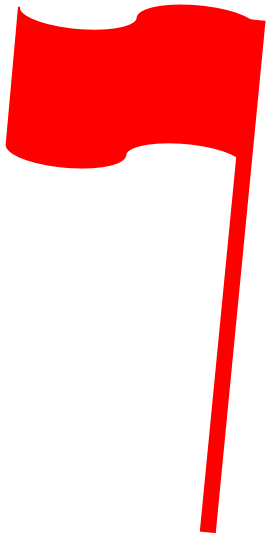
"If powder drugs are handled, procedures must be established and followed to appropriately manage cross-contamination risk (see § 211.100). This is particularly important if the powder is cytotoxic or highly sensitizing. FDA recommends the physical segregation of areas in which powder drugs are exposed to the environment. For penicillin products, a separate facility is required (see § 211.42(d))."

--Current Good Manufacturing Practice —Draft Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (January 2020)

Process and Facility Design

Red flags

- Lack of air control system
- Loose cleanroom ceiling tiles
- Disinfectants and cleaning agents used in ISO 5 not sterile
- Surfaces not cleanable surfaces



Environmental & Personnel Monitoring

WHY?

Sterility tests alone do not provide an adequate assurance of sterility.
Quality is built in, not tested in.

Environmental & Personnel Monitoring

Control systems to prevent contamination during aseptic processing include “a system for monitoring environmental conditions.”
--21 CFR 211.42(c)(10)(iv)

“Evaluating the quality of air and surfaces in the cleanroom environment should start with a well defined written program and scientifically sound methods. The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures.”

“A vigilant and responsive personnel monitoring program should be established.”
--Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice Guidance for Industry

Pressure Differential Limits

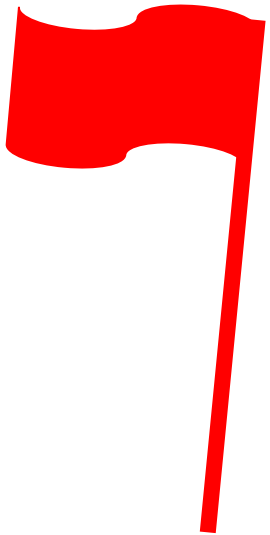
"A system for environmental monitoring must include the establishment of pressure differential limits (see § 211.42), and control systems should include built-in alarms to detect excursions. An adequate control system includes monitoring for pressure differentials, humidity, and temperatures during production and taking prompt action to correct adverse conditions, which are necessary activities to prevent contamination during aseptic processing (see § § 211.42, 211.46, 211.58)."

--Current Good Manufacturing Practice —Draft Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (January 2020)

Environmental & Personnel Monitoring

Red flags

- Infrequent environmental monitoring
- Environmental monitoring not representative of operational conditions
- Adverse trends in environmental monitoring



Product Inspection & Component Control

WHY?

Contaminants and impurities in ingredients can end up in a finished drug

Contaminants can form during processing

Breaches in the container/closure system can lead to product contamination or degradation

Component Control

"Controls over the source and quality of components are required (§ § 211.82, 211.84, 211.87, 211.113). When producing sterile drug products, one aspect of such controls is the consideration of whether the incoming components are non-sterile."

--Current Good Manufacturing Practice —Draft Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (January 2020)

Container/Closures and Equipment

"If the outsourcing facility does not use presterilized and depyrogenated single-use disposable equipment (e.g., filters, transfer tubing, temporary holding vessels), the equipment must be sterilized and depyrogenated before use through processes that have been validated (see §§ 211.65, 211.67(a) and (b), 211.100, 211.113)."

--Current Good Manufacturing Practice —Draft Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (January 2020)

Product Inspection & Component Control

Red flags

- Visible contamination: “floaters,” particles, discoloration, leaking in finished product
- Condition of container and closure
- Container not suitable for intended use
- Bulk drug substances not suitable for drug manufacturing (e.g. chemical grade, lack of COA)

Packaging and Labeling Control

WHY?

To ensure that mislabeling of product does not occur.

Potential for serious patient harm with incorrect labeling.

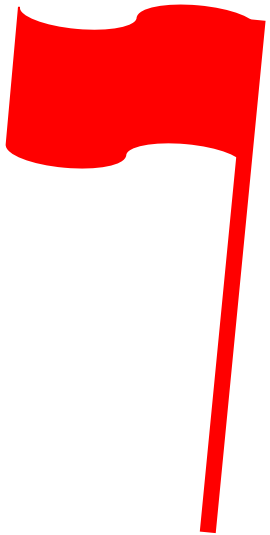
Packaging and Labeling Control

"There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product." *21 CFR 211.122(a)*

Packaging and Labeling Control

Red flags

- Product containers that are not immediately labeled
- Multiple types of products being compounded in a single cleanroom with inadequate segregation of product and associated labels



Records Review

WHY?

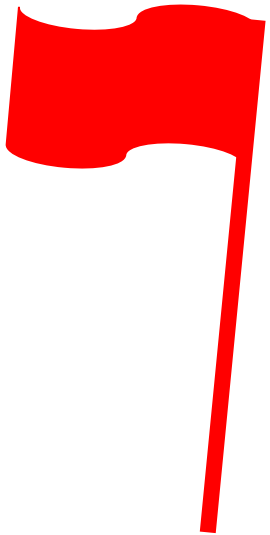
Documentation of key quality controls such as release testing and environmental monitoring.

Shows how facility identifies and addresses problems.

Records Review

Red flags

- Depyrogenation in inappropriate equipment (e.g., toaster oven or autoclave).
- Lack of records, lack of investigation into OOS results, lack of COA's.
- Multiple complaints regarding adverse events or product quality issues.



THANK YOU!

Contact

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