

FDA Inspections of Outsourcing Facilities

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CGMPs for Outsourcing Facilities

- 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 - See draft guidance, “Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act,” which, when finalized, will reflect FDA’s current thinking on compliance with CGMP requirements for 503B facilities.

CGMPs for Outsourcing facilities

- FDA recognizes the differences between compounding outsourcing facilities and conventional drug manufacturers, and the need, to some extent, to appropriately tailor CGMP requirements for outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.

Insanitary Conditions

- Outsourcing facilities are subject to the prohibition on 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.”

Initial Facility Walk-Through

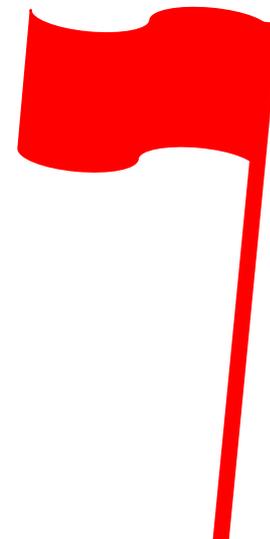
WHY?

Opportunity to observe conditions as they actually are, and identify obvious issues

Initial Facility Walk-Through

Red flags for CGMP Noncompliance

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



Aseptic Operators and Operations

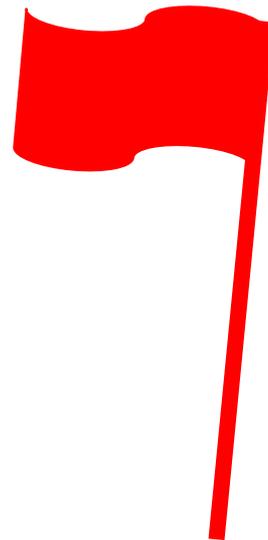
WHY?

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

Aseptic Operators and Operations

Red flags for CGMP Noncompliance

- Improper aseptic gowning techniques
- Materials not being cleaned and sanitized prior to entering into the ISO-5 classified area
- Poor aseptic technique (i.e. blocking first air)
- Items in cleanroom that have not been cleaned and disinfected
- Filters used to render a product sterile 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, that “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.”

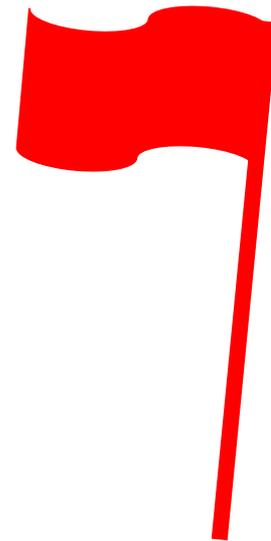
Cross Contamination

FDA's Draft Guidance states: "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))."

Process and Facility Design

Red flags for CGMP Noncompliance

- Lack of air control system
- Loose cleanroom ceiling tiles
- Dirty/Damaged HEPA filters
- Disinfectants and cleaning agents used in ISO 5 not sterile
- Surfaces that are not cleanable



Environmental & Personnel Monitoring

WHY?

Sterility tests alone do not provide an adequate assurance of sterility.

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)*

“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

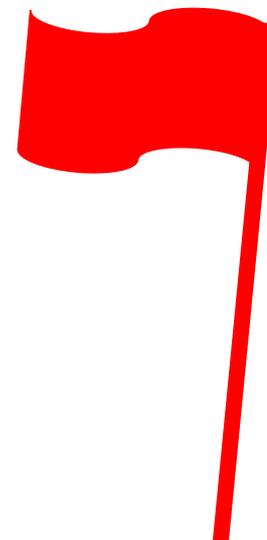
Pressure differential limits must be established, (see § 211.42) and control systems should include built-in alarms to detect excursions.

Monitoring for pressure differentials, humidity, and temperatures should occur during production, and prompt action should be taken to correct inappropriate conditions.

Environmental & Personnel Monitoring

Red flags for CGMP Noncompliance

- Infrequent environmental monitoring
- Environmental monitoring is 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 product
 - 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.”

- FDA Draft Guidance Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act

Container/Closures and Equipment

“If [an] 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 and 211.113)

- FDA Draft Guidance Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act

Product Inspection & Component Control

Red flags for CGMP Noncompliance

- 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 (i.e. do not conform to an applicable USP/NF monograph, lack of COA)



Packaging and Labeling Control

WHY?

To ensure that mislabeling of product does not occur.

To ensure product mix up does not occur

Potential for serious patient harm with incorrect labeling.

Packaging and Labeling Control

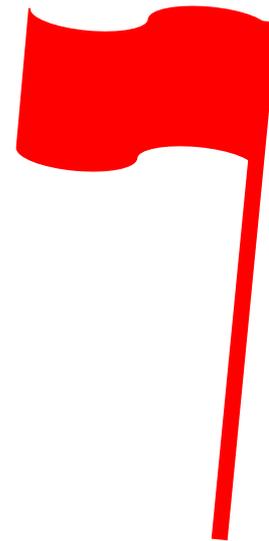
“There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, 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 for CGMP Noncompliance

- 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

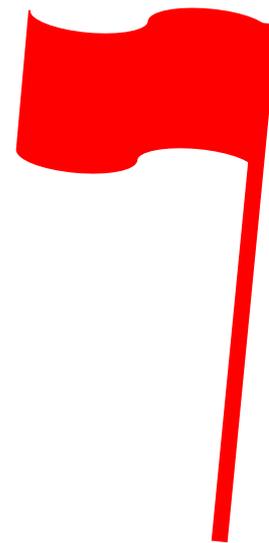
WHY?

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

Records Review

Red flags for CGMP Noncompliance

- Lack of records, lack of investigation into OOS results, lack of COAs
- Multiple complaints regarding adverse events or product quality issues.
- Potential data integrity concerns



Top 483 Citations



21 CFR 211.42(c)(10)(iv)	Environmental Monitoring System	Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically, ***
21 CFR 211.113(b)	Procedures for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***
21 CFR 211.192	Investigations of discrepancies, failures	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. Specifically, ***
21 CFR 211.42(c)(10)(v)	Cleaning System	Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the [room] [equipment] to produce aseptic conditions. Specifically, ***
21 CFR 211.113(b)	Validation lacking for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include [adequate] validation of the [aseptic] [sterilization] process. Specifically, ***

THANK YOU!

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