

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 - See draft guidance, “Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act,” which, when finalized,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?

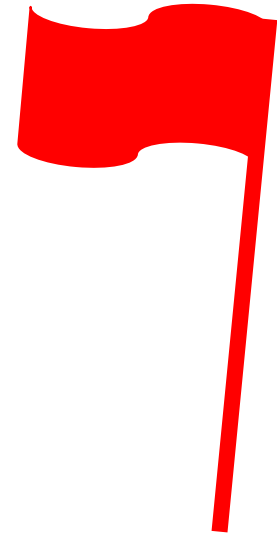
Opportunity to observe conditions as they actually are, and identify obvious issues

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

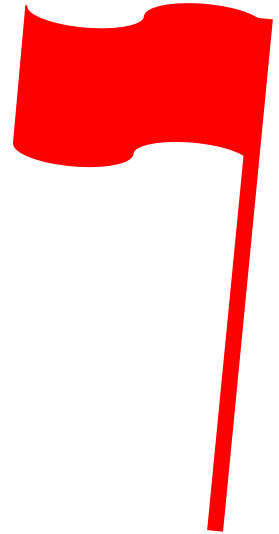
WHY?

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.”

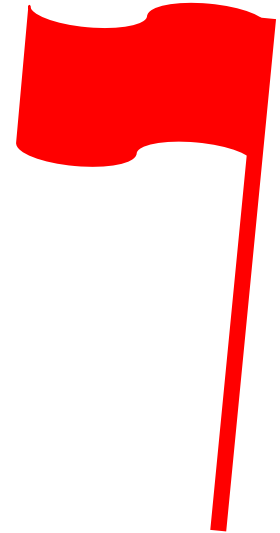
Cross Contamination

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



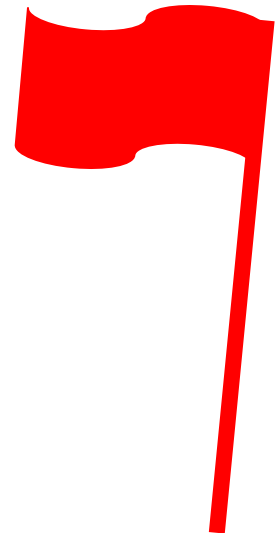
“If [an] outsourcing facility does not use presterilized and depyrogenated single-use disposable equipment (e.g., filters, transfer tubing, temporary holding vessels) the equipment, must be sterilized and depyrogenated before use through processes that have been validated. (see §§211.65, 211.67(a) and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

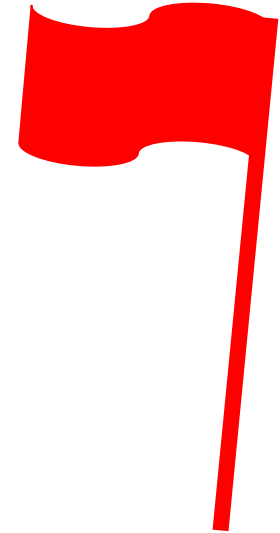
“There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled,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

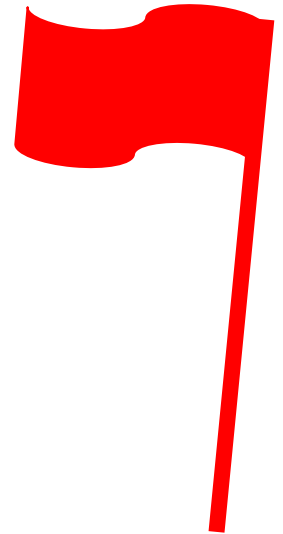
WHY?

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 Five 483 Citations

1. 21 CFR 211.42(c)(10)(iv)-Environmental Monitoring System
2. 21 CFR 211.113(b)-Procedures for sterile drug products
3. 21 CFR 211.192- Investigations of discrepancies, failures
4. 21 CFR 211.42(c)(10)(v)-Cleaning System
5. 21 CFR 211.113(b)-Validation lacking for sterile drug products

THANK YOU!

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FDA Inspections of Outsourcing Facilities

What to Expect on an Inspection: Section 503B Compliance Evaluation

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Branch 3

Division of Compounding II

Office of Compounding Quality and Compliance

Outsourcing Facilities (OF)

- Elect to register as an OF
- Comply with all the conditions of section 503B of the FDCA
- Are engaged in the compounding of sterile human drugs
- Are inspected by FDA on a risk-based schedule
- May or may not obtain prescriptions for identified individual patients

Section 503B of the FDCA

The human drug products compounded by outsourcing facilities are eligible for exemptions from requirements under three sections of the FDCA. These three sections are:

- New drug approval requirements in section 505
- Labeling with adequate directions for use in section 502(f)(1)
- Drug supply chain security requirements in section 582

Section 503B: Facility



During an inspection, FDA will:

- Evaluate the facility to ensure that all drug products produced at the FDA-registered facility are compounded in accordance with section 503B.
- Drugs compounded by an OF are not eligible for the exemptions provided under section 503A.
- If a firm chooses to also compound drug products under the different conditions of section 503A, this must be done in a separate establishment. Operations must be completely segregated, i.e., do not share rooms and fixed equipment or supplies, have separate entrances/exits, do not share an internal pass-through opening, areas are separated by permanent physical barriers, etc.

Section 503B: Facility

Additionally, FDA will:

- Confirm the address that was registered with FDA as an OF and confirm it is the actual location where 503B compounding operations occur.
- Confirm that the outsourcing facility's drug product labels clearly identify the outsourcing facility as the producer of the drug product.

Section 503B: Facility

Important Notes:

- If the firm's 503A operations are **not** completely segregated from the 503B operations, we generally intend to consider the 503A operations to be part of the OF and subject to the conditions of section 503B and CGMP requirements
- If the firm is a 510-registered manufacturer *and* a registered outsourcing facility, the compounded drug products must meet the conditions of section 503B to qualify for the exemptions from FDCA sections 502(f)(1), 505, and 582. Approved drug products and drug products compounded under section 503B may be produced in the same facility

Section 503B: Licensed Pharmacist Supervision

Under section 503B, an OF is not required to be a licensed pharmacy, *however*, compounding at an OF must be ***by or under*** the direct supervision of a licensed pharmacist

Section 503B: Licensed Pharmacist Supervision



During the inspection, FDA will:

- Verify that the firm has a licensed pharmacist providing oversight of compounding operations.
- Collect information regarding the role of the pharmacist(s), e.g., the number of pharmacists employed, pharmacist licensure information, the hours the pharmacist(s) are on site, and whether a pharmacist is present during compounding operations.
- Collect documents such as copies of pharmacist licenses.

Conditions of Section 503B

Conditions include:

- Drug product reporting requirements (sections 503B(a)(1) and 503B(b)(2))
- Adverse event reporting requirements (sections 503B(a)(1) and 503B(b)(5))
- Labeling requirements (section 503B(a)(10))
- Prohibition on compounding drugs that appear on the list of drugs at 21 CFR 216.24 that have been withdrawn or removed from the market because the drugs or components of the drugs have been found to be unsafe or not effective (section 503B(a)(4))
- Limitations on bulk drug substances that can be used in compounding (section 503B(a)(2))
- Prohibition on compounding drugs that are essentially a copy of one or more FDA-approved drugs (section 503B(a)(5))
- Prohibition on wholesaling (section 503B(a)(8))

Section 503B: Drug Product Reporting



- Section 503B requires outsourcing facilities to electronically submit a report about the drug products compounded at the facility, initially upon registration as an OF, and twice a year (In June and December)
- If no drugs are compounded during the reporting period, the OF must *still* submit a report

Section 503B: Drug Product Reporting



- The product report must identify all drugs compounded (even if not distributed) by the OF during the reporting period, including all sterile, non-sterile, and patient-specific drugs
- Prior to an OF inspection, FDA will verify whether or not a firm has submitted the required product reports

Section 503B: Drug Product Reporting



- During the FDA inspection, we will collect documents such as a complete drug production log to verify that a facility has properly reported all drugs compounded during the corresponding reporting period to FDA

Deficiencies in drug product reporting may be documented as an observation on the Form FDA 483

Section 503B: Adverse Drug Reporting



- Under section 503B of the FDCA, outsourcing facilities must submit adverse event reports to FDA in accordance with the content and format requirements established through guidance or regulation under section 310.305 of title 21, Code of Federal Regulations.

Section 503B: Adverse Drug Reporting



- Outsourcing facilities must electronically report to FDA all **serious and unexpected** adverse drug experiences associated with the use of their compounded prescription drug products.
- FDA strongly recommends that outsourcing facilities report all serious adverse drug experiences associated with their compounded drug products. Reporting all serious adverse drug experiences, whether expected or unexpected, would provide important information about potential product quality issues or public health risks associated with drug products compounded by outsourcing facilities.

Section 503B: Adverse Drug Reporting



- Section 310.305 requires that OFs report adverse drug experiences received or otherwise obtained that are both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information along with a copy of the drug product's current labeling.
- The regulation also requires establishment and maintenance of records for 10 years of all adverse drug experiences required to be reported.

Section 503B: Adverse Drug Reporting



During an inspection, FDA will:

- Determine if the OF has received any adverse event reports
- Obtain copies of all adverse event reports received by the OF
- Determine if the OF submitted adverse events to FDA in accordance with content and format requirements established through guidance or regulation under 21 CFR 310.305.

Section 503B: Adverse Drug Reporting



Additionally, during an inspection, FDA will:

- Determine if the OF has adequate written processes for the surveillance, receipt, evaluation, and reporting of adverse events for the drug products it compounds in accordance with the content requirements established through guidance or regulation under section 503B(b)(5) of the FDCA.
- Obtain copies of the OF's adverse event and complaint SOPs

Failure to submit an adverse drug event report to FDA within 15 calendar days of receipt by the OF may be documented as an observation on the Form FDA 483

Section 503B: Labeling



Section 503B includes a condition that outsourcing facilities label their drugs and containers with specific information.

Section 503B: Labeling

- During the inspection, FDA will:
 - Obtain copies of a random sample of drug product labels and container labeling for approximately 10 to 15 products
 - Review the labels and labeling to determine whether or not all the required labeling elements are present

Labeling deficiencies may be documented as an observation on the Form FDA 483

Section 503B: Drugs on the Withdrawn/Removed List

Section 503B prohibits the compounding of drugs that appear on the list of drugs at 21 CFR 216.24. This list identifies drugs that have been withdrawn or removed from the market because the drug products, or components of the drug products, have been found to be unsafe or not effective (section 503B(a)(4))

Section 503B: Drugs on the Withdrawn/Removed List

During an inspection, FDA will review the following information to determine compliance:

- Complete drug product list
- Bi-annual drug product reports submitted by the OF
- Other documents may also be collected, such as batch records and shipping records

Deficiencies may be documented as an observation on the Form FDA 483

Section 503B: Bulk Drug Substances



Section 503B limits the bulk drug substances (BDS) that outsourcing facilities can use in compounding to those that:

1. Are used to compound drugs that appear on FDA's Drug Shortage List at the time of compounding, distribution, and dispensing, or
2. Appear on a list developed by FDA of bulk drug substances for which there is a clinical need (503B Bulks List).

While the 503B Bulks List is being developed, FDA does not intend to take action against an outsourcing facility for compounding a drug using BDS that does not appear on the 503B Bulks List and is not used to compound a drug on the FDA drug shortage list so long as certain conditions are met.

Section 503B: Bulk Drug Substances



Additionally, bulk drug substances used in compounding under section 503B must:

- Be accompanied by a valid certificate of analysis (COA)
- Have been manufactured by an establishment registered with FDA under section 510 of the FDCA, and
- Comply with an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if one exists.

Section 503B: Bulk Drug Substances

During an outsourcing facility inspection, FDA will review the following information to determine compliance with the bulk drug substance condition:

- A list of all drug products produced from bulk drug substances (BDS) to determine eligibility of the BDS for use in compounding
- COAs for each BDS to determine:
 - If each BDS is accompanied by a valid COA
 - If each BDS was manufactured by an establishment registered with FDA under section 510 (including foreign establishments).
- SOPs
- Other documents may also be collected, such as batch records, shipping records, and invoices

Section 503B: Bulk Drug Substances



If the OF compounds drugs using bulk drug substances that are ineligible for use in compounding under section 503B, we may document this as an observation on the Form FDA 483

Section 503B: Essentially a Copy



Under section 503B, an OF may not compound a drug product that is “essentially a copy” of one or more approved drugs.

Section 503B: Essentially a Copy

A compounded drug is "essentially a copy of an approved drug" if:

- It is **identical or nearly identical** to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, it is on FDA's drug shortage list at the time of compounding, distribution, and dispensing; or
- It is not identical or nearly identical, but it **contains a bulk drug substance that is a component of an approved drug** or a marketed drug that is not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug.

Section 503B: Essentially a Copy



FDA does not intend to take action against an outsourcing facility regarding this provision if it fills orders for a compounded drug that is essentially a copy of an approved drug that has been discontinued, for reasons other than lack of safety or effectiveness, and is no longer marketed.

Section 503B: Essentially a Copy



During an outsourcing facility inspection, FDA will:

- Review drug production logs and drug product reports to identify potential copies
- Discuss potential copies with the OF
- Collect other documents related to potential copies such as batch records, prescriptions, purchase orders, product and container labels, invoices, shipping records, documentation of a provider's clinical difference determination, etc.

Section 503B: Essentially a Copy



If the OF appears to be compounding drug products that are essentially a copy of an approved drug or a marketed drug not subject to section 503(b), and not subject to approval in an application submitted under section 505, FDA may cite this deficiency as an observation on the Form FDA 483.

Section 503B: Wholesaling

- Section 503B prohibits the wholesaling of compounded drugs.
- Compounded drugs will not be sold or transferred by an entity (e.g., a commercial distributor) other than the outsourcing facility that compounded such drug.

Section 503B: Wholesaling

During an outsourcing facility inspection, FDA will determine whether the drug products made by the outsourcing facility are distributed to an entity other than a:

- Health care entity;
- Health care practitioner; or
- Patient.

FDA will review and collect documents such as drug orders, sales invoices, customer lists, and distribution/shipping records



Section 503B: Compliance Evaluation

Inspection: Preliminary determination of 503B compliance. Any findings during the inspection may be cited as observations on the Form FDA483.

Post-inspection: Final determination of 503B compliance. Regulatory action, if indicated, will be determined based on this evaluation, in conjunction with the evaluation of CGMP compliance.

THANK YOU!