FDA Inspections of Outsourcing Facilities

What to Expect on an Inspection:

Section 503B Compliance Evaluation

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Outsourcing Facilities (OF)

- Elect to register as an OF
- Comply with all of the conditions of section 503B
- 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 FD&C Act

The human drug products compounded by outsourcing facilities are eligible for exemptions from requirements under three sections of the FD&C Act. 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 FD&C Act 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 your firm has a licensed pharmacist providing oversight of your compounding operations.
- Collect information regarding the role of the pharmacist(s) in your operation (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 your 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 your 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 FD&C Act, 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 FD&C Act, 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!