Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2016
Compounding and Related Documents

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended for entities that are registered or are considering registering with the Food and Drug Administration (FDA or Agency) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[2] Section 503B defines an outsourcing facility, in part, as "a facility at one geographic location or address." FDA has received questions from outsourcing facilities and other stakeholders about the meaning of this term, such as whether multiple suites used for compounding human drugs at a single street address constitute one or multiple facilities, or whether a single location where human drugs are compounded can be subdivided into separate operations compounding under different standards. FDA is issuing this guidance to answer these questions.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 503B, added to the FD&C Act by the Drug Quality and Security Act in 2013, created a new category of compounders called *outsourcing facilities*. Section 503B describes the conditions that must be satisfied for human drug products compounded by or under the direct

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) and in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] A new section 503B was added to the FD&C Act by the Drug Quality and Security Act (DQSA). See Pub. L. No.113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

supervision of a licensed pharmacist in an outsourcing facility to qualify for exemptions from three sections of the FD&C Act:

- section 502(f)(1) (concerning labeling requirements);
- section 505 (concerning drug approval requirements); and
- section 582 (concerning Drug Supply Chain Security Act requirements).

Section 503B(d)(4) of the FD&C Act defines an outsourcing facility as a facility at one geographic location or address that— (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. In addition, an outsourcing facility is not required to be a licensed pharmacy, and it may or may not obtain prescriptions for identified individual patients.[3] Because drugs compounded by outsourcing facilities are not exempt from section 501(a)(2)(B) of the FD&C Act, outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements.[4,5]

One of the conditions that must be met for a compounded drug to qualify for the exemptions under section 503B is that it must be compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance with this section (section 503B(a)(11)). FDA's final guidance document, *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*,[6] clarifies that:

> If you register a facility as an outsourcing facility, you are indicating your intent for the facility's compounded drugs to be regulated under section 503B of the FD&C Act. Under section 503B(a)(11), a compounded drug can only qualify for the exemptions from sections 502(f)(1), 505, and 582 of the FD&C Act if ***all*** of the facility's compounded drugs are compounded in accordance with section 503B (page 4).

The guidance further states that:

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[3] See section 503B(d)(4)(C).

[4] See section 503B(a).

[5] FDA has issued a draft guidance entitled, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* ("Interim CGMP Guidance"). The Interim CGMP Guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

> All FDA guidances are available on the FDA guidance Webpage at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. FDA updates guidances regularly. To ensure that you have the most recent version, please check this web page.

[6] See the guidance *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

> By registering as an outsourcing facility, an entity is electing to have its compounded drugs regulated under section 503B of the FD&C Act, not section 503A. Drugs compounded at an outsourcing facility are not eligible for the exemptions provided in section 503A, even if the conditions in that section are met with respect to the particular drug (page 5).

Some outsourcing facilities compound drugs both according to patient-specific prescriptions as well as in response to orders that are not patient-specific, as section 503B permits them to do.[7] FDA has been asked whether an outsourcing facility can create a separate area within its facility for compounding according to patient specific prescriptions under section 503A, and not follow CGMP requirements in that area. For example, can the drugs be compounded according to patient-specific prescriptions in an adjacent area or room, or in a separate suite, but with the same staff and the same components used in 503B compounding? The CGMP regulations[8] contain requirements for facility design, staff training and competency testing, control of incoming components, aseptic processing, air quality, environmental monitoring, and related requirements designed to ensure the quality of the finished product. The application of different CGMP requirements or the different conditions in section 503A and 503B to commingled compounding activities can cause confusion about what requirements apply and could lead to the production of substandard drugs.

For that reason, and because it is a condition of eligibility for the exemptions in section 503B that all of the drug products compounded in an outsourcing facility must be compounded in accordance with section 503B and with CGMP requirements, this guidance clarifies what constitutes a "facility."

III. POLICY

Section 503B(d) defines an outsourcing facility, in part, as "a facility at one geographic location or address." FDA interprets "facility at one geographic location or address" to mean a business or other entity under one management, direct or indirect, engaged in human drug compounding at a geographic location or street address. The agency considers all activities, equipment, appurtenances, and materials part of such a facility if they are related to human drug compounding under the supervision of the facility's management at the same street address, or in the same building, or in buildings located in close proximity to one another.

As noted above, all drug products compounded in an outsourcing facility are regulated under section 503B[9] and subject to CGMP requirements.[10] These conditions cannot be avoided by segregating or subdividing compounding within an outsourcing facility. For example, even if an

[7] See note 3, supra.

[8] See CGMP regulations at Title 21, Parts 210 and 211 of the Code of Federal Regulations.

[9] See section 503B(a)(11).

[10] See section 503B(a).

outsourcing facility divides its site at one street address into multiple sections with temporary or permanent physical barriers, conducts patient-specific and non-patient specific compounding in different areas (e.g., in different hoods or different rooms), or conducts patient specific and non-patient specific compounding on different days or different times of the day, all of the drug products compounded at that street address must meet the conditions of section 503B or none of the outsourcing facility's drug products would qualify for the exemptions in section 503B. Furthermore, all of the drug products compounded at that street address must be compounded in accordance with CGMP requirements or the outsourcing facility could be cited for violations of section 501(a)(2)(B) of the FD&C Act.

A. Segregating Compounding of Drug Products Under Section 503A From Compounding of Drug Products Under Section 503B

FDA is interpreting facility in this way to be consistent with the intent of section 503B. To be eligible for the exemptions in section 503B(a), a drug product must be compounded in an outsourcing facility in which drugs are compounded only in accordance with section 503B (see section 503B(a)(11)). Outsourcing facilities may or may not obtain prescriptions for identified individual patients, and they are not subject to the interstate distribution restrictions in section 503A. Therefore, the intent of this provision is to ensure that all drugs compounded at an outsourcing facility without the restrictions in section 503A (e.g., the prescription requirement and the restrictions on interstate distribution) are compounded in accordance with CGMP requirements, labeled appropriately, subject to adverse event reporting, and otherwise compounded in accordance with the conditions of section 503B.

If compounding under sections 503A and 503B were to take place in the same geographic location or address, it could appear that all drug products compounded in the outsourcing facility were being made under higher standards, when in fact some or all were made under lesser controls (e.g., the drugs produced under the conditions of 503A would not be produced in accordance with CGMP requirements).

In addition, this definition is designed to prevent commingling of compounding activities under sections 503A and 503B to evade the conditions of section 503B and CGMP requirements. A drug product compounded under section 503A may be indistinguishable from a drug product compounded under section 503B except for the conditions under which it is compounded. It is important to be able to follow the production of drug products compounded in an outsourcing facility to ensure that the products are made under CGMP requirements from the time the bulk drug substances are received at the facility through production of the finished dosage form. If a firm compounds drug products in the same general location under different standards, it will be difficult to ensure that all of the products were made under the correct standards, particularly if the activities are commingled (e.g., because compounding under both standards draws on the same supplies, equipment, personnel, storage, or processing areas), or if compounded drug products are marketed under the same firm name or from the same location. And because drug products compounded under section 503A must be compounded in accordance with a prescription while drug products made under section 503B may or may not be compounded in accordance with a prescription, if the drug products are made in neighboring suites in the same

building, it may be impossible to determine whether a prescription was obtained for the a particular product before it was distributed. The agency's interpretation also provides clarity during inspections with regard to which standards apply to the location that is being inspected.

It is in the best interest of the public health to be clear about the separation between 503A and 503B facilities to ensure that those obtaining the drugs will know the standards under which they were compounded. Furthermore, the public health is best served, and an important objective of section 503B is achieved, if all drug products compounded in an outsourcing facility, whether patient-specific or non-patient specific, are compounded in accordance with CGMP requirements and other requirements imposed in section 503B of the FD&C Act.

B. Compounding Drug Products Under Section 503B and Conventionally Manufacturing Drug Products at the Same Facility

If a conventional manufacturer registers a facility as an outsourcing facility and makes both approved drug products and compounded drug products in the outsourcing facility, the compounded drug products would need to meet the conditions of section 503B to qualify for the exemptions from sections 502(f)(1), 505, and 582.[11]

All of the drug products produced at the facility would be subject to the CGMP requirements in 21 CFR parts 210 and 211. As stated above,[12] FDA has issued a draft guidance that, when finalized, will describe FDA's expectations regarding outsourcing facilities and these CGMP requirements. When a facility both manufactures conventional drug products and compounds drug products under section 503B, the policies described in this guidance would apply to the facility's compounded drug products, except with respect to CGMP requirements that must be implemented throughout a manufacturing facility and cannot be applied differently to different drug products in the same facility, such as environmental monitoring and pressure differential monitoring requirements.

The compounding of drug products under section 503B and the manufacture of approved drug products in the same facility does not present the complications described above regarding the compounding of drug products under sections 503A and 503B in the same facility. For example, an outsourcing facility could not commingle its compounded and approved drug products to avoid manufacturing the approved drug products in accordance with applicable CGMP requirements or to avoid compounding drug products in accordance with the conditions of section 503B. An outsourcing facility's compounded drug products are easily differentiated from its approved drug products; the approved drug products are the subject of approved drug applications and are listed with FDA under section 510 of the FD&C Act, while the compounded drug products are unapproved and are generally not listed. Furthermore, outsourcing facilities

[11] We do not read "compounding" in section 503B(a)(11) of the Act to refer to the manufacture of an approved drug product. Therefore, a drug product may be compounded in an outsourcing facility in accordance with section 503B even if an approved drug product is manufactured in that outsourcing facility not in accordance with section 503B.

[12] See footnote 5.

must label compounded drug products with the statement, "This is a compounded drug,"[13] so purchasers of compounded drug products from an outsourcing facility that also manufactures approved drug products will know that the drug products that they purchased were compounded. FDA verifies during inspections that outsourcing facilities are producing their compounded and approved drug products in accordance with the applicable standards, including that the drug products are labeled appropriately.

[13] See section 503B(a)(10).