Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact Sara Rothman, CDER Office of Unapproved Drugs and Labeling Compliance (OUDLC) at 301-796-3110.

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

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 AND SCOPE

Pharmacies located within a hospital or standalone pharmacies that are part of a health system frequently provide compounded drug products for administration within the hospital or health system. Some of these compounders have registered with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) and others are state-licensed pharmacies subject to section 503A of the FD&C Act. This guidance describes how FDA intends to apply section 503A of the FD&C Act to drugs compounded by licensed pharmacists or physicians in state-licensed hospital or health system pharmacies for use within the hospital or health system.

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

A. Overview

1. Compounding Under the FD&C Act

Sections 503A and 503B of the FD&C Act address human drug compounding.

[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.

Section 503A, added to the FD&C Act by the Food and Drug Administration Modernization Act in 1997, describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State licensed pharmacy or Federal facility, or by licensed physician, to be exempt from the following three sections of the FD&C Act:

- section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements);
- section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and
- section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

A list of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A of the FD&C Act appears in the guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.[2]

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 of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by or under the direct 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);
- section 505; and
- section 582 (concerning track and trace requirements).

The guidance, *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* lists the conditions that are set forth in section 503B of the FD&C Act.

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 CGMP requirements, among other requirements under the FD&C Act (section 503B(a)).[3] In addition, outsourcing facilities will be inspected by FDA on a risk-based schedule (section 503B(b)(4)). An outsourcing facility is not required to be a licensed pharmacy and may or may not obtain prescriptions for identified individual patients.[4]

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[2] 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.

[3] FDA has issued a draft guidance for industry *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act.* Once finalized, that guidance will represent the Agency's thinking on this topic.

[4] Although an outsourcing facility may send prescription drugs to health care facilities without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain subject to the

2. Compounding in Hospitals and Health Systems

Compounded drug products can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as a patient who has an allergy and needs a medication to be made without a certain dye, or an elderly patient or a child who cannot swallow a pill and needs a medicine in a liquid form that is not otherwise available.

Hospital and health system[5] drug compounding and distribution practices vary. For example, some hospital pharmacies compound drugs only for use in the hospital in which the pharmacy is located (e.g., for the treatment of patients admitted to the hospital, or for use in the hospital's emergency room), while other hospital and health system pharmacies compound and distribute their compounded drug products to other facilities within their health system (e.g., to other hospitals, clinics, infusion centers, or long-term care facilities within the health system for administration or dispensing).

In some cases, a hospital or health system pharmacy compounds drugs only after receipt of a prescription or order for an identified individual patient. Hospital and health system pharmacies may also compound drugs and distribute them within the hospital or health system before the receipt of a patient-specific prescription. The hospital or health system then holds the drug products until a patient presents with a need for the drug, for example in an operating room, where emergency procedures cannot be scheduled in advance, or in emergency departments.

Many hospitals and health systems purchase compounded drug products from compounders that have registered with FDA as outsourcing facilities under section 503B of the FD&C Act. Outsourcing facilities are subject to increased federal oversight through FDA inspection on a risk-based schedule, and quality standards CGMP requirements) that help to assure the quality of their compounded drug products. Some hospital and health system compounders have registered with FDA as outsourcing facilities to serve as centralized compounding facilities where drug products are compounded with or without first receiving patient-specific prescriptions, and they then distribute the drugs within their health system or to affiliated health care facilities.

3. Risks Associated with Compounded Drug Products

Although compounded drugs can serve an important need, they pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. In

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requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a prescription drug to a patient without a prescription.

[5] FDA regards a health system as collection of hospitals that are owned and operated by the same entity and that share access to databases with drug order information for their patients. There is no definition of "health system" that applies to all sections of the FD&C Act. However, this is the definition of a "health system" used in section 506F of the Act concerning hospital repackaging of drugs in shortage.

addition, licensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not required to comply with CGMP requirements. Furthermore, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products and seek to qualify for the exemptions under section 503A of the FD&C Act for the drug products they compound because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint such as a report of a serious adverse event or visible contamination.

In 2012, contaminated injectable drug products that a compounding pharmacy shipped to patients and healthcare practitioners across the country caused a fungal meningitis outbreak that resulted in over 60 deaths and over 750 cases of infection.[6] This was the most serious of a long history of outbreaks associated with contaminated compounded drugs. Since the 2012 fungal meningitis outbreak, FDA has investigated numerous other outbreaks and other serious adverse events, including deaths, associated with compounded drugs that were contaminated or otherwise compounded improperly.

FDA has also identified many pharmacies that compounded drug products under insanitary conditions whereby the drug products may have been contaminated with filth or rendered injurious to health and that shipped the compounded drug products made under these conditions to patients and health care providers in large volumes across the country.[7] The longer a compounded sterile drug product that is contaminated is held by a pharmacist or physician before distribution, or the longer it is held in inventory in a healthcare facility before administration, the greater the likelihood of microbial proliferation and increased patient harm.

As noted previously, compounders that elect to become outsourcing facilities must register with FDA, must comply with CGMP requirements, and are inspected by FDA according to a risk-based schedule. This mitigates the risk that their drug products will be contaminated or otherwise made under substandard conditions.

Because compounded drugs have not undergone premarket review for safety, effectiveness, and quality, they should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient. As described further below, the exemptions under sections 503A and 503B of the FD&C Act are only available to compounded drugs that meet certain conditions.

B. The Prescription Requirement in Hospitals and Health Systems

[6] See http://www.cdc.gov/HAI/outbreaks/meningitis.html

[7] See FDA actions, including warning letters and injunctions, related to insanitary conditions at compounding facilities, on FDA's website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm

As described above, compounded drug products are not approved and, therefore, do not undergo premarket review for safety, effectiveness, and quality. In addition, drug products compounded by licensed pharmacists and licensed physicians under section 503A of the FD&C Act are exempt from CGMP requirements. As reflected in the policies set forth below, FDA believes that the conditions in sections 503A and 503B provide important protections to patients, including those treated in a hospital or other facility within a health system, from the risks associated with compounded drugs and help ensure that compounders do not operate like conventional manufacturers. Therefore, FDA generally intends to apply these conditions to compounding in health system and hospital pharmacies, and sets forth an enforcement policy below regarding the prescription requirement in section 503A.

The prescription requirement in section 503A ensures that drug products are only exempt from three key provisions of the FD&C Act designed to assure safety, efficacy, and quality if they are compounded for identified individual patients. However, as stated above, FDA recognizes that a hospital may need to maintain a supply of certain compounded drug products within the hospital but outside of the pharmacy (e.g., in an emergency department or operating room) in anticipation of a patient presenting with a critical need for the drug when there is no time for the hospital pharmacy to compound and provide the drug upon receipt of a prescription or order for that patient.

FDA also recognizes that certain characteristics of hospital pharmacies differentiate them from pharmacies that are not owned and controlled by hospitals, and from conventional manufacturers. For example, generally, the scope of distribution of drug products compounded by hospital pharmacies is limited. Hospital pharmacies usually compound drug products based on orders from practitioners who work in the hospital, distribute the drug products only within the hospital or to related healthcare facilities under common ownership and control and located within close proximity to the hospital, and administer them only to patients within the hospital or healthcare facility. Because the hospital or healthcare facility and the pharmacy are under common ownership and control, the hospital or healthcare facility is responsible for both the compounding of the drug and treatment of the patient, and the cause of any compounding-related adverse events can be more readily identified. FDA believes that the policies set forth in this guidance, based on the way a hospital pharmacy normally functions with regard to compounding for its patients, will prevent hospital pharmacies from operating like conventional manufacturers.

III. POLICY

A. Hospital or Health System Compounding Under Section 503A of the FD&C Act

To qualify for the exemptions under section 503A of the FD&C Act from sections 501(a)(2)(B), 502(f)(1), and 505(a), a drug product compounded by a licensed pharmacist in a state-licensed pharmacy or Federal facility, or by a licensed physician, must be compounded in accordance with all of the provisions of section 503A. Section 503A does not distinguish between stand-alone pharmacies and pharmacies within hospitals and health systems. Therefore, the provisions of section 503A apply to pharmacists, pharmacies, and physicians that compound drugs within a hospital or a health system that is not registered as an outsourcing facility under section 503B.

Drug products compounded by a licensed pharmacist or licensed physician that are not compounded in accordance with all of the provisions of section 503A may be subject to regulatory action for violations of the new drug approval, adequate directions for use, and CGMP requirements of the FD&C Act.

For example, under section 503A, a licensed pharmacist or a licensed physician within a hospital or health system must compound drug products for an identified individual patient. The compounding must either be (a) after the receipt of a valid prescription or order for an identified individual patient or (b) in limited quantities in advance of receipt of a valid prescription or order for an identified individual patient, and the drug must be distributed after receipt of the prescription or order.

However, FDA does not intend to take action if a hospital pharmacy distributes compounded drug products without first receiving a patient-specific prescription or order provided that:

(1) The drug products are distributed only to healthcare facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located within a 1 mile radius of the compounding pharmacy;
(2) The drug products are only administered within the healthcare facilities to patients within the healthcare facilities[8], pursuant to a patient specific prescription or order; and
(3) The drug products are compounded in accordance with all other provisions of section 503A, and any other applicable requirements of the FD&C Act and FDA regulations (e.g., the drug products are not made under insanitary conditions (section 501(a)(2)(A)) or misbranded (e.g., section 502(g)).

The 1-mile radius in our policy is intended to distinguish a hospital campus from a larger health system. As explained in section II.B of this guidance, certain characteristics of hospital pharmacies distinguish them from conventional manufacturers. However, a health system pharmacy that compounds drug products without patient-specific prescriptions for facilities within its health system across a broader geographic area could function as a large manufacturing operation, but without the necessary standards to assure drug quality. If such a pharmacy contaminates or otherwise adulterates or misbrands a compounded drug, the drug has the potential to harm many patients. Outsourcing facilities, which are subject to CGMP requirements and other conditions that help to assure drug quality, can compound and distribute drug products to healthcare facilities nationwide without first receiving prescriptions for identified individual patients.

B. Hospital or Health System Compounding Under Section 503B of the FD&C Act

A compounder can register as an outsourcing facility if it intends to provide compounded drugs to facilities such as other hospitals or clinics outside the 1 mile radius of the pharmacy in which the drug is compounded without first obtaining a prescription for an identified individual patient.

[8] This does not include dispensing a drug product to a patient for use outside the hospital.

To qualify for the exemptions under section 503B from sections 502(f)(1), 505, and 582 of the FD&C Act, hospitals and health system compounders that elect to register with FDA as outsourcing facilities must comply with all of the provisions of section 503B. Outsourcing facilities must also comply with CGMP requirements in section 501(a)(2)(B) of the FD&C Act.