Drug Compounding: FDA Authority and Possible Issues for Congress

Agata Dabrowska
Analyst in Health Policy

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Summary

Drug compounding is a process by which a pharmacist or physician combines, mixes, or alters various drug ingredients to create a drug to meet the unique needs of an individual patient for whom an approved drug may not be appropriate (e.g., due to an allergy to a dye in the product).

The Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes the Food and Drug Administration (FDA) to regulate the manufacturing and sale of drugs in the United States, including compounded drugs. Generally, a drug may not be sold unless the FDA, through its drug approval process, has determined that the drug is safe and effective for its intended use. Although compounded drugs are considered new drugs, it would not be practicable for pharmacies to obtain FDA approval for each drug compounded for an individual patient. Thus, compounded drugs are not evaluated by FDA prior to marketing for safety, effectiveness, or quality.

In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA, P.L. 105-115), which attempted to clarify FDA's authority to regulate compounded drugs. The act set forth, in a new FFDCA Section 503A, the conditions that must be met for a compounded drug to be exempt from certain statutory requirements related to new drug approval. Following the 2012 fungal meningitis outbreak and a series of adverse event reports and quality problems linked to compounding facilities, Congress passed the Drug Quality and Security Act (DQSA, P.L. 113-54). Title I of the DQSA, the Compounding Quality Act (CQA), created a new category of drug compounders called *outsourcing facilities*, a term that describes entities that compound drugs in circumstances that go beyond what 503A compounding pharmacies are allowed to do (i.e., compounding drugs in bulk for use in hospitals and other facilities, referred to as "office-use").

Since the enactment of the CQA, FDA has issued various guidance documents to facilitate implementation of the law and a draft memorandum of understanding (MOU) addressing the interstate distribution of certain compounded drug products. FDA has also increased its enforcement efforts with respect to compounding, conducting over 400 inspections of drug compounders, issuing over 150 warning letters, and overseeing 120 recalls involving compounded drugs. Additionally, FDA has communicated with stakeholders and state regulators via listening sessions, meetings, and information posted on the FDA website. Some stakeholders have found FDA guidance and communication to be helpful; others have reported communication challenges and disagreement with the agency's interpretation of the statutory provisions. These reported challenges have resulted in certain actions by some in Congress, including letters to FDA, report directives, and the introduction of legislation that would amend certain compounding provisions in the FFDCA.

In working to address the issues raised by stakeholders and maintain public health protections, policymakers may consider issues such as patient access, drug quality, and the necessity of compounded drugs. For patients with a legitimate medical need, preserving timely access to compounded medications has been identified as a concern by supporters of office-use compounding. However, in the context of patient safety, drug quality is also a consideration. Compounded drugs are not evaluated by FDA prior to marketing, and pharmacies that compound pursuant to FFDCA Section 503A are not required to register with FDA or report adverse events to the agency. For these reasons, among others, FDA maintains that compounded drugs pose a higher risk than FDA-approved drugs. A third consideration is necessity, specifically whether pharmacies need to compound for office-use. If a hospital, clinic, or health care practitioner wants to keep compounded drugs in stock for office-use, these entities can generally obtain non-patient-specific compounded products from outsourcing facilities that are registered with FDA and subject to more stringent regulatory requirements.

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Background

Drug compounding is a process by which a pharmacist or physician combines, mixes, or alters various drug ingredients to create a drug to meet the unique needs of an individual patient.[1] Compounded drugs include both nonsterile products (e.g., capsules and ointments) and sterile products (e.g., injectable and ophthalmic products). In situations where a product approved by the Food and Drug Administration (FDA) would not be medically appropriate to treat a patient, a pharmacist or physician may formulate and dispense or administer a compounded drug product.[2] For example, a patient with an allergy may need a medication without a certain dye, or an elderly person with a limited ability to swallow may need a medication in liquid form that is not commercially available.

The Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes FDA to regulate the manufacturing and sale of drugs in the United States, including compounded drugs.[3] Generally, a new drug may not be sold unless the FDA, through its drug approval process, has determined that the drug is safe and effective for its intended use. The FFDCA defines a *new drug* to be a drug "the composition of which is such that such drug is not generally recognized ... as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof."[4] Although compounded drugs are considered new drugs, it would not be practicable for pharmacies to obtain approval for each drug compounded for an individual patient.[5] Thus, compounded drugs are not evaluated by FDA prior to marketing for safety or effectiveness and until the 1990s, responsibility for overseeing and regulating drug compounding has generally been left to the states.[6]

Legislative History

Historically, drug compounding has been overseen at the state level by state regulatory bodies such as boards of pharmacy or medicine.[7] During the 1990s, the number of entities engaging in drug compounding increased, as did concern that compounding pharmacies were functioning like drug manufacturers, producing large quantities of compounded drugs not captured by the FDA drug approval process.[8] To address the growing number of compounding entities, in 1992, the FDA issued a Compliance Policy Guide (CPG) for compounding to "delineate FDA's

[1] Food and Drug Administration (FDA), "Compounding and the FDA: Questions and Answers," https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm.

[2] FDA, "FDA's Human Drug Compounding Progress Report: Three Years after Enactment of the Drug Quality and Security Act," January 2017, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.

[3] 21 U.S.C. §301 et seq.

[4] FFDCA §201(p).

[5] See *Thompson v. W. States Medical Ctr.*, 535 U.S. 357, 369 (2002) ("[I]t would not make sense to require compounded drugs created to meet the unique needs of patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs.").

[6] *Id.* at 362.

[7] CRS Report R40503, *FDA's Authority to Regulate Drug Compounding: A Legal Analysis*.

[8] G Gianutos, "Regulatory and Safety Issues in Compounding," *U.S. Pharmacist*, October 2015, https://www.uspharmacist.com/ce/regulatory-and-safety-issues-in-compounding.

enforcement policy on pharmacy compounding."[9] The CPG remained in effect until 1997 when Congress provided statutory authority for portions of it through the FDA Modernization Act (FDAMA, P.L. 105-115). Among other things, FDAMA added new FFDCA Section 503A, "Pharmacy Compounding," designed to clarify FDA's authority to regulate compounded drugs.

FFDCA Section 503A, as created in 1997, set forth the conditions that must be met for a compounded drug to be exempt from three statutory requirements: (1) the new drug approval process, (2) labeling with adequate directions for use, and (3) current good manufacturing practice (CGMP) requirements.[10] Among these conditions is that the drug must be compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician, based on the receipt of a valid prescription for an identified patient. In addition, drug compounding may be performed in limited quantities before the receipt of a valid prescription order if there is a history of receiving orders solely within an established relationship between the pharmacist or physician and the patient or other licensed prescriber.

Moreover, Section 503A included a provision that a drug could be compounded only if a physician or pharmacist did not advertise or promote the compounding of any particular drug, class, or type of drug.[11] The advertising provisions were challenged by several compounding pharmacies, and, in 2002, the provisions were found by the Supreme Court to be unconstitutional.[12] However, the Supreme Court did not address a lower court's conclusion that the advertising prohibition was not severable from the rest of Section 503A and that the entire section was, therefore, invalid.[13] FDA interpreted the Supreme Court's 2002 ruling as invalidating Section 503A in its entirety and issued guidance that it would exercise its enforcement discretion to exempt small pharmacies that only manufactured drugs for individual patients.[14] However, in 2008 another federal appellate court disagreed with FDA's interpretation of the legal effect of the 2002 ruling, holding that Section 503A was severable from the rest of the section and leaving much of it in force.[15] As a result, FDA considered the remaining provisions of Section 503A effective, but only in the states where the 2008 ruling had effect, resulting in a fractured and confusing legal landscape for pharmacy compounding.[16]

In 2012, the interstate distribution of contaminated compounded drug products led to an outbreak of fungal meningitis, resulting in more than 60 deaths and 750 cases of infection.[17] The entity responsible for compounding and shipping the contaminated drugs, the New England Compounding Center (NECC), had been the subject of prior complaints and had been

[9] FDA, Guidance for FDA Staff and Industry, Compliance Policy Guides Manual, Sec. 460.200 Pharmacy Compounding, May 2002, https://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf.

[10] According to FDA, "CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities" to assure "the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations," https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm.

[11] *See* Thompson v. Western States Med. Ctr., 535 U.S. 357, 364-65 (2002).

[12] *Id.* at 377.

[13] *Id*. at 366.

[14] FDA, Guidance for FDA Staff and Industry, Compliance Policy Guides Manual, Sec. 460.200 Pharmacy Compounding, May 2002, https://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf.

[15] *See* Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383, 401 (5th Cir. 2008).

[16] *See Pharmacy Compounding After the Drug Quality and Security Act*, 26 No. 4 Health Law 1, 3-4(2014).

[17] FDA, "FDA's Human Drug Compounding Progress Report: Three Years after Enactment of the Drug Quality and Security Act," January 2017, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.

investigated by both FDA and the Massachusetts state board of pharmacy. However, because, in part, of the uncertainty over the validity of Section 503A, it was not clear who had authority over compounding pharmacies (the state or FDA), and the NECC continued to operate.[18] The NECC outbreak was not an isolated incident, and FDA studies had found quality problems with drugs compounded by other pharmacies, including sub- and super-potent drugs and contamination. According to one report, from 1990 to 2005, FDA became aware of almost 240 serious illnesses and deaths associated with improperly compounded products, with the actual number likely being greater since pharmacies are not required to report adverse events to FDA.[19] A 2014 report published by the Pew Charitable Trusts identified more than 25 reported compounding errors or potential errors linked to 1,049 adverse events between 2001 and 2013.[20]

Following the NECC event and numerous other reports of problems resulting from compounded drugs, Congress passed the Compounding Quality Act (CQA) as Title I of the Drug Quality and Security Act (DQSA; P.L. 113-54). The CQA removed the advertising provisions that the Courts had determined were unconstitutional, clarifying FDA's authority to regulate pharmacy compounding practice under FFDCA Section 503A.[21] The CQA also added a new FFDCA Section 503B and created a new category of drug compounders called *outsourcing facilities*, a term that describes entities that compound sterile drugs in circumstances that go beyond what 503A compounding pharmacies are allowed to do (e.g., compounding drugs in large volumes without obtaining patient-specific prescriptions). Unlike 503A compounding pharmacies, registered outsourcing facilities must comply with CGMPs and are subject to certain registration, reporting, and inspection requirements. The differences between these two types of compounding entities are discussed in more detail below and are summarized in **Table A-1**.

Since the enactment of the CQA, FDA has issued numerous draft and final guidance documents, proposed and final rules, and a draft memorandum of understanding (MOU) to implement the compounding provisions.[22] The agency has communicated with stakeholders and state regulators via annual listening sessions, notice-and-comment guidance development, intergovernmental meetings, and information posted to FDA's website, among other things. Some states have found FDA communication to be helpful, while others have reported several communication challenges.[23] In addition to the issues raised by some states, other stakeholders (e.g., pharmacist and physician groups) have expressed concern with FDA guidance and interpretation of certain compounding-related statutory provisions. In response to these concerns, some Members of Congress have sent letters to FDA, and appropriators have included directives to the agency in report language. In addition, legislation has been introduced that would amend certain compounding provisions in the FFDCA.

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[18] G Gianutos, "Regulatory and Safety Issues in Compounding," *U.S. Pharmacist*, October 2015, https://www.uspharmacist.com/ce/regulatory-and-safety-issues-in-compounding.

[19] FDA, "2006 Limited FDA Survey of Compounded Drug Products," https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm204237.htm.

[20] Pew Charitable Trusts. "U.S. Illnesses and Deaths Associated with Compounded or Repackaged Medications, 2001-Present," September 2014, http://www.pewtrusts.org/~/media/Assets/2014/09/CompoundingOutbreaks_ChartSept2014_v3.pdf?la=en.

[21] FDA, "FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act," January 2017, p. 7, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.pdf.

[22] Ibid.

[23] GAO, "Drug Compounding: FDA has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges," November 2016, http://www.gao.gov/assets/690/681096.pdf.

This report provides an overview of the requirements for compounding pharmacies under FFDCA Section 503A and the requirements for outsourcing facilities under Section 503B. It also discusses FDA activities related to implementation of the compounding provisions, the issues that have been raised by stakeholders, and considerations for policymakers.

Pharmacy Compounding

Historically, pharmacy compounding has been regulated by state entities (e.g., state boards of pharmacy), and the frequency of inspections and level of oversight by state regulators has varied.[24] In response to concerns surrounding the practice of large-scale compounding that resembled drug manufacturing, in 1992, FDA issued guidance explaining the types of compounding that may be subject to enforcement action by the agency.[25] Congress provided statutory authority for portions of the guidance in FFDCA Section 503A.

FFDCA Section 503A

FFDCA Section 503A describes the conditions that must be satisfied for a compounded drug to be exempt from three sections of the FFDCA:[26]

- Section 501(a)(2)(B) concerning compliance with CGMP requirements,
- Section 502(f)(1) concerning the labeling of drugs with adequate directions for use, and
- Section 505 concerning drug approval under a new drug application (NDA) or abbreviated new drug application (ANDA).

If a drug is not compounded in accordance with the conditions set forth in Section 503A, it does not qualify for these exemptions and is subject to the same requirements as conventional manufacturers, including CGMP, labeling with adequate directions for use, and new drug approval requirements.

Pursuant to Section 503A, a drug product is exempt from the above requirements if it is compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician, for an identified patient based on the receipt of a valid prescription, or in limited quantities before the receipt of a prescription for an identified patient. In these cases, the compounding must be based on a history of the licensed pharmacist or physician receiving prescription orders for the compounding of the product, and the orders must have been "generated solely within an established relationship" between the licensed pharmacist or physician and either such patient for whom the prescription will be provided or the practitioner who will write the prescription.[27]

[24] National Conference of State Legislatures (NCSL), "State Regulation of Compounding Pharmacies," October 1, 2014, http://www.ncsl.org/research/health/regulating-compounding-pharmacies.aspx.

[25] FDA, Guidance for FDA Staff and Industry, Compliance Policy Guides Manual, Sec. 460.200 Pharmacy Compounding, May 2002, https://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf.

[26] FFDCA §503A(a).

[27] FFDCA §503A(a).

A drug product may be compounded if the licensed pharmacist or licensed physician

- compounds using bulk drug substances[28] that comply with specified requirements;[29]
- compounds using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph, if a monograph exists, as well as the USP chapter on pharmacy compounding;[30]
- does not compound a product that appears on the Health and Human Services Secretary's list of drugs that have been withdrawn or removed from the market because they were found to be unsafe or not effective;[31] and
- does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.[32]

A drug product may be compounded if it

- has not been identified by the Secretary, by regulation, as presenting "demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product,"[33] and
- is compounded in a state that has entered into an MOU with the Secretary addressing "the interstate distribution of inordinate amounts of compounded drug products interstate" and provides for appropriate state investigations of complaints about distribution outside the state. If a drug product is compounded in a state that has not entered into an MOU with the Secretary, the pharmacist, pharmacy, or licensed physician may not distribute or cause to be distributed compounded drugs outside that state in quantities that exceed 5% of the total prescriptions dispensed or distributed by that pharmacy or physician.[34]

[28] 21 C.F.R. 207.3 defines a bulk drug substance as an active pharmaceutical ingredient (API). 21 C.F.R. 207.1 defines an API as "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."

[29] Pursuant to FFDCA §503A(b)(1)(A), the bulk drug substance must comply with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph if such monograph exists, and the USP chapter on pharmacy compounding. If such monograph does not exist, the bulk drug substance must be a component of an FDA-approved drug. If a monograph does not exist and the drug substance is not a component of an approved drug, the bulk drug substance must be on the Secretary of Health and Human Services' of bulk drug substances, developed through regulation. In addition, bulk drug substances used in compounding under 503A must be manufactured by an establishment registered with FDA under FFDCA §510 and must be accompanied by a valid certificate of analysis. The law requires the Secretary to issue regulations to implement the provision regarding pharmacy compounding using bulk drug substances.

[30] FFDCA §503A(b)(1)(B).

[31] FFDCA §503A(b)(1)(C).

[32] FFDCA §503A(b)(1)(D).

[33] FFDCA §503A(b)(3)(A).

[34] FFDCA §503A(b)(3) requires the Secretary, in consultation with the National Association of Boards of Pharmacy (NABP), to develop a standard MOU for use by the states that "addresses the interstate distribution of inordinate amounts of compounded drug products interstate" and provides for appropriate state investigations of complaints about distribution outside the state.

Compounding pharmacies are not required to report to FDA adverse events or the type of drugs being compounded. Compounding pharmacies are not required to register with FDA, and the agency generally does not inspect them unless it is for cause (e.g., in response to adverse event reports or if there is visible contamination). FDA has the authority to inspect, "at reasonable times and within reasonable limits and in a reasonable manner," pharmacies and "all pertinent equipment, finished and unfinished materials, containers, and labeling therein," with some limitations.[35] Although compounded drugs subject to Section 503A are exempt from CGMP requirements, other FFDCA requirements apply, such as the prohibition against adulteration and misbranding.[36]

Outsourcing Facility Compounding

In response to the 2012 fungal meningitis outbreak and a series of adverse event reports and quality problems linked to compounding facilities, Congress held a series of hearings, which led to the enactment of the CQA in November 2013. The law established FFDCA Section 503B and created a new category of drug compounders called *outsourcing facilities*. Entities that compound drugs in ways that exceed the circumstances described in Section 503A (i.e., facilities that compound drugs in bulk for use in hospitals or other facilities) may register with FDA as such. An outsourcing facility is defined as a facility at one geographic location or address that is engaged in the compounding of sterile drugs, has elected to register as an outsourcing facility, and complies with all the requirements of Section 503B.[37]

FFDCA Section 503B

A registered outsourcing facility that complies with the requirements described in Section 503B is exempt from three sections of the FFDCA:[38]

- Section 502(f)(1) concerning labeling of drugs with adequate directions for use,
- Section 505 concerning drug approval under an NDA or ANDA, and
- Section 582 concerning track and trace requirements.

Unlike 503A compounding pharmacies, outsourcing facilities are not exempt from CGMP requirements. If a drug is not compounded in accordance with the conditions of Section 503B, it does not qualify for these exemptions and would be subject to the same requirements as conventional drug manufacturers, including the requirements for labeling, new drug approval and supply chain management. Section 503B includes requirements that focus on the drug and the outsourcing facility.

[35] FFDCA §704(a). The CQA also added new FFDCA Sections 744J and 744K, authorizing the Secretary to collect annual establishment and reinspection fees from outsourcing facilities.

[36] Pursuant to FFDCA §501(a)(2)(A), a drug shall be deemed 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." For examples of insanitary conditions, see FDA draft guidance, *Insanitary Conditions at Compounding Facilities*, August 2016, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm514666.pdf. A drug shall be deemed misbranded if, among other things, "its labeling is false or misleading in any particular" (FFDCA §502(a)).

[37] FFDCA §503B(d)(4)(A).

[38] FFDCA §503B(a).

A drug may be compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility if

- it is not compounded using bulk drug substances unless they comply with specified limitations;[39]
- it is compounded using ingredients (other than bulk drug substances) that comply with the applicable USP or NF monograph, or any other compendium or pharmacopeia recognized by the Secretary;[40]
- it does not appear on the Secretary's list, established by regulation, of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective;[41]
- it is not "essentially a copy of one or more approved drugs";[42]
- it does not appear on the Secretary's list, established by regulation, of "drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients" unless compounding is done "in accordance with all applicable conditions identified on the list ... as conditions that are necessary to prevent" such difficulties;[43]
- the drug is subject to a Risk Evaluation and Mitigation Strategy (REMS), the outsourcing facility must demonstrate a plan to use "controls comparable to the controls applicable" under the REMS;[44]
- it will not be sold or transferred by any entity other than the outsourcing facility that compounded it;[45]
- it is compounded in an outsourcing facility that had paid fees pursuant to FFDCA Section 744K;[46]

[39] Pursuant to FFDCA §503B(a)(2), an outsourcing facility may not compound using bulk drug substances unless the bulk drug substance (1) appears on a list, established by the Secretary, identifying bulk drug substances for which there is a clinical need, or the drug compounded from such bulk drug substance appears on the drug shortage list under FFDCA §506E; (2) complies with an applicable monograph under the USP, NF, or other compendium or pharmacopeia recognized by the Secretary, if one exists; (3) is manufactured by an establishment registered with FDA under FFDCA §510; and (4) is accompanied by a valid certificate of analysis.

[40] FFDCA §503B(a)(3).

[41] FFDCA §503B(a)(4).

[42] FFDCA §503B(a)(5). Section §503B(d)(2) defines the term "essentially a copy of an approved drug" to mean "(A) a drug that 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, the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing; or (B) a drug, a component of which is 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."

[43] FFDCA §503B(a)(6).

[44] FFDCA §503B(a)(7). Pursuant to FFDCA §505-1, FDA may require a REMS when the agency determines that it is necessary to ensure that the benefits of a drug outweigh its risks. A REMS may include instructions to patients and clinicians, or elements to assure safe use (such as required training or certification of prescribers, pharmacies, or healthcare settings; laboratory tests; or patient monitoring or registries). See CRS Report R44810, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development*.

[45] FFDCA §503B(a)(8).

- the drug label bears the statement "this is a compounded drug" or a comparable statement; the name, address, and phone number of the outsourcing facility; and the following specified information with respect to the drug: the lot or batch number; the established name of the drug; dosage form and strength; statement of quantity or volume; date that the drug was compounded; expiration date; storage and handling instructions; National Drug Code (NDC) number, if available; the statement "not for resale," and if the drug is dispensed or distributed other than pursuant to a prescription for an individual identified patient, the statement "Office-use Only," as well as a list of active and inactive ingredients by established name and quantity or proportion of each ingredient;[47] and
- the container "from which individual units of the drug are removed for dispensing or administration" includes a list of active and inactive ingredients (if there is not space on the label), adverse event reporting information, and directions for use (e.g., dosage and administration).[48]

To qualify for the exemptions under Section 503B, an entity that elects to register as an outsourcing facility must

- register with the Secretary annually (electronically, unless waived) and indicate whether it intends to compound a drug that appears on FDA's drug shortage list;[49]
- submit a report to the Secretary twice a year identifying the drugs compounded, including the active ingredient and its source, National Drug Code numbers, and other specified information;[50]
- be subject to inspection (pursuant to FFDCA Section 704, which applies to manufacturing facilities) according to a risk-based schedule based on factors such as the compliance history of the outsourcing facility, inherent risk of the drugs being compounded, and other specified factors;[51] and
- submit adverse event reports to FDA.[52]

Outsourcing facilities may compound drugs with or without a patient-specific prescription.[53] To meet the definition of an outsourcing facility, an entity must compound sterile drugs and may compound nonsterile drugs as well.[54]

(...continued)

[46] FFDCA §503B(a)(9).

[47] FFDCA §503B(a)(10)(A).

[48] FFDCA §503B(a)(10)(B).

[49] FFDCA §503B(b)(1) and (3).

[50] FFDCA §503B(b)(2).

[51] FFDCA §503B(b)(4). While 503A compounding pharmacies are subject to "general" inspections, 503B outsourcing facilities are subject to enhanced FDA inspections, which include inspection of the facilities' records.

[52] FFDCA §503B(b)(5).

[53] FFDCA §503B(d)(4)(C).

[54] FFDCA §503B(d)(4)(A). FFDCA §503B(d)(5) defines a sterile drug as a "drug that is intended for parenteral administration [i.e., by a route other than the gastrointestinal tract], an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law."

CQA Implementation and Possible Issues for Congress

Since the enactment of the CQA, FDA has issued numerous draft and final guidance documents to explain its policy on certain requirements and facilitate implementation of the compounding provisions under FFDCA Sections 503A and 503B. The agency also has issued a draft MOU addressing the interstate distribution of certain compounded drug products. Additionally, since enactment of the CQA, FDA has conducted over 400 inspections of drug compounders, issued more than 150 warning letters advising compounders of violations of federal law, and overseen more than 125 recall events.[55] FDA also has communicated with stakeholders and state regulators via annual listening sessions, a notice-and-comment guidance development process, intergovernmental meetings, and information posted to the FDA website, among other things. As of December 2017, FDA's website lists 73 entities that have registered as outsourcing facilities.[56] Because 503A compounding pharmacies are not required to register with FDA and are generally overseen by state regulatory bodies, it is difficult to quantify the total number of these entities.

In November 2016, the Government Accountability Office (GAO) published a report on drug compounding that included results from a survey of state pharmacy regulatory bodies. According to the report, most states that participated in the intergovernmental meetings found them to be helpful.[57] Of the 40 states that reported having had compounding-related communication with FDA, 60% (24 states) reported being very or somewhat satisfied with the communication, whereas 23% (9 states) reported being very or somewhat dissatisfied. Respondents in 15 states reported experiencing one or more communication challenges with FDA, citing issues such as timeliness and difficulties getting the agency to respond to requests for information.[58] Other stakeholders, including certain compounding pharmacist and physician groups, have voiced concern regarding FDA's interpretation and implementation of certain statutory provisions (e.g., the prescription requirement and draft MOU). Stakeholders in this space include state regulators, pharmacists and physicians who compound drugs, outsourcing facilities, and the groups that represent these entities. In response to the issues flagged by stakeholders, Congress has responded by sending letters to FDA, issuing directives in report language, and introducing legislation to amend the statutory provisions concerning compounding.

The following sections discuss some of the issues that have been raised in response to FDA's implementation of the compounding provisions, as well as the actions taken by Congress. This is not a comprehensive list of all of the issues flagged by interested parties, but rather a summary of selected issues that have been the subject of congressional letters to the agency, report directives, and legislation. The three issues discussed are: (1) the prescription requirement and compounding for office-use, (2) the draft MOU addressing interstate distribution of compounded drugs, and (3) inspections under CGMP requirements.

[55] FDA Statement, "Statement from FDA Commissioner Scott Gottlieb, M.D., on the importance of the Drug Quality and Security Act and overseeing the safety of compounded drugs," June 26, 2017, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm564681.htm.

[56] FDA, "Registered Outsourcing Facilities," accessed December 20, 2017, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm.

[57] GAO, "Drug Compounding: FDA has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges," November 2016, http://www.gao.gov/assets/690/681096.pdf.

[58] Ibid.

The Prescription Requirement and Compounding for Office-Use

As previously discussed, to qualify for the exemptions under FFDCA Section 503A, a drug product must satisfy certain statutory conditions.[59] Generally, under Section 503A, a drug product may be compounded upon the receipt of a valid prescription for an identified patient, or in limited quantities before the receipt of a prescription for an identified patient, based on a history of prescription orders for that drug product within an established relationship between the pharmacist, patient, and the prescriber (see "FFDCA Section 503A").[60] This second circumstance is sometimes referred to as *anticipatory compounding*.

With respect to the provision for anticipatory compounding, there has been some disagreement as to whether it authorizes compounding for office-use. While anticipatory compounding refers to compounding done in limited quantities before the receipt of a patient-specific prescription, office-use refers to compounding that is not for an identified, individual patient pursuant to a prescription, but rather for the purpose of keeping compounded drugs in stock for use by hospitals, clinics, or health care practitioners.[61] In some cases, for example, a provider may need to administer a compounded drug to a patient immediately rather than writing a prescription and waiting for the drug product to be compounded and shipped to the provider. FDA has generally taken the position that 503A pharmacies may not compound for office-use.[62]

In FY2016 report language (H.Rept. 114-205), the House Committee on Appropriations directed FDA to "issue a guidance document on how compounding pharmacists can continue to engage in 'office-use' compounding before the receipt of a patient-specific prescription consistent with the provisions of 503A within 90 days after the enactment of this Act." On April 15, 2016, the agency issued draft guidance stating that the law provides for drug compounding in two situations: (1) in response to a patient-specific prescription, or (2) in limited quantities, pursuant to the anticipatory compounding provision under section 503A and in accord with the limitations proposed by FDA in the draft guidance.[63] The draft guidance did not allow for office-use compounding under Section 503A, stating that hospitals, clinics, and health care practitioners can obtain non-patient-specific compounded drugs to keep in stock for office-use from outsourcing facilities registered under Section 503B.[64] The agency further explained that the limitations on anticipatory compounding differentiate traditional compounding by licensed pharmacists or physicians from compounding by registered outsourcing facilities, which are subject to additional FDA requirements, including compliance with CGMPs, registration and reporting, and inspections.

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[59] These exemptions are from three sections of the FFDCA: Section 501(a)(2)(B) concerning CGMP requirements, Section 502(f)(1) concerning the labeling of drugs with adequate directions for use, and Section 505 concerning premarket approval of new drug applications.

[60] FFDCA §503A(a).

[61] FDA, *Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act*, draft guidance issued April 2016 and final guidance issued in December 2016, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf.

[62] Ibid.

[63] FDA states that it does not consider a compounder to have exceeded the limited quantity conditions if (1) the compounder holds for distribution no more than a 30-day supply of a particular compounded product to fill valid prescriptions it has not yet received and (2) "the amount of the supply is based on the number of valid prescriptions that the compounder has received for identified individual patients in a 30-day period over the past year that the compounder selected." The guidance *Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act* provides examples to illustrate the agency's policy on anticipatory compounding.

[64] FDA, *Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf.

These additional requirements reduce the risk of quality problems such as production mistakes or contamination.[65]

In FY2017 report language (H.Rept. 114-531), the House Appropriations Committee wrote that compounding for office-use is authorized in the majority of states and was intended to be allowed under the CQA. The committee directed FDA to issue a final guidance that provides for office-use compounding of drugs "in appropriate circumstances."

In December 2016, FDA finalized the guidance, maintaining that compounding for office-use is not allowed under Section 503A and that the prescription requirement is necessary to ensuring that compounding is based on individual patient need, and that the requirement helps to distinguish between drug compounding and conventional manufacturing.[66] FDA also responded to the committee's report language, stating that "the policies set forth in FDA guidance documents implement the statutory provisions that provide for compounding and distribution of drugs for office-use by outsourcing facilities under section 503B ... and anticipatory compounding by compounders under section 503A."[67]

It remains to be seen how the issue of compounding for office-use will be resolved. Although the FDA has maintained its position that compounding for office-use is not permitted under current law, legislation introduced in Congress would, among other things, allow office-use compounding if permitted by the state in which the compounding is being performed.[68] According to a GAO survey of state pharmacy regulatory bodies, respondents in 27 states reported that compounding for office-use is authorized in their state. Of those, respondents in four states added that only FDA-registered outsourcing facilities may compound for office-use, and a respondent in one state reported that the state was working to prohibit this practice "to align with federal restrictions on pharmacies under section 503A."[69] Some Members of Congress have sent letters to the FDA, stating that Congress did not intend to prohibit office-use compounding.[70]

Interstate Distribution of Compounded Drugs

Another issue flagged by some stakeholders has been FDA's draft MOU addressing the distribution of inordinate amounts of compounded drug products interstate.[71] Section 503A prohibits a pharmacist, pharmacy, or physician from distributing compounded drug products outside of the state in which they are compounded in quantities that exceed 5% of the total prescription orders dispensed or distributed by that pharmacy or physician, unless the state performing the compounding has entered into an MOU with the Secretary. Pursuant to the statute,

[65] Ibid.

[66] FDA, *Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act*, draft guidance issued April 2016 and final guidance issued in December 2016, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf.

[67] FY2018 FDA Justification of Estimates for Appropriations Committees, pg. 250, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM559923.pdf.

[68] See, for example, H.R. 2871 in the 115th Congress.

[69] GAO, "Drug Compounding: FDA has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges," November 2016, http://www.gao.gov/assets/690/681096.pdf.

[70] See, for example, the letter to FDA, from Congressman Buddy Carter and other members of Congress, May 23, 2017, https://buddycarter.house.gov/uploadedfiles/officecompounding.pdf, and the letter to FDA, from Congressman Chris Stewart and other members of Congress, June 20, 2016, http://stewart.house.gov/sites/stewart.house.gov/files/Office%20Use%20Letter%20FDA-Final%5B1%5D.pdf.

[71] The statute delegates defining the term *inordinate amounts* to the Secretary of Health and Human Services.

the MOU must address the distribution of inordinate amounts of compounded products interstate and provide for appropriate investigation by a state agency of complaints relating to compounded drug products distributed interstate.[72] The law further requires the Secretary, in consultation with the National Association of Boards of Pharmacy (NABP), to develop such an MOU for use by the states.[73]

In February 2015, FDA issued a draft MOU, which if finalized, would establish an agreement between FDA and a state regarding the distribution of inordinate amounts of compounded human drug products interstate. The draft MOU defines *inordinate amounts* and addresses how states would handle complaints about drug products compounded by pharmacies within their borders.[74] While the law created a 5% limit on interstate distribution for 503A pharmacies operating in a state that has not entered into an MOU with FDA,[75] the draft MOU proposes a 30% upper limit for 503A pharmacies operating in a state that enters into the MOU. The MOU and the interstate distribution restrictions do not apply to registered outsourcing facilities under section 503B. As of the date of this report, FDA has not issued a final MOU.[76]

One criticism of the draft MOU is the inclusion of the act of *dispensing* in the definition of *distribution*.[77] FFDCA Section 503A does not define these two terms; however, in the draft MOU, FDA defines *distribution* to mean "that a compounded human drug product has left the facility in which the drug was compounded. Distribution includes delivery or shipment to a physician's office, hospital, or other health care setting for administration and dispensing to an agent of a patient or to a patient for the patient's own use."

According to one pharmacy group, by including the word *dispensing* within the definition of *distribution*, FDA is attempting to regulate not only interstate *distribution* of compounded drugs, but also interstate *dispensing* of compounded drugs, the latter of which has traditionally been overseen by state regulators.[78] The group states that the statute clearly distinguishes between the acts of dispensing and distribution, and authorizes FDA to issue an MOU that addresses only the interstate distribution of inordinate amounts of compounded drugs. As evidence of this distinction, the group also states that in the Controlled Substances Act (CSA) and FDA regulations, the terms *dispense* and *distribute* refer to different activities.[79] Conversely, the FDA's

[72] FFDCA §503A(b)(3)(B)(i).

[73] Ibid.

[74] Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products between the State of [insert STATE] and the U.S. Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM434233.pdf.

[75] FFDCA §503A(b)(3)(B)(ii).

[76] FDA, Food and Drug Law Institute (FDLI) Presentation titled "Title I Implementation- Pharmacy Compounding in 2016," see http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM491054.pdf.

[77] Compounders on Capitol Hill, "Support Letter to Chairman Chaffetz and Ranking Member Cummings to Request House Oversight and Government Reform Hearing on FDA Implementation of the DQSA," https://c.ymcdn.com/sites/iacp.site-ym.com/resource/resmgr/CCH_2016/FINAL_House_Oversight_Hearin.pdf.

[78] International Academy of Compounding Pharmacists (IACP), Docket No. FDA-2014-N-1459, July 20, 2015.

[79] As provided by IACP in the letter to FDA, CSA §102(10) [21 U.S.C. §802(10)] defines *dispense* to mean "to deliver a controlled substance to an ultimate user or research subject by, or pursuant to the lawful order of, a practitioner, including the prescribing and administering of a controlled substance and the packaging, labeling or compounding necessary to prepare the substance for such delivery." CSA §102(11) [21 U.S.C. §802(11)] defines *distribute* to mean "to deliver (other than by administering or dispensing) a controlled substance or a listed chemical." FDA regulations at 21 C.F.R. §208.3(b) define *dispense to patients* to mean "the act of delivering a prescription drug product to a patient or an agent of the patient either: (1) by a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct (continued...)

position has been that 503A pharmacies, unlike outsourcing facilities, are primarily overseen by the states, are exempt from CGMP requirements, and are not required to register with FDA. If a substantial proportion of drugs compounded by 503A pharmacies are distributed outside of a state's borders, adequate regulation of those drugs can be challenging, and may make it more difficult to investigate and address multistate outbreaks.[80] In 2012, the interstate distribution of contaminated compounded drug products resulted in an outbreak of fungal meningitis, with an estimated 14,000 patients receiving injections from lots of contaminated drug product.[81]

In the explanatory statement accompanying the FY2017 omnibus, Congress stated that it "did not intend to include dispensing of compounded drugs over state lines within the scope of the MOU," and allowed FDA to only regulate distribution.[82] Legislation has also been introduced in the 115th Congress that would exclude from the definition of the terms *distribute* or *distribution* the act of dispensing a compounded drug product under Section 503A.[83]

The definition of the term *distribution* is significant because of its relationship to the issue of compounding for office-use. While FDA's view is that the agency's draft MOU does not alter the prescription requirement under 503A, others maintain that it goes against congressional intent. More specifically, some argue that by distinguishing between the two terms, Congress intended to exclude the act of dispensing from the definition of distribution, therefore allowing compounding for office-use.[84]

Pharmacy Inspections Under CGMP Requirements

The FDA's implementation of CQA has raised another issue: the inspection of compounding entities under CGMPs. Unlike outsourcing facilities, 503A compounding pharmacies are not subject to CGMP requirements, are not required to register with FDA, and are not routinely inspected by the agency.[85] Thus, the majority of compounding facilities in the United States do not register with FDA and, unless they elect to become outsourcing facilities, they are primarily overseen by state regulatory authorities. This means that FDA often is unaware of potential problems with the drug products or facility conditions unless the agency receives a complaint (e.g., a report of a serious adverse event or visible contamination).[86]

(...continued)

supervision; or (2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner." FDA regulations at 21 C.F.R. §208.3(c) define *distribute* to mean "the act of delivering, other than by dispensing, a drug product to any person."

[80] 80 *Federal Register* 8874. See also FDA presentation, "Draft Standard MOU," https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM446238.pdf.

[81] FDA, "FDA's Human Drug Compounding Progress Report, Three Years after Enactment of the Drug Quality and Security Act," January 2017, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.pdf.

[82] *Congressional Record*, vol. 163, part 76 (May 3, 2017), p. H3334.

[83] See, for example, H.R. 2871 in the 115th Congress, which would define *dispense* to mean "the act of the drug product leaving the facility in which it was compounded for delivery to a patient, patient's agent, or health care facility (including a hospital, physician's office, or other health care setting) pursuant to a valid prescription order for an identified patient."

[84] International Academy of Compounding Pharmacists (IACP), Docket No. FDA-2014-N-1459, July 20, 2015.

[85] FDA, draft guidance, *Insanitary Conditions at Compounding Facilities*, August 8, 2016, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf.

[86] Ibid.

Compounding pharmacies are not exempt from the prohibition on preparing drugs under insanitary conditions, and FDA has the authority to inspect these pharmacies, within certain limitations.[87] As of June 1, 2017, since the enactment of the CQA, the agency had conducted more than 400 inspections of compounding entities, the majority of which were 503A compounding pharmacies. FDA has issued more than 150 warning letters advising compounders of significant violations of federal law and more than 50 letters referring inspection findings to state regulatory agencies. In addition, the FDA has overseen over 125 recalls involving compounded drugs and worked with the Department of Justice on a number of civil and criminal enforcement actions.[88]

One issue raised by stakeholders is that FDA has been inspecting 503A compounding pharmacies under CGMP standards, from which they are exempt. Upon conducting an inspection, the agency issues an FDA Form-483 ("483"), which lists the observations identified during inspection.[89] Observations may include deficiencies related to the prohibition on insanitary conditions or deviations from drug production practices that could lead to quality problems. A 483 does not represent a final determination by FDA regarding a firm's compliance. Some pharmacy groups have said that FDA has listed deviations from CGMP as observations on the 483, even though 503A pharmacies are not subject to CGMP requirements.[90] In response to concern from stakeholders, House appropriators wrote (H.Rept. 114-531):

> The Committee reminds the FDA that compounding pharmacies are not drug manufacturers, but rather, are state licensed and regulated health care providers that are inspected by state boards of pharmacy pursuant to state laws and regulations that establish sterility and other standards for the pharmacies operating within their states. Compounding pharmacies are more appropriately inspected using USP standards or other pharmacy inspection standards adopted by state law or regulation in the state in which a pharmacy is licensed.

FDA has stated that it identifies CGMP deviations on the 483 only when it has evidence to suggest that the compounding pharmacy does not qualify for the exemptions under Section 503A because it does not meet the statutory requirements.[91] For example, if a pharmacy is engaging in compounding without a patient-specific prescription and not within the limitations of anticipatory compounding, it does not satisfy the conditions of Section 503A and therefore does not qualify

[87] FFDCA §704(a).

[88] FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D., on the importance of the Drug Quality and Security Act and overseeing the safety of compounded drugs," June 26, 2017, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm564681.htm.

[89] FDA, FDA Form 483 Frequently Asked Questions, https://www.fda.gov/ICECI/Inspections/ucm256377.htm.

[90] FDA Law Blog, "FDA Releases "Notice" Advising of a Change in Inspections of Pharmacies Compounding Drug Products within FDCA Section 503A: Let's Watch What Happens Next…," July 20, 2016, http://www.fdalawblog.net/2016/07/fda-releases-notice-advising-of-a-change-in-inspections-of-pharmacies-compounding-drug-products-with/; American Pharmacists Association, "FDA announces major change in pharmacy inspections," July 18, 2016, https://www.pharmacist.com/sites/default/files/files/APhA%20Comments%20to%20FDA%20re%20Rx%20Requirement-%20FINAL%20071816.pdf; and support letter to Chairman Chaffetz and Ranking Member Cummings to Request House Oversight and Government Reform Hearing on FDA's Implementation of the DQSA, https://c.ymcdn.com/sites/iacp.site-ym.com/resource/resmgr/CCH_2016/FINAL_House_Oversight_Hearin.pdf.

[91] FDA, "Notice to Industry regarding procedure for inspections of entities that are seeking to compound human drugs in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act," July 11, 2016, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm510684.pdf. See also FY2018 FDA Justification of Estimates for Appropriations Committees, p. 251, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM559923.pdf.

for the exemptions under that section, including the CGMP exemption. In response to stakeholder input, FDA issued a notice regarding a change in inspection procedures of 503A pharmacies, stating that it will now make a preliminary assessment regarding a facility's compliance with Section 503A before closing the inspection.[92] Per the notice, the 483 will not include observations that represent CGMP deviations unless the investigator determines that the pharmacy does not meet the conditions of Section 503A. After the inspection, FDA is to review the evidence to evaluate whether the facility compounds all of its drugs in accordance with certain conditions of Section 503A and other applicable provisions of federal law, as specified.[93] Despite this notice, at least one pharmacy stakeholder group alleges that FDA has continued to apply 503B outsourcing facility standards during inspection of 503A compounding pharmacies and to cite CGMP noncompliance.[94]

Policy Considerations

In working to address the issues raised by stakeholders and maintain public health protections, policymakers may consider issues such as patient access to compounded drugs, drug quality, and necessity of compounding. With respect to patient access, some patients have a legitimate medical need for compounded drugs, whereby an FDA-approved product would not be medically appropriate treatment. For these patients, preserving timely access to compounded medications is important, a concern raised by those who support compounding for office-use.[95]

Drug quality is also a consideration, particularly in the context of patient safety. Pharmacies that compound pursuant to Section 503A are exempt from CGMP requirements, are not subject to FDA registration, and are generally not inspected by the agency unless it is for cause. Because these pharmacies are not required to register with FDA, the agency is often unaware of potential issues with the compounded products or compounding practices until it receives a complaint or adverse event report, which pharmacies are not required to submit. For these reasons, among others, FDA maintains that compounded drugs pose a higher risk than FDA-approved drugs.[96]

A related policy consideration is necessity. As discussed, FDA's interpretation of the prescription requirement has been met with some opposition, and certain stakeholders have argued that compounding for office-use by 503A pharmacies should be allowed because health care providers need to keep certain compounded drugs in stock for immediate administration. However, FDA and outsourcing facility groups have generally disagreed that 503A pharmacies need to compound for office-use.[97] Outsourcing facilities created by the CQA are able to produce in bulk while also

[92] Ibid.

[93] Ibid.

[94] Statement of the American Pharmacists Association, Stacie S. Maass, Senior Vice President, Pharmacy Practice and Government Affairs, FDA Listening Session: Drug Compounding, June 5, 2017, https://www.pharmacist.com/sites/default/files/files/FDA%20Compounding%20Listening%20Session%20June%205%2017%20Final.pdf.

[95] Comment from the American Academy of Dermatology Association, RE: [Docket No. FDA-2016-D-0269] Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry, July 2016.

[96] FDA, *Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act*, draft guidance issued April 2016 and final guidance issued in December 2016, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf.

[97] FY2018 FDA Justification of Estimates for Appropriations Committees, p. 250, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM559923.pdf. See also, Comments from the Outsourcing Facility Association, Re: Docket No. FDA-2016-D-0269: Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act, March 29, 2017.

providing additional patient protections since they are subject to more stringent regulatory requirements; as such, allowing 503A compounding pharmacies to produce for office-use may not be necessary. If a hospital, clinic, or health care practitioner wants to keep compounded drugs in stock for office-use, they can generally obtain non-patient-specific compounded drugs from outsourcing facilities that are registered under Section 503B. FDA also has stated that allowing pharmacies to compound without a patient-specific prescription may provide less incentive for such entities to register as outsourcing facilities.[98] To help health care providers determine which outsourcing facilities compound the drugs they need for purposes of office-use, FDA has issued a list of the drugs that registered outsourcing facilities have produced.[99] Several other stakeholders, including the pharmaceutical industry, have generally supported FDA's prescription requirement guidance.[100]

[98] FY2018 FDA Justification of Estimates for Appropriations Committees, pg. 250, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM559923.pdf.

[99] FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D., on new efforts to encourage compounding of better quality drugs under DQSA and help health care professionals access compounded medications needed for patient care from outsourcing facilities," September 26, 2017, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577590.htm.

[100] Comments from the Biotechnology Innovation Organization (BIO), Re: Docket No. FDA-2016-D-0269: Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act, July 18, 2016. See also, PEW, Comments on Draft Guidance Documents for Industry Regarding Compounding Under the Federal Food, Drug, and Cosmetic Act Docket Nos. FDA-2016-D-0269/ FDA-2016-D-0271/ FDA-2016-D-0238.

Appendix. Comparison of 503A Compounding Pharmacies and 503B Outsourcing Facilities

Table A-1. Federal Requirements for Compounding Under FFDCA §503A and 503B

Summary of Requirements

	503A Compounding Pharmacies	503B Outsourcing Facilities
FFDCA exemptions	• Section 502(f)(1) concerning labeling with adequate directions for use • Section 505 concerning new drug approval • Section 501(a)(2)(B) concerning CGMP requirements	• Section 502(f)(1) concerning labeling with adequate directions for use • Section 505 concerning new drug approval • Section 582 concerning supply chain security and track and trace requirements
Who may compound	A licensed pharmacist in a state-licensed pharmacy or federal facility or a licensed physician.	A licensed pharmacist or individual under the direct supervision of a licensed pharmacist in a facility that registers as an outsourcing facility.
Prescription requirement	May compound (1) based on the receipt of a prescription for an identified individual patient; or (2) in limited quantities if the compounding is based on a history of the licensed pharmacist or physician receiving prescription orders for the compounding of the product, and the orders have been generated within an established relationship between the licensed pharmacist or physician doing the compounding and the patient or prescriber of the order (i.e., anticipatory compounding).	May compound a drug with or without a prescription.
Types of drugs that may be compounded	May compound sterile or nonsterile drugs.	Must compound sterile drugs and may also compound nonsterile drugs.
Bulk drug substances	May compound using bulk drug substances that are manufactured by an establishment that is registered with FDA under FFDCA §510 and are accompanied by a valid certificate of analysis. In addition, such bulk drug substances must • comply with the standards of an applicable USP or NF monograph if such monograph exists, and the USP chapter on pharmacy compounding; • if such monograph does not exist, be drug substances that are components of FDA-approved drugs; or • if such monograph does not exist and the drug substance is not a component of an approved drug, appear on the HHS Secretary's list of bulk drug substances, developed through regulation.	May compound using bulk drug substances that are manufactured by an establishment that is registered with FDA under FFDCA §510 and are accompanied by a valid certificate of analysis. In addition, such bulk drug substances must • appear on a list, established by the Secretary, identifying bulk drug substances for which there is a clinical need, or the drug compounded from such bulk drug substance appears on the drug shortage list under FFDCA §506E; and • comply with an applicable monograph under the USP, NF, or other compendium or pharmacopeia recognized by the Secretary, if one exists.

	503A Compounding Pharmacies	503B Outsourcing Facilities
Other ingredients	May compound using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if a monograph exists, as well as the USP chapter on pharmacy compounding.	May compound using ingredients (other than bulk drug substances) that comply with the applicable USP or NF monograph, or any other compendium or pharmacopeia recognized by the HHS Secretary.
Drugs that may not be compounded	May not compound a drug that (1) appears on the Secretary's list, established by regulation, of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective, or (2) is a "drug product" identified by the Secretary by regulation as one that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on its safety or effectiveness.	May not compound a drug that (1) appears on the Secretary's list, established by regulation, of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective, or (2) are "drugs or categories of drugs" identified by the Secretary by regulation as those that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on its safety or effectiveness, "taking into account the risks and benefits to patients" unless the compounding is done "in accordance with all applicable conditions identified on the list ... as conditions that are necessary to prevent" such difficulties.
Limits on interstate distribution	May be compounded in a state that has entered into an MOU with the Secretary addressing "the distribution of inordinate amounts of compounded drug products interstate" and that provides "for appropriate investigation by a State agency of complaints relating to the compounded drug products distributed outside such State." If the drug product is compounded in a state that has not entered into an MOU with the Secretary, the pharmacist, pharmacy, or licensed physician may not compound drugs outside that state in quantities that exceed 5% of that entity's total prescription orders.	No statutory restriction on interstate distribution.
Compounded drugs that are essentially copies of commercial drugs	May not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are "essentially copies of commercially available drug products."	May not compound a drug that is essentially a copy of one or more approved drugs.
Labeling	No labeling requirements. Note: While there are no specific labeling requirements listed under §503A, other FFDCA labeling requirements apply to compounded drugs (e.g., the drug product's labeling, advertising, and promotion must not be false or misleading).	The label of the drug must include the statement "this is a compounded drug" or a comparable statement, and the name, address, and phone number of the outsourcing facility. The label must also include specified information with respect to the drug (e.g., lot or batch number, established name of the drug, dosage form and strength, the statement "not for resale"). The container "from which individual units of the drug are removed for dispensing or administration" must include a list of active and inactive ingredients (if there is not space on the label), FDA adverse event reporting information, and directions for use.

	503A Compounding Pharmacies	503B Outsourcing Facilities
Registration	Not required.	Must register with the Secretary annually the facility name, place of business, unique facility identifier, and a point of contact email address, and must indicate whether the facility intends to compound a drug on the drug shortage list under FFDCA §506E.
Inspection	May be inspected pursuant to FFDCA §704(a), which allows FDA to inspect, "at reasonable times and within reasonable limits and in a reasonable manner," pharmacies and "all pertinent equipment, finished and unfinished materials, containers, and labeling therein." Are generally are exempt from 704(a)(2)(A), which pertains to inspection of records.	Must be inspected pursuant to FFDCA §704. Not exempt from §704(a)(2)(A), which pertains to inspection of records. Inspections of outsourcing facilities must be conducted on a risk-based schedule established by the Secretary, as specified in §503B(b)(4).
Quality standards	Compounding pharmacies are exempt from CGMP requirements, but are subject to other quality requirements, such as the prohibition on preparing, packing, or holding drugs under insanitary conditions.	Must comply with CGMP requirements.
Fees	Not required.	Must pay an annual establishment fee for each outsourcing facility and a reinspection fee from each outsourcing facility subject to reinspection.
Reporting to FDA of drugs compounded	Not required.	Must submit to the Secretary, twice a year as specified, a report identifying the drugs compounded in the past 6 months, and specified information with respect to each identified drug (e.g., active ingredient and source, NDC or source drug or bulk active ingredient).
Reporting to FDA of adverse events	Not required.	Must submit adverse event reports to the Secretary.

Source: Created by CRS based on FFDCA §§503A and 503B and Table 1 in the Government Accountability Office (GAO) report, "Drug Compounding: FDA has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges," November 2016, http://www.gao.gov/assets/690/681096.pdf.

Notes: This table addresses only federal reporting requirements. States may have their own laws regarding adverse event reporting. FFDCA= Federal Food, Drug, and Cosmetic Act; CGMP= Current Good Manufacturing Practice; FDA= Food and Drug Administration; HHS= Health and Human Services; NF= National Formulary; MOU= Memorandum of Understanding; NDC=National Drug Code; USP= United States Pharmacopeia.

Author Contact Information

Agata Dabrowska
Analyst in Health Policy
adabrowska@crs.loc.gov, 7-9455