



**American Pharmacists Association**<sup>®</sup>  
Improving medication use. Advancing patient care.

July 18, 2016

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

[Submitted electronically to [www.regulations.gov](http://www.regulations.gov)]

**Re: Prescription Requirement under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry (FDA-2016-D-0269)**

Dear Sir/Madam:

APhA is pleased to submit these comments on the FDA's draft guidance on the Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act (the "Guidance")<sup>1</sup>. Founded in 1852 as the American Pharmaceutical Association, APhA represents more than 62,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings, and the uniformed services.

APhA is committed to working with FDA and other stakeholders to make certain that nothing like what occurred at the New England Compounding Center (NECC) happens again. As FDA is aware, compounding is an important part of pharmacy practice because it permits patients with unique medical needs to access vital medications when commercially available dosage forms do not exist. APhA supports FDA's efforts to ensure drug quality and security as the provision of safe, effective medications, including compounded medications, is of paramount importance to our members. However, APhA continues to have concerns that FDA's interpretation and implementation of the Drug, Quality and Security Act ("DQSA") is negatively impacting patients' access to these necessary compounded medications. Specifically, APhA is troubled that the Guidance prohibits compounding for office use/administration, further restricts the quantity of product that can be compounded in advance of a patient-specific prescription, overestimates the ability of 503B facilities to meet patient compounding needs, and appears to define what constitutes a valid prescription.

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<sup>1</sup> The draft guidance addresses compounding after the receipt of a prescription for an identified individual patient, compounding before the receipt of a prescription for an identified individual patient (anticipatory compounding), and compounding for office use (or "office 24 stock").

## I. Compounding Medications for Office Use

APhA disagrees with FDA's position in the Guidance that compounding for office use or administration is prohibited by 503A. The Guidance articulates that 503A does not provide for the distribution of a compounded drug before receiving a valid prescription order for an identified individual patient, typically referred to as compounding for office use or administration. This new interpretation is inconsistent with FDA's previous and longstanding position and the DQSA's congressional intent.<sup>2</sup> Congress left 503A virtually untouched by the DQSA, signifying its desire to continue the allowance of office use compounding under 503A—a fact confirmed by Members of Congress in numerous communications with FDA since the DQSA's passage.<sup>3</sup> If FDA believes additional safeguards are necessary with regard to this practice, it can look to states, many of which have laws and regulations on office use, to identify successful policies balancing patient/public safety with patients' legitimate need for these medications.

Furthermore, while FDA lists in the Guidance alternative mechanisms in which providers can utilize to obtain compounded products for office use, many of them are not viable. For example, FDA notes that pharmacies can register as 503B facilities if they wish to do office use compounding. However, 503B registration is only for those entities compounding sterile products, therefore, pharmacies, which compound only non-sterile products, are unable to register as a 503B outsourcing facility. In addition, because 503B registration triggers CGMPs to be applicable to all compounded products, including patient-specific and non-sterile compounding, it is simply unrealistic to assume a traditional pharmacy could ever register as a 503B facility because of the costs and time associated with CGMP compliance. The Guidance

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<sup>2</sup> See House Report 114-205. – which states “The Committee is concerned that, since passage of the Drug Quality and Security Act (DQSA) of 2013, the FDA has interpreted provisions of Section 503A of the FDCA in a manner inconsistent with its legislative intent and with the agency's own previous positions. Specifically, the FDA has taken the position that under 503A, a pharmacist may not compound medications prior to receipt of a prescription and transfer the drugs to a requesting physician or other authorized agent of the prescriber for administration to his or her patients without a patient-specific prescription accompanying the medication. This practice, which is often referred to as “office-use” compounding, is authorized in the vast majority of states and was intended to be allowable under DQSA. The Committee is aware that in 2012, prior to passage of the DQSA, FDA was working on a draft compliance policy guide for 503A of the FDCA that provided guidance on how “office-use” compounding could be done consistent with the provisions of 503A. The Committee understands the intent of the DQSA was not to prohibit compounding pharmacists from operation under existing 503A exemptions; therefore, the Committee directs the 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.

Available at: <https://www.congress.gov/congressional-report/114th-congress/house-report/205>

<sup>3</sup> See Statement of Rep. Buddy Carter, *Congressional Record* (Apr. 27, 2016). “...congressional intent was clear that 503A community pharmacies could continue to provide office-use compounded medication as they had always done.” Available at: <https://www.congress.gov/congressional-record/2016/4/27/house-section/article/h2047-5?resultIndex=36>; Statement of Rep. Tom Coburn, *Congressional Record* (Nov. 18, 2013). “There has been a lot of concern that by reaffirming Section 503(a) of the Food, Drug, and Cosmetic Act, office-use compound[ing] of drugs is not recognized as a permissible compounding activity. Therefore, I want to make clear that this legislation does not change current law or authority over the dispensing or distribution of medications by pharmacists, compounded or manufactured, for a prescriber’s administration to or treatment of a patient within their practice.”; Statement of Sen John Boozman, *Congressional Record* (Nov. 18, 2013) “The practice of pharmacy, including pharmacy compounding, is a state issue. Nothing in this law changes that. Compounded drugs for office-use is a state issue. Nothing in this law changes that.”

also offers that hospitals, clinics, and health care facilities can rely on 503B facilities for their office-use compounded products. As discussed in more detail below, reliance on 503B facilities for all office use compounding is also unworkable because these same time/ cost limitations. Accordingly, APhA requests that FDA return to its previous interpretation of 503A to allow office use compounding, and if additional protections are necessary, APhA recommends FDA work with states to identify successful workable policies.

## **II. Anticipatory Compounding**

Section 503A(a)(2) of the FD&C Act, allows a licensed pharmacist or licensed physician to compound “limited quantities”<sup>4</sup> before the receipt of a valid prescription order when there is a relationship between the prescriber and pharmacist or physician receiving the prescription, or the patient and pharmacist or physician receiving the prescription. The Guidance defines “limited quantity” as “a 30-day supply of a particular compounded drug” if that supply “is based on the number of valid prescriptions that the compounder has received for an identified individual patient in a 30-day period over the past year” (i.e., referred to as “anticipatory compounding”). While APhA appreciates FDA acknowledging “larger batch sizes can increase efficiency and reduce the likelihood of human error,”<sup>5</sup> because FDA is now defining “limited quantity,” we believe it is minimizing the value and benefit of anticipatory compounding.

The Guidance defines “limited quantities,” as a 30-day supply based on the past year and outlines a myriad of factors to be included in the computation. In addition to being complex to calculate and record, the arbitrary 30-day supply constraint fails to take into account the inconsistencies and variability in and between pharmacy practices. It also treats all compounded products similarly, ignoring the fact that some products benefit greatly from larger batch compounding or certain preparations have long beyond use dates (BUD).

APhA strongly recommends that any enumerated quantity threshold cannot be limited to historical order patterns and must allow for anticipatory compounding when there is an expectation of physicians’ and patients’ demand. Allowing for situations when there is a real and expected need will ensure that pharmacies maintain the ability to anticipatorily compound to protect public health and patient safety (e.g., drug shortages), despite there not being a history of orders. Such additional language would have been necessary to cover the Tamiflu suspension shortage a few years ago. After the first one or two patients presented at pharmacies and pediatric offices, and parents began outreach to providers, it was clear the demand would exceed the supply. Compounding in anticipation allowed the caregivers to quickly receive this shortaged medication. In addition, in many cases, a prescriber can reasonably predict how many units of a particular compounded product are required in a given time frame, thus providing a reasonable control to the quantity to be anticipatorily compounded. Therefore, it is in the public interest to allow 503A pharmacists to compound to meet an impending need, such as drug shortages; to reduce potentially dangerous physician and patient wait times for medications; and to prevent the disruption of patient care and treatment plans. Consequently, APhA does not believe further clarification is needed as the current language in 503A allowing a “limited quantity” of anticipatory compounding in situations where there is an established relationship is

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<sup>4</sup> See 21 U.S. Code § 353a - Pharmacy compounding. Available at: <https://www.law.cornell.edu/uscode/text/21/353a>

<sup>5</sup> In addition, compounding larger supplies of products often encourages quality control testing because costs can be spread out among a larger number of products.

a clear and reasonable standard. However, if FDA is committed to further defining the quantity of anticipatory compounding allowed under 503A, APhA recommends including a limit better aligned with products' established BUDs, derived from peer-reviewed literature, or evidenced by direct analytical testing.

### **III. Capabilities of 503B Facilities**

As mentioned above, FDA states in the Guidance that 503A prohibits office use compounding, even in states that explicitly authorize the practice, and highlights other mechanisms that can be accessed to satisfy the demand for office use compounding. FDA suggests that pharmacies can register as 503B facilities if they wish to do office use compounding or physician offices can obtain these compounded medications from 503B facilities. However, in practice, prohibiting office use compounding by 503A pharmacies will likely prevent patient access to a significant amount of medications that pharmacists have long-provided to physicians for use in their offices.

FDA states in the Guidance that 503A pharmacies compounding for office use can continue to do so by simply registering as outsourcing facilities. For numerous reasons this is simply impractical. First, some pharmacies are ineligible to register under 503B because they do not sterile compound. Second, because 503B registration triggers CGMPs to be applicable to all compounded products, the time and costs associated with CGMP makes it unfeasible for most pharmacies to provide the diversity of products that they currently compound because the quantity of product required by physicians and patients is small.

The Guidance also provides that hospitals, clinics, and health care facilities can rely on 503B facilities for their office use compounded products. While some entities obtain a portion of their office use products from 503B facilities, 503B facilities cannot supply all their compounding products because compliance with CGMPs makes it cost and/or time prohibitive to fulfill all the compounding demands of health care facilities, providers and patients, which is why many 503B facilities have defined formulary lists<sup>6</sup>. CGMP requirements include: procurement of bulk drug product(s) which meets CGMP; authoring procedures to compound the medication which meet CGMP; proper testing (validation, release testing, stability testing) and other requirements.<sup>7</sup> APhA members' conversations with 503B facilities have confirmed the inability of these facilities to supply many small batch medications commonly associated with office use (e.g., numbing creams/sprays, etc.). In addition, because of the time required to meet CGMPs, including, but not limited to the testing requirements, 503Bs are unable to immediately meet the needs of providers and patients unless facilities are currently compounding the product(s). Therefore, APhA strongly urges FDA to follow its previous long-standing policy, as well as the intent of Congress, and continue to allow 503A pharmacies to compound limited quantities without a patient-specific prescription and defer to states for statutory or regulatory authority over pharmacies' office use compounding.

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<sup>6</sup> See SCA Pharmaceuticals. Product Catalog. 2016; Cantrell Drug Company. Product Catalog. 2016; and Leiter's Compounding Product Catalog, 2016.

<sup>7</sup> See FDA. Guidance for Industry Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act. July 2014. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf>

#### IV. Definition of Valid Prescription

APhA is troubled by language in the Guidance that appears to define what is considered a valid prescription order.<sup>8</sup> From the language, it is unclear whether the requirement to note that the prescriber confirmed the need for a compounded drug pertains only to situations in which a prescription order is unclear or if it applies to all 503A compounding. APhA believes that in order to be consistent with the statute and states' authority, it is the former, and requests that FDA clarify this language in its final guidance.

#### V. Pharmacists' Ongoing DQSA Concerns

##### A. Draft Memorandum of Understanding (MOU)

As stated to FDA in previous comments, APhA believes FDA's current draft MOU<sup>9</sup> is a marked departure from established regulatory practices. The draft MOU redefines "distribution" to include "dispensing", resulting in what is essentially another ban on office use compounding, which, is in conflict with previous FDA policy and Congress's intent when it passed the DQSA.

The plain language of the FD&C Act directs FDA to develop an MOU that addresses "the distribution of inordinate amounts of compounded drug products interstate."<sup>10</sup> While DQSA does not explicitly define "distribution", the statutory text differentiates between "distribution" and "dispensing" in a number of places—a clear indication that Congress ascribed different meanings to the two terms.<sup>11</sup> Historically, the terms "dispense" and "distribute" refer to two different activities. In both FD&C<sup>12</sup> and the Controlled Substances Act<sup>13</sup>, Congress and FDA expressly recognized the different usage of "dispense" and "distribute", defining "dispensing" as something that is intrinsically clinical in nature, while defining "distribution" as the act of shipping or delivering a medication outside of the patient-provider relationship. To treat

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<sup>8</sup> The Guidance states, "To serve as a basis for compounding under section 503A, a notation must document the prescriber's determination that a compounded drug is necessary for the identified patient . . .". See Lines 272-274. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf>

<sup>9</sup> FDA. Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drugs Products Between [insert state] and the U.S. Food and Drug Administration. February 13, 2015. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM434233.pdf>

<sup>10</sup> See 21 U.S.C. § 353a(3)(B). Available at: <https://www.law.cornell.edu/uscode/text/21/353a>

<sup>11</sup> See e.g., *id.* at (3)(B)(ii) (differentiating the "dispensed" and "distributed" through the use of the disjunctive "or", indicating that the terms are not interchangeable).

<sup>12</sup> Drug Supply Chain Security Act, §581(5) (2013) (defining distribute as "the sale, purchase, trade, delivery, handling, storage, or receipt of a product", but stating that it "does not include the dispensing of a product pursuant to a prescription executed in accordance with section 503(b)(1) or the dispensing of a product approved under section 512(b)").

<sup>13</sup> See 21 U.S.C. §802(10)-(11). Available at: <http://www.deadiversion.usdoj.gov/21cfr/21usc/802.htm> ; See also 21 C.F.R. §208.3 defining "distribute" as "the act of delivering, other than by dispensing, a drug product to any person", thereby expressly excluding dispensing from the act of distribution). Available at: <https://www.law.cornell.edu/cfr/text/21/208.3>

“distribution” and “dispensing” as interchangeable only in the context of DQSA not only creates confusion, it also implies that FDA is entering into the regulation of clinical decision-making related to prescribing—an area meant to be governed by states. Thus, in keeping with congressional intent, we believe that the MOU should only address “distribution” of compounded medications across state lines and should have no effect on dispensing of prescriptions for identified patients by 503A pharmacies.

*B. Interpretation of Distribution Across State Lines (5%/30%)*

APhA members continue to voice serious concern regarding the imposition of percentage limitations on interstate distribution of compounded drug products. As the draft MOU currently reads, the limitations will apply to all compounded medications distributed across state lines, including those dispensed pursuant to a valid prescription. While these limitations have serious consequences for patient access, the FDA offers no justification for the numbers chosen and cites no data or studies linking a higher volume of out-of-state sales of compounded medications to unsafe practices or an increased risk to patient safety. Because the FDA has failed to provide any basis for the 5% / 30% thresholds, the limits appear arbitrary.

Enforcing these limitations could result in hardship for patients who trust and rely on specific pharmacists/pharmacies for their compounded drug products, especially patients who live near state borders or contiguous states (e.g., MD-VA-DC, NY-NJ-CT) or are reliant on medications that are in shortage. For example, in a small pharmacy, a single pharmacist may not fill a large number of prescriptions, thus the number of compounded medications it takes to reach either the 5% or 30% threshold is relatively small. As an illustration, if a pharmacist located in a non-MOU state near a state border fills 100 compounded prescriptions per month, that pharmacist can distribute only 5 of those prescriptions to out-of-state patients. In an MOU state, the pharmacist can distribute 30 prescriptions to out-of-state patients, which is still a small number. In order to ensure that he/she is treated as a traditional pharmacist under 503A, the pharmacist may be forced to turn away customers with compounding requirements. In some areas, particularly those that are rural, it may be very difficult for patients to find another pharmacist or pharmacy providing certain compounded preparations. Thus, while FDA’s exemption of prescribed medications carried across state lines from the calculation of “inordinate amounts”<sup>14</sup> will help patients with the financial and logistical means to make regular trips to the pharmacy (e.g., those who can drive or who caretakers who can pick up medications), many patients face significant transportation, mobility, and financial challenges that make such trips impossible. Should a drug shortage or other emergency situation arise, the MOU provides no exemptions to, or safeguards against, investigations for pharmacies whose output temporarily spikes in response to increased patient need. Furthermore, this policy could have the unintended consequence of preventing specialized patient populations from accessing pharmacies with the capability to compound the medications necessary to meet their critical needs (e.g. oncology, pediatric TPN, etc.).

APhA acknowledges that constructing an effective regulatory framework that adequately delineates between compounding and manufacturing presents a number of challenges, and

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<sup>14</sup> See FDA. Draft MOU. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm434233.pdf>

appreciates FDA's openness to input from pharmacists and pharmacies. During the April 30, 2015 listening session for 503A compounders, in the context of discussions regarding the MOU's definition of "distribution", a suggestion was made that the MOU should apply only to interstate distribution of medications compounded for office use (e.g., without a prescription for an individually identified patient). Such an MOU could resolve a number of the issues, including the necessity to carve dispensing activities out of the MOU's definition of "distribution" and the access issues created by applying arbitrary restrictions to interstate shipment of medications compounded pursuant to patient-specific prescriptions. Further, Congress noted that for the MOU, "inordinate" amounts or quantities refers to "amounts typically associated with ordinary commercial drug manufacturing", but the 5% / 30% limitations set forth in the draft MOU in no way resembles commercial drug manufacturing output, particularly because FDA would apply them to patient-specific prescriptions.<sup>15</sup> This approach, as opposed to the imposition of arbitrary percentage limitations on all 503A-compounded medications, would harmonize well with the focus on the established or historical relationship between a prescriber and a pharmacist to determine the relative risk associated with compounding. Given that the MOU will guide compounding practice for many years, APhA strongly encourages the FDA to carefully evaluate this option, as it would offer solid oversight without threatening patient and provider access to safe, high-quality compounded medications.

### *C. Inspections*

APhA is pleased that FDA has responded to APhA and our members' feedback and issued a notice of a change to its procedure for inspections of human drug compounders.<sup>16</sup> APhA members appreciate that starting August 1, FDA inspectors will make a preliminary assessment as to whether pharmacies are compliant with 503A before applying 503B standards in "Form FDA-483" investigations and will *not* include observations in its Form-FDA 483 based "solely" on FDA's CGMP requirements under 503B, unless it appears that pharmacies are compounding drugs that do not qualify for the 503A exemptions.<sup>17</sup> While we appreciate FDA's action to address serious concerns of pharmacists and pharmacies throughout the country, the change in policy is not effective for more than two weeks, nor is it retroactive. Accordingly, APhA recommends FDA apply these new standards retroactively to past inspections/Form-FDA-483s.

In addition, it is clear from language in the notice that FDA still intends to include observations regarding CGMP compliance on Form FDA-483s when performing inspections of 503A pharmacies. Holding pharmacies to standards that they should not have to meet wastes FDA and pharmacies' resources, negates opportunities to improve pharmacies' processes and procedures, and exceeds language of the DQSA and congressional intent.

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<sup>15</sup> See Senate Committee Report 105-43, Food and Drug Modernization Act of 1997. p.68. Available at: <https://www.congress.gov/congressional-report/105th-congress/senate-report/43/1>

<sup>16</sup> See FDA. Notice of Change in Process for Inspections of Certain Compounders. July 12, 2016. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCMS10684.pdf>

<sup>17</sup> FDA acknowledges that "because a Form FDA-483 does not represent a final Agency determination regarding a firm's compliance, formerly, FDA investigators have been identifying deviations from drug production practices on Forms FDA-483 that could lead to quality problems without regard to whether the observations related to CGMP deficiencies or other deficiencies. . . ."

Lastly, we remain troubled by the fact that the FDA continues to inspect pharmacies, those not registered as 503B facilities, which are under the purview of State Boards of Pharmacy, absent a complaint or a request by a State Board.

*D. Nuclear Pharmacy/Radiopharmaceutical Guidance*

There continues to be ambiguity regarding the applicability of FDA's DQSA regulatory activity on the practice of nuclear pharmacy because it is specifically exempted from 503A and preexisting FDA guidance exempts it from CGMPs.<sup>18</sup> Only adding to the confusion is the fact that most of the work of nuclear pharmacies or of pharmacists handling radiopharmaceuticals is not actually compounding. While compounding pharmacies create what are essentially new drug products designed to meet patient needs, most nuclear pharmacies are preparing radiopharmaceuticals from kits that are FDA-approved—activity which falls outside of the Food, Drug, and Cosmetic Act's definition of compounding.<sup>19</sup> Therefore, APhA requests that FDA expeditiously issue regulatory documents to provide clarity to nuclear pharmacists and pharmacies when compounding drugs to meet the demands of identified patients.

In closing, APhA looks forward to continuing to work with the FDA and other stakeholders to construct a framework in accordance with current statutory authority and congressional intent that ensures patients have access to safe and effective compounded medications. It is important in developing and implementing DQSA, FDA remembers Congress' objective to secure an appropriate place for customized compounding of medications in today's modern health care system. We hope to be a resource for FDA and are happy to be of assistance in any way possible. Thank you again for the opportunity to provide comments on this important issue. If you have any questions or require additional information, please contact Michael Baxter, Director of Regulatory Affairs, at [mbaxter@aphanet.org](mailto:mbaxter@aphanet.org) or by phone at (202) 429-7538.

Sincerely,



Thomas E. Menighan, BSPHarm, MBA, ScD (Hon), FAPhA  
Executive Vice President and CEO

cc: Stacie S. Maass, RPh, JD, Senior Vice President, Pharmacy Practice and Government Affairs

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<sup>18</sup> See FDA. Guidance for Industry. Nuclear Pharmacy Guideline. Criteria for Determining When to Register as a Drug Establishment. 1984. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070293.pdf>

<sup>19</sup> See 21 U.S.C. §353a(f). Available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376733.htm>