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Physician Compounding Comes Under Scrutiny

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Physician compounding of sterile products occupies a borderland between the practice of medicine and the practice of pharmacy and, until recently, has lived in a regulatory gap. However, in 2012, when 64 patients died of fungal meningitis and 753 were injured as a result of contaminated products from a single compounding pharmacy in Massachusetts, safety of compounded drugs became a public health concern and physician compounding came under scrutiny.

Compounded drugs are necessary to patient care where the dosage, concentration, formulation, or method of delivery of a drug is not commercially available in a manufactured form. In such cases, a compounded product prepared either by the physician or a compounding pharmacy may be the only option. Examples of physician sterile compounding include mixing and administration of allergen immunotherapy injections; mixing of lidocaine with dilutions of sodium bicarbonate to reduce injection pain; diluting of steroids for intralesional injections; pediatric preparations; and reconstituting botulin toxin type A.

Physicians who compound products for their own patients argue that this is part of the practice of medicine and should not be subject to regulations that apply to compounding pharmacies or outsourcing facilities. They point out that many compounded products are integral to their practice and are often for immediate use during a procedure or treatment. This article examines the evolving regulatory and legal climate that may impact physician office compounding and the potential consequences of such changes.

Food and Drug Administration

In reaction to the 2012 tragedy, Congress, in 2013, enacted the Drug Quality and Security Act (DQSA) that created a new regulatory category of "outsourcing facilities."[\[1\]](#) At the same time, Congress left intact Section 503A of the Federal Food, Drug, and Cosmetic Act (Act) governing small-scale compounding by physicians and compounding pharmacies.[\[2\]](#) That Section permits physicians and pharmacists that meet certain requirements to compound drugs based on a prescription from the patient's practitioner, without a new drug approval, and without having to meet labeling and good manufacturing practices. Physicians have long relied on this provision to prepare and administer compounded drugs to their own patients and to obtain compounded products from compounding pharmacies based on a patient prescription.[\[3\]](#)

Since the Act's passage, the Food and Drug Administration (FDA) has issued several draft and final guidance documents setting forth its interpretation of the Act. The FDA guidance has been controversial and is viewed by many as potentially jeopardizing the ability of physicians to compound and administer drugs to their own patients—a service physicians consider to be within the practice of medicine.

One draft guidance that has raised particular alarm, *Insanitary Conditions at Compounding Facilities*, would require physicians' offices to maintain a certified International Organization for Standardization (ISO) Class 5 area or "clean room" with a buffer area and high efficiency particulate arrestance (HEPA) filters and conduct sampling of airborne particulates and surface areas, among other things.[\[4\]](#) Although this may not be a burden for larger compounding pharmacies, most physician offices would be challenged to meet these requirements. In reaction to concerns raised by physicians and other stakeholders, the FDA, in its 2018 Priorities Plan, stated that in finalizing this

guidance, it will adopt a risk-based approach and drugs that create "negligible patient risk" would be subject to a less stringent compliance policy.[\[5\]](#)

At the same time, the FDA has taken a more moderate approach in its recently finalized guidance, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*.[\[6\]](#) Although Section 503A of the Act does not apply to biologics, the FDA states that it will use its enforcement discretion to permit outsourcing facilities and compounding pharmacies to "mix, dilute or repackage" biological products without an approved license. In addition, the guidance allows physicians to prepare allergen immunotherapy "prescription sets" and provides for a beyond-use date of up to 12 months.

United States Pharmacopeia

Concurrent with FDA activity, the United States Pharmacopeia (USP) began its scheduled ten-year review of its chapters 795 and 797 that set forth standards for non-sterile and sterile compounding. USP is a non-governmental, nonprofit scientific standard-setting organization, and, although it does not enforce its standards, the USP's standards have been adopted by at least 32 states and are referenced in Section 503 of the Act.

The USP's definition of compounding is broader than the FDA's and includes biologics, as well as drugs and even preparations mixed in accordance with the manufacturer's labeled instructions.[\[7\]](#) USP draft sterile compounding standards (Ch. 797) issued for comment in the fall of 2015 were an entire rewrite of existing USP standards and, if adopted, would impose more stringent engineering controls such as use of "clean rooms" and frequent testing for airborne particulate matter and microbial testing of gloves, surfaces, and the like. All of these could require significant outlays of capital. One area of concern is more stringent "beyond use dates" that would require clinicians to discard compounded drugs within shorter time frames, thereby creating increased expense and wastage. The USP proposal also would eliminate special rules created by USP in 2007 for allergen immunotherapy that allows physicians to prepare allergen extract vials for their patients using aseptic technique.

In response to physician outcry, the USP pulled back its proposal and will issue new draft standards that will be released for comment in July 2018. Final standards are to be published by June 1, 2019, with an effective date of December 1, 2019.[\[8\]](#)

The USP delegated the development of the sterile compounding standards to its Expert Committee on Sterile Compounding, a group comprised primarily of pharmacists and with no physician representation. Recently, however, perhaps in recognition of the potential impact of its standards on physicians, the USP created an informal physician advisory group.

Closing the Regulatory Gap?

Physician compounding has, for the most part, been loosely regulated, if at all. The FDA views it as the responsibility of the states, but very few states exercise any oversight. State boards of pharmacy regulate compounding pharmacies but do not view their authority as extending to physician offices. While physicians are under the authority of state medical licensing boards, those entities are complaint driven and do not engage in routine inspections. Unless a patient is harmed and files a complaint, there is unlikely to be oversight by state medical boards. As a result, physician compounding occupies a regulatory gap that many are advocating be closed.

The Government Accountability Office (GAO), in response to a request in the DQSA, undertook a study of regulatory activities by the FDA and the states and reported on significant gaps in regulation of physician compounding.[\[9\]](#) While 48 states have laws or regulations related to drug compounding generally, only nine have laws or policies specific to physician or practitioner compounding.[\[10\]](#) A similar gap was identified by the Federation of State Licensing Boards (FSMB), which entered the debate with a 2018 draft Position Statement. The FSMB recommended that physicians compounding in their offices comply with USP standards. It also suggested that state medical boards

communicate with state boards of pharmacy surrounding physician compliance issues, although it did not put forth any specifics. The FSMB draft statement has been interpreted by some as a suggestion that state boards of medicine cede authority to boards of pharmacy when it comes to physician compounding.

Ohio is at the vanguard in terms of regulating physician compounding. The Ohio legislature enacted a law that requires practitioners engaged in compounding drugs for administration to their patients to obtain a Terminal Distributor license.^[11] Through regulation, the State of Ohio Board of Pharmacy requires that most compounded products be prepared in a "clean room" unless used within six hours. It also incorporates USP Ch. 797.^[12] While a number of other states have also enacted laws or adopted new regulations on compounding, they apply primarily to pharmacists and compounding pharmacies and not physicians. One exception is North Carolina whose Medical Board has issued a position statement that physicians who compound in their offices must follow FDA and USP policies.^[13]

Physician compounding may be regulated indirectly when a physician practices within a hospital system that is accredited by The Joint Commission. If the physician practice location falls under the hospital's licensure, it will be reviewed by The Joint Commission as part of the hospital's accreditation. The Joint Commission requires that sterile compounding conform to requirements of USP Ch. 797 and has even created a medication compounding certification program for hospitals.^[14] As a result, compounding that might otherwise be done by physicians in their offices takes place in the hospital's pharmacy.

What to Watch for

Several FDA guidance documents are still pending with the agency. Physicians should pay special attention to the 2016 draft guidance on *Insanitary Conditions at Compounding Facilities* that would require all compounding be performed in an ISO Class 5 environment. In addition, the USP's draft Ch. 797 will be issued in July of 2018. Some issues to watch for are whether the new USP proposal will ease up on standards for "immediate use" products and preparation of allergen immunotherapy prescription sets. Also important will be the extent to which USP standards will subject physician office compounding to engineering controls such as maintaining an ISO Class 5 environment, microbial testing, and beyond use dates, all of which could have significant cost and access implications.

Because USP standards are incorporated by reference into state laws and regulations in at least 32 states, the new rules could dramatically alter the state regulatory landscape.^[15] At the same time, most states do not enforce compounding laws against physicians. The state boards of pharmacy generally have no jurisdiction over the practice of medicine, and state medical boards are only just beginning to look at the issue. In addition, they lack the resources to carry out inspections and would likely act only in response to complaints. Nevertheless, this issue is on the FSMB's radar screen, and collaboration with the National Association of Boards of Pharmacy to encourage their respective boards to close the regulatory gap is a possibility.

Even in the absence of regulation or enforcement, physicians should consider the level of risk associated with products compounded in their offices and whether USP or FDA standards might be viewed by a court as establishing the standard of care for purposes of negligence.

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[1] Drug Quality and Security Act, Pub. L. No. 113-54, §102, 127 Stat. 587, 588-93 (2013) (Section 503B of the Federal Food, Drug, and Cosmetic Act) (codified at 21 U.S.C. § 353b).

[2] 21 U.S.C. § 353a.

[3] The FDA defines compounding to exclude "mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer . . ." 21 U.S.C. § 353a(e).

[4] FDA, *Insanitary Conditions at Compounding Facilities* (Aug. 2016), available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm514666.pdf> (Draft Guidance). Although FDA guidance is not binding, it does represent the agency's current thinking of the topic. As of the date of publication, this guidance had not been finalized.

[5] Scott Gottlieb, *2018 Compounding Policy Priorities Plan*, FDA (Jan. 2018), available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm>.

[6] FDA, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* (Jan. 2018), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434176.pdf>.

[7] USP Ch.797—Pharmaceutical Compounding—Sterile Preparations.

[8] See USP, *General Chapter <797> Pharmaceutical Compounding—Sterile Preparations*, available at <http://www.usp.org/compounding/general-chapter-797> (last visited May 8, 2018).

[9] U.S. Gov't Accountability Office, GAO-17-64, *Drug Compounding: FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges* (2016), available at <https://www.gao.gov/assets/690/681096.pdf>.

[10] *Id.*

[11] Ohio Rev. Code Ann. § 4729.54.

[12] *Id.* § 4729.541.

[13] North Carolina Medical Board, *Physician Compounding*, available at [https://www.ncmedboard.org/images/uploads/article_images/Compounding_Position_Statement_Revised_\(1\)_\(2\).pdf](https://www.ncmedboard.org/images/uploads/article_images/Compounding_Position_Statement_Revised_(1)_(2).pdf) (last visited May 8, 2018).

[14] See The Joint Commission, *Medication Compounding Certification*, available at https://www.jointcommission.org/certification/medication_compounding.aspx (last visited May 8, 2018).

[15] Pew Charitable Trusts & Nat'l Ass'n of Boards of Pharmacy, *State Oversight of Drug Compounding* (Feb. 2018), available at http://www.pewtrusts.org/~media/assets/2018/02/drug_safety_assesment_web.pdf.