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The Practice of Compounding, Associated Compounding Regulations, and the Impact on Dermatologists

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ABSTRACT

Medication compounding gained national attention in the fall of 2012 after contaminated compounded medications produced in the New England Compounding Center infected 800 people with fungal meningitis and led to several fatalities. This prompted Congress to pass regulations on compounding through the Drug Quality and Security Act (DQSA) in 2013. The act increased oversight of patient-specific drug compounding taking place in compounding pharmacies, created 503(b) outsourcing facilities to obtain compounded drugs, and added regulations for obtaining compounded drugs from traditional 503(a) pharmacies. These regulations also had a broader overall impact by triggering federal and state-specific policies, which have ultimately limited a physician's ability to perform low-risk, in-office compounding. This article provides an overview of the different types of compounding restrictions, reviews the current federal and state regulations and/or guidelines, discusses how newly proposed policies may affect the practice of dermatology, and presents an algorithm on how the practicing dermatologist should approach compounding.

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INTRODUCTION

Medication compounding gained national attention in 2012 after contaminated compounded medications produced in the New England Compounding Center caused an infectious outbreak that led to several fatalities. In addition, rising costs and national shortages of medications have sparked new interest in the practice of compounding. Regulations and guidelines related to sterile and non-sterile compounding by physicians and pharmacists, however, have never been more complex. The United States (U.S.) Food and Drug Administration (FDA) has released several non-binding draft guidance documents on clinical compounding. Meanwhile, the United States Pharmacopeia (USP) General Chapter <797> Pharmaceutical Compounding - Sterile Preparations is currently undergoing revisions to set standards that prioritize patient safety and assure quality of all compounded medications. These changes have significant implications on the practice of medicine in certain specialties and they may profoundly impact the ability of dermatologists to provide care to their patients. Amid such flux in regulations and guidelines, it is imperative for dermatologists to be abreast of new information, incorporate established standards into their practice, and understand the risks associated with compounding. This article provides an overview of the different types of compounding, reviews the current regulations and guidelines, and discusses how the practice of dermatology may be affected by new proposed policies.

Definition of Compounding

The FDA defines compounding as combining, mixing, or altering the ingredients of a drug to create a distinct medication tailored to a patient. Compounding must be performed by a licensed pharmacist, a licensed physician, or a person under the direct supervision of a licensed pharmacist in an outsourcing facility. Importantly, compounded medications are not FDA-approved and have not undergone FDA pre-market review for safety, effectiveness, and quality.[1]

Background

In September 2012, tainted steroid injections compounded by the New England Compounding Center caused a multi-state fungal meningitis outbreak that led to several fatalities. Prior to this, the regulations surrounding compounding were more lenient. In

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response to these injuries and fatalities, Congress passed regulations on compounding through the Drug Quality and Security Act (DQSA). The DQSA amended Section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), which led to increased oversight of patient-specific drug compounding taking place in traditional compounding pharmacies and other healthcare settings, including physicians' offices. Additionally, the DQSA created Section 503B, establishing a new compounding entity, known as outsourcing facilities, to provide safe, non-patient-specific compounding for "office-use" and institutional settings.[2] These outsourcing facilities must be registered with the FDA, meet Federal manufacturing standards (ie, follow current good manufacturing practice [cGMP]) and undergo routine inspections.

Traditional 503A pharmacies compounding products pursuant to a valid, patient-specific prescriptions and satisfying other conditions are exempt from cGMP compliance and are, instead, subject to only state regulation, which generally requires USP compliance. Prior to the formation of the FDA, the USP established national safety standards for medicines, foods, and dietary supplements. The USP is a private, nongovernmental organization whose role in public health has evolved in American history. Beginning in the early 1900s, all medications in the U.S. must, by law, meet certain USP standards.[3] Today, the USP publishes a compendium of drug information to ensure the appropriate identity, quality, purity, and potency of products, that all drugs are manufactured to USP standards.[4] USP General Chapter <797> on sterile compounding describes requirements for compounders, including responsibilities of compounding personnel, staff training, facilities, environmental monitoring, and testing and storage of finished preparations. These requirements help ensure patient benefit and reduce risks such as contamination, infection or incorrect dosing. Standards for compounded preparations outlined within the USP may be enforced by both the states and the FDA. Because the needs of clinical medicine are constantly evolving, USP guidelines are continually updated. In fact, the USP is currently revising Chapter <797>, and the American Academy of Dermatology is working on educating government bodies on the repercussions of restrictive guidelines on dermatology, especially as it relates to products such as lidocaine and botulinum toxin. State pharmacy boards often adopt USP recommendations when implementing regulations, but are free not to do so, and thus these laws can vary by state. For example, several states, like Colorado and Connecticut, require that sterile compounding pharmacies comply with the USP and state-specific regulations. Still, other states, like Arizona, have neither state-specific language, nor USP compliance requirements.[5]

Obtaining Compounded Medications

Currently, compounded medications may be obtained through three main avenues: 1) traditional 503A compounding pharmacies, 2) 503B outsourcing facilities, or 3) physician-guided "in-office" compounding. Traditional compounding pharmacies, also known as 503A compounding pharmacies, abide by the standards set forth in section 503A of the FDCA. These compounded medications are dispensed after receipt of an individual-specific prescription. Compounded drug products obtained by 503A compounding pharmacies can only be distributed in limited quantities (ie, no more than a 30-day supply) before the receipt of a valid prescription when based on a history of prior valid prescription orders with the same entities within the last year. The compounding of the drug product must be performed by a state licensed pharmacy or by a licensed physician and comply with the standards of the USP and National Formulary (NF).[6] Ideally, traditional pharmacies satisfy conditions of section 503A to qualify for exemptions specified in that section. For example, a compounder may be exempt from cGMP and labeling of drugs with adequate directions for use if they satisfy certain conditions.[7] However, all other applicable provisions of the FDCA remain in effect for compounded drugs, even if the conditions in section 503A are met. For example, a compounded drug cannot be contaminated or made under insanitary conditions.[8]

Outsourcing facilities, also known as 503B compounding pharmacies, can produce sterile and non-sterile compounded medications in large batches with or without patient-specific prescriptions to be sold by healthcare providers presuming the compounded medication is not an essential copy of a commercially available drug (see below). Outsourcing facilities must comply with current good manufacturing practice (cGMP) requirements. This is distinct from 503A compounding pharmacies which may be exempt from cGMP compliance if they satisfy certain conditions. In addition, outsourcing facilities undergo regular FDA inspection per a risk-based schedule and have adverse event reporting requirements. Thus, outsourcing facilities may provide a higher quality drug product than other facilities and the FDA encourages individuals to obtain compounded drugs through this method.[9]

"In-office" compounding occurs when physicians and their staff prepare medications in the outpatient clinic setting. Several medical specialties, including dermatology, allergy, and oncology, rely on in-office compounding regularly to treat their patients. Advocates in dermatology have suggested use of the term in-office "preparations," rather than "compounding", since this is routine clinical practice as opposed to a pharmaceutical function. For example, dermatologists often buffer lidocaine with sodium bicarbonate to reduce pain on injection, they dilute triamcinolone with saline to achieve an optimal concentration, and reconstitute botulinum toxin for medical and cosmetic purposes. These are just a few common routine clinical compounding uses for dermatologists.

Medications Eligible for Compounding

When compounding under section 503A or 503B of the FDCA, licensed pharmacists and physicians may use only certain bulk active ingredients. The FDA, with input from the public and medical evidence for their safety, has developed criteria to categorize potential bulk active ingredients to be used in compounding into three safety categories. Category 1 includes substances that are eligible for

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compounding. Category 2 includes substances that are significant safety concerns and cannot be used in compounding. Category 3 includes ingredients that have insufficient evidence for their safety by FDA standards. Under section 503A of the FDCA, compounding pharmacies may use bulk active ingredients if they meet one of three criteria: the substances comply with USP or NF monograph standards, are FDA-approved human drug products, or FDA category 1 active ingredients.[10] Notable medications used in dermatology that appear under 503A Category 1 include cantharidin, capsaicin, glycolic acid, kojic acid, glutathione, and squaric acid dibutyl ester. Under section 503B of the FDA, an outsourcing facility cannot use bulk active ingredients unless they are in FDA category 1 or exist on the FDA drug shortage list when the medication is compounded, distributed, and dispensed.[11] The FDA allows for new nominations and re-nominations of bulk drug substances. Following review of these agents, the FDA categorizes the drug and updates the bulk substance list monthly. Currently until the FDA finalizes its lists of bulk active ingredients on the 503A and 503B lists, it does not plan to take action against a compounding facility that does not meet the above stated FDCA conditions so long as the following conditions are met: the active ingredient is manufactured by a company registered with the FDA under section 510 of the FDCA, it includes a valid certificate of analysis, it complies with USP, and is compounded in compliance with other stipulations in the FDCA.[10,11]

Pharmacy and In-Office Compounding Regulations versus Recommendations and How This Affects Clinicians

All physicians must adhere to compounding regulations set forth by the FDA and their respective state medical, pharmacy, and health boards. Legally, pharmacies and clinicians must adhere to regulations, while recommendations that are not set forth by regulations are not binding. Provisions of the DQSA are considered law. For other aspects of the FDCA, however, the FDA has published several draft documents providing guidance on compounding human drug products, prescription requirements, and facilities in which compounding occurs. While these are technically non-binding recommendations, many authorities interpret these draft guidelines as the law. This distinction between recommendations and regulations is often poorly understood in the clinical community, leading to confusion among practitioners on what can and cannot be done in the office setting.

Oversight of in-office compounding occurs at the state level by the medical and pharmacy boards. In fact, states are responsible for their own laws and regulations pertaining to compounding medications. Consequently, there is significant inter-state variability on policies related to compounding and often these policies are not specific to nonpharmacists (eg, physicians). In 2016, the U.S. Government Accountability Office (GAO) surveyed state pharmacy boards in all 50 U.S. states on the settings in which drugs are compounded, state laws and policies, and communication between the states and the FDA. Highlights from this survey include: 1) there is a lack of quantitative and qualitative data on compounded drugs within states, 2) less than 20 percent of states reported having physician-specific compounding laws, regulations, and policies, and 3) while most states are satisfied with their communication with the FDA, there are still challenges. Despite these shortcomings, nearly all states reported having drug compounding laws, regulations and policies that are enforceable if upon inspection the state finds the compounding facility noncompliant.[12] A second national assessment survey of 43 U.S. states commissioned by the Pew Charitable Trusts highlighted the inter-state variability in policies and dissension from federal law.This survey found that nearly half of the states that responded to the survey required adherence to the USP General Chapter <797> on sterile compounding, 60 percent were not required to report adverse events related to compounding, and 65 percent allowed pharmacies to dispense compounded medications without a prescription. The latter survey responses conflict with recently clarified federal law that commands receipt of a patient-specific prescription prior to dispensing compounded drugs.[13]

The Joint Commission has published a chart called "Pharmacy Rules/Regulations by State for Compliance with USP 797 Medication Compounding" as a resource for pharmacists to clarify the state-specific laws. For instance, in NewYork, the State Board of Pharmacy oversees compounding in pharmacies and does not require full compliance with the USP General Chapter <797>.[5]This chart, however, only references regulations as they pertain to pharmacists and the rules may differ for physicians. According to a representative at the New York State Board of Pharmacy, the NewYork State Board of Medicine oversees physician compounding and physicians are expected to follow both USP and FDA regulations. This highlights the point that state compounding laws often do not specifically address compounding outside of pharmacies. Physicians must familiarize themselves with their respective state's regulations and which governing board oversees compounding practices.

A major factor influencing a physician's ability to compound are the upcoming changes to the USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. The previous edition of this chapter was published June 2008 and is being updated. Revisions were proposed in September 2015 with plans for these to be finalized in September 2018 after an opportunity for public comment. Proposed revisions include consolidating the previous three compounding sterile preparations (CSPs) risk categories into two categories – Category 1 and Category 2 – based primarily on the conditions under which they are made and the time within which they will be used. Category 1 CSPs have a shorter beyond use date (BUD) and may be prepared in a segregated compounding area; Category 2 CSPs have a longer BUD and must be prepared in a cleanroom environment. For example, Category 1 CSPs are assigned a maximum BUD of 12 hours or less at controlled room temperature or 24 hours or less if refrigerated if made in accordance with all the applicable standards for Category 1 CSPs. Category 2 CSPs have longer BUDs based on

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the conditions in which they are prepared and stored.[14,15] The consequences of these USP revisions remain uncertain, but if state pharmacy boards adopt the finalized USP guidelines, this may impact physician's ability to continue in-office compounding.

Penalties

Current compounding guidelines are evolving rapidly, but it is important for physicians, pharmacies, and healthcare facilities to have a basic understanding of the laws set forth by State and Federal regulatory entities. The FDA conducts for-cause inspections of compounding pharmacies, and FDA will take aggressive action, including enforcement actions, as appropriate, to protect the public health. Facility and responsible individuals may be subject to Federal regulatory actions including, but not limited to, a warning letter, seizure of product, fines, and/or injunction, or referral for criminal prosecution by the United States Department of Justice. For example, the FDCA prohibits physicians from regularly compounding prescriptions that are essentially copies of commercially available drugs. A first violation is considered a criminal act and the penalty could include up to a year of imprisonment or a fine of up to $1,000, or both. A second violation is punishable by up to 3 years in prison, a fine of up to $10,000, or both, as well as mandatory exclusion from Medicare and Medicaid.[16]

How Compounding Affects Patient Care in Dermatology

Advocates for dermatology have been involved with educating Congress, FDA, USP, and other policymakers and stakeholders on the differences between low-risk compounding in the medical office versus compounding in commercial facilities. The field of dermatology relies on low-risk in-office compounded medication to provide care to patients; some examples include buffering lidocaine, diluting triamcinolone, and reconstituting botulinum toxin.

Many of the agents used by dermatologists are for topical use or for intradermal injection, which inherently carries less risk than medications used for intravenous infusion, intraocular, or intrathecal purposes. It is common practice in dermatology to take multi-use vials of 1% lidocaine with epinephrine and buffer with bicarbonate to reduce pain on injection. This compound has been shown to maintain its anesthetic and vasoconstrictive properties for up to 1 week after being prepared.[17] In addition, a 2016 study by Pate et al analyzed syringes of plain 1% lidocaine and 1% lidocaine with epinephrine and/or sodium bicarbonate that were drawn from multi-use vials using routine clinic aseptic technique. They concluded that prefilled lidocaine syringes stored at controlled room temperature or controlled cold temperature are not subject to bacterial or fungal growth after 4 weeks.[18] This may be due to the preservatives in multi-use vials and/or the intrinsic antimicrobial properties of lidocaine itself.[19] With this information and considering national shortages, it seems reasonable for physicians to add bicarbonate or epinephrine to multi-use vials of lidocaine using aseptic technique in the clinical setting.

With growing concerns of the liability associated with compounding, at least one hospital has adopted a one vial, one patient policy to ensure patient safety when injecting medications.[20] Misguided legislation surrounding compounding and the associated risks have the potential to encourage other medical facilities to do the same. This superfluous approach is not only wasteful but will also amplify healthcare costs.

Access is another major concern if regulations continue to heighten. Dermatologists frequently use compounded medications manufactured from outside sources for office-use. Examples of "office-use" compounded medications include pre-formulated topical numbing creams, compounded wart treatment formulations, and aluminum chloride. When obtained through traditional 503A compounding pharmacies, these frequently utilized drugs may be readily available in small amounts at an affordable price, but now, they must be patient specific. Alternatively, physicians can acquire these compounded drugs at the 503B compounding facilities, but there may be a significant delay, they may only be available in large batches a that create waste and high costs or the medications may not be available at an affordable price. While some of these products may be intended for use in the office, they may also be intended for home use. The physician is held accountable to ensure such products are produced at FDA-registered and -compliant facilities keeping in mind that FDA registration is not synonymous with meeting all FDA requirements outlined in the FDCA. There is concern from the FDA that while compounding without meeting the requirements of 503A or registering as a 503B is illegal, registration is voluntary and there may still be rogue compounding pharmacies supplying medications to unsuspecting physicians. This contradicts FDA position to direct healthcare providers towards more heavily regulated outsourcing facilities, and it creates a hurdle for patient access.

Confusion surrounding compounding may discourage dermatologists from compounding in the clinical setting. In particular, dermatologists may be weary to perform such practice out of fear of hefty fines associated with the creation of an essential copy of a commercially available drug. However, if the physician compounds a product that is similar to but slightly different for a particular patient need, this may not be an essential copy. For example, when a surgeon dilutes lidocaine with epinephrine for a patient with a sensitivity to the epinephrine component, this is not an essential copy of a commercially available drug because this cannot be readily purchased. This product is different from the commercial product and is permitted by law so long as the medical necessity is documented.

State legislatures, while well intentioned, continue to misinterpret the intent of the DQSA, draft guidance on pharmacy compounding, and recommendations on compounding in insanitary conditions. Already, concerns over patient safety have prompted 27 states to prohibit office-use compounding. Other state pharmacy boards

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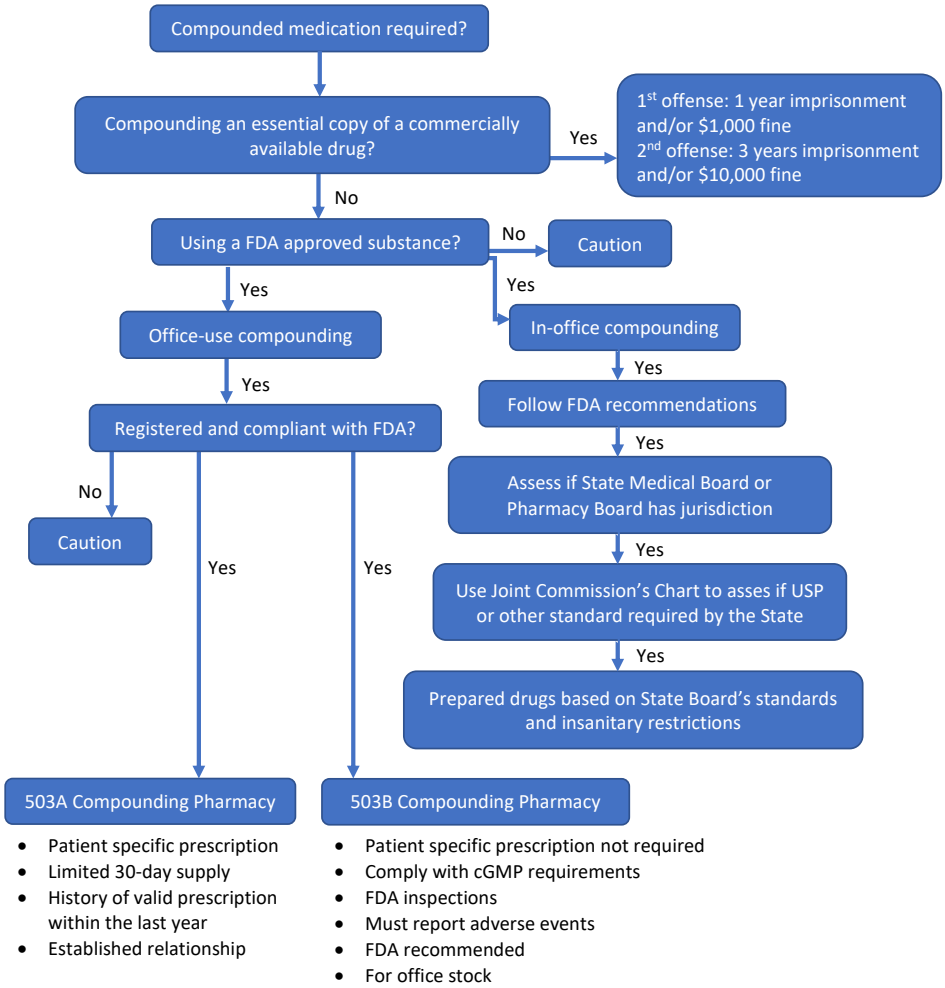
are adopting USP General Chapter <797> revisions before they are finalized. Furthermore, physicians may be subject to more restrictive requirements set forth in the FDA's draft guidance on insanitary conditions if prematurely adopted by state pharmacy boards. The impetus for these moves by the FDA resulted from dead insects and dog hairs being discovered near sterile compounding rooms at various compounding facilities. In the FDA's draft guidance document, there are several examples of what may be considered insanitary conditions, such as performing aseptic manipulations outside a laminar flow hood, putting on gown apparel improperly, or having loose ceiling tiles.[21] If implemented, it would essentially make in office compounding prohibitive for the majority of practitioners.

While state pharmacy board regulations typically pertain only to pharmacists and compounding facilities, at least one state is extending its policies to physicians. The State of Ohio Board of Pharmacy enacted new sanctions on physician compounding in April 2017, which has hindered dermatologists' ability to provide care for their patients. The new law requires a "Terminal Distributor of Dangerous Drugs" license for physicians who compound two or more prescription medications in-office. In addition, the rule outlines the requirements for prescribers compounding drug products. For example, non-hazardous drugs used within 6 hours of preparation (eg, lidocaine mixtures) must be prepared using aseptic technique with proper hand hygiene and powder-free gloves in a designated clean medication area.[22] In contrast, the State of California requires that such medications be used within a 1 hour time frame, but currently does not require a license.[23] In further contrast, the state of NY allows for compounding of medications based on the most restrictive use requirements of the components mixed together as opposed to an arbitrary time limit. In other words, if one component has an in-use time of 12 hours and another has an in-use time of 6 hours, then the compounded medications must be used within 6 hours of mixing.[24] Thus, compounding restrictions by the states vary widely with little consistency as to the rationale behind the restrictions. In addition, Isedeh et al noted that if physicians fall subject to the same rules and regulations imposed on compounding pharmacies, then most dermatology offices would

FIGURE 1. Compounding options algorithm.



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be considered an insanitary environment unfit for in-office compounding.[25] This would limit dermatologists' ability to provide care for many of their patients due to the inability to compound certain low-risk medications.

To assist dermatologists with compounding, we propose the following algorithm as a guideline to comply with scrutiny by State and/or Federal agencies. See Figure 1.

CONCLUSION

Compounding serves an important role in the field of medicine and quality assurance is paramount to ensure patient safety. While some forms of compounding require strict adherence to FDA requirements, low-risk in-office compounding by dermatologists or any physician should not be held to the same burdensome requirements proposed in the FDA's draft guidance pharmacy compounding and insanitary conditions. Such requirements have the potential to delay treatments, raise health care costs and negatively affect patient satisfaction. Physicians, pharmacists and policymakers should work together to formulate a risk stratification scheme for compounded drugs in various healthcare settings based on reproducible data. In the meantime, physicians can use the algorithm proposed, to minimize their risk of exposure while trying to help their patients.

DISCLOSURE

Dr. Desai serves on the US Food & Drug Administration Pharmacy Compounding Advisory Committee (PCAC). His views and opinions are his own and do not represent his role at the FDA. In addition, this manuscript was drafted on a scientific basis without any governmental affiliation.

Dr. Harper is a speaker and advisor for Aclaris, LaRoche Posay, and Ortho, a speaker, consultant, and advisor for Allergan and Galderma, a consultant for Aqua, BioPharmX, and Sun, and a speaker, consultant, and investigator for Bayer.

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