Prescriber, Beware: Understanding and Protecting Drug Compounding

Compounding has been an integral part of the specialty, but changing regulations and new players may converge to bring change.

BY PAUL WINNINGTON, EDITORIAL DIRECTOR

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that there are some drug products that are not commercially available that are considered therapeutically important, but a doctor could not get them simply because there’s no FDA-approved source,” observes Sheldon Bradshaw, JD, a partner at King and Spalding in Washington, DC and former Chief Counsel at FDA. “One of the examples that dermatologists often use would be lidocaine to help relieve pain associated with particular procedures.”

Seemal R. Desai, MD, a dermatologist in Plano, TX, explains that there are two main types of compounding: in-office compounding and office use compounding. In-office compounding can be further classified. In states that allow in-office pharmacies, physicians may order and the practice-based pharmacy may dispense compounded formulations for the individual patient’s use. If an in-office pharmacy is not permitted or does not exist, the physician can order a compounded drug product via prescription (this form of compounding is established by section 503A of the FDCA, discussed more below). As such, “office-use” compounding includes products intended for the patient’s home use.

In any practice, the preparation of topical or injected products for use during or in association with a procedure may also be considered “in-office” compounding. Increasingly, dilution of drug products like lidocaine or botulinum toxin for injection, for example, could be considered in-office compounding.

“According to the FDA, any mixing, adulterating, of diluting...by a strict reading, that’s compounding,” Dr. Desai says. He notes that his comments are his own and not those of any governmental agency and/or related to any of his appointments.

“Diluting Botox or diluting lidocaine—is that really compounding?” Dr. Kiricik asks. “You’re diluting, right? If I have 2 moles of Botox and I’m putting normal saline in it, is that considered compounding or just diluting the drug? So the definition of compounding is also very gray.”

Additionally, Dr. Desai says, anticipated regulations would limit when and how dilutions could be done in the practice setting. Whereas many practices may dilute a day’s worth of specific drugs each morning—properly storing and handling materials to preserve efficacy and sterility—new restrictions could prevent the practice. The alternative, having to dilute product for each patient, “will slow workflow and create inconvenience for doctors and patients,” Dr. Desai says.

Mr. Bradshaw suspects that the FDA will continue to allow physicians to dilute and prepare agents for in-office use and even notes that dilution is part of the labeling for some agents. However, he does caution that practices need to be attentive to patient safety and product purity. For example, FDA prefers single-use vials as a means to reduce risk of contamination.

Office-use compounding, familiar to all dermatology practices, involves the acquisition of prepared drug products, usually in large (but not excessive) quantities, for use during in-office procedures. Cantharidin to treat warts, or aluminum chloride, noted above, would fall into this category. These drug products are increasingly provided by 503B facilities (Section 503B of the FDCA), which are outsourcing facilities intended to produce large batches with or without prescriptions to be sold to healthcare facilities as office use only.

Some 503A facilities interpret current or proposed regulations to mean that they cannot dispense office-use agents in bulk to the practice. Instead, they may require a prescription for each individual patient in order to dispense the drug product, which, at face value, is not feasible.

However, Mr. Bradshaw points to “one small exception to the requirement for having a prescription”: anticipatory compounding. Assuming there is no FDA approved version of the drug being compounded, the practice is “based on a known quantifiable use of the product by that doctor in that office. So say you have a dermatologist who knows that based on the type of procedures they regularly perform in their office in a month’s course, that every month they average 25 or 30 uses of a particular product. The doctor could ask a 503A pharmacy to make a batch of 30, rather than making a batch of one, 30 separate times. But it has to be based on known use and it can’t be for an extended period of time, so it might be a one-month supply. And then you would sync back up with the pharmacy with the prescription after the fact,” he explains. “So they would still be compounding for individual patients, and that would allow the traditional pharmacy compounding to make a batch of say 30 rather than waiting on a prescription and doing them one at a time.”

The Preserving Patient Access to Compounded Medications Act of 2017 (H.R.2871) introduced in the House of Representatives in June seeks to preserve office-use compounding by authorizing office-use compounding by state-licensed pharmacies.

**COMPUNDED HOME-USE PRODUCTS**

Dermatology has a legacy of innovation related to the use of compounded drug products, and many physicians are known for their “recipes.” TriLuma (Galderma) is essentially a commercialized formulation of what was once known as Kligman’s Solution, after dermatologist Albert Kligman, who popularized the mixture. FDA allows the compounding of drug products—by prescription—when a few specific requirements are met. Traditionally, such compounded drug products have been provided by 503A facilities (after section 503A of the FDCA), which are local pharmacies or in-office pharmacies (where allowed by law) that produce products only for use by the patient in his/her home.

At 503A facilities, the drug product should be compounded for an identified individual patient with a valid...
prescription from a prescribing practitioner, indicating that a compounded product is necessary for the identified patient. The prescription cannot be for a drug product that was withdrawn or removed from the market, because such drug products or components of such drug products have been found to be unsafe or not effective. Additionally, the pharmacy may not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product. FDA maintains and publishes a list of “bulk substances” that may be compounded by 503A facilities. Not every active agent used in commercially available drug products is on the list.

The 503B provision permits for more large-scale production of compounded products, but critics say some facilities
may be stretching the limits of the regulation. For example, certain 503B compounding pharmacies actively advertise the availability of formulations that apparently mimic existing, commercially available, FDA-approved drug formulations. Such practices appear to undermine the spirit of compounding—which is intended to give patients access to drug products that are not already available.

"Compounding is for non-existing drugs," Dr. Kircik maintains. "I'll give you an example. Let's say you want to mix vitamin D—calcipitriol 0.005%—with betamethasone 0.064% in suspension. That's illegal because it exists as Taclonex. But if you mix vitamin A—that's tazarotene—plus Vitamin D, plus betamethasone, that's legal because it doesn't exist."

"A number of entities are still really acting like the New England Compounding Center was acting," asserts Mr. Bradshaw. "They're still manufacturing in bulk but they're not complying with FDA's cGMP requirements. They're often compounding drugs using ingredients that aren't on the list provided by the FDA. And importantly, they're also often compounding drugs that are essentially copies of an FDA approved drug product.

"They often try to cover their unlawful actions by saying, 'Look, we're registered with the FDA.' This may be true. But they want doctors to believe that registration is sort of the equivalent of the FDA's Good Housekeeping seal of approval—that because they're registered, they're somehow in compliance with FDA regulations. But registration with the FDA is only one small portion of what they have to do," he explains.

The onus is on doctors to assure that they direct patients to compliant pharmacies, Mr. Bradshaw warns. "In sourcing these medicines, prescribing physicians have to ask whether or not the 503B facility is in compliance with all of these other provisions. And in many cases, candidly, they're not," he says.

There are often warning signs of non-compliance. "One red flag for a doctor is anytime a pharmacy is essentially saying you should use one of our compounded drugs in lieu of the FDA-approved drugs that you normally use," Mr. Bradshaw says. "In essence, they're trying to get doctors to switch from an FDA-approved product to one of theirs, when the whole idea is that outsourcing facilities are only supposed to be filling a niche where there isn't an FDA-approved drug available." Non-compliant pharmacies may slightly tweak the formulation so it has different inactive ingredients or may combine two active ingredients together to try to create something that is not commercially available. "But that all still runs afoul of the Act," Mr. Bradshaw maintains.

There are clinical concerns about the efficacy of some of the 503B drug products. "Vehicles matter, and not only do vehicles matter, but there's more to consider," Dr. Kircik insists. "How much active goes there, how much of it stays there, how much of it is being absorbed? We have no idea what's going on with some of these formulations."

Recently, new companies have emerged that provide dermatology practices with equipment and supplies intended to automate in-office compounding. Some observers are concerned about the efficacy and legality of these services. Even if the medical practice is permitted by state law to dispense prescription drug products from the office, there are outstanding questions, including those related to copying commercially available formulations.

Mr. Bradshaw points to a few potential pitfalls for practices that engage in such compounding activities. For one, to assure full compliance, the practice should probably be registering with FDA as 503B outsourcing facilities, which is an extensive undertaking that utilizes a good deal of resources. Additionally, prescribers may be subjecting themselves to increased liability, he warns. "At least when doctors are sourcing drugs from the pharmacy, they can at least try to argue that they themselves were not the ones that made the drugs—they received it from what they thought was a reputable company. They may not have done much due diligence, but that's what they thought," Mr. Bradshaw says. "But now, if an injury is caused by a product that was compounded in the doctor's office, they don't even have that extra layer of insulation in defending a suit. So, it seems like doctors are needlessly taking on a lot of extra liability in moving a compounding operation right into their office."

Industry is taking note, as well. In September, Allergan filed suit in the US District Court for the Central District of California against Imprimis Pharmaceuticals, Inc., Prescriber’s Choice, Inc., and Sincerus Florida, LLC alleging that those companies are unlawfully manufacturing and selling unapproved new drugs and violating the Lanham Act and state law by engaging in false and misleading advertising and promotion of their unapproved new drugs.

Finally, there are questions about the touted practical “benefit” to patients associated with these compounded drug products. For example, Dr. Kircik says they may cost patients more out-of-pocket than a branded drug obtained with a rebate.

A CALL TO ACTION

Dr. Desai and Dr. Kircik urge their dermatologist peers to become more aware of issues associated with compounding and to get involved. The AADA is keeping abreast of developments and working with dermatologists, law makers, and regulators. Because it is such an integral part of the specialty, dermatologists may take compounding for granted. "We want to educate our members of the AAD. We want to protect in-office and office use compounding for dermatology," Dr. Desai insists. "We want to clarify and protect the legal value of compounding."