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COMPOUNDING & the Practicing Urologist

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Most urologists are aware of pharmacy compounding, but few are familiar with federal regulations regarding compounding that may affect their practice. Inappropriate use of compounding has legal consequences for the prescribing physician. One urologist recently sat down with the former Chief Counsel of the FDA to learn more.

Pharmacy compounding is a process whereby pharmacists mix bulk ingredients to produce medications that are not available commercially. Compounded drugs, however, are not approved by the United States Food and Drug Administration (FDA) as safe and efficacious.[1,2] The FDA recognizes that, under certain well-defined circumstances, compounded medications can play an important role in our healthcare system, e.g., when a pharmacist compounds a drug product pursuant to a doctor's prescription for an individual patient with a specific medical need, such as preparing a drug product in liquid form for someone with swallowing difficulty.

While many compounding pharmacies operate within the FDA's narrow and specific boundaries, others do not. Inappropriate compounding creates significant safety risks for patients and potential liability issues for healthcare professionals.

From malpractice implications to reimbursement, considerations every practicing urologist needs to know are covered here in the conversation between Jed C. Kaminetsky, MD, FACS, practicing urologist with University Urology Associates, New York, and clinical assistant professor of urology at NYU School of Medicine and former Chief Counsel of the FDA, Sheldon Bradshaw, JD.

Dr. Kaminetsky: What is the FDA's position on pharmacy compounding?

Mr. Bradshaw: The FDA recognizes the value of "traditional pharmacy compounding." It is important to note, however, that the Agency defines "traditional pharmacy compounding" very narrowly. In short, the traditional practice of pharmacy compounding involves the preparation of a drug product pursuant to a doctor's prescription for an individual patient with a specific medical need, e.g., a patient who is allergic to one of the inactive ingredients in the FDA-approved drug, a child who cannot tolerate the FDA-approved drug without the addition of a flavoring, a patient who needs the FDA-approved drug in a different dosage form, etc. Of particular note, in its Compliance Policy Guide ("CPG") on Pharmacy Compounding, the FDA states that traditional pharmacy compounding does not include the "[c]ompounding [of] drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products." The FDA's CPG further states that a pharmacy may compound a drug product that is slightly different than an FDA-approved drug only if (1) it does so in "small quantit[ies]" and (2) there "is documentation of the medical need for the particular variation of the compound for the particular patient." The CPG on pharmacy compounding is available on the FDA's website at www.fda.gov.[4]

Dr. Kaminetsky: What is the FDA's position on doctors prescribing compounded drugs?

Mr. Bradshaw: The FDA's position on this is crystal clear. They expect physicians to prescribe FDA-approved drug products when they are available and compounded drugs should only be used if there is no available FDA-approved alternative appropriate for a patient's treatment. And where an FDA-approved alternative is available, the FDA expects the prescribing physician to document the clinical rationale for their decision to prescribe a compounded drug product. In a document entitled "The Special Risks of Pharmacy Compounding," the FDA goes so far as to specifically recommend that consumers "protect themselves against inappropriate drug-compounding practices" by "ask[ing their] doctor if an FDA-approved drug is available and appropriate for [their] treatment."[1]

Dr. Kaminetsky: Why are compounded drug products disfavored by the FDA?

Mr. Bradshaw: FDA has explained that its efforts to circumscribe the use of compounded drugs are due to the fact that "compounded drugs are not FDA-approved," which "means that FDA has not verified their safety and effectiveness." It also means that compounded medications, unlike FDA approved medications, are not manufactured in compliance with current good manufacturing practices ("cGMP") or in facilities subject to inspection by the FDA. As a result, the Agency has cautioned "that poor practices on the part of drug compounders can result

in contamination or in products that don't possess the strength, quality, and purity required," which is of particular concern for sterile or implantable drug products.[1] Doctors need to know that the FDA views compounded drugs as unapproved new drugs under the Food, Drug and Cosmetic Act ("FD&C Act").[5]

Dr. Kaminetsky: May a doctor be held liable for prescribing compounded products?

Mr. Bradshaw: There absolutely can be medical liability in this situation and, in addition, many malpractice carriers will not cover the use of compounded medications when an FDA-approved product is available. If a patient is injured by a compounded medication, which, unlike FDA-approved medications, is not manufactured in compliance with cGMPs or in facilities subject to inspection by the FDA, the physician may be left personally liable.[6] Consider, for example, the possible exposure to the doctors who prescribed the unapproved compounded drugs at issue below.

Recently, the FDA reported that 12 patients in Florida and four patients in Tennessee contracted eye infections that led to increased vision loss and, in some cases, blindness when compounding pharmacies re-packaged the drug Avastin® (Genentech/Roche), which is approved for cancer, for use in macular degeneration. In this case, the compounded drug was shown to contain bacteria that would not have been present had the doctors simply used the FDA-approved drug Lucentis® (Genentech/Roche), which has the same mode of action as Avastin®, but is actually approved by FDA as an eye treatment and is manufactured and packaged in an FDA-approved facility that follows cGMPs and tests drug products for sterility before releasing them.[7]

Another example occurred in Walnut Creek, CA, where 10 hospitalizations and 3 deaths occurred due to bacterial meningitis caused by compounded cortisone injections. When officials investigated the facility, they found that drugs were being mixed by technicians wearing long-sleeved sweaters and jewelry, who were not wearing clean gloves and did not thoroughly wash their hands. Near the compounding area, there was a tropical fish tank and, on a shelf behind a laminar flow hood where sterile products were made, cans of cat food used to flavor drugs for pets were found.

Serratia bacteria, which was the type determined to cause at least one of the deaths, was detected on the sink drain board, sink handles and on the instrument used to mix the betamethasone.[8] These are just a few examples of which there are many. Without an effective way to track adverse reactions globally, we will probably never know the full extent of this issue.

Dr. Kaminetsky: Can you describe appropriate vs. inappropriate uses of compounded product?

Mr. Bradshaw: As previously mentioned, the appropriate use of compounded products is narrow and only covers a need that is truly unmet by an FDA-approved product. An example would be a child that is unable to swallow a tablet. In this case, the drug can be compounded into liquid form so that this individual patient can receive the treatment they need. The caveat is this drug can only be made in small supply for this individual patient upon receipt of a prescription for that patient, as compounded products may not be manufactured in large quantities.

Compounding is inappropriate whenever there is an FDA-approved alternative that will effectively treat a patient; it's that simple. Having a slightly different dosage strength or a small variation in the inactive excipients without medical justification does not warrant the use of compounded drugs. If someone is using compounded products that are made in large quantities in anticipation of patients who will need the drug product—that is also inappropriate. As mentioned earlier, all compounded drug products are viewed as unapproved new drugs by the FDA and physicians must be able to document the clinical reason why they chose to use this product in place of an FDA-approved alternative.

In the CPG on pharmacy compounding, the FDA clearly defined the following criteria as unacceptable:[4]

- Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.
- Compounding drugs that were withdrawn or removed from the market for safety reasons.
- Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA-sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312.[9]
- Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
- Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
- Using commercial-scale manufacturing or testing equipment for compounding drug products.
- Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state-licensed persons or commercial entities for resale.
- Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available

FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.

- Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

Dr. Kaminetsky: What if the cost of compounded drugs is lower?

Mr. Bradshaw: There are several issues to consider in response to this question. First, if there is an FDA-approved alternative, a lower price would not justify the use of a compounded product based on the criteria set forth by the FDA. Why lower prices do not justify the use of compounded medications is nicely illustrated in the recent case involving the use of contaminated Avastin® that I discussed previously.[7] In that case, doctors were using compounded versions of the cancer-drug Avastin® to treat macular degeneration, rather than Lucentis®, which has the same mode of action as Avastin® and is actually approved by the FDA as an eye treatment, because the compounded Avastin® was less expensive than the FDA-approved Lucentis®. That decision, of course, had tragic consequences. Second, although the cash price may be lower, the out-of-pocket cost to the patient is often higher as many insurance carriers will not provide reimbursement for compounded drugs.

Dr. Kaminetsky: Are there any reimbursement-related issues when using compounded drugs?

Mr. Bradshaw: With regard to billing for office administered preparations, while an office can attempt to bill for a compounded preparation using an un-assigned code in addition to submitting an invoice, some government programs and most private payors will not cover the use of compounded medications as they are viewed as unapproved new drugs. Where physicians expose themselves to liability is when they use an FDA-approved product's Healthcare Procedure Coding System (HCPCS) code or National Drug Code (NDC) number in billing for a compounded product. The Office of Inspector General of the U.S. Department of Health and Human Services (OIG-HHS) refers to this practice, i.e., "billing for a more expensive service than the one actually performed," as "upcoding." OIG-HHS has identified upcoding as "among the most frequent subjects of investigations and audits by the OIG."[10]

This practice may also violate the False Claims Act when the federal government is the payor, as the government is paying for an FDA-approved, cGMP-compliant product, but is actually receiving an unapproved drug product compounded without regard to cGMPs.[11]

(continued)

Important Risks to Consider When Using Compounded Drug Products

- **The FDA does not inspect facilities compounding drugs:** Pharmacies engaged in compounding medications are not required to follow FDA's cGMPs and FDA does not inspect such facilities to confirm such compliance. The lack of a sterile manufacturing area can (and often does) compromise the ingredients used to make compounded medicines.
- **Unknown drug stability:** It is common for compounded drugs (which are not FDA-approved) to come without an expiration date and after potency has diminished, or with an expiration date that is not supported by any stability testing.
- **Super-potency:** The strength of the compounded medication may be higher than the labeling indicates.
- **Sub-potency:** The strength of the compounded medication may be lower than the labeling indicates and, in some cases, the compounded drug may not include any active ingredient.
- **Wrong active ingredient:** In some cases, compounded drug products may even contain the wrong active ingredient.
- **Malpractice insurance:** Injuries associated with inappropriate use of compounded agents may not be covered by malpractice carriers.
- **Reimbursement:** Use of compounded drugs may not be covered by private or government payors and the billing of compounding drug under FDA approved drug codes is considered "upcoding" by the OIG.

Dr. Kaminetsky: Can you give me examples of cases in which the FDA has taken action against compounding pharmacies?

Mr. Bradshaw: The FDA routinely sends warning letters to compounding pharmacies. Recently, Wyeth petitioned the FDA to take action against pharmacies compounding bio-identical hormone therapy (BHT) drugs. In response to Wyeth's petition, the FDA sent Warning Letters to seven pharmacies compounding such drugs and issued a press release urging patients to use FDA-approved hormones whenever possible.[12] In addition to sending Warning Letters, as the FDA did in the case of pharmacies compounding BHT drugs, doctors should be aware that FDA-initiated regulatory action may include seizures, injunctions, and/or prosecutions.

Dr. Kaminetsky: You know, we don't learn this in medical school. If I were to educate my residents on rules of the road for understanding pharmacy compounding, what are 3 or 4 bullet points I should give them?

Mr. Bradshaw: It's really pretty simple. I would let them know that compounding is only appropriate when there is no FDA-approved drug that can effectively treat their patient's ailment. This typically occurs in the following circumstances:

- An individual patient has an allergy to an ingredient used in an FDA-approved medication.
- A patient requires a medication for which there is no suitable FDA-approved formulation.
- The FDA-approved drug is not currently available.

Under any other circumstance, they would be taking an unnecessary risk that could cause harm to their patient and ultimately leave them personally liable for their actions.

With regard to reimbursement and billing, I would make sure they understood that, in most circumstances, compounded products will not be covered by insurance as they are viewed as unapproved medications, and that using codes for established FDA-approved products when using a compounded product would likely be considered fraud, which is serious business.

Dr. Kaminetsky: Thank you, Sheldon. As a busy urologist, I'm seeing more and more of this and other forms of counterfeiting FDA-approved medications. I think this is important information that all of my peers should have.

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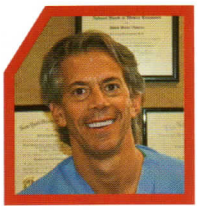

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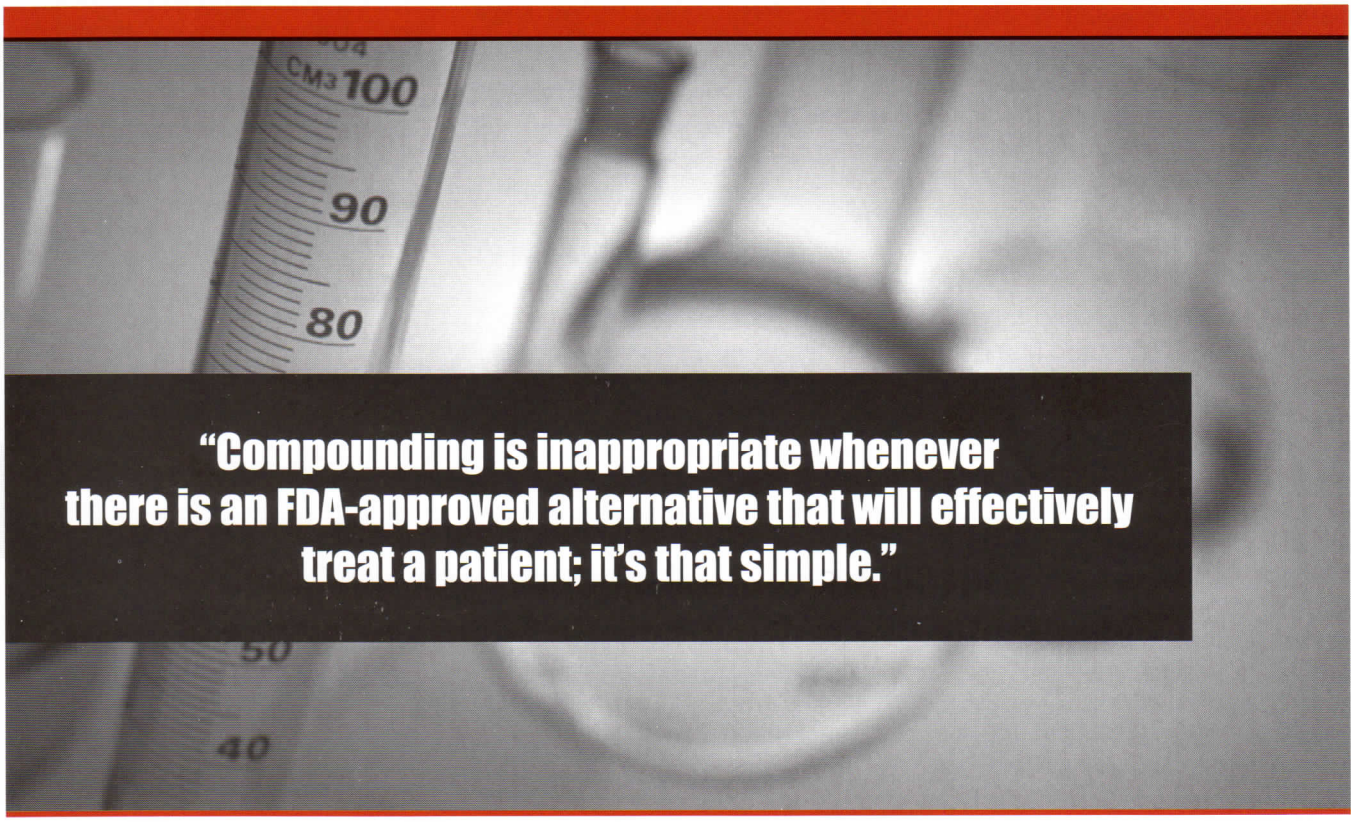
Sheldon Bradshaw, JD, served as Chief Counsel of the FDA. As Chief Counsel, he was responsible for providing legal advice to the Secretary and Deputy Secretary of the U.S. Department of Health and Human Services and to the FDA's senior leadership—including the Commissioner, the Deputy Commissioner and the Directors of the various FDA centers—on issues related to products regulated under the Federal Food, Drug and Cosmetic Act and the Public Health Service Act. In addition, he oversaw all FDA-related litigation and reviewed and approved every significant regulation and guidance document promulgated by the FDA. In fulfilling his duties, Mr. Bradshaw regularly advised the FDA on issues related to the practice of pharmacy in general and pharmacy compounding in particular. Prior to his service at the FDA, Mr. Bradshaw held several senior positions at the U.S. Department of Justice. He is currently the co-chair of the food and drug practice group at the international law firm of Hunton & Williams, LLP. At Hunton, he advises clients in the same areas in which he worked while Chief Counsel of the FDA.



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Useful Links to Compounding Regulations and Information You Should Know

http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm

http://www.pharmwatch.org/comp/sellers.shtml

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm#Conclusions