Practitioners Take Huge Risks Dealing With Rogue Drug Compounders

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Medical practitioners in general (and ophthalmologists, dermatologists, and plastic surgeons in particular) are increasingly being approached by entities who mass manufacture drugs – under the guise of compounding – that they claim are lower-cost or more convenient alternatives to the FDA-approved drugs the practitioners are already administering or dispensing in their practices. These entities often promise that their products will yield higher profits for practitioners than the FDA-approved alternatives. In some cases they are even offering to help practitioners compound their own special blends of drugs right in their offices or clinics.

But let the buyer beware. Entities making such claims are typically not engaged in lawful drug compounding. Indeed, the rogue actors are neither engaged in the time-honored practice of traditional pharmacy compounding (where a pharmacist, pursuant to a prescription, prepares a drug product that is tailored to the medical needs of a specific patient), nor engaged in the well-accepted practice of compounding medically necessary therapies that are currently unavailable in the marketplace. Rather, they are brazenly circumventing FDA's drug manufacturing and compounding laws to increase their own profits and, in doing so, they put both patients and practitioners at risk.

This paper is intended to: (1) provide background on the laws related to legal compounding, (2) summarize the risks to patients and practitioners provided by rogue actors manufacturing drugs under the guise of lawful compounding, and (3) provide concrete steps that practitioners can easily undertake to protect their patients and practices by ensuring they are sourcing their drugs from reputable suppliers.

Federal Laws Regulating Legal Compounding

Traditional drug compounding is a practice in which a licensed pharmacist (or a physician), pursuant to a valid prescription, combines, mixes or alters the ingredients of a drug to create a new medication that is tailored to the specific needs of an individual patient (whose needs cannot otherwise be met by an FDA-approved drug). For example, if a patient is allergic to a specific inactive ingredient in an FDA-approved medication, a licensed pharmacist can, pursuant to a physician's prescription, create a new version of the medication without the offending ingredient. Similarly, if a pediatric patient cannot tolerate the taste of the FDA-approved medication, a licensed pharmacist can, pursuant to a physician's prescription, create a new version of the medication by adding a flavoring. This is a medically necessary practice and is perfectly lawful.

Over the course of the last several decades, however, compounding has grown beyond its historic focus on individual patients. Indeed, rogue players have begun manufacturing and distributing drug products in bulk – under the guise of engaging in traditional pharmacy compounding – in violation of federal drug manufacturing laws. In fact, this unlawful practice led to a multistate outbreak of fungal meningitis in 2012 that killed 64 patients and affected nearly 800 others. The outbreak was caused by the New England Compounding Center ("NECC"), which shipped over 17,000 vials of an injectable steroid solution from three contaminated lots to healthcare facilities in 23 states.

In response to that public health tragedy, Congress in November 2013 enacted the Compounding Quality Act ("CQA") as part of the Drug Quality and Security Act ("DQSA") of 2013 (Pub. L. 113-54). The CQA amended the Federal Food, Drug and Cosmetic Act ("FD&C Act") by re-enacting one regulatory pathway (and then creating a second pathway) for entities that wish to lawfully compound drug products.

The first pathway is set forth in Section 503A of the FD&C Act. Under 503A, Congress once again recognized the importance of traditional pharmacy compounding. Entities engaged in traditional pharmacy compounding are exempt from three specific federal rules applicable to drug manufacturers (i.e., compliance with current good manufacturing practices ("cGMPs"), labeling with adequate directions for use, and FDA approval prior to marketing) provided that they (1) limit their compounding to prescriptions for identified individual patients and make no more than limited quantities of compounded drugs in advance of receiving prescriptions, (2) do not make drugs (either regularly or in inordinate amounts) that are essentially copies of commercially available drugs, and (3) use permissible bulk ingredients. Products prepared by traditional pharmacy compounders also must not be contaminated or prepared under insanitary conditions; the drugs must be the correct strength and purity; and the drug product's labeling, advertising, and promotion must not be false or misleading.

The second pathway is set forth in Section 503B of the FD&C Act. Under 503B, so-called "outsourcing facilities" may compound drugs in unlimited quantities (without first receiving prescriptions) if they are compounding drugs for which there is a drug shortage or compounding drugs using specific bulk ingredients, as identified on a list published by FDA, for which there is a clinical need. However, outsourcing facilities, similar to traditional pharmacy compounders, cannot compound drugs that are

essentially a copy of one or more approved drugs. Outsourcing facilities must also, among other things: (1) register with FDA, (2) comply with the FDA's stringent cGMP regulations; (3) open its operations to FDA inspections; (4) report adverse events to the FDA; and (5) provide the FDA with detailed information about the products they compound. If an outsourcing facility comports with all of the requirements contained in Section 503B, the product need not have labeling that contains adequate directions for use or obtain FDA drug approval prior to marketing.

Risks to Patient Health Posed by Illegally Compounded Products

Despite the passage of the CQA following the NECC tragedy, rogue actors still persist in mass manufacturing and marketing compounded drugs without complying with either of the two legal pathways or FDA's drug manufacturing requirements. This unlawful practice continues to expose countless patients to experimental and potentially dangerous products.

FDA has repeatedly cautioned that although legally compounded drugs "can serve an important need, they also pose higher risks to patients than FDA-approved drugs. Compounded drugs are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality." FDA has further cautioned that "[t]here can be health risks associated with compounded drugs that do not meet federal quality standards. Compounded drugs made using poor quality practices may be sub- or super-potent, contaminated, or otherwise adulterated. Additional health risks include the possibility that patients will use ineffective compounded drugs instead of FDA-approved drugs that have been shown to be safe and effective."

The dangers of illegal compounding are also underscored by two risk alerts recently issued by FDA. On August 4, 2017, FDA announced that a compounded curcumin injectable product has been associated with two serious adverse events, including one death. In addition, on July 28, 2017, FDA announced that it had received adverse event reports for at least 43 patients who had invitreal (eye) injections of a compounded mixture of triamcinolone and moxifloxacin during cataract surgery. The adverse events included blurred and decreased vision.

Because compounded products are not subject to FDA preapproval, FDA is often unaware of violative and dangerous products until they have actually injured patients. The government can take action at the time, but often it is too late to protect patients. For example:

- In June 2017, the owner and head pharmacist of the NECC was sentenced to nine years in prison after causing a 2012 multistate meningitis outbreak that sickened over 750 individuals and resulted in 64 deaths. The government also indicted at least 14 others in connection with the outbreak.
- In June 2017, the owner and compliance director of an Indiana compounding pharmacy were indicted in connection with their distribution of over- and under-potent drugs, including the opioid morphine sulfate that was nearly 25 times the correct potency – the super-potent drug was administered to three infants at a hospital, and one had to be taken by emergency helicopter to a nearby children's hospital.
- In July 2017, a U.S. District Court in Alabama entered a permanent injunction against a compounding pharmacy and its executives. The Justice Department said the pharmacy failed to adequately address insanitary conditions that resulted in contaminations in sterile areas. The government's investigation was prompted in part by a 2015 outbreak of staphylococcus aureus infections that were potentially linked to products manufactured by the pharmacy.
- In April 2017, a court entered a preliminary injunction against a pharmacy after dozens of patients in the Dallas area were harmed by antibiotic injections used in "dropless" cataract surgeries. Several patients lost vision in one eye, and immediate malpractice litigation was launched against the ophthalmologist and his practice as a result of the event.
- In June 2016, two pharmacists from a compounding pharmacy in Alabama were sentenced to prison, following a 2011 outbreak in which 19 cases of serratia marcescens bacterial infections were reported, including nine deaths, associated with contaminated IV nutrition formula from the pharmacy.

Risks to Practitioners' Practices Posed by Illegally Compounded Products

The publicity surrounding the tragedy caused by NECC in 2012 rightfully focused on the impact to the public health. But following the passage of the CQA, these tragedies can put practitioners at risk too. Drug products that are unlawfully mass manufactured and marketed under the guise of compounding are adulterated and misbranded, and the FD&C Act prohibits their sale and use. As a result, violators may be subject to criminal prosecution and sanctions under FD&C Act. In addition, practitioners may be subjected to the loss of a medical license and patient lawsuits. The use or sale of unlawfully compounded drugs could also give rise to civil liability under patent or other laws.

Moreover, the rogue compounders have tried to scapegoat practitioners. For example, in reaction to FDA's risk advisory regarding the curcumin emulsion, the compounding pharmacy quickly blamed the practitioner, stating in a press release that one event was related to "the apparent improper administration

of a medication to a patient by a practitioner who prescribed the medication for one patient and summarily, and without our knowledge, gave it to a completely different patient."

Another potential risk to practitioners is malpractice liability. When doctors buy misbranded, non-FDA-approved or adulterated drugs from rogue compounders, it is imperative that they understand that such drugs may:

- Contain harmful ingredients;
- Be ineffective, containing incorrect amounts of active ingredients or no active ingredient at all;
- Cause adverse health events; or
- Have been produced, stored and shipped under unsanitary or incorrect conditions, with the risk of contamination.

If a patient suffers an adverse event from one of these drugs, a medical malpractice carrier may balk when asked to provide assistance. Many medical malpractice policies (following the NECC tragedy) typically exclude liability caused by the administration of unapproved or misbranded/adulterated drugs, which include drug products that are not legally compounded.

Even more concerning for practitioners, the lure of large potential financial gains have given rise to significant fraud investigations associated with drug compounding. Importantly, the FDA and the Department of Justice will not hesitate to prosecute practitioners who are viewed as participating in claims fraud against private and governmental payors. For example, in March 2017 and May 2017, the Justice Department announced that fifteen people (including two doctors) had been sentenced in a $172 million insurance fraud scheme. According to the Justice Department:

The defendants prepared medications in bulk quantities, which they alleged to be compounded medications for specific individualized patient needs. The defendants falsely represented to the health insurance providers that these medications were prepared in limited quantities for individual patients and were exempt from FDA inspection. The health insurance providers compensated the defendants for the alleged costs of the ingredients for such medications. The defendants concealed from the health insurance providers that the defendants paid illegal kickbacks to physicians for the issuance of the compounded medications. [The] defendants unlawfully provided the physicians with pre-printed prescription pads.

In fact, a practitioner should be especially leery about a compounding pharmacy that promises increased profits for administering and prescribing their drug products. They should be even leerier about a compounding pharmacy that offers to pay a practitioner for every compounded drug that they order. What the practitioner may view as a new profit center may be viewed by the government as claims fraud or an illegal kickback. To get some sense of the scope of fraud associated with drug compounding, put the following search request into Google: "fraud and drug compounding site:justice.gov" (and these hundreds of examples are just the cases the government has caught!). For further background, see "Compounding the Problem: The Government Cracks Down on Compounding Pharmacy Fraud and Abuse" (ABA Health eSource, 2015).

Concrete Precautions Practitioners Should Take When Using Compounded Products

The FDA generally expects practitioners to use FDA-approved drug products whenever they are available. The reason, of course, is that compounded medications (unlike their FDA-approved counterparts) have not been clinically studied or found by FDA to be safe and effective. But, as FDA's Commissioner, Dr. Scott Gottlieb, recently observed, a practitioner may use compounded drugs "when the needs of their patients cannot be met by FDA-approved drugs." Therefore, in those limited instances when practitioners use compounded drugs, they should take the following concrete steps to ensure that they are only purchasing high quality (and legal) products.

- Be wary of compounders who offer to provide products that are less expensive alternatives to the FDA-approved drug products the practitioner currently prescribes or administers to their patients. Indeed, a loud alarm bell should go off in the practitioner's ears. Under federal law, compounders may not compound drugs that are essentially just copies of FDA-approved drugs that are commercially available. If an FDA-approved drug works and is commercially available, there is no legitimate basis for switching to a compounded drug.
- Be wary of compounders who offer to provide products that have slight (and clinically irrelevant) differences from an FDA-approved product, such as different inactive ingredients or strengths. Such products will likely be considered to be essentially copies of FDA-approved products and, therefore, unlawful.
- Be wary of compounders who offer a single drug product that simply combines the active ingredients found in two separate FDA-approved drug products. Such products may be considered to be essentially copies of FDA-approved products, and they may be unlawful.

If the compounder is not obviously engaged in traditional pharmacy compounding, e.g., they are not universally asking for prescriptions for individually identified patients or are

manufacturing in large quantities, a practitioner should make sure that the compounder is lawfully operating as an outsourcing facility prior to sourcing any drugs from them. To do so, there are four FDA-generated lists that a practitioner should consult. The four lists – all of which were prepared by FDA following the passage of the CQA – are easy to access and the exercise is almost always educational (and, more often than it should be, very sobering).

1. Make sure that the outsourcing facility is registered with FDA. Lawfully registered facilities are listed here:

   https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm

   Practitioners may be surprised to learn that a number of compounders manufacturing drugs in bulk have still not registered with FDA as the FD&C Act explicitly requires.

2. Make sure that the drug being compounded is either on FDA's drug shortage list or that the bulk ingredients (ie, active ingredients) are on FDA's 503B Category 1 list, which can be accessed here:

   https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf

   Practitioners may be astonished to learn that many compounded drugs being offered for sale contain an active ingredient that does not appear on the list published by FDA, despite the fact that such products are unlawful. A practitioner should immediately be skeptical about the credibility of an outsourcing facility that offers to compound such drugs.

3. Make sure that the compounded drug you want to order is on the list of products that the outsourcing facility has reported to FDA, which can be accessed here under the heading "Product Reporting Information":

   https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm#reporting.

   Practitioners may be shocked to learn that the very drug formulations they are being vigorously lobbied to purchase have not been reported to FDA as federal law explicitly requires. In fact, the list published by FDA reveals a large gap between the list of drug formulations that certain outsourcing facilities offer to sell to practitioners and the list of drug formulations those same outsourcing facilities report to FDA. For example, one large outsourcing facility that supplies practitioners with a catalogue listing over 300 unique drug formulations does not have even one single drug formulation on the FDA list. Another large outsourcing facility that on its website touts its ability to compound numerous drug formulations has one (and only one) drug on the FDA list. Offering to compound a drug formulation that the outsourcing facility has not reported to FDA is an obvious red flag that should not be ignored.

4. Make sure that the compounded drug you want to order was manufactured in a facility that is in compliance with FDA's strict cGMP regulations. As noted above, FDA maintains a list of all the outsourcing facilities registered with the Agency at the following easily accessible link:

   https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm.

   For each outsourcing facility, FDA has conveniently provided a link to the most recent Form 483 (which contains the inspectional observations made by FDA during a cGMP inspection) and, of critical importance, a link to any Warning or Untitled Letter that FDA issued to the facility due to manufacturing violations. Practitioners may find it sobering to read the inspectional observations contained in a Form 483 or the list of violations enumerated in a Warning or Untitled Letter. It is important to know, however, whether the outsourcing facility from which the practitioner plans on sourcing critical drug products is in compliance with federal law, particularly as it relates to the facility's ability to compound safe medications. Based on my own experience, a practitioner is unlikely to hear about a compounder's manufacturing problems during a marketing pitch by the compounder.

FDA Commissioner Scott Gottlieb Responds

Notwithstanding the urging of the compounding pharmacy lobby, Dr. Gottlieb is likely to continue to enforce fully the law applicable to compounding. On September 26, 2017, Dr. Gottlieb, who has a long history of seeking to address problems associated with improper drug compounding, issued a statement where he re-emphasized the importance of outsourcing facilities complying with the requirements of the CQA. In so doing, Dr. Gottlieb stressed the importance of outsourcing facilities complying with FDA's cGMP regulations and specifically encouraged the medical community to only source compounded drugs when FDA-approved alternatives were not available and, even then, only from the lists described above.

Following the NECC tragedy, Dr. Gottlieb co-wrote an article (with the author of this paper), "A Compounding Fracture at the FDA," Wall St. Journal, Nov. 13, 2012, in which he criticized the FDA for failing to use its authority to prevent the tragedy, since it had sent NECC a Warning Letter in 2006. In that WSJ article, he wrote that NECC "was hardly a pharmacy as generally

understood; it was manufacturing unapproved duplicates of FDA-approved drugs and distributing them for a large-scale market without first receiving valid prescriptions for the individual drugs." During a May 26, 2017, Congressional hearing, Dr. Gottlieb signaled to proponents of loosening compounding restrictions that for there to be changes, Congress would have to "revisit it as a matter of statute."

On June 26, 2017, Dr. Gottlieb issued yet another statement reiterating the "importance of the [DQSA] and overseeing the safety of compounded drugs." His statement noted that the FDA had conducted more than 400 inspections, including 109 inspections of outsourcing facilities; issued more than 150 warning letters advising compounders of significant violations of federal law; issued more than 50 letters referring inspectional findings to state regulatory agencies; overseen over 125 recalls involving compounded drugs; and worked with the Department of Justice on a number of civil and criminal enforcement actions. He also noted that the FDA has issued 21 draft guidance documents, ten final guidance documents, three proposed rules, a final rule, and a draft memorandum of understanding.

Caveat Emptor

Selling or administering compounded drugs produced in violation of federal law puts practitioners (and their patients) at serious risk. Given the current enforcement posture of the FDA, the potential rewards available to whistleblowers, and the press' hunger for sensational news stories, the question isn't whether, but when, the FDA, medical licensing boards, and the public will find out about unlawful compounding activities. Practitioners should take all precautions to insulate their patients and practices from these activities. When FDA goes after an illegal drug compounder, it can be expected to look for the compounder's customer list. Practitioners who are purchasing these illegally compounded drugs should immediately stop doing so. And, in light of the government's vigorous enforcement of anti-fraud rules against rogue drug compounding, practitioners who have done business with these compounders should also talk to their lawyers.

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