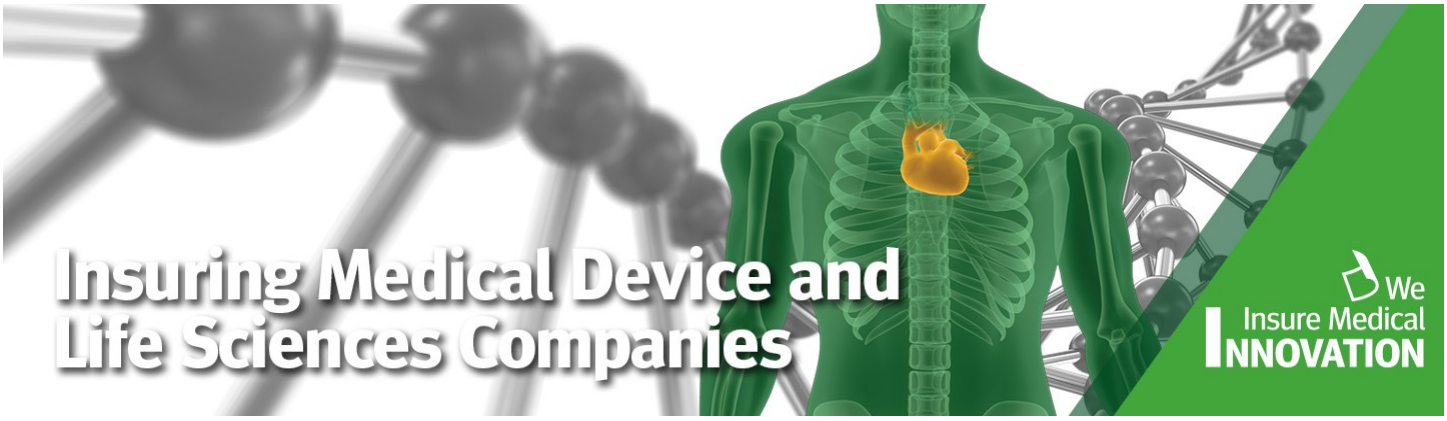

Risk Management 101: Pharmaceutical Compounding

Since a fungal meningitis outbreak tied to a compounding center exposed common misuse of pharmaceutical compounding in 2012, compounding has become the target of significant media and governmental attention. While there are serious risks associated with compounding—largely stemming from the fact that the resultant drugs are not FDA-approved and, as such, have not undergone the rigors of safety testing and clinical trials—compounding is not altogether dubious and there are several legitimate and necessary uses of compounding in healthcare.

□ What Is Compounding?

The Food and Drug Administration (FDA) defines pharmaceutical compounding as "a practice in which a licensed pharmacist combines, mixes, or alters ingredients in response to a prescription to create a medication tailored to the medical needs of an individual patient."

□ Why Are Drugs Compounded?

Compounding may be done for medically necessary reasons, such as to change the form of the medication from a solid pill to a liquid, to avoid a non-essential ingredient that the patient is allergic to, or to obtain the exact dose(s) needed of particular active pharmaceutical ingredient(s). It may also be done for more discretionary reasons, like to add flavors to a medication or otherwise alter the taste or texture to make it more palatable to the patient (often to enhance the likelihood of medication compliance in children, for example).

Key Points

- Most legitimate compounding is done on a patient-by-patient basis, although exceptions exist for populations like animals and children, for whom the dosage or concentration of approved drugs may not be suitable.
- Because compounded drugs have not been subject to FDA approval and generally not tested in clinical settings or on multiple subjects, they are significantly more risky than approved drugs.
- Compounding should be done in compliance with USP Convention, and specifically Chapter <797> for sterile preparations and <795> for non-sterile preparations.
- Non-traditional compounders— those establishments that compound in bulk— should register with the FDA as 503B "outsourcing facilities"
- Compounding cannot be undertaken to produce a drug product that is "essentially a copy" of a mass-produced drug product.

Compounding is most routine in the case of intravenous/parenteral medication, typically by hospital pharmacists, but is also offered by certain retail pharmacies for various forms of medication.

Compounding is also frequently undertaken in the veterinary context. Because drug companies generally spend more time, money, and R&D efforts on drugs for human populations, there are not as many approved drugs specifically for animals. Veterinarians and vet pharmacies frequently compound human drugs for animal consumption.

□ Traditional vs. Non-Traditional Compounding

Traditional compounding is done on a patient-by-patient basis. It is done any time a given drug product is made or modified to have characteristics that are uniquely desired and specifically contemplated for an individual patient. Traditional compounding has been a long-standing practice in the medical industry and one that has obvious necessity for those patients who, for whatever reason, cannot be treated with an FDA-approved medication.

"Non-traditional" compounding is the production of compound drugs for more than one patient. It takes place when "compounding" effectively becomes small-scale mass production of a given drug. Non-traditional compounding has become increasingly commonplace as drug shortages and cost pressures have led some hospitals to rely on larger-scale compounding pharmacies to meet their regular supply needs, particularly for sterile-injectable medications.

Compounding on a larger scale is sanctioned by the FDCA Compounding Quality Act, Section 503B. Section 503B lays out procedures by which compounders can register as Outsourcing Facilities. They must follow the regulation, including producing drugs in accordance with CGMPs and track and trace requirements. So long as they do this, their preparations are exempt from significant drug requirements, like the clinical trial and drug application approval processes.

□ **Why Is Compounding A Concern?**

When done for other than a patient-specific population, compounding raises serious safety concerns for those ingesting the products, which translates to potential products liability and regulatory repercussions for the compounders and, potentially, original drug manufacturers. It is important to remember that the compounded products have not been tested in clinical trials nor approved by the FDA.

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.

Unless a complaint is filed or a patient is harmed, drugs made by compounders are seldom tested. In Texas—one of only two states that does random testing—significant problems have been found. Random tests by the state's pharmacy board over the last several years have found that as many as one in four compounded drugs was either too weak or too strong. In Missouri, the only other state that does testing, potency varied by as much as 300 percent.

□ **Oversight & Regulation**

Traditionally, compounding pharmacies have been licensed and regulated by their respective state boards of pharmacy like all other pharmacies, and were outside the purview of the FDA. (State boards of pharmacy have varying but limited inspection authority and generally do not execute the kind of oversight that the FDA does.)

The U.S. Pharmaceopeial Convention (USP) provides the industry standards for compounding practices, and many state pharmacy boards have integrated the USP standards into their own requirements.

◊ *The DQSA & "Outsourcing Facilities"*

The Drug Quality and Security Act (DQSA) was passed in November 2013 largely in response to the widely publicized misuses of compounding. The law clarifies the FDA's authority over compounding and provides a regulated pathway for non-traditional compounders to operate, allowing them to register with the FDA as "outsourcing facilities."

Under the DQSA and the regulations the FDA promulgated after its passage, the Agency will not exercise oversight over traditional (patient-specific) compounding. Pharmacies compounding only by prescription remain exclusively under state-level pharmacy regulation.

For non-traditional compounders, the DQSA creates a new class of FDA-regulated entities called "outsourcing facilities. Registration with the FDA as an outsourcing facility is currently voluntary. Once registered, these facilities are subject to registration fees, various reporting requirements, and regular inspections.

FDA has also published the following requirements for compounding "outsourcing facilities":

1. Drugs are compounded by or under the direct supervision of a licensed pharmacist.
2. The facility does not compound using "bulk drug substances" (unless certain exceptions apply) and its drugs are manufactured by an FDA-registered establishment.
3. Other ingredients used in compounding the drug must comply with the standards of the applicable U.S. Pharmacopeia or National Formulary monograph, if a monograph exists.
4. The drug does not appear on a list published by the FDA of unsafe or ineffective drugs.
5. The drug is not "essentially a copy" of one or more marketed drugs or categories of drugs that present "demonstrable difficulties" for compounding.
6. The compounding pharmacist demonstrates that he or she will use controls comparable to the controls applicable under any applicable risk evaluation and mitigation strategy (REMS).
7. The drug will not be sold or transferred by an entity other than the outsourcing facility.
8. The label of the drug states that it is a compounded drug, as well as the name of the outsourcing facility, the lot or batch number of the drug, dosage form and strength, and other key information.