

Ensuring the Safety of Compounded Products: Best Clinician Practices and an Existing Solution

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Without doubt, tragedy has struck hundreds of people due to the contamination of a batch of injectable medication produced by the New England Compounding Center (NECC) of Framingham, Massachusetts. Now fear grips the unaware, the unknowing, and the naïve.

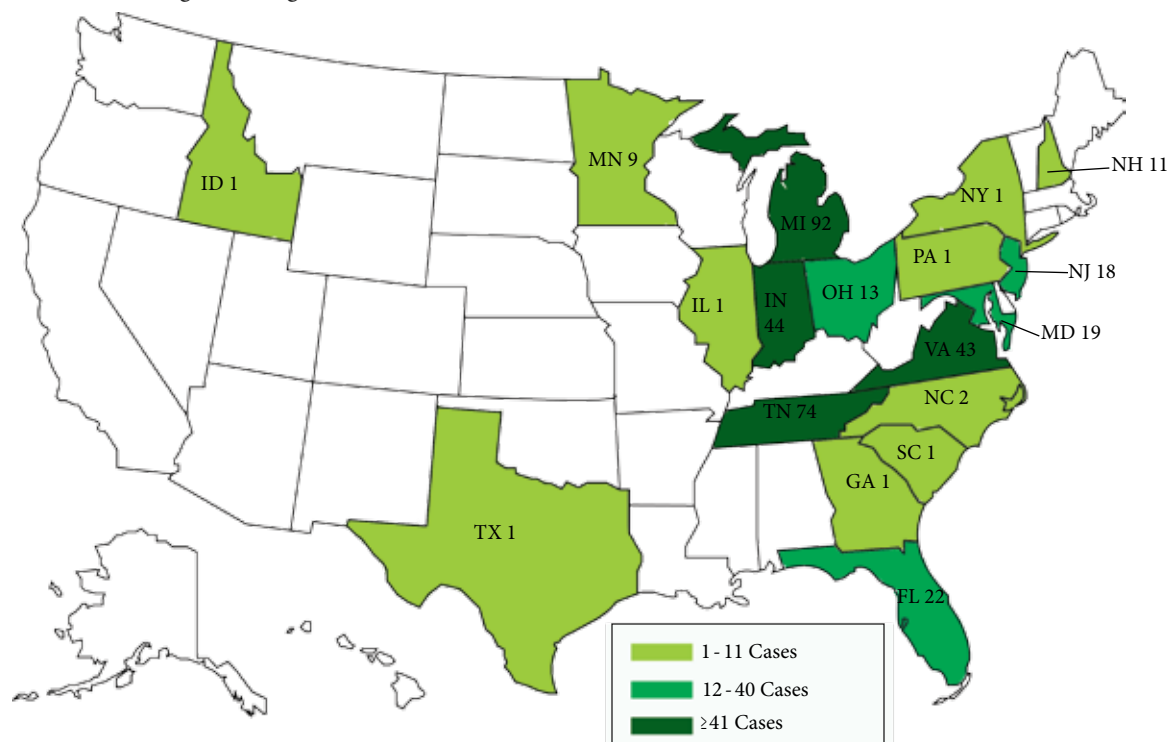
As of October 27, 2012, the Center for Disease Control (CDC) has reported 344 patients diagnosed with fungal meningitis, a potentially life-threatening infection. To date there have been 25 reported deaths from 18 states (Figure 1) and the number has risen as this journal is being prepared for distribution.¹

The CDC and the US Food and Drug Administration (FDA) have confirmed the presence of a fungus known as *Exserohilum rostratum* in unopened medication vials of preservative-free methylprednisolone acetate from one of the three implicated lots from NECC. The laboratory confirmation further links steroid injections from these lots from NECC to the multistate outbreak of fungal meningitis and joint infections.² Over 800 products produced by NECC have been voluntarily recalled.³

It is important to note that an investigation is still in progress with no definitive conclusions officially released at the time of this writing. The CDC and FDA continue to examine all aspects of these patients' treatment—administered medications, syringes, alcohol swabs, physician and nurse procedure, and the clinic environment.

According to the *Wall Street Journal* of October 24, NECC had its products tested at an independent lab in May, which stated that samples from a batch of steroids—later implicated in the meningitis—were “sterile.” But experts said the sample size that apparently was tested was

Figure 1. Cases of Fungal Meningitis¹



too small to be meaningful and didn't comply with industry guidelines.⁴

Physician's View of Compounding Medications

I have been a physician for over 25 years, first in emergency medicine/trauma, then this past decade in integrative age-management medicine. In both practices, the use of compounded medications is a daily occurrence. Physicians understand that medications have risks and benefits, including unwanted and potentially dangerous side effects. But most physicians assume that medications ordered for patients are safe, effective, high quality, and free of dangerous infectious agents.

Most physicians, however, are not aware of the compounding of medications, of US Pharmacopeia regulations 795 and 797, or of independent voluntary organizations like the Pharmacy Compounding Accreditation Board (PCAB). Often, physicians do not know what a compounding pharmacy does, even when they order medication from the compounding pharmacy.

Commercially Manufactured Medications

Commercial medications are produced by Big Pharma. High-blood-pressure pills, diabetic medication, statins, chemotherapy, and antibiotics are but a few of the thousands of types of medications available today. The majority of medications used by patients are commercial medications.

Commercial manufacturers are regulated by the FDA, and their products are dispensed by local pharmacies and in hospitals. Potentially dangerous events can and do occur at commercial manufacturing plants, including contamination of products used in the manufacturing of medications. Contamination can and does occur in every aspect of pharmacy, including commercial manufacturing plants.

"Within the past few years, commercial manufacturing, like compounding, has seen the federal government increase enforcement of Good Manufacturing Practices (GMPs) regulations, allowing more inspectors to visit and assess manufacturing sites domestically and abroad," noted Mark Mandel, PharmD, owner of Mark Drugs, a compounding pharmacy in Chicago. "This increased enforcement by the FDA has led to numerous discoveries of problematic conditions in commercial manufacturing facilities. This has been cited as a major cause of significant nationwide and worldwide drug shortages."

Compounding Medications vs Manufacturing Medications

Compounding of medications is different from commercial manufacturing. Compounding pharmacies ("compounders") take commercially manufactured products and produce (or "compound") that medication in an alternate form or size. Compounding provides individualized and customized therapy that does not meet the definition of manufacturing as described by state boards of pharmacy, the FDA, the US Drug Enforcement Administration (DEA), and the US Supreme Court.

Compounding is an essential component of health care because commercially manufactured medications cannot account for the specific needs of every individual patient or meet the demand of the nation. Compounding is a component of the profession of pharmacy that is and has always been regulated by individual state boards of pharmacy.

Modern Medicine and the Role of Compounding Pharmacies

Compounding occurs for various and essential reasons. Compounders can prepare established medications for use in alternate forms other than those provided by the manufacturer; perhaps an injectable medication made without the preservative is desired. For example, the reason NECC compounded preservative-free methylprednisolone acetate injections is because alcohol is believed by some physicians to cause irritation of the lining of the brain and damage to nerves.

Compounders can also divide commercially produced drugs into smaller, more affordable, easier-to-store amounts to be used by hospitals or physicians. Avastin, used by ophthalmologists to treat macular degeneration, is a good example. Manufactured in 4- to 16-mL vials, it is expensive to obtain. A compounding pharmacy is able to repackage a 4-mL vial of Avastin into smaller, more affordable doses, making this off-label use of Avastin affordable for patients.

When needed, compounders can produce medications that are not currently available or are in short supply. When methotrexate, an effective cancer-fighting medication, was in short supply earlier this year and threatened the well-being of thousands of children with cancer, compounding pharmacies were able to bolster availability of the drug until the manufacturer could ramp up the supply.⁵

Compounding exists in every hospital across the United States. Hospital pharmacies are responsible for preparing intravenous (IV) solutions that contain antibiotics, chemotherapy, and parental nutrition, to name only a few examples. Compounders can produce medications like natural bioidentical hormones, such as estrogens, testosterone, and progesterone, which a physician may desire to treat patients with hormone imbalances like menopause and male low testosterone. Even though many natural hormones are produced by Big Pharma (Vivelle-dot, Testim, Androgel, Prometrium), a physician may request a hormone to be compounded due to cost, availability, dosage, or when judged by the doctor to be in the best interest of the patient.

Compounding Is Regulated

US Pharmacopeia regulation 795 requires compounding pharmacies to follow guidelines in the compounding of nonsterile products (like creams and tablets),⁶ while US Pharmacopeia regulation 797 requires compounding pharmacies to follow guidelines in the compounding of sterile products (like eye drops and injections).

Unfortunately, more often than not, these regulations tend to be enforced retroactively, after an event such as the contamination of corticosteroid preparation such as in the NECC case. Proactive policing of these regulations does not occur with enough regularity, if at all, to ensure that out-of-hospital compounding pharmacies are adhering to these regulations.

Joint Commissions

Physicians, and most laypeople, are quite familiar with Joint Commission for hospital accreditation. An independent, not-for-profit organization, the Joint Commission accredits and certifies more than 19 000 health care organizations and programs in the United States. The Joint Commission accreditation and certification is recognized nationwide as a symbol of quality that reflects an organization's commitment to meeting certain performance standards.

The Joint Commission's mission is to continuously improve health care for the public by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value.⁷ This voluntary, independent organization to which hospitals apply for accreditation ensures an unbiased evaluation of the hospital or health care facility, ensuring that the facility meets the qualifications of excellence in quality assurance and processes required to keep patients as safe from unintentional harm as possible.

So, why isn't there an organization to which compounding pharmacies can voluntarily apply for accreditation, which inspires them to excel in providing safe and effective care of the highest quality and value? Well, there is.

Pharmacy Compounding Accreditation Board

As the demand for compounded medications increased, the pharmaceutical profession saw a need for a system of standards by which each compounding pharmacy can test its quality processes. Compounding pharmacists also wanted a mechanism to allow them to know that they are producing a high quality compound, and in doing so, providing the best quality to their patients. Pharmacy Compounding Accreditation Board (PCAB) accreditation gives patients, prescribers, and third-party payers a way to select a pharmacy that meets or exceeds US Pharmacopeia's high quality standards. Eight of the nation's leading pharmacy organizations joined together, contributing their time, money and leadership, to create PCAB: a voluntary quality accreditation designation for the compounding industry.

Organizations that founded PCAB and that make up the PCAB Board of Directors include⁸:

- American College of Apothecaries
- National Community Pharmacists Association
- American Pharmacists Association
- National Alliance of State Pharmacy Associations
- International Academy of Compounding Pharmacists
- National Home Infusion Association
- National Association of Boards of Pharmacy
- United States Pharmacopeia

"PCAB accreditation requires us to make a significant investment of both time and money," said Executive Vice President of Diplomat Specialty Pharmacy, Jeff Rowe. "This preparation has involved reviewing all of our procedures to make sure they meet PCAB's exacting standards."

When asked about the costs for PCAB accreditation, Rowe noted that "PCAB bases the charges associated for accreditation on the volume of compounds a pharmacy fills. This variable pricing model does encourage smaller volume and start-up compounding pharmacies to seek accreditation, since it makes it more affordable."

"PCAB offers many tools to help develop policies and procedures to help compounders meet and exceed state board of pharmacy and USP standards," continues Rowe. "Obtaining that accreditation gives patients, physicians, and Diplomat the peace of mind that our compounding meets the highest quality standards."

The main issue is that PCAB is a voluntary accreditation process and to date only 163 of the more than 7000 US compounding pharmacies have gone the extra mile to achieve this accreditation. With greater participation in accreditation, no further regulations need to be enacted and no watchdog group needs to be founded. What ought to happen, all things considered, is a push by the government, physicians, compounding pharmacies, third-party payers, the media, and most importantly the patients to require accreditation by PCAB for all compounding pharmacies.

This goal cannot be accomplished immediately, since there is a limit to the rate at which new applicants can be evaluated by PCAB. Requiring immediate accreditation would eliminate the majority of compounding pharmacies, causing a shortage of compounded medications—a situation that would compromise the care of thousands of patients. This is a long-term solution for the industry. Until the time comes that PCAB accreditation becomes the standard for compounding pharmacies, the following points provide practitioners and patients some questions and guidelines for evaluating the safety and procedures of compounding pharmacies.

Key Points for Health Care Practitioners

Choose a PCAB-accredited compounding pharmacy, or one that is in the process of becoming accredited. Or:

1. Practitioners should ask the compounder:
 - a. Are compounding technicians routinely trained? How often and by whom?
 - b. Where are the compounding material (ingredients) sourced from? Are these sources foreign or domestic? This author recommends domestic sources.
 - c. How many human compounds are prepared each week? This author recommends more than 300 human compounds per week to demonstrate sufficient volume.
 - d. If making sterile medications (IVs or injectable medications), what sterile processes and quality assurance are employed?
 - e. Do they belong to organizations such as International Academy of Compounding Pharmacists

(IACP), which promotes, educates, and supports the specialty of compounding?

2. Practitioners should ask if the compounds are made in a dedicated laboratory space (and not a back counter).
3. Practitioners should be aware of the process of quality assurance that the pharmacy engages to verify that the products that they are using are of the highest quality and sterile. Original source material is not verified to be sterile. The physician should be aware if the compounder conducts testing to ensure that the compounded preparation is verified to be sterile according to USP <71> sterility tests. The pharmacy may not have a test for the specific product that you are ordering but they should have reports on testing so that you can confirm that testing is being performed.
4. Practitioners should be aware of whether the pharmacy has standard operating procedures (SOPs) for tracking all lots of compounds per physician order as well as SOPs for a product recall if necessary.
5. Practitioners should be aware if their compounding pharmacists are licensed and in good standing with their state board of pharmacy.
6. Practitioners should be aware if their compounding pharmacy is licensed in any other states to which it could be dispensing/distributing/providing the medication.

Key Points for Patients

1. Know your health care provider. A quality health care provider should have recommendations for compounding pharmacies and be able to provide you with answers regarding the safety and quality required.
2. Ask your health care practitioner if you are receiving any compounded products, and if so, how the safety and quality of the compounder is determined. This is doubly important if you receive IV therapy, injections, or implanted medications.

Key Points for Compounding Pharmacies

1. Demonstrate a commitment to compounding and take specific classes and training to learn the current level of compounding technology.
2. Do not overstep your training, equipment or abilities when it comes to making a preparation. It is better to decline a compound and send it to somewhere that specializes in compounding than to potentially hurt a patient.
3. Strongly consider becoming PCAB accredited.

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