

STERILE PRODUCT COMPOUNDING:

DEVELOPING QUALITY-BASED STANDARDS FOR PHARMACY PRACTICE



Learn more about pharmacy compounding regulations at the upcoming NHIA 12th Annual Conference in San Antonio!

By Eric S. Kastango, R.Ph., M.B.A., FASHP and Brian D. Bradshaw, C.R.Ph., FASCP

Compounding pharmacists and pharmacies are invaluable in delivering patient-specific health care in the United States. Today, pharmacists continue a centuries-old tradition of extemporaneously compounding medications because many physicians choose to prescribe compounded drugs for their patients, a practice which is becoming more prevalent for a variety of reasons (see Exhibit 1).^{1,2} But as the practice of specialty compounding grows, so does the perceived need for governmental oversight. As a profession, we can do better by regulating our practices and ourselves.



Exhibit 1 Why Compound Medications?

There are a variety of reasons physicians prescribe compounded medications.

- **Commercial Availability.** Certain medications may not be available in commercial form or the patient may require a customized form.
- **Concentration.** Patients with chronic or intractable pain regularly require narcotic/analgesic medications compounded in higher concentrations than are commonly available. Often these medications are prescribed in combination with other medications.
- **Inactive Ingredients.** Some patients can experience an allergic or other untoward reaction to inactive ingredients in medications—ingredients such as dyes or fillers which have no therapeutic role. A compounding pharmacist is able to make a similar drug with alternative or no inactive ingredients.
- **Dosage/Form.** The appropriate dosage, strength, or form may not be readily available for every patient. Commercial products, for example, are often not available in strengths that can be easily and safely dosed for children. For those who can't easily swallow tablets or capsules, such as children and the elderly, pharmacists can prepare the medication in another form that can be tolerated.
- **Flavor.** Some children refuse to swallow a medicine, even in liquid form, if it tastes bad. Many times, pharmacists can customize a drug in a child's favorite flavor—cherry, grape, orange, or raspberry—in an effort to increase its appeal and increase compliance to achieve positive outcomes.
- **Market Availability.** The medication may not be available due to shortages, recalls, plant closures, or other manufacturer or FDA related issues.
- **Price.** There may be a significant economic advantage to compounding medications from components compared with using a commercially available medication.

Source: Nordenberg T. Pharmacy compounding: Customizing prescription drugs. *FDA Consumer Magazine* 2000; July-August [serial online]. Available at: http://www.fda.gov/fdac/features/2000/400_compound.html.

THE GROWTH OF NICHE COMPOUNDING

Since the 1980s, Food and Drug Administration (FDA)-regulated pharmaceutical manufacturers have drastically reduced the number of commercially available drugs and their dosage forms, making it difficult for physicians to prescribe and for patients to obtain those medications. Over 7,000 medication-dosage forms have been withdrawn from the market primarily due to economic reasons.³

This void has spawned a niche industry of pharmacies and pharmacists who offer specialized compounding services. Likewise, the popularity

of automated medication dispensing systems, such as central fill, unit-dose repackaging, and admixture operations, is growing. Individual state boards of pharmacy are left struggling to create standards for these new compounding activities and other pharmacy practices, which have been largely left to the principles of "professional discretion."

It is important to realize that compounding suspensions, emulsions, gels, ophthalmic, and especially injectable dosage forms requires considerable knowledge of pharmaceuticals and processes to ensure that the compounded dosage meets intended purity, potency, and sterility. While fla-

vorering a medicine may seem innocuous, it can alter the active ingredient's chemical stability to the point of diminishing its effectiveness.

As the specialty pharmacy niche continues to grow, so does the number of patient injuries or deaths related to improperly compounded medications.⁴⁻¹⁰ Increased oversight is sure to follow—and is already being discussed in public media outlets such as the Associated Press and National Public Radio to name a few.^{6,10,11} Most would expect tighter regulations to originate with individual state boards of pharmacy that regulate pharmacies. But the effect the FDA can have upon pharmacy operations should not be ignored. Recently pharmacies in California and South Carolina were closed through cooperative actions between those state boards and the FDA. In addition, pharmacists have lost their licenses and Pharmacists-In-Charge (PICs) and owners have been named as defendants in multi-million dollar lawsuits—even though all state pharmacy practice acts were followed.

At the same time, the FDA continues its pursuit of pharmacies and pharmacists engaging in activities that may be construed as "manufacturing," and, thus, outside the scope of typical pharmacy practice. This despite the fact that pharmacists nationwide are working without a clear state or federal definition of "manufacturing" as opposed to legitimate pharmacy compounding.

SAMPLES AND EXAMPLES

The FDA recently published a study that would appear to add credence to the agency's concerns over under-regulated compounding pharmacies.¹² Regulators sampled 29 drugs from 12 pharmacies and found that more than one-third of the samples (10 of 29) failed either a drug assay or pyrogen test—nine out of 10 were found to be sub-potent and one in 10 was pyrogenic. The complete study is available at <http://www.fda.gov/cder/pharmcomp/communityPharmacy/default.html>.



California Drafting New Sterile Product Regulations

In response to patient safety concerns, the California legislature has enacted two new laws addressing pharmacy practice: One requiring all pharmacies to develop quality assurance (QA) programs to study and evaluate medication errors. The other is more specific to infusion pharmacies: It requires that pharmacies that compound injectable sterile drug products obtain a separate pharmacy license and comply with new state regulations related to sterile product compounding.

The sterile product standards are still being developed by the California Board of Pharmacy, having already undergone a series of revisions. Scheduled to take effect on July 1, 2004, they address facility and equipment standards; policies and procedure requirements; labeling; record-keeping; protective clothing; training of staff, patient, and caregiver; disposal of waste material; quality assurance; and use of reference materials. For example, pharmacies compounding sterile injectable products from one or more non-sterile ingredients must perform the aseptic processing of such products in a class 100 laminar airflow hood within a class 10,000 cleanroom, with a positive air pressure differential relative to adjacent areas; or in a class 100 cleanroom with a positive air pressure differential; or in a barrier isolator that provides a class 100 compounding environment.

A copy of the latest version of the regulations is available on the members-only section of the NHIA website (www.nhianet.org/members/sterileproductrule.pdf).

The purpose of the study, according to the FDA, was to gather information about the quality, purity, and potency of marketed compounded drug products and to assist the agency in developing a regulatory strategy for compounded drug products. The pharmacies examined by the FDA were selected for their ability to fill prescriptions ordered over the Internet; the sampled drugs were selected based on their common use and potential health risk if improperly compounded.

Unfortunately, similar errors have surfaced in pharmacy practice. In one example, Doc's Pharmacy, a California-based compounding pharmacy, began extemporaneously compounding betamethasone (Celestone®, Shering) in early 2001 in response to a national shortage.¹³ According to the Contra Costa County Health Services, on May 17, 2001, a batch of betamethasone was prepared and dispensed to the Sierra Surgery Center in Walnut Creek, California. The drug was contaminated with *serratia* bacteria, and over the next two weeks, 38 people received spinal injections of the contaminated betamethasone. Dozens of people were hospitalized and treated with antibiotics. Five people developed cases of *serratia* meningitis infections. Three of

those patients died as a result of the infection.¹⁴

Examples like this coupled with the FDA drug sample make a stronger case for tighter control of compounding pharmacies.

SELF-REGULATION AND PROFESSIONAL CHALLENGES

It may be that unless the pharmacy profession voluntarily acts to stem the tide of extensive state regulation and/or FDA interdiction, the privilege of compounding will be legislated away from pharmacists. There are opportunities for pharmacists and pharmacies to work collaboratively with the state boards to develop robust operating principles that will ensure patient safety, allow the pharmacy practice to provide critical services, and assure the FDA and the public that self-regulation and control is in place.

As a profession, our experience has dictated that we can no longer rely on professional discretion as the guiding force in pharmacy practice. Although we may think that we are capable of self-regulating under the current standards of practice, we may be operating under a false sense of security. Just because a pharmacy's operations have

never resulted in a tragedy doesn't mean that a problem doesn't exist. When the FDA or the media shows up at your doorstep, it is too late.

With such a strong case for self-regulation, the next question is how should oversight begin? At the most recent United States Pharmacopoeia (USP) Pharmacy Compounding Stakeholders meeting (held August 2002) there was considerable discussion about board certification for compounding pharmacists. The USP's Board of Pharmaceutical Specialties currently certifies four pharmacy specialties—therapeutics, nutrition, oncology, and psychotherapeutics. While specialty pharmacy could be added, the program would take five to seven years to get up and running, according to Executive Director Richard Bertin, Pharm. D.¹⁵

One challenge facing the pharmacy today involves the various split groups within the profession—characterized by the USP's many specialty groups. Each represents a sub-specialty, important in its own right and with special interests and concerns of its own. However, with the current external challenges to pharmacy practice, the profession as a whole could benefit from putting aside the special interests of each sector in favor of the greater good.

At the same time, we must realize that the longer we continue practicing in an environment that is perceived to be under-regulated and continues to produce patient injuries and compounding errors, we are slowly and quietly losing ground to external regulatory groups. Now is the time for pharmacists to be proactive in guiding the direction of pharmacy compounding. If we can't prove that we can handle it, someone else will.

While the authors recognize the important symbiotic relationship between pharmacy practice and the U.S. Food and Drug Administration, we view FDA regulation of pharmacy practice as intrusive. The agency legitimizes the practice of pharmacy, but should not oversee it. We believe that, if approached in a collaborative manner, the pharmacy profession can demonstrate the principles of self-reg-

ulation and adopt consistent standards of practice that will safeguard patient safety and product quality.

OTHER MODELS

Outside of the International Standards Organization (ISO), an internationally recognized quality organization based in Geneva, Switzerland, there is no current organization that is viewed as the principle authority of pharmacy compounding quality in the United States. None of the current accrediting organizations—the Accreditation Commission for Health Care, Inc. (ACHC), the Community Health Accreditation Program (CHAP), and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)—addresses the specific needs of the specialty compounding pharmacy industry, and there is limited help from professional and trade organizations

for the local compounding pharmacy. Although many of these organizations publish and sell policies and procedures and offer on-site training programs, none offers the necessary depth and breadth to withstand the scrutiny of either a legal or FDA audit, especially in the event of a patient injury.

We may find that a quality-based method of self-regulation would serve the profession best. By embracing a quality-based group of standards—rather than simply following procedures—we can ensure the health and safety of patients receiving compounded pharmaceuticals.

We hope to spark a dialogue within the profession in order to create a mechanism that will guide pharmacists in preparing compounded pharmaceuticals and restore confidence in the final dispensed product from the public and the FDA. Can we adopt and follow a model of self-regulation and consumer education to the regulatory and legal satisfaction of the individual boards of pharmacy, the National Association of Boards of Pharmacy (NABP), and the FDA? One way or another, we'll soon find out. ■

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15. USP Pharmacy Compounding Stakeholders Meeting, August 12, 2002, Rockville, MD



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