

Pulmonary Perspectives

The Perils of Pseudo-Compounded Medications

Physicians have a major responsibility to ensure the safety of their patients' medications.

Recently, there has been a significant rise in public concern about drug safety. The concern encompasses FDA-approved pharmaceuticals and, even more troubling, imported drugs that are not well regulated. Many less heavily publicized pharmaceuticals are mass-manufactured drugs prepared in the United States that masquerade as traditionally compounded products. These drugs should be of great concern to clinicians and their patients. Physicians who specialize in respiratory diseases need to be especially vigilant, because many of these medications are used in nebulizers. Hormones and dermatologic preparations are other commonly "compounded" drugs.

The age-old practice of compounding drugs is when a pharmacist prepares a pharmaceutical by mixing ingredients, in response to a physician's prescription, to meet the needs of a specific patient. This is an invaluable service rendered for patients who require special drug combinations that are not commercially available, people who may be allergic to inactive ingredients in FDA-approved products, and children who may need flavors added to encourage them to take a medicine.

However, so-called "compounding pharmacies" exist that are engaged in the mass manufacturing of drugs under the guise of a traditional compounding practice. They produce millions of doses of their product in anticipation of a physician's order. The problems with this practice are that the drugs are not FDA-approved and that the FDA does not regulate the manufacturing process. Pharmacists running these operations take the position that compounding is supposed to be regulated at a state level by state pharmacy boards. Yet the FDA can intervene, and has intervened, when it can prove that there is mass manufacturing taking place.

There are several consequences of the compounding practice that are very troubling. States do not have the resources necessary to inspect compounding pharmacies, and some states have only a handful of inspectors to cover the entire state, which allows for some extremely shoddy practices by the "compounders." The raw materials used for their preparations are not FDA-approved, so it is impossible to determine their provenance, purity, or potency. Manufacturing processes are often not sterile, and preparations have been unevenly potent, causing the overtreatment or undertreatment of patients. In addition, plastic ampules of drugs for nebulizer formulations have paper labels

with ink that can leach into the solutions, unlike FDA-approved preparations where the labeling is embossed in the plastic, to avoid this problem. There are well-documented instances of each of these problems where patient injury has resulted.

The FDA states that it knows of 200 adverse events involving 71 compounded products since 1990 (US FDA. Consumer Update, May 3, 2007: The Special Risks of Pharmacy Compounding. Available at www.fda.gov/consumer/updates/compounding053107.html), despite the fact that pharmacies are not required to report adverse events like commercial drug manufacturers. Examples of these adverse events include: (1) three patients who died of infections acquired by cardioplegic solutions during open-heart surgery; (2) two patients whose eyes were damaged by infected solutions during cataract surgery; (3) three patients who died of *Serratia*-infected injectable beclomethasone; and (4) 18 cases of *Serratia marcescens* in several states due to contaminated magnesium sulfate IV solution (Sunenshine et al. *Clin Infect Dis* 2007; 45:527). A particularly egregious and instructive case involved a Kansas City, MO, pharmacy that prepared 4,000 L of respiratory solutions to be used nationwide to 18,000 patients. These medications were contaminated with *Pseudomonas cepacia*. The pharmacy never notified doctors or patients about the contamination and destroyed critical records. It was ultimately disciplined by the state Board of Pharmacy, which, in Missouri, is more aggressive and effective than in many other jurisdictions (Missouri Board of Pharmacy Takes Action Against Kansas City Company [press release]. Jefferson City, MO, March 10, 2003).

In some instances, "compounding" manufacturers claim that they have generic versions of drugs, which are, in fact, not FDA-approved; therefore, they are not available in this country. An example is the medication budesonide, for use in nebulizers. The only approved form of this drug is Pulmicort Respules (AstraZeneca; Wilmington, DE), a special formulation that is aqueous-soluble. Budesonide is notoriously insoluble in water, so these "compounders" dissolve it in high concentrations of ethanol. Their preparations are then sold and administered to patients, including children, via nebulization. Ethanol is very irritating to the lungs and, in these cases, is being given to patients who already have inflammatory lung disease.

These drugs are marketed in ways that are deceptive to physicians and patients. In one marketing method, suppliers of durable medical equipment link up with the mass manufacturers. When a patient

submits an order for a nebulizer, the supplier will offer a free nebulizer if the patient gets his medication from the supplier, which is delivered to his home. The supplier bills the insurance company or Medicare, and the medication is virtually cost-free. This sounds like a good deal, except for the fact that the medications are unreliable and can even be dangerous.

Physician approval for compounded drugs may also be obtained deceptively. The request for approval is faxed to the physician from the pharmacy; however, frequently, the form does not make it clear that a substitution is being requested. In addition, the form does not indicate that these drugs are not FDA-approved, and that many other combination drugs offered are available in FDA-approved versions. A major example of this is the albuterol/ipratropium combination, available as DuoNeb (Dey, L.P.; Napa, CA), which seems to be a favorite of mass manufacturers. Another example is budesonide, as previously noted. Physicians may be unaware that they are signing off on drugs that are not FDA-approved and of inferior quality. One could speculate that the "compounding" manufacturers and distributors are counting on physicians being too busy to scrutinize what they are signing.

Is there any peril to physicians if a patient becomes ill as a result of taking such a medicine? In fact, it is the physician who becomes liable for the adverse events. Once the physician approves the medication, the pharmacist preparing the drug is no longer at risk for liability.

One might ask what is being done to protect patients and physicians from these unscrupulous pharmacies. The FDA issued a Compliance Policy Guide in 2002 outlining the circumstances that would trigger its intervention. To the extent the FDA can intervene with limited resources, it has intervened. This list also is instructive in identifying the behaviors of these pharmacies that put them in conflict with proper manufacturing practices. These behaviors include:

- ▶ Compounding drug products that have been pulled from the market because they were found to be unsafe or ineffective.
- ▶ Compounding drugs that are essentially copies of a commercially available drug.
- ▶ Compounding drugs in advance of receiving prescriptions, except in very limited quantities relating to the amounts of drugs previously compounded based on valid prescriptions.
- ▶ Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs, without an FDA-sanctioned, investigational new drug application.

▶ 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.

▶ Failing to conform to applicable state law regulating the practice of pharmacy (US FDA. Consumer Update, May 3, 2007: The Special Risks of Pharmacy Compounding. Available at www.fda.gov/consumer/updates/compounding053107.html).

Compounding has been a major concern for patient advocacy groups and specialty societies. Allergy and Asthma Network/Mothers of Asthmatics took the lead in forming a coalition of patient groups, specialty societies, and pharma-

ceutical companies to address this problem. The coalition, called Consumer Health Alliance for Safe Medications, has helped raise public awareness through lobbying, education programs, and media events. It has brought the problem to the attention of the Centers for Medicare

and Medicaid Services and, as a result, Medicare is no longer providing reimbursement for medications not approved by the FDA. Attempts to secure federal legislation are ongoing.

Consumers can protect themselves by ensuring that the medication they get from pharmacies or durable medical equipment companies is FDA-approved. They should check with their physicians and pharmacies.

Physicians have a major responsibility to ensure the safety of their patients' medications. They must read all their faxes for prescriptions before they sign them. They also need to read the fine print to ensure that the concentrations of combination medications are the same as in their commercial preparations. They must insist that the medications they prescribe are dispensed as written and their patients' medications are FDA-approved. They need to be aware that, if their patients are not doing well using their nebulized medication, the problem could be that the medication was obtained from a compounding pharmacy and underpotent.

Physicians must insist that whatever medication their patients inhale, ingest, or apply, it conforms to the highest possible manufacturing standards and that "compounded" products are not surreptitiously substituted for FDA-approved medications. ■

Dr. Daniel Ein
Chief, Division of Allergy
and Clinical Professor of Medicine
George Washington University
School of Medicine
Washington, DC

Dr. Gene L. Colice, FCCP
Editor,
Pulmonary Perspectives