Compounding Challenges & Opportunities

By Bruce R. Siecker, Ph.D., R.Ph.

Bruce Siecker is president of Paradigm Research & Advisory Services, Inc. based in Stone Ridge, Virginia. He trains, writes, consults, and testifies on drug program, regulatory, and corporate compliance.

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Goals and Objectives

Pharmacists:
Goals: Based on historical and professional developments, to provide the pharmacist with the challenges and opportunities associated with compounded prescriptions in the contemporary community pharmacy.

After completing this lesson a pharmacist should be able to:
1. Briefly explain early attempts at compounding.
2. Explain how MTM concepts affect the role of the pharmacist as a compliance specialist.
3. Define prescription compounding vs. drug manufacturing.
4. Explain the role that the FDA Modernization Act of 1997 plays in compounding.
5. Define what constitutes a drug that can be compounded.
6. Give three examples of why a prescription would be compounded.
7. Explain how the U.S. Court of Appeals of the Fifth Circuit impacts compounding.
8. Explain what these organizations do:
   ▪ International Academy of Compounding Pharmacists
   ▪ Professional Compounding Centers of America
9. Define the purpose of the Pharmacy Compounding Accreditation Board.

Pharmacy Technicians:
Goals: Based on historical and professional developments, to provide the pharmacist with the challenges and opportunities associated with compounded prescriptions in the contemporary community pharmacy.
A Lengthy and Compelling History

The art and science of pharmaceutical compounding is more than 10,000 years old. Hunter-gatherer societies developed knowledge of plants, molds, fungi, and bacteria. Ancient civilizations used “pharmaceutical compounding” for religious and grooming purposes, treating the ill, and preparing the dead for burial.

These early “druggists” compounded a variety of medicines, dyes, incense, perfumes, preservatives, and cosmetics. They also drove the Alchemy movement in their search for the fountain of youth and gold. According to Christian beliefs, men traveled to Bethlehem more than 2000 years ago with gifts of gold, frankincense, and myrrh.

The aromatic resin myrrh, valued for its medicinal and cosmetic purposes, is still used today. Myrrh is not approved by the U.S. Food and Drug Administration to treat inflammation of the mouth and pharynx (and other conditions), but the medicinal use of this unapproved drug may become legally acceptable under a new FDA law (the FDA Modernization Act of 1997, see below).

In the medieval Islamic world, Muslim chemists developed advanced methods of compounding drugs. The first drugstores were opened in Baghdad in 754 A.D. The era of compounding began in the 19th century when attempts were made to isolate compounds from coal tar in order to make synthetic dyes. During this time early pharmacists focused on preparing and formulating concoctions of crude drugs, extracting the drugs with water or alcohol to make a final preparation.

In time, efforts were directed at isolating the active ingredients of these crude mixtures, such as morphine from the opium extract preparation. From this saw the beginnings of the modern pharmaceutical industry. These large commercial laboratories were based on economies of scale, while pharmacists focused their attention on preparing (or compounding) prescriptions from the larger-scale products made by the pharmaceutical companies.

The 20th century brought greater regulation to the practice of medicine and forced the pharmaceutical companies to prove the safety (and later, the effectiveness) of their products. Pharmaceutical compounding began to decline in popularity when penicillin was discovered, and modern marketing techniques and “branding” became commonplace. Mass-produced drugs saved time, effort, and cost, and compounding became a specialty available only at a limited number of pharmacies.

Still, compounding never died and has remained a part of pharmacy practice since the beginning. It remains viable today! In 2006 it is estimated that 30 million compounded prescriptions were dispensed. Hospitals easily added upwards of 100 million compounded injectable and admixtures drugs to the entire picture.

In the latest part of the 20th century and early 21st century the pharmacist shifted from an emphasis on drug product distributor to a medication therapy manager. Along with this change in emphasis came the recognition that traditional medications carried a significant non-compliance problem.

As the medication therapy manager, pharmacists were responsible for providing ways for patients to become compliant with medicines. Because commercially available products from the nation’s pharmaceutical manufacturers are limited in terms of drug strengths, dosage forms, and flavors, the most obvious solution to compliance problems was to customize therapies through compounding.

As such, a pharmacist is more a compliance-solution specialist than simply a drug product distributor. No other health care specialist has the training and experience to modify the pH, particle size, protein binding, flavor, structure to activity relationship, and economics to assist the prescriber in overcoming very real compliance problems.

It is becoming more evident that matching a patient’s life style and daily habits to the needs of drug therapy is far more complex than it was once thought. It is much easier to provide a “compounded solution,” along with enhanced pharmacist-patient communication, to improve compliance. These and other reasons continue to support the growth and interest in compounding.

What Is Compounding?

What is, and is not, compounding is a question that raises the issue of who is responsible for compounding. Compounded medications are
prepared for specific patients with individual needs by pharmacists acting on a physician’s order.

**Pharmacist compounding is:**
the preparation, mixing, assembling, packaging, or labeling of a drug or device by a pharmacist as the result of a practitioner’s prescription drug order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice; or for the purpose of, or as an incident to research, teaching, or chemical analysis and not for sale or dispensing.

**Drug Manufacturing is:**
the production, preparation, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or labeling or relabeling of its container, and the promotion and marketing of such drugs or devices.

The fundamental issue is when does compounding become manufacturing. First and foremost, the drug in question must have been prescribed for a specific patient to qualify as compounded. Second, the drug is a chemical. According to the FDA Modernization Act of 1997, a drug substance can qualify for use in compounding in one of three ways; it is:

1. Recognized as approved by the FDA,
2. Listed in a book of widely used drug substances published by the United States Pharmacopeial Convention (considered an independent standards setting organization), or
3. Listed in an FDA rule as acceptable for pharmacy compounding (such as found in the January 7, 1999 *Federal Register*, including myrrh)

A drug substance does not qualify if it has previously been shown to be unsafe or ineffective. Also restricted are those drugs that have proven difficult to compound. The law also prohibits compounding that profits from the research and development of drug manufacturers. As such, there are limitations on copying manufactured drugs.

The line between compounding and manufacturing is difficult to draw. On the one hand, the definition should not allow manufacturers to use the label “compounded” to escape the formal drug approval process. At the same time, pharmacists should not be allowed to end run the drug approval process by claiming that a drug is compounded.

**Why Do Pharmacists Compound Today**
A wide variety of situations occur that compounding can address. Physicians may prescribe an individual compounded medication—something pharmaceutically unique—for a specific patient. Patients may request that oral preparations be flavored to mask the “mediciney” taste. And, pharmacists may also suggest to the prescriber ways to make sure the drug gets used effectively.

It really does not matter who suggests that a drug be “compounded” (except legally); what matters is that nothing produced by a pharmaceutical company, or generally available, will do the job for the patient. This is where the pharmacist adds his skills and training to make a specific compounded prescription exactly right for a specific patient! In reality, pharmaceutical compounding is simply a matter of tailoring a product to a specific patient.

Compounded prescriptions results from patients that require:

- Topical mixtures not available from commercial sources
- Discontinued or unavailable products (or strengths)
- A drug no longer or never manufactured
- Products produced without specific non-active ingredients, dyes or fragrances
- Allergen-free medication, e.g., gluten-free
- A limited or very small dosage
- Change in dosage formulation, e.g., cannot swallow a tablet because of a disability
- A unique dosage formulation
- Flavor additives to liquid drugs to improve palatability
- Veterinary medicines—change in dose, something more easily administered, or adding a palatable flavor
The Government’s Viewpoint

In January 2008, the FDA sent warning letters to about a half-dozen compounding pharmacies claiming that each had violated federal law. The pharmacies were guilty of unsupported claims that compounded hormone therapy was “bio-identical” to FDA-approved therapy for treatment of menopausal symptoms. In short, FDA was saying that a claim that the use of estradiol as a form of bio-identical hormone replacement therapy (BHRT) was unproven. Those wishing to make such claims and use estradiol for these purposes would have to submit an investigational or new drug application (NDA) and undergo a formal review.

This action brought immediate response from pharmacies. It was pointed out that estradiol, though not approved by the FDA, had a USP monograph prior to 1997. Congress in the FDA Modernization Act of 1997 had said that unapproved drugs, which had a USP monograph, could be compounded when prescribed by a licensed practitioner.

The American Pharmaceutical Association led an action that resulted in a letter and meeting to discuss the issue. The FDA refused to rescind its stand and the matter ended up in federal court. The U.S. Court of Appeals (for the Fifth Circuit) ruled that FDA had jurisdiction over compounded drugs as new drugs, but if compounded pursuant to the FDA Modernization Act of 1997 the FDA cannot claim that they are misbranded or mislabeled. This means that the FDA cannot go after a pharmacy for compounding BHRT on the basis of misbranding or mislabeling in the Fifth Circuit (Texas, Louisiana, or Mississippi). Whether the FDA would attempt enforcement in the other federal districts, given the result in the Fifth District, is open to debate.

In another case involving compounded drugs, the Supreme Court of Iowa ruled that compounding which mixes non-prescription (over-the-counter) drugs to make a new product and sells that product without a prescription is guilty of manufacturing. If a prescription is not present, the pharmacist is engaging in manufacturing.

Misuses and Abuses of Compounding

A news report on May 12, 1998 focused on dangerous compounding in Florida’s pharmacies. Done in cooperation with the Florida Board of Health (including pharmacy), the segment reported on the compounding of albuterol and the lack of regulatory oversight of these products. Prescriptions were sent to independent laboratories for potency and stability analyses. Several products were judged super-potent. Reporters also raised the possibility of bacterial contamination, but did not test for it.

These and other news efforts attack compounding on various levels, but do little to document or quantify a problem with compounded medicines. What is needed is a well designed study to map out the quality of compounded prescriptions in terms of who prepared them. In other words, to test the idea that experience and skill really makes a differences in preparing compounded medicines, not that there is a problem with compounding per se.

Organizations of Interest

There are several organizations that focus on compounding. The IACP — short for the International Academy of Compounding Pharmacists — is a membership organization with about 1,000 member pharmacists located in Sugar Land, Texas. It is highly political and fights for the right to compound. It attempts to raise the awareness of the general public, Congress, and courts of the value of compounding, to reverse the FDA’s policy of maintaining that all compounded drugs are new drugs (and therefore must follow the rules for new drug approval for manufactured drugs), and to maintain state’s authority over the practice of compounding. (See A Compounding Controversy below.)

The PCCA of Houston, Texas (see www.pccarx.com) as it has become known in pharmacy is short for the Professional Compounding Centers of America. It has about 2,400 members worldwide. It encourages compounding, offers courses in compounding and compounding issues, and sells various products and equipment associated with compounding.
The Pharmacy Accreditation Board

Compounding pharmacies are licensed by a state board of pharmacy in the same manner they are licensed as a pharmacy. A pharmacy license by a state board of pharmacy also implies that it is a compounding pharmacy. There are no unique requirements, and no federal licensure. The FDA does not inspect or register compounding pharmacies because they are not considered manufacturing sites.

In 2004, the Pharmacy Compounding Accreditation Board (PCAB) was created in response to an increase in the demand for compounded drugs. The PCAB is a separate accreditation process that is voluntary and profession-driven. Its focus is on the safety of the process, it serves no regulatory or licensing role.

Once certified, a pharmacy can claim to be a “PCAB Accredited Compounding Pharmacy.” The PCAB maintains an Internet-accessible site (www.pcab.infor) to allow consumers access to a list of PCAB-approved pharmacies.

Available Resources

The Art, Science, and Technology of Pharmaceutical Compounding is a comprehensive reference. Pharmacy Compounding Accreditation: A How to Manual is available to pharmacists wishing to seek accreditation as a compounding pharmacy (see www.pharmacist.com for both). The International Journal of Pharmaceutical Compounding is a bimonthly, independent journal featuring peer-reviewed scientific articles, professional articles, and news. CompoundingToday newsletter is available on a weekly basis for those interested in compounding. (See info@compoundingtoday.com.)

There are courses taught around the country which focus on various aspects of compounding. These include courses in aseptic technique, USP 797 guidelines, compounding various specialty medications (pain, nutritional, aging, women/men, etc.) veterinary compounding, quality assurance, and marketing compounding. These and others are typically promoted via direct mail and through the pharmacy literature. (See Gallipot, www.gallipot.com and Professional Compounding Centers of America.)

A Compounding Controversy

There is current controversy regarding who should regulate compounding pharmacies. FDA is concerned that compounding pharmacies are active like manufacturers and therefore should be regulated federally as manufacturers. The FDA maintains that all compounded drugs are new drugs. As such, compounded medications are illegal unless regulated by the FDA. However, FDA will use its “enforcement discretion” in the process.

The International Academy of Compounding argues that compounded drugs are not new, unapproved drugs. Compounding pharmacies only dispense them on the doctor’s prescription. And, to the extent that there are safety issues, state boards of pharmacy will summarily deal with them.

Recent court rulings, such as Medical Center Pharmacy vs. Gonzales, 2006, appear to support the position taken by the IACP.

The Future of Pharmaceutical Compounding

Even with U.S. demand for compounded prescriptions increasing each year, compounded medications account for only about 1% to 2% of total annual prescriptions (exclusive of institutional prescriptions). Though not the preponderant type of prescription, compounded medications for pain, pediatrics, and pets and the like appear to have their place. They offer a unique set of challenges and opportunities.