Pharmacy Compounding

Background

Compounding pharmacists play an essential role in their patients' lives by allowing physicians to prescribe customized medication therapy to best meet the needs of their patients. And for the growing number of people with unique health care needs that cannot be addressed with commercially available products, a compounded product may be the only viable treatment option. Compounding enables a pharmacist to utilize their medication knowledge and expertise to produce individualized medications that meet a patient's needs. Compounding is also in great demand for treating animals because of the relatively narrow selection of medications that are manufactured for them.

Compounding of medications for patient use has been a significant component of the practice of pharmacy and medicine since time immemorial. Virtually all practicing pharmacists will be involved with compounding activities at some point during their career. Compounding pharmacies are licensed and regulated in the 50 states and the District of Columbia by their respective state boards of pharmacy.

Friction remains regarding which agency should regulate pharmacy compounding. APhA continues to support the regulation of pharmacy compounding at the state level through state boards of pharmacy. APhA believes that the Food and Drug Administration (FDA) should only step in, working with the boards of pharmacy, when compounding "crosses the line" into manufacturing. However, despite our continuing efforts to make this case, we have seen an increase in attempts to federally regulate compounding.

Meeting Unmet Needs

It is impractical for a manufacturer to make numerous, slightly different products to address the entire range of patients' needs. Generally, only a few or even one dosage form will be commercially available. Physicians and pharmacists recognize that the healthcare needs of some individuals do not always fall within the confines of commercially available dosage strength and formulations. Because large-scale manufacturers cannot tailor a medication for a single patient or even a handful of patients cost-effectively, many patients need custom-made medication dosages to solve specific medical problems. Compounding allows for a myriad of concentrations and combinations that can be used to meet individual patients' needs in various care settings.

Examples of some of the most commonly compounded products include lotions, ointments, creams, gels, suppositories, intravenously administered fluids and medications, total parenteral nutrition products, oral suspensions, and troches. Pediatric or geriatric patients may need extremely small doses, cancer patients may need specific combinations of chemotherapy drugs to treat their disease, or special dosage forms may be necessary to care for patients with AIDS, chronic pain or other maladies. Some therapies, such as parenteral nutrition, can only be provided to patients using compounded dosage forms. Other patients need preservative-free products, liquids with special flavors, or delivery systems that are not commercially available.

Additionally, some medications, such as radiopharmaceuticals, may not have sufficient shelf life to withstand the commercial distribution process and therefore need to be prepared at the time of dispensing. Many manufactured "finished pharmaceutical" products are only "finished" in the sense of being ready to ship and then store in the pharmacy. The products must still be compounded to provide a dosage form suitable for a patient's treatment.

Types of Compounding

- Compounding in Cancer Treatment: Almost all chemotherapy involves drugs and drug combinations that are compounded by pharmacists. It is imperative that a patient receive the correct drug dosage based upon the patient's body size, the type of cancer, the size and type of tumor, and the clinical condition of the patient. This can only be accomplished using compounded patient-specific medication preparations.
- Compounding for Pediatric Patients: Many drugs used in pediatric treatment are not commercially available in dosage forms appropriate for pediatric patients. Consequently, commercial products manufactured for use in adults must be modified and compounded for use in children. It has been estimated that more than 40% of doses given in pediatric hospitals require compounding to prepare a suitable dosage form.[1] Indeed, utilization of compounded medications is essential for the provision of medical care to hospitalized children.
- Compounding in Hospitals: Extemporaneous compounding services within the hospital pharmacy provide hospital physicians with literally any form or strength of medication needed for a specific situation. For example, compounded intravenous admixtures are highly individualized and facilitate administration of drugs not suitable for other routes of administration. Because daily intravenous therapy is provided through compounding of medications, nearly every person who has ever been admitted to a hospital has received a compounded product, including those patients receiving outpatient surgery.
- Compounding in Hospice Care: Medications to alleviate pain and to control nausea and vomiting are the most common prescriptions for patients in the hospice setting. If commercial products that provide the

[1] Winckler, S. C. Extemporaneous compounding: a return to regulatory limbo? J Pain Palliat Care Pharmacother, 16(4): 71-78, 2002.

precise dose(s) required are not available, they can often be supplied by extemporaneous compounding. One of the problems for many hospice patients is that pain medications are not manufactured in the required dosages. Additionally, patients often are not physically capable of swallowing the number of commercially manufactured tablets required. A pharmacist can compound a stronger product by transforming a tablet dosage form into a liquid that is easily swallowed. Often patients cannot take any medication by mouth, and often their veins are not accessible to inject medications. In these situations, physicians and pharmacists must modify traditional medications into products that may be applied topically or delivered rectally.

APhA Position

APhA supports pharmacy compounding as a critical component of the health care system, allowing physicians to prescribe medication therapy that best meets the needs of their patients. In providing compounding services, pharmacists work hand-in-hand with physicians to solve health care problems not addressed by commercially available medications, and in doing so fill a unique need in our health care system.

APhA supports compounding that is done within the triad relationship of the physician, pharmacist and patient working together to individualize care for maximum patient benefit. This triad should control the preparation of a drug product; consequently, pharmacy compounding is performed in response to a prescription from a licensed prescriber, or in preparation for a reasonably anticipated prescription, based upon prior experience and expected needs of individual patients. Furthermore, compounded drugs are not for resale, but rather, are personal and responsive to a patient's immediate needs. Finally, compounding should not occur when a commercially available product is available.

The profession's definition of compounding does not encompass the preparation of massive amounts of a drug product with the contemplation of distribution to a mass market of unknown users in unknown venues. Rather, the definition supports our assertion that the purpose of pharmacist compounding is to prepare an individualized drug treatment for a patient based on an order from a licensed prescriber.

Congress Activity

In May 2008, in response to FDA action described below, Representative Ross (D-AR) and Senator Cornyn (R-TX) introduced House of Representatives and Senate Resolutions that urged FDA to reverse its position on compounding estriol.

In July 2008, Senate Majority Leader Reid (D-NV) introduced the Drug and Device Accountability Act of 2009 (S. 3409) on behalf of Senator Kennedy (D-MA) that would implement FDA oversight over pharmacists' compounding activities. The bill would require pharmacies engaged in compounding to test products for purity and identity, establish electronic pedigree requirements, and subject these pharmacies to inspection. The legislation has not been reintroduced to date although compounding remains an important issue for some Members of Congress and action is likely in 2009.

Regulatory Activity

In the past year, FDA took action around bio-identical hormone replacement therapy (BHRT). Specifically, the Agency sent warning letters to pharmacies compounding BHRT, responded to the Wyeth Citizen Petition on compounding BHRT, and announced a new public education campaign on BHRT. The FDA's warning letters to the compounding pharmacies focused on the use of the term "bio-identical", the "safe & effective" marketing claims, and the use of estriol, which is not FDA approved.

APhA led a pharmacy-wide effort to respond to FDA's letters. While APhA agreed that the cited marketing claims were inappropriate absent supporting science, we disagreed that FDA has authority to regulate compounded drugs as "new drugs" under the Food, Drug and Cosmetics Act. We also argued that FDA's use of its compounding compliance policy guide (CPG) was inappropriate; and we disagreed with limiting ingredients to components of FDA-approved drugs.

In July 2008, FDA issued a guidance indicating that an investigational new drug application (IND) would be required by physicians who prescribe products containing estriol. APhA and other groups opposed this requirement because of burdens [particularly the requirement for an institutional review board (IRB)] placed on physicians to receive approval for the product and, as a result, the negative effect on patient access to these products.

In November 2008, APhA joined the International Academy of Compounding Pharmacists, the National Alliance of State Pharmacy Associations, the National Community Pharmacists Association, and the American College of Apothecaries in a joint letter to FDA Commissioner Andrew von Eschenbach objecting to FDA enforcement actions against pharmacists that compound BHRT using estriol as an ingredient. The organizations found that according to FDA's Compliance Policy Guide for compounding established pursuant to the Food and Drug

Marketing Act of 1997 (FDAMA), estriol is a permissible ingredient for use in compounding based on its recognition in national compendia. In the letter, APhA urged FDA to amend the compounding CPG through a public comment process and not take additional enforcement actions until the issue has been resolved. The organizations note that CPGs do not have the force and effect of law and that the current action is based upon the "current thinking of FDA" that is an overextension of authority.

The letter also recommends that FDA cease enforcement activity until litigation involving compounding is resolved.

Litigation

The FDA's authority over pharmacy compounding is further complicated by litigation pending in several federal district courts across the United States. FDAMA sought to establish appropriate procedures for pharmacy activities by including a safe harbor with a list of permitted activities that would exempt compounded products from FDA's "new drug" definition. This provision also included restrictions on the ability of pharmacists to advertise compounding services. In 2002, pharmacies engaged in compounding sued Health and Human Services (HHS) on the advertising restrictions noting that it unconstitutionally limits 1st amendment commercial speech. In *Thompson* v *Western States*, the Supreme Court invalidated the advertising restrictions from FDAMA but also rescinded the statutory provisions for acceptable compounding practice and left open the question regarding whether compounded products are new drugs. This situation creates problems in determining the boundaries of FDA enforcement of compounding practices and federal district courts across the country have interpreted these provisions differently.

In *Medical Center Pharmacy et al* v. *Mukasey*, the Federal District Court of Appeals found that the Food, Drug, and Cosmetic Act permits limited exceptions to the definition of new drug under FDAMA and that the advertising provisions can be considered separately from the other provisions. The ten pharmacies involved in this litigation are located in the states of Louisiana, Mississippi, and Texas. After reviewing the Court's findings, FDA determined that it will apply the FDAMA provisions to pharmacies in the three states involved in the litigation and thus permit compounding with estriol. However, outside of the three states involved in the case, compounding with estriol is pursuant to the CPG and therefore is not permitted. This creates much confusion across the United States.

APhA and other interested pharmacy organization find that litigation in federal appeals' court must be resolved and settled before FDA can take any additional enforcement action against pharmacies.

State Activity

In December 2008, APhA responded to the California Worker's Compensation Division's (CWCD) proposed policy that topical compounded analgesics would be considered "not recommended" for beneficiaries. APhA noted that this restriction would unfairly affect individuals covered by workman's compensation benefits. This action would also restrict the ability of physicians to work with pharmacists to ensure the most appropriate medication for patients. Although the CWCD rescinded its initial proposal of a blanket restriction, a second draft continues to prevent full patient access to these products. In a February 20, 2009 letter to the CWCD, APhA expressed its remaining concerns with the proposal and recommended engaging pharmacists in the process of determining what medications work best for worker compensation claimants by expanding the membership of the Medical Evidence Evaluation Advisory Committee to include a pharmacist.

Next Steps

Looking into the future, we expect the release of the Congressional Research Service (CRS) study of state regulation of pharmacy compounding. The study was requested in April 2007 by Senator Smith (R-OR) in response to comments made at a hearing on BHRT that he chaired. The study is intended to identify whether there are any gaps in state regulations of pharmacy compounding. Depending on the study's findings, it may be used by Members of Congress and others to support federal regulation of compounding practice.

Legislation will likely be introduced in 2009 to address the issue of whether compounded products are considered new drugs under FDA authority or whether a compromise will be reached to allow for compounded products under certain circumstances subject to certain FDA oversight or restriction.

Pharmacy Compounding Accreditation Board (PCAB)

As the demand for compounded medications increased, the pharmacy profession saw a need for an enhanced, profession-wide system of standards by which each compounding pharmacy can test its quality processes. In 2004, eight of the nation's leading pharmacy organizations joined together to establish PCAB, a voluntary system of standards for compounding pharmacies. PCAB accreditation, which requires pharmacies to comply with stringent standards, provides patients and prescribers a way to select a pharmacy that meets high quality standards.

PCAB's mission is:

- To serve the public good by serving pharmacy, patients and prescribers.
- To organize and carryout a comprehensive program of voluntary accreditation in the practice of pharmacy compounding.
- To promote, develop and maintain principles, policies and standards for the practice of pharmacy compounding in the public interest and to apply these in the accreditation of pharmacies that offer pharmacy compounding

to improve the quality and safety of pharmacy compounding provided to the general public.
- To offer to the public and prescribers a way to identify the pharmacies that satisfy accreditation criteria.
- To provide a public forum for information on the practice of pharmacy compounding, and to educate the public on the importance of pharmacy compounding.

PCAB's member organizations include:
- American College of Apothecaries
- American Pharmacists Association
- International Academy of Compounding Pharmacists
- National Association of Boards of Pharmacy
- National Community Pharmacists Association
- National Council of State Pharmacy Association Executives
- National Home Infusion Association
- United States Pharmacopeia Convention (USP)

APhA Statements

The following documents are available on the APhA Government Affairs Web site at www.pharmacist.com/GA:
- 2/2009 and 12/2008 APhA Letters to California Workers' Compensation Division Regarding Compounded Topical Analgesics
- 11/2008 APhA Joint Letter to FDA Regarding Compounding Enforcement Actions Related to BHRT
- 7/2008 5th Circuit Court of Appeals Decision Regarding Compounding and New Drugs
- 2/1/2008 APhA Joint Response on FDA Governing Pharmaceutical Compounding.
- 3/7/2007 APhA Statement on the Safety Drug Compounding Act of 2007
- 3/7/2007 APhA Joint Response on the Safe Drug Compounding Act of 2007
- 4/19/2007 APhA Testimony on Bio-identical Hormone Therapy to Senate Committee on Aging

Resources

- Additional information about PCAB can be found at http://www.pcab.org/ and at http://www.pcab.info/
- APhA House of Delegates: www.pharmacist.com/HoD

APhA Government Affairs Resources
www.pharmacist.com/GA