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PHARMACY COMPOUNDING: NON-PATIENT SPECIFIC

Statement of the Issue

Periodically, interest arises in legislation that would authorize a pharmacy licensed in Florida to compound prescription drugs that are not to be dispensed by the pharmacy to a named patient but are to be provided to a hospital, ambulatory surgical center, or physician's office for administration to a patient who is unknown at the time the medication is provided to the hospital, ambulatory surgical center, or physician's office. This practice is commonly referred to as compounding for office use.

The current regulatory environment accommodates compounding on a per-prescription basis or in anticipation of receipt of a prescription when a drug that is not commercially available is needed for a specified patient. This regulatory environment is intended to balance the potential health risks associated with pharmaceutical compounding while meeting specific patient medication needs.

The federal and state laws and enforcement efforts concerning pharmacy compounding conflict, and are at best, confusing. This brief sets forth regulatory and other considerations applicable to pharmacy compounding, focusing on issues related to pharmacy compounding for office use.

Discussion

Summary

Compounding is the process of combining, mixing, or altering ingredients, or preparing drugs by a pharmacist (or physician) to fit the unique needs of an individual patient.¹ Compounding does not include mixing, reconstituting, or other acts that are performed in accordance with directions contained in approved labeling or other directions provided by the product's manufacturer. A health care practitioner might prescribe a compounded preparation rather than a commercially available drug in several situations. For example, a practitioner might prescribe a compounded preparation when a patient requires a different dosage form, such as turning a pill into a liquid for a patient who cannot swallow pills or into a lollipop or flavored medication for children; a different dosage strength, such as for an infant; or allergen-free medication. In addition, the practitioner might want a pharmacist to compound medications that are not commercially available.

The Federal Food, Drug, and Cosmetic Act (FDCA) and federal regulations establish the minimum standards for drug products in this country. Specifically, the FDCA regulates the manufacture and distribution of drugs. The regulation of the professional practices of medicine and pharmacy is deferred to the states. In most instances the FDCA does not preempt states from enacting duplicative or more stringent licensure and regulatory provisions for activities involving drugs and drug products. Pharmacists and pharmacies are also subject to regulation under The Florida Pharmacy Act² and The Florida Drug and Cosmetic Act³ (The Florida Act).

¹ United States Food and Drug Administration Consumer Update: The Special Risks of Pharmacy Compounding, found at: <http://www.fda.gov/consumer/updates/compounding053107.html> (Last visited on September 23, 2008).

² Chapter 465, Florida Statutes (F.S.).

³ Part I of ch. 499, F.S.

Drugs for animals may be compounded and although many of the issues are similar, this paper concentrates on drugs intended for human use.⁴

Historical Overview of Drug Regulation

Before mass production of medications (manufacturing) became commonplace, compounding was a routine activity of physicians and pharmacists. The art of pharmaceutical compounding has ancient roots.

Federal controls over the drug supply in this country began in 1848 with the Drug Importation Act, which required U.S. Customs inspection to stop entry of adulterated drugs from overseas. Congress enacted the original Food and Drugs Act in 1906. It prohibited misbranded and adulterated foods, drinks, and drugs in interstate commerce. No government pre-approval was granted; the federal government could act only after products were on the market. Major revisions to drug regulation occurred in the FDCA of 1938, which started a new system of drug regulation – requiring new drugs to be shown safe before marketing via submission of a new drug application⁵ to the Food and Drug Administration (FDA).⁶ Then in 1962, in addition to demonstrating a new drug's safety, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them. The Food and Drug Administration Modernization Act of 1997 (FDAMA) amended numerous provisions of the FDCA, one of which specifically addressed pharmacy compounding.⁷

Specific Drug Regulations

New Drug Approval

The FDCA requires new drugs to undergo an approval process demonstrating that the drug is safe and effective for its intended use.⁸ A new drug is defined in the FDCA and in the Florida Act as any drug that is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.⁹ Both the FDCA and the Florida Act¹⁰ prohibit a person from selling ... or distributing any new drug unless an approved application has become effective under s. 505 of the FDCA. The Florida Act continues with the phrase, "... or unless otherwise permitted by the Secretary of the United States Department of Health and Human Services for shipment in interstate commerce."¹¹

The FDA approval means not only that the drug has been reviewed for safety and effectiveness, it means that the FDA has reviewed manufacturing quality, inspected manufacturing controls, and has reviewed the product labeling to ensure it adequately conveys the drug's benefits and risks. It also means that the drug product is consistently monitored for safety, effectiveness, and adherence with manufacturing quality standards.¹² Accordingly, manufacturing establishments must register with the FDA, including facilities located in other countries if the drugs manufactured in those establishments are to be marketed in this country. Most states also license and inspect facilities that manufacture drugs within their state for compliance with good manufacturing practices.

⁴ New animal drugs are regulated in 21 U.S.C. §360(b)(1).

⁵ If a drug obtained approval, the FDA allowed drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval and they could be marketed without independent approval. Source: Marketed Unapproved Drugs – Compliance Policy Guide, June 2006, found at: <<http://www.fda.gov/cder/guidance/6911fn1.pdf>> (Last visited on September 23, 2008).

⁶ The FDA had been created in 1927 under a different organizational name.

⁷ 21 U.S.C. 353a or Sec. 503A of the FDCA, effective November 21, 1998.

⁸ 21 U.S.C. 355 or Sec. 505 of the FDCA. There are various procedures to obtain drug approval.

⁹ For the complete definition see 21 USC 321(p) or Sec. 201(p) of the FDCA and s. 499.003(32), F.S.

¹⁰ Section 499.023, F.S.

¹¹ This phrase is significant because it authorizes compounding in accordance with the exercise of FDA's enforcement discretion as discussed later in this brief.

¹² FDA's Questions and Answers for Consumers about Unapproved Drugs, found at:

<http://www.fda.gov/cder/drug/unapproved_drugs/qaConsumers.pdf> (Last visited on September 23, 2008).

Adulteration

Under the FDCA and the Florida Act, a drug is adulterated if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the safety requirements of the FDCA and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.¹³ Current good manufacturing practice standards address personnel; facilities; equipment; control of components, drug product containers, and closures; packaging and labeling control; holding and distribution; laboratory controls; records and reports; and returned and salvaged drug products.¹⁴

Misbranding

A drug is misbranded under the FDCA and the Florida Act if its labeling is false or misleading in any way and if its labeling fails to bear adequate directions for use. Additionally, the FDCA and the Florida Act require a drug label to include, among other things, the name and place of business of the manufacturer, repackager, or distributor of the drug unless the drug is dispensed pursuant to a prescription of a practitioner licensed by law to prescribe such drug. If the drug is dispensed, the label must, among other things, identify the pharmacy as well as the name of the patient to whom the drug is dispensed.¹⁵

Status of Compounded Drugs Under Federal Law

In the early 1990s, the FDA became concerned that some pharmacies were purchasing bulk quantities of drug substances, “compounding” them into specific drug products before receiving individual prescriptions, and marketing those drugs to doctors and patients. Although the FDA had long refrained from regulating pharmacist compounding, it believed that pharmacies engaging in large-scale bulk compounding were effectively manufacturing drugs under the guise of compounding them.

In 1992, the FDA issued a Compliance Policy Guide¹⁶ asserting the applicability of the FDCA to compounded drugs, but declaring its intention to generally defer to state regulation of the day-to-day practice of retail pharmacy and related activities. Nevertheless, the FDA warned that it may, in the exercise of its enforcement discretion, initiate federal enforcement actions when the scope and nature of a pharmacy’s activity raises the kind of concerns normally associated with a manufacturer. Compounding pharmacies were concerned about relying on the largess of the FDA’s enforcement discretion with respect to pharmacy compounding. As a result, in 1997 Congress amended the FDCA by enacting the FDAMA.¹⁷

The FDAMA exempts drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient from three key provisions of the FDCA: the adulteration provision concerning the good manufacturing practice requirements; the misbranding provision concerning the labeling of drugs with adequate directions for use; and the new drug provision concerning the approval of drugs under new drug or abbreviated new drug applications so long as the provider of the compounded drug abides by certain restrictions.

Soon after enactment of the FDAMA, several licensed pharmacies brought action challenging a restriction in the FDAMA that prohibited the advertising and promotion of particular compounded drugs. The United States Supreme Court held¹⁸ in 2002 that these provisions were unconstitutional restrictions of commercial speech. However, the lower court, the Court of Appeals for the Ninth Circuit, had also determined that the other restrictions related to compounding in the FDAMA could not be severed from the unconstitutional advertising and promotional restrictions. The severability issue was not brought before the Supreme Court, and accordingly, the Supreme Court did not rule on that

¹³ For the complete definition see 21 USC 351 or Sec. 501 of the FDCA found at: <http://www.fda.gov/opacom/laws/fdcaact/fdcaact5a.htm#ftn1> (Last visited on September 23, 2008) and s. 499.006, F.S.

¹⁴ 21 C.F.R. 211.

¹⁵ 21 USC 352 or Section 502(a) of the FDCA, s. 499.007, F.S., and s. 893.04(1)(e), F.S., for controlled substances.

¹⁶ Compliance Policy Guide No. 7132.16 (Mar. 1992).

¹⁷ Pharmacies characterized Congress’ action as a “reaction to the FDA’s 1992 policy” and the FDA characterized it as “a confirmation of it.” From *Medical Center Pharmacy, et. al. vs. Mukasey* 536 F.3rd 383, 390 (5th Cir. 2008).

¹⁸ *Thompson v. Western States Medical Center, et.al.*, 535 U.S. 357 (2002)

issue. The FDA shares the Ninth Circuit's view that this entire compounding section in the FDAMA is now void¹⁹ and compounded drugs are subject to all provisions of the FDCA.

Accordingly, the FDA determined that it needed to issue guidance to the compounding industry on what factors the FDA would consider in exercising its enforcement discretion regarding pharmacy compounding. The FDA's enforcement policy, with respect to the compounding of human drugs, is articulated in Compliance Policy Guide (CPG) section 460.200, issued by the FDA on May 29, 2002.²⁰ The following includes key provisions from this CPG:

The FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription *for an individually identified patient* from a licensed practitioner. The FDA stated that this traditional activity is not the subject of the guidance. Generally, the FDA will continue to defer to state authorities regarding less significant violations of the FDCA related to pharmacy compounding of human drugs. However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA, the FDA has determined that it should seriously consider enforcement action. In determining whether to initiate such action, the FDA will consider whether the pharmacy engages in any of the following acts:²¹

- Compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amount of drugs compounded after receiving valid prescriptions;
- Compounding drugs that were withdrawn or removed from the market for safety reasons;²²
- 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;
- Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements;
- Using commercial scale manufacturing or testing equipment for compounding drug products;
- Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale;
- Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products unless there is documentation of the medical need for the particular variation of the compound for the particular patient; and
- Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

Although there are some differences in the set of restrictions between the FDAMA and the FDA's CPG, the major difference is that the FDAMA specifically exempts pharmacies that compound in accordance with the specified criteria from violating the adulteration, misbranding, and new drug provisions of the FDCA. On the other hand, the CPG articulates that compounding is subject to regulation under the FDCA but that the FDA may exercise enforcement discretion with respect to taking action against a pharmacy for violating the adulteration, misbranding, and new drug provisions of the FDCA for compounded products.

On July 18, 2008, the United States Court of Appeals for the Fifth Circuit opined²³ that the other restrictions related to compounding in the FDAMA could be severed from the unconstitutional advertising and promotional restrictions so

¹⁹ Footnote 2 in seven FDA Warning Letters dated January 7, 2008, related to compounded menopause hormone therapy drugs, found at <<http://www.fda.gov/cder/pharmcomp/>> (Last visited on September 23, 2008).

²⁰ Found at: <http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html> (Last visited on September 23, 2008)

²¹ The CPG states that the list of factors is not intended to be exhaustive and that other factors may be appropriate for consideration in a particular case. The CPG also provides that other FDA guidance interprets or clarifies the FDA's positions concerning nuclear pharmacy, hospital pharmacy, shared service operations, mail order pharmacy, and the manipulation of approved drug products.

²² The CPG provides a list of drugs, which is also in 21 C.F.R. 216.24. The CPG provides that this list will be updated in the future, as appropriate.

²³ *Medical Center Pharmacy v. Mukasey*, 536F.3d 383, (5th Cir. 2008).

that a compounding pharmacy that complies with the remaining restrictions in the FDAMA does not violate the adulteration, misbranding, and new drug provisions of the FDCA. Since a split in decisions by the circuit courts of appeal exists, in all likelihood the U.S. Supreme Court will take up the matter at some point in the future.

Wholesale Distribution

Wholesale distribution means distribution of prescription drugs to persons other than a consumer or patient, with certain exemptions. Both federal and state laws distinguish and specifically exempt dispensing a prescription drug from the licensure laws regulating the wholesale distribution of prescription drugs.²⁴ Under Florida law, dispensing involves a pharmacist or licensed practitioner transferring possession of a properly labeled prescription drug to a patient or patient's agent.²⁵ Compounded drugs may be delivered to a practitioner's office for administration to the patient if the drug is dispensed for a specified patient at the time of delivery; this is not considered a wholesale distribution. However, if the drug is not so dispensed, the distribution of the compounded drug to the practitioner is a wholesale distribution under both the FDCA and the Florida Act.

Although the distribution of prescription drugs to practitioners for office use constitutes wholesale distribution under the FDCA, federal regulations exempt the sale of minimal quantities of drugs by retail pharmacies to licensed practitioners for office use. In this context, sales of prescription drugs by a retail pharmacy to licensed practitioners for office use are considered to be minimal if the total annual dollar volume of prescription drugs sold to licensed practitioners does not exceed 5 percent of the dollar volume of that retail pharmacy's annual prescription drug sales.²⁶

Florida's law does not have a similar exemption and requires a retail pharmacy drug wholesale distributor permit for the wholesale distribution of prescription drugs by a retail pharmacy up to a certain level of sales, and if the sales volume for wholesale distributions exceeds that threshold, then a prescription drug wholesale distributor permit is required.^{27,28} However, a pharmacy in Florida that compounds sterile products, such as eye drops and parenteral/enteral nutritional preparations or other injectables, must be licensed by the Board of Pharmacy in a manner that makes the pharmacy ineligible for a permit under the Florida Act that authorizes the wholesale distribution of prescription drugs. This type of compounding pharmacy is a health care entity under the Florida Act.²⁹

When a medical provider authorized to purchase and possess prescription drugs in Florida acquires prescription drugs that have not been dispensed to a patient, the transaction is a wholesale distribution. The medical provider must obtain the prescription drug from an authorized source,³⁰ i.e., a wholesale distributor permitted under the Florida Act to distribute prescription drugs to that type of medical provider. In addition, a pharmacy that distributes prescription drugs in a wholesale distribution is required to provide a pedigree paper³¹ to the recipient medical provider.³²

Practitioner Need for Compounded Medications for Office Use

Senate professional staff surveyed associations representing pharmacies and pharmacists, hospitals, health-system pharmacists, medical and osteopathic physicians, and hospices to determine whether compounding for office use is needed in various health-care settings. Senate professional staff also requested input on strategies that might be

²⁴ 21 C.F.R. 203.3(cc) and s. 499.003(53), F.S.

²⁵ The Florida Pharmacy Act in s. 465.003(6), F.S. (2007).

²⁶ Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures, Final Rule, December 3, 1999, Comments on the Proposed Rule on Page 67748, found at: <<http://www.fda.gov/OHRMS/DOCKETS/98fr/120399a.txt>> (Last visited on September 23, 2008).

²⁷ s. 499.01(2)(f), F.S.

²⁸ A pharmacy registered to dispense controlled substances may distribute such substances (without being registered with the DEA as a distributor) to another pharmacy or to a practitioner to dispense, provided that several conditions are met, including, the total number of dosage units of controlled substances distributed by the pharmacy does not exceed five percent of all controlled substances dispensed by that pharmacy during a calendar year. Source: 21 C.F.R. §1307.11(a)(1).

²⁹ See the definitions of "closed pharmacy," "health care entity," and "retail pharmacy" in s. 499.003, F.S.

³⁰ s. 499.005(14), and s. 499.0051(4), F.S.

³¹ A pedigree paper is a document containing information regarding the sales and distributions of a prescription drug. See s. 499.003(36), F.S.

³² s. 499.005(28) and (29) and s. 499.0051, F.S.

available to minimize or reduce the risk to the ultimate patient related to non-patient specific compounding. In addition, Senate professional staff received input from individual pharmacists and practitioners in the state.

Without exception, all parties communicated the medical necessity for patient-specific compounding. However, Senate professional staff was unable to document an immediate medical need for a non-patient specific compounded drug where the timeframe precluded ordering the medication for the specified patient.³³ Some parties cited convenience to both the practitioner and patient as justifying compounding for office use. For example, a compounding pharmacist explained that if a practitioner has compounded anesthetic gels in the office, then the practitioner might be able to perform certain tests or procedures during an initial office examination without scheduling a follow-up appointment. Although commercially available anesthetic gels exist for these types of routine procedures, the compounding pharmacist explained that some practitioners may prefer to use combination products that act more quickly or have additional substances in them. Practitioners in Florida may be obtaining these compounded medications from pharmacies located in other states.

Hospices provided conflicting comments on the need for Ativan, Benadryl, Haldol, and Reglan (ABHR) suppositories immediately upon admission of patients. Some suggested that this very common compounded medication, or something similar, should be made available as floor stock for inpatient hospices to expedite care and eliminate wastage that frequently occurs despite the hospice filling the prescription on a 3-day supply basis.

Compounding for Office Use in Other States

At least 15 states specifically authorize pharmacies to compound medication for physician office use. These states have varying levels of authorizations and requirements. Some states authorize a compounded medication that is not patient specific to be provided to other pharmacies, clinics, or institutional pharmacies for administration while some states restrict this practice to providing the medication to practitioners. Some states require a pharmacy to adhere to detailed standards that are similar to good manufacturing practices that a manufacturer must follow, while other states specify less detail in regulating the compounding process.

In May 2005, the FDA responded to the Texas Department of State Health Services' request to clarify the FDA's regulatory approach to pharmacy compounding of human drugs and to comment generally on proposed Senate Bill 492 (2005), which addresses pharmacy compounding under Texas state law.³⁴ The FDA stated that it believes that the legislation would disserve Texans because it would purport to legalize conduct that is illegal under federal law. The FDA further stated that although the FDA generally defers to state authorities regarding the regulation of pharmacy compounding, the agency remains prepared to enforce the FDCA as appropriate to protect the public health and vindicate the integrity of the new drug approval process.

Notwithstanding the FDA's concerns that the specific bill purports to authorize conduct that would run afoul of federal law and the FDA's regulatory approach, the FDA discussed provisions that should be included in any bill that would be consistent with the FDA's regulatory approach. Some of this discussion includes:

The FDA recognizes that it may be appropriate in some circumstances for pharmacists to compound limited supplies of drugs solely for administration in a practitioner's office, but the FDA is concerned that this proposed bill fails to include sufficient limitations and safeguards. The FDA believes that any bill should [not] become a back door for the sale of compounded drugs to other pharmacies, health facilities and wholesalers ... The FDA believes that any bill that would be consistent with the FDA's regulatory approach should ... provide that pharmacies may compound and deliver only a "limited" quantity of drugs to a practitioner "solely" for administration in a practitioner's office ... The FDA would also suggest that the bill require that any drug compounded and delivered pursuant to these provisions be labeled "for Office Use Only" and "Not for Resale."

³³ The Florida Hospital Association was not aware of any regulatory obstacles that make it difficult or impossible for hospitals to obtain needed drugs. Cardioplegia solutions used in emergency heart surgeries, other admixtures used by hospitals, and certain radiopharmaceuticals have unique state and federal regulatory provisions to address availability of these products.

³⁴ Correspondence to Karen Tannert, R.Ph., Drug and Medical Devices Group, Texas Department of State Health Services from Steven D. Silverman, Director, Division of New Drugs and Labeling Compliance CDER, Office of Compliance, dated May 4, 2005.

Florida's Compounding Rule

On October 7, 2008, the Florida Board of Pharmacy amended a rule to authorize compounding for office use.³⁵ This rule may not comport with FDA's guidance related to its exercise of enforcement discretion regarding compounding for office use by:

- Authorizing a pharmacist to dispense and deliver a compounded drug to a practitioner to administer in a health care facility or treatment setting, including a hospital, ambulatory surgical center, or pharmacy;
- Authorizing a pharmacy to compound a "reasonable quantity" as defined in the rule³⁶ versus a "limited quantity;" and
- Omitting the suggested labeling of compounded products for office use.

Another concern with this rule is that it purports to legalize conduct related to the wholesale distribution of certain compounded drugs that may not be lawful under the Florida Act.

Risks Associated with Compounded Drugs³⁷

Compounded drugs can pose both direct and indirect health risks. Compounded drugs may be unsafe and pose direct health risks because of the use of poor quality compounding practices. They may be sub- or super-potent, contaminated, or otherwise adulterated. Indirect health risks include the possibility that patients will use ineffective compounded drugs instead of FDA-approved drugs that have been shown to be safe and effective.

Some pharmacists are well-trained and well-equipped to compound certain medications safely. But not all pharmacists have the same level of skills³⁸ and equipment, and some drugs may be inappropriate for compounding. In some cases, compounders may lack sufficient controls (e.g., equipment, training, testing, or facilities) to ensure product quality or to compound complex drugs like sterile or extended-release drugs. The quality of the drugs that these pharmacists compound is unknown and these drugs pose potential risks to the patients who take them.

When pharmacy compounders both operate like drug manufacturers and engage in high-volume distribution, the risk of patient harm increases. Over the past several years, the FDA has become aware of serious adverse events, including deaths, associated with compounded drugs. For example, the FDA:

- Issued a warning letter³⁹ to a pharmacy in Alabama related to its compounding activities for producing large volumes of injectable and non-injectable products which may be copies, or essentially copies, of FDA-approved, commercially available products. A consumer complaint of an adverse incident related to a compounded injectable suspension prompted an FDA inspection, which revealed that the compounding firm had received at least 70 complaints associated with that injectable suspension. The day following the FDA inspection, the firm issued a voluntary recall on two lots of the product.
- Issued warning letters to five firms about their standardized compounded, high-strength topical anesthetic creams. Two deaths were connected to the topical anesthetics compounded by two of the pharmacies.

³⁵ Rule 64B16-27.700, F.A.C.

³⁶ The rule states that the quantity of compounded drug for any practitioner and all practitioners as a whole, is not greater than an amount the pharmacy is capable of compounding in compliance with pharmaceutical standards for identity, strength, quality, and purity of compounded drug that are consistent with USP guidelines and accreditation practices.

³⁷ FDA's Compounded Menopausal Hormone Therapy Questions and Answers, found at <http://www.fda.gov/cder/pharmcomp/BHRT_qa.htm> (Last visited on September 23, 2008).

³⁸ A survey sent to 82 deans of pharmacy schools throughout the country in 2005 revealed that instruction provided to pharmacy students in preparing compounded sterile preparations varied widely. Only 7 of the 53 respondents (13 percent) believed that their students had adequate training in the compounding of sterile preparations via didactic and laboratory courses before graduation ... and 88.7 percent of the respondents believed that students could only become fully competent in such compounding over time in practice. *Instruction on compounded sterile preparations at U.S. schools of pharmacy* by Mac Hellums, Susan P. Alverson, and Mary R. Monk-Tutor, *American Journal of Health-System Pharmacy*, Vol. 64, Issue 21, 2267-2274 (2007).

³⁹ A copy of the warning letter is available at: <http://www.fda.gov/foi/warning_letters/s6529c.pdf> (Last visited on September 23, 2008).

- Warned three firms to stop manufacturing and distributing thousands of doses of unapproved inhalation drugs under the guise of compounding. Warning letters to these firms identify a range of serious concerns including inadequate quality control, concerns about potency, and compounding copies of FDA-approved drugs.

The FDA receives adverse drug reaction reports⁴⁰ from manufacturers as required by regulation. Health care professionals and consumers send reports voluntarily through the MedWatch program. These reports support the FDA's post-marketing safety surveillance program for all approved drugs and therapeutic biologic products. The FDA may take regulatory actions to improve product safety and protect the public health, such as updating a product's labeling information, sending out a "Dear Health Care Professional" letter, or re-evaluating an approval decision, based on analysis of these reports.⁴¹ Compounded drugs are not similarly tracked.⁴²

USP Standards and Compounding Accreditation

USP Standards

The United States Pharmacopeia (USP) is an official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured or sold in the United States.⁴³ The FDCA designates the USP/NF (National Formulary) as the official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the USP/NF standards for strength, quality, purity, packaging, and labeling of medicines to avoid possible charges of adulteration and misbranding. The Florida Act also refers to and requires compliance with this official compendium.⁴⁴

The USP has two chapters related to pharmaceutical compounding. USP Chapter 795 addresses pharmaceutical compounding for nonsterile preparations. The newest version of USP Chapter 797 Pharmaceutical Compounding—Sterile Preparations (USP Chapter 797) became effective on June 1, 2008. Both USP Chapters are enforceable by the FDA; however since the FDA defers to the states to regulate the practice of pharmacy and to perform inspections, individual states are adopting some or all of the standards, especially with respect to compounding sterile preparations. The Florida Board of Pharmacy recently adopted by rule Standards of Practice for Compounding Sterile Preparations⁴⁵ that a pharmacist in Florida must follow when compounding low, medium, and high-risk sterile preparations. This rule closely tracks USP Chapter 797.⁴⁶

Compounding Accreditation

The Pharmacy Compounding Accreditation Board (PCAB) was created in 2004 as a voluntary accreditation body to establish high quality standards for compounding pharmacies. The PCAB was formed by eight national pharmacy organizations, including the USP and the National Association of Boards of Pharmacy. Pharmacies that successfully meet the PCAB's requirements, including documented compliance with USP Chapter 797, receive the designation "PCAB Accredited™ compounding pharmacy" and are able to display the PCAB Seal of Accreditation. Three pharmacies in Florida are accredited and four applications for accreditation of pharmacies located in Florida are pending.⁴⁷

⁴⁰ Adverse event reporting is required on prescription and non-prescription drugs and, as of December, 2007, on dietary supplements as required by Public Law 109-462.

⁴¹ Additional information on the FDA Adverse Event Reporting System may be obtained at <http://www.fda.gov/cder/aers/default.htm> (Last visited on September 23, 2008).

⁴² *Ibid* at 38.

⁴³ U.S. Pharmacopeia, About USP – an Overview found at: <http://www.usp.org/aboutUSP/index.html?USP> (Last visited on September 23, 2008).

⁴⁴ See for example, s. 499.003(35) and s. 499.006, F.S.

⁴⁵ Rule 64B16-27.797, effective June 18, 2008.

⁴⁶ Hospital pharmacies may still be assessing their ability to fully comply with the applicable practice standards for compounding sterile preparations. Source: Response for the Senate staff survey from the Florida Society of Health-System Pharmacists, Inc., dated September 12, 2008.

⁴⁷ See <http://www.pcab.org/find-a-pharmacy.shtml#fl> (Last visited on September 23, 2008).

Conclusion

Although contrary to the FDCA, and whether or not the compounding provisions in the FDAMA are determined by the courts to be valid, the FDA appears to have opened the door through the exercise of enforcement discretion for state law to authorize, in a limited manner with adequate safeguards, pharmacies to compound medications for a practitioner's office use. If the Legislature determines that the need for and benefits from this activity outweigh the associated risks,⁴⁸ in addition to providing parameters consistent with the factors the FDA considers in determining whether to exercise enforcement discretion, several key statutory provisions would need to be addressed and possibly amended, including but not limited to providing for:

- Compounding practice standards and accreditation to help ensure patient safety;
- Modification of the definition of an adulterated drug so that the compounded preparation does not run afoul of the adulteration provisions;
- Labeling conventions so that the compounded preparation is not misbranded;
- A new permit to authorize the compounding pharmacy to engage in the wholesale distribution of compounded preparations to a practitioner for office use; and
- Exempting the wholesale distribution of compounded preparations to a practitioner for office use from certain recordkeeping requirements or providing for specific recordkeeping provisions related to the wholesale distribution of prescription drugs.

⁴⁸ In addition to risk of direct or indirect physical harm to the patient, there may also be financial risk to third party payers related to inappropriate billing for a compounded medication, such as using a "similar" commercially available product's billing code to effectuate payment.