Pharmacy compounding of high-risk level products and patient safety

TAMIRA MULLARKEY

Purpose. Issues surrounding pharmacy compounding as well as patient safety concerns surrounding compounding of high-risk level products are discussed.

Summary. The practice of traditional pharmacy compounding is an established activity of pharmacists that serves a vital function to meet the prescribed medical needs of individual patients. However, legal and regulatory debate concerning the oversight of pharmacy compounding has arisen in recent decades, driven mostly by patient harm that has occurred as a result of compounding errors or deceptive practices. Federal and state government agencies and professional organizations have reported errors in pharmacy compounding, including subpotent and contaminated products that have caused patient harm. The *United States Pharmacopeia* (*USP*) chapter 797 serves to protect patients by requiring best practice and quality standards for the safe preparation and handling of compounded sterile preparations (CSPs). High-risk level CSPs pose the greatest risk to patients since nonsterile ingredients or containers are used, which mandates final product sterilization prior to dispensing. Pharmacists should understand and comply with federal, state, and *USP* chapter 797 requirements when preparing CSPs, particularly high-risk level CSPs. Professional pharmacy organizations, such as the American Society of Health-System Pharmacists (ASHP) and the National Association of Boards of Pharmacy (NABP), continue to support the practice of traditional pharmacy compounding through their guidelines, with patient safety as a central theme.

Conclusion. Until the regulatory debate is resolved, pharmacists engaged in pharmacy compounding, particularly in the preparation of high-risk level CSPs, should remain competent in their skills and practice in accordance with federal, state, and *USP* chapter 797 requirements and, thereby, protect patients and the professionalism of pharmacy.

Index terms: Compounding; Contamination; Control, quality; Errors, medication; Guidelines; Organizations; Pharmacists; Pharmacy; Regulations; Sterile products; Sterilization; Toxicity

Am J Health-Syst Pharm. 2009; 66(Suppl 5):S4-13

In the United States, the boundary between medicine and pharmacy began to emerge during the 1800s.[1] Previously, physicians were inclined to combine the practice of medicine and pharmacy in their offices, homes, or doctor's shops.[1] When physician training transitioned from preceptorships to experiential learning in hospitals and clinics, the practice of writing prescriptions began. Specially trained chemists and druggists who staffed apothecaries became almost exclusively responsible for preparing and dispensing medications. Today, compounding, or the preparation of customized dosage forms for the specific problems of individual patients, remains a unique science and art of pharmacy practice.[1]

Despite advances in the practice of pharmacy during the 1800s, the U.S. drug market remained largely unregulated and chaotic.[2] Inconsistencies in compounded medications and compounding techniques existed.[1] Peddlers with traveling medicine shows sold elixirs and herbal remedies made with secret ingredients such as liquor, mercury or arsenic.[2] To strengthen the professionalism of pharmacy and to circumvent patient harm, pharmacy societies and associations were founded, and federal government intervention intensified.[1] With the passage of the Pure Food and Drug Act to protect consumers, the Food and Drug Administration (FDA) was established in 1906.[3]

A growth in drug manufacturing by the pharmaceutical industry be-

TAMIRA MULLARKEY, M.S., is Staff Pharmacist, Department of Pharmacy, Clara Maas Medical Center, Saint Barnabas Health Care System, Scotch Plains, NJ; at the time of writing she was employed by IDEAS, South Plainfield, NJ.

Address correspondence to Ms. Mullarkey at Department of Pharmacy, Clara Maas Medical Center, Saint Barnabas Health Care System, 1989 Birch Street, Scotch Plains, NJ 07076 (tmullarkey@sbhcs.com).

This activity is supported by an educational grant from Medtronic, Inc., administered by IDEAS, a full-service medical communications company.

IDEAS is part of Livingston Services Corporation, which is owned by Saint Barnabas Health Care System.

Ms. Mullarkey was employed by IDEAS at the time of writing.

 1079-2082/09/0901-00S4$06.00.

DOI 10.2146/ajhp0108b

gan after World War II and traditional compounding by pharmacists declined significantly.[1,4] Approximately 75% of prescriptions filled in the United States during the 1930s required some form of compounding, compared with more recent estimates of 1–8% of prescriptions annually.[1,4] Within the last 30 years, a resurgence in pharmacy compounding of customized drug preparations has occurred, perhaps motivated by a shift towards pharmaceutical care services that improve patient outcomes and quality of life.[4] In addition, reductions in hospital length of stay began to occur in 1983 with the passage of Medicare's prospective pricing system for hospital inpatient reimbursement based on diagnostic-related groups.[5] Consequently, the numbers of patients receiving care from clinic-based services and home infusion services increased, leading to expansion in the preparation of compounded sterile preparations (CSPs) by home infusion services or specialized compounding pharmacies.

While pharmacy compounding is inherent to the profession of pharmacy, often providing an important mechanism to improve patient care, debate has arisen concerning its legal status and risk to patients, particularly if performed inappropriately. Several adverse events or errors associated with pharmacy-compounded formulations have been reported since 2000, often resulting in patient harm and, at times, legal action.[4,6-11] When compared with compounded nonsterile preparations, the preparation of CSPs is associated with greater risk to patients. Therefore, organizations such as the United States Pharmacopeia (USP) and the American Society of Health-System Pharmacists (ASHP) have provided guidance for the preparation of CSPs.[12] Compounding pharmacists must remain diligent in their compounding skills and decisions related to compounded formulations, particularly in the preparation of high-risk CSPs, which pose the greatest risk to patients. In addition to practice skills, compounding pharmacists must understand the legal and regulatory implications associated with the preparation of high-risk CSPs in order to protect both patient welfare and professionalism of pharmacy.

Definitions

Under Section 510(g) of the Federal Food, Drug and Cosmetic Act (FDCA) of 1938, which replaced the Pure Food and Drug Act of 1906, registration as producers of drugs and devices (i.e., manufacturers) does not apply to:

> ". . . pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail."[13]

Under this provision, traditional compounding by pharmacists is exempt from the FDCA requirements for manufacturers, including manufacturer licenses and regulations regarding current Good Manufacturing Practices (cGMPs). Pharmacies that repackage, change the original container, or alter the labeling of any medication for distribution to individuals other than the ultimate user (i.e., patients) are defined as and should register as manufacturers (FDCA Section 510[a][1]).[13] While FDA regulates manufacturing through the FDCA, its jurisdiction over professional practice (i.e., compounding) is deferred to state authorities, unless misbranding or adulteration occurs.[4] Controversy exists over when compounding has crossed the boundary into manufacturing.[4]

FDA has defined compounding as "the combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription. Compounding does not generally include mixing or reconstituting commercial products in accordance with the manufacturer's instructions or the product's approved labeling."[14] FDA states that traditional compounding typically occurs when an FDA-approved drug is unavailable or when a licensed health care professional determines that an FDA-approved drug is not appropriate for a patient's medical need.[15] FDA regards virtually all compounded drugs as unapproved new drugs. However, FDA recognizes the importance of traditional compounding and directs its enforcement activity only to those pharmacies engaged in large scale manufacture of unapproved new drugs under the guise of traditional compounding.[15]

To strengthen the practice of compounding and to promote professionalism, pharmacy organizations have published definitions of compounding (Table 1).[16-19]

Sterile compounding differs from nonsterile compounding primarily because maintenance of sterility is required when compounding exclusively with sterile ingredients and components and the achievement of sterility is required when compounding nonsterile ingredients and components.[19] Standards for sterile compounding include International Standards Organization (ISO)-classified air environments, personnel garbing and gloving, personnel training and testing in aseptic manipulation, environmental quality specifications, and disinfection of gloves and surfaces. All CSPs must be

Table 1.
Definitions of Compounding from Professional Pharmacy Organizations

Organization	Publication	Definition Of Compounding
American Society of Health-System Pharmacists (ASHP)	ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products	"The mixing of ingredients to prepare a medication for patient use [including] dilution, admixture, repackaging, reconstitution, and other manipulations of sterile products."[16]
National Association of Boards of Pharmacy (NABP)	Model State Pharmacy Act and Model Rules	"The preparation of components into a drug product (1) as the result of a practitioner's prescription drug order based on the practitioner–patient–pharmacist relationship in the course of professional practice, or (2) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding includes the preparation of limited amounts of drugs or devices in anticipation of receiving prescription drug orders based on routine, regularly observed prescribing patterns."[17]
United States Pharmacopeia (USP)	*The United States Pharmacopeia*	Compounding differs from manufacturing through "the existence of specific practitioner–patient–compounder relationship, the quantity of medication prepared in anticipation of receiving a prescription or a prescription order, and the conditions of sale, which are limited to specific prescription orders."[18] The finished preparation must be dispensed in accordance in compliance with Boards of Pharmacy and other regulatory agency requirements. Sterile compounding requires the maintenance of sterility and stratifies products by potential risk for microbial, chemical, and physical contamination.[19] Mixing and reconstitution of products in accordance to manufacturer instructions are subject to *USP* sterility requirements.

prepared in ISO Class 5 or better air quality conditions.

CSPs may be classified as low-risk, medium-risk, or high-risk.[19] Low-risk CSPs are simple admixtures compounded using closed system transfer methods. Examples of low-risk CSPs include single-volume transfers of sterile dosage forms from ampuls, bottles, bags, or vials, using sterile syringes with sterile needles. Medium-risk CSPs are admixtures compounded using multiple additions or small volumes and may be used for batch preparations (e.g., transfer into syringes) or may involve complex manipulations (e.g., total parenteral nutrition). High-risk CSPs incorporate nonsterile ingredients (e.g., bulk powder) or involve open system transfers. One example of a high-risk CSP is dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized.

Regulatory oversight of compounding: Legal debate

Since pharmacies are registered and licensed by their respective state boards of pharmacy, compounding is regulated by state government agencies.[4] According to the FDCA, FDA enforcement is limited to manufacturers, unless adulteration or misbranding occurs.[4] With the resurgence of pharmacy compounding in recent decades, controversy over FDA regulation of compounding has intensified.

In 1990, FDA, acting as public health advocates, issued an alert in response to concern over patient injuries associated with compounding and batch preparation of sterile products by pharmacies.[4] Although traditional compounding was not discouraged by the letter, pharmacy organizations became concerned that FDA intended to eliminate the right of pharmacists to compound medications.[20] To clarify its position, FDA published its first Compliance Policy Guide (CPG), Section 7132.16, in March 1992, much of which was codified in 1997 by the FDA Modernization Act (FDAMA), which amended the FDCA (Section 503A).[20] The law attempted to clarify activities of compounding versus

manufacturing and supported FDA's historic exemption of traditional compounding from cGMPs and the misbranding and adulteration provisions of the FDCA. However, the law disagreed with FDA's long-standing position that compounded drugs are "new drugs", and thereby repealed FDA's authority to regulate pharmacies engaging in compounding as manufacturers. In 2002, the Supreme Court in *Thompson* v. *Western States Medical Center*, No. 01-344, agreed with the Court of Appeals for the Ninth Circuit that Section 503A prohibitions on pharmacy compounding advertisement and promotion (i.e., commercial speech) were unconstitutional.[21] Since the inseverability of the advertising provisions from Section 503A (as determined by the Court of Appeals) was not challenged, Section 503A was in effect invalidated by the Supreme Court decision. This decision returned pharmacy compounding to an activity that is neither clearly federally regulated nor unregulated.

After the Supreme Court decision, FDA drafted the revised CPG (Section 460.200) in May 2002, to provide guidance on the types of compounding subject to FDA enforcement action.[22] FDA continues to recognize the adulteration and misbranding exemptions of traditional pharmacy compounding. However, FDA maintains that while a compounded drug is exempt from manufacturing requirements, it could still be considered a new drug, especially since Section 503A is now invalid. This contention has resulted in legal challenges of FDA jurisdiction over pharmacy compounding (Table 2).[23-25] The most recent ruling in *Medical Center Pharmacy* v. *Mukasey*, No. 06-51583, has resulted in a split decision in the circuit courts, a matter which may be brought to the Supreme Court.

The proposed Safe Drug Compounding Act of 2007 aimed to amend the FDCA to provide safe and appropriate compounding of drugs by licensed pharmacists and physicians.[26,27] Many of the provisions of the Act seemed to reflect key elements of Section 503A, without the breach of commercial free speech. However, the bill has yet to be introduced, and the likelihood of its passage is unclear.[27]

Advocacy for and benefits of pharmacy compounding

FDA recognizes the importance of traditional compounding, which is defined in the 2002 CPG as extemporaneously compounded and manipulated drugs in reasonable quantities upon receipt of a valid prescription for an individual patient from a licensed practitioner.[22]

The International Academy of Compounding Pharmacists (IACP), a nonprofit advocacy organization for compounding pharmacists, states that the use of a compounded drug should be based on the patient–physician–pharmacist relationship.[28] According to the IACP, reasons to prescribe a compounded medication instead of a manufactured medication for human use may include the unavailability of an FDA-approved medication due to discontinuation or shortages; patient contraindications to specific ingredients; the need for tailored dosage strengths (e.g., for use in infants) or dosage forms (e.g., creams,

Table 2.
Court Rulings on FDA Jurisdiction over Compounding[a]

Court Case	Summary of Major Rulings
Thompson v. *Western States Medical Center*[21]	U.S. Supreme Court ruling that certain provisions of Section 503A of the FDCA placed unconstitutional restrictions on commercial free speech under the First Amendment. This decision, in effect, invalidated Section 503A as ruled by a lower Court of Appeals (Ninth Circuit).
Wedgewood Village Pharmacy, Inc., in the Matter of Establishment Inspection of: d/b/a Wedgewood Pharmacy v. *United States of America*[23]	Court of Appeals (Third Circuit) found that compounding pharmacies are not exempt from FDA inspections, and FDA can use the 2002 CPG and pharmacy prescription volume to gauge a compounding pharmacy's eligibility of exemption from inspections.
Medical Center Pharmacy v. *Gonzales*[24]	District Court for the Western District of Texas ruled that compounded drugs are "implicitly exempt" from the FDCA new drug provision; the decision was appealed.
Medical Center Pharmacy v. *Mukasey*[25]	Court of Appeals (Fifth Circuit) rejected District Court for the Western District of Texas and ruled that compounded drugs are subject to FDA regulations, unless qualifying FDCA exemptions for compounded drugs are met. Additionally, the advertising prohibitions in Section 503A of the FDCA can be severed leaving the remaining parts of Section 503A valid.[b]

[a]FDA = the Food and Drug Administration, FDCA = Federal Food, Drug, and Cosmetic Act, CPG = Compliance Policy Guide.
[b]FDA will follow the court's decision in the Fifth Circuit while following 2002 CPG enforcement elsewhere.

liquids); to improve adherence; and to improve palatability through flavor additives.[28]

The positions of both FDA and IACP seem to possess one central theme—to provide effective pharmaceutical care while protecting the safety of patients and the practice of traditional pharmacy compounding.

Issues surrounding pharmacy compounding

Activities of compounding pharmacists. With the resurgence of pharmacy compounding in recent decades, questions have arisen about the motivation of compounding pharmacies and the safety of compounded drugs, particularly with CSPs. Prohibited activities by compounding pharmacies, as described in FDA's 2002 CPG, include the use of large quantities of bulk drug substances to prepare large quantities of drugs in anticipation of receiving prescriptions; the sale of prepared drugs to physicians and patients with whom only a remote relationship exists; the use of commercial scale manufacturing equipment for compounding; and the preparation of products that are essentially copies of commercially available FDA-approved drugs.[22]

Pharmacists engaging in practices more similar to manufacturing and large-scale drug distribution than those of traditional compounding without the more stringent oversight required for pharmaceutical manufacturers (i.e., cGMPs) may result in inferior preparations, ineffective treatments, regulation noncompliance, malpractice, and patient harm. While FDA conducts roughly 3,500 annual inspections of manufacturers to ensure cGMPs are being met,[29] the number of compounding pharmacy inspections by state authorities is not well documented. The risk of patient harm associated with high-risk level CSPs could be greater due to deviations in sterility assurance, final product concentrations, or stability accuracy since ineffective oversight of pharmacy compounding may exist.

Quality of CSPs. Aseptic manipulations of CSPs usually result in a greater risk of contamination and lower sterility assurance levels (SALs) than those associated with manufactured products. As established by cGMPs, terminal sterilization of manufactured products typically results in a SAL of less than 10^{-6} (i.e., the risk of viable microorganisms is one in one million).[30] In contrast, the extensive aseptic manipulations required during pharmacy compounding of high-risk level CSPs may result in a SAL of 10^{-3} (i.e., the risk of viable microorganisms is one in one thousand).[31]

Concentration deviations in CSPs of drugs with narrow therapeutic ranges could greatly affect clinical outcomes (e.g., the occurrence of toxicity symptoms, loss of clinical effectiveness). Additionally, if verification of compounding accuracy of CSPs is insufficient, drug concentration variations among CSP batches could result in fluctuations of patient response to therapy over time. cGMPs require the evaluation of decontaminated manufactured products for uniform distribution of defined concentrations.[30]

Although articles describing the chemical stability of CSPs are often based on well-conducted studies, the data cannot be extrapolated to concentrations or time periods beyond those studied. Generally, minimal direct data are available for CSPs in terms of the effect on stability of sterile containers, product handling during storage and shipment, and in vivo, particularly for long-term infusions. Conversely, cGMPs for a manufactured product require extensive stability testing on product quality, purity, and strength under a variety of environmental conditions during the product's shelf life.[32] Clinical trials during the FDA-approval process for a manufactured product validate its in vivo stability and effectiveness. However, cGMPs govern the production of a manufactured product prior to reconstitution or dilution. Therefore, the quality of commercially available products requiring such manipulations before administration depend on the technique and skill of the individual responsible for these tasks.

Therapy management issues. Therapy management could also be complicated when a compounded CSP is used instead of a manufactured product. Third party reimbursement may be rejected, depending on the insurer's policies, or insurance fraud can occur if inappropriate codes or drug identification numbers are knowingly documented. The mechanism for reporting medication errors associated with compounding, such as through FDA's MedWatch program, is unclear, which may contribute to a lack of reporting and a lack of dissemination of adverse event information. Technical support from manufacturers of devices (e.g., infusion pumps) or drug information from manufacturers of the equivalent FDA-approved product may not be applicable. Informed patient consent and physician authorization for use of CSPs, which requires diligent education and communication, should be considered to avoid negligence.

FDA survey results and CPGs. Concern over an increase in number of reports of problems and recalls related to compounded products led FDA to conduct a limited survey of compounded products from 12 retail pharmacies across the United States in 2001.[14] The goal of the study was to assess the quality, purity, and potency of compounded drugs ordered over the Internet. While 37 products were identified for analytical testing, only 29 products were tested; eight products were excluded from the analysis because either a commercial version was supplied in place of the compounded product or the products were not supplied in sufficient

time for testing. The dosage forms included nonsterile products (i.e., for inhalation or oral use) and CSPs (i.e., pellet implants, ophthalmics, and injectables). Five of the 29 tested products did not have expiration dates listed on their labels. Ten products (34%) failed one or more standard quality tests. Nine products failed assay (potency) testing, ranging from only 59% to 89% of expected potency, and one injectable product failed limulus amebocyte lysate bacterial endotoxin testing. The analytical testing failure rate for commercially manufactured products at the time of the survey was less than 2% for all tests and approximately 0.1% for potency testing.[33] FDA concluded that the analytical testing failure rate (34%) was higher than expected despite the limitations of the survey (i.e., small sample size, inability of repeat collection and analyses).[14]

Due to the 2001 survey results and to fill the void left by invalidation of Section 503A of the FDCA, FDA published CPG Section 460.200 in May 2002, which still guides FDA action today.[22] The 2002 CPG verifies that drugs compounded by pharmacists in reasonable quantities, pursuant to valid prescriptions, and for individual patients are not subject to FDA enforcement. Guidance from and enforcement by FDA is directed at activities typically associated with manufacturing and result in violations of the new drug, adulteration, or misbranding provisions of the FDCA. While FDA defers less significant violations of the 2002 CPG to state authorities, significant violations of delineated restricted activities are subject to enforcement action by the FDA.

Between 1990 and 2005, FDA learned of at least 240 serious illnesses and deaths associated with improperly compounded products.[15] FDA stated that since adverse event reporting to FDA by pharmacists is not mandated, additional unreported adverse events associated with pharmacy compounding may have occurred. In 2006, FDA conducted a second limited survey of compounded drug products to further explore potency and contamination quality issues. This survey did not examine sterility but did analyze active ingredient identity, potency, and uniformity of oral, topical, or inhalation dosage forms. Of 198 samples that were collected through unannounced visits to U.S. compounding pharmacies listed on the Internet or in telephone directories, 37 samples were excluded from analysis for various reasons. Of the remaining 161 samples, 125 consisted of active pharmaceutical ingredients and 36 were compounded finished product samples. Twelve of the compounded finished product samples (33%) failed analytical testing. The majority of the products that failed analysis failed assay (potency) or content uniformity testing, demonstrating subpotency, superpotency, or nonuniformity of individual dosage units. Potency ranged from 67.5% to 268.4%, and both subpotent and superpotent active components were found in products containing multiple active pharmaceutical ingredients. Since all active pharmaceutical ingredient samples passed analytical testing, FDA suggested that failures of the compounded finished product samples could be attributed to the compounding processes of pharmacies. While recognizing the limitations of the study, FDA concluded that the wide range in potency and uniformity of compounded finished drug products leads to uncertainty in the amount of drug received by the patient, and that such uncertainty can lead to medication errors that pose a health risk for patients who rely on compounded drugs.[15]

ASHP survey of CSPs. In 2002, the compliance of U.S. hospital pharmacies with the 2000 ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products was assessed through surveys mailed to 600 pharmacy directors.[34] Quality assurance was defined in terms of risk level (1 through 3) based on the vulnerability to contamination during preparation (lowest to highest risk respectively). The survey assessed the types of preparations compounded by risk level and evaluated compliance with recommendations in specific quality domains. Survey results from 182 respondents of varying geographic regions and hospital bed size indicated low compliance with the ASHP guidelines for some quality domains, particularly for hospitals that compounded Risk Level 3 preparations (Table 3).[34] Because this survey was conducted before the implementation of *USP* chapter 797, the findings may not reflect current practice.

***USP* chapter 797.** As the number of patients discharged from hospitals on parenteral preparations increased during the 1980s and early 1990s, injuries and deaths related to CSPs began to rise dramatically.[35,36] Tragic events and public attention brought pharmacy compounding under regulatory scrutiny, and the development of pharmacy compounding standards was prompted. FDA considered possibly prohibiting some types of high risk compounded preparations as unapproved new drugs.[35] Since sterile compounding was deemed vital to the preparation of previously unavailable commercial products, (i.e, phenytoin, nitroglycerin, and concentrated morphine injections), practice recommendations were issued by various organizations to provide assistance to personnel in the preparation of CSPs, including *USP* and *National Formulary* (*USP–NF*) Chapter 1206 entitled *Sterile Products for Home Use*, published in 1995.[35]

USP chapter 1206 began to evolve from informational (i.e., chapters numbered above 1000) to required chapter 797 (i.e., chapters numbered less than 1000 are required) in June 2000, with the establishment of a voluntary advisory panel to USP

that is now called the Sterile Compounding Expert Committee.[35] The renumbering of the chapter was an effort to reduce or prevent patient harm from CSPs and was in part due to invalidation of Section 503A of the FDCA. In January 2004, *USP* general chapter 797 *Pharmaceutical Compounding–Sterile Preparations* became the first official publication to describe required conditions and practice standards for CSPs. Based on feedback and comments from affected parties, USP published the revision bulletin of general chapter 797 in December 2007 and gave practitioners until June 1, 2008, to comply with the requirements.[36] Compliance with *USP* chapter 797 standards is enforced through agencies such as FDA, state boards of pharmacy, and accrediting agencies such as the Joint Commission and the Pharmacy Compounding Accreditation Board. FDA will defer to state authorities when evaluating *USP* chapter 797 compliance but will intervene when patient injury or death occurs.[36]

Table 3.
Compliance of Hospital Pharmacies with the 2000 ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products During 2002[34]

Quality Domain	Weighted % Compliance (*n* = 182)
Personnel education, training, and evaluation	62.7
Facilities and equipment	
Risk level 1	81.8
Risk level 2	9.3
Risk level 3	9.3
Garb	
Risk level 1	5.2
Risk level 2	2.9
Risk level 3	2.2
Expiration dating	95.5
Labeling	61.1
Documentation	
Risk level 1	85.0
Risk level 2	29.2
Risk level 3	4.7
End-product evaluation by visual inspection	
Risk level 1	99.2
Risk level 2	100
Risk level 3	95.1
End-product evaluation by microbial testing	
Risk level 1	36.8
Risk level 2	42.6
Risk level 3	48.0
End-product evaluation by pyrogen or endotoxin testing	
Risk level 1	9.4
Risk level 2	11.2
Risk level 3	24.4
Evaluation includes quarantine of preparations while awaiting microbial, pyrogen, or endotoxin testing results	
Risk level 1	13.0
Risk level 2	22.0
Risk level 3	40.6
End-product drug concentration testing	
Risk level 1	17.5
Risk level 2	17.5
Risk level 3	20.7

The NABP has shown support for *USP* chapter 797 by incorporating its requirements into its Model Rules.[36] Individual states vary on their adoption of *USP* chapter 797, with some states adopting the chapter in its entirety and most states incorporating portions into their laws and regulations. Other states have instead developed official policies and procedures without changing regulations, and some states have taken no definite action. Selected states will also enforce some regulations for nonpharmacy professionals and organizations, such as physicians and their offices.

USP chapter 797 is organized to provide a foundation of essential procedures for the safe preparation of CSPs, as classified by potential for microbial, chemical, and physical contamination, in an effort to prevent patient harm.[19] Specifically, minimum practice and quality standards based on scientific data and best practice guidelines are provided for the maintenance of sterility when compounding low-risk and medium-risk CSPs (i.e., compounding exclusively with sterile ingredients and containers) and for the achievement of sterility when compounding high-risk CSPs (i.e., compounding when nonsterile components or containers). Within each category, practice standards are provided for personnel garbing and gloving, personnel training, competency assessment, environmental control, quality assurance,

storage, handling, and beyond-use date (BUDs) assignment. [Immediate-use CSPs, preparations with a low risk of contamination that are needed for emergency or immediate administration to a patient, cannot include medium-risk or high-risk CSPs and are exempt from the requirements for low-risk CSPs provided that defined criteria are met.]

USP chapter 797 standards apply to any location where CSPs are prepared, stored, and transported, including hospitals, clinics, pharmacies, physician offices, and other applicable places.[19] While *USP* recognizes that CSPs are generally prepared under the supervision of pharmacists, the standards also apply to physicians, nurses, and technicians. The standards apply to all CSPs and to manufactured sterile products prepared according to FDA-approved labeling or off-label variations, which is more stringent than FDA standards that exclude manufacturer-guided mixing or reconstitution from compounding regulations. *USP* chapter 797 addresses environmental and beyond-use storage and exposure conditions that manufacturer labeling does not provide.

High-risk level CSPs, which involve the use of nonsterile components or containers, are subject to more stringent requirements and must be sterilized prior to administration to patients.[19] *USP* chapter 797 warns that "careful consideration and evaluation of nonsterile ingredient sources is especially warranted when the CSP will be administered into the vascular system, CNS, or eyes."[19] Bulk nonsterile ingredients should preferably be *USP-NF* grade ingredients, stored appropriately, and may require testing of the accuracy of expected active chemical moiety per the amount of drug substance weighed. When assigning BUDs, pharmacists should consider the nature of the drug and its degradation method, the CSP container or delivery device, the expected storage conditions, the intended duration of therapy, and the expiration dates of all ingredients used. If a drug has a narrow therapeutic range, quantitative stability assays (i.e., high-performance liquid chromatography) could further ensure the compounding accuracy of CSPs.

Compounding errors and high-risk level CSPs. Pharmacies are not required to report adverse events associated with compounded drugs to FDA, unlike commercial drug manufacturers. Since reporting is voluntary, the actual number of adverse events associated with compounded drugs may be skewed. While many adverse events are truly accidents, deceptive practices for profit or for convenience, including insurance fraud (i.e., purposeful potency alterations) and error concealment (i.e., unreported contamination) by compounding pharmacists or pharmacies, have been reported.[37] The following two case reports represent complications that can occur when high-risk level CSPs are prepared inappropriately. The first case report illustrates patient harm that occurred as a result of a potency error, while the second report illustrates patient harm that occurred as a result of a contamination error.

At the American Academy of Physical Medicine and Rehabilitation 2008 Annual Assembly, a poster was presented involving a patient who had acute baclofen withdrawal because of a pharmacy compounding error.[38] A 52-year-old woman with tetraplegia went to an emergency room one week after her intrathecal baclofen pump was refilled, complaining of pain, headache, increasing spasms, and decreased ability to perform typical activities for the past few days. Upon admission, her hypertension and symptoms worsened, with frequent whole body spasms and tachycardia. She was transferred to the intensive care unit for treatment of sustained hypertension despite medical intervention. A pump-imaging study confirmed proper functioning of her intrathecal infusion pump. At that time, her infusion pump was refilled with compounded baclofen 4000 mg/mL, a concentration that is two-fold greater than the highest commercially available strength. Upon sample analysis from the pump reservoir, the baclofen concentration was found to be 7% of expected strength. After replacement with commercially available baclofen (2000 mg/mL concentration), the patient's symptoms began to resolve immediately. The authors concluded that intrathecal baclofen delivery carries a risk for complications, even after years of treatment, including baclofen withdrawal symptoms that mimic other conditions. The use of a compounded medication must be considered as a cause for withdrawal symptoms and warrants consideration of quality control procedures. The findings support the need for determining final drug concentration accuracy when preparing a CSP of a drug with a narrow therapeutic range.

In the second report, eleven patients were infected with *Serratia marcescens* (culture confirmed, n = 8; or clinical infection, n = 3) after receiving epidural or intraarticular injections of compounded betamethasone prepared by a community pharmacy in California on a single day in May 2001.[39] Five of the patients were diagnosed with meningitis, three of whom subsequently died. Complications in the other patients included epidural abscess (n = 5) and hip infection (n = 1). The compounded betamethasone injection was prepared by a local pharmacy because of a national shortage of commercially manufactured betamethasone injection. Investigation by state authorities found numerous deficiencies in the compounding process of the local pharmacy. Deficiencies were identified in the cleanroom environment, terminal sterilization, autoclave temperature, staff training,

labeling practices, and supervision of technicians.[39,40] Although stock solutions were autoclaved, the individual vials of betamethasone injection were not autoclaved, contrary to previous practices at the pharmacy, because of previously observed discoloration of the final product. The 5-mL vials were cleaned with alcohol pads prior to pipetting the betamethasone product. Investigators isolated *S. marcescens* from 35 of 51 betamethasone vials (69%) and from a 1% carboxymethylcellulose stock solution. In addition to deficiencies in the compounding process, investigators also determined that the pharmacy was preparing compounded quantities in excess of anticipated need, in contrast to FDA guidance.[40] The findings in this report support the principle of absolute compliance with *USP* chapter 797 practice standards when preparing a high-risk level CSP.

Role of compounding pharmacists

The central theme of compounding practice guidelines and standards set forth by ASHP, NABP, and *USP* chapter 797 is that pharmacists are responsible for the protection of patient safety by ensuring that CSPs are properly prepared, labeled, stored, dispensed, and delivered.[36] Pharmacists must demonstrate high competence, participate in constant training, and practice with the utmost ethical code. Pharmacists should be aware of their state's position on *USP* chapter 797. Compliance with facility and equipment requirements as well as quality assurance programs is essential to ensure product potency and patient safety. Since pharmaceutical manufacturers are subject to strict FDA regulation and cGMPs, there is reasonable certainty that commercially available products are prepared in optimal conditions. Compounding pharmacies must be consistently committed to the highest level of quality and patient care. Since the greatest potential for patient harm exists with high-risk level CSPs, attention is particularly important when compounding high-risk level CSPs.

Conclusion

Compounding has been an important service of pharmacists since the profession began, enabling physicians to prescribe customized medications to meet patients' individual needs. Since pharmaceutics and chemical incompatibilities are incorporated into the pharmacy curriculum, pharmacists possess a unique advantage when the concepts of optimal compounding are understood. However, pharmacists should recognize the risk of compounding, particularly if their training is inadequate or if quality assurance is insufficient. Although requirements such as those in *USP* chapter 797 serve to protect patients from inferior CSPs, potency and contamination errors can occur. Furthermore, the legal status and regulatory oversight of compounding appears controversial, which may further compromise patient safety. Since the greatest harm to patients can occur with high-risk level CSPs, these products should only be compounded when medically necessary and in accordance with state laws and strict best practice requirements.

References

1. Higby GJ. Evolution of pharmacy. In Troy DB, Remington JP, Beringer P, eds. Remington: the science and practice of pharmacy. 21st ed. Philadelphia: Lippincott Williams & Wilkins; 2005:7-19.
2. Chemical Heritage Foundation. Pharmaceutical achievers: aspirin adventures. Something new at the apothecary shop: snake oil. www.chemheritage.org/educationalservices/pharm/asp/asp21a.htm (accessed 2008 Dec 8).
3. Swann JP. History of the FDA. www.fda.gov/oc/history/historyoffda/default.htm (accessed 2008 Dec 8).
4. Thompson JE. A practical guide to contemporary pharmacy practice. 2nd Philadelphia: Lippincott Williams & Wilkins; 2004.
5. Monk-Tutor MR. The U.S. home infusion market. *Am J Health-Syst Pharm*. 1998; 55:2019-25.
6. Vivian J. Pharmacy compounding and the FDA. *US Pharm*. 2003; 28:32-45.
7. Gebhart F. Fatal meningitis linked to compounding by Calif. pharmacy. *Drug Topics*. 2001; 13:32.
8. Romano MJ. A 1000-fold overdose of clonidine caused by a compounding error in a 5-year-old child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001; 108:471-2.
9. Food and Drug Administration. Warnings for makers of compounded pain products. www.fda.gov/fdac/features/2007/207_compound.html (accessed 2008 Dec 8).
10. Food and Drug Administration. FDA warns five firms to stop compounding topical anesthetic creams. www.fda.gov/bbs/topics/NEWS/2006/NEW01516.html (accessed 2008 Dec 8).
11. Food and Drug Administration. Colistimethate (marketed as Coly-Mycin M and generic products) information. www.fda.gov/cder/drug/infopage/colistimethate/default.htm (accessed 2008 Dec 8).
12. Treadway AK, Craddock D, Leff R. Practices of pharmacies that compound extemporaneous formulations. *Am J Health-Syst Pharm*. 2007; 64:1403-9.
13. Food and Drug Administration. Federal Food, Drug, and Cosmetic Act. Amended through December 31, 2004. www.fda.gov/opacom/laws/fdcact/fdcact5a3.htm#ftn31 (accessed 2008 Dec 10).
14. Food and Drug Administration. Limited FDA survey of compounded drug products. www.fda.gov/cder/pharmcomp/survey.htm (accessed 2008 Dec 10).
15. Food and Drug Administration. 2006 limited FDA survey of compounded drug products. www.fda.gov/cder/pharmcomp/survey_2006.htm (accessed 2008 Dec 10).
16. American Society of Health-System Pharmacists. ASHP policy and positions: drug distribution and control: preparation and handling. www.ashp.org/DocLibrary/BestPractices/QualityAssurance.aspx (accessed 2008 Dec 12).
17. National Association of Boards of Pharmacy. Model State Pharmacy Act and Model Rules (Model Act). www.nabp.net/ftpfiles/NABP01/ModelActFINAL.doc (accessed 2008 Dec 12).
18. U.S. Pharmacopeia. General information chapter 795: pharmaceutical compounding—nonsterile preparations. www.pharmacopeia.cn/v29240/usp29nf24s0_c795.html (accessed 2008 Dec 12).
19. Pharmaceutical compounding—sterile preparations (general information chapter 797). www.usp.org/pdf/EN/USPNF/PF797.pdf (accessed 2008 Dec 12).
20. Abood RR. Pharmacy practice and the law. 5th ed. Sudbury, MA: Jones and Bartlett; 2008.
21. *Thompson* v. *Western States Medical Center*, 535 U.S. 357 (2002).
22. Food and Drug Administration. Compliance policy guides manual sec. 460.200: pharmacy compounding. www.fda.gov/

ora/compliance_ref/cpg/cpgdrg/cpg460-200.html (accessed 2008 Dec 12).
23. *Wedgewood Village Pharmacy, Inc.* v. *United States*, 421 F.3d 263 (3rd Cir. 2005).
24. *Medical Center Pharmacy* v. *Gonzales*, 451 F. Supp. 2d 854, 856 (W.D. Tex. 2006).
25. *Medical Center Pharmacy* v. *Mukasey,* 536 F.3rd 383, 390 (5th Cir. 2008).
26. Safe Drug Compounding Act of 2007 (discussion draft), 110th Cong., 1st Sess., 2007.
27. Paul R. New bill on pharmacy compounding stirs concern: Safe Drug Compounding Act of 2007. *Drug Topics.* http://drugtopics.modernmedicine.com/drugtopics/article/articleDetail.jsp?id=414436 (accessed 2008 Dec 16).
28. International Academy of Compounding Pharmacists. What is pharmacy compounding? www.iacprx.org/site/PageServer?pagename=What_is_compounding (accessed 2008 Dec 17).
29. Food and Drug Administration. Generic drugs: questions and answers. www.fda.gov/buyonlineguide/generics_q&a.htm (accessed 2008 Dec 18).
30. Food and Drug Administration. Guidance for industry: sterile drug productions produced by aseptic processing—current good manufacturing practice. www.fda.gov/Cder/guidance/5882fnl.pdf (accessed 2008 Dec 18).
31. General information Chapter 1211: Sterilization and sterility assurance. In: The United States Pharmacopeia, 20th rev., and The national formulary, 20th ed. Rockville, MD: United States Pharmacopeial Convention; 2006.
32. Food and Drug Administration. Guidance for industry: container and closure system integrity testing in lieu of sterility testing as a component of the stability protocol for sterile products. www.fda.gov/cber/gdlns/contain.pdf (accessed 2008 Dec 18).
33. Galson SK. Statement before the senate committee on health, education, labor, and pensions hearing on "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients." www.fda.gov/ola/2003/pharmacycompound1023.html (accessed 2008 Dec 18).
34. Morris AM, Schneider PJ, Pedersen CA et al. National survey of quality assurance activities for pharmacy-compounded sterile preparations. *Am J Health-Syst Pharm.* 2003; 60:2567-76.
35. The United States Pharmacopeial Convention. USP Patient Safety CAPSLink. www.usp.org/pdf/EN/patientSafety/capsLink2005-06-01.pdf (accessed 2008 Dec 22).
36. American Society of Health-System Pharmacists. ASHP discussion guide on USP chapter 797 for compounding sterile preparations. www.ashp.org/s_ashp/docs/files/DiscGuide797-2008.pdf (accessed 2008 Dec 22).
37. National Association of Boards of Pharmacy. Missouri Board of Pharmacy. www.nabp.net/ftpfiles/newsletters/MO/MO082003.pdf (accessed 2008 Dec 31).
38. Kanter DM, Logan L, Turk MA et al. Acute baclofen withdrawal in a patient receiving compounded intrathecal baclofen: a case report. *Arch Phys Med Rehabil.* 2008; 89:E94. Abstract.
39. Civen R, Vugia DJ, Alexander R et al. Outbreak of *Serratia marcescens* infections following injection of betamethasone compounded at a community pharmacy. Clin Infect Dis. 2006; 43:831-7.
40. Peques DA. Improving and enforcing compounding pharmacy practices to protect patients. *Clin Infect Dis.* 2006; 43:838-40.