
Chapter 1

Guidelines for Compounding Practices

CHAPTER AT A GLANCE

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Compounding is an integral part of pharmacy practice and is essential to the provision of health care.¹ Compounding is defined in several ways; one definition in Chapter 795 of the *United States Pharmacopeia (USP 795)* is as follows:

The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner–patient–pharmacist–compounder relationship in the course of professional practice. Compounding includes the following:

- Preparation of drug dosage forms for both human and animal patients,
- Preparation of drugs or devices in anticipation of prescription drug orders, on the basis of routine, regularly observed prescribing patterns,
- Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients,
- Preparation of drugs or devices for the purposes of, or as an incident to, research (clinical or academic), teaching, or chemical analysis, and
- Preparation of drugs and devices for prescriber's office use where permitted by federal and state law.

Compounding can be as simple as the addition of a liquid to a manufactured drug powder or as complex as the preparation of a multicomponent parenteral nutrition solution. In general, compounding differs from manufacturing in that compounding involves a specific practitioner–patient–pharmacist relationship, the preparation of a relatively small quantity of medication, and different conditions of sale (i.e., specific prescription orders). The side-

Distinguishing Compounding from Manufacturing

Compounding is the act of preparing, mixing, assembling, packaging, and/or labeling a drug or device as the result of a practitioner's prescription drug order or initiative based on the practitioner–patient–pharmacist relationship in the course of professional practice, or for the purpose of, or incident to, research, teaching, or chemical analysis and not for sale or dispensing. *Compounding* also includes the preparation of drugs or devices in anticipation of prescription drug orders, on the basis of routine, regularly observed prescribing patterns.²

Manufacturing is the production, preparation, propagation, conversion, and/or processing of a drug or device, either directly or indirectly, through extraction from substances of natural origin or independently through means of chemical or biological synthesis; the term includes any packaging or repackaging of the substance(s) or labeling or relabeling of its container and the promotion and marketing of such drugs or devices. *Manufacturing* also includes the preparation and promotion of commercially available products from bulk compounds for resale by pharmacies, practitioners, or other persons.²

Guidelines for distinguishing between compounding and manufacturing are as follows:

- Pharmacists may compound, in reasonable quantities, drug preparations that are commercially available in the marketplace if a pharmacist–patient–prescriber relationship exists and a valid prescription is presented.
- Pharmacists may compound nonprescription medications in commercially available dosage forms or in alternative dosage forms to accommodate patient needs as allowed by individual state boards of pharmacy.
- Pharmacists may compound drugs in limited quantities prior to receiving a valid prescription, on the basis of a history of receiving valid prescriptions that have been generated solely within an established pharmacist–patient–prescriber relationship, and provided that the prescriptions are maintained on file for all such preparations dispensed at the pharmacy.
- Pharmacists should not offer compounded medications to other pharmacies for resale; however, a practitioner may obtain compounded medication to administer to patients, but it should be labeled with the following: "For Office Use Only," date compounded, use-by date, and name, strength, and quantity of active ingredients. An exception to this may be the outsourcing of some compounded preparations by hospitals to contract compounding pharmacies.
- Compounding pharmacies and pharmacists may advertise or otherwise promote the fact that they provide prescription compounding services.

bar above more fully defines compounding and manufacturing and provides guidelines for differentiating the two activities.

The pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity, with appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and current scientific principles. Pharmacists should continually expand their compounding knowledge by participating in seminars, studying current literature, and consulting with colleagues.

Regulatory Framework

In general, professions such as medicine and pharmacy are established as legal entities within a state by the professional practice acts of each state that are enacted by the state lawmakers (legislature). Once a profession is established, the state legislatures make laws to govern its practice. The lawmakers also establish a governing board to oversee the practice of the profession in their state. In some states, the governing board may oversee more than one profession. Usually, the board creates regulations to govern the practice.² Whereas a state's laws must be changed by the legislature, regulations can be changed by the state boards.

Physicians are regulated by state boards of medicine that govern practice by enacting and enforcing regulations and disciplining practitioners who do not abide by the laws and regulations. Similarly, state boards of pharmacy govern pharmacy practice by enacting and enforcing regulations and disciplining practitioners who do not abide by the laws and regulations. In addition to state laws and regulations, pharmacists must comply with various standards of practice, including those in *United States Pharmacopeia* Chapter 795, Pharmaceutical Compounding—Nonsterile Preparations, and Chapter 797, Pharmaceutical Compounding—Sterile Preparations, when these standards are addressed by the individual state board of pharmacy.

Since 1820, a nongovernmental organization, the United States Pharmacopeial Convention (USP), has established some of the standards of quality for compounded and manufactured pharmaceuticals and published them in its compendium the *United States Pharmacopeia* (USP). In the 1906 Federal Food and Drugs Act, both the USP and the *National Formulary* (NF) were designated as official compendia of the United States, and this designation has been reaffirmed since that time. It is up to the state boards of pharmacy to enforce these standards, as the USP has no enforcement powers.

The 1906 Federal Food and Drugs Act prohibited the sale of adulterated or misbranded drugs, but it did not require that drugs be approved by any agency. The Food and Drug Administration (FDA) was formally organized in 1938 under the Federal Food, Drug, and Cosmetic Act; this law required FDA to approve marketed drugs on the basis of safety. In 1962, the Kefauver-Harris Amendments required that marketed drugs (those approved by FDA) also be effective. Thus, FDA is responsible for ensuring the safety and effectiveness of manufacturers' marketed drugs.

The 1938 Federal Food, Drug, and Cosmetic Act established FDA to monitor the relatively young pharmaceutical industry, which at that time had no enforceable standards. That act does not refer to pharmaceutical compounding. Recently, court decisions have stated that FDA has no authority over pharmacy compounding done by a pharmacy that is in compliance with the pharmacy practice laws of the state.

Compounding has long been recognized as a legal and vitally important core component of traditional pharmacy practice. In 1938, the USP had already been providing compounding instructions for 118 years. Compounding occupied such an important role in U.S. pharmacy practice in the early 20th century that a number of state pharmacy practice acts not only regulated compounding but specifically included the term *compounding*. Before 1938, states considered every location where compounding occurred and where drugs, medicines, or chemicals were sold or dispensed to be a pharmacy. In other words, wherever compounding took place, the facility was termed a pharmacy and was thus subject to that state's pharmacy practice act.³

Furthermore, before 1938, states and the District of Columbia restricted compounding, dispensing, or selling drugs, medicines, or poisons and compounding physicians' prescriptions to pharmacists or assistant pharmacists registered or licensed by the state board of

pharmacy. A number of jurisdictions, while restricting pharmacy compounding (and other pharmacy practices) to registered or licensed pharmacists (or, in some cases, assistant pharmacists under the personal supervision of registered pharmacists), expressly noted that such restrictions did not apply to licensed medical practitioners compounding their own prescriptions. The states, far from banning compounding, restricted persons who could engage in the activity to specific state-registered or licensed health professionals.

As further evidence of the importance of compounding to pharmacy practice, by 1938 a number of states required applicants for pharmacist registration and licensure to prove they had spent specific amounts of time gaining practical experience in locations where drugs, medicines, and poisons were compounded, dispensed, and retailed and medical practitioners' prescriptions were compounded. The jurisdictions, far from discouraging compounding, sought to ensure that a pharmacist had a certain amount of experience in compounding.

At that time, a number of jurisdictions allowed only licensed or registered pharmacists to operate pharmacies for retailing, dispensing, or compounding drugs, medicines, or poisons or for compounding physicians' prescriptions. In addition, before 1938 it was illegal for the owner or manager of a pharmacy to permit anyone but a licensed pharmacist to engage in pharmacy compounding.

Clearly, registered pharmacists were compounding drugs as part of their practice in 1938, and they have continued to do so since then. Pharmacists in 1938 were compounding more than 250 million prescriptions annually, or approximately two prescriptions for every person in the United States. In 1940, the federal government recognized the importance of compounding in the practice of pharmacy within the armed forces and civil service.

The intent of the Federal Food, Drug, and Cosmetic Act had nothing to do with compounding. At the time of its passage, the state boards of pharmacy, pharmacists, and other health care professionals would have opposed any measure that attempted to ban pharmacy compounding. Congress did not intend to outlaw compounding any more than it intended to prohibit dispensing and selling drugs, medicines, and poisons, the other traditional pharmacy practices that were then and are still regulated by the states.

Unapproved Drugs

FDA is looking at all unapproved drug products that are being marketed in the United States. This is of interest to compounding pharmacists because FDA has decided that compounded preparations are now considered "unapproved new drugs." The Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That act prohibited the sale of adulterated or misbranded drugs. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act, which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938.

Under the 1938 grandfather clause, a drug product that was on the market prior to passage of the 1938 act and that contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that act was not considered a *new drug* and therefore was exempt from the requirement of having an approved new drug application.

FDA estimates that several thousand unapproved drug products are being commercially manufactured and marketed. FDA also considers all compounded preparations as unapproved drugs; this includes all intravenous admixtures in hospitals, pediatric oral liquids, pain management injections, and other preparations that are compounded. Thus, other agencies of the federal government—including the Department of Veterans Affairs, the Indian Health Service, all branches of the armed services, and the Federal Bureau of Prisons—are involved

TABLE 1-1 Examples of Pre-1938 Drugs That Remained on the Market as Unapproved Drugs

Acetaminophen, codeine phosphate, and caffeine capsules and tablets	Morphine sulfate oral solution and tablets
Amobarbital sodium capsules	Nitroglycerin sublingual tablets
Amyl nitrate inhalant	Opium tincture
Chloral hydrate capsules, syrup, and suppositories	Oxycodone tablets
Codeine phosphate injection, oral solution, and tablets	Oxycodone hydrochloride oral solution
Codeine sulfate tablets	Paregoric
Colchicine injection and tablets	Phenazopyridine hydrochloride tablets
Digitoxin tablets	Phenobarbital capsules, elixir, and tablets
Digoxin elixir and tablets	Phenobarbital sodium injection
Ephedrine sulfate capsules and injection	Pilocarpine hydrochloride ophthalmic solution
Ergonovine maleate injection and tablets	Potassium bicarbonate effervescent tablets for oral solution
Ergotamine tartrate tablets	Potassium chloride oral solution
Hydrocodone bitartrate tablets	Potassium gluconate elixir and tablets
Hydrocodone bitartrate, aspirin, and caffeine tablets	Potassium iodide oral solution
Hydromorphone hydrochloride suppositories	Salsalate capsules
Levothyroxine sodium for injection	Sodium fluoride oral solution and tablets
	Thyroid tablets

in compounding unapproved illegal drugs. Many state agencies (e.g., hospitals, prisons, welfare programs) also are involved in compounding unapproved illegal drugs.

It is an interesting situation in which we find ourselves. FDA has determined that an action (compounding) widely practiced by other agencies of the U.S. government is illegal, as compounding creates unapproved new drugs. Even the U.S. courts disagree with FDA. According to a recent court decision—*Medical Center Pharmacy v Mukasey*, 536 F3d 383 (5th Cir 2008)—the definition of a new drug was never intended to apply to compounded medications. According to that decision, compounded medications are not new drugs and are legal drugs under the law (except in the view of FDA). Compounding is anything outside the approved labeling of a drug.

Examples of drugs marketed prior to 1938 that were grandfathered and allowed to stay on the market as unapproved drugs are shown in Table 1-1.

Certification and Accreditation

An exciting recent development is the opportunity for a compounding pharmacy to obtain accreditation; other health care organizations have had that opportunity for years. Compounding pharmacies now have an external standard-setting entity to which they can apply for accreditation, the Pharmacy Compounding Accreditation Board (PCAB).⁴

The mission of PCAB is to serve the public good by serving patients, prescribers, and the pharmacy profession. The comprehensive accreditation program is completely voluntary and is structured to improve quality and safety through standard practices. The PCAB Principles of Compounding and PCAB Standards are the two main tools through which PCAB carries

out its mission. A core concept contained in the principles is that compounding is the result of a practitioner's prescription drug order based on a valid practitioner–patient–pharmacist relationship. The principles state, moreover, that compounding is a part of the practice of pharmacy subject to regulation and oversight by the state boards of pharmacy. The PCAB standards cover several core areas of both sterile and nonsterile compounding, including training of personnel, storage of chemicals, proper equipment usage, beyond-use dating, packaging, labeling, patient education, and quality assurance. PCAB uses two methods to determine compliance: an extensive review of the standard operating procedures (SOPs) of the facility, and an on-site survey of the pharmacy.⁵

PCAB requires that a facility seeking accreditation have a set of comprehensive SOPs for use by the pharmacy staff. PCAB looks at whether SOPs (1) are in writing, (2) reflect what the organization actually does, and (3) are being implemented as written. Well-written purchased or downloaded SOPs usually include reference information such as USP requirements, the FDA negative list (i.e., list of substances not to be used in compounding), and SOPs that should be followed throughout the industry. Some organizations develop their own SOPs, and others purchase or download prewritten SOPs available from various sources. Either approach can be used, but both require a great deal of work.

PCAB places a lot of emphasis on SOPs because it is usually not possible to test every compounded preparation prior to dispensing. However, compounders can rely on a set of consistent, uniform procedures which, if followed, ensure that the preparation is made correctly each time and that the appropriate documentation is generated. SOPs ensure that the procedures are standardized and documented to provide consistency and continuity.

A general approach to developing an SOP manual is to (1) review the PCAB standards and make a list of required SOPs, (2) assess whether your organization has SOPs that address the PCAB requirements, and (3) conduct another review of your written SOPs to determine whether the SOP and the actual procedure match.⁶

Today, pharmacy and other professions are increasingly emphasizing quality assurance and the need for continuing competence of practitioners. In many areas of practice, certification is used to recognize individuals who meet a certain standard. Certification probably will not be required in the future for the compounding of simple preparations, but it may be required for the compounding of complex preparations, such as high-risk sterile compounding and the compounding of biotechnology preparations and those used in nuclear pharmacy. We need to begin now to prepare for such requirements.

It is important to distinguish *certification* (and *certified practitioners*) from programs that award a *certificate* for completion of a prescribed course of study. A *certificate program* may involve simply attending a seminar, reading a book, or viewing an audiovisual course. For certification, the standard must be high. Certified practitioners must have experience in the specialized field and must demonstrate an advanced level of practice. Usually, they must pass an examination and demonstrate mastery of core knowledge. In the past, they might have been called “masters” of their disciplines or trades.

Compounding Facility and Equipment

Pharmacies that engage in compounding should have a designated area with adequate space for the orderly placement of the equipment and materials used in compounding activities. The pharmacist is also responsible for the proper maintenance, cleanliness, and use of all equipment involved in the compounding practice. A detailed discussion of the physical facility is included in Chapter 3, which also describes the specific equipment and supplies needed in the compounding process.

In addition, *USP* Chapter 795, Pharmaceutical Compounding—Nonsterile Preparations, and *USP* Chapter 797, Pharmaceutical Compounding—Sterile Preparations, should be consulted for comprehensive discussion of the compounding facility and equipment and the other topics covered in the following sections.

Personnel

Only personnel authorized by the responsible pharmacist should be in the immediate vicinity of the drug-compounding operation. Any person with an apparent illness or open lesion that may adversely affect the safety or quality of a drug preparation being compounded should be excluded from direct contact with components, drug preparation containers, closures, in-process materials, and drug preparations until the condition is corrected or determined by competent medical personnel to not jeopardize the safety or quality of the preparation being compounded. All personnel who assist in compounding procedures should be instructed to report to the responsible pharmacist any health conditions that may have an adverse effect on drug preparations.

Duties

The pharmacist has the responsibility and authority to inspect and approve or reject all components, drug preparation containers, closures, in-process materials, and labeling, as well as the authority to prepare and review all compounding records to ensure that no errors have occurred in the compounding process. In addition to compounding, the pharmacist provides other services, such as the following:

- Publicizes the availability of both prescription and nonprescription compounding services. These services may include chemicals, devices, and alternative dosage forms,
- Provides drug searches on specific chemicals in different dosage forms, strengths, bases, and the like to accommodate physicians' specific needs,
- Provides follow-up information in response to a practitioner's request for information regarding a compounded medication, and
- Consults with practitioners regarding a particular dosage form when discussing services with a health care provider.

Qualifications

Pharmacists should possess the education, training, and proficiency necessary to properly and safely perform compounding duties at the level at which they are involved. All pharmacists who engage in the compounding of drugs should be proficient in the art and science of compounding and should maintain that proficiency through current awareness and training.

Instruction for compounding pharmacists should cover the following:

- Proper use of compounding equipment such as balances and measuring devices, including guidelines for selecting proper measuring devices, limitations of weighing equipment and measuring apparatus, and the importance of accuracy in measurements,
- Pharmaceutical techniques needed to prepare compounded dosage forms (i.e., comminution, trituration, levigation, pulverization by intervention, and geometric dilution),
- Properties of dosage forms to be compounded and related factors, such as stability, storage considerations, and handling procedures,
- Literature regarding stability, solubility, and other physicochemical properties of the ingredients,

- Handling of nonhazardous and hazardous materials in the work area, including protective measures for avoiding exposure, emergency procedures to follow in the event of exposure, and the location of material safety data sheets (MSDSs) in the facility (see Chapter 4 for a discussion of MSDSs),
- Use and interpretation of chemical and pharmaceutical symbols and abbreviations in medication orders and in formulation directions, and
- Review of pharmaceutical calculations.

Attire

Personnel engaged in the compounding of drugs should wear clean clothing appropriate to the operation being performed. Protective apparel, such as coats or jackets, aprons, or hand or arm coverings, should be worn as necessary to protect drug preparations from contamination. A clean laboratory jacket usually is considered appropriate attire for non-sterile compounding procedures. Work with hazardous materials, such as chemotherapeutic agents, may require the use of goggles, gloves, masks or respirators, double gowns, and foot covers; showers and eyewash stations should be provided. Clean room apparel is required for the compounding of sterile preparations in a controlled environment (clean room).

Ingredient Standards

Throughout history, pharmacists have used chemicals and other materials for prescription compounding. In the past, these chemicals and materials were obtained from natural preparations, raw materials, and household ingredients. Today, compounding pharmacists use chemicals from various sources, depending on availability.

Chemical companies may place a disclaimer on their chemicals for a number of reasons, including the following:

- Companies do not want to be required to label the materials under the Food, Drug, and Cosmetic Act of 1938 (FDC Act); consequently, they state that the materials are not to be used as drugs. This exempts the companies from having to comply with the FDC regulations.
- The source of the chemicals may be companies that do not meet current good manufacturing practices as stipulated in parts 210 and 211 of the Code of Federal Regulations; thus, when drugs are repackaged, only select information concerning the levels of potency and impurities and other miscellaneous characterization data are provided.
- The disclaimer protects the companies from liability associated with the use of their products that have not undergone the full safety and effectiveness testing required by FDA for the manufacturing of drug products.

USP Chapter 795 states that “The pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and relevant scientific data and information.”¹ The compounding of quality preparations must involve the use of high-quality chemicals. If *USP/NF* grade ingredients (Table 1-2) are used to prepare compounded formulations, the preparation must meet the requirements of compendial monographs.

TABLE 1-2 Description of Chemical Grades

Grade	Description
USP/NF	Meets the minimum purity standards; conforms to tolerances set by the <i>United States Pharmacopeia/National Formulary</i> for contaminants dangerous to health
ACS reagent	High purity; conforms to minimum specifications set by the Reagent Chemicals Committee of the American Chemical Society
CP (chemically pure)	More refined than technical or commercial grade but still of unknown quality
Technical or commercial	Indeterminate quality

USP Chapter 795 also states the following:

A USP or an NF grade substance is the preferred source of ingredients for compounding all other preparations. If that is not available, or when food, cosmetics, or other substances are or must be used, the use of another high quality source, such as analytical reagent (AR), certified American Chemical Society (ACS), or Food Chemicals Codex (FCC) grade, is an option for professional judgment. For any substance used in compounding not purchased from a registered drug manufacturer, the pharmacist should establish purity and safety by reasonable means, which may include lot analysis, manufacturer reputation, or reliability of source.¹

In addition to the USP, NF, AR, ACS, and FCC grades mentioned above, other high-purity chemical grades include analytical reagent, high-performance liquid chromatography, spectroscopic grade, and primary standard. These grades are used primarily in the analytical chemistry and pharmaceutical analysis field.

Manufactured drug products such as injectables, tablets, or capsules may be sources of active ingredients. If such a product is the source of the active ingredient used in the compounding of a prescription, only a manufactured drug from a container labeled with a batch control number and a future expiration date is acceptable. If a manufactured drug product is used, it is important that all the ingredients in the drug product be considered relative to the intended use and the potential effect on the overall efficacy (strength, quality, purity, stability, compatibility) of the compounded preparation.

Appendix I lists drug products that have been withdrawn or removed from the market because of safety or efficacy concerns. According to FDA, preparing compounded formulations of any of these products will be subject to enforcement action.

For consistent quality in compounded preparations, it is important to use high-quality suppliers of chemicals for compounding. Using the same suppliers also helps ensure consistent quality. If different suppliers are used, variations in physicochemical characteristics, such as particle size, may alter the expected response of drug preparations. It is wise to have a secondary supplier available in the event of unexpected shortfalls in supply.

Certificates of analysis should be obtained and kept on record as documentation of the quality of chemicals used in compounding preparations. These can be easily maintained in a standard three-ring notebook system.

The Compounding Process

Before the first step in the compounding process is taken, the following questions must be considered:

- What are the physical and chemical properties and medicinal and pharmaceutical uses of the drug substance?
- Are the quantity and quality of each active ingredient identifiable?
- Given the purpose of the prescription, will the preparation and route of administration provide adequate absorption, either locally or systemically?
- Are excipients present from any source (manufactured products) that may be expected to cause an allergic reaction, irritation, toxicity, or an undesirable organoleptic response by the patient?
- For preparations that are to be administered orally, are the active ingredients stable in the normal gastric pH range, or are they subject to extensive hepatic first-pass metabolism?

The steps to be followed before, during, and after compounding can be grouped into five categories: preparatory, compounding, final check, sign-off, and cleanup steps. These are summarized in the sidebar below.

General Steps in the Compounding Process

Preparatory

1. Judging the suitability of the prescription in terms of its safety and intended use and the dose for the patient.
2. Performing the calculations to determine the quantities of the ingredients needed.
3. Selecting the proper equipment and making sure it is clean.
4. Donning the proper attire and washing hands.
5. Cleaning the compounding area and the equipment, if necessary.
6. Assembling all the necessary materials and ingredients to compound and package the prescription.

Compounding

7. Compounding the prescription according to the formulary record or the prescription, using techniques according to the art and science of pharmacy.

Final Check

8. Checking, as indicated, the weight variation, adequacy of mixing, clarity, odor, color, consistency, and pH.
9. Entering the information in the compounding log.
10. Labeling the prescription.

Sign-Off

11. Signing and dating the prescription, affirming that all of the indicated procedures were carried out to ensure uniformity, identity, strength, quantity, and purity.

Cleanup

12. Cleaning and storing all equipment.
13. Cleaning the compounding area.

Continuous Quality Improvement

Before dispensing the prescription to the patient, the pharmacist should ensure the accuracy and completeness of the compounded preparation by reviewing each step in the preparatory, compounding, final check, and sign-off phases. In the preparatory review, the pharmacist checks that all preparations for the compounding process were handled appropriately. Aspects to be reviewed include the following:

- Appropriate ingredients, adjuvants, and equipment were selected for the specific preparation.
- Calculations are correct.
- Measurements were performed accurately with properly functioning equipment.
- The formulation is appropriate for the intended use and stability limits of the preparation.

The pharmacist then reviews the compounding steps to ensure that the procedures and techniques used to prepare the formulation were faithfully followed and appropriately documented. This review also ensures that the formulation is reasonably aesthetic and uniform in content.

The pharmacist's review of the final check phase should be comprehensive. It is intended to verify the following:

- The calculated yield is consistent with the actual yield.
- The tolerance for individual dose weight variation has been met by a sampling technique when appropriate (e.g., capsule weight).
- The physical characteristics (clarity, color, odor) of the preparation are consistent with those predicted for the preparation.
- Physical tests have been performed when appropriate, and the preparation meets the test limits.
- The preparation is suitably labeled, and the contents have been verified with the prescription order. All legal requirements have been imprinted on the label and in the compounding record.
- The preparation is suitably packaged for patient use, and the container that is selected will protect the preparation from undue environmental exposure until at least the discard-after or beyond-use date.
- Documentation is appropriate, as listed in Chapter 4.
- The patient or caregiver has been adequately informed about ways to identify obvious evidence of instability in the compounded preparation.
- The preparation is labeled with explicit storage and administration instructions.

The pharmacist may also decide to submit samples of compounded preparations to an analytical testing laboratory or test it within the pharmacy. Such analytical testing could include dissolution rates and concentrations of compounded medications. Additional tests, assays, or visual observations of samples of the preparation may be performed to ensure the content, stability, pH, sterility, and nonpyrogenicity. The pharmacist may use an analytical testing laboratory to perform some of the testing; this would involve testing samples of a compounded preparation.

Packaging, Storage, and Labeling

The pharmacist should inspect and approve all components, drug preparation containers, closures, labeling, and other materials involved in the compounding process. These materials should be handled and stored in a manner that will prevent contamination.

Packaging

Compounded preparations should be packaged according to the specifications in *USP 34/NF 29* (i.e., the current edition). The selection of a container depends on the physical and chemical properties of the compounded preparation and the intended use of the preparation.

To help maintain potency of the stored drug, packaging materials should not interact physically or chemically with the preparation. Materials that are reactive, additive, or absorptive can alter the safety, identity, strength, quality, or purity of the compounded drug beyond the specifications for an acceptable preparation. Container characteristics of concern include inertness, visibility, strength, rigidity, moisture protection, ease of reclosure, and economy of packaging.

Plastic containers have become increasingly popular because they are less expensive and lighter in weight than glass. Only plastic containers that meet *USP 34/NF 29* standards should be used.

Storage

Chemicals should be stored according to either the manufacturers' directions or the appropriate *USP 34/NF 29* monographs. In general, compounding chemicals should be stored in tightly closed, light-resistant containers at room temperature; some chemicals, however, require refrigeration. Chemicals should be stored off the floor, preferably on shelves in a clean, dry environment. Commercial drugs to be used in the compounding process should be removed from cartons and boxes before they are stored in the compounding area.

Temperature requirements for storage of substances are detailed in the appropriate *USP 34/NF 29* monographs. The temperatures of the storage areas, including refrigerators and freezers, should be monitored and recorded at least weekly.

Flammable or hazardous products should be stored appropriately in safety storage cabinets and containers, which are available from many laboratory suppliers.

Labeling

Labeling should be done according to state and federal regulations. Usually, labeling information includes the (1) generic or chemical names of the active ingredients, (2) strength or quantity, (3) pharmacy lot number, (4) beyond-use date, and (5) any special storage requirements.

When a commercial drug product has been used as a source of the drug, the generic name of the drug product, not the proprietary name, should be placed on the label. Inactive ingredients and vehicles should also be listed on the label. If no expiration date is provided on the chemicals or materials that are used, a system of monitoring should be established (e.g., placing the date of receipt of the materials on the label of the container, or whatever the state board of pharmacy requires). Monitoring expiration dates will ensure that materials, ingredients, and supplies are rotated so that the oldest stock is used first.

The use of specially coined names or short names for convenience should be discouraged. Such names can cause difficulty in emergency departments if an overdose or accidental poisoning has occurred or if health professionals treating the patient need to know what the patient has been taking. If batch quantities of a preparation are compounded, a

lot number should be assigned and placed on the labels. Surplus prepared labels should be destroyed.

If excess preparation is compounded or additional quantities are prepared in anticipation of future requests for the preparation, the pharmacist should have written procedures for the proper labeling of the excess preparation. Labeling should include the (1) complete list of ingredients, (2) preparation date, (3) assigned beyond-use date, (4) appropriate testing/published data, and (5) control numbers. The preparation should then be entered into the inventory and stored appropriately to help ensure its strength, quality, and purity. When the compounding process is completed, the excess preparation should be reexamined for correct labeling and contents.

IACP Recommended Labeling

The International Academy of Compounding Pharmacists (IACP) has developed recommendations for labeling preparations compounded in response to a prescription for a specific patient. The primary label of each compounded medication should include a statement notifying the patient that the medication has been compounded. If space limitations or clinical reasons preclude inclusion on the primary label, the information may be affixed through auxiliary labeling (e.g., if a label applied directly to the primary container could affect the quality of the medication, the label and statement should instead be applied to exterior packaging). In either case, the statement should be prominently displayed in the medication labeling. IACP recommends the following statement: “This medicine was specially compounded in our pharmacy for you at the direction of your prescriber.” Alternative language that clearly states that the medication has been compounded may be used.

In addition, IACP supports state regulations that require the following pieces of information on all prescription labels, including compounded medication labels: (1) patient’s name, (2) prescriber’s name, (3) name, address, and phone number of the pharmacy preparing the medicine, (4) prescription number, (5) medication’s established or distinct common name, (6) strength, (7) statement of quantity, (8) directions for use, (9) date prescription is filled, (10) expiration/beyond-use date, (11) storage instructions, and (12) any other state labeling requirements.

Further, IACP recommends including the following language as an insert with the package of the compounded medication:

This medicine was compounded specifically for you in a pharmacy to fill the prescription your doctor wrote for you. It was specially made to meet your individual needs. For this reason, no standardized information or literature is available with your prescription. If you have not done so, please discuss this medicine with your doctor to ensure that you understand (1) why you have been prescribed a compounded medicine, (2) how to properly take this medicine, and (3) the interactions, if any, this medicine may have with any other medicines you are taking.

Compounding is a long-standing pharmacy practice that allows doctors to treat their patients’ individual needs without being restricted only to off-the-shelf medicines or devices. This medicine was prepared in a compounding pharmacy to meet the specifications ordered by your doctor.

1. Call your doctor if
 - You experience any side effects.
 - You are taking additional medicines that may interact with this compounded medicine.
 - You have allergies or other medical conditions that should be noted.

2. Call our pharmacists if
 - Information on the label is not clear to you.
 - You have any concerns regarding precautions, ingredients, or proper storage.

Our pharmacists will be happy to help with any additional questions or concerns.

Clear labeling of compounded medications will help ensure that patients are properly and consistently informed.

IACP Recommended Labeling for Medications Compounded for Office Use

Physicians and institutions occasionally ask pharmacists to compound non-patient-specific medications that are not commercially available and that must be administered by the prescriber. For example, FDA requires certain medications to be administered by the prescriber. In other cases, preparations for office use must be compounded in advance and immediately available for the physician to use in emergencies.

For these medications, IACP recommends language to be included on the primary label of each package. If space limitations or clinical reasons preclude inclusion on primary labeling, the information may be affixed through auxiliary labeling (e.g., if a label applied directly to the primary container could affect the quality of the medication, the label and statement should instead be applied to exterior packaging). In either case, the statement should be prominently displayed in the medication labeling. IACP recommends the following statement to help ensure (1) that the medication is administered properly and (2) that the prescriber and the patient are aware that the medication has been compounded: “This medicine was compounded in our pharmacy for use by a licensed professional only.” Alternative language clearly stating that the medication has been compounded and is intended for in-office administration only may be used.

In addition, IACP supports state regulations that require the following pieces of information on the labels of office-use compounds: (1) name, address, and telephone number of the pharmacy preparing the medicine, (2) lot number, (3) the medication’s established or distinct common name, (4) strength, (5) statement of quantity, (6) date prescription is filled, (7) beyond-use date, (8) storage instructions; and (9) any other state labeling requirements.

Quality Control

The pharmacist should review all compounding records for accuracy and conduct in-process and final checks to ensure that errors have not occurred in the compounding process. Written procedures for the compounding of drugs should be available and followed to ensure the identity, strength, quality, and purity of the finished preparation. Such procedures should include a listing of the ingredients, quantities, order of mixing or preparation, and a detailed description of the compounding process. The equipment and utensils used should be listed, as well as the container and closure packaging system. Information concerning stability and compatibility should be included, along with any documentation related to the preparation.

Ingredients should be accurately weighed, measured, or subdivided as indicated. The compounding pharmacist should check and recheck these operations at each step in the compounding process to ensure that weights or measures are correct.

Standard operating procedures (SOPs) should be prepared that describe the tests or examinations to be conducted on the finished preparation. These tests could include physi-

cal examination and measurements of pH, weight, and volume. Such procedures are established to monitor the output of the compounding pharmacy and to validate the performance of compounding processes that may cause variability in the completed drug preparation.

Stability, Expiration, and Beyond-Use Dating

USP 34/NF 29 defines *stability* as the “extent to which a dosage form retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its preparation.”⁷⁷ The compounding pharmacist must avoid formulation ingredients and conditions that could result in a subpotent preparation that leads to poor clinical results. Knowledge of the chemical reactions by which drugs degrade can enable the pharmacist to establish conditions that minimize the rate of degradation. At all steps in the compounding, dispensing, and storage processes, the pharmacist should observe the compounded drug preparation for signs of instability. A discard-after or beyond-use date is the date after which a compounded preparation should be discarded. This period should be based on available stability information and reasonable patient needs with respect to the intended drug therapy. When a commercial drug product is used as a source of active ingredients, its expiration date can often be used as a factor in determining a discard-after date, which cannot exceed the expiration date of any of its components.

In determining a discard-after date, the pharmacist may consider the following:

- The nature of the drug and its degradation kinetics,
- The container in which the drug is packaged,
- The storage conditions to which the preparation is expected to be exposed,
- The expected length of therapy,
- The expiration date of similar commercial products, if the active ingredient is a USP/NF substance,
- Published literature, and
- Information obtained from the manufacturer by telephone, if no printed information is supplied with the product.

The beyond-use date assigned to a specific preparation should be based on the following:

- Physical and chemical properties of the ingredients,
- Use of preservatives or stabilizers,
- Dosage form of the preparation,
- Storage conditions, and
- Scientific, laboratory, or reference data.

It is difficult to assign a beyond-use date. The pharmacist should consult all available stability information and then make a conservative estimate, keeping in mind several general guidelines. First, when a manufactured commercial product is used as the source of the active ingredient for a solid or nonaqueous nonsterile dosage form, the time until the beyond-use date should be no more than 25% of the time remaining until the manufacturer’s expiration date or 6 months, whichever is less. For example, if a product received on April 1, 2011, has an expiration date of December 31, 2011, 8 months remain until the expiration date. Therefore, the beyond-use date for the compounded preparation should be 2 months (25% of 8 months) from the date of its compounding. Second, when a USP or an NF pure chemical is used, the beyond-use date should be no more than 6 months for dry preparations. (See Chapter 5 for cases that do not fall within either of these guidelines.)

All compounded preparations should be observed periodically for signs of physical instability, including evidence of microbiological and fungal contamination of any preparations whose formulas lack preservatives. If large quantities of a preparation have been legitimately prepared, it may be advisable to conduct potency and stability assays to assure the compounding pharmacist of the preparation's potency up to the assigned beyond-use date. Chapter 5 provides additional information on beyond-use dates.

Records and Reports

Pharmacists should maintain at least four sets of records for compounding: (1) formulation records, (2) compounding records, (3) SOPs, including equipment maintenance records, and (4) ingredients records, including certificates of analysis and MSDSs. Records and reports should be retained for the period of time required by state laws and regulations for the retention of prescription files. All records and reports should be readily available in the pharmacy for authorized inspection during the retention period. The proper recording of information is so vital to ensuring consistent preparation of a formulation that an entire chapter (Chapter 4) is devoted to the subject, discussing each type of record in detail.

Patient Counseling

Compounded prescriptions offer an excellent opportunity for patient counseling. The pharmacist can explain that the particular prescription has been prepared especially for the patient and can describe steps that are required before its administration. This occasion can also be used to discuss other routine subjects with the patient.

Disposing of Expired Chemicals and Medications

Daily, weekly, and monthly, compounding pharmacists face the challenge of responsibly disposing of expired medications and chemicals. In years past, pharmacists avoided accumulating out-of-date drugs by incinerating them on the premises, washing them down the sink, flushing them down the toilet, or attempting to return them indirectly (via sales representatives) or directly to the manufacturer.

We now know that the on-site incineration of expired drugs pollutes the air and that discarding medications in the dumpster or trash bin can result in drug diversion or in accidental poisoning because many pharmaceutical agents are hydrophilic, biologically active, and persistent and often resist wastewater treatment. Drugs currently detected in environmental samples include lipid regulators, hormones, antidepressants, beta-blockers, antibiotics, oral contraceptives, antiepileptics, antineoplastics, tranquilizers, nonopioid analgesics, and anti-inflammatory agents. Medications can remain unused for many reasons, including noncompliance, death of the patient, expiration dates, low utilization, overstocking due to a one-time use for a patient, special needs, a change in prescribing practices, and withdrawal of the drug from the U.S. market. Regardless of the reason for disposal, compounding pharmacists, like their institutional and retail colleagues, are increasingly pressured to find environmentally friendly and affordable methods of disposing of expired products.

When disposing of pharmaceutical waste, pharmacists must comply with all pertinent state and federal regulations according to the U.S. Environmental Protection Agency (EPA). Specific chemicals are listed as hazardous waste in the Resource Conservation and Recovery Act (RCRA). RCRA has classified hazardous pharmaceutical waste into three categories: the

“P” list, the “U” list, and the “D” list. All RCRA hazardous waste must be managed and disposed of according to specific guidelines and cannot be discarded in sewers or landfills. Over the past decade, the disposal of hazardous pharmaceutical waste has become a science, and companies with expertise in that specialty are increasing in number.^{8,9}

Reference Library

Regarding nonsterile preparations, *USP* Chapter 795 states that “The pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and relevant scientific data and information.”¹

The compounding of quality preparations requires access to up-to-date, reliable drug information as well as pharmacy compounding information. Compounding pharmacists must have ready access to reference materials on all aspects of compounding, including reprints of journal articles. These materials may include on-site books, reprints, and journals, as well as telephone access to information from a compounding or drug information center. Computer access to such information is also important.

The contents of a reference library at a particular practice site will depend in part on the type of compounded formulations being prepared. For example, references on aseptic compounding practices are needed if the site compounds sterile preparations. The following references should be a part of every pharmacy reference library:

- Allen LV Jr. *Remington: The Science and Practice of Pharmacy*. 22nd ed. Chicago: Pharmaceutical Press; 2012.
- Allen LV, Popovich NG. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. 9th ed. Baltimore: Lippincott Williams & Wilkins; 2008.
- Ansel HC, Stokksa MJ. *Pharmaceutical Calculations*. 12th ed. Baltimore: Lippincott Williams & Wilkins; 2005.
- McEvoy GK, Snow EK, Miller J. *AHFS Drug Information 2011*. Bethesda, Md: American Society of Health-System Pharmacists; 2011.
- *The Merck Index*. 14th ed. Rahway, NJ: Merck & Co; 2006.
- Reynolds JEF. *Martindale: The Extra Pharmacopoeia*. 33rd ed. London: The Pharmaceutical Press; 2011.
- Rowe RC, Sheskey PJ, Owen SC. *Handbook of Pharmaceutical Excipients*. 6th ed. Washington, DC: American Pharmacists Association; 2009.
- *Secundum Artem*. Minneapolis, Minn: Paddock Laboratories [quarterly journal].
- Shrewsbury R. *Applied Pharmaceutics in Contemporary Compounding*. 2nd ed. Englewood, Colo: Morton; 2008.
- *United States Pharmacopoeia 34/National Formulary 29*. Rockville, Md: United States Pharmacopoeial Convention; 2011.

Some editions of these references should be retained in a “previous editions” section of the reference library because they contain valuable information that was not carried forward to new editions; examples include *Remington: The Science and Practice of Pharmacy* and *Martindale: The Extra Pharmacopoeia*. Older editions of some references should be discarded, however, if new research has shown that previously published information is incorrect; examples include the *United States Pharmacopoeia/National Formulary*, *Handbook on Injectable Drugs* (L. A. Trissel), and *King Guide to Parenteral Admixtures*.

Establishing a Reference Library

1. Determine the books required by the state board of pharmacy.
2. Determine the scope of practice, or “breadth,” required for the pharmacy.
3. Determine the “depth” of the scope of practice.
4. Select core books that will be required (both paper and electronic).
5. Select supplemental books that will be required (both paper and electronic).
6. Create a list of the core and supplemental books; mark with an asterisk those required by the board of pharmacy.

Maintaining a Reference Library

1. Annually (e.g., the first week in January), review the reference library and order updates (new book editions or supplements) and recently published references as required (see step 2).
2. As new editions of pharmacy references are announced, check the edition on hand to determine whether to order the latest edition.
3. Mark the books that should be retained in a “previous editions” section of the reference library.
4. Mark the books that should be discarded when replaced by a new edition.

References

1. Pharmaceutical Compounding Expert Committee. Pharmaceutical compounding. In: *United States Pharmacopeia 34/National Formulary 29*. Rockville, Md: United States Pharmacopeial Convention; 2011.
2. Good compounding practices applicable to state-licensed pharmacies. In: *Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy*. Park Ridge, Ill: National Association of Boards of Pharmacy; 1993:C.1–C.5.
3. Houck LK. Compounding: a well-established practice in 1938. *Int J Pharm Compound*. 2005; 9(5):364–7.
4. Cabaleiro J. Obtaining accreditation by the Pharmacy Compounding Accreditation Board, part 4: tips for “last minute” preparations. *Int J Pharm Compound*. 2008;12(5):432–3.
5. Murry T. Accreditation by the Pharmacy Compounding Accreditation Board: raising the bar for patient care. *Int J Pharm Compound*. 2008;12(2):174–5.
6. Cabaleiro J. Obtaining accreditation by the Pharmacy Compounding Accreditation Board, part 2: developing essential standard operating procedures. *Int J Pharm Compound*. 2007;11(5):397–9.
7. Stability considerations in dispensing practice. In: *United States Pharmacopeia 34/National Formulary 29*. Rockville, Md: United States Pharmacopeial Convention; 2011.
8. Vail J. Disposing of expired drugs and chemicals: new options for compounders. *Int J Pharm Compound*. 2008;12(1):38–47.
9. Vail J. Consumer options for the disposal of unused medications. *Int J Pharm Compound*. 2008; 12(1):87.