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# Chapter 1

# Laws, Regulations, Standards, and 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. Compounding is defined in the Introduction to this book according to Chapter <795> of the *United States Pharmacopeia (USP)*<sup>1</sup> and the definitions in the Drug Quality and Security Act (H.R. 3204, 113th Cong., 2013).

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 section, “Distinguishing Compounding from Manufacturing,” later in this chapter, more fully defines compounding and manufacturing and provides guidelines for differentiating the two activities.

A 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 that state that are enacted by the state lawmakers (legislature). Once a profession is established, the state legislatures enact 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. Although 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 *USP* Chapter <795>, Pharmaceutical Compounding—Nonsterile Preparations, and *USP* 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*. 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. The state boards of pharmacy can be responsible for enforcing these standards, because 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 U.S. 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.

*FDA* was established in part to monitor the relatively young pharmaceutical industry, which had no enforceable standards at the time. The Federal Food, Drug, and Cosmetic Act does not refer to pharmaceutical compounding. Court decisions have stated that *FDA* lacks authority over a pharmacy's compounding that is performed in compliance with the pharmacy practice laws of the state. However, some specific criteria of the Drug Quality and Security Act must be met as described later in this chapter; if not, then *FDA* may become involved.

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 also specifically included the term *compounding*. Before 1938, states considered every location where compounding occurred and where drugs, medications, or chemicals were sold or dispensed to be a pharmacy. In other words, wherever compounding took place, the facility was termed a pharmacy and thus was subject to that state's pharmacy practice act.<sup>2</sup>

Furthermore, before 1938, states and the District of Columbia restricted the compounding, dispensing, or selling of drugs, medications, or poisons and the compounding

of physicians' prescriptions to pharmacists or assistant pharmacists registered or licensed by the state board of pharmacy. However, 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 restricted persons who could engage in the activity to specific state-registered or state-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, medications, and poisons were compounded, dispensed, and retailed and medical practitioners' prescriptions were compounded. The jurisdictions 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 of drugs, medications, or poisons or for compounding of physicians' prescriptions. In addition, before 1938 the owner or manager of a pharmacy could not legally 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. In 1938, pharmacists 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. This began with the Durham-Reynolds Bill of 1943 (Public Law 130) establishing the Pharmacy Corps in the U.S. Army. Compounding was the norm at large military posts; a number of products, such as cough syrups, irrigating solutions, and ointments, were routinely compounded.

The intent of the Federal Food, Drug, and Cosmetic Act had nothing to do with compounding. At the time of the act's 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 of drugs, medications, and poisons, the other traditional pharmacy practices that were then, and are still, regulated by the states.

## Unapproved Drugs

FDA looks at all unapproved drug products that are being marketed in the United States. This is of interest to compounding pharmacists because FDA has determined that compounded preparations are now considered "unapproved new drugs." In fact, any modification to a drug outside the approved labeling of a drug can be considered to be compounding.

The Federal Food and Drugs Act of 1906 first brought drug regulation under federal law. That act prohibited the sale of adulterated or misbranded drugs. The Federal Food, Drug, and Cosmetic Act of 1938 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 before passage of the 1938 act and that contained in its labeling the same representations concerning the conditions of use as it did before passage of that act was not considered a *new drug*. Therefore, it was exempt from the requirement of having an approved new drug application.

FDA estimates that several thousand unapproved drug products are currently being commercially manufactured and marketed. It also considers all compounded preparations as unapproved drugs; these include 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 U.S. Department of Veterans Affairs, the Indian Health Service, all branches of the armed services, and the Federal Bureau of Prisons—are involved in compounding unapproved drugs. Many state agencies (e.g., hospitals, prisons, and welfare programs) also are involved in compounding unapproved drugs. In addition, most of the commercially manufactured veterinary drug products are not FDA approved; they are unapproved drugs. Nonprescription drug products are not FDA approved but follow the over-the-counter (OTC) monograph system that allows them to be manufactured if they comply with the OTC monographs.

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

## Distinguishing Compounding from Manufacturing

*Compounding* is defined in the Introduction of this book. *Manufacturing* is the production, preparation, propagation, conversion, and 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

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

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

of commercially available products from bulk compounds for resale by pharmacies, practitioners, or other persons.

Guidelines for distinguishing between compounding and manufacturing are as follows:

- Under certain situations (drug shortages, presence of excipients patients cannot tolerate, etc.), 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 before 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 if allowed by state law, 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.

## FDA Modernization Act of 1997

In 1997, the efforts of many organizations, including FDA, politicians, and pharmacists resulted in section 503A of the Food and Drug Administration Modernization Act of 1997 (FDAMA97) (Public Law 105-115, § 127), supporting pharmacists’ right to compound.

The purpose of section 127 of Public Law 105-115 was to ensure patient access to individualized drug therapy and prevent unnecessary FDA regulation of health professional practice. This legislation exempted pharmacy compounding from several regulatory requirements, but did not exempt drug manufacturing from the act’s requirements. The legislation also set forth conditions that must be met in order to qualify for exemption from the act’s requirements. Thus, compounding, according to FDAMA97, would exempt pharmacists from having to meet the *new drug* requirements for each preparation compounded.

In November 1998, the solicitation and advertising provisions of section 503A were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech. The U.S. District Court for the District of Nevada ruled in the plaintiffs’ favor. FDA appealed to the U.S. Court of Appeals for the Ninth Circuit. On February 6, 2001, the Court of Appeals declared section 503A invalid in its entirety (*Western States Medical Center v Shalala*, 238 F.3rd 1090 [9th Cir. 2001]). The U.S. Supreme Court affirmed the Court of Appeals decision that found section 503A of the act invalid in its entirety because it contained unconstitutional restrictions on commercial speech (i.e., prohibitions on soliciting of prescriptions for and advertising of specific compounded drugs). The Court did not rule on, and therefore left in place, the holding of the Court of Appeals that the unconstitutional restrictions on commercial speech could not be severed from the rest of section 503A. Thus, section 503A was removed from FDAMA97.

Generally, FDA continued to defer to state authorities regarding less significant violations of the act related to pharmacy compounding of human drugs. FDA anticipated that, in such cases, cooperative efforts between the states and the agency would result in coordinated investigations, referrals, and follow-up actions by the states.

However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the act, FDA determined that it should seriously consider enforcement action. In determining whether to initiate such an action, the agency considered whether the pharmacy was engaged in any of the following acts:

1. Compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.
2. Compounding drugs that have been withdrawn or removed from the market for safety reasons. Appendix I provides a list of such drugs that will be updated in the future, as appropriate.
3. Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA-sanctioned Investigational New Drug application in accordance with 21 U.S.C. § 355(i) and 21 C.F.R. 312.
4. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
5. Receiving, storing, or using drug components that are not guaranteed or otherwise determined to meet official compendial requirements.
6. Using commercial-scale manufacturing or testing equipment for compounding drug products.
7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state-licensed persons or commercial entities for resale.
8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. Certain circumstances may be appropriate for allowing a pharmacist to compound a small quantity of a drug that is only slightly different than a commercially available FDA-approved drug. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.
9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

The foregoing list of factors is not intended to be exhaustive. Other factors may be appropriate for consideration in a particular case.

## **Events Leading Up to the Drug Quality and Security Act**

The following example involves a pharmacy that was actually manufacturing under the guise of compounding. In 2012, an outbreak of fungal meningitis in the United States was traced to fungal contamination in three lots of compounded methylprednisolone suspension for epidural steroid injections. Doses from those three lots were administered to 14,000 patients. The New England Compounding Center (NECC) case was a tragedy for the 64 individuals who died, the hundreds who were sickened, and their families and loved

ones. The case is discussed in detail in Chapter 33, “Pharmaceutical Compounding Errors,” of this book.

The tragic events associated with NECC are a stark lesson in what can happen when quality assurance, quality control, and legal requirements are not followed. The quality assurance and quality control requirements of *USP* Chapter <797>, *USP* Chapter <71>, and other applicable *USP* chapters are designed to establish systems that ensure sterile medications are safe and that verify the medications’ quality through sterility testing and other tests. These standards establish a redundant system of processes to ensure the quality of compounded sterile preparation. However, when these processes are not performed properly or their results are ignored, as is alleged in the NECC case, serious injury or death to patients can occur.

For many years, pharmacists have been reminded that *USP* <797> requirements are legally enforceable in all states. The prosecution of NECC personnel based on noncompliance with *USP* standards may set a precedent for future civil and criminal cases alleging that patients were injured as a result of noncompliance with *USP* standards. The tragic case of NECC is a call for all sterile-compounding pharmacists to scrutinize their operations to ensure full compliance with regulatory, quality, and safety standards.

The new Drug Quality and Security Act (DQSA) (H.R. 3204, 113th Cong., 2013), a direct result of the NECC tragedy, specifically prohibits traditional compounding pharmacies from dispensing for non-patient-specific office use. However, FDA is afforded flexibility in enforcement discretion. Sterile compounding facilities that register as outsourcing facilities under H.R. 3204, section 503B, may dispense non-patient-specific medications provided they meet several requirements, including compliance with Current Good Manufacturing Practices.

## H.R. 3204: Drug Quality and Security Act

The new law—DQSA (H.R. 3204)—incorporates and brings up to date the court decisions regarding FDAMA97. A summary of the law is as follows:<sup>3</sup>

- “Drug Quality and Security Act - **Title I: Drug Compounding** - Compounding Quality Act - (Sec. 102) Amends the Federal Food, Drug, and Cosmetic Act (FFDCA) with respect to the regulation of compounding drugs. Exempts compounded drugs from new drug requirements, labeling requirements, and track and trace requirements if the drug is compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility and meets applicable requirements.”
- Establishes requirements for pharmacies under section 503A.
- Establishes requirements for outsourcing facilities under section 503B.
- “Requires the Secretary to: (1) publish a list of drugs presenting demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug, taking into account the risk and benefits to patients; and (2) convene an advisory committee on compounding before creating the list.”
- “(Sec. 103) Prohibits the resale of a compounded drug labeled ‘not for resale,’ or the intentional falsification of a prescription for a compounded drug. Deems a compounded drug to be misbranded if its advertising or promotion is false or misleading in any particular.”
- “(Sec. 105) Requires the Secretary to receive submissions from state boards of pharmacy: (1) describing any disciplinary actions taken against compounding pharmacies or any recall of a compounded drug, and (2) expressing concerns that a compounding pharmacy may be violating the FFDCA.”

- “(Sec. 106) Revises compounding pharmacy requirements to repeal prohibitions on advertising and promotion of compounded drugs by compounding pharmacies and repeal the requirement that prescriptions filled by a compounding pharmacy be unsolicited.”
- “(Sec. 107) Requires the Comptroller General ([Government Accountability Office]) to report on pharmacy compounding and the adequacy of state and federal efforts to assure the safety of compounded drugs.”

### **H.R. 3204, Section 503A: Pharmacies**

Section 503A of H.R. 3204 likely affects more than an estimated 98% to 99% of the pharmacies in the United States, most of which do some traditional compounding. The law is summarized as follows:<sup>4</sup>

- “FDA expects State boards of pharmacy to continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding.”
- “FDA also intends to continue to cooperate with State authorities to address pharmacy activities that may be violative of the [Federal Food, Drug, and Cosmetic] Act, including section 503A.”
- A drug must be “compounded for an identified individual patient based on the receipt of a valid prescription order, or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.”
- “The compounding of the drug product is performed:
  - “By a licensed pharmacist in a State licensed pharmacy or a Federal facility, or by a licensed physician on the prescription order for an individual patient . . . or
  - “By a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient when” there is documentation of need.”
- “The drug is compounded in compliance with the [USP] chapters on pharmacy compounding using bulk drug substances [active pharmaceutical ingredients (APIs)] that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists.”
  - “If such a monograph does not exist, the drug substance(s) must be a component of an FDA-approved human drug product.”
  - “If a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it must appear on a list of bulk drug substances for use in compounding developed by FDA through regulation.”
- The drug product is compounded using bulk drug substances that are
  - “manufactured by an establishment that is registered . . . (including a foreign establishment).”
  - “accompanied by valid certificates of analysis for each bulk drug substance.”
- “The drug product is compounded using [excipients] that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding.”
- “The drug product does not appear on the list [of] drug products that have been withdrawn or removed from the market because [they] have been found to be unsafe or not effective.”
- Drug products “that are essentially copies of commercially available drug products” are not compounded “regularly or in inordinate amounts.”

- Drug products listed by FDA that present “demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product” are not compounded.
- “The drug product is compounded in a State that has entered into a memorandum of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or in States that have not entered into such an MOU with FDA, the licensed pharmacist, licensed pharmacy, or licensed physician does not distribute, or cause to be distributed, compounded drug products out of the State in which they are compounded, more than 5% of the total prescription orders dispensed or distributed by such pharmacy or physician.”

### **H.R. 3204, Section 503B: Outsourcing Facilities**

Some highlights of section 503B of H.R. 3204 include the following.

Section 503B defines an outsourcing facility as follows:

a facility at one geographic location or address that—

- (i). is engaged in the compounding of sterile drugs;
- (ii). has elected to register as an outsourcing facility; and
- (iii). complies with all of the requirements of this section.

In addition, an outsourcing facility does not have to be a licensed pharmacy and may or may not acquire prescriptions for identified individual patients. A “sterile drug” is one that “is intended for parenteral administration, an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law.”

A facility that elects or chooses to register with FDA as an outsourcing pharmacy involved with sterile compounding is required to use bulk drug substances that

- appear on a list established by FDA.
- appear on the drug shortage list in effect at the time of compounding, distribution, and dispensing.
- comply with monographs in the *USP/NF* or other compendium or pharmacopeia recognized by FDA.
- are manufactured by an establishment registered with FDA.
- are accompanied by valid certificates of analysis.

The facility must comply with the following:

- Use other ingredients that comply with standards of the *USP/NF* if such monograph exists, or of another compendium or pharmacopeia recognized by FDA.
- Do not use drugs that have been withdrawn or removed by FDA because they have been found to be unsafe or ineffective.
- Do not prepare drugs that are essentially copies of one or more approved drugs (except in the case of an approved drug that appears on the drug shortage list).
- Do not prepare drugs that present demonstrable difficulties for compounding.
- Comply with FDA requirements if preparing any drugs that are the subject of a risk evaluation and mitigation strategy.

- Do not sell drugs for resale.
- Pay all applicable fees.
- Adhere to the requirements for the label, containers, and any other required information.
- Register with FDA between October 1 and December 31 of each year.
- Provide reports during June and December of each year to FDA of the drugs compounded during the previous six months.
- Comply with Good Manufacturing Practices.
- Be subject to FDA inspections.
- Submit adverse event reports.

At the time of the publication of this book, approximately 50 facilities were registered as human drug compounding outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

### **The Triad**

The DQSA states that a compounded product is exempt from meeting the *new drug* requirements if the drug product is compounded for an individual patient on the basis of the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order indicating that a compounded product is necessary for the specific patient—if the product meets certain requirements. A pharmacist may compound a drug when a prescription clearly requires compounding (because the drug is not commercially available in the form needed or a physician authorizes compounding). Also, a pharmacist may compound a drug if—with the physician’s approval—the pharmacist determines that a compounded drug is necessary and notes that information on the prescription. This method allows pharmacists to suggest therapeutic switches to a compounded drug, just as they do for other types of medications. The physician, the patient, and the pharmacist form the legal compounding “triad.”

### **Licensed Pharmacist or Physician**

The product must be compounded by a licensed pharmacist—in a state-licensed pharmacy or federal facility—or by a licensed physician or other licensed practitioner authorized by state law to prescribe drugs.

### **Anticipatory Compounding**

Limited quantities of products can be compounded in advance—if there is a history of receiving valid prescription orders for the product, generated by an established relationship between the licensed pharmacist and individual patients for whom the prescriptions are provided. An established relationship with the physician or other licensed professional who wrote the prescription must also exist.

### **Substances That May Be Used in Compounding**

Substances that may be used for compounding include the following:

- Bulk drug substances that have monographs in the *USP/NF*, and comply with *USP* Chapter <795>
- Drug substances that are components of FDA-approved drugs or drug products, including any ingredient that is contained in commercially available FDA-approved drug products

- Bulk drug substances that appear on a list of approved bulk-drug substances developed by FDA
- Substances that are manufactured by facilities registered with FDA—including foreign facilities—and comply with standards of any monograph in the *USP/NF* (if a monograph exists), as well as with the *USP* Chapter <795>. Table 1-2 describes the chemical grades of substances.

### Substances That May *Not* Be Used in Compounding

Compounding should not be performed using substances or involving products that are in the following categories:

- Products listed in Appendix I should not be used in compounding, because they are on the list of drug products withdrawn or removed from the market (because they have been found to be unsafe or ineffective).
- Inordinate amounts of commercially available drug products (not including drug products in which a change has been made for an individual patient, such as omitting a dye, flavor, sweetener, preservative, or the like) to which the patient may be sensitive should not be compounded. According to the DQSA, pharmacists are allowed to compound copies of commercially available drug products included in the FDA definition. In other words, the quantity described as “inordinate amounts” has yet to be defined. Much latitude is given to a prescribing practitioner in this area. One should note, however, that a small variation in strength, such as from 50 mg to 45 mg, would likely not be determined a significant difference.

### Memorandum of Understanding

Section 503A(b)(3)(B) of H.R. 3204 established that to qualify for the exemptions in section 503A, the drug product must be compounded in accordance with either of the following:

1. It was compounded in a state that had entered into an MOU with FDA that addressed the interstate distribution of inordinate amounts of compounded drug products and provided for investigation by a state agency of complaints related to compounded drug products distributed outside such state; or
2. It was compounded in a state that had not entered into such an MOU, but the licensed pharmacist, pharmacy, or physician distributes (or causes to be distributed) compounded drug products outside of the state in which they were compounded—in quantities not exceeding 5 percent of the total prescription orders dispensed or distributed by the pharmacy or physician.

**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> (USP/NF) for contaminants dangerous to health
ACS reagent	High purity; conforms to minimum specifications set by the Reagent Chemicals Committee of the American Chemical Society (ACS)
CP (chemically pure)	More refined than technical or commercial grade but still of unknown quality
Technical or commercial	Indeterminate quality

### Implementation of DQSA: Draft Guidances

FDA has issued five documents related to drug compounding and repackaging that will help entities comply with important public health provisions. The documents are applicable to pharmacies, federal facilities, outsourcing facilities, and physicians.

The documents are as follows:

- Guidance: For Entities Considering Whether to Register as Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act<sup>5</sup>
- Draft Guidance for Industry: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities<sup>6</sup>
- Draft Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application<sup>7</sup>
- Draft Guidance for Industry: Adverse Event Reporting for Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act<sup>8</sup>
- Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert STATE] and the U.S. Food and Drug Administration<sup>9</sup>

The above documents are the latest in a series of policy documents related to FDA oversight of drugs produced by state-licensed pharmacies, federal facilities, and outsourcing facilities.

### Implementation of DQSA: Organization and Lists

The provisions of section 503A require rulemaking or other action by FDA. Some of these actions require decisions regarding the following.

*Organization and Formation of the Pharmacy Compounding Advisory Committee*  
H.R. 3204, section 503B(c)(2) states the following: “Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.” FDA, in consultation with the Pharmacy Compounding Advisory Committee, will make decisions regarding the following lists to be developed.

*Lists to Develop: FDA, in Consultation with the Pharmacy Compounding Advisory Committee*

In consultation with the Pharmacy Compounding Advisory Committee, FDA will make decisions regarding the following.

#### The Negative List

The first committee developed and approved a negative list consisting of drugs that have been removed from the market for safety reasons. The DQSA Pharmacy Compounding Advisory Committee reviews and recommends modifications to this list of drug products that may not be compounded as a result of having been withdrawn or removed from the market because they have been found to be unsafe or not effective. See Appendix I. To obtain the current list, visit [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=216.24](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=216.24).

### The Positive List of APIs

The FDA Pharmacy Compounding Advisory Committee evaluates bulk drug substances that (1) do not contain a *USP* or *NF* monograph, (2) are not components of FDA-approved drug products, or (3) do not contain a monograph in another compendium or pharmacopeia recognized by FDA to determine their suitability for use in compounding.

### Demonstrable Difficulties in Compounding

The FDA Pharmacy Compounding Advisory Committee evaluates drug products that present demonstrable difficulties for compounding and that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product.

A major problem involving implementation of the law is FDA's actions in going well beyond what the law states and extending its reach into the authority of the individual state boards of pharmacy. Also, FDA is extending the law to include veterinary drug compounding and broadening the scope of section 503B compounding facilities to allow them to compound both nonsterile and sterile preparations.

## ***United States Pharmacopeia***

In 1990, the United States Pharmacopeial Convention approved the appointment of an Expert Advisory Panel on Pharmacy Compounding Practices. Initially, the panel's activities were (1) to prepare a chapter on compounding for the *USP/NF* and (2) to begin the process of preparing monographs of compounded products for inclusion in the *NF*.

The prepared chapter, <1161>, "Pharmacy Compounding Practices," was published and became official in 1996. With the mention of this chapter in FDAMA97, the chapter was renumbered as Chapter <795>; subsequently, its title was also changed to "Pharmaceutical Compounding—Nonsterile Preparations."<sup>1</sup> (One should note that *USP* chapters with numbers greater than <1000> are informational, whereas numbers less than <1000> are enforceable.)

The first of the compounding monographs became official in November 1998, and these monographs are published in the *USP* section of the *USP/NF*. Each published monograph involves a considerable amount of work, including a detailed, validated stability study. Some monographs that were previously published in the *USP/NF* are being reintroduced into the compendia. A second chapter related to compounding in the *USP/NF* was Chapter <1206>, "Sterile Drug Products for Home Use"; it was renumbered as <797> and was extensively revised and rewritten and then retitled as "Pharmaceutical Compounding—Sterile Preparations."<sup>1</sup>

Three additional *USP* chapters were written: <1075>, "Good Compounding Practices"; <1160>, "Pharmaceutical Calculations in Prescription Compounding"; and <1163>, "Quality Assurance in Pharmaceutical Compounding." Thereafter, Chapters <795>, "Pharmacy Compounding—Nonsterile Preparations," and <1075>, "Good Compounding Practices," were combined and expanded into a new General Chapter—<795>, Pharmacy Compounding—Nonsterile Preparations. In addition, Chapter <797>, Pharmacy Compounding—Sterile Preparations, has been updated.

## **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).<sup>10</sup> PCAB is now administered by the Accreditation Commission for Health Care (ACHC). ACHC also accredits (1) community retail pharmacies, (2) home infusion therapy pharmacies, (3) long-term care pharmacies, and (4) specialty pharmacies. In addition, it accredits (1) behavioral health organizations, (2) durable medical equipment providers, (3) home health agencies, (4) hospices, (5) private duty nursing services, and (6) sleep centers. PCAB-ACHC can now provide services whereby multiple-service pharmacies can obtain their accreditation from a single organization.

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. PCAB carries out its mission through two main tools: PCAB Principles of Compounding and PCAB Standards. A core concept of 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.<sup>11</sup>

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 the organization's actual activities, 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 purchase or download the prewritten SOPs available from various sources, whereas others develop their own SOPs. Either approach can be used, but both require extensive work.

PCAB places considerable emphasis on SOPs because testing every compounded preparation before dispensing is not possible. Compounders can rely on a set of consistent, uniform procedures that, if followed, ensure the preparation is made correctly each time and the appropriate documentation is generated. SOPs are designed to ensure that methods are standardized and documented to provide consistency and continuity.

A general approach to developing an SOP manual involves (1) reviewing the PCAB standards and creating a list of required SOPs, (2) assessing whether an organization has SOPs that address the PCAB requirements, and (3) conducting another review of the written SOPs to determine whether the SOP and the actual procedure match.<sup>12</sup>

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 rise to meet a certain standard. Certification likely 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 preparing for such requirements now. Currently, accreditation is required for some types of insurance reimbursement for third-party companies.

An important difference exists between *certification* (and *certified practitioners*) and 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 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 competent medical personnel determine the condition does 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 condition that may adversely affect drug preparations.

### Duties

A pharmacist has (1) the responsibility and authority to inspect and approve or reject all components, drug preparation containers, closures, in-process materials, and labeling and (2) the authority to prepare and review all compounding records to ensure that no errors have occurred in the compounding process. In addition to compounding, a pharmacist provides other services, such as the following:

- Publicizes the availability of both prescription and nonprescription compounding services, which may involve chemicals, devices, and alternative dosage forms
- Provides drug searches on specific chemicals in different dosage forms, strengths, bases, and the like to accommodate specific needs of physicians and patients
- Provides follow-up information in response to a practitioner’s request for information regarding a compounded medication
- 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 state-of-the-art 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
- Current 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) (also called safety data sheets [SDSs]) in the facility (see Chapter 5 of this book for a discussion of MSDSs and SDSs)
- Use and interpretation of chemical and pharmaceutical symbols and abbreviations in medication orders and in formulation directions
- 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 nonsterile 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, and showers and eyewash stations should be provided. Clean room apparel is required for the compounding of sterile preparations in a controlled environment (clean room).

### Compounding Process

Before the first step in the compounding process is taken, the following questions should 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: preparation, compounding, final check, sign-off, and cleanup steps. These are summarized here.

### General Steps in the Compounding Process

#### *Preparation*

1. Judge the suitability of the prescription in terms of its safety and intended use and the dose for the patient.
2. Perform the calculations to determine the quantities of the ingredients needed.
3. Select the proper equipment, and ensure it is clean.
4. Don the proper attire, and wash hands.

5. Clean the compounding area and the equipment, if necessary.
6. Assemble all the necessary materials and ingredients to compound, and package the prescription.

### *Compounding*

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

### *Final Check*

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

### *Sign-Off*

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

### *Cleanup*

12. Clean and store all equipment.
13. Clean the compounding area.

## **Packaging, Storage, and Labeling**

A 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 the current *USP/NF*. The selection of a container depends on the physical and chemical properties of the compounded preparation and the intended use of the preparation.

To 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 current *USP/NF* standards should be used.

### **Storage**

Chemicals should be stored according to either the manufacturers' directions or the appropriate current *USP/NF* 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 current *USP/NF* 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 a 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 as required. 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 following any requirement of the individual state board of pharmacy). 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 care 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, a pharmacist should have written procedures for the proper labeling of the excess preparation. Labeling should include (1) a complete list of ingredients, (2) a preparation date, (3) an assigned beyond-use date, (4) an appropriate testing and published data, and (5) control numbers. The preparation should then be entered into the inventory record 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.

## Office-Use Compounding

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 a physician to use in emergencies.

For these medications, the International Academy of Compounding Pharmacists (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.”

IACP encourages pharmacists to consider the following when dispensing a compounded preparation to an authorized prescriber for office use:

1. In the judgment of the dispensing pharmacist, the quantity being compounded and dispensed for office use is consistent with accepted practice.
2. All compounds dispensed on an office-use prescription or medication order should be labeled “For Institutional or Office Use Only—Not for Resale” or as otherwise required by state pharmacy practice acts.
3. For each dispensing of an office-use compounded preparation, a pharmacist should provide to the authorized prescriber the name and strength of the preparation or a list of active ingredients and strengths, the pharmacy’s lot number, a beyond-use expiration date as determined by the pharmacist using appropriate documented criteria, and any necessary and appropriate ancillary instructions or cautionary statements.
4. A pharmacy should have written procedures for notifying each authorized prescriber or facility to which the office-use compounded preparation was dispensed in the event of a recall.

IACP encourages pharmacists to advise prescribers that the resale or redispensing of any office-use compounded product may lead to violations of practice acts or other state regulations involving labeling and record keeping.

In addition, IACP supports state regulations that require the following information be placed on the labels of office-use compounds: (1) name, address, and telephone number of the pharmacy preparing the medication; (2) lot number; (3) established or distinct common name of the medication; (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.

## Reference Library

Regarding nonsterile preparations, *USP* Chapter <795> states: “The compounding is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good compounding practices, official standards, and relevant scientific data and information.”<sup>21</sup>

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. These materials may include on-site books, reprints, and journals; access to information from a compounding or drug information center; and Internet access to compounding databases.

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 and consist of the most current editions:

- Allen LV Jr. *Remington: The Science and Practice of Pharmacy*. London: Pharmaceutical Press.
- Allen LV Jr., Popovich NG. *Ansel’s Pharmaceutical Dosage Forms and Drug Delivery Systems*. Baltimore: Lippincott Williams & Wilkins.

- Ansel HC, Stockton SJ. *Pharmaceutical Calculations*. Baltimore: Lippincott Williams & Wilkins.
- *AHFS Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists.
- *The Merck Index*. Rahway, NJ: Merck and Co.
- *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press.
- Rowe RC, Sheskey PJ, Cook WG, Fenton ME. *Handbook of Pharmaceutical Excipients*. Washington, DC: American Pharmacists Association.
- *Secundum Artem*. Minneapolis, MN: Paddock Laboratories [quarterly journal].
- Shrewsbury R. *Applied Pharmaceutics in Contemporary Compounding*. Englewood, CO: Morton Publishing Co.
- *United States Pharmacopeia–National Formulary*. Rockville, MD: United States Pharmacopeial Convention.

Some editions of these references should also 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 Complete Drug Reference*. 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 Pharmacopeia/National Formulary*, *Handbook on Injectable Drugs* (L. A. Trissel; American Society of Health-System Pharmacists, Bethesda, MD), and *King Guide to Parenteral Admixtures* (King Guide Publications, Napa, CA).

### 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.

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5. U.S. Food and Drug Administration. Guidance: for entities considering whether to register as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. Available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434171.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434171.pdf).
6. U.S. Food and Drug Administration. Draft guidance for industry: repackaging of certain human drug products by pharmacies and outsourcing facilities. Available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434174.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434174.pdf).
7. U.S. Food and Drug Administration. Draft guidance for industry: mixing, diluting, or repackaging biological products outside the scope of an approved biologics license application. Available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434176.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM434176.pdf).
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9. U.S. Food and Drug Administration. Draft memorandum of understanding addressing certain distributions of compounded human drug products between the state of [insert STATE] and the U.S. Food and Drug Administration. Available at: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM434233.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM434233.pdf).
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## Chapter 2

# Compounding Ingredient Considerations

### CHAPTER AT A GLANCE

Compounding with Hydrates and Solvates  
Compounding with Organic Salts  
Compounding with Esters  
Compounding with Inorganic Salts  
Compounding with Potency-Designated Ingredients  
Compounding with Complex Organic Molecules  
Compounding with Aliquots, Dilutions, and Concentrates  
Compounding with Commercial Products  
Disposing of Expired Ingredients and Medications

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Throughout history, pharmacists have used natural products, 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.

Chapter <795>, Pharmaceutical Compounding—Nonsterile Preparations, of the *United States Pharmacopeia (USP)* states: “The compounder is responsible for compounding preparations of acceptable strength, quality, and purity and in accordance with the prescription or medication order. The compounder is also responsible for dispensing the finished preparation, with appropriate packaging and labeling, and in compliance with the requirements established by the applicable state agencies, state boards of pharmacy, federal law, and other regulatory agencies where appropriate.”<sup>1</sup> The compounding of quality preparations must involve the use of high-quality chemicals. If *USP* and *National Formulary (NF)* grade ingredients are used to prepare compounded formulations, the ingredients must meet the requirements of compendial monographs.

*USP* Chapter <795> also states the following:<sup>1</sup>

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 compounder should establish purity and

safety by reasonable means, which may include lot analysis, manufacturer reputation, or reliability of source.

In addition to the USP, NF, AR, ACS, and FCC grades mentioned above, other high-purity chemical grades include 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, consideration of all the ingredients in the drug product relative to the intended use and the potential effect on the overall efficacy (strength, quality, purity, stability, compatibility) of the compounded preparation is important.

Some drug substances and products have been withdrawn or removed from the market because of safety or efficacy concerns. According to the U.S. Food and Drug Administration (FDA), preparing compounded formulations of any of these products will be subject to enforcement action.

For consistent quality in compounded preparations, use of high-quality suppliers of chemicals for compounding is important. 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. Having a secondary supplier available in the event of unexpected shortfalls in supply is wise.

Knowing the purity and form of all ingredients used in compounding, especially active pharmaceutical ingredients, is important. A number of factors must be considered to ensure that the final compounded preparation falls within the strength requirements (e.g., 90%–110%) for compounded preparations or within the requirements of the *USP* monograph.

The form of the drug (base, salt, or ester) can be determined from the *USP* monograph or from the manufacturer's package insert in the case of a commercially manufactured product. Another source of information is the *United States Pharmacopeia/National Formulary (USP/NF)* monographs for bulk products.

For example, albuterol sulfate tablets USP are based on the albuterol content (present as the sulfate form). The *USP* monograph for albuterol sulfate tablets states, "Albuterol Tablets USP contain an amount of albuterol sulfate equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of albuterol ( $C_{13}H_{21}NO_3$ )." In contrast, diphenhydramine hydrochloride capsules USP are based on the total molecule (i.e., diphenhydramine hydrochloride). The *USP* monograph states, "Diphenhydramine Hydrochloride Capsules USP contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diphenhydramine hydrochloride ( $C_{17}H_{21}NO \cdot HCl$ )." Examples of drugs in the ester form are discussed later in this chapter.

Also, some drugs are either obtained as an aliquot or dilution or prepared as aliquots or dilutions to be weighed or measured later for compounding purposes. Finally, a number of drugs are available with labeled potency designations; for example, the *USP* monograph states that gentamicin sulfate USP "has a potency equivalent to not less than 590  $\mu$ g of gentamicin per mg, calculated on the dried basis."

So, where do practitioners turn to obtain information on whether a drug is a salt, base, acid, ester, hydrate, solvate, or other type of substance? Most commonly, they look at the *USP/NF*, certificates of analysis (COAs), and the chemical structure or the empirical formula of the drug (for solvates and hydrates). COAs are discussed in Chapter 5 of this book; Figure 2-1 shows an example of a COA.

CERTIFICATE OF ANALYSIS		
Morphine Sulfate, USP	CAS 62111-15-0	
$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$	Lot No. ___XYZ___	
MW 758.83		
TEST	LIMIT	RESULTS
	<u>Min.</u> <u>Max.</u>	
Assay	98.0% 102.0% (anhydrous basis)	100.5%
Identification	To pass test	Passes test
Specific rotation	-107 °   -109.5°	-108.1°
Acidity	To pass test	Passes test
Water	10.4% 13.4%	12.5%
Residue on ignition	nmt 0.1%	0.06%
Chloride	To pass test	Passes test
Ammonium salts	To pass test	Passes test
Limit of foreign alkaloids	To pass test	Passes test
Physical appearance: White, feathery, silky crystals, cubical masses of crystals, or white, crystalline powder.	To pass test	Passes test
Manufacturer name Manufacturer address Manufacturer telephone		
Signature of Certificate of Analysis Coordinator	_____	

**FIGURE 2-1** Example of a certificate of analysis.

## Compounding with Hydrates and Solvates

Figure 2-2 shows a portion of a *USP/NF* monograph. A hydrate is apparent because the chemical structure contains water. The more molecules of water that are present in a molecule of the substance, the greater is the amount of chemical that must be weighed to obtain the actual active drug. Table 2-1 lists drugs commonly used in compounding and their allowable water content as specified in the *USP/NF*.

Let's look at different forms of dexamethasone as an example of a drug that is available with different amounts of water. Dexamethasone contains less than 0.5% of its weight in water. Dexamethasone acetate has one molecule of water of hydration and contains between 3.5% and 4.5% water; the anhydrous form contains less than 0.4% water. Dexamethasone sodium phosphate contains a sum of water and alcohol that may be up to 16.0%.

Another example is lidocaine hydrochloride. Lidocaine hydrochloride occurs as a monohydrate and as the anhydrous form. The water content may be between 5% and 7%.

### Calculations

How much adjustment should be made if using lidocaine hydrochloride monohydrate in place of lidocaine hydrochloride anhydrous for a compounded prescription?

Lidocaine HCl monohydrate	$C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$	MW 288.81
Lidocaine HCl anhydrous	$C_{14}H_{22}N_2O \cdot HCl$	MW 270.80

A comparison of the molecular weights reveals that a factor of 1.066 can be used for the adjustment because  $288.81/270.80 = 1.066$ .

*Example: If a prescription for lidocaine hydrochloride 2% gel (100 g) is to be made, then 2 g of anhydrous lidocaine HCl could be used:*

$$2 \text{ g} \times 1.066 = 2.132 \text{ g of lidocaine HCl monohydrate}$$

Also, a direct comparison of the molecular weights and the physical quantity required can be used, as follows:

$$\frac{\text{MW hydrate}}{\text{MW anhydrous}} = \frac{\text{Weight of hydrated form}}{\text{Weight of anhydrous form}}$$

$$\frac{288.81}{270.80} = \frac{x}{2 \text{ g}}$$

$$x = 2.133 \text{ g}$$

Further, the *USP* monograph for lidocaine hydrochloride jelly *USP* states, "It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of lidocaine hydrochloride ( $C_{14}H_{22}N_2O \cdot HCl$ )." Note that this is the anhydrous form.

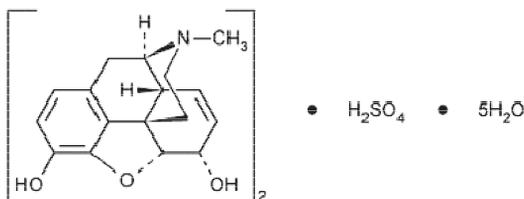
Checking the COA for the lidocaine hydrochloride being used to determine the water content is also important. Fortunately, most pure powders (anhydrous) contain only 0.2%–0.5% moisture, which can be insignificant; nevertheless, it needs to be checked.

### Packaging, Storage, and Weighing

Solvates and hydrates must be packaged in tight containers to prevent the loss or gain of moisture. In fact, all chemicals used in compounding are best stored in tight containers

## Morphine Sulfate

(mor' feen sul' fate)



(C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>·5H<sub>2</sub>O 758.83  
 Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, (5 $\alpha$ ,6 $\alpha$ )-, sulfate (2:1) (salt), pentahydrate.  
 7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate (2:1) (salt) pentahydrate [6211-15-0].

Anhydrous 668.77 [64-31-3].

» Morphine Sulfate contains not less than 98.0 percent and not more than 102.0 percent of (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>, calculated on the anhydrous basis.

**Packaging and storage**—Preserve in tight, light-resistant containers. Store up to 40° as permitted by the manufacturer.

USP REFERENCE STANDARDS (11)—  
 USP Morphine Sulfate RS

### Identification—

**A:** *Infrared Absorption* (197K): dried at 145° for 1 hour.

**B:** To 1 mg in a porcelain crucible or small dish add 0.5 mL of sulfuric acid containing, in each mL, 1 drop of formaldehyde TS: an intense purple color is produced at once, and quickly changes to deep blue-violet (*distinction from codeine, which gives at once an intense violet-blue color, and from hydromorphone, which gives at first a yellow to brown color, changing to pink and then to purplish red*).

**C:** To a solution of 5 mg in 5 mL of sulfuric acid in a test tube add 1 drop of ferric chloride TS, mix, and heat in boiling water for 2 minutes: a blue color is produced, and when 1 drop of nitric acid is added, it changes to dark red-brown (*codeine and ethylmorphine give the same color reactions, but hydromorphone and papaverine do not produce this color change*).

**D:** A solution (1 in 50) responds to the tests for *Sulfate* (191)

**SPECIFIC ROTATION** (781S): between -107° and -109.5°.

*Test solution:* the equivalent of 20 mg per mL, in water.

**Acidity**—Dissolve 500 mg in 15 mL of water, add 1 drop of methyl red TS, and titrate with 0.020 N sodium hydroxide: not more than 0.50 mL is required to produce a yellow color.

**WATER, Method I** (921): between 10.4% and 13.4% is found.

**RESIDUE ON IGNITION** (281): not more than 0.1%, from 500 mg.

**Chloride**—To 10 mL of a solution (1 in 100) add 1 mL of 2 N nitric acid and 1 mL of silver nitrate TS: no precipitate or turbidity is produced immediately.

**Ammonium salts**—Heat 200 mg with 5 mL of 1 N sodium hydroxide on a steam bath for 1 minute: no odor of ammonia is perceptible.

**Limit of foreign alkaloids**—Dissolve 1.00 g in 10 mL of 1 N sodium hydroxide in a separator, and shake the solution with three successive portions of 15, 10, and 10 mL of chloroform, passing the chloroform solutions through a small filter previously moistened with chloroform. Shake the combined chloroform solutions with 5 mL of water, separate the chloroform layer, and carefully evaporate on a steam bath to dryness. To the residue add 10.0 mL of 0.020 N sulfuric acid, and heat gently until dissolved. Cool, add 2 drops of methyl red TS, and titrate the excess acid with 0.020 N sodium hydroxide: not less than 7.5 mL is required (1.5%).

### Assay—

**Mobile phase**—Dissolve 0.73 g of sodium 1-heptanesulfonate in 720 mL of water, add 280 mL of methanol and 10 mL of glacial acetic acid, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

**Standard preparation**—Dissolve an accurately weighed quantity of USP Morphine Sulfate RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.24 mg per mL. Prepare a fresh solution daily.

**System suitability preparation**—Dissolve suitable quantities of USP Morphine Sulfate RS and phenol in *Mobile phase* to obtain a solution containing about 0.24 and 0.15 mg per mL, respectively.

**Assay preparation**—Transfer about 24 mg of Morphine Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

**Chromatographic system** (see *CHROMATOGRAPHY* (621))—The liquid chromatograph is equipped with a 284-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation* and the *System suitability preparation*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.7 for phenol and 1.0 for morphine sulfate; the resolution, *R*, between phenol and morphine sulfate is not less than 2.0; the tailing factor for the morphine sulfate peak is not more than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

**Procedure**—Separately inject equal volumes (about 25  $\mu$ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub> in the portion of Morphine Sulfate taken by the formula:

$$100C(r_u/r_s)$$

in which *C* is the concentration, in mg per mL, of anhydrous morphine sulfate in the *Standard preparation*, as determined from the concentration of USP Morphine Sulfate RS corrected for moisture content by a titrimetric water determination; and *r<sub>u</sub>* and *r<sub>s</sub>* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

**FIGURE 2-2** Portion of a USP/NF monograph.

**TABLE 2-1** Maximum Allowable Water Content for Selected Substances

<b>Drug</b>	<b>Maximum Water Content (%)</b>	<b>Drug</b>	<b>Maximum Water Content (%)</b>
Acetylcysteine	1.0	Estriol	0.5
Acyclovir	6.0	Estrone	0.5
Albuterol	0.5	Fluconazole	0.5
Albuterol sulfate	0.5	Gentamicin sulfate	18.0
Ammonium alum	48.0	Glycopyrrolate	0.5
Potassium alum	46.0	Heparin sodium	5.0
Amikacin	8.5	Homatropine hydrobromide	1.5
Aminophylline	7.9	Hydrocodone bitartrate	12.0
Amitriptyline hydrochloride	0.5	Hydrocortisone	1.0
Amoxapine	0.5	Hydrocortisone sodium phosphate	5.0
Amoxicillin	14.5	Hydromorphone hydrochloride	1.5
Aspartic acid	0.5	Hydroxyzine hydrochloride	5.0
Aspirin	0.5	Ibuprofen	1.0
Atenolol	0.5	Ipratropium bromide	4.4
Atropine sulfate	4.0	Ketorolac tromethamine	0.5
Azathioprine	1.0	Labetalol hydrochloride	1.0
Azithromycin	6.5	Levothyroxine sodium	11.0
Beclomethasone dipropionate	3.8	Lidocaine hydrochloride	7.0
Hydrous benzoyl peroxide	26.0	Lincomycin hydrochloride	6.0
Benztrapine mesylate	5.0	Liothyronine sodium	4.0
Betamethasone acetate	4.0	Lithium carbonate	1.0
Betamethasone sodium phosphate	10.0	Lithium citrate	28.0
Bupivacaine hydrochloride	6.0	Morphine sulfate	13.4
Buprenorphine hydrochloride	1.0	Nalorphine hydrochloride	0.5
Calcium carbonate	2.0	Nifedipine	0.5
Capsaicin	1.0	Nystatin	5.0
Captopril	1.0	Ondansetron hydrochloride	10.5
Cephalothin sodium	1.5	Papaverine hydrochloride	0.5
Chloramphenicol sodium succinate	5.0	Phentolamine mesylate	0.5
Citric acid, anhydrous	1.0	Prednisolone	7.0
Citric acid, monohydrate	9.0	Progesterone	0.5
Cocaine hydrochloride	1.0	Saccharin sodium	15.0
Codeine phosphate	3.0	Scopolamine hydrobromide	13.0
Codeine sulfate	7.5	Sodium chloride	0.5
Colchicine	2.0	Dibasic sodium phosphate	64.0
Cyanocobalamin	12.0	Monobasic sodium phosphate	26.5
Desmopressin acetate	6.0	Testosterone	1.0
Dexamethasone sodium phosphate	16.0	Tetracycline	13.0
Dextroamphetamine sulfate	1.0	Tetracycline hydrochloride	2.0
Dextromethorphan	0.5	Thyroid	6.0
Dextromethorphan hydrobromide	5.5	Tobramycin	8.0
Dextrose	9.5	Tobramycin sulfate	2.0
Edetate disodium	11.4	Vancomycin hydrochloride	5.0
Estradiol	3.5	Zinc gluconate	11.6

that are kept thoroughly closed at all times except for the short time during a weighing step. Storing chemicals at the indicated temperatures and minimizing exposure to very high humidity are also important.

### Hygroscopic, Deliquescent, and Efflorescent Powders

Hygroscopic powders are those that will tend to absorb moisture from the air. Deliquescent powders are those that will absorb moisture from the air and even liquefy. Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty. Extra care must be taken in working with these powders; storage in tight containers will generally prevent difficulties. The *USP* description of a powder usually states whether it has hygroscopic, deliquescent, or efflorescent properties.

If a hygroscopic or deliquescent powder is being weighed on a balance and the compounder leaves for a short time and then returns, the powder may have absorbed moisture from the air and may therefore weigh heavier than it should. Weighing should be done quickly after opening the bulk chemical containers, and the containers should then be resealed.

### Water and Solvent Content of Powders

If the chemical structure or the empirical formula does not show water in the molecule, checking the *USP* monograph for tests that may be related to water content of powders, such as “Loss on Drying” and “Residual Solvents,” is important.

*USP* Chapter <731>, Loss on Drying, concerns the amount of volatile matter, including water, of any kind that is driven off under the conditions specified in the monograph. For substances appearing to contain water as the only volatile constituent, the test procedure is given in *USP* Chapter <921>, Water Determination, and the allowable range is specified in the individual monograph. The loss on drying may be significant; it should be detailed on the COA, and necessary calculations should be undertaken for adjustments.

Whereas loss on drying involves any volatile matter, many substances in the *USP/NF* are hydrates or contain water in adsorbed form. Consequently, water content is important in demonstrating compliance with the *USP/NF* standards. As detailed in *USP* Chapter <921>, water content is generally determined by titrimetric, azeotropic, or gravimetric methods.

All substances used in drug products or preparations are subject to standards related to the amount of residual solvents that are likely to be present. These standards are designed to ensure that the amounts of residual solvents in pharmaceuticals are acceptable for the safety of the patient. For our purposes, residual solvents are organic volatiles (including alcohol) that are used in the preparation of drug substances, products, or preparations. Residual solvents generally are not completely removed by practical and ordinary techniques. However, residual solvent content should be evaluated and justified, as described in *USP* Chapter <467>, Residual Solvents.

### Compounding with Organic Salts

Knowing the form of a drug being used in determining the dose for administration is important. Many drugs are salts, and the dose may be based on the total salt form or just the base form of the drug. In the albuterol example given earlier in this chapter, *USP* states, “Albuterol Tablets *USP* contain an amount of albuterol sulfate equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of albuterol ( $C_{13}H_{21}NO_3$ ).” In other words, sufficient albuterol sulfate is present to provide the labeled amount of the albuterol base.

*Example: A prescription calls for 10 mL of fentanyl 50 µg/0.1 mL (as the citrate) topical gel. How much fentanyl citrate will be required?*

1.  $50\ \mu\text{g}/0.1\ \text{mL} = x/10\ \text{mL}$                        $x = 5\ \text{mg}$
2. Fentanyl MW = 336.47  
Fentanyl citrate MW = 528.59
3.  $336.47/5\ \text{mg} = 528.59/x$                        $x = 7.85\ \text{mg}$
4. Each milligram of fentanyl equals  $528.59/336.47 = 1.57\ \text{mg}$  fentanyl citrate

In the diphenhydramine example earlier in this chapter, diphenhydramine hydrochloride capsules USP are based on the total molecule—diphenhydramine hydrochloride. The weight of the hydrochloride is considered in the dose of the drug.

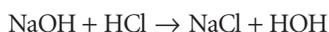
*Example: A prescription calls for 30 capsules of diphenhydramine hydrochloride 35 mg each. How much diphenhydramine hydrochloride will be required?*

Because the total salt molecule is part of the dose:

$$30 \times 35\ \text{mg} = 1.05\ \text{g of diphenhydramine hydrochloride}$$

### Advantage of the Salt Form

Most people are familiar with the following reaction, in which an acid reacts with a base by double decomposition to produce a salt and water:



This reaction is also called a neutralization reaction. However, most drugs are weak acids or weak bases, not strong acids and strong bases.

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used in their salt forms to increase their aqueous solubility. For example, sodium salts are often made from weak acids; sodium salicylate is the salt of the weak acid salicylic acid and the strong base sodium hydroxide. A salt can also be made from a weak base and a strong acid; ephedrine hydrochloride can be prepared from the weak base ephedrine and the strong acid hydrochloric acid. The combination of a weak base and a weak acid can also be used; an example is codeine phosphate made from the weak base codeine and the weak acid phosphoric acid.

When salts are placed in an aqueous environment, they will dissolve to some extent, depending on their solubility in the aqueous medium and the pH of the medium. A portion of the drug will be dissolved, and some may remain undissolved. Of the dissolved portion, a part will be ionized and the remainder will be unionized, depending on the pH of the medium. Usually, the unionized portion of the drug in solution will be absorbed for systemic effect. The portion that is either ionized or unionized is described by the dissociation constant, or  $\text{pK}_a$  of the drug, and the pH of the medium.

Thus, the purpose of the salt form is usually to enhance the solubility of the drug. Use of the salt form may also enhance the drug's stability and change other attributes to make the drug easier to manipulate for producing dosage forms.

Only the unionized portion of the drug will ultimately exert its effect in the body. Some of the remainder of the salt molecule may no longer follow the base, or unionized, form of the drug to its site of action in the body.

## Determining Which Form to Use

Why are some drugs dosed according to their base form (whether they be weak acids or weak bases) and some according to the total weight of their salt form? A review of revisions to the *USP* over many years reveals no apparent basis for determining which way the salts are dosed. Both the official monographs and the package insert information on FDA-approved drugs appear to be inconsistent in how they determine which way a drug is dosed. Pharmacists involved in compounding must be aware of the correct use of the terminology.

*USP XII* (1942) listed about 20 tablet monographs, all based on the salt form of the drug; for example, “Morphine Sulfate Tablets USP contain not less than 93 per cent and not more than 107 per cent of the labeled amount of morphine sulfate  $[(C_{17}H_{19}O_3N)_2 \cdot H_2SO_4 \cdot 5H_2O]$ .” In that time period, monograph names were quite clear; if the salt was to be used, the salt name was part of the official name. For example, “Barbital Tablets USP” was based on the labeled amount of barbital ( $C_8H_{12}N_2O_3$ ), but “Barbital Sodium Tablets” was based on the labeled amount of barbital sodium ( $C_8H_{11}N_2O_3Na$ ).

The *USP XVI* (1960) monograph for amodiaquine hydrochloride tablets USP stated, “Amodiaquine Hydrochloride Tablets contain an amount of amodiaquine hydrochloride ( $C_{20}H_{22}ClN_3O \cdot 2HCl \cdot 2H_2O$ ) equivalent to not less than 93% and not more than 107% of the labeled amount of amodiaquine base ( $C_{20}H_{22}ClN_3O$ ).” This monograph shows that the dose is calculated on the base form of the drug.

The formulator (the compounding pharmacist) is responsible for determining whether the base/acid or salt form of the drug is to be used in calculating the amount of the active pharmaceutical ingredient. When receiving a prescription, a compounder should follow a routine procedure to correctly determine whether the salt or the base/acid form of the drug is to be used as the basis for the dose. Information can be obtained from the *USP* monograph, the product package insert, or a call to the manufacturer or the physician as necessary. Table 2-2 shows the forms (salts and bases/acids) to be used for various dosage forms of drugs from *USP/NF*. Note that whereas the drugs listed in Table 2-2 are those with official *USP* monographs, many drug products on the market do not have *USP* monographs.

**TABLE 2-2** Form (Salt or Base/Acid) Used as Basis of Label Content

Substance	Capsules	Liquids <sup>a</sup>	Injections	Suppositories
Amikacin sulfate			B/A	
Amitriptyline hydrochloride			S	
Doxycycline		B/A		
Doxycycline calcium		B/A		
Doxycycline hyclate	B/A			
Erythromycin estolate	B/A	B/A		
Erythromycin ethylsuccinate		B/A	B/A	
Erythromycin lactobionate			B/A	
Morphine sulfate	S		S	S
Oxycodone hydrochloride		S		
Scopolamine hydrobromide		S	S	
Tetracycline hydrochloride	S	S	S	
Thiamine hydrochloride		S	S	

B/A = base or acid; S = salt.

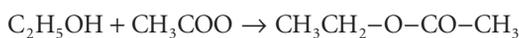
<sup>a</sup>Liquids include oral solutions, suspensions, emulsions, elixirs, syrups, ophthalmics, nasal solutions, and otic solutions.

## Compounding with Esters

Some drugs (e.g., atropine, cocaine, many local anesthetics) are esters by virtue of their internal chemical structure. Others are esters because a moiety has been added to form an ester for certain purposes. Only the latter are discussed here; those that are esters because of their basic molecular structure are not included.

An ester is a compound of the general formula  $R-C-O-R_1$ , where R and  $R_1$  may be the same or different and may be either aliphatic or aromatic. The term *aliphatic* refers to an acyclic or cyclic, saturated or unsaturated carbon compound, excluding aromatic compounds. The term *aromatic* was originally used to describe compounds that smelled; these were later found to contain either benzene or a fused benzene ring in the structure. The term *aromatic* has been generalized to include aromatic heterocyclic structures.

An ester can be formed through the dehydration of a molecule of an alcohol and a molecule of an organic acid. For example, ethanol reacts with acetic acid to form ethyl acetate, an ester:



### Advantages of the Ester Form

After salts, esters are the most important acid derivatives used in pharmacy. Esters may be prepared for a number of reasons, including solubility, stability, resistance to degradation after administration, and use as prodrugs.

Some drugs are very soluble but tend to degrade rapidly when in solution. One approach to increasing their stability and shelf life is to prepare esters that are poorly soluble. This results in a suspension dosage form instead of a solution dosage form. A drug in suspension degrades much more slowly than a drug in solution. After oral administration, the ester is cleaved and the active drug moiety is released for absorption.

Some drugs may cause pain at the site of injection, especially if they precipitate and damage the surrounding tissue. This can be overcome by preparing a drug with increased solubility. Chloramphenicol has low water solubility, but the succinate ester is formed to increase the drug's water solubility and facilitate parenteral administration. The succinate ester is inactive but is hydrolyzed to release the active chloramphenicol moiety.

The use of esters is an important means of preparing prodrugs, because esterases present in various parts of the body will cleave the ester linkage, releasing the active moiety. Carboxylic acid esters are common in pharmacy; they are neutral liquids or solids that can be hydrolyzed slowly by water and rapidly by acids or alkalis into their components.

Some of the simple esters are soluble in water, but those with more than four carbon atoms are practically insoluble in water.

One cannot simply look at the name of a compound and determine whether that drug is a salt or an ester. For example, *acetate salts* include calcium acetate, chlorhexidine acetate, desmopressin acetate, flecainide acetate, gonadorelin acetate, guanabenz acetate, leuprolide acetate, lysine acetate, mafenide acetate, and zinc acetate, and *acetate esters* include cortisone acetate, desoxycorticosterone acetate, dexamethasone acetate, fludrocortisone acetate, fluorometholone acetate, hydrocortisone acetate, isoflupredone acetate, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, methylprednisolone acetate, norethindrone acetate, paramethasone acetate, prednisolone acetate, trenbolone acetate, and betamethasone acetate. Further, *succinate salts* include sumatriptan succinate, doxylamine succinate, loxapine succinate, and metoprolol succinate, and *succinate esters* include chloramphenicol sodium succinate, hydrocortisone sodium succinate, hypromellose acetate succinate, methylprednisolone sodium succinate, and prednisolone sodium succinate.

Let's look at cefuroxime axetil as an example of an ester that is dosed according to the base form.

1. Cefuroxime axetil is  $C_{20}H_{22}N_4O_{10}S$ , with a molecular weight of 510.47. Cefuroxime axetil is described as a mixture of the diastereoisomers of cefuroxime axetil and contains the equivalent of not less than 745  $\mu\text{g}$  and not more than 875  $\mu\text{g}$  of cefuroxime ( $C_{16}H_{16}N_4O_8S$ ) per milligram, calculated on the anhydrous basis.
2. Cefuroxime axetil tablets USP contain the equivalent of not less than 90.0% and not more than 110.0% of the labeled amount of cefuroxime ( $C_{16}H_{16}N_4O_8S$ ).
3. Ceftin tablets (cefuroxime axetil tablets) provide the equivalent of 250 mg or 500 mg of cefuroxime as cefuroxime axetil.
4. Ceftin for oral suspension (cefuroxime axetil powder for oral suspension) provides the equivalent of 125 mg or 250 mg of cefuroxime as cefuroxime axetil per 5 mL of suspension.
5. After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime; the axetil moiety is metabolized to acetaldehyde and acetic acid.
6. The molecular weight of cefuroxime axetil is 510.47. The molecular weight of cefuroxime is 424.39. Therefore, 1 mg of cefuroxime is contained in  $510.47/424.39 = 1.2$  mg of cefuroxime axetil. A 250 mg cefuroxime tablet will contain  $250 \times 1.2 = 300$  mg of cefuroxime axetil.
7. Therefore, if the compounding is using a commercial product in preparing a dosage form, no conversion should be required. However, if a bulk active ingredient is used, the required amount of cefuroxime axetil that is equivalent to the desired dosage of cefuroxime must be calculated.

### Labeling of Official Monographs

Let's look again at the example of dexamethasone. Labeled strengths of dexamethasone pose an interesting problem because they do not consistently name either the base or the ester form. "Dexamethasone" dosage form monographs are based on the labeled amount of dexamethasone. The "dexamethasone acetate" dosage form monograph is based on the labeled amount of dexamethasone. "Dexamethasone sodium phosphate" dosage form monographs are based on the labeled amount of dexamethasone phosphate.

Because some drugs may occur as salt forms, ester forms, or salt-ester forms, documenting which form is being used and whether it is a salt, ester, or combination is important. An example of a drug that occurs as both salt and ester forms is erythromycin. Erythromycin estolate is a salt; erythromycin ethylsuccinate is an ester; erythromycin gluceptate is a salt; erythromycin lactobionate is a salt; and erythromycin stearate is a salt.

Table 2-3 lists USP-monographed drugs that occur as esters and whether dosing for various dosage forms is based on the ester or the base form of the drug. Checking each formula for confirmation before making any necessary calculations is always best.

### Compounding with Inorganic Salts

Characteristics of inorganic salts that can affect their physical and chemical properties, including particle size, tendency to absorb or give off water, and pH, are of interest for compounding pharmacists. When exposed to air, a hygroscopic powder will absorb moisture, a deliquescent powder will absorb moisture to the point of liquefaction, and an efflorescent powder will give off its water of crystallization. These effects are associated with the humidity in the immediate

**TABLE 2-3** Form (Ester or Base) Used as Basis of Label Content

<b>Drug</b>	<b>Topical</b>	<b>Capsules/ Tablets</b>	<b>Liquids<sup>a</sup></b>	<b>Injections</b>	<b>Suppositories</b>
Betamethasone benzoate	E				
Betamethasone dipropionate	B (Cr/Oint/Lot)		B		
Betamethasone valerate	B (Cr/Lot/Oint)				
Hydrocortisone acetate	E (Cr/Lot/Oint)		E	E	
Hydrocortisone sodium succinate				B	
Hydroxyprogesterone caproate				E	
Medroxyprogesterone acetate		E		E	
Megestrol acetate		E	E		
Methylprednisolone acetate	E (Cr)			E	
Methylprednisolone sodium succinate				B	
Prednisolone acetate			E	E	
Prednisolone sodium succinate				B	

E = ester; B = base; Cr = cream; Lot = lotion; Oint = ointment.

<sup>a</sup>Liquids include oral solutions, suspensions, emulsions, elixirs, syrups, ophthalmics, nasal solutions, and otic solutions.

environment. Some powders will either absorb or liberate water, depending on the humidity. These effects are especially important during pharmaceutical processes such as weighing and may result in incorrect quantities of materials being weighed. Eutectic formation is another phenomenon that results when certain materials are mixed together and become pasty or even liquefy. Eutectic mixtures can be advantageous or deleterious, depending on how they are used. Pharmacists can use numerous methods to overcome these occurrences.

### Incompatibilities

Incompatibility is defined as the inability of a substance to maintain its identity or to exercise its inherent properties when brought into contact with or into the sphere of influence of another substance or a physical force. For pharmacists, incompatibilities can be either desirable or undesirable. An example of a desirable incompatibility is the addition of effervescent salts to water. An example of an undesirable incompatibility is a pH change resulting in hydrolysis and drug degradation.

Incompatibilities can be physical, chemical, or physiologic; the chemical and physical incompatibilities are of interest to compounding pharmacists. Physical incompatibilities include insolubility, immiscibility, heat, pressure, cold, light, and percussion (violent reactions). Chemical incompatibilities commonly include hydrolysis, condensation, oxidation, reduction, precipitation, gas evolution, heat liberation, and heat absorption. Some of these characteristics are mentioned in Table 2-4.

**TABLE 2-4** Properties of Selected Inorganic Salts

Name	Formula	MW	H <sub>2</sub> O Solubility	Use	Notes <sup>a</sup>
Potassium alum	$\text{AlK}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$	474.39	FS	Astringent Styptic	With phenol, salicylates, or tannic acid, a green or gray color owing to traces of iron in the alum may be developed.
Ammonium carbonate	$(\text{NH}_4\text{HCO}_3)$ and $(\text{NH}_2\text{COONH}_4)$		FS	Alkalinizing agent Buffer	Consists of ammonium bicarbonate and ammonium carbamate in varying proportions. Contains between 30% and 34% $\text{NH}_3$ . Is alkaline to litmus.
Boric acid	$\text{H}_3\text{BO}_3$	61.83	Sol	Buffer Weak germicide	Acids and acid salts decompose ammonium carbonate. Resorcinol gives a brown color that changes to blue. With sodium bicarbonate and moisture, liberation of carbon dioxide occurs. Traces of iron have sometimes caused discoloration in powders with phenol.
Calamine	$\text{ZnO}$ with $\text{Fe}_2\text{O}_3$		IS	Astringent Protectant	Contains zinc oxide with a small amount of ferric oxide. Reacts slowly with fatty acids in oils and fats to produce lumpy masses of zinc oleate or stearate. Vanishing creams tend to dry out and crumble.
Calcium chloride	$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	147.01	FS	Desiccant Diuretic	Levigate with mineral oil to a smooth paste before incorporation into ointments. pH 4.5–9.2. Deliquescent.
Calcium hydroxide	$\text{Ca}(\text{OH})_2$	74.09	SIS	Protectant Astringent	Is precipitated by borates, carbonates, citrates, oxalates, phosphates, sulfates, and tartrates. Precipitates most alkaloids and metals (as the hydroxide).
Magnesium carbonate			PrIn	Antacid Cathartic	Liberates carbon dioxide when mixed with acids. Precipitates free alkaloids from alkaloidal salt solutions. (continued)

**TABLE 2-4** Properties of Selected Inorganic Salts (Continued)

Name	Formula	MW	H <sub>2</sub> O Solubility	Use	Notes <sup>a</sup>
Magnesium sulfate	MgSO <sub>4</sub> · xH <sub>2</sub> O	138.36 (Monohydrate)	FS	Cathartic Soak or compress for skin disorders	Efflorescent. pH 5.0–9.2.
Potassium bromide	KBr	119	FS	Sedative	Is alkaloidal precipitant. Strong oxidizing agents liberate bromine.
Potassium chloride	KCl	74.55	FS	Electrolyte source	Is neutral to litmus. Forms precipitates by reaction with lead and silver salts.
Potassium hydroxide	KOH	56.11	FS	Alkalinizing agent Caustic	Deliquescent. Reacts with acids; liberates alkaloids from aqueous solutions of alkaloidal salts.
Potassium iodide	KI	166	VS	Expectorant Iodine source Antifungal therapy	Hygroscopic. Is decomposed with acids. Oxidizing agents liberate iodine.
Sodium bicarbonate	NaHCO <sub>3</sub>	84.01	Sol	Alkalinizing agent Antacid Antipruritic	Is alkaline to litmus. Is decomposed by acids and salts; acid reaction liberates carbon dioxide. Intensifies the darkening with solutions of salicylates. Precipitates some alkaloids.
Sodium chloride	NaCl	58.44	FS	Electrolyte Tonicity- adjusting agent	May react with atmospheric moisture or water of crystallization from other ingredients. Precipitates form with lead and silver salt solutions. Strong oxidizing agents liberate chlorine from acidified solutions.
Sodium hydroxide	NaOH	40	FS	Alkalinizing agent Caustic	Hygroscopic. Absorbs carbon dioxide and is converted to sodium carbonate. Forms soluble soaps with fats and fatty acids.

Sodium hypochlorite	NaClO	74.44	FS	Disinfectant Germicidal Dissolves necrotic tissue Deodorant	In solution. pH 7.8–8.2 (0.3% solution).
Sodium dibasic phosphate	Na <sub>2</sub> HPO <sub>4</sub> · xH <sub>2</sub> O	141.96 (anhy)	FS	Buffer Cathartic	Hygroscopic. Produces alkaline reaction. Precipitates heavy metals. pH 4.1–4.5. Deliquescent. Is incompatible with carbonates and alkalis in general.
Sodium monobasic phosphate	NaH <sub>2</sub> PO <sub>4</sub> · xH <sub>2</sub> O	119.98	FS	Buffer Urinary acidifier	Forms strongly alkaline solutions.
Sodium tribasic phosphate	Na <sub>3</sub> PO <sub>4</sub>	163.94 (anhy)	FS	Ingredient in detergents, buffers, water softening	
Zinc oxide	ZnO	81.39	IS	Mild astringent, protectant, and antiseptic	Reacts slowly with fatty acids in oils and fats to produce lumpy masses of zinc oleate or stearate. Vanishing creams tend to dry out and crumble. Levigates with mineral oil to a smooth paste prior to incorporation into ointments.
Zinc sulfate	ZnSO <sub>4</sub> · xH <sub>2</sub> O	161.46 (anhy)	FS	Astringent, emetic, and weak antiseptic	Efflorescent. Acid to litmus. Precipitates with lead, barium, strontium, and calcium salts. May dehydrate methylcellulose suspensions, leading to precipitation. Acacia, proteins, and tannins may precipitate.

anhy = anhydrous.

\*pH values are provided in aqueous solutions. Check USP for concentrations used for these descriptions.

## Solubility of Inorganic Salts

Some general rules regarding the solubility of inorganic salts are of interest:

1. If both the cation and the anion of an ionic compound are monovalent, the solute–solute attractive forces are usually easily overcome; therefore, these compounds are generally water soluble (e.g., NaCl, LiBr, KI,  $\text{NH}_4\text{NO}_3$ ,  $\text{NaNO}_2$ ).
2. If only one of the two ions in an ionic compound is monovalent, the solute–solute interactions also are usually easily overcome, and the compounds are water soluble (e.g.,  $\text{BaCl}_2$ ,  $\text{MgI}_2$ ,  $\text{Na}_2\text{SO}_4$ ,  $\text{Na}_3\text{PO}_4$ ).
3. If both the cation and the anion are multivalent, the solute–solute interaction may be too great to be overcome by the solute–solvent interaction, and the compound may have poor water solubility (e.g.,  $\text{CaSO}_4$ ,  $\text{BaSO}_4$ ,  $\text{BiPO}_4$ ) (exceptions:  $\text{ZnSO}_4$ ,  $\text{FeSO}_4$ ).
4. Common salts of alkali metals (e.g., Na, K, Li, Cs, Rb) are usually water soluble (exception:  $\text{Li}_2\text{CO}_3$ ).
5. Ammonium and quaternary ammonium salts are water soluble.
6. Nitrates, nitrites, acetates, chlorates, and lactates generally are water soluble (exceptions: silver and mercurous acetate).
7. Sulfates, sulfites, and thiosulfates generally are water soluble (exceptions: calcium and barium salts).
8. Chlorides, bromides, and iodides are water soluble (exceptions: salts of silver and mercurous ions).
9. Acid salts corresponding to an insoluble salt will be more water soluble than the original salt.
10. Hydroxides and oxides of compounds other than alkali metal cations and the ammonium ion generally are water insoluble.
11. Sulfides are water insoluble except for their alkali metal salts.
12. Phosphates, carbonates, silicates, borates, and hypochlorites are water insoluble except for their alkali metal salts and ammonium salts.

If these factors are not addressed before compounding, the effectiveness, stability (physical and chemical), and elegance of a prescription compounded with inorganic salts may be adversely affected. Properties of some inorganic salts are given in Table 2-4.

## Compounding with Potency-Designated Ingredients

For some active pharmaceutical ingredients (APIs), including some antibiotics, endocrine products, biotechnology-derived products, and biological agents, the potency is based on *activity* and expressed in terms of units of activity, micrograms per milligram, or other standard terms of measurement. Table 2-5 includes examples of these substances with the *USP* description of their potency.

Regarding biologicals, the following is found in the *USP* General Notices:

### 5.50.10 Units of Potency (Biological):

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by *USP*

**TABLE 2-5** Potency Designations as Described in *USP*

<b>Active Pharmaceutical Ingredient</b>	<b>Potency Designation</b>
Amikacin sulfate	Contains the equivalent of not less than 674 µg and not more than 786 µg of amikacin per mg, calculated on the dried basis
Amoxicillin	Contains not less than 900 µg and not more than 1050 µg of amoxicillin per mg, calculated on the anhydrous basis
Amphotericin B	Has a potency of not less than 750 µg of amphotericin B per mg, calculated on the dried basis
Ampicillin	Contains not less than 900 µg and not more than 1050 µg of ampicillin per mg, calculated on the anhydrous basis
Ampicillin sodium	Contains not less than 845 µg and not more than 988 µg of ampicillin per mg, calculated on the anhydrous basis.
Calcitonin salmon	One mg of acetic acid-free, anhydrous calcitonin salmon is equivalent to 6000 USP calcitonin salmon units
Cefuroxime sodium	Contains the equivalent of not less than 855 µg and not more than 1000 µg of cefuroxime, calculated on the anhydrous basis
Cephalexin	Has a potency of not less than 950 µg and not more than 1030 µg of cephalexin per mg, calculated on the anhydrous basis
Cephalexin hydrochloride	Contains the equivalent of not less than 800 µg and not more than 880 µg of cephalexin per mg
Cephalothin sodium	Contains the equivalent of not less than 850 µg of cephalothin per mg, calculated on the dried basis
Colistin sulfate	Has a potency equivalent to not less than 500 µg of colistin per mg
Gentamicin sulfate	Has a potency equivalent to not less than 590 µg of gentamicin per mg, calculated on the dried basis
Heparin sodium	Has a potency of not less than 140 USP heparin units in each mg, calculated on the dried basis
Insulin	Has a potency of not less than 26.5 USP insulin units in each mg, calculated on the dried basis; insulin labeled as purified contains not less than 27.0 USP insulin units in each mg, calculated on the dried basis
Insulin human	Has a potency of not less than 27.5 USP insulin human units in each mg, calculated on the dried basis
Insulin lispro	Has a potency of not less than 27.0 USP insulin lispro units per mg, calculated on the dried basis
Neomycin sulfate	Has a potency equivalent to not less than 600 µg of neomycin per mg, calculated on the dried basis
Nystatin	Has a potency of not less than 4400 USP nystatin units per mg, or, where intended for use in the extemporaneous preparation of oral suspensions, not less than 5000 USP nystatin units per mg
Oxytocin	Has oxytocic activity of not less than 400 USP oxytocin units per mg
Streptomycin sulfate	Has a potency equivalent to not less than 650 µg and not more than 850 µg of streptomycin per mg
Tobramycin	Has a potency equivalent to not less than 900 µg of tobramycin per mg, calculated on the anhydrous basis
Tobramycin sulfate	Has a potency of not less than 634 µg and not more than 739 µg of tobramycin (C <sub>18</sub> H <sub>37</sub> N <sub>5</sub> O <sub>9</sub> ) per mg
Vancomycin hydrochloride	Has a potency equivalent to not less than 900 µg of vancomycin per mg, calculated on the anhydrous basis
Vasopressin	Has vasopressor activity of not less than 300 USP vasopressin units per mg

Reference Standards as “USP Units.” For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined.

There is no relationship between the units of potency of one drug and those of another drug. In the case of potency-designated drugs, there must be a reference standard for comparison. In actual usage, the potency specifications often include a range or “not less than \_\_\_” and “not more than \_\_\_.” In some cases, only a lower range is given, and in a few cases, there is no upper limit.

The determinations of potency are generally done on the dried or anhydrous basis. In the case of hygroscopic APIs, precautions must be taken to maintain the substance in a dried state in tight containers. In some cases, solvent-free conditions are specified.

In the case of dihydrostreptomycin, there are different potencies depending on the use of the API. The potency may be not less than 450 µg, 650 µg, or 725 µg, depending on its form or usage (route of administration).

In some cases, as in erythromycin ethylsuccinate and erythromycin stearate, the potency is based on the sum of the percentages of three different erythromycins that make up the API. Usually, the potency designation is determined on the base of the drug, but in a few instances the salt or ester form is used.

The potency of antibiotics is commonly expressed as micrograms of activity per milligram of substance. Obviously, there will be different equivalents for the base versus the salt form of the drug. For example, as shown in Table 2-5, tobramycin has a potency of not less than 900 µg of tobramycin per milligram, and tobramycin sulfate has a potency of not less than 634 µg of tobramycin per milligram, all on the anhydrous basis. In another example, ampicillin contains not less than 900 µg and not more than 1050 µg of ampicillin per milligram, and ampicillin sodium contains not less than 845 µg and not more than 988 µg of ampicillin per milligram, both calculated on the anhydrous basis. Because of these differences, checking the labels accompanying each batch of each API for the necessary values to be used in calculations is extremely important.

In some drugs (e.g., heparin, insulin), the actual dose may be expressed in units instead of milligrams. Other examples include enzymes (pancreatin, pancrelipase, papain) and antibiotics.

Each container must be labeled with the actual potency, and this information must be used in calculations involving dosing that occur before compounding activities. These calculations must be done, checked, and documented, because different lots of the same API may have different potencies.

*Example: A formula calls for 500 mg of neomycin sulfate. The label on the API shows 650 µg of neomycin activity per milligram of powder. How much of this powder is required to provide the 500 mg of neomycin sulfate?*

$$\frac{650 \mu\text{g}}{1000 \mu\text{g}} = \frac{500 \text{ mg}}{x}$$

$x = 769 \text{ mg}$  of the powder is required to provide 500 mg of actual neomycin sulfate.

## Compounding with Complex Organic Molecules

Most complex molecules and biotechnology products are proteins; however, some may be smaller, peptide-like molecules. Proteins are inherently unstable molecules and require special handling; furthermore, their degradation profiles can be quite complex. Pharmacists

involved in compounding with biologically active proteins must be interested in their stabilization, formulation, and delivery to the site of action.

In working with complex molecules, one must be cognizant of both the active drug constituent and the total drug formulation in which it is contained. This is true when converting a commercial product into a compounded preparation. Protein drugs are very potent and are generally used in quite low concentrations. The bulk of many manufactured products and compounded preparations may be the excipients, including the vehicle, buffers, and stabilizers that are often incorporated into these products.

A number of different stabilizers from different chemical classes can be used; these include surfactants, amino acids, polyhydric alcohols, fatty acids, proteins, antioxidants, reducing agents, and metal ions. Table 2-6 describes agents that may be used as stabilizers in complex molecule and protein formulations.

**TABLE 2-6** Stabilizing Agents for Complex Molecule and Protein Preparations

Class	Agent	Action
Amino acids	Alanine	Solubilizer
	Arginine	Buffer
	Aspartic acid	Inhibits isomerism
	Glycine	Stabilizer
	Glutamic acid	Thermostabilizer
	Leucine	Inhibits aggregation
Antioxidants	Ascorbic acid, cysteine hydrochloride, glutathione, thioglycerol, thioglycolic acid, thiosorbitol	Help stabilize protein conformation
Chelating agents	Ethylenediaminetetraacetic acid salts	Inhibit oxidation by removing metal ions, glutamic acid, and aspartic acid
Fatty acids	Choline, ethanolamine, phosphatidyl	Stabilizers
Proteins	Human serum albumin	Prevents surface adsorption; stabilizes protein conformation; serves as a complexing agent and cryoprotectant
Metal ions	Ca <sup>++</sup> , Ni <sup>++</sup> , Mg <sup>++</sup> , Mn <sup>++</sup>	Help stabilize protein conformation
Polyhydric alcohols	Ethylene glycol	Stabilizer
	Glucose	Strengthens conformation
	Lactose	Stabilizer
	Mannitol	Cryoprotectant
	Propylene glycol	Prevents aggregation
	Sorbitol	Prevents denaturation and aggregation
	Sucrose	Stabilizer
	Trehalose	Stabilizer
Polymers	Polyethylene glycol, povidone	Prevent aggregation
Surfactants	Poloxamer 407	Prevents denaturation and stabilizes cloudiness
	Polysorbate 20 and polysorbate 80	Retard aggregation

## Stabilization

A key factor in formulating a stable preparation is pH. The optimal pH range can be achieved through the selection of appropriate physiologic buffers, usually in buffer concentration ranges of 0.01 M to 0.1 M. In general, an increase in the buffer concentration means an increase in pain on injection, so the concentration is usually kept as low as is reasonable.

Chelating agents are incorporated to bind trace metals such as copper, iron, calcium, and manganese and minimize rates of degradation. Ethylenediaminetetraacetic acid (EDTA) is commonly used at a concentration of about 0.01% to 0.05%.

Because oxidation is one of the major factors in protein degradation, antioxidants are often incorporated. Examples include ascorbic acid, sodium disulfide, monothioglycerol, and  $\alpha$ -tocopherol.

Especially in preparation of multidose vials, preservatives are usually necessary if compatible with the active ingredient. Examples of preservatives include phenol (0.3% to 0.5%), chlorobutanol (0.3% to 0.5%), and benzyl alcohol (1% to 3%).

Other excipients may include the polyols, which are good stabilizers and are commonly used in concentrations from 1% to 10%, and tonicity-adjusting agents, which include sodium chloride and dextrose in concentrations necessary to achieve isotonicity of approximately 290 mOsm/L.

## Preparation

Formulations and procedures with complex molecules should be kept as simple as possible. Sterility must be achieved and maintained in many preparations, and because most do not contain a preservative, preparation of only one dose from each vial or container is recommended in order to minimize contamination. Sometimes this is not practical, and specific manipulations are needed to meet patient needs. The standards of *USP Chapter <797>*, Pharmaceutical Compounding—Sterile Preparations, should be met while working with these sterile preparations. Two special considerations in working with biotechnologically derived preparations are the use of filters and the sorption of these drugs to containers.

The use of filters in manipulating biotechnology products can cause sorption, resulting in loss of some of the drug available to the patient. Sorption is “sticking,” by either absorption into the filter or adsorption onto the surface of the filter. Special filters have been prepared to minimize this problem. For example, muromonab-CD3 (Orthoclone OKT3) injection should be filtered with a low-protein-binding filter of 0.2 to 0.22  $\mu\text{m}$ . Many biotechnology products should not be filtered at all. If a filtration device is part of the intravenous administration apparatus, large-molecule drugs generally should be administered distal to the site of the filter. Filters that have been shown to minimize protein adsorption are those made from polyvinylidene difluoride, polycarbonate, polysulfone, and regenerated cellulose. As a precaution, low-protein-binding filters should be used.

Drug loss through sorption of proteins to containers (glass or plastic) can be minimized either by the use of albumin or by siliconization. Adding about 0.1% albumin to the product can decrease the sorption of proteins to containers. If glass containers are used, the albumin solution should be added and manipulated to coat the interior surface before the drug is added. If siliconization is used, one can prepare a silicone solution or emulsion and soak or rinse the glass vials in it. The drained vials should then be placed in an oven at about 250°C for 5 to 6 hours. This procedure will minimize protein adsorption to glass; it can be used for both the preparation equipment and the packaging containers.

## Physicochemical Considerations

Several considerations can help ensure retention of a large-molecule drug's activity up to the time of administration to the patient. These include selecting an appropriate vehicle for

drug delivery, individualizing dosages, administering drugs through novel drug-delivery systems, preparing drugs for delivery through these systems, monitoring their efficacy, and counseling patients on their use. Information on specific products is given in Table 2-7.

Physicochemical issues relevant to large-molecule drugs include the following:

- Effect of agitation or frothing on a preparation's stability
- High molecular weight and potential for aggregation (i.e., a small change in structure can result in a change in activity)
- Assignment of potency to the reference standards (whereas traditional pharmaceuticals are about 98% pure, these materials may be only 0.1% to 1% active, with their activity assigned by potentially variable assays)
- Use of micropipets, which can require frequent calibration
- Stability potentially less than with lyophilized preparations
- Interaction of the product with the inner wall of the glass vial and with the elastomeric closure
- Effectiveness of the preservative if a multidose product is mixed with other products
- Immunogenic potential, because some are produced by a fermentation-type process and proteins can co-purify with proteins

Physicochemical factors to be considered in compounding protein drug products also include the structure of the protein drug, isoelectric point, molecular weight, solubility and factors affecting solubility (e.g., surfactants, salts, metal ions, pH), stability and factors affecting stability (e.g., pH, temperature, light, oxygen, metal ions, freeze-thaw cycles, mechanical stress), polymorphism, stereoisomers, filtration media compatibility, shear, and surface denaturation.

Solubility can vary with changes in chemical structure, pH, and temperature. Proteins are generally more soluble in their native environment or medium or in a matrix that is similar to their native environment, which may include sodium chloride, trace elements, lipids, and other proteins in an aqueous medium. One must consider the ingredients' effects on the solubility of the active drug, especially because most of the products are currently administered parenterally. This is critical because the actual drug is present in a small quantity and can go unnoticed if it precipitates. Sterile water for injection and 0.9% sodium chloride solution usually are good vehicles for use in a formulation.

The pH of the compound should be maintained close to the pH of the original approved, manufactured product. Changes in pH can affect proteins in numerous ways and result in altered activity. Chemical degradation rate constants are related to pH, and the hydrogen ion concentration can affect the actual structure of proteins (i.e., quaternary structure). Buffer systems may be needed in compounding; they should be prepared at the minimum buffer strength required to produce the most stable drug product.

Chemical and physical instability must be considered and addressed appropriately. *Chemical instability* of proteins is the modification of protein structures by bond formation or cleavage to yield a new compound. *Physical instability* generally involves changes in structure, conformation, or behavior in a particular environment. Stability, both chemical and physical, depends on pH, temperature, and agitation, as well as on the overall environment in which the drug is contained.

Sorption is a problem with colony-stimulating factors and with aldesleukin (Proleukin) at low concentrations. To minimize sticking of the protein to the glass, the addition of about 0.1% albumin to the product to occupy the potential binding sites in the container is often helpful. Pharmacists must consider this problem before making any changes in packaging.

**TABLE 2-7** USP Monograph Information on Selected Complex Molecules

Generic Name	Trade Name	Strength Designation	pH of Solution	Notes
Alteplase	Activase	Units	7.1–7.5	Endotoxins: <1 per mg Reconstitute by directing stream of SWFI directly into lyophilized cake. It is preservative free, because it is incompatible with preservatives. Use within 8 hours. Dilute further if necessary with equal volume of NS or D5W. Alteplase may also contain arginine, polysorbate 80, and phosphoric acid and/or sodium hydroxide to adjust pH.
Insulin injection, human	Humulin	Units		Endotoxins: nmt 80 per 100 USP insulin human units Humulin may also contain glycerin, metacresol, zinc oxide, and sodium hydroxide and/or hydrochloric acid to adjust pH.
Sargramostim	Leukine	Units	7.1–7.7	Endotoxins: nmt 50 per mg Avoid foaming during dissolution. Do not shake or vigorously agitate. If final concentration is less than 10 µg/mL, 0.1% human albumin should be added to the saline before adding the sargramostim. Do not use an in-line membrane filter.
Somatropin	Genotropin, Humatrope, Norditropin	Units		Sargramostim may also contain mannitol, sucrose, and tromethamine. Endotoxins: nmt 20 per mg Genotropin 5 mg also contains glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, m-cresol, and SWFI.

SWFI = sterile water for injection; NS = 0.9% sodium chloride injection; D5W = 5% dextrose injection; nmt = not more than.

Agitation resulting in frothing can create difficulties in two ways. First, frothing can cause difficulties in using a syringe to withdraw the required amount of drug from a vial. To avoid this problem, the formulator should mix the product by rolling the vial in the hands or gently swirling it. Second, excessive agitation can cause changes in a protein's quaternary structure that often reduce or eliminate a drug's therapeutic activity. Some products, such as filgrastim (Neupogen) and sargramostim (Leukine), are reconstituted by directing a soft stream of diluent against the inside of the container wall. Others, such as recombinant tissue plasminogen activator (tPA; alteplase), are reconstituted by directing a stream of diluent directly into the product at the bottom of the vial.

### Packaging

The container used for packaging and storage after compounding must be chosen carefully. For example, the manufacturer's directions for interleukin-2 (aldesleukin) suggest the use of a plastic bag because that type of dilution container enhances consistent drug delivery. Unless otherwise specified, USP type I glass should be used for packaging when storage for extended time periods is indicated. A pharmacist should be aware of the potential for sorption of the drug to the glass walls. Closures and stoppers should be selected that are compatible and flexible; have low levels of particulates; and experience few problems with adsorption, absorption, and permeation.

### Storage and Labeling

The recommended storage temperature depends on the specific preparation and may include room temperature (15°C–25°C), refrigerator temperature (2°C–8°C), or frozen (–20°C) or ultrafrozen temperature (down to –80°C). Freezing does affect the activity of certain products; for instance, the activity of filgrastim decreases if it is frozen. Some products can retain potency at room temperature after reconstitution. Sargramostim retains potency for up to 30 days at 25°C. However, most manufacturers recommend refrigeration at 2°C to 8°C, regardless of the product's potency at room temperature.

The short shelf life of these products after reconstitution can be due to chemical, physical, or microbiological instability. The manufacturer's recommendations or recommendations validated by the published literature should be followed for products after they are reconstituted and manipulated. One example is tPA, which has been used in treating intraocular fibrin formation after a vitrectomy and in managing subconjunctival hemorrhage after glaucoma filtration surgery. The prepared solution is stable in a pH range of 5 to 7.5 and is incompatible with bacteriostatic agents. To prepare a compounded preparation, a pharmacist reconstitutes the commercial product according to the manufacturer's directions, using sterile water for injection without preservatives to yield a concentration of 1 mg/mL. This solution is further diluted with 0.9% sodium chloride injection to yield a concentration of 25 µg/100 µL. Aliquots of 0.3 mL are withdrawn into 1-mL tuberculin syringes and capped. The syringes are stored in an ultrafreezer at –70°C. This product has been shown, by both bioassay and clinical use, to retain its activity for at least 1 year. This type of specific product information is not included in the manufacturer's label information and is usually obtained from the literature or by asking the manufacturer directly.

### Stability

Physical stability can involve degradation by aggregation, denaturation, and precipitation. Aggregation can be the result of covalent or noncovalent processes and can be either physical or chemical in nature. Aggregate formation can actually begin when primary particles are formed from protein molecules as a result of Brownian movement.

Denaturation can result from heat, cold, extreme pH values, organic solvents, hydrophilic surfaces, shear, agitation, mixing, filtering, shaking, freeze–thaw cycles, ionic strength, and other factors. Denaturation can be quite complex and can be either reversible or irreversible.

Precipitation can result from shaking, heating, filtration, pH, and chemical interactions. The first step in a precipitation process usually is aggregation. When the aggregates gain a sufficient size, they precipitate out of solution and are clearly evident. Precipitation can occur on membrane filters, in equipment, in tubing, and in contact with other equipment and supplies.

## Compounding with Aliquots, Dilutions, and Concentrates

Substances are available as aliquots, dilutions, and concentrates for a number of reasons. First, the quantities required for dosing or compounding may be so small they cannot be accurately weighed, so dilutions are prepared, assayed, and used. Second, some items, such as nitroglycerin, are explosive and must be diluted in order to be safely handled. Third, many substances, such as acids and bases, are commercially available in percentage strengths that vary from one acid to another and depend on the solubility and stability of the solute in water and on the manufacturing process. The diluted acids are aqueous solutions, usually 10% weight-in-volume (w/v), although diluted acetic acid is 6% w/v. The concentrations of the official undiluted acids are expressed as percentages weight in weight (w/w), but the strengths of official diluted acids are expressed as percentages weight in volume. Therefore, a pharmacist must consider the specific gravities of the concentrated acids when calculating the volume required to make a given quantity of diluted acid.

### Triturations, Dilutions, and Concentrates

Triturations or dilutions were, at one time, official and consisted of diluting one part by weight of the drug with nine parts of finely powdered lactose; they were 10% mixtures of the drug. These dilutions were a means of conveniently obtaining small quantities of a drug for compounding purposes. Many aqueous concentrates are available and are convenient to use; a notable example in compounding is benzalkonium chloride solutions. Table 2-8 lists examples of other substances available as triturations, dilutions, and concentrates.

*Example: How many milliliters of a benzalkonium chloride 17% solution would be required to prepare 4000 mL of a 1:10,000 solution?*

$$1 : 10,000 :: x : 4000$$

$$10,000x = 4000$$

$x = 0.4$  g of benzalkonium chloride substance is required.

$$17 \text{ g} : 100 \text{ mL} :: 0.4 \text{ g} : x$$

$$17x = 40$$

$x = 2.35$  mL of the benzalkonium chloride 17% solution is required.

**TABLE 2-8** Examples of Substances (Official and Nonofficial) Available as Triturations, Dilutions, and Concentrates

Substance	Strength (%)	Comments
Acetic acid NF	36.0%–37.0% w/w	
Acetic acid, diluted NF	5.7%–6.3% w/v	
Alcohol, USP	94.9%–96.0% v/v; 92.3%–93.8% w/w	Sp gr 0.812–0.816
Alcohol, diluted NF	48.4%–49.5% v/v	Sp gr 0.935–0.937
Ammonia solution, strong NF	27%–31% w/w	
Ammonium lactate 70% solution	70%	
Ammonium lauryl sulfate 28%	28%	
Formaldehyde solution USP	Nlt 34.5% w/w	
Glutaraldehyde 25% aqueous solution	25%	
Glycolic acid 70%	70%	
Hydrochloric acid NF	36.5%–38.0% w/w	
Hydrochloric acid, diluted NF	9.5%–10.5% w/v	
Hydrogen peroxide concentrate USP	29.0%–32.0% w/w	Strong oxidant
Hydrogen peroxide topical solution USP	2.5%–3.5% w/v	
Hypophosphorous acid NF	30.0%–32.0%	
Isopropyl rubbing alcohol USP	68.0%–72.0%	Sp gr 0.872–0.883
Lactic acid USP	88.0%–92.0% w/w	
Nitroglycerin, diluted USP	10% usually w/w	
Phenol, liquefied USP	90% w/w	
Phosphoric acid NF	85.0%–88.0% w/w	
Phosphoric acid, diluted NF	9.5%–10.5% w/v	
Sodium hypochlorite solution USP	4.0%–6.0% w/w	
Sorbitol solution	Nlt 64.0%	
Zinc pyrithione 48% (min) aqueous dispersion	48%	

Nlt = not less than.

Methods of calculation using dilutions or triturations can include ratio and proportion, allegation alternate, and allegation medial. These procedures are described in pharmacy calculation textbooks.

## Nitroglycerin

Diluted nitroglycerin contains the following cautionary labeling:

Caution—Taking into consideration the concentration and amount of nitroglycerin ( $C_3H_5N_3O_9$ ) in Diluted Nitroglycerin, exercise appropriate precautions when handling this material. Nitroglycerin is a powerful explosive and can be detonated by percussion or excessive heat. Do not isolate nitroglycerin ( $C_3H_5N_3O_9$ ).

Isosorbide dinitrate and isosorbide mononitrate have similar warnings.

*Example: To obtain 40 mg of nitroglycerin to prepare 100 nitroglycerin 0.4 mg dosage units:*

A 10% nitroglycerin trituration contains 1 g of nitroglycerin per 10 g of mixture.

$$40 \text{ mg} = 0.04 \text{ g}$$

$$1 \text{ g} : 10 \text{ g} :: 0.04 \text{ g} : x \text{ g}$$

$x \text{ g} = 400 \text{ mg}$  of the dilution would be required.

### Acids and Bases

Checking the label of each lot of concentrated acid or base used for a prescription or procedure is always best, because lots can sometimes vary. The following relationship can be used:

$$\frac{\text{Strength of diluted acid} \times 1000}{\text{Strength of undiluted acid} \times \text{sp gr of undiluted acid}}$$

*Example: To make 1000 mL of diluted HCl USP, using HCl assayed at 37.5% HCl with sp gr of 1.18, the amount required is*

$$\frac{10 \times 1000}{37.5 \times 1.18} = 226 \text{ ml is required}$$

Dilution concentrations can be done by allegation, ratio and proportion, or other calculation methods described in pharmacy calculation textbooks.

## Compounding with Commercial Products

In compounding prescriptions for humans, pharmacists can use either bulk drug substances or commercial preparations. With a few exceptions, veterinary compounding requires the use of commercial products.

The Federal Food, Drug, and Cosmetic Act recognizes the *USP/NF* as the official compendia of the United States. Compounded drugs prepared pursuant to a practitioner's prescription must meet compendial requirements if the prescription uses the compendial name. According to *USP* Chapter <795>, a *USP* or an *NF* grade substance is the preferred source of ingredients for compounding all preparations. If that is not available, or when food, cosmetics, or other substances are or must be used, then use of another high-quality source, such as analytical reagent, certified American Chemical Society, or Food Chemicals Codex grade is an option for professional judgment. A manufactured drug product may also be a source of active ingredient.

### Commercial Products as Source of Active Drugs

Is the use of commercial products in compounding wise? When doing so, can a pharmacist be assured of a quality preparation? Can the standards of *USP* Chapter <795>; Chapter <797>; and Chapter <1075>, Good Compounding Practices, be met by using commercial products as the source of drugs? The answer to these questions is "sometimes, but not always." Pharmacists are placed in an interesting position: although the federal government dictates that commercial products be used in compounding veterinary preparations, doing so sometimes results in preparations that are outside *USP* standards and specifications. Box 2-1 describes an example of out-of-specification compounding.

**BOX 2-1 Example: Out-of-Specification Compounding**

In compounding for human patients, pharmacists have the choice of using bulk chemicals or commercial products. When using commercial products as the source of active drugs, a pharmacist does not know whether the final compounded preparation meets USP standards. An example is a relatively simple intravenous admixture containing gentamicin injection 80 mg in 50 mL of 5% dextrose injection. To prepare this, a pharmacist adds 2 mL of Garamycin injection (40 mg/mL) to an empty piggyback bag and adds 48 mL of 5% dextrose injection to make a final volume of 50 mL. The finished compounded preparation is allowed a variance of 90.0% to 110.0% of the labeled potency. The USP specification for gentamicin injection is not less than 90.0% and not more than 125.0% of the labeled amount of gentamicin. If the specific batch analyzed at the manufacturer was at 120%, then it met the USP specifications and entered the marketplace distribution system. A pharmacist who adds 2 mL of that gentamicin injection to 48 mL of 5% dextrose injection has just compounded a drug preparation that does not meet the USP compounding specifications of 90.0% to 110.0% of the labeled quantity; that is, 2 mL of 40 mg/mL at 120% of labeled quantity equals 96 mg of gentamicin present. The acceptable range would be 72 to 88 mg of gentamicin, so the preparation with 96 mg of drug does not meet the USP standard for compounding. If this solution were selected for analysis by a regulatory agency, it would be found to be beyond specifications and superpotent. This is the current regulatory situation, and it must be followed until such time that most compounding can be done using compendial standard (*USP/NF*) or other high-quality bulk drug substances.

Historically, pharmacists have used commercially available medications to prepare different dosage forms. The most common examples are the use of oral tablets and capsules to prepare oral liquids (solutions and suspensions) for pediatric patients and the use of injectable drugs to prepare intravenous admixtures. Even though FDA-approved commercial products are used, the final compounded preparation does not have FDA approval.

Considerations concerning commercial product use include the following:

1. Using commercial products as a source of active drugs usually will result in a higher prescription cost to the patient than would using bulk drug substances. This is especially true when injectables are used as the drug source.
2. All the excipients present in the commercial dosage form must be considered for their effects on the efficacy, safety, stability, and assay potency of the final compounded preparation.
3. When using solutions as the source of drugs, a pharmacist must be aware of the pH of the solution and the pH of the compounded preparation. If there is a significant difference in pH (i.e., 2 to 3 pH units), the solubility and stability of the drug and formulation may change. If the pH of the final solution is insufficient to keep the drug in solution, the preparation may be a suspension rather than a solution.
4. The presence of buffers in the commercial drug product can affect the pH of the final compounded preparation.
5. Before a pharmacist uses a commercial product to compound large batches, assaying the product for potency may be advisable. An assay is especially important

if the USP allowable range for the commercial product exceeds the 90%–110% potency range acceptable for compounded preparations. For most commercial drugs, the potency range is 95%–105% or 90%–110% of the labeled quantity; for some, the range is 80%–120%. Some *USP* monographs for commercial products go as high as 165% of the labeled quantity; although this is unusual, it is a variable a pharmacist must consider. Even if the compounding pharmacist performed every step correctly, the final preparation could fail to meet specifications because wide variability was allowed in the commercial product.

6. Some dosage forms should not be used in compounding. Modified-release dosage forms (e.g., extended release, delayed release, repeat action, targeted release) should not be used unless their suitability for use in compounding has been documented.
7. When commercial products are used in compounding, listing their manufacturer and lot number is important. This is especially important in the case of multisource generic drugs, because different excipients may be used by different manufacturers.
8. A limiting factor can be the quantity of commercial product that must be used to provide the required amount of active drug. Often, the required quantity makes use of the commercial product impractical.

In addition to these factors, some commercial dosage forms are inappropriate for use in compounding particular dosage forms, as summarized in Table 2-9. The reasons are discussed in the following sections.

### Excipients in Various Dosage Forms

*Powders and granules* generally consist of the active drug and diluents. Medicated powders for external use may use cornstarch or talc as a diluent and adherent and may also contain water-repelling agents. Those for internal use may be intended for local effects (laxatives) or systemic effects; they may use a water-soluble or dispersible diluent, anticaking agent, coating agents, flavors or perfumes, sweeteners, and solubilizing agents.

*Capsules* usually consist of the active drug and diluent and may also contain lubricants, disintegrating agents, glidants, and coating agents. Some of these ingredients are water soluble and some are not.

*Tablets* contain the active drug and possibly diluents or fillers, disintegrating agents, glidants, lubricants, binders, antiadherents, colorants, sweeteners, and flavorants. In some cases, coating materials and plasticizers may need to be considered.

*Ointments* may be of the oleaginous, absorption, water-removable, or water-soluble type. The oleaginous bases consist primarily of hydrocarbon vehicles, such as petrolatum and mineral oil. Absorption bases may have, in addition, water-in-oil emulsifying agents, such as lanolin and cholesterol. Water-removable bases usually contain emulsifying agents or surfactants, and water-soluble bases are usually polymer based. Additional materials may include flavors or perfumes, stiffening agents, and water-repelling additives.

*Creams* generally are oil-in-water emulsions or water-in-oil emulsions and contain the aqueous and oil phases along with surfactants or emulsifying agents and possibly preservatives. Some may also contain perfumes, antioxidants, buffering agents, chelating agents, humectants, and stiffening agents.

*Gels* are semisolid systems usually containing a polymeric gelling agent and preservative; they may contain acidifying or alkalizing agents, antioxidants, buffering agents, chelating agents, flavors or perfumes, humectants, and sweeteners.

*Suppositories and inserts* are solid forms that usually consist of a base that melts at body temperature or dissolves in body fluids. (Compressed-tablet inserts are covered under tablets,

**TABLE 2-9** Compounded Dosage Forms and Potential Commercial Drug Sources

Source of Dosage Form	Form to Be Compounded													
	Pwdrs	Grans	Caps	Tab	Oints	Crms	Gels	Solns	Susps	Emuls	Parens	Ophths	Nasal Solns	Otic Solns
Powders and granules	+		+	+	+	+	+	?	+	+	-	-	-	+
Capsules	+		+	+	+	+	+	-	+	+	-	-	-	+
Tablets	+		+	+	+	+	+	-	+	+	-	-	-	+
Ointments	-		-	-	+	+	-	-	-	?	-	-	-	+
Creams	-		-	-	+	+	?	-	-	+	-	-	-	+
Gels	-		-	-	?	+	+	+	+	+	-	-	+	+
Solutions	?		?	?	+	+	+	+	+	+	-	+	+	+
Suspensions	?		?	?	+	+	+	?	+	+	-	-	-	+
Emulsions	-		-	-	?	+	+	?	+	+	-	-	-	+
Parenterals	+		+	+	+	+	+	+	+	+	+	+	+	+
Ophthalmics	+		?	?	?	+	+	+	+	+	-	+	+	+
Nasal solutions	+		?	?	?	+	+	+	+	+	-	-	+	+
Otic solutions	-		?	?	?	+	+	+	+	+	-	-	+	+

+ = Generally okay to use; ? = Possible; use only if necessary; - = Generally not to be used

above.) The suppository bases may be complex mixtures of fatty acids to achieve a certain melting range or may be water soluble. These dosage forms may also contain stiffening agents or softening agents.

*Solutions* may contain the active ingredient, vehicle, solvents, preservative, sweetener, flavors, tonicity-adjusting agents, viscosity-adjusting agents, buffers, pH-adjusting agents, antifoaming agents, antioxidants, chelating agents, humectants, and wetting or solubilizing agents.

*Suspensions* may contain the active ingredient, vehicle, preservative, surfactants, sweetener, flavors, viscosity-adjusting agents, buffers, pH-adjusting agents, antifoaming agents, antioxidants, chelating agents, humectants, and wetting agents.

*Emulsions* may contain the active ingredient, vehicle, preservative, sweetener, surfactants or emulsifying agents, buffers, pH-adjusting agents, antifoaming agents, antioxidants, chelating agents, flavors, humectants, viscosity-increasing agents, and sweeteners.

*Injectables (parenterals)* may contain the active drug, vehicle, preservative, solvents, tonicity-adjusting agents, antioxidants, chelating agents, buffers, pH-adjusting agents, antifoaming agents, and wetting or solubilizing agents.

*Ophthalmics* may contain the active drug, vehicle, preservative, solvents, tonicity-adjusting agents, antioxidants, chelating agents, buffers, pH-adjusting agents, and viscosity-increasing agents.

*Nasal solutions* may contain the active drug, vehicle, preservative, solvents, tonicity-adjusting agents, antioxidants, chelating agents, buffers, pH-adjusting agents, antifoaming agents, flavors, humectants, and wetting or solubilizing agents.

*Otic solutions* may contain the active drug, vehicle, preservative, solvents, antioxidants, chelating agents, buffers, pH-adjusting agents, acidifying or alkalizing agents, humectants, and viscosity-increasing agents.

## Compounded Dosage Forms and Potential Commercial Drug Sources

### *Powders and Granules*

Powders and granules generally can be made from commercial dosage forms such as powders, granules, capsules, and tablets. Particle size is important, and pulverization and sieving should be considered to produce uniform and physically stable mixtures. Ointments, creams, gels, suppositories, and inserts are not practical to use in compounding powders and granules. Solutions and suspensions may be considered if they can be evaporated to dryness to obtain the desired quantity of active drug. Emulsions are not practical to use. Parenterals may be used if they are powders for reconstitution or can be evaporated to dryness. Ophthalmics, nasal solutions, and otic solutions are usually not practical.

### *Capsules*

For compounding capsules, both powders and granules may serve as a source, depending on the quantity of powder present and the size of the capsule to be prepared. Granules may require pulverization before blending and encapsulation. Capsules can be used under the same conditions; pulverizing the contents before blending may be necessary. Immediate-release tablets can be pulverized with the other ingredients required to make a capsule. Ointments, creams, gels, suppositories, and inserts are not appropriate as a drug source for capsules, unless a suitable quantity of an oleaginous-based ointment can be placed in a hard-gelatin capsule to prepare a semisolid-filled capsule. Solutions and suspensions can be used only if the solvent systems are evaporated to provide the drug. Parenterals may be appropriate if they are lyophilized powders or powders for reconstitution. Liquid

parenterals would require evaporation, as would ophthalmics, nasal solutions, and otic preparations.

### *Tablets*

Powders, granules, capsules, and tablets can be used if pulverized uniformly and blended to form tablets. Most compounded tablets are of the molded type, and these sources of drug work well if the volume of powder is not too great. Ointments, creams, gels, suppositories, and inserts do not work well for this category. Solutions and suspensions would require evaporation of the solvent, as would parenterals, ophthalmics, nasal solutions, and otic solutions, if aqueous based. Lyophilized powders or powders for reconstitution for injection may work well.

### *Ointments*

Powders, granules, capsules, and tablets may work well if the powders are thoroughly pulverized and the bulk volume of the powders is not too great. If excess powders are used, the ointment may become too thick to be used effectively. Ointments and creams may be appropriate if the phases are compatible (i.e., water and oil phases). Gels may be used in absorption, oil-in-water, and water-soluble-based ointments. Suppositories and inserts may be appropriate if the phases are compatible (i.e., oleaginous). Some inserts are actually tablets and could be considered, as previously discussed.

Solutions and suspensions may be appropriate for absorption, emulsion, and to some degree, water-soluble ointments. Care must be exercised to retain the viscosity of the preparation. Emulsions can be used if they are compatible with the final preparation (i.e., water-in-oil or oil-in-water). Oil-in-water emulsions may be incorporated into oil-in-water emulsions, absorption bases, and water-soluble bases. Water-in-oil emulsions may be incorporated into absorption bases and water-in-oil emulsion bases. Parenterals, ophthalmics, nasal solutions, and otic solutions may be satisfactory depending on compatibility considerations.

### *Creams*

Powders, granules, capsules, and tablets may be satisfactory if the bulk volume of the excipients is not too great. Ointments and creams can be used if consideration is given to the compatibility of the different aqueous and lipophilic phases. Gels can usually be incorporated into oil-in-water creams.

Suppositories and inserts are not good choices as drug sources for creams. Solutions, suspensions, and emulsions may be suitable if the required volume is not excessive. If the volume is too large, evaporation to a suitable volume may be needed. Parenterals, ophthalmics, nasal solutions, and otic solutions may be suitable.

### *Gels*

Powders, granules, capsules, and tablets usually are not suitable to produce clear gels. If a clear gel is not required, then they may be suitable. In an aqueous-based gel, many of the water-soluble excipients will dissolve. Ointments usually are not suitable, except for water-soluble ointments; the oil-in-water emulsion ointments (creams) may be miscible, however. The oleaginous, absorption, and water-in-oil emulsion (creams) type of ointments will not work well. Gels should work satisfactorily if there are no problems with differing pH or gelling agents. Suppositories and inserts generally will not work well. Solutions, suspensions, and oil-in-water emulsions may be satisfactory, depending on the volume to be incorporated. Parenterals, ophthalmics, nasal solutions, and aqueous otic solutions may be used if the volume is not too great.

### *Suppositories and Inserts*

Powders, granules, capsules, and tablets generally can be used as a source of active drug in compounding suppositories and inserts, provided the volume of powder required to obtain the active drug is not excessive. Ointments and creams can sometimes be used in small quantities if the bases are compatible. Gels are not recommended unless the base is a polyethylene glycol or glycerinated gelatin base that would be compatible with gels. Suppositories and inserts can be used as appropriate if the bases are compatible. Solutions and suspensions in very small quantities can often be incorporated into suppository vehicles, but concentrating the active drug by evaporation of the water, either partially or to complete dryness, may be necessary. Emulsions may be suitable if the suppository base will take up the phases and be stable. Parenterals may be used if they are highly concentrated or if they are powders for injection. Ophthalmics, nasal solutions, and aqueous otic solutions can be used only if they are sufficiently concentrated or can be evaporated to meet the required volume limitations. Otic solutions that are oil based may be miscible with many suppository and insert bases.

### *Solutions*

A primary consideration in preparing solutions is whether they are for internal or external use. Powders and granules may or may not be suitable, depending on whether all the excipients are soluble in the vehicle or insoluble excipients can be appropriately removed by filtration. Similarly, capsules and tablets may be suitable when they can be pulverized, placed into solution, and filtered, provided that all the excipients are soluble in the vehicle.

Oleaginous and absorption ointment bases are suitable only for nonaqueous solutions. Generally, emulsion bases are not suitable without a specific solvent blend to dissolve both phases. Active drugs contained in water-soluble ointment bases can be used to prepare aqueous solutions. Gels can often be used to prepare solutions, because the process is actually one of diluting the gel and maintaining a clear solution.

Suppositories and inserts are not suitable for solutions in most circumstances. If nonaqueous solutions are desired, then oleaginous suppository bases may be considered. If aqueous solutions are desired, then polyethylene glycol suppository-based active drugs may work.

Solutions are obviously fine to use to compound other solutions. Suspensions and emulsions can be used only if the solvent system in the compounded formulation will dissolve the suspended or emulsified materials.

Parenterals, ophthalmics, nasal solutions, and otic solutions may be appropriate, depending on the concentration required and solubility. Parenteral powders for reconstitution may be appropriate.

### *Suspensions*

Powders, granules, capsules, and tablets usually work well. The quantity of powders and granules may need to be considered. Ointments and creams generally do not work well unless the solvent system is nonaqueous or a blend of solvents. Gels usually can be used if their base is miscible with the suspension vehicle.

Suppositories and inserts are usually not appropriate unless they are of a water-soluble base (polyethylene glycol or glycerinated gelatin) for an aqueous suspension. Nonaqueous vehicles may be satisfactory for oleaginous suppositories and inserts. Solutions and other suspensions generally are appropriate. Emulsions can be used only if the vehicle in the compounded suspension can dissolve both phases of the emulsion; otherwise, a suspension emulsion would result. Parenterals, ophthalmics, nasal solutions, and aqueous-based otic solutions or suspensions usually can be used with little difficulty.

### *Emulsions*

Powders, granules, capsules, and tablets generally can be used as the drug source for preparing emulsions; however, emulsion suspensions can result because of the excipients present in the commercial dosage form. Ointments and creams may be appropriate, depending on the presence of additional emulsifying agents and the quantity of commercial product that must be incorporated. Gels can easily be used with oil-in-water emulsions, because they will blend into the external phase. Suppositories and inserts are not generally advisable, but using heat to melt the suppositories or inserts and incorporating them into the heated emulsion vehicle, possibly with additional surfactant and with shearing, potentially may result in a suitable emulsion.

Solutions are a good source of active drugs for preparing emulsions. Suspensions may be appropriate, and the final preparation may be an emulsion suspension. Emulsions can often be blended to form a new or even a multiple emulsion. Parenterals, ophthalmics, nasal solutions, and aqueous otic solutions may be appropriate to use. If oil-based otic solutions are used, incorporating an additional emulsifying agent or surfactant for oil-in-water emulsions may be necessary; in water-in-oil emulsions, the oil-based otic solution may be readily miscible.

### *Parenterals*

Nonsterile commercial dosage forms of powders, granules, capsules, and tablets usually should not be used for compounding parenterals. Ointments, creams, gels, suppositories, and inserts are likewise inappropriate. Nonsterile solutions, suspensions, and emulsions should not be used even if sterilized, because of the potential endotoxin load and the presence of inappropriate excipients for parenteral administration. Parenterals can be used. In general, using ophthalmics, nasal solutions, and otic solutions would be inappropriate because of the potential endotoxin load and the presence of inappropriate excipients for parenteral administration.

### *Ophthalmic Preparations*

Powders, granules, capsules, and tablets generally are inappropriate sources of active drugs for ophthalmic products because of the presence of excipients. Ointments may be used only if sterilization and other processes would not adversely affect the preparation of an ophthalmic ointment. Creams are not appropriate. Gels generally are not appropriate except under certain circumstances. Suppositories and inserts are inappropriate. Solutions may be considered if they are appropriate for the specific situation and the requirements for ophthalmics can be met. Suspensions and emulsions are not appropriate because of the particle size and irritant properties of these dosage forms. Parenterals are generally appropriate to use in compounding ophthalmic preparations. Nasal solutions and aqueous otic solutions should be used only if necessary and with due consideration of the excipients they contain.

### *Nasal Preparations*

Powders, granules, capsules, and tablets generally are not suitable because of the presence of insoluble excipients. Ointments are generally not appropriate unless they have water-soluble bases. Creams are not usually suitable. Gels may work satisfactorily. Suppositories and inserts are not suitable. Solutions and suspensions may be considered if the quantity to be used is reasonable. Generally, emulsions should not be used. Parenterals, ophthalmics, and aqueous otic solutions usually can be used satisfactorily.

### *Otic Preparations*

Powders, granules, capsules, and tablets should be used only if the presence of the excipients is considered. The insoluble excipients tend to build up in the ear canal and mix with

cerumen, which can cause problems. Generally, ointments, creams, and gels should be considered as a source of active drug if small quantities can be incorporated into a liquid otic preparation. Suppositories and inserts are not appropriate. Solutions, suspensions, and emulsions may be appropriate sources. Parenterals, ophthalmics, and nasal solutions can often be used; in some cases, all that is needed is to add viscosity-enhancing agents.

## Disposing of Expired Ingredients 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.<sup>1</sup>

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 because of 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. 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.<sup>2,3</sup>

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