

# ASHP Technical Assistance Bulletin on Compounding Nonsterile Products in Pharmacies

## Introduction

Pharmacists are the only health care providers formally trained in the art and science of compounding medications.<sup>1,2</sup> Therefore pharmacists are expected, by the medical community and the public, to possess the knowledge and skills necessary to compound extemporaneous preparations. Pharmacists have a responsibility to provide compounding services for patients with unique drug product needs.

This Technical Assistance Bulletin is intended to assist pharmacists in the extemporaneous compounding of nonsterile drug products for individual patients. Included in this document is information on facilities and equipment, ingredient selection, training, documentation and record keeping, stability and beyond-use dating, packaging and labeling, and limited batch compounding. This document is not intended for manufacturers or licensed repackagers.

## Facilities and Equipment

**Facilities.** It is not necessary that compounding activities be located in a separate facility; however, the compounding area should be located sufficiently away from routine dispensing and counseling functions and high traffic areas. The area should be isolated from potential interruptions, chemical contaminants, and sources of dust and particulate matter. To minimize chemical contaminants, the immediate area and work counter should be free of previously used drugs and chemicals. To minimize dust and particulate matter, cartons and boxes should not be stored or opened in the compounding area. The compounding area should not contain dust-collecting overhangs (e.g., ceiling utility pipes, hanging light fixtures) and ledges (e.g., window-sills). Additionally, at least one sink should be located in or near the compounding area for hand washing before compounding operations. Proper temperature and humidity control within the compounding area or facility is desirable.

Work areas should be well lighted, and work surfaces should be level and clean. The work surface should be smooth, impervious, free of cracks and crevices (preferably seamless), and nonshedding. Surfaces should be cleaned at both the beginning and the end of each distinct compounding operation with an appropriate cleaner or solvent. The entire compounding facility should be cleaned daily or weekly (as needed) but not during the actual process of compounding.

**Equipment.** The equipment needed to compound a drug product depends upon the particular dosage form requested. Although boards of pharmacy publish lists of required equipment and accessories, these lists are not intended to limit the equipment available to pharmacists for compounding.<sup>2</sup> Equipment should be maintained in good working order. Pharmacists are responsible for obtaining the required equipment and accessories and ensuring that equipment is properly maintained and maintenance is documented.

**Weighing Equipment.** In addition to a torsion balance, pharmacists who routinely compound may need to use a top-loading electronic balance that has a capacity of at least 300 g, a

sensitivity of  $\pm 1$  mg (or 0.1 mg), and 1-mg, 100-mg, 1-g, and 100-g weights for checking. Balances should be maintained in areas of low humidity and should be stored on flat, nonvibrating surfaces away from drafts. At least annually, the performance of balances should be checked according to the guidelines found in *Remington's Pharmaceutical Sciences*,<sup>3</sup> *USP XXII NF XVII: The United States Pharmacopeia—The National Formulary (USP–NF)*,<sup>4</sup> or *USP DI Volume III: Approved Drug Products and Legal Requirements*<sup>5</sup> or the instructions of the balance manufacturer. Performance should be documented.

Weights should be stored in rigid, compartmentalized boxes and handled with metal, plastic, or plastic-tipped forceps—not fingers—to avoid scratching or soiling. Since most Class III prescription balances are only accurate to  $\pm 5$  or 10 mg, Class P weights may be used for compounding purposes.<sup>4</sup> The *USP–NF* recommends that the class of weights used be chosen to limit the error to 0.1%. In practical terms this means that Class P weights can be used for weighing quantities greater than 100 mg.

The minimum weighable quantity must be determined for any balance being used for compounding. To avoid errors of 5% or more on a Class III balance with a sensitivity requirement of 6 mg, quantities of less than 120 mg of any substance should not be weighed. Smaller quantities may be weighed on more sensitive balances. If an amount is needed that is less than the minimum weighable quantity determined for a balance, an aliquot method of measurement should be used.

**Measuring Equipment.** The pharmacist should use judgment in selecting measuring equipment. The recommendations given in the *USP–NF* General Information section on volumetric apparatus should be followed. For maximum accuracy in measuring liquids, a pharmacist should select a graduate with a capacity equal to or slightly larger than the volume to be measured. The general rule is to measure no less than 20% of the capacity of a graduate. Calibrated syringes of the appropriate size may be preferred over graduated cylinders for measuring viscous liquids such as glycerin or mineral oil, since these liquids drain slowly and incompletely from graduated cylinders. Viscous liquids may also be weighed if this is more convenient, provided that the appropriate conversions from volume to weight are made by using the specific gravity of the liquid. Thick, opaque liquids should be weighed. For example, if a formulation specifies 1.5 mL of a liquid, it is better to use a 3-mL syringe with appropriate graduations to measure 1.5 mL than to use a 10-mL graduated cylinder, since quantities of less than 2.0 mL cannot be accurately measured in a 10-mL graduate. Also, if an opaque, viscous chemical, such as Coal Tar, USP, must be measured, it is more accurate to weigh the substance than to try to read a meniscus on a graduated cylinder or a fill line on a syringe.

For volumes smaller than 1 mL, micropipettes are recommended, in sizes to cover the range of volumes measured. Two or three variable pipettes can usually cover the range from about 50  $\mu$ L to 1 mL.

Although conical graduates are convenient for mixing solutions, the error in reading the bottom of the meniscus increases as the sides flare toward the top of the graduate.

Therefore, for accurate measurements, cylindrical graduates are preferred. Conical graduates having a capacity of less than 25 mL should not be used in prescription compounding.<sup>4</sup>

**Compounding Equipment.** Pharmacists need at least two types of mortars and pestles—one glass and one Wedgwood or porcelain. The sizes of each will depend on the drug products being compounded. Glass mortars should be used for liquid preparations (solutions and suspensions) and for mixing chemicals that stain or are oily. Generally, glass mortars should be used for antineoplastic agents. Because of their rough surface, Wedgwood mortars are preferred for reducing the size of dry crystals and hard powder particles and for preparing emulsions. Porcelain mortars have a smoother surface than Wedgwood mortars and are ideal for blending powders and pulverizing soft aggregates or crystals. When Wedgwood mortars are used for small amounts of crystals or powders, the inside surface may first be lightly dusted with lactose to fill any crevices in which the crystals or powders might lodge. If the contact surfaces of the mortar and pestle become smooth with use, rubbing them with a small amount of sand or emery powder may adequately roughen them. Over extended use, a pestle and a mortar become shaped to each other's curvature. Thus, to ensure maximum contact between the surface of the head of each pestle and the interior of its corresponding mortar, pestles and mortars should not be interchanged.<sup>3</sup>

The compounding area should be stocked with appropriate supplies. Although supply selection depends on the types of products compounded, all areas should have weighing papers, weighing cups, or both to protect balance pans and spatulas. Glassine weighing papers (as opposed to bond weighing paper) should be used for products such as ointments, creams, and some dry chemicals. Disposable weighing dishes should also be stocked for substances like Coal Tar, USP.

Each compounding area should have stainless steel and plastic spatulas for mixing ointments and creams and handling dry chemicals. The pharmacist should exercise judgment in selecting the size and type of spatula. Small spatula blades (6 inches long or less) are preferred for handling dry chemicals, but larger spatula blades (>6 inches) are preferred for large amounts of ointments or creams and for preparing compactible powder blends for capsules. Plastic spatulas should be used for chemicals that may react with stainless steel blades. A variety of spatulas should be stocked in the compounding area, including 4-, 6-, and 8-inch stainless steel spatulas (one each) and 4- and 6-inch plastic spatulas (one each). Imprinted spatulas should not be used in compounding, since the imprinted ink on the spatula blade may contaminate the product.

The compounding area should contain an ointment slab, pill tile, or parchment ointment pad. Although parchment ointment pads are convenient and reduce cleanup time, parchment paper cannot be used for the preparation of creams because it will absorb water. Therefore, an ointment slab or pill tile is necessary. If suppositories are compounded, appropriate suppository molds, either reusable or disposable, should be available.

Other useful equipment and supplies may include funnels, filter paper, beakers, glass stirring rods, a source of heat (hot plate or microwave oven), a refrigerator, and a

freezer—in some cases, an ultrafreezer capable of maintaining temperatures as low as  $-80^{\circ}\text{C}$ .

## Ingredients

Ideally, only USP or NF chemicals manufactured by FDA-inspected manufacturers should be used for compounding. Although chemicals labeled USP or NF meet *USP-NF* standards for strength, quality, and purity for human drug products, the facilities in which the chemicals were manufactured may not meet FDA Good Manufacturing Practice (GMP) standards. In the event that a needed chemical is not available from an FDA-inspected facility, the pharmacist should, by next best preference, obtain a USP or NF product. If that is not available, the pharmacist should use professional judgment and may have to obtain the highest-grade chemical possible. Chemical grades that may be considered in this situation are ACS grade (meeting or exceeding specifications listed for reagent chemicals by the American Chemical Society) and FCC grade (meeting or exceeding requirements defined by the Food Chemicals Codex). Additional professional judgment is especially necessary in cases of chemical substances that have not been approved for *any* medical use. Particularly in these cases, but also in others as needed, the pharmacist, prescriber, and patient should be well informed of the risks involved.

Selection of ingredients may also depend on the dosage form to be compounded. In most cases, the prescriber specifies a particular dosage form, such as a topical ointment, oral solution or rectal suppository. Sometimes, however, the prescriber relies on the pharmacist to decide on an appropriate form. Irrespective of how the drug order is written, the pharmacist should evaluate the appropriateness of ingredients and the drug delivery system recommended. Factors to consider in selecting the dosage form include (1) physical and chemical characteristics of the active ingredient, (2) possible routes of administration that will produce the desired therapeutic effect (e.g., oral or topical), (3) patient characteristics (e.g., age, level of consciousness, ability to swallow a solid dosage form), (4) specific characteristics of the disease being treated, (5) comfort for the patient, and (6) ease or convenience of administration.

In checking the physical form of each ingredient, the pharmacist should not confuse drug substances that are available in more than one form. For example, coal tar is available as Coal Tar, USP, or Coal Tar Topical Solution, USP; phenol is available as Liquified Phenol, USP, or Phenol, USP; sulfur is available as Precipitated Sulfur, USP, or Sublimed Sulfur, USP. If ingredients are liquids, the pharmacist should consider compounding liquid dosage forms such as solutions, syrups, or elixirs for the final product. If ingredients are crystals or powders and the final dosage form is intended to be a dry dosage form, options such as divided powders (powder papers) or capsules should be considered. If ingredients are both liquids and dry forms, liquid formulations such as solutions, suspensions, elixirs, syrups, and emulsions should be considered.

Care must be exercised when using commercial drug products as a source of active ingredients. For example, extended-release or delayed-release products should not be crushed. Also, since chemicals such as preservatives and excipients in commercial products may affect the overall stability and bioavailability of the compounded product, their presence should not be ignored. Information on preservatives and excipients in specific commercial products can be found in

package inserts and also in the dosage form section of selected product monographs in *USP DI Volume I*.<sup>6</sup>

If an injectable drug product is a possible source of active ingredient, the pharmacist should check the salt form of the injectable product to make sure it is the same salt form ordered. If it is necessary to use a different salt because of physical or chemical compatibility considerations or product availability, the pharmacist should consult with the prescriber. Some injectable products contain active constituents in the form of prodrugs that may not be active when administered by other routes. For example, if an injectable solution is a possible source of active ingredient for an oral product, the pharmacist must consider the stability of the drug in gastric fluids, the first-pass effect, and palatability. Also, if injectable powders for reconstitution are used, expiration dating may have to be quite short.

### Storage

All chemicals and drug products must be stored according to *USP–NF* and manufacturer specifications. Most chemicals and drug products marketed for compounding use are packaged by the manufacturer in tight, light-resistant containers. Chemicals intended for compounding should be purchased in small quantities and stored in the manufacturer's original container, which is labeled with product and storage information. This practice fosters the use of fresh chemicals and ensures that the manufacturer's label remains with the lot of chemical on hand. Certificates of purity for chemical ingredients should be filed for a period of time no less than the state's time requirement for retention of dispensing records.

The manufacturer's label instructions for storage should be followed explicitly to ensure the integrity of chemicals and drug products and to protect employees. Most chemicals and commercial drug products may be stored at controlled room temperature, between 15 and 30 °C (59 and 86 °F); however, the pharmacist should always check the manufacturer's label for any special storage requirements. Storage information provided for specific commercial drug products in *USP DI Volume I* and on product labels follows the definitions for storage temperatures found in the General Notices and Requirements section of *USP–NF*. An acceptable refrigerator maintains temperatures between 2 and 8 °C (36 and 46 °F); an acceptable freezer maintains temperatures between –20 and –10°C (–4 to +14 °F)

To protect pharmacy employees and property, hazardous products such as acetone and flexible collodion must be stored appropriately. Safety storage cabinets in various sizes are available from laboratory suppliers.

### Personnel

Compounding personnel include pharmacists and supportive personnel engaged in any aspect of the compounding procedures.

**Training.** The pharmacist—who is responsible for ensuring that the best technical knowledge and skill, most careful and accurate procedures, and prudent professional judgment are consistently applied in the compounding of pharmaceuticals—must supervise all compounding activities and ensure that supportive personnel are adequately trained to perform assigned functions. Both pharmacists and the compounding personnel they supervise should participate in programs designed to enhance

and maintain competence in compounding. Training programs should include instruction in the following areas:

- Proper use of compounding equipment such as balances and measuring devices—including guidelines for selecting proper measuring devices, limitations of weighing equipment and measuring apparatus, and the importance of accuracy in measuring.
- Pharmaceutical techniques needed for preparing compounded dosage forms (e.g., levigation, trituration, methods to increase dissolution, geometric dilution).
- Properties of dosage forms (see *Pharmaceutical Dosage Forms in USP–NF*) to be compounded and related factors such as stability, storage considerations, and handling procedures.
- Literature in which information on stability, solubility, and related material can be found (see suggested references at the end of this document).
- Handling of nonhazardous and hazardous materials in the work area, including protective measures for avoiding exposure, emergency procedures to follow in the event of exposure, and the location of Material Safety Data Sheets (MSDSs) in the facility.<sup>7–10</sup>
- Use and interpretation of chemical and pharmaceutical symbols and abbreviations in medication orders and in product formulation directions.
- Pharmaceutical calculations.

Procedures should be established to verify the ability of staff to meet established competencies. These procedures may include observation, written tests, or quality control testing of finished products.

**Attire.** Personnel engaged in compounding should wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face hand, and arm coverings, should be worn as necessary to preclude contamination of products and to protect workers.

Generally, a clean laboratory jacket is considered appropriate attire for most personnel performing nonsterile compounding activities. Personnel involved in compounding hazardous materials should wear safety goggles, gloves, a mask or respirator, double gowns, and foot covers as required, depending on the substance being handled. To avoid microbial contamination of compounded drug products, written policies should be established that address appropriate precautions to be observed if an employee has an open lesion or an illness. Depending on the situation, an affected employee may be required to wear special protective apparel, such as a mask or gloves, or may be directed to avoid all contact with compounding procedures.

### Reference Materials

Pharmacists and supportive personnel must have ready access to reference materials on all aspects of compounding (see suggested references at the end of this document). Earlier editions of some references, such as *Remington's Pharmaceutical Sciences*, provide more comprehensive compounding information than do the later editions. Information on compounding extemporaneous dosage forms from commercially available products can sometimes be obtained from the product's FDA-approved labeling (package insert), the manufacturer, a local pharmacy college, or a drug information center. It is essential

that the stability and proper storage conditions for extemporaneous products be thoroughly researched. Therefore, the availability of adequate references and appropriate training in the use of the references is important.

## Documentation and Record Keeping

Each step of the compounding process should be documented. Pharmacists should maintain at least four sets of records in the compounding area: (1) compounding formulas and procedures, (2) a log of all compounded items, including batch records and sample batch labels (see section on packaging and labeling), (3) equipment-maintenance records, including documentation of checks of balances, refrigerators, and freezers, and (4) a record of ingredients purchased, including certificates of purity for chemicals (see section on ingredient selection) and MSDSs.

Compounding procedures should be documented in enough detail that preparations can be replicated and the history of each ingredient can be traced. Documentation should include a record of who prepared the product (if the compounder is not a pharmacist, the supervising pharmacist should also sign the compounding record); all names, lot numbers, and quantities of ingredients used; the order of mixing, including any interim procedures used (such as preparing a solution and using an aliquot); the assigned beyond-use date; and any special storage requirements (see section on stability and expiration dating). Compounding formulas and procedures should be written in a typeface that can be read easily. If formulas originate from published articles, copies of the articles should be attached to or filed with the written procedures.

Equipment maintenance and calibrations should be documented and the record maintained in an equipment-maintenance record file. Refrigerator and freezer thermometers should be checked and documented routinely, as should alarm systems indicating that temperatures are outside of acceptable limits.

Follow-up contact with patients who have received extemporaneously compounded products is recommended to ascertain that the product is physically stable and that no adverse effects have occurred from use of the product. Documentation of the contact and the findings is recommended.

## Stability, Expiration, and Beyond-Use Dating

The *USP–NF*<sup>4</sup> defines stability as the extent to which a dosage form retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its preparation. The *USP–NF* lists the following five types of stability:

- Chemical
- Physical
- Microbiological
- Therapeutic
- Toxicological

Factors affecting stability include the properties of each ingredient, whether therapeutically active or inactive. Environmental factors such as temperature, radiation, light, humidity, and air can also affect stability. Similarly, such factors as particle size, pH, the properties of water and other solvents employed, the nature of the container, and the presence of other

substances resulting from contamination or from the intentional mixing of products can influence stability.<sup>4</sup>

Since compounded drug products are intended for consumption immediately or storage for a very limited time, stability evaluation and expiration dating are different for these products than for manufactured drug products. According to criteria for assigning dating in the *USP–NF*<sup>4</sup> General Notices and Requirements section and the Code of Federal Regulations,<sup>11</sup> the pharmacist labeling extemporaneously compounded drug products should be concerned with the beyond-use date as used by *USP–NF* or the expiration date as used by the Code of Federal Regulations. For uniformity, the term *beyond-use date* will be used in the remainder of this bulletin. The beyond-use date is defined as that date after which a dispensed product should no longer be used by a patient.

Determination of the period during which a compounded product may be usable after dispensing should be based on available stability information and reasonable patient needs with respect to the intended drug therapy. When a commercial drug product is used as a source of active ingredient, its expiration date can often be used as a factor in determining a beyond-use date. For stability or expiration information on commercial drug products, the pharmacist can refer to *USP DI Volume I*.<sup>6</sup> If no information is available, the manufacturer should be contacted. When the active ingredient is a USP or NF product, the pharmacist may be able to use the expiration dating of similar commercial products for guidance in assigning a beyond-use date. In addition, the pharmacist can often refer to published literature to obtain stability data on the same active ingredient under varying conditions and in different formulations.<sup>12</sup>

The pharmacist must assess the potential for instability that may result from the new environment for the active ingredients—from the combination of ingredients and the packaging materials. According to *USP–NF*,<sup>4</sup> hydrolysis, oxidation-reduction, and photolysis are the most common chemical reactions that cause instability. When the possibility of such reactions exists, the pharmacist should seek additional stability data or consider other approaches. These could, in extreme cases, include the preparation and dispensing of more than one compounded drug product or the use of alternative methods of dosing. For some drugs, the latter methods might include, for example, crushing a tablet or emptying the contents of a hard gelatin capsule into an appropriate food substance at each dosing time.

In assigning a beyond-use date for compounded drug products, the pharmacist should use all available stability information, plus education and experience in deciding how factors affecting product stability should be weighted. In the absence of stability data to the contrary or any indication of a stability problem, the following general criteria for assigning maximum beyond-use dates are recommended. It must be emphasized that these are *general* criteria. Professional judgment as discussed elsewhere in this section must be used in deciding when these general criteria may not be appropriate.

- When a manufactured final-dosage-form product is used as a source of active ingredient, use no more than 25% of the manufacturer's remaining expiration dating or six months, whichever is less;
- When a USP or NF chemical not from a manufactured final-dosage-form product is used, use no more than six months;

- In other cases, use the intended period of therapy or no more than 30 days, whichever is less.

All compounded products should be observed for signs of instability. Observations should be performed during preparation of the drug product and any storage period that may occur before the compounded drug product is dispensed. A list of observable indications of instability for solid, liquid, and semisolid dosage forms appears in *USP–NF*.

## Packaging and Labeling

The packaging of extemporaneously compounded products for ambulatory patients should comply with regulations pertaining to the Poison Prevention Packaging Act of 1970. These regulations can be found in *USP–NF*.<sup>4</sup>

Containers for compounded products should be appropriate for the dosage form compounded. For example, to minimize administration errors, oral liquids should never be packaged in syringes intended to be used for injection.

The drug product container should not interact physically or chemically with the product so as to alter the strength, quality, or purity of the compounded product. Glass and plastic are commonly used in containers for compounded products. To ensure container inertness, visibility, strength, rigidity, moisture protection, ease of reclosure, and economy of packaging, glass containers have been the most widely used for compounded products.<sup>3</sup> Amber glass and some plastic containers may be used to protect light-sensitive products from degradation; however, glass that transmits ultraviolet or violet light rays (this includes green, blue, and clear [“flint”] glass) should not be used to protect light-sensitive products.

The use of plastic containers for compounded products has increased because plastic is less expensive and lighter in weight than glass. Since compounded products are intended for immediate use, most capsules, ointments, and creams should be stable in high-density plastic vials or ointment jars. Only plastic containers meeting *USP–NF* standards should be used.<sup>4</sup> Reclosable plastic bags may be acceptable for selected divided powders that are intended to be used within a short period of time.

Each compounded product should be appropriately labeled according to state and federal regulations. Labels should include the generic or chemical name of active ingredients, strength or quantity, pharmacy lot number, beyond-use date, and any special storage requirements. If a commercial product has been used as a source of drug, the generic name of the product should be used on the label. The trade name should not be used because, once the commercial drug product has been altered, it no longer exists as the approved commercial product. Listing the names and quantities of inactive ingredients on labels is also encouraged. The coining of short names for convenience (e.g., “Johnson’s solution”) is strongly discouraged; these names provide no assistance to others who may need to identify ingredients (e.g., in emergency circumstances).

Capsules should be labeled with the quantity (micrograms or milligrams) of active ingredient(s) per capsule. Oral liquids should be labeled with the strength or concentration per dose (e.g., 125 mg/5 mL or 10 meq/15 mL). If the quantity of an active ingredient is a whole number, the number should not be typed with a decimal point followed by a zero. For example, the strength of a capsule containing 25 mg of active ingredient should be labeled as 25 mg and not 25.0 mg. In

cases where the dosage strength is less than a whole number, a zero should precede the decimal point (e.g., 0.25 µg).<sup>3</sup>

In expressing salt forms of chemicals on a label, it is permissible to use atomic abbreviations. For example, HCl may be used for hydrochloride, HBr for hydrobromide, Na for sodium, and K for potassium.

Vehicles should also be stated on labels, especially if similar products are prepared with different vehicles. For example, if a pharmacist prepares two potassium syrups, one using Syrup, USP, as the vehicle and one using a sugar-free syrup as the vehicle, the name of the vehicle should be included on the labels.

Liquids and semisolid concentrations may be expressed in terms of percentages. When the term “percent” or the symbol “%” is used without qualification for solids and semisolids, percent refers to weight in weight; for solutions or suspensions, percent refers to weight in volume; for solutions of liquids in liquids, percent refers to volume in volume.<sup>4</sup>

Labels for compounded products that are prepared in batches should include a pharmacy-assigned lot number. Assignment of a pharmacy lot number must enable the history of the compounded product to be traced, including the person compounding the product and the product’s formula, ingredients, and procedures. Being able to trace the history of a batch is essential in cases of a drug product recall or withdrawal.

In the preparation of labels for batches of compounded products, all extra labels should be destroyed, since pharmacy lot numbers change with each batch. If computers, memory typewriters, or label machines are used to print batch labels, care must be taken to ensure that the memory and printing mechanism have been cleared and the correct information is programmed before any additional labels are made. It is a good practice to run a blank label between each batch of labels to ensure that the memory has been erased or cleared. To document the information printed on each set of labels, a sample label printed for the batch should be attached to the compounded-product log. If labels are sequentially prepared for different drug products, procedures should exist to minimize the risk of mislabeling the compounded products. These procedures should ensure, for example, that labels for one drug product are physically well separated from labels for any other drug product.

Auxiliary labels are convenient for conveying special storage or use information. Auxiliary labels should be attached conspicuously to containers, if possible. If the container is too small for both a general label and an auxiliary label, special storage and use instructions should appear on the label in a format that will emphasize the instructions.

## Limited Batch Compounding

The purpose of extemporaneously compounding products is to provide individualized drug therapy for a particular patient. When a pharmacist is repeatedly asked to prepare identical compounded products, it may be reasonable and more efficient for the pharmacist to prepare small batches of the compounded product.

Batch sizes should be consistent with the volume of drug orders or prescriptions the pharmacist receives for the compounded product and the stability of the compounded product. The pharmacist should use judgment in deciding reasonable batch sizes. Product assays should be performed by a chemical analysis laboratory on a regular basis to ensure product

consistency among various lots, product uniformity, and stability. Analyses should be repeated every time an ingredient (active or inert) or procedure is changed. Documentation of assay findings should be filed for a period no less than the state's time requirement for the retention of dispensing records.

## General Compounding Considerations

To provide the patient with the most stable drug product, the pharmacist should take the following steps upon receiving a prescription order that requires compounding.

First, the pharmacist should determine if a similar commercial product is available. A pharmacist can refer to various reference texts to check the availability of identical or similar products. Package inserts from commercially available products also contain information on inactive ingredients that can be compared with the requested formulation. If there is a commercially manufactured identical product, the local availability of the product should be determined.

When a similar product is commercially available, the pharmacist should determine which ingredients are different from the requested formulation to decide whether or not the commercial product can be used. At this stage, the pharmacist should seek answers to the following questions:

- Are all of the ingredients appropriate for the condition being treated?
- Are the concentrations of the ingredients in the drug order reasonable?
- Are the physical, chemical, and therapeutic properties of the individual ingredients consistent with the expected properties of the ordered drug product?

If the answers to these questions are positive, the pharmacist should consult the prescriber about the possibility of dispensing the commercial product. (In some states, pharmacists may not be required to obtain permission from the prescriber to dispense a commercial product if the formulation is identical to the drug order.) Dispensing a commercial product is preferable to extemporaneously compounding a drug product because commercial products carry the manufacturer's guarantee of labeled potency and stability.

If there is not a commercial product available with the same or similar formulation, the pharmacist should consider asking the prescriber the following questions:

- What is the purpose of the order? There may be another way to achieve the purpose without compounding a product.
- Where did the formula originate (article, meeting, colleague)?
- How will the drug product be used?
- Does the patient have other conditions that must be considered?
- For how long will the drug product be used?

If possible, the pharmacist should obtain a copy of the original formula to determine the extent to which the formulation has been tested for stability. When documentation is not available, the pharmacist should review the ingredients for appropriateness and reasonable concentrations.

For drug products that must be compounded, the pharmacist should closely observe the compounded drug product

for any signs of instability. Such observations should be performed during preparation of the drug product and during any storage period that may occur before the compounded drug product is dispensed.

If specific packaging information is not available, a light-resistant, tight container, such as an amber vial or bottle, should be used to maximize stability (see section on packaging and labeling).

The pharmacist should label the compounded drug product, including an appropriate beyond-use date and storage instructions for the patient.

## Specific Compounding Considerations

Accepted, proven compounding procedures for products including solutions, suspensions, creams, ointments, capsules, suppositories, troches, emulsions, and powders may be found in reference sources or the pharmacy literature. For additional information, pharmacists should check references cited in this document or consult colleagues or colleges of pharmacy with known expertise in compounding.

## Glossary

*For the purposes of this document, the following terms are used with the meanings shown.*

**Active Ingredient:** Any chemical that is intended to furnish pharmacologic activity in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body of man or other animals.<sup>4</sup>

**Batch:** Multiple containers of a drug product or other material with uniform character and quality, within specified limits, that are prepared in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.

**Cold:** Any temperature not exceeding 8 °C (46 °F).<sup>4</sup>

**Commercially Available Product:** Any drug product manufactured by a producer registered with the Department of Health and Human Services as a pharmaceutical manufacturer.

**Compounding:** The mixing of substances to prepare a drug product.

**Container:** A device that holds a drug product and is or may be in direct contact with the product.<sup>3</sup>

**Cool:** Any temperature between 8 and 15 °C (46 and 59 °F).<sup>4</sup>

**Drug Product:** A finished dosage form that contains an active drug ingredient usually, but not necessarily (in the case of a placebo), in combination with inactive ingredients.<sup>4</sup>

**Extemporaneous:** Impromptu; prepared without a standard formula from an official compendium; prepared as required for a specific patient.

**Inactive Ingredient:** Any chemical other than the active ingredients in a drug product.<sup>4</sup>

**Manufacturer:** Anyone registered with the Department of Health and Human Services as a producer of drug products.<sup>14</sup>

**Sensitivity Requirements:** The maximal load that will cause one subdivision of change on the index plate in the position of rest of the indicator of the balance.<sup>4</sup>

**Stability:** The chemical and physical integrity of a drug product over time.<sup>4</sup>

**Trituration:** The reducing of substances to fine particles by rubbing them in a mortar with a pestle.<sup>3</sup>

**Warm:** Any temperature between 30 and 40 °C (86 and 104 °F).<sup>4</sup>

## Suggested References

### Product Availability

*American Drug Index*

*Drug Facts & Comparisons*

*Physicians' Desk Reference*

*The Extra Pharmacopoeia (Martindale)*

*CHEMSOURCES*

*AHFS Drug Information*

### Compounding Techniques

Compounding Companion PC-Based Software

King's *Dispensing of Medications*

*Remington's Pharmaceutical Sciences*

Contemporary Compounding column in *U.S. Pharmacist*

### Pharmaceutical Calculations

Stoklosa and Ansel's *Pharmaceutical Calculations*

Math—Use It or Lose It column in *Hospital Pharmacy*

Calculations in Pharmacy column in *U.S. Pharmacist*

### Drug Stability and Compatibility

*American Journal of Hospital Pharmacy*

ASHP's *Handbook on Extemporaneous Formulations*

ASHP's *Handbook on Injectable Drugs*

*International Pharmaceutical Abstracts*

*Journal of the Parenteral Drug Association* (now *Journal of Pharmaceutical Science and Technology*)

Canadian Society of Hospital Pharmacists *Extemporaneous Oral Liquid Dosage Preparations*

*Pediatric Drug Formulations*

*Physicians' Desk Reference*

Contemporary Compounding column in *U.S. Pharmacist*

*AHFS Drug Information*

*The Merck Index*

## References

1. Pancorbo SA, Campagna KD, Devenport JK, et al. Task force report of competency statements for pharmacy practice. *Am J Pharm Educ.* 1987; 51:196–206.

2. Allen LV Jr. Establishing and marketing your extemporaneous compounding service. *US Pharm.* 1990; 15(Dec):74–7.
3. Remington's pharmaceutical sciences. 18th ed. Gennaro AR, ed. Easton, PA: Mack Publishing; 1990; 1630–1, 1658, 1660.
4. The United States Pharmacopeia, 22nd rev., and The National Formulary, 17th ed. Rockville, MD: The United States Pharmacopeial Convention; 1989.
5. USP DI Volume III: Approved drug products and legal requirements. 14th ed. Rockville, MD: The United States Pharmacopeial Convention; 1994.
6. USP DI Volume I: Drug information for the health care professional. 14th ed. Rockville, MD: The United States Pharmacopeial Convention; 1994.
7. 29 §C.F.R. 1910.1200(1990).
8. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990; 47:1033–49.
9. Feinberg JL. Complying with OSHA's Hazard Communication Standard. *Consult Pharm.* 1991; 6:444, 446, 448.
10. Myers CE. Applicability of OSHA Hazard Communication Standard to drug products. *Am J Hosp Pharm.* 1990; 47:1960–1.
11. 21 C.F.R. §211.137.
12. Connors KA, Amidon GL, Stella VJ. Chemical stability of pharmaceuticals: a handbook for pharmacists. 2nd ed. New York: Wiley; 1986.
13. American Society of Hospital Pharmacists. ASHP guidelines on preventing medication errors in hospitals. *Am J Hosp Pharm.* 1993; 50:305–14.
14. Fitzgerald WL Jr. The legal authority to compound in pharmacy practice. *Tenn Pharm.* 1990; 26(Mar):21–2.

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