

Content Uniformity Test—Content uniformity testing on the test and reference product lots should be performed as described in *USP*.

WAIVER REQUIREMENTS

Waiver of in vivo bioequivalence study requirements for the 200-mg strength of the generic tablet product may be granted pursuant to 21 CFR 320.22(d)(2) provided the following conditions are met:

1. The 200-mg tablet is proportionally similar in both active and inactive ingredients to the firm's 600-mg tablet which has been demonstrated to be bioequivalent to the reference product in vivo.
2. The 200-mg tablet of the generic product meets dissolution test requirements.■

Add the following:

■(1161) PHARMACY COMPOUNDING PRACTICES

Compounding is an integral part of pharmacy practice and is essential to the provision of health care. The purpose of this chapter and applicable monographs on formulation is to provide general information to enhance the pharmacist's ability in the pharmacy to extemporaneously compound preparations that are of acceptable strength, quality, and purity. Compounding can be as simple as adding a liquid to a manufactured drug powder, which has been formulated to produce a solution or a suspension, and as complex as the extemporaneous creation of a preparation from unformulated active ingredients and added substances.

Compounding is different from manufacturing, which is guided by GMPs (see *Good Manufacturing Practices* (1077)). Some of the characteristics or criteria that differentiate compounding from manufacturing include the existence of specific practitioner-patient relationships; the quantity of medication prepared in anticipation of receiving a prescription or a prescription order; and the conditions of sale, which are limited to specific prescription orders.

The pharmacist's responsibilities in compounding drug preparations are to dispense the finished preparation in accordance with a prescription or a prescriber's order or intent and to dispense those preparations in compliance with requirements established by Boards of Pharmacy and other regulatory agencies. Pharmacists must be familiar with statutes and regulations that govern compounding because these requirements vary from state to state.

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

COMPOUNDING ENVIRONMENT

Facilities

Pharmacy areas designated for compounding should have adequate space for the orderly placement of equipment and materials to prevent mixups between ingredients, containers, labels, in-process materials, and finished preparations. The compounding area should also be designed, arranged, used, and maintained to prevent adventitious cross-contamination. Areas used for sterile preparations should be separate and distinct from the non-sterile compounding area (see *Sterile Drug Products for Home*

Use (1206)). The entire compounding area should be well lighted. Heating, ventilation, and air conditioning systems should be controlled to avoid decomposition of chemicals (see *Storage Temperature under Preservation, Packaging, Storage, and Labeling in the General Notices* and the manufacturers' labeled storage conditions). Storage areas should provide an environment suitably controlled to ensure quality and stability of bulk chemicals and finished preparations.

Potable water should be supplied for hand and equipment washing. This water should meet the standards prescribed in the Environmental Protection Agency's National Primary Drinking Water Regulations (40 CFR Part 141). *Purified Water* must be used for compounding nonsterile drug preparations when formulations indicate the inclusion of water. *Purified Water* must also be used for rinsing equipment and utensils. In those cases when a water is used to prepare a sterile preparation, *Water for Injection*, *Sterile Water for Injection*, or *Bacteriostatic Water for Injection* must be used (see *Water for Pharmaceutical Purposes* (1231) and *Sterile Drug Products for Home Use* (1206)).

Compounding areas should be maintained in a clean and sanitary condition. Adequate washing facilities should be provided, including hot and cold water, soap or detergent, and air driers or single-service towels. Sewage, trash, and other refuse in the compounding area should be disposed of in a safe, sanitary, and timely manner. Equipment should be thoroughly cleaned promptly after use to avoid cross-contamination of ingredients and preparations. Special precautions should be taken to clean equipment and compounding areas meticulously after compounding preparations that contain allergenic ingredients (e.g., sulfonamides or penicillins).

Equipment

Equipment should be of appropriate design and size for compounding and suitable for the intended uses. The types and sizes of equipment will depend on the dosage forms and the quantities compounded (see *Weights and Balances* (41), *Prescription Balances and Volumetric Apparatus* (1176), and equipment manufacturers' instruction manuals). All equipment should be constructed so that surfaces that contact pharmaceutical components, in-process materials, or finished preparations are not reactive, additive, or adsorptive to avoid altering the safety, identity, strength, quality, or purity of the preparation. Equipment and accessories used in compounding should be inspected, maintained, and cleaned at appropriate intervals to ensure the accuracy and reliability of their performance.

STABILITY OF COMPOUNDED PREPARATIONS

Stability is defined as the extent to which a preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding. See the table *Criteria for Acceptable Levels of Stability* under *Stability Considerations in Dispensing Practices* (1191).

The compounding pharmacist must avoid formulation ingredients and processing conditions that would result in a potentially toxic or ineffective preparation. The pharmacist's knowledge of the chemical reactions by which drugs degrade provides a means for establishing conditions under which the rate of degradation is minimized. The factors that influence the stability of preparations compounded by pharmacists are generally the same as those for manufactured drug products (see *Factors Affecting Product Stability and Responsibility of the Pharmacist* under *Stability Considerations in Dispensing Practice* (1191)).

Primary Packaging

Compounded preparations should be packaged in containers meeting USP standards (see *Containers under Preservation, Packaging, Storage, and Labeling in the General Notices, Containers* (661), and *Containers—Permeation* (671)). The container used depends on the physical and chemical properties of the compounded preparation. Container-drug interaction should be considered with substances such as phenolic compounds and sorptive materials (e.g., polypeptides and proteins).

Sterility

Assurance of sterility in a compounded sterile preparation is mandatory. Compounding and packaging of sterile drugs, such as ophthalmic solutions, will require strict adherence to guidelines presented in the general information chapter *Sterile Drug Products for Home Use* (1206) and in the manufacturers' labeling instructions.

Stability Criteria and Beyond-use Dating

The beyond-use date is the date after which a compounded preparation should not be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

Pharmacists should consult and apply drug-specific and general stability documentation and literature when available, and should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy when assigning a beyond-use date (see *Expiration Date* under *Labeling* in the *General Notices*). Beyond-use dates should be assigned conservatively. When using manufactured solid dosage forms to prepare a solution or aqueous suspension, the pharmacist should also consider factors such as hydrolysis and the freeze-thaw property of the final preparation before assigning a beyond-use date. In assigning a beyond-use date for a compounded drug preparation, in addition to using all available stability information, the pharmacist should also use his or her pharmaceutical education and experience.

When a manufactured product is used as the source of active ingredient for a nonsterile compounded preparation, the product expiration date cannot be used to extrapolate directly a beyond-use date for the compounded preparation. However, a pharmacist may refer to the *USP DI* or to the manufacturer for stability information. The pharmacist may also refer to applicable publications to obtain stability, compatibility, and degradation information on ingredients. All stability data must be carefully interpreted in relation to the actual compounded formulation.

At all steps in the compounding, dispensing, and storage process, the pharmacist should observe the compounded drug preparation for signs of instability. For more specific details of some of the common physical signs of deterioration, see *Observing Products for Evidence of Instability under Stability Considerations in Dispensing Practice* (1191). However, excessive chemical degradation and other drug concentration loss due to reactions may be invisible more often than they are visible.

In the absence of stability information that is applicable to a specific drug and preparation, the following maximum beyond-use dates are recommended for nonsterile compounded drug preparations* that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated.

For nonaqueous liquids and solid formulations (Where the manufactured drug product is the source of active ingredient)—The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier.

A USP or NF substance is the source of active ingredient—The beyond-use date is not later than 6 months.

For water-containing formulations (prepared from ingredients in solid form)—The beyond-use date is not later than 14 days when stored at cold temperatures.

For all other formulations—The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier. These beyond-use date limits may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation (i.e., the same drug concentration range, pH, excipients, vehicle, water content, etc.). See also the beyond-use dating information in the *Labeling* section under *Single-unit Containers and Unit-dose Containers for Nonsterile Solid and Liquid Dosage Forms* in the general test chapter *Containers* (661).

* For guidelines applicable to dating sterile compounded preparations, see *Storage and Expiration Dating* under *Sterile Drug Products for Home Use* (1206). "Copied with permission from *Supplement 5 to USP-NF*

BEYOND-USE LABELING

Federal law requires that manufactured drug products be labeled with an expiration date. Some state laws may require a beyond-use date. The label on the container or package of an official compounded preparation must bear a beyond-use date. Good pharmacy practice dictates beyond-use labeling for all compounded preparations.

INGREDIENT SELECTION AND CALCULATIONS

Ingredients

Active Ingredient(s)—An *active ingredient* in this *Pharmacopeia* means an official substance. The term active ingredients usually refers to chemicals, substances, or other components of articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in humans or other animals or for use as nutritional supplements.

Added Substances—*Added substances* in this *Pharmacopeia* mean ingredients that are necessary to prepare the dosage form but are not intended or expected to cause a human pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded dosage form. The term added substances is usually used synonymously with the terms *inactive ingredients*, *excipients*, and *pharmaceutical ingredients*.

Sources

A USP or an NF grade drug substance is the preferred source of ingredients for compounding all drug preparations. If that is not available, or when food, cosmetics, or other substances are used, then 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 drug substance used in compounding that is not official in the USP or NF, the pharmacist should establish purity and safety by reasonable means, which may include lot analysis, manufacturer reputation, or reliability of source.

A manufactured drug product may be a source of active ingredient. Only manufactured drugs from containers labeled with a batch control number and a future expiration date are acceptable as a potential source of active ingredients. When compounding with manufactured drug products, the pharmacist must consider all ingredients present in the drug product relative to the intended use of the compounded preparation.

Calculations

The pharmacist must be able to calculate the amount or concentration of drug substances in each unit or dosage portion of a compounded preparation at the time it is dispensed. Pharmacists must perform calculations and measurements to obtain, theoretically, 100% of the amount of each ingredient in compounded formulations. Calculations must account for the active ingredient, or active moiety, and water content of drug substances, which includes that in the chemical formulas of hydrates. Official drug substances and added substances must meet the requirements under *Loss on Drying* (731), which must be included in the calculations of amounts and concentrations of ingredients. The pharmacist should consider the effect of ambient humidity on the gain or loss of water from drugs and added substances in containers subjected to intermittent opening over prolonged storage. Each container should be opened for the shortest duration necessary and then closed tightly immediately after use.

The nature of the drug substance that is to be weighed and used in compounding a prescription must be known exactly. If the substance is a hydrate, its anhydrous equivalent weight may need to be calculated. On the other hand, if there is adsorbed moisture present that is either specified on a certificate of analysis or that is determined in the pharmacy immediately before the drug substance is used by the procedure under *Loss on Drying* (731), this information must be used when calculating the amount of drug substance that is to be weighed in order to determine the exact amount of anhydrous drug substance required.

There are cases in which the required amount of a dose is specified in terms of a cation [e.g., Li(+), netilmicin (n+)], an anion [e.g., F(-)], or a molecule (e.g., theophylline in aminophylline). In these instances, the drug substance weighed is a salt or complex, a portion of which represents the pharmacologically active moiety. Thus, the exact amount of such substances weighed must be calculated on the basis of the required quantity of the pharmacological moiety.

The following formula may be used to calculate the exact theoretical weight of an ingredient in a compounded preparation:

$$W = \frac{ab}{de}$$

in which *W* is the actual weighed amount; *a* is the prescribed or pharmacist-determined weight of the active or functional moiety of drug or added substance; *b* is the chemical formula weight of the ingredient, including waters of hydration for hydrous ingredients; *d* is the fraction of dry weight when the percent by weight of adsorbed moisture content is known from the loss on drying procedure (see *Loss on Drying* (731)); and *e* is the formula weight of the active or functional moiety of a drug or added substance that is provided in the formula weight of the weighed ingredient.

Example 1: Triturate Morphine Sulfate USP and Lactose NF to obtain 10 g in which there are 30 mg of Morphine Sulfate USP for each 200 mg of the morphine-lactose mixture. [NOTE—Clinical dosages of morphine mean Morphine Sulfate USP, which is the pentahydrate.]

Equation Factor	Numerical Value
<i>W</i>	weight, in g, of Morphine Sulfate USP
<i>a</i>	1.5 g of morphine sulfate pentahydrate in the prescription
<i>b</i>	759 g/mole
<i>d</i>	1.0
<i>e</i>	759 g/mole

$$W = \frac{1.5 \text{ g (759 g/mole)}}{1.0 \text{ (759 g/mole)}} = 1.5 \text{ g.}$$

Example 2: Accurately weigh an amount of Aminophylline USP to obtain 250 mg of anhydrous theophylline. [NOTE—The powdered aminophylline dihydrate weighed contains 0.4% w/w adsorbed moisture as stated in the Certificate of Analysis.]

Equation Factor	Numerical Value
<i>W</i>	weight, in mg, of Aminophylline USP (dihydrate)
<i>a</i>	250 mg of theophylline
<i>b</i>	456 g/mole
<i>d</i>	0.996
<i>e</i>	360 g/mole

$$W = \frac{250 \text{ mg (456 g/mole)}}{0.996 \text{ (360 g/mole)}} = 318 \text{ mg.}$$

Example 3: Accurately weigh an amount of Lithium Citrate USP (containing 2.5% moisture as stated in the Certificate of Analysis) to obtain 200 mEq of lithium (Li+). [NOTE—One mEq of Li+ is equivalent to 0.00694 g of Li+.]

Equation Factor	Numerical Value
<i>W</i>	weight, in g, of Lithium Citrate USP (tetrahydrate)
<i>a</i>	200 mEq of Li+ or 1.39 g of Li+
<i>b</i>	282 g/mole
<i>d</i>	0.975
<i>e</i>	3 × 6.94 g/mole or 20.8 g/mole

$$W = \frac{1.39 \text{ g (282 g/mole)}}{0.975 \text{ (20.8 g/mole)}} = 19.3 \text{ g.}$$

Example 4: Accurately weigh an amount of Netilmicin Sulfate USP, equivalent to 2.5 g of netilmicin. [NOTE—Using the pro-

cedure under *Loss on Drying* (731), the Netilmicin Sulfate USP that was weighed lost 12% of its weight.]

Equation Factor	Numerical Value
<i>W</i>	weight, in g, of Netilmicin Sulfate USP
<i>a</i>	2.5 g
<i>b</i>	1442 g/mole
<i>d</i>	0.88
<i>e</i>	951 g/mole

$$W = \frac{2.5 \text{ g (1442 g/mole)}}{0.88 \text{ (951 g/mole)}} = 4.31 \text{ g.}$$

CHECKLIST FOR ACCEPTABLE STRENGTH, QUALITY, AND PURITY

The following questions should be considered carefully before compounding:

- (1) Have the physical and chemical properties and medicinal and pharmaceutical uses of the drug substances been reviewed?
- (2) Is the quantity and quality of each active ingredient identifiable?
- (3) Will the active ingredients be effectively absorbed, locally or systemically according to the prescribed purpose, from the preparation and route of administration?
- (4) Are there added substances (confirmed or potentially present) from manufactured products that may be expected to cause an allergic reaction, irritation, toxicity, or undesirable organoleptic response from the patient? Are there added substances (confirmed or potentially present) that may be unfavorable (e.g., unsuitable pH or inadequate solubility)?
- (5) Are the active ingredients stable in the normal gastric pH range and not subject to extensive hepatic first-pass metabolism when oral administration is prescribed?
- (6) Were all calculations and measurements confirmed to ensure that the preparation will be compounded accurately?

COMPOUNDED DOSAGE FORMS

The terms *compounded dosage forms*, *compounded drugs*, *compounded formulations*, and *compounded preparations* mean finished dosage forms that are prepared by or under the direct supervision of a licensed pharmacist. When controlled substances are used, check with state and federal authorities concerning their policies. Compounded dosage forms include, but are not restricted to, the following pharmaceutical dosage forms described under *Pharmaceutical Dosage Forms* (1151).

Capsules, Powders, Lozenges, and Tablets

When compounding these dosage forms, the pharmacist should prepare an amount of the total formulation sufficient to allow the prescribed amount or quantity to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- Implementing appropriate checks to ensure that all ingredients are blended to achieve a homogeneous mixture.
- Monitoring humidity if moisture might cause hydrolysis, dosage form adhesion to containers, or softening or partial dissolution of capsule shells.
- Accurately performing weighings to ensure that each unit shall be not less than 90% and not more than 110% of the theoretically calculated weight for each unit.
- Packaging dosage units according to container specifications for capsules and tablets of the specific active ingredient unless specified otherwise in individual monographs (see *Containers* (661)).

Emulsions, Solutions, and Suspensions

When compounding these dosage forms, the pharmacist should prepare a 2% to 3% excess amount of the total formulation to allow the prescribed amount to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- For single-unit containers, the weight of each filled container, corrected for tare weight, shall be the equivalent of not less than 100% and not more than 110% of the labeled volume.
- Aqueous suspensions should be prepared by levigating the powder mixture to a paste with an appropriate wetting agent. This paste is converted to a free-flowing fluid by adding adequate vehicle. Successive portions of vehicle are used to wash the mortar, or other vessel, to transfer the suspension quantitatively to a calibrated dispensing bottle or graduate.
- Solutions shall contain no visible undissolved matter when dispensed. [NOTE—An exception may occur with supersaturated solutions such as *Potassium Iodide Oral Solution*.]
- Emulsions and suspensions should be labeled, "Shake well before using."

Suppositories

When compounding suppositories, the pharmacist should prepare an excess amount of total formulation to allow the prescribed quantity to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- Not using ingredients that are caustic or irritating, and thoroughly comminute solids that are abrasive to the mucous membranes.
- Selecting a base that allows active ingredients to provide the intended local or systemic therapeutic effect.
- Weighing a representative number of suppositories to ensure that each is not less than 90% and not more than 110% of the average weight of all suppositories in the batch.

Creams, Topical Gels, Ointments, and Pastes

When compounding semisolid dosage forms, the pharmacist should prepare an excess amount of total formulation to allow the prescribed quantity to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- Not using ingredients that are caustic, irritating, or allergenic to the skin or other application sites unless they are necessary for a treatment.
- Selecting a base or vehicle that allows active ingredients to provide the intended local or systemic therapeutic effect.
- Reducing solid ingredients to the smallest reasonable particle size achievable by trituration or levigation.
- Geometrically incorporating the active ingredients with the added substances to achieve a uniform liquid or solid dispersion in the dosage form.
- Observing the uniformity of the dispersion by spreading a thin film of finished formulation on a flat transparent surface (e.g., clear glass ointment slab).

COMPOUNDING PROCESS

The pharmacists should consider using the following steps to minimize error and maximize the prescriber's intent:

- (1) Judge the suitability of the prescription to be compounded in terms of its safety and intended use.
- (2) Perform necessary calculations to establish the amounts of ingredients needed.
- (3) Identify equipment needed.
- (4) Don the proper attire and wash hands.
- (5) Clean the compounding area and needed equipment.
- (6) Only one prescription should be compounded at one time in a specified compounding area.
- (7) Assemble all necessary materials to compound the prescription.
- (8) Compound the preparation following the formulation record or prescription (see *Compounding Records and Documents* below), according to the art and science of pharmacy.
- (9) Assess weight variation, adequacy of mixing, clarity, odor, color, consistency, and pH as appropriate.
- (10) Annotate the compounding log and describe the appearance of the formulation.
- (11) Label the prescription containers to include the following items: a) the name of the preparation; b) the date of compounding; c) the internal identification number; d) the be-

- yond-use date (see *Beyond-use Labeling*); e) the initials of the pharmacist who prepared the label; and f) any storage requirements.
- (12) Sign and date the prescription affirming that all procedures were carried out to ensure uniformity, identity, strength, quantity, and purity.
- (13) Thoroughly and promptly clean all equipment, and store it properly.

COMPOUNDING RECORDS AND DOCUMENTS

All pharmacists who dispense prescriptions must comply with the record keeping requirements of their individual states. If the pharmacist compounds a preparation according to the manufacturer's labeling instructions, then further documentation is not required. All other compounded preparations require further documentation. Such compounding documents should list the ingredients and the quantity of each in the order of the compounding process.

The objective of the documentation is to allow another pharmacist to reproduce the identical prescription at a future date. The formulation record provides a consistent source document for preparing the preparation (recipe), and the compounding record documents the actual ingredients in the preparation and the person responsible for the compounding activity. These records should be retained for the same period of time that is required for any prescription under state law. The record may be a copy of the prescription in written or machine readable form that includes a formulation record, a compounding record, and a Material Safety Data Sheets (MSDS) file.

Formulation Record

The formulation record is a file of individually compounded preparations. This record must list the name, strength, and dosage form of the preparation compounded, all ingredients and their quantities, equipment needed to prepare the preparation, when appropriate, and mixing instructions. Mixing instructions should include the order of mixing, mixing temperatures or other environmental controls, such as the duration of mixing, and other factors pertinent to the replication of the preparation as compounded. The formulation record must include an assigned beyond-use date, the container used in dispensing, the storage requirements, and any quality control procedures.

Compounding Record

The compounding record contains documentation of the name and strength of the compounded preparation, the formulation record reference for the preparation, and the sources and lot numbers of ingredients. The compounding record also should include information on the total number of dosage units compounded, the name of the person who prepared the preparation and the name of the pharmacist who approved the preparation, the date of preparation, the assigned internal identification number or the prescription number and an assigned beyond-use date, and the prescription number. For all compounded preparations, results of quality control procedures should be recorded (e.g., weight range of filled capsules).

MSDS File

The MSDS File contains the Material Safety Data Sheets for any drug substance or bulk chemical located on the pharmacy premises not in a solid dosage form. The MSDS should be requested from the supplier of each substance and kept on file in the pharmacy. Employees should be instructed as to the location of the file and its content.

QUALITY CONTROL

The safety, quality, and performance of compounded preparations depend on correct ingredients and calculations, accurate and precise measurements, appropriate formulation conditions and procedures, and prudent pharmaceutical judgment. As a final check, the pharmacist should review each procedure in the compounding process. To ensure accuracy and completeness, the

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pharmacist should observe the finished preparation to ensure that it appears as expected and should investigate any discrepancies and take appropriate corrective action before the prescription is dispensed to the patient (see the *Checklist for Acceptable Strength, Quality, and Purity*, the appropriate pharmaceutical dosage form under *Compounded Dosage Forms*, and the steps under *Compounding Process*).

PATIENT COUNSELING

The patient or the patient's agent should be counseled about proper use, storage, and evidence of instability in the compounded preparation at the time of dispensing (see *Responsibility of the Pharmacist under Stability Considerations in Dispensing Practice* (1191)).

(1206) STERILE DRUG PRODUCTS FOR HOME USE

Change to read:

RESPONSIBILITY OF THE DISPENSING PHARMACIST

A pharmacist dispensing any HSD is responsible for ensuring that the product has been prepared, labeled, controlled, stored, dispensed, and distributed properly. This includes the responsibility for ensuring that the HSD is kept under appropriate controlled conditions at the location of use and that it is administered properly through adequate labeling and verbal or written instructions. The dispensing pharmacist is also responsible for ensuring that the HSD retains its quality attributes within acceptable limits through a written quality assurance program. This program should ensure that for the entire labeled life of the product, or until manipulated by the patient or caregiver, the potency, pH, sterility, freedom from pyrogens, particulate limits, container integrity, appearance, and other qualities or characteristics that the HSD is expected to have do exist. The quality assurance program should encompass every HSD under the pharmacy's control and includes all phases of its preparation, distribution, storage, administration, and use. The dispensing pharmacy should employ proper analytical testing, where appropriate, to ensure the microbiological, chemical, and physical quality of all HSDs. These responsibilities apply equally to commercially available injectable drug products that are dispensed to patients without compounding or other manipulation and to HSDs that have been repackaged, reconstituted, diluted, admixed, blended, or otherwise manipulated (collectively referred to as "Compounded") in any way prior to dispensing. The pharmacist is responsible for ensuring that quality is built into the preparation of products, with key factors including at least the following general principles:

- (1) Personnel are capable and qualified to perform their assigned duties.
- (2) Ingredients used in compounding have their expected identity, quality, and purity.
- (3) Critical processes are validated to ensure that procedures, when used, will consistently result in the expected qualities in the finished product.
- (4) The production environment is suitable for its intended purpose (addressing such matters as environmental cleanliness, control, monitoring, and the setting of action limits, as appropriate).
- (5) Appropriate release checks or testing procedures are performed to ensure that finished products have their expected potency, purity, quality, and characteristics at the time of release.
- (6) Appropriate stability evaluation is performed or determined from the literature for establishing reliable expiration dating to ensure that finished products have their expected potency, purity, quality, and characteristics at least until the labeled expiration date.
- (7) There is assurance that processes are always carried out as intended or specified and are under control.

- (8) Preparation conditions and procedures are adequate for preventing mixups.
- (9) There are adequate procedures and records for investigating and correcting failures or problems in preparation, testing, or in the product itself.
- (10) There is adequate separation of quality control functions and decisions from those of production.

Emphasis in this chapter is placed upon the quality and the control of the processes utilized, personnel performance, and the environmental conditions under which the processes are performed. Other factors, such as testing and stability, are addressed to the extent necessary for the limited quantities of products with relatively short expiration dating periods normally associated with home care pharmacy practice. This chapter is not intended to address issues concerning the manufacture of sterile drug products.

Change to read:

RISK LEVELS

With reference to the microbiological quality (i.e., sterility) of the finished drug product, an HSD, in general, is compounded under either relatively *low-risk* or *high-risk* conditions, as determined by the potential for the introduction of microbial contamination. This contamination may result from the use of non-sterile components; novel, complex, or prolonged aseptic processes; or open exposure of the drug product or product containment devices to the atmosphere. In addition, long storage time between compounding and initiation of administration may affect the microbiological quality of the finished drug product.

The characteristics itemized below to distinguish between the high-risk and low-risk levels are intended to provide conceptual guidance and are not intended to be prescriptive. The pharmacist is expected to exercise professional judgment on a case-by-case basis when determining the risk level that would be appropriate for a particular process.

Low-Risk

An HSD is considered to be aseptically processed under low-risk conditions when all of the following conditions prevail:

- (1) The finished product is compounded with commercially available, sterile drug products.
- (2) Compounding involves only basic, and relatively few, aseptic manipulations that are promptly executed.
- (3) "Closed system" transfers are used: the container-closure system remains essentially intact throughout the aseptic process, compromised only by the penetration of a sterile, pyrogen-free needle or cannula through the designated stopper or port to affect transfer, withdrawal, or delivery in accordance with the labeled instructions for the pertinent, commercially available devices. Opened ampuls should be regarded as if they are closed systems for purposes of this chapter.

Examples of low-risk processes include the following:

- (1) Transferring sterile drug products from vials or ampuls into sterile final containers using a sterile needle and syringe.
- (2) Transferring sterile drug products into sterile elastomeric infusion containers with the aid of a mechanical pump and an appropriate sterile transfer tubing device, with or without the subsequent addition of sterile drug products to the infusion container with a sterile needle and syringe.
- (3) Compounding sterile nutritional solutions by combining *Dextrose Injection* and *Amino Acids Injection* via gravity transfer into sterile empty containers, with or without the subsequent addition of sterile drug products to the final container with a sterile needle and syringe.

High-Risk

Category I—A high-risk HSD may fall into either of two sub-classifications. High-risk HSDs in *Category I* are those prepared from commercially available, sterile components where one or more of the following conditions prevail:

- (1) Compounding involves the intermediate closed system pooling of sterile drug products. Pooling of additives is

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