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Blueprint for Inspection of Pharmacies

Module II – Compounding Nonsterile Preparations

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United States Pharmacopeia (USP)

Categories of Compounded Nonsterile Preparations

SIMPLE

Making a preparation that has a *United States Pharmacopeia (USP)* compounding monograph or that appears in a peer-reviewed journal article that contains specific quantities of all components, compounding procedure and equipment, and stability data for that formulation with appropriate BUDs; or reconstituting or manipulating commercial products that may require the addition of one or more ingredients as directed by the manufacturer. Examples include *Captopril Oral Solution*, *Indomethacin Topical Gel*, and *Potassium Bromide Oral Solution, Veterinary*.

MODERATE

Making a preparation that requires special calculations or procedures (such as calibration of dosage unit mold cavities) to determine quantities of components per preparation or per individualized dosage units; or making a preparation for which stability data for that specific formulation are not available. Examples include *Morphine Sulfate Suppositories*, diphenhydramine hydrochloride troches, and mixing two or more manufactured cream products when the stability of the mixture is not known.

COMPLEX

Making a preparation that requires special training, environment, facilities, equipment, and procedures to ensure appropriate therapeutic outcomes. Examples of possible complex preparation types include transdermal dosage forms, modified-release preparations, and some inserts and suppositories for systemic effects.

[Abstracted from *2016 USP Compounding Compendium*, current with USP-39/NF-34 through First Supplement]

General Operations Information

- 01.00** Does the pharmacy *dispense* nonsterile compounded preparations pursuant to a prescription?
- 01.01** Are patient profiles complete and DUR performed for each prescription?
- 01.02** Do the compounded prescriptions produce a significant difference from a commercially available drug that is justified by a documented medical need of the individual patient as determined by the prescribing practitioner?
- 01.03** Are nonsterile compounded prescriptions picked up at the pharmacy?
- 01.04** Are nonsterile compounded prescriptions delivered to patients in their homes or residential facilities?
- 01.05** Are nonsterile compounded prescriptions delivered to practitioner for administration to the patient in the office, clinic, or facility?
- 02.00** Does the pharmacy *distribute* nonsterile compounded preparations?
- 02.01** Does the pharmacy distribute nonsterile compounded preparations to practitioners for office use?
- 02.02** Does the pharmacy distribute nonsterile compounded preparation to hospitals, clinics, or surgery centers?
- 02.03** Does the pharmacy have a sales force that distributes samples containing active ingredients?
- 03.00** Does the pharmacy provide nonsterile compounded preparations to other pharmacies for dispensing?
- 03.01** If so, does the pharmacy have central fill contracts or agreements with these pharmacies for patient-specific preparations?
- 04.00** Does the pharmacy compound oral preparations (tablets, capsules, liquids, lozenges, etc.)?
- 05.00** Does the pharmacy compound topical (creams, ointments, inserts, suppositories, patches, sprays including nasal sprays, etc.)?
- 06.00** Does the pharmacy compound vitamin or nutritional supplements?
- 07.00** Does the pharmacy compound investigational drugs?

- 08.00** Does the pharmacy make a copy of an approved commercial product?
- 08.01** Products are verified as not available via FDA list and/or the manufacturer and documented.
- 08.02** FDA list and manufacturer information is monitored, and when item is taken off the list or becomes available, any remaining stock is quarantined for destruction and not dispensed or distributed.
- 09.00** Does the pharmacy perform compounding identified as *simple*? If so, indicate percentage of total compounding activity designated as such. This activity includes:
1. Making a preparation that has a USP compounding monograph or that appears in a peer-reviewed journal article that contains specific quantities of all components, compounding procedure and equipment, and stability data for that formulation with appropriate beyond-use dates (BUDs).
 2. Reconstituting or manipulating commercial products that may require the addition of one or more ingredients as directed by the manufacturer.
- 10.00** Does the pharmacy perform compounding identified as *moderate*? If so, indicate percentage of total compounding activity designated as such. This activity includes:
1. Making a preparation that requires special calculations or procedures (such as calibration of dosage unit mold cavities) to determine quantities of components per preparation or per individualized dosage units.
 2. Making a preparation for which stability data for that specific formula is not available.
- 11.00** Does the pharmacy perform compounding identified as *complex*? If so, indicate percentage of total compounding activity designated as such. This activity includes making a preparation that requires special training, environment, facilities, equipment, and procedures to ensure appropriate therapeutic outcomes.
- 12.00** Does the pharmacy perform compounding with *hazardous drugs*? If so, indicate percentage of total compounding activity designated as such.
- 12.01** Is the pharmacy aware of the more stringent requirements of the proposed USP Chapter <800>?
- 12.02** Does the pharmacy have a hazardous waste handling and collection system? For example, empty bottles that contained chemotherapy medications or warfarin, hazardous drug compounding waste.

- 12.03 Do patient/caregiver training programs or materials contain information and precautions regarding the handling and disposal of hazardous products such as chemotherapy medications?
- 13.00 Are Safety Data Sheets (SDS) [formerly known as Material Safety Data Sheets (MSDS)] available to personnel for drugs and chemicals used in the pharmacy (including those for compounding, if applicable)?
- 14.00 Does the pharmacy compound using any *controlled substances*? If so, indicate percentage of total compounding activity designated as such.
- 15.00 *APIs*: Does the pharmacy make any nonsterile compounded preparations using bulk powder Active Pharmaceutical Ingredients (APIs)?
- 15.01 Does the pharmacy purchase APIs directly from the manufacturer?
- 15.02 Does the pharmacy verify that the manufacture of the API is an FDA-registered facility? How?
- 15.03 Does the pharmacy use active ingredients that are not from an FDA-registered facility?
- 15.04 Does the pharmacy computer track on-hand quantities of APIs used for compounding?
- 16.00 Does the pharmacy perform any testing in-house (not sent to an outside lab)?
- 17.00 Does the pharmacy send samples to an outside lab to perform testing?
- 18.00 *Quality Assurance/Quality Improvement*: Does the pharmacy's continuous quality improvement program include nonsterile compounding measures?
- Quality Related Events (QREs) related to the preparation of compounded products;
 - Personnel testing and validation;
 - Equipment calibration, testing, and validation;
 - End product testing, such as potency, particulates, consistency, etc.; and
 - Patient or prescriber reports or complaints regarding nonsterile compounded preparations.
- 18.01 Does the facility QA program identify action limits or thresholds and the appropriate follow-up mechanisms when action limits or thresholds are exceeded including a recall system?
- 18.02 Does the recall system include communication with both the patient and the prescriber regarding the affected nonsterile compounded preparation?

- 18.03 Are QREs involving nonsterile compounded preparations or all pharmacy recall campaigns reported to the Board of Pharmacy?

Component Selection and Use

- 19.00 All bulk drug substances (APIs) used are:
- (1) Compliant with the standards of an applicable USP or NF monograph, if one exists; or
 - (2) A component of an FDA-approved human drug product; or
 - (3) On the list of bulk drug substances for use in compounding developed by the FDA and issued through regulation. [*Note: must comply with (1) or (2) above until the FDA list is issued*]
- 19.01 Certificates of Analysis (COAs) obtained for all bulk APIs used for compounding.
- 19.02 USP- or NF-grade substances used, if available.
- 19.03 If compendial quality components are not available, chemically pure, analytical reagent grade or ACS [American Chemical Society]-certified components are used and are determined to be free from impurities.
- 19.04 APIs or other components have labeling indicating use for pharmaceutical compounding or manufacturing. Labels do not indicate “for research purposes only”, “not for drug use”, or are handwritten labels from other pharmacies.
- 19.05 If compounding for both humans and animals, APIs or other components that are labeled for veterinary use only are segregated or marked in such a way to prevent them from being used for human compounding.
- 19.06 All substances and components have a complete label including a batch control or lot number, and an expiration date.
- 19.07 For APIs without an expiration date assigned by the manufacturer or supplier, the pharmacy assigns a conservative expiration date. The expiration date assigned does not exceed three years for ingredients used for nonsterile compounding and does not exceed one year for ingredients used for sterile compounding. The pharmacy may perform purity and quality testing to further extend their expiration date.
- 19.08 All APIs and components received without an expiration date are labeled with the date they were received.
- 19.09 If the pharmacy repackages APIs into smaller containers for ease

of use, the expiration date assigned is conservative (typically, the lesser of one year or the actual expiration date from the original container). Product may be tested to extend the expiration date, but may not exceed the original package expiration date.

- 19.10** Bulk component containers are labeled with appropriate OSHA hazard communication labels and hazardous substances (including hormones) are segregated.
- 19.11** Components from foreign sources that are derived from ruminant animals (cow, sheep, goat) have documentation that the component is in compliance with federal laws governing processing, use, and importation – that the animals were free from disease, and that they were born, raised, and slaughtered in locations where bovine spongiform encephalopathy and scrapie are not known to exist.
- 20.00** Where water is an ingredient, purified or distilled water is used.
- 21.00** Ingredients used for dietary or nutritional supplements meet USP, Food Chemicals Codex (FCC), or NF standards, or the pharmacy has alternate means to determine if the ingredients meet food-grade quality.
- 22.00** No preparations are made or ingredients used that appear on the FDA's list of drug products withdrawn or removed from the market for safety reasons. The facility has a copy of the list or other way to determine.
- 23.00** When manufactured products are used for compounding, all the other excipients in the product (in addition to the active ingredient) are considered relative to the use, effectiveness, and stability of the compounded preparation to be made.
- 24.00** For animal compounding, the compounding meets the same standards as compounding for human patients.
 - 24.01** The pharmacist is knowledgeable or has references regarding the individual species' limitations in physiology and metabolic capacity that can result in toxicity when certain drugs or excipients are used.
 - 24.02** It is determined and documented if the animal is used for food (meat, milk, eggs, etc.) or that the animal is a pet.
 - 24.03** The pharmacist is familiar with or has a reference regarding drug residues in the food chain and withdrawal times if compounding for food-producing animals.
 - 24.04** The facility has a list of drugs and components not allowed when compounding for food-producing animals.

- 24.05 The pharmacist is familiar with or has a reference regarding regulations for drug use in performance animals (e.g., race or show horses, racing dogs).

Beyond Use Dating (BUD)

- 25.00 BUDs are assigned from the day of preparation.
- 26.00 BUDs for nonaqueous formulations are not later than the remaining time until the earliest expiration date of any API and not later than six months.
- 27.00 BUDs for water-containing oral formulations are not later than 14 days when stored at controlled cold temperatures (refrigerated).
- 28.00 BUDs for water-containing topical/dermal and mucosal liquid and semisolid formulations are not later than 30 days.
- 29.00 BUDs are assigned based on dispensing in tight, light-resistant contains/overpacks.
- 30.00 Extended BUDs are supported by testing data.

Environment

- 31.00 The nonsterile compounding area is a controlled environment and separate from the general pharmacy.
- 32.00 There is sufficient space available for the type and amount of compounding performed and the space is orderly to prevent mix-ups between ingredients, containers, labels, in-process materials, and finished preparations.
- 33.00 Only one preparation is compounded at a time.
- 34.00 Procedures are implemented to prevent cross-contamination, especially when compounding with drugs such as hazardous drugs and known allergens like penicillin that require special precautions.
- 35.00 The compounding area is well-lit.
- 36.00 The pharmacy performs hazardous nonsterile compounding in a ventilated cabinet such as a BSC, CAI, or CACI; however, CAI may not be used for hazardous drugs that may volatilize. *{USP Chapter <800> will change hazardous drug compounding requirements.}*
- 36.01 Ventilated cabinets (BSC, CAI, CACI) used for hazardous compounding are certified or tested periodically.

- 36.02 Hood prefilters are checked and replaced regularly.
{*Recommended*}
- 36.03 If the hoods or isolators are not located in a closed, controlled room environment, there is documentation from the manufacturer and site testing to verify proper functioning of equipment under dynamic conditions for the safety of personnel.
- 37.00 Appropriate protective attire (gowns, gloves, masks, etc.) is available including appropriate personal protective equipment (PPE) for hazardous drug compounding if hazardous drugs are used.
- 38.00 There is a sink in the compounding area with hot and cold potable water, soap or detergent, and air-driers or single-use towels.
- 39.00 There is adequate space to wash equipment and utensils including access to water for rinsing. {*Purified water is recommended, but not required.*}
- 40.00 The temperature of the compounding area is controlled by a thermostat and an air conditioning system is in place.
- 41.00 *Temperature* in the compounding area is maintained to provide controlled room temperature storage of 20° to 25°C (68° to 77°F), or more restrictive if warranted by specific drug product storage requirements.
- 41.01 Temperature monitoring is in place to detect any excursions (24/7) by continuous monitoring or retroactive detection using min/max. Temperature records are maintained.
- 41.02 Excursion action plan is in place, including evaluating excursion effects on drug product integrity.
- 41.03 Temperature monitoring is also performed in drug storage areas, if separate from the compounding areas.
- 42.00 *Humidity* in the compounding area is maintained to provide humidity in the ranges warranted by specific drug product storage requirements. If drug products require storage in a 'dry place', humidity is not to exceed 40%. Generally recommended range is 35-60%.
- 42.01 Humidity monitoring in place to detect any excursions (24/7) by continuous monitoring or retroactive detection using min/max. Humidity records are maintained.
- 42.02 Excursion action plan in place including evaluating excursion effects on drug product integrity.

- 42.03** Humidity monitoring is also performed in drug storage areas, if separate from the compounding areas.
- 43.00** The bulk component storage area is adequately arranged and maintained in a clean and sanitary condition.
- 44.00** All components, equipment, and containers are stored off the floor, and handled and stored to prevent contamination.
- 45.00** All components and packaging containers and closures are properly rotated to use oldest first.
- 46.00** Hazardous drugs are appropriately identified and marked, received, handled and stored by appropriately trained personnel (OSHA regulations and NIOSH Alerts).
- 47.00** Trash is disposed of in a safe, sanitary, and timely manner including hazardous waste.
- 48.00** Environmental testing is performed to detect contamination by drug residue in the pharmacy area or areas served by the same ventilation system. *{Recommendation: drug residue may cause cross contamination to other products or expose staff. Not required but is recommended if compounding with hazardous materials or known allergens such as penicillin, not using a hood, or the compounding room is not segregated.}*

Training

- 49.00** All personnel of reproductive capability who handle or compound hazardous drugs or chemicals have confirmed in writing that they understand the risks of handling hazardous drugs, including teratogenicity, carcinogenicity, and reproductive issues.
- 50.00** There is documentation that all personnel that perform compounding are appropriately trained including policies and procedures, documentation, hazardous drug handling, and compounding technique and are not allowed to compound or supervise compounding until training is successfully completed.
- 51.00** There is documentation that the training process for the preparation of compounds includes demonstration of the compounding procedure first, followed by the trainee performing the procedure under supervision successfully before being allowed to perform compounding.
- 52.00** There is documentation that training includes the operation of any equipment that may be used when preparing compounded products; documentation includes operation and troubleshooting.

- 53.00** There is documentation available showing employees performing nonsterile compounding are evaluated at least annually (including hazardous drug handling).
- 54.00** If the pharmacy uses relief personnel from outside agencies to perform nonsterile compounding there is documentation that training is verified.

Compounding Equipment

- 55.00** Appropriate equipment and utensils are available, clean, and in good working order. Automated, mechanical, or electronic equipment (including capsule machines, autoclaves, ovens, etc.) are periodically inspected and calibrated.
- 56.00** Scales, balances, or other equipment used for measurement is validated and calibrated at least annually. If scales are not validated and sealed by a state or local weights and measures agency, describe procedure used.
- 57.00** Powder hoods used for nonsterile compounding are certified or tested periodically to ensure proper function. Hood filters are checked regularly and replaced when necessary.
- 58.00** All equipment is cleaned promptly after each use. Equipment and utensils washing using potable water with a soap or detergent, and rinsed.
{*Recommendation: rinse with purified water.*}
- 59.00** The pharmacy uses separate equipment and utensils to compounding allergenic, cytotoxic, or hazardous products, or has detailed procedures for meticulous cleaning of equipment and utensils immediately after use to prevent cross contamination or exposure.

Documentation

- 60.00** The pharmacy creates a *Master Formulation Record* the first time before compounding a new preparation.
- 60.01** Every formulation is evaluated for incompatibilities and the potential for being ineffective or toxic.
- 60.02** The *Master Formulation Record* contains:
- 60.02.01** Official or assigned name, strength, and dosage form;
 - 60.02.02** All necessary calculations;
 - 60.02.03** Description of all ingredients and their quantities;

- 60.02.04 Compatibility and stability information including references (when available);
- 60.02.05 Equipment used for the preparation;
- 60.02.06 Mixing instructions (order of mixing, temperatures, duration of mixing, and other pertinent factors);
- 60.02.07 Container used and packaging requirements;
- 60.02.08 Assigned BUD information;
- 60.02.09 Labeling information, including the name of and quantity or concentration of each active ingredient;
- 60.02.10 Description of the finished preparation;
- 60.02.11 Storage requirements; and
- 60.02.12 Quality control procedures and expected results (e.g., dose measurement of capsule in the dose calibrator).

61.00 The pharmacy creates a *Compounding Record* for each compound prepared.

61.01 The *Compounding Record* includes:

- 61.01.01 Official or assigned name, strength, and dosage of the preparation;
- 61.01.02 Master Formulation Record reference;
- 61.01.03 Sources, lot numbers, and expiration dates of all components;
- 61.01.04 Total quantity or number of dosage units compounded;
- 61.01.05 Person compounding the preparation;
- 61.01.06 Person performing the quality control procedures;
- 61.01.07 Person who approved the preparation;
- 61.01.08 Date of compounding;
- 61.01.09 Assigned internal identification number or prescription number;
- 61.01.10 Description of the final preparation;

- 61.01.11 Assigned BUD;
- 61.01.12 Duplicate label;
- 61.01.13 Results of quality control procedures (weight range of filled capsules, pH of aqueous liquids, etc.); and
- 61.01.14 Documentation of any quality control issues, and any adverse reactions or preparation problems reported by the patient or caregiver including investigation and recall, if appropriate.

Compounding Procedures

- 62.00 The *Master Formulation Record* and the *Compounding Record* has been reviewed by the compounder to ensure it is error free.
- 63.00 Compounding personnel ascertain that ingredients for compounded preparations are of the correct identity and appropriate quality including a unit-by-unit physical inspection of the components.
- 64.00 The containers and closures selected meet USP standards (from container supplier).
- 65.00 Container selection determined by physical and chemical properties of the preparation.
- 66.00 Compounding personnel maintain good hand hygiene and wear clean and appropriate clothing for the compounding being performed.
- 67.00 Personnel don appropriate protective garb when compounding includes hazardous compounding.
- 68.00 Routine compounding procedures for batch preparation completed and verified according to written procedures, including: calculations correct, weighing and measuring performed correctly, order of mixing correct, compounding techniques performed correctly.
- 69.00 Procedures for in-process checks followed. These checks indicate that appropriate procedures and packaging are followed for each step, including addressing pharmacist verification of steps performed by non-pharmacists that includes visual inspection of product, and documentation of the compounding accuracy is performed to ensure proper measurement, reconstitution, and component usage. *{Recommendation: compounding accuracy checked by a person other than the compounder.}*
- 70.00 If there are any deviations from the master formulation record, these

deviations are recorded.

71.00 There is a plan for cleaning, e.g., after each preparation, daily tasks, monthly tasks, etc.

72.00 Personnel are appropriately garbed for protection when cleaning.

72.01 Compounding employees are using appropriate techniques.

Finished Preparation Release Checks and Tests

73.00 The finished preparation is observed to appear as expected in the Master Formulation Record and documented.

74.00 As appropriate, the final completed preparation is assessed for weight, mixing, clarity, color, consistency, pH, and strength, and is documented.

75.00 There are established written processes that describe test or examinations conducted on the compounded preparation e.g., degree of weight variation in capsules.

76.00 Preparations with extended BUDs that are not supported by testing data are sampled and tested for physical, chemical, and microbiological characteristics.

76.01 If any failed tests or discrepancies are observed, there is an investigation and appropriate corrective actions taken before dispensing to patient.

76.02 If products are being tested are dispensed or distributed before the test results are obtained, there is a recall procedure if the test results indicate an issue.

77.00 There are appropriate control procedures to monitor the output and to verify the performance of compounding processes and equipment that may be responsible for causing variability in the final compounded preparations, e.g., validation of equipment and personnel performance documentation.

78.00 Labels on immediate patient-specific containers include identifiers for the persons preparing the compound and performing the final verification, BUD, and indication that this is a compounded preparation, special requirements for storage, and appropriate packaging and labeling of hazardous materials.

79.00 Batch preparations (in anticipation of prescriptions) are of an appropriate volume and batch preparations in stock are all within their BUD (not outdated).

- 80.00** Labels on batch preparations include the name and quantity of all contents, date of preparation (or internal code indicating this information), preparer and verification pharmacist identifiers, stability (BUD), and any auxiliary labels indicated including appropriate packaging and labeling of hazardous materials. *{Recommendation: include time of preparation with the date.}*
- 81.00** Preparations are stored properly prior to dispensing based upon conditions upon which BUD was assigned.
- 82.00** Preparations are examined immediately after preparation and again immediately prior to dispensing for any signs of instability.

Patient Counseling and Communication

- 83.00** Patient/caregiver training programs or materials contain information and precautions regarding the handling and disposal of hazardous products such as chemotherapy medications.
- 84.00** The required printed drug information materials (drug information sheets, patient package inserts, MedGuides, etc.) are provided for the compounded preparations.
- 85.00** Patients are instructed on the signs of product instability or contamination (as appropriate) and how to report any changes in the physical characteristics of the preparation to the pharmacy.
- 86.00** Product recalls include documentation that both the patient and the physician/prescriber of the potentially contaminated compounded preparation are notified of the potential risk.

Revision History

08-30-2017 **Version 1.1** **80.00** Adjusted labeling requirement for batches, to change the inclusion of the preparation time from a required element to a recommendation for best practice.