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Association of Portuguese Hospital Pharmacists

The USP and Compounding Nonsterile Medications

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USP’s Beginning

USP was founded in 1820 by 11 physicians, in Washington, D.C.
The first Pharmacopoeia (1820)

The first Pharmacopoeia of the United States contained 217 of the “most fully established and best understood” medicines in the U.S. It was published “by the authority of the medical societies and colleges.”
USP Today

- Scientific non-profit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements

USP’s Mission:
To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.
What We Do Today

- Establish and disseminate public written standards for the quality, purity, identity, strength, and labeling of medicines
- Provide recommendations to practitioners on the safe use of medicines
- Work with international health agencies to improve the quality of medicines worldwide
- Educate practitioners, producers and others seeking information on quality and USP standards
USP Standards

- The United States Pharmacopeia National Formulary (USP–NF)
- Food Chemicals Codex (FCC)
- USP Dietary Supplements Compendium (DSC)
- USP Medicines Compendium (MC)
- Herbal Medicines Compendium (HMC)
- Reference Standards
- Other Resources
  - Pharmacopeial Forum (PF)
  - FCC Forum (FCCF)
  - USP Dictionary
  - Chromatographic Columns
New Publication includes:

- Mission & Preface
- General Notices & Requirements
- Compounding Related Chapters
  - 5 essential compounding chapters
- Supporting General Chapters
  - Over 40 referenced Chapters
- Compounded Preparation Monographs
  - 175 formulations

Downloadable pdf
Annual Subscription
Legal Recognition in the US

- **1848 Drug Import Act** recognized USP standards to stop the dumping of drugs by Europeans.

- **1906 Pure Food and Drugs Act** enforced USP and NF standards for strength, quality, and purity.

- **1938 Food, Drug and Cosmetic Act** recognized USP & NF standards for strength, quality, purity, packaging, and labeling.

- **1994 Dietary Supplement Health Education Act** recognize USP standards for dietary supplements.
Legal Recognition in the US

- **1997 FDA Modernization Act**
  Sec. 503A stated that compounding must comply with USP-NF standards and chapter on pharmacy compounding

- **2003 Medicare Modernization Act**
  Requested USP to develop and revise the Model Guidelines for Medicare Formularies

- **2010 Affordable Care Act**
  Recognizes USP Model Guidelines to assess coverage of *Essential Health Benefits*

- **2013 Drug Quality and Security Act**
  Recognize USP monographs for bulk drug substances and USP chapters on pharmacy compounding
Compounding

Definition
– The preparation of a drug in accordance with a licensed practitioner’s prescription or medication order based on the triad relationship.

Why compound?
– Pediatric patients
– Geriatric patients
– Animal patients
– Non-standard doses
– Allergen-free medication
– HRT
– Sports Injuries
– Pain Management
– Drug Shortages
– Discontinuation by manufacturer
– Intravenous Medications
In 2012, 85.5% of community (outpatient) pharmacies provide compounding service\(^1\)
- 72% provide non-sterile compounding services only
- 28% provide sterile compounding services

In 2012, 92% of hospitals (inpatient) used compounded sterile preparations\(^2\)
- 92% used sterile-to-sterile preparations
- 25% used nonsterile-to-sterile preparations
- 85% outsourced some sterile preparations

National Drug Shortages: New Shortages by Year

New Drug Shortages by Year
Jan 2001 – Mar 2014

1. Data collected by the University of Utah Drug Information Service.
Compounding Expert Committee
Compounding General Chapters

- <795> Pharmaceutical Compounding – Nonsterile Preparations
- <797> Pharmaceutical Compounding - Sterile Preparations
- <1163> Quality Assurance in Pharmaceutical Compounding
- <1160> Pharmaceutical Calculations in Prescription Compounding
- <1176> Prescription Balances & Volumetric Apparatus
Review of USP Compounding
General Chapters
General Chapters can be:

- **Enforceable**
  - Numbered below <1000>

- **Informational**
  - Numbered above <1000>

- **Specific for dietary supplements**
  - Numbered above <2000>

**Terminology**

- “Shall” requirements
- “Should” recommendations
General Chapter <795>

Pharmaceutical Compounding – Nonsterile Preparations
USP <795>: Revision History

- **First Published** in USP24-NF19 (2000)
  - Revision from <1161> Pharmacy Compounding Practices
  - 1997 FDA Modernization Act
- **Revised** in USP34-NF29 (2011)
  - Incorporation of <1075> Good Compounding Practices
- **Revision Bulletin** posted November 22, 2013
  - Official Jan 1, 2015
Purpose

– To provide guidance on applying good compounding practices for nonsterile formulations for humans or animals.
– To provide general information to enhance the compounder's ability to extemporaneously compound preparations that are of acceptable strength, quality, and purity.
USP <795>: Major Elements

Categories of Compounding

Responsibilities of the Compounder

Compounding Facilities

Component Selection, Handling and Storage

Stability Criteria and Beyond-Use Dating

Compounding Documentation

Compounding for Animal Patients
USP <795>: Categories of Compounding

Simple
- Preparation with USP compounding monograph
- Preparation in peer-reviewed literature
  - e.g. Captopril Oral Solution

Moderate
- Preparation with special calculations or procedures
- Preparation with no stability data
  - e.g. Morphine Sulfate Suppositories

Complex
- Special training, environment, facilities, equipment and procedures
  - e.g. transdermal dosage forms, modified release preparations, inserts and suppositories
USP <795>: Responsibilities of the Compounder

- General Principles of Compounding
  - Training and documentation of competency
  - Compounding ingredients
  - Hazardous component containers
  - Equipment
  - Facilities
  - Authorized entry
  - Quality control and assurance
  - Error prevention
  - Documentation
  - Investigations
Recommend USP, NF, or FCC substance manufactured in an FDA-registered facility

The water used in all aspects of compounding should meet the requirements of *Waters for Pharmaceutical Purposes* <1231>

Non-FDA registered facility

- Use professional judgment and establish purity and safety to include certificate of analysis

Non-compendial quality

- Use high quality ingredients such as those chemically pure, analytical reagent grade, or American Chemical Society (ACS)-certified
  - Caution: ACS grade materials do not consider impurities that raise patient safety concerns
Manufactured drug products as the active ingredient
– Labeled with batch control number and expiration date
– Consider all ingredients (e.g. excipients) effect on therapeutic appropriateness and stability

Compounding for dietary and nutritional supplement
– Ingredients that meet FCC standards or acceptable food-grade quality

Components derived from ruminant animals
– Require written assurance for compliance with federal laws
BUD considerations
- the nature of the drug and its degradation mechanism
- the dosage form and its components
- the potential for microbial proliferation in the preparation
- the container in which it is packaged
- the expected storage conditions
- the intended duration of therapy
For Nonaqueous Formulations

- The BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.

For Water-Containing Oral Formulations

- The BUD is not later than 14 days when stored at controlled cold temperatures.

For Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations

- The BUD is not later than 30 days.
### Master Formulation Record
- Name, strength, and dosage form
- Calculations / Verifications
- Ingredients / Quantities
- Compatibility & Stability Information
- Equipment, when appropriate
- Mixing instructions
- Example labeling
- Assigned BUD
- Storage conditions
- Prescription or control number
- Container
- Packaging and storage requirements
- Description of final preparation
- Quality control

### Compounding Record
- Name, strength, and dosage
- Master Formulation Record reference
- Names & quantities of all components
- Sources, lot numbers, & expiration dates of components
- Total quantity compounded
- Personnel
- Date of preparation
- Assigned control or prescription number
- Assigned BUD
- Duplicate label
- Description of final preparation
- Quality Control Procedures
- Issues or any adverse reactions

Documentation enables a compounder to systematically trace, evaluate, and replicate the steps included throughout the preparation process.
Nature of the animal patient shall be determined

- Companion Animals
- Performance Animals
  - Strictly regulated by federal and state governments
- Food-Producing Animals
  - Accurate length of time to withhold treated animal tissues from the human food supply.
  - Withdrawal time (WDT) must be included on the dispensing label

- Species’ limitations in physiology and metabolic capacity that can result in toxicity when certain drugs or excipients are used
General Chapter <1163>

Quality Assurance in Pharmaceutical Compounding
History

– First Published in USP30-NF25 2S (2007)
– Revised in USP34-NF29 (2011)

Introduction

– A quality assurance program is guided by written procedures that define responsibilities and practices that ensure compounded preparations are produced with quality attributes appropriate to meet the needs of patients and health care professionals.
USP <1163>: Overview

Training

SOP’s

Documentation

Verification

Testing

Cleaning & safety

Containers, packaging, & labeling

Outsourcing

Responsible personnel
To describe how to perform routine and expected tasks in the compounding environment, including but not limited to procedures involving:

1. Beyond-Use dating
2. Chemical & physical stability
3. Cleaning & disinfecting
4. Component quality evaluation
5. Compounding methods
6. Dispensing
7. Documentation
8. Environmental quality
9. Equipment
10. Formulation development
11. Labeling
12. Materials & preparation handling & storage
13. Measuring & weighing
14. Packaging & repackaging
15. Patient monitoring
16. Patient education
17. Personnel cleanliness & garb
18. Purchasing
19. Quality Assurance & Continuous Quality Monitoring
20. Safety
21. Shipping
22. Testing
23. Training

SOPs must be reviewed regularly and updated as necessary.
- Periodic auditing and verifying compliance with established SOPs
- SOP should be specific to each device and process
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<tr>
<th>Table 1</th>
<th>Chapter Title</th>
<th>Chapter</th>
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Options for testing

- Onsite (in-house) testing
  - Appropriate qualified equipment
- Outsourced to contract laboratories
  - Follow USP general chapters
  - Registered with U.S. Food and Drug Administration

Selection of testing method

- Quantitative (strength, concentration)
- Semiquantitative (tolerance levels)
- Qualitative (presence/absence)
- Physical/Chemical characteristics of the analyte
## USP <1163>: Testing

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*a, b, c, d* testing methods and additional information may vary depending on specific substances and dosage forms. Please consult the USP <1163> for detailed guidance.
USP <1163>: Testing

- Physical Testing of Dosage Units
  - Weight Assessment
  - Visual inspection
  - pH

- Microbiological Testing
  - Preservative Effectiveness Testing
  - Microbial Limit Testing

- Additional QA Checks
  - Visual inspection
  - pH
New General Chapters In Development
New Chapters or Major Revisions

Proposal for new General Chapter or major revision comes from staff, committee member, or external source

Committee, subcommittee, or panel evaluates idea and develops a *Pharmacopeia Forum* (PF) proposal

Public comment solicited
- Stimuli Article (common for new General Chapter) or draft chapter published in *PF*
- "Design phase" of workshop or other public meeting scheduled for "high-impact" chapters (required chapters with broad industry impact)

Comments collected from public forums and shared with committee/panel
General Chapter <800>

Hazardous Drugs – Handling in Healthcare Settings
New proposed standard to protect personnel and environment when handling hazardous drugs (HDs)

**Purpose:** To define processes intended to provide containment of hazardous drugs to as low as reasonably achievable

The chapter addresses:
- Standards that apply to all personnel who compound HDs preparations and all places where HDs are prepared, stored, transported, and administered
- Receiving, storing, compounding, dispensing, administering, and disposing of both nonsterile and sterile products and preparations
- Altering, counting, crushing, and pouring HDs.
HD includes any drug identified by at least one of the following six criteria:

- Carcinogenicity
- Teratogenicity or developmental toxicity
- Reproductive toxicity in humans
- Organ toxicity at low doses in humans or animals
- Genotoxicity
- New drugs that mimic existing HDs in structure or toxicity

Chapter refers to NIOSH List

http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf
General Chapter <1168>

Compounding for Investigational Studies
Purpose:

– To provide additional standards for compounding for investigational preclinical and early phase I investigations


– Public comments period closed Nov 30, 2013

– Committee currently reviewing the chapter and working with stakeholders
Review of USP Compounding Preparation Monographs
Monograph Titles

1. Substance monograph
   Amlodipine Besylate

2. Product monograph
   Amlodipine Besylate Tablets

3. Compounded Preparation monograph
   Amlodipine Oral Suspension

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**Amlodipine Oral Suspension**

**DEFINITION**

Amlodipine Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine (C_{20}H_{25}ClN_{3}O_{3}).

Prepare Amlodipine Oral Suspension 1 mg/mL as follows (see Pharmaceutical Compounding—Nonsterile Preparations (795)).

<table>
<thead>
<tr>
<th>Amlodipine tablets</th>
<th>equivalent to</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle: A 1:1 mixture of Ora-Sweet(^{b}) and Ora-Plus(^{b}), a sufficient quantity to make</td>
<td>100 mL</td>
<td></td>
</tr>
</tbody>
</table>

\(^{b}\)Norvasc 5-mg tablets, Pfizer, Inc., Groton, CT.

\(^{b}\)Paddock Laboratories, Minneapolis, MN.

Calculate the required quantity of each ingredient for the total amount to be prepared. Place the required number of tablets in a suitable mortar and comminute to a fine powder. Add the Vehicle in small portions, and triturate to make a smooth paste. Add increasing volumes of the Vehicle to make an amlodipine liquid that is pourable. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough of the Vehicle to bring to final volume, and mix well. [NOTE—To ensure component uniformity, homogenization is recommended.]

flask, and swirl to disintegrate the Tablets. Add 300 mL of Mobile phase, insert the stopper into the flask, and
**Amlodipine Oral Suspension**

**DEFINITION**
Amlodipine Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine (C_{17}H_{21}N_{3}O_{4}).

Prepare Amlodipine Oral Suspension 1 mg/mL as follows:

1. Take of Jalap in powder;
2. Rhubarb in powder;
3. Castile soap, each one ounce;
4. Submuriate of mercury six drachms and two scruples;
5. Tartarized antimony, twenty eight grains.

With water form a mass and divide into four hundred pills.

### Amlodipine Tablets: equivalent to

<table>
<thead>
<tr>
<th>Quantity</th>
<th>ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>100 mL</td>
<td></td>
</tr>
</tbody>
</table>

*Nerax 5-mg tablets, Pfizer Inc., Croton, CT.*
*Paddock Laboratories, Minneapolis, MN.*

Calculate the required quantity of each ingredient for the total amount to be prepared. Place the required number of tablets in a suitable mortar and comminute to a fine powder. Add the Vehicle in small portions, and triturate to make a smooth paste. Add increasing volumes of the Vehicle to make an amlodipine liquid that is pourable. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough of the Vehicle to bring to final volume, and mix well. [Note—To ensure component uniformity, homogenization is recommended.]

### ASSAY

#### Procedure
1. **Mobile phase:** Acetonitrile, methanol, and 40 mM ammonium acetate, (50:15:35). Filter through a nylon 66 filter of 0.45-μm pore size, and degas.
2. **Standard stock solution:** Dissolve an appropriately weighed amount of USP Amlodipine Besylate RS in methanol, equivalent to 1.0 mg/mL of amlodipine (approximately equal to 1.4 mg/mL of amlodipine besylate). Standard solution: Transfer 1.0 mL of the Standard stock solution into a 50-mL volumetric flask, and dilute with Mobile phase to volume to obtain a solution with a nominal concentration of about 20 μg/mL of amlodipine.
3. **Centrifuge** Sample solution: Shake thoroughly by hand each bottle of Oral Suspension. Pipet 1.0 mL of Oral Suspension into a 50-mL volumetric flask, rinse the pipet three times with Mobile phase, and dilute with Mobile phase to volume to obtain a solution with a nominal concentration of about 20 μg/mL of amlodipine. Centrifuge.

### Chromatographic system

(See Chromatography (621), System Suitability)
- **Mode:** LC
- **Detector:** UV 240 nm
- **Column:** 3.0-mm × 15-cm; 5-μm packing L10
- **Flow rate:** 0.4 mL/min
- **Injection size:** 10 μL

### System suitability

**Sample:** Standard solution

[Note—The retention time for amlodipine is about 10.1 min.]

### Suitability requirements

- Column efficiency: NLT 4000 theoretical plates
- Tailing factor: NMT 2.0
- Relative standard deviation: NMT 2.0% for replicate injections

### Analysis

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of amlodipine (C_{17}H_{21}N_{3}O_{4}) in the portion of Oral Suspension tablets

\[ \text{Result} = \left( \frac{r}{r_s} \right) \times \left( \frac{C_s}{C} \right) \times 100 \]

- \( r_s \) = peak response of amlodipine from the Standard solution
- \( r \) = peak response of amlodipine from the Sample solution
- \( C_s \) = concentration of amlodipine in the Standard solution (μg/mL)
- \( C \) = nominal concentration of amlodipine in the Sample solution (μg/mL)

### SPECIFIC TESTS

- **pH (791):** 4.0-5.0

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Package in tight, light-resistant containers. Store at controlled room temperature or controlled cold temperature.
- **Labeling:** Label to indicate that it is to be well-shaken before use, and to state the Beyond-Use Date.
- **Beyond-Use Date:** NMT 90 days after the date on which it was compounded when stored at controlled cold temperature; NMT 60 days when stored at controlled room temperature
- **USP Reference Standards (11)**
  - USP Amlodipine Besylate RS
Currently, **175** official monographs (for human and veterinary use)
- Oral Suspensions
- Oral Solutions
- Suppositories
- Injections
- Topicals
- Ophthalmics

Monographs are based on peer-reviewed literature studies and laboratory conducted stability studies.

- **2012**: 26 monographs became official
- **2013**: • 16 monographs proposed in PF
- **2014**: • 12 monographs proposed in PF
  • 12 monographs in development
Monograph Development Process

- Identified through stakeholder survey results
- Prioritized by patient need and frequency of use
- Contracted to independent analytical labs
  - Assay developed and validated
  - Stability study conducted for BUD determination
- Laboratory studies funded by USP
Clinical Case

S: 4 lb 6 month old baby boy

O: At 3 months developed “cradle cap” then widespread weeping cutaneous lesions, impaired digestion & seizures

A:

P:

Acrodermatitis enteropathica is an autosomal recessive metabolic disorder affecting the uptake of zinc, characterized by periorificial and acral dermatitis, alopecia, and diarrhea. Fatal if untreated.
Clinical Case

123 Pharmacy Road  
Rockville, MD  
(123)555-0123

Name: Baby Johnson  Age: 6 months  
Date: June 26, 2013

Zinc Sulfate 44 mg/mL Oral Solution

Sig: 3.5 mL/day of zinc  
(equiv 154 mg/day Zinc)  
Disp: 50 mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc sulfate, granular (heptahydrate)</td>
<td>4.4 g</td>
</tr>
<tr>
<td>Cherry syrup, NF</td>
<td>45 mL</td>
</tr>
<tr>
<td>Purified Water, NF, a sufficient quantity to make</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

Note: Elemental zinc 1 mg is equivalent to zinc sulfate 2.47 mg or zinc sulfate heptahydrate 4.4 mg.
Questions
Thank You