Nonsterile Compounding: USP and Best Practices for Community Pharmacists
Target Audience: Pharmacists and Pharmacy Technicians

ACPE#: 0202-0000-18-033-L07-P/T

Activity Type: Knowledge-based
Disclosures

Brenda Jensen and Patricia Kienle are members of the USP Compounding Expert Committee, but this talk is not affiliated with or endorsed by USP.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

At this completion of this knowledge-based activity, participants will be able to:

1. Describe the role of key personnel and environmental requirements when compounding nonsterile preparations
2. Explain risk management strategies for handling hazardous drugs, including those in U.S. Pharmacopeial Convention General Chapter <800>
3. List important elements on a certificate of analysis
4. Identify challenges pharmacists and support staff may encounter when compounding practices are surveyed by regulators and surveyors
1. Assessment Question

Which of the following is correct

A. USP sets and enforces standards
B. USP enforces standards set by other federal agencies
C. USP sets standards which are enforced by other agencies
D. USP enforces standards when specifically written
2. Assessment Question

A certificate of analysis should be reviewed for

A. Only API (active pharmaceutical ingredients)
B. Only inactive ingredient components
C. Only hazardous components
D. All components
3. Assessment Question

An assessment of risk approach may be used when compounding with hormones.

A. Yes, since hormones are on NIOSH Tables 2 and 3
B. Yes, if using concentrated hormone solutions
C. Yes, if using only conventionally-manufactured products as ingredients
D. No
4. Assessment Question

Which of the following documents describes the specific components of a compound?

A. Master Formulation Record
B. Compounding Record
C. USP <795>
D. USP <800>
USP General Chapters


- These standards have been recognized in the Federal Food, Drug and Cosmetic (FD&C) Act since it was first enacted in 1938. The FD&C Act defines the term "official compendium" as the official USP, the official NF, the official Homeopathic Pharmacopeia of the United States, or any supplement to them.

http://www.usp.org/about/legal-recognition/standard-categories#compounded-prep
USP: Compounded Preparations

- USP provides both general chapters and monographs for compounded preparations
- Compounded preparation monographs include formulas, specific directions to correctly compound the particular preparation, packaging and storage information, labeling information, pH, beyond-use dates based on stability studies, and detailed assays (majority of monographs).
- Standards in USP–NF for compounded preparations may be enforced by both the states and FDA

http://www.usp.org/about/legal-recognition/standard-categories#compounded-prep
Regulatory Issues

- USP sets standards
- Regulators enforce standards
  - Federal
  - State

Photo courtesy of USP
Status of USP Compounding Chapters

- <795> Nonsterile Compounding
- <797> Sterile Compounding
- <800> Hazardous Drugs
  - Will become official on December 1, 2019
Health-System Accreditation Organizations

- The Joint Commission
- DNV Healthcare
- Healthcare Facilities Accreditation Program
  - Will be transitioning to Accreditation Association for Hospitals/Health Systems
- Center for Improvement in Healthcare Quality
Ambulatory Accreditation/Credentialing Organizations

- ACHC (Accreditation Commission for Health Care)/PCAB (Pharmacy Compounding Accreditation Board)
- URAC (formerly the Utilization Review Accreditation Commission)
- NABP VPP (Verified Pharmacy Program)
- FocusScript
- PersonalMed
Best Practices

- Professional organizations develop guidance documents to supplement standards
- These often provide more procedural information
Major Elements to Consider

- Compounds Prepared
- Facilities and Equipment
- Work Practices
Compounds Prepared

Non-Hazardous

Hazardous
What Drugs are Hazardous?

- The National Institute for Occupational Health and Safety (NIOSH) defines the list of drugs that are hazardous to healthcare personnel.

- Any Active Pharmaceutical Ingredient (API) and any antineoplastics that must be manipulated that are on the list must be handled with all containment strategies and work practices defined in <800>
  - Other dosage forms of drugs on the NIOSH list may be entity-exempt from some or all of the strategies if an Assessment of Risk is performed and implemented.
Facilities

- Adequate space designed for compounding
- Lighting
- Water
- Temperature
  - Controlled Room Temperature 20° to 25°C (68°-77°F)
  - Controlled Cold Temperature 2° to 8°C (36°-46°F)
  - Frozen Temperature –25° to –10°C (–13° to 14°F)
- Appropriate humidity
- No storage on floor
Equipment

- Clean
- Properly maintained
  - Verification
  - Calibration
  - Certification
- Used appropriately
Selecting Components ...

- Excipients
  - Use USP/NF when available
  - If not available, Analytical Reagent (AR), Certified American Chemical Society (ACS), Food Chemicals Codex (FCC) when appropriate
Selecting Components ...

- Vendor FDA registered
- APIs - Use USP/NF when available or component of FDA-approved drugs or on FDA Bulk Substance List
  - Not on the FDA ‘negative’ list except as permitted
  - Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act
Certificate of Analysis

- CAS number
- Molecular Weight (to correct for salt form)
- Assay
- Water
- Impurities
- Appearance
- Must be kept for two years
### Certificate Of Analysis

<table>
<thead>
<tr>
<th>Item Number</th>
<th>Item</th>
<th>CAS Number</th>
<th>Molecular formula</th>
<th>Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES122</td>
<td>Estradiol, Micronized Powder, USP</td>
<td>50-28-2</td>
<td>( C_{16}H_{24}O_2 )</td>
<td>2AK0841</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification min max</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSAY ((C_{16}H_{24}O_2))</td>
<td>97.0 - 103.0 %</td>
<td>101.80%</td>
</tr>
<tr>
<td>MELTING RANGE</td>
<td>173 - 179 C</td>
<td>177 - 179 C</td>
</tr>
<tr>
<td>SPECIFIC ROTATION ([a]_D)</td>
<td>+76 to +83</td>
<td>+80</td>
</tr>
<tr>
<td>CHROMATOGRAPHIC PURITY</td>
<td>TO PASS TEST</td>
<td>PASSES TEST</td>
</tr>
<tr>
<td>WATER</td>
<td>3.50%</td>
<td>3.30%</td>
</tr>
<tr>
<td>OTHER IMPURITIES</td>
<td>TO PASS TEST</td>
<td>PASSES TEST</td>
</tr>
<tr>
<td>IDENTIFICATION</td>
<td>TO PASS TEST</td>
<td>PASSES TEST</td>
</tr>
<tr>
<td>EXPIRATION DATE</td>
<td>17-Mar-16</td>
<td></td>
</tr>
<tr>
<td>RESIDUAL SOLVENTS</td>
<td>TO PASS TEST</td>
<td></td>
</tr>
<tr>
<td>CLASS 2 (SOLVENT) / METHANOL</td>
<td>&lt; 3000 ppm</td>
<td></td>
</tr>
<tr>
<td>CLASS 3 (solvent) / ETHANOL</td>
<td>&lt; 5000 ppm</td>
<td></td>
</tr>
<tr>
<td>APPEARANCE</td>
<td>WHITE POWDER</td>
<td></td>
</tr>
<tr>
<td>MANUFACTURE DATE</td>
<td>17-Mar-11</td>
<td></td>
</tr>
</tbody>
</table>
Correction for Salt Form

- MW of Salt Form/MW of Base
- Example
  - Ketamine HCL MW 274.185 g/mol
  - Ketamine MW 237.727 g/mol
  - \( \frac{274.185}{237.727} = 1.153 \)
- For each 1 g of ketamine needed, use 1.153 g of ketamine HCL
Correction for Assay

- $\frac{100}{\text{assay}}$

- Example
  - Estradiol assay 99.8%
  - $\frac{100}{99.8} = 1.002 \text{ g}$
- For each 1 g of estradiol needed, use 1.002 g
Correction for Water

- \( \frac{100}{100 - \text{water}} \)

Example

- Estradiol water 3.3%
  - \( \frac{100}{100 - 3.3} = \frac{100}{96.7} = 1.034 \)

- For each 1 g of estradiol needed, use 1.034 g
Putting It All Together

- Salt correction x assay correction x water correction

- Example
  - Estradiol (no salt correction)
  - Assay correction x water correction
  - $1.002 \times 1.034 = 1.036$

- For each 1 g of Estradiol needed use 1.036 g

- Additional information USP <1160> *Pharmaceutical Calculations in Pharmacy Practice*
Master Formulation Record ...

- Name, strength, and dosage form
- Name (including salt form), grade and quantity of each active and inactive ingredient
- Calculations
- Compatibility and stability information
- Equipment needed
- Mixing instructions
... Master Formulation Record

- Sample labeling information
- Container used in dispensing
- Packaging and storage requirements
- Description of final preparation
- Quality control procedures and expected results
Compounding Record ...

- Preparation name, strength, and dosage form
- Master formulation record referenced
- Name (including salt form), grade and quantity measured of each active and inactive ingredient
- Sources, lot numbers, and expiration date for each active and inactive ingredient
... Compounding Record ...

- Total quantity compounded
- Name of person who prepared the preparation, performed the QC procedures, and approved the preparation
- Date prepared
- Assigned control or prescription number
... Compounding Record

- Assigned BUD
- Duplicate label as described in the Master Formulation Record
- Description of final preparation
- Results of quality control procedures (e.g., weight range of filled capsules, pH of aqueous liquids, accuracy of dispensing devices)
- Documentation of any quality control issues or adverse reactions or problems reported by patients
Weighing on Balance

- Level
- Calibrated
  - Internal
  - External – Are calibration weights calibrated?
- Stable: Wait for stability indicator before reading
- Error: Could be from equipment or user

Minimum Accurate Weighable Quantity (MAWQ)*
  - Linearity/Percent error allowed

*USP <1176> Prescription Balances and Volumetric Apparatus used in Compounding
Weighing on Balance

- Example
  - Linearity on a balance reading 0.000 is 0.002
  - A 5% error is allowed
  - MAWQ = 0.002/0.05 = 0.040 g
Measuring Liquids

- Capacity
- Calibrated
- Select graduated cylinders with capacity equal to or just exceeding capacity to be measured
- Know minimum volume
  - Example: Use 4 mL minimum volume in 10 mL cylinder for 5% error
- Cylinders calibrated either ‘to contain’ or ‘to deliver’
Mixing: Geometric Dilution

- Select a mortar large enough for the entire quantity
- Add the smallest quantity to mortar
- Add an equivalent amount of the next smallest quantity and mix until uniform using pestle
- Add a quantity equal to the combined quantities and mix until uniform
- Repeat as necessary to mix all components
Establishing Beyond Use Dates (BUDs)

<table>
<thead>
<tr>
<th>Type of Formulation</th>
<th>Maximum BUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonaqueous</td>
<td>Not later than the time remaining until the earliest expiration date of any API, or 6 months, whichever is earlier</td>
</tr>
<tr>
<td>Water-containing oral</td>
<td>Not later than 14 days when stored at cold temperatures</td>
</tr>
<tr>
<td>Water-containing topical/dermal and mucosal liquids and semi-solid</td>
<td>Not later than 30 days</td>
</tr>
</tbody>
</table>
Labeling

- Chemical name
  - including salt form when required
- Strength
- Dosage form
- Quantity
- BUD
- Indication that ‘this is a compounded preparation’
- Storage
- Warnings or hazards
- Additional state law requirements
Compounding Hazardous Preparations

- All elements required for compounding non-hazardous preparations must be followed for compounding hazardous preparations
- Additional containment strategies and work practices are required when compounding hazardous drugs in order to protect healthcare workers
What’s the Big Deal?

Working with or near hazardous drugs in health care settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.

Hazardous Drugs

- Carcinogen
- Genotoxin
- Teratogen
- Reproductive toxin
- Organ toxicity at low dose in humans or animals
- New drugs that mimic existing HDs in structure or toxicity
NIOSH List of Hazardous Drugs

- Three Tables
  - 1 – Antineoplastics
  - 2 – Non-antineoplastics
  - 3 – Reproductive only hazards
- Table 5 provides recommendations for Personal Protective Equipment (PPE)

www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf
Ideal Situation

- Handle every drug in every dosage form on the NIOSH list with all the containment strategies and work practices identified in <800>
- Is that possible in every case?
- Is that practical in every case?
- Is that necessary in every case?
Your Options

- Handle all drugs and dosage forms with all containment and work practices listed in <800>
- Perform an Assessment of Risk to determine alternative containment strategies and work practices
What’s the Assessment of Risk All About?

- USP <800> establishes the containment strategies and work practices best known to control hazardous drug contamination
  - Engineering controls
  - Protective equipment
  - Work practices
Hierarchy of Controls

1. Elimination
   - Physically remove the hazard.

2. Substitution
   - Replace the hazard.

3. Engineering Controls
   - Isolate people from the hazard.

4. Administrative Controls
   - Change the way people work.

5. PPE
   - Protect the worker with Personal Protective Equipment.

https://www.cdc.gov/niosh/topics/hierarchy/
HD Life Cycle in Your Pharmacy

Receive → Store → Compound

Dispense → Dispose
Your Hazardous Drug List

1. Review the NIOSH list of hazardous drugs
2. Identify the drugs and dosage forms you handle
3. Perform an Assessment of Risk
4. Document review of the list annually
Required Assessment of Risk Elements

- Drug
- Dosage form
- Risk of exposure
- Packaging
- Manipulation
- Documentation of alternative containment strategies and/or work practices

Review annually and document
Your HD List

<table>
<thead>
<tr>
<th>Require ALL containment strategies detailed in &lt;800&gt;</th>
<th>Alternative containment strategies can be considered and implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Active Pharmaceutical Ingredient (API) of any HD on the list</td>
<td>• Antineoplastics you only need to count or package</td>
</tr>
<tr>
<td>• Antineoplastics that require manipulation</td>
<td>• Non-antineoplastics</td>
</tr>
<tr>
<td>• Dosage forms that don’t fit your Assessment of Risk</td>
<td>• Reproductive only hazards</td>
</tr>
</tbody>
</table>
So What Happens With ...

- Active Pharmaceutical Ingredient (API)
- Antineoplastic dosage form dispensed in unit-of-use
- Antineoplastics that must be repackaged
- Antineoplastic oral dosage form that must be crushed
- Oral agents on Tables 2 and 3
API of Any Drug on the NIOSH List

- Active Pharmaceutical Ingredient of any antineoplastic, non-antineoplastic, or reproductive hazard
- **No option** → must treat with all the containment strategies and work practices in <800>
<800> Containment

- Containment Primary Engineering Control (C-PEC)
  - Powder Hood

- Containment Secondary Engineering Control (C-PEC)
  - Room with fixed walls separate from non-hazardous compounding
  - Negative pressure
  - Vented to the outside
  - At least 12 air changes per hour

Photo courtesy of Labconco
Antineoplastic Agents

- For antineoplastic agents that only require counting or packaging
  - Methotrexate tablets
  - Megestrol suspension
  - Conventionally-manufactured fluorouracil cream

- You can consider these dosage forms in your Assessment of Risk
HDs Other Than Antineoplastics

- Non-antineoplastics
- Reproductive only hazards

- All can be considered for your Assessment of Risk
  - But some are concerning
Approach to Assessment of Risk

- The NIOSH list has links and information concerning why the drug is on the list
- Look at that information, and evaluate it based on your circumstances
- Some are situational hazards
  - Hazards in third trimester
Assessment of Risk Requirements

- If you exempt specific drugs and dosage forms in your entity, you must identify the alternative containment strategies and/or work practices

- Determine how you will document this
  - Spreadsheet?
  - Separate form for each dosage form?
Examples of Work Practices

- Identify HDs by bins or shelf stickers
- Buy in unit-of-use when possible
- Use separate equipment for chemo
  - Designated counting tray and spatula
  - Wear chemo gloves tested to ASTM D6978
  - Decontaminate tray after use
Drug Storage

- Identify as HDs
- Store in yellow, lidded bins
- Clearly note what must be done if manipulation of the dose is required
Finished Dosage Forms

- Determine where they will be stored
- Waiting for patient pick-up
Resources

- USP Compounding Compendium
- USP FAQs
- The Chapter <800> Answer Book (ASHP)
- Safe Handling Practices for Hazardous Drugs (Joint Commission Resources/BD: www.hazmedsafety.com)
- Ready for 800? (bbraun: www.readyfor800.com)
- Perform an Assessment of Risk to Comply with USP <800>: www.pppmag.com, March 2017
Challenges You May Encounter

- The regulations/rules/standards may not align
  - Prioritize who you are trying to please
  - Know the rules
  - Develop and implement policies and procedures
  - Train staff and ensure competency
  - Track customer concerns
  - Track variances and unexpected outcomes
  - Perform compliance audits and mock inspections
  - Document, Document, Document
Common Issues

- Documentation lacking or incomplete
  - Policies and Procedures
  - Formulation/Compounding Records
  - Training Files
  - Calibration Logs
  - Hood Certification Reports
  - Cleaning Logs
  - Quality Control Records
  - Investigations of variances or unexpected outcomes
Common Issues: Formulation/Compounding Record

- Missing required information
- Calculations not performed for salt form, assay or water
- Purified Water, USP (or better) not used
- BUD inappropriate or not referenced
  - BUD exceeds the expiration of component
- Missing pharmacist double-check on chemicals and quantities
- Missing Quality Control
  - Description of the preparation
  - pH
  - Weight variation testing
  - Visual inspection
Common Issues: Training and Competency

- Initially, at least annually, and upon evidence of poor technique
  - USP <795>
  - Calculations
  - Equipment
  - Compounding processes
  - PPE
- Training is not the same as competency
  - Training should include some sort of knowledge check
  - Demonstrating competency involves a visual assessment
Common Issues: Cross-Contamination

- Hood must be powered on with safety shield in place
- Powders need to be weighed, mixed to the wet stage or made into capsules in hood
- Crush tablets in hood
- Operate mixers and blenders (for powders) in hood
- Mix troches, suppositories, etc. in hood
- Wet capsule machine, mortars, utensils, weigh boats etc. with water before leaving the hood or discard through attached trash chute
- Compound one preparation at a time
- Open one container at a time in hood
Common Issues: Cross-Contamination

- Close and wipe down container before removing
- Cover weigh boats
- Do not store excess chemicals or supplies in hood
- Do not bring bins or compounding logs into hood
- Towels are one time use
- Weigh boats, weigh paper and syringes are one time use
- Syringes stored in bottles add to risk
- Store glassware upside down. Cover tops of cylinders/funnels.
- Store utensils, pestles, devices, etc. in closed drawers or covered container
Common Issues: Potency Test Failures

- No correction for salt form, assay and/or water
- Inadequate mixing
- Chemical instability
- Weighing or measuring issue
  - Balance or measuring device not calibrated
  - Incorrect quantity weighed or measured
  - Remaining quantity left on weigh boat, cylinder, etc.
  - Spills
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QUESTIONS?