Pharmacy Compounding: Infection Prevention

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What is compounding?
What is compounding?

• NC Board of Pharmacy
  » taking two or more ingredients and combining them into a dosage form of a drug, exclusive of compounding by a drug manufacturer, distributor, or packer

• FDA
  » “combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient”
  » “Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling”

• USP
  » “The preparation, mixing, assembling, altering, packaging, and labeling of a drug or drug-delivery device”
    • Specifically includes: “Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients.”

1. Pharmacy Practice Act, N.C. Gen. Stat. § 90-85.3.(c)
2. FDA FAQ on compounding published 10/06/2015
3. [21 USC 321 (k) and (m)].
4. USP <795> Pharmaceutical Compounding-Nonsterile Preparations
Why do we care?

- **Federal**
  - USP Chapters <1000 → enforceable
  - FDA currently using “Enforcement Discretion”

- **State**
  - State Boards of Pharmacy can enforce only if FD&C Act is within regulations or if they have adopted its own version
  - The NCBOP has incorporated into its regulations USP 795 and 797 standards (and will include 800)
Why do we care?

- Scope of applicability
  - Health care organizations
  - Pharmacies
  - Physician practice facilities
  - Any and all facilities where CSPs are prepared, stored, and dispensed

- The Joint Commission
  - “TJC expects compliance.”
  - “Applies to all personnel who are preparing sterile products that are going to be used but are going to stored until used”
CSPs Incidents
Beyond Use Dates

- What is a Beyond Use Date (BUD)?

- How does a BUDs compare to:
  - Spike by time
  - Discard after time
  - Expiration date
  - Hang time
# USP 795 Risk Categories

<table>
<thead>
<tr>
<th>Categories</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>Compound has a USP monograph or appears in peer-reviewed literature</td>
<td>Captopril Oral Solution</td>
</tr>
<tr>
<td>Moderate</td>
<td>Compound that has special calculations or procedures</td>
<td>Morphine sulfate suppositories</td>
</tr>
<tr>
<td>Complex</td>
<td>Compound that requires special training, environment, facility, equipment, or procedures</td>
<td>Transdermal dosage forms</td>
</tr>
</tbody>
</table>
### SF - Captopril Oral Suspension 1 mg/mL

<table>
<thead>
<tr>
<th>Preparation:</th>
<th>Batch Size:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril Oral Suspension 1 mg/mL</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

### Source of Formula:
Am J Health-Syst. Pharm. 1997; 54:2483-2487

<table>
<thead>
<tr>
<th>Ingredients and Grade:</th>
<th>Amount:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril 50 mg tablets</td>
<td>2 tablets</td>
</tr>
<tr>
<td>Syrup BP</td>
<td>Qs ad 100ml</td>
</tr>
</tbody>
</table>

### Preparation Instructions:

1. Place the tablets in a mortar. Reduce the tablets to a fine powder.
2. Add a small amount of Syrup BP and mix to a uniform paste.
3. Add increasingly larger amounts of Syrup BP until it is incorporated into the suspension, working in each addition until uniform suspension is formed.
4. Transfer the contents of the mortar to a graduated cylinder and add enough Syrup BP to bring the final volume to 100 mL.
5. Transfer suspension back to mortar and mix until contents are uniform.

### Equipment:
Normal Room Ventilation- Gloves-Protect Exposed Skin

### Auxillary Labels:
- Shake well
- Protect from light
- Refrigerate

### Expiration Date:
30 days

### References:
Captopril Oral Suspension 1 mg/mL
# BUD Assignment – Non-sterile

<table>
<thead>
<tr>
<th>Categories</th>
<th>BUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonaqueous formulations</td>
<td>No later than the expiration of the earliest API or 6 months, whichever is earlier</td>
</tr>
<tr>
<td>Water containing oral formulation</td>
<td>No later than 14 days when stored at controlled room temp</td>
</tr>
<tr>
<td>Water containing Topical/Dermal and Mucosal Liquid and Semisolid Formulation</td>
<td>No later than 30 days</td>
</tr>
</tbody>
</table>

Note: no BUD should never be longer than any ingredient’s expiration.

Stability data that is longer can override these limits, however microbial growth should be considered.
Sterile compounding - Operational issues

Operational Process  Equipment  Environment
Training  CSP Preparation  Cleaning  Personnel
Literature

- **Accuracy/Sterility** - Trissel 2003\(^1\) and 2005\(^2\)
  - Estimated microbial contamination for Low and Medium-risk CSPs
  - Evaluated aseptic technique of pharmacists and technicians from 2002-2003 (\(n=267\))
    - 0.1% contamination for Low-risk CSPs (\(n=1058\))
    - 5.8% overall contamination rate for Medium-risk CSPs (\(n=539\))
      - Even worse rate for staff who regularly compounded

1. Am J Health Syst Pharm. 2003; 60:1853-55
Follow CSP Policy Before Entering:

1. Remove all Jewelry
2. Put on Hair and Face Covers
3. Put on shoe covers
4. Wash Hands and Forearms to Elbows
5. Put on Non-shedding Approved Gown / Coat
6. **BEFORE working in hood** and as needed Re-sanitize Hands
7. Put on Gloves
8. Sanitize Gloves
Environmental quality/control

## Cleanroom Particle Count Classifications

<table>
<thead>
<tr>
<th>ISO 14644-1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>FS 209E&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Maximum Particle Concentration (0.5 micrometers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Particles/m&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>352</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>35,200</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>352,000</td>
</tr>
<tr>
<td>6</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>100,000</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>International Organization of Standardization

<sup>b</sup>Federal Standards
Environmental quality/control

- Necessary ISO cleanroom components
  - Airborne particulate count
    - PEC (LAFWs/RABS/Barrier isolators): ≤ISO Class 5
    - Buffer zone: ≤ISO Class 7
    - Anteroom: ≤ISO Class 8
  - Air exchanges
    - >30 exchanges/hour (At least 15 from the PEC)
  - Positive pressure (non-hazardous)
    - At least 0.02-inch water column
  - Materials of construction
    - Limit ledges, crevices, etc.
    - Where is the sink?
Storage and Dating

- Single-dose vial
  - Opened or needle punctured single-dose
    - >ISO Class 5 → used within 1 hour
    - <ISO Class 5 → used up to 6 hour period*
      *(must be continuously exposed)
Storage and Dating

- Multiple-dose vial
  - Opened or needle punctured multiple-dose
    - 28 days or manufacturer specifications
Microbiological BUD

- Information resources
  - Chemical stability limits from literature or testing
  - USP Chapter <797>

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Room (25-35°C)</th>
<th>Refrigeration (2-8°C)</th>
<th>Frozen (≤-10°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate-use¹</td>
<td>1 hour</td>
<td>1 hour</td>
<td>N/A</td>
</tr>
<tr>
<td>Low w/12-hr BUD</td>
<td>&lt;12 hours</td>
<td>≤12 hours</td>
<td>N/A</td>
</tr>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Medium²</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>

¹Excludes hazardous medications; ²Entails >3 ingredients and/or batch/multiple dose preparations

It is your professional obligation to determine the “risk level”
Putting it all together

Risk Level

Beyond-Use Dating (point in time)

Chemical Stability Microbial Stability Aseptic technique

ASSUMPTION! CSP is stored at its optimal temperature at all times.

Proper garb Engineering controls DCA and First-Air
Case studies

- Your hospital has just purchased an ENT clinic and has asked your advice on reducing drug costs for the clinic. At nearly $1000 a vial, the Botox they are using to treat torticollis represents more than half their drug expenditure.
- Unfortunately, the average dose is only 0.1 mL of the 1 mL vial, leaving most of each vial wasted. In a dramatic cost savings move, a physician who is new to the clinic has started drawing up doses for all of his patients for the day from a single vial. This innovative practice is anticipated to save hundreds of thousands of dollars a year for the clinic.
- What would you advise the new clinic leadership to do?
Case studies

• At a clinic visit, a nurse expresses concern that a patient’s family is violating USP 797 and asks you to speak with the mother.

• When asked, the mother describes how she draws up two doses at a time from her son’s vial of filgrastim. One dose she gives immediately and the other she stores in the refrigerator for the next day.

• You know that filgrastim vials are single dose vials and you also know that they are quite expensive and this patient has poor insurance coverage.

• How do you respond to the nurse’s concerns and what do you advise the mother?
Video Tour of Pharmacy
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