Risk Level Determination and Assignment of Beyond-Use Dates

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October 9, 2013
Determination of Risk Level

• Responsibility of the person completing the compounding
• No single ‘iron-clad’ determination
• Requires professional judgment
• General descriptive statements to aid people performing compounding (not prescriptive)

Exception:
Non-sterile raw materials or equipment always high risk level
## USP <797> Risk Levels

<table>
<thead>
<tr>
<th>Ingredient: CSP Relationship</th>
<th>Risk Level</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>One to One (1:1)</td>
<td>Low-Risk Compounding</td>
<td>• Reconstitution and transfer of a 1 gram vial of cefazolin into one syringe or minibag</td>
</tr>
</tbody>
</table>
| One to Many or Many to One (1:? or ? to 1) | Medium-Risk Compounding | • A bulk 10 gram vial of vancomycin distributed among several final doses  
                                 |                   | • The combination of several ingredients (>3) into one final dose (TPN) |
| Any ingredient-CSP relationship using nonsterile ingredients and/or devices or a CSP that requires terminal sterilization (filtration, steam, heat, gas or ionizing radiation) | High-Risk Compounding | • Alum bladder irrigation  
                                 |                   | • PCA or epidural from powdered ingredients |

Polling Question

It is possible for a particular type of CSP to represent all risk levels depending on how it is prepared.

1. True

2. False
Risk Levels: It depends...

- If a vial/bag system is used or a premixed IV is dispensed
  - Not applicable
- If prepared as stat dose outside ISO Class 5 PEC
  - Immediate-use
- One dose for one patient made in a cleanroom
  - Low-risk level
- Prepared in a segregated compounding area
  - Low risk level with 12 hour BUD
- Batch of identical dosage forms made in a cleanroom
  - Medium risk level
- Prepared from non-sterile ingredients
  - High risk level
Single/Multiple Dose Vials

• Definitions of SDV and MDV are in the USP General Notices and Requirements

• Single dose vials:
  – Punctured in ISO 5 environment may be used for up to 6 hours
  – Punctured in worse than ISO 5 must be used within 1 hour or discarded

• Single dose ampules must be discarded after opening and not stored for any time period

Image courtesy [www.flickr.com](http://www.flickr.com)
Multiple Dose Vials

- Multiple dose vials – contain antimicrobial preservative(s)
- Designed for entry on multiple occasions
  - BUD: 28 days after initial entry unless specified otherwise by the manufacturer.
- Based on USP <51> Antimicrobial Preservative Testing
- Expiration date on vial is based on an unopened, properly stored vial

Image courtesy of www.pfizerinjectables.ca
Pharmacy Bulk Package (PBP)

- **USP <1> Injections**
- Sterile preparation for parenteral use that contains many single doses
- Restricted to the preparation of admixtures for infusion or filling empty sterile syringes
- Closure penetrated only once
- Used in a suitable work area such as a laminar flow hood
- Includes a statement limiting the time frame in which the container may be used once it has been entered

Image courtesy of [http://www.hospira.com](http://www.hospira.com)
Cefazolin 20 gram PBP

• Typical package insert
  – After entry, use entire contents of the vial promptly
  – Dispense and discard PBP within 4 hours of initial entry

Image courtesy of http://www.wgcriticalcare.com
Beyond-Use Dating (BUD)
Parameters for Establishing BUD

- Recognizes the probability of contamination even under best conditions:
  - Optimal employee performance
    - 0.1% (1 contaminated dose out of 1,000)
  - Contamination rates published in the literature
    - 0.3% – 16%
- Patient Safety: Protect patients from dangerous or even fatal overgrowths of microorganisms that may have been accidentally introduced
- Storage time: needs to be greater than zero but less than positive infinity*
  - (> 0 and < +∞)

* Personal conversation with Dr. David W. Newton, September 30, 2009
Responsibilities of Compounding Personnel

“Beyond-use dates are appropriate and based on valid scientific criteria”
Products vs. Preparations

- Manufactured Products
  - have Expiration Dates
- Compounded Preparations
  - have Beyond-Use Dates (or times)
  - Commonly used terms for Beyond-Use date include:
    - Discard after
    - Use before
    - Use by
    - Administer by
Expiration Dates

• Applies to manufactured drug products
• Determined by multiple, scientifically valid, product/package-specific research studies
• Based on the Arrhenius Equation \( k = Ae^{-\frac{E_a}{RT}} \) in statistical analysis
• Strict, specific, and proven to be valid
• Approved by the FDA

\[
k = Ae^{-\frac{E_a}{RT}} \quad \text{or} \quad \ln k = -\frac{E_a}{RT} + \ln A
\]

Where:
- \( k \) = Chemical Reaction Rate
- \( A \) = Pre-exponential Factor
- \( E_a \) = Activation Energy
- \( R \) = Gas Constant
- \( T \) = Temperature in Kelvin

Image courtesy [www.chemwiki.ucdavis.edu](http://www.chemwiki.ucdavis.edu)
Beyond-Use Dates

• The date (or time) beyond which the drug should not be stored

• Assigned by the facilities doing compounding
  – Needs to be consistent

• Deviates from the official labeling (package insert)
  – Considered compounding

• Should be based on drug-specific, scientifically valid research studies
  – Original articles and print and electronic compilations

• May use more general guidelines when specific information is unavailable
  – USP <795>
**Traditional BUD Paradigm**

- Assume the compounded preparation is sterile
- Base the BUD solely on the drug’s chemical stability
• Recognize the possibility that the preparation was inadvertently contaminated during compounding

• Based the BUD on
  1. the drug’s chemical stability in conjunction with
  2. microbiological limits for patient safety
BUD: Microbiological Limits

- Most shelf life labels or listed expiration dates are used as guidelines based on normal handling of products.
- Use prior to the BUD does not necessarily guarantee the safety of the drug.
- Immediately after the date, a CSP is not always dangerous nor ineffective*
- BUD storage limits are applied whenever an actual sterility test in accordance with USP Chapter <71> has not been performed

Sources of Stability Information for BUD

• Drug manufacturers, including the package insert
• Valid testing of the specific preparation and container
• Relevant published stability information in original articles or reliable print compilations and electronic databases
Chemical Stability Information

- Slow and difficult to collect adequate data
- Expensive to obtain adequate data
- Technically challenging, not usually within the capability of most pharmacists, nurses, and physicians
- Often unavailable
- Chapter <797> recognizes this
Beyond-Use Guidance

• In the absence of specific chemical stability information, follow the guidelines of USP Chapter <795>

  – Nonaqueous Formulations
    • BUD not later than the time remaining until the earliest expiration of any API or 6 months, whichever is earlier

  – Water-Containing Oral Formulations
    • BUD not later than 14 days when stored at controlled cold temperatures

  – Water-Containing Topical, Dermatologic, Mucosal Liquid and Semisolid Formulations
    • BUD not > 30 days
Polling Question

You are inspecting a pharmacy that is compounding hydration bags (in a LAFW inside a cleanroom) for a patient. They are adding electrolytes to liter bags of D5%/0.45%NS. Though they are only dispensing enough bags for 1 week at a time, you notice the label bears instructions to refrigerate and a “do not use after” date that is 2 weeks from the date compounded. What is your concern?

1. No concern. It is acceptable for low risk level CSPs to have a storage time of 14 days refrigerated.

2. Medium risk level BUDs refrigerated are only 9 days.
# Microbiological Beyond Use Dating

## Beyond-use dating for CSPs according to Risk-Level

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>BUD at Room Temperature (20 to 25°C)</th>
<th>BUD under Refrigeration (2° to 8°C)</th>
<th>BUD with Frozen Storage (-25 to -10°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Use</td>
<td>1 hour</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Low Risk with 12h BUD</td>
<td>12 hours</td>
<td>12 hours</td>
<td>N/A</td>
</tr>
<tr>
<td>Low Risk</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Medium Risk</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High Risk</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>

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Assigning Beyond Use Dating for Batch Prepared CSPs

Single Dose Container (SDC) bag, vial or ampule or Pharmacy Bulk Package (PBP)

1 Dose
- Inside ISO Class 5
- Outside ISO Class 5

# doses SDC/PBP used to make
- Preparation conditions
- Inside ISO Class 5
- Outside ISO Class 5

More than 1 dose
- Storage
- Entire contents not used
- Entire contents used in 6 hours (or manufacturer’s instructions if less)
- Do Not Use for multiple patients. After entry, discard

Microbial Risk Level of Final CSP

- Low Risk Level
  - 14 days cold temp.
  - 3 days room temp.
  - Use immediately

- Use immediately

- Medium Risk Level
  - 9 days cold temp.
  - 30 hours room temp.

- DO NOT STORE
  - Medium Risk Level
  - Discard contents of vial after 6 hours
  - 30 hours room temp.

- Medium Risk Level
  - 9 days cold temp.

- With no intervening steps once punctured

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Summary of Risk Level and Assignment of BUD

• It is important that consistent approach be established and uniformly applied when establishing and assigning BUDs to CSPs.

• It is strongly recommended that pharmacies establish a standardized compounding methodology for each CSP they compound.

• That methodology and all elements are best memorialized in a master compounding worksheet.

• With a standardized methodology, the microbial risk level is always the same each time the CSP is compounded.

• The risk level AND stability together determine BUD limited by whichever is shorter.

• Sterility testing according is the requirement of USP Chapter <71> are required when the default BUDs in the chapter for all risk levels are exceeded.