USP Chapter <797>: Beyond Use Dating, Stability, and Storage

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Continuing Education Objectives

After reading this monograph, the participant should be able to:

• Interpret and discuss the scope and intent of USP Chapter <797> the U.S. standard for pharmacy sterile compounding.
• Describe the various risk levels indicated in USP Chapter <797> for differing compounded sterile preparations, and the impact these have on beyond use dating (BUD).
• Discuss the factors that must be considered in establishing a safe beyond use date for various types of compounded sterile preparations.

USP Chapter <797>

The United States Pharmacopeia (USP) General Chapter <797> “Pharmaceutical Compounding—Sterile Preparations” was published in the fall of 2003 and went into effect on January 1, 2004. The chapter has had a tremendous impact on home infusion pharmacy operations and will continue to do so as it evolves.*

Indeed, USP <797> is the U.S. standard for pre-administration manipulations of compounded sterile preparations, including compounding, transportation, and storage. The guidelines apply to all compounding personnel without distinction as to site or profession—all patients deserve to be protected from errors and contamination.

Chapter <797> was created through the collective work of the USP Sterile Compounding Expert Committee, which is made up of:

• Pharmacists in academia
• Pharmacists from hospital practice
• Pharmacists from retail sterile practice
• Pharmacists from government

The experts on the committee did not participate in order to promote the business of compounding pharmacies or the profession of pharmacy, nor did they wish to apply good manufacturing processes (GMPs) to compounding pharmacy or to find a lowest common denominator by which the profession could operate. Instead, the experts, guided by USP, were foremost interested in patient safety—reducing the number of injuries and deaths from compounding, regardless of the site of practice.

The guidelines that resulted from their work are designed to describe current sterile compounding best practices and to help bring lagging pharmacies—and others—to speed with current best practices.

Products vs. Preparations

There is a clear differentiation between drug products that are manufactured by pharmaceutical companies for widespread use and sterile preparations that are compounded by pharmacists, technicians, physicians, and nurses for small-scale, individualized administration. As such, the dating requirements and language applied to each differs. For example, in order to avoid confusion caused by using language with regulatory meaning, USP adopted its own language for Chapter <797>, which includes “compounded preparations” rather than “products.”

* USP released a draft revision of General Chapter <797> in May 2006 with an associated comment period. A final revision, which will take comments into consideration, is expected to go into effect sometime in 2007.
"Products," manufactured by drug companies under federal standards—FDA good manufacturing practices (GMPs)—carry expiration dates. Expiration dates are determined by multiple, scientifically valid, product- and package-specific research studies. They are based on the Arrhenius Equation with statistical analysis and approved by the FDA. Expiration dates are very strict, specific, and proven to be valid.

Alternatively, "compounded preparations," compounded by pharmacy personnel, carry beyond use dates (BUD). BUD is the date or time beyond which the drug should not be used and is assigned by the compounding personnel. A BUD can deviate from the official labeling (package insert) of one or more of the preparation’s ingredients. However, that deviation should be based on drug-specific, scientifically valid research studies when possible. When specific information is not available, compounding personnel may use more general guidelines.

Shifting BUD Paradigms
USP Chapter <797> and its subsequent revision(s) reflect a shifting BUD paradigm that puts an increased emphasis on patient safety and protection from contamination.

In the past, compounding personnel worked under the assumption that the compounded preparation was sterile. BUD was based solely on the chemical stability of the drug. This dating method is simple, but not necessarily safe, given that the drug and/or other ingredients are not always sterile—they may be contaminated with microorganisms. In addition, this mindset fails to recognize the possibility that the preparation was inadvertently contaminated during compounding. Practitioners must embrace the mindset that if you’re mixing preparations all day, some of those batches may have bugs in them and you don’t know which ones.

The new BUD paradigm accepts this precept and bases BUD on the drug’s chemical stability in conjunction with microbiological limits for increased patient safety. For non-sterile preparations, BUD is based on chemical stability of the drug in the formulation and packaging at specific storage conditions. For sterile preparations, BUD is based on: 1.) chemical stability in conjunction with microbiological limits—whichever is shorter.

The addition of microbiological limits is designed to protect patients from dangerous, or even fatal, overgrowths of microorganisms that may have been accidentally introduced. These limits vary in duration by the likelihood, or risk level. They are applied whenever an actual sterility test in accordance with USP Chapter <797> has not been performed.

Microbiological Limits and Risk
USP designated risk levels for compounded preparations because different sterile preparations represent different amounts of risk and because pharmacists and other compounding personnel have not always recognized these differences.

Ultimately, improved patient safety requires a change of mindset—we owe it to our patients and ourselves to adopt a different way of thinking about risk. Not only is there a risk of compounded preparations being contaminated, there are associated risks to the patient’s health, risks to the compounder’s career and financial well-being, and risks to our profession and our compounding privilege.

Generally, complexity in compounding can lead to contamination. With this in mind, USP designated three risk levels for compounded sterile preparations (CSPs). Following is a brief overview of each:

- **Low-Risk**. Compounded from sterile, commercial drugs using commercial sterile devices. Maintained in an ISO Class 5 environment at all times. Compounded using only a few basic, closed-system aseptic transfers and manipulations.
- **Medium-Risk**. Multiple pooled, sterile, commercial products compounded for multiple patients or one patient multiple times. Complex aseptic manipulations where the compounding covers a long duration. No bacteriostat is used and the preparation is administered over several days.
- **High-Risk**. Prepared from non-sterile ingredients, or from sterile ingredients but exposed to less than ISO Class 5 environment. Involving a delay of more than six hours from compounding to sterilization. Purity of components is assumed but not verified by documentation.

It is the responsibility of the compounder to determine the risk level for each preparation. With the exception of a preparation made from non-sterile raw materials, which is always a High-Risk preparation, USP’s general descriptive statements (above) are designed to aid compounding personnel in their decision-making. There is no iron-clad way of making this determination—it requires professional judgment and must consider a variety of factors. For
Case Studies

Microbiological Limits and Risk

Determine the risk level (low, medium, or high) for each compounded sterile preparation using the stability information provided. Answers and explanations are listed below.

1. Cefazolin 1 g admixed into 50 mL of 0.9% Sodium Chloride for IV use
   - **Stability information:** 7% loss in 5 days at RT
     - 5% loss in 24 days at 4º C

2. TPN with AA 4.5%, dextrose 22%, 4 electrolytes, multiple vitamins, trace elements, insulin, ranitidine.
   - **Stability information:** No stability data on this specific formulation but other data allows for extrapolation of 15-30 days refrigerated

3. Morphine 50 mg/mL + Bupivacaine 10 mg/mL in NS for use in a SynchroMed® pump (18 mL) for IT use. Prepare 40 mL and package in two 20-mL syringes.
   - **Stability Information:** No loss of either drug in 60 days at RT or 4º C

4. Alprostadil 12.5 mcg/mL, Papaverine HCl 4.5 mg/mL, Phentolamine mesylate 0.125 mg/mL for intracavernosal injection.
   - **Stability Information:** 8% loss in 5 days at RT
     - 6% loss in 30 days at 4º C

Answers:

1. **Low Risk Level** - 48 hours at room temperature and 14 days refrigerated, per USP Microbiological limits
2. **Medium Risk Level** - 36 hours at room temperature and 7 days refrigerated.
3. **High Risk Level** - Must be prepared from non-sterile powder; 24 hours at room temperature and 3 days refrigerated, per USP Microbiological limits.
4. Risk Level determined by preparation techniques – see below:
   - If a single vial is prepared from commercial sterile vials: **Low Risk Level**
     - 48 hours at room temperature and 14 days refrigerated.
   - If prepared in a large batch of vials using commercial sterile drugs: **Medium Risk Level** - 36 hours at room temperature and 7 days refrigerated.
   - If prepared from non-sterile powders: **High Risk Level** - 24 hours at room temperature and 3 days refrigerated.

Example:

- Consider a 10 mL vial of diphenhydramine 10 mg/0.2 mL drawn into tuberculin syringes for pediatric IM administration:
  - **Stability Considerations**

Drugs and CSPs are subject to chemical and physical instabilities, which must also be considered when assigning a BUD.

Chemical processes, such as hydrolysis, oxidation, reduction, and racemization are occurring all the time. CSPs are also affected by physical factors, including temperature, exposure to light and oxygen, varying formulation components, water content, pH, containers and closures, and more. The result can be a preparation that is hazy or turbid, contains precipitation, color changes, or gas formation. See Exhibit 1 for more on how temperature affects BUD.

Since it is so difficult for pharmacists alone to judge drug stability, the new, patient safety-oriented paradigm suggests that they apply the “iceberg rule” of chemical stability. Only 10 percent of an iceberg is visible above the surface of the water, leaving 90 percent undetected until it is often too late. When considering chemical stability, pharmacists should assume that they won’t know about 90 percent of the problems associated with any mixture.

There are a variety of sources for stability information that can aid in the decision-making process. Using external, documented sources allows for professional judgment while providing sound footing in the event that the compounding’s decision is called into question. Pharmacists can consider the...
following stability sources:

- Stability information from drug manufacturers, including the package insert
- Stability information derived from valid testing of the specific preparation and container
- Relevant published stability information in original articles or reliable print compilations and electronic databases

The above sources aside, it is often challenging to locate appropriate chemical stability information. It is a slow and expensive process to collect adequate data and is not usually within the capability of most pharmacists, nurses, and physicians. USP recognizes this and provides an alternative method for determining BUD in the absence of specific stability information: following the guidelines of USP Chapter <795>.

For example, USP <795> guidelines recommend that for solids and non-aqueous liquids, the BUD should be 25 percent of the remaining expiration period or six months. For USP bulk substances, the BUD should not be more than six days, and for aqueous formulations, 14 days refrigerated. For all others, not more than 30 days or the intended duration of therapy. When you can’t find any other standard, benchmark your activity as you go.

### Professionalism in BUD

It should go without saying that it is unacceptable to subject patients to increased risk of harm for convenience or profit. But as professionals we must go beyond ill intent and take the steps necessary to reduce risk to the patient through inadvertent actions.

That is why all standard operating procedures should include specific BUD guidelines. Compounding personnel must also recognize that accuracy and consistency are critical in their processes, as is proper documentation—we all know the saying, “If it isn’t written, it didn’t happen.”

### Recommended Reading


Trissel is best known as the author of the Handbook on Injectable Drugs, a core pharmacy reference work found in nearly every hospital and home care pharmacy in the United States—and most of the rest of the world. First appearing in 1977, this work has been in continuous publication for nearly 30 years. In addition to the Handbook, Trissel has written the Pocket Guide to Injectable Drugs, Trissel's Stability of Compounded Formulations, Trissel's Tables of Physical Compatibility, and for 10 years wrote the National Cancer Institute's Investigational Drug - Pharmaceutical Data Book. He recently authored the new book Trissel's Calcium and Phosphate Compatibility in Parenteral Nutrition. Much of his published works are now collected in electronic format in Trissel's 2 Clinical Pharmacetics Database.

Trissel has served as a consultant to several pharmaceutical companies and the FDA on sterile drug product design, formulation and clinical use and served on the Pharmacy Professional Advisory Committee to the Surgeon General of the United States. He has been the recipient of a number of awards and honors throughout his career, including the APhA Distinguished Achievement Award in 2002 and the Award for Sustained Contributions to the Published Literature from ASHP in 1996.

### About the Author

Lawrence Trissel, B.S., R.Ph., FASHP, has more than 30 years experience in drug research with approximately 150 original publications to his credit—mostly in the area of drug stability. He serves as the Vice Chair of the USP Sterile Compounding Expert Committee, and along with other committee members is a principal author of the USP Chapter <797> Beyond Use Dating requirements.

Exhibit 1

Beyond Use Dating and Temperature

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Room Temperature</th>
<th>Refrigerator</th>
<th>Freezer (&lt; -20º C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>7 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>

Source: USP
1. The intent of USP Chapter <797> is to make sure that all compounding pharmacies apply good manufacturing processes (GMPs).
   a. True
   b. False

2. Which of the following is NOT considered one of the steps in the pre-administration manipulations of compounded sterile preparations (CSPs)?
   a. Compounding
   b. Storage
   c. Length of infusion

3. The U.S. Food and Drug Administration (FDA) determines the beyond use dates (BUD) for compounded sterile preparations.
   a. True
   b. False

4. A CSP that is compounded from multiple pooled sterile commercial products for use by multiple patients is considered to be:
   a. low-risk
   b. medium-risk
   c. high-risk

5. The determination of USP risk-level is the responsibility of the licensed health care professionals who supervise compounding.
   a. True
   b. False

6. A CSP that is compounded from non-sterile ingredients is always a high-risk preparation
   a. True
   b. False

7. Drawing a drug up into a syringe for IM administration would always be considered a low-risk preparation
   a. True
   b. False

8. When considering beyond use dating (BUD) for a CSP which of the following sources of information should be considered
   a. Chemical stability information
   b. Risk-level of the CSP
   c. Time and temperature at which the preparation is stored and used
   d. All of the above

9. USP Chapter <795>, Pharmaceutical Compounding—Nonsterile Preparations, provides guidance on determining chemical stability when specific published information is not available
   a. True
   b. False

10. Microbiological beyond-use dating (BUD) recommendations published in USP Chapter <797> apply only to preparations that are not tested for sterility
    a. True
    b. False
Continuing Education Application

JANUARY 15, 2007
Expires JANUARY 15, 2010

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   Email ______________________________________________________________________________________________________________________
   Soc. Sec. No. ____________________________________________________ Date Quiz Taken ________________

Quiz: Shade In Your Choice

Circle your choice

11. Is this program used to meet your mandatory C.E. requirements?
   A. Yes       B. No

12. Job description
   A. Owner     B. Manager    C. Employee

13. Age Group
   A. 21-30     B. 31-40    C. 41-50     D. 51-60     E. Over 60

14. How long have you been practicing as a home infusion pharmacist?
   A. 2 years or less     B. 5 years or less
   C. 10 years or less    D. More than 10 years

   15. Did this module achieve its stated objectives?
       A. Yes       B. No

   16. How much of this program can you apply in practice?
       A. All       B. Some
       C. Very little   D. None

   17. How long did it take you to complete both the reading and the quiz? _________ minutes

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