USP Compounding Standards and Beyond-Use Dates

On November 1, 2022, USP published updates to the USP General Chapters on compounding nonsterile and sterile preparations.

The revisions to the chapters, including updates to the beyond-use dates (BUDs), reflect advancements in science and clinical practice, clarify topics that were not consistently understood, and incorporate input from stakeholder engagements and from more than 1,400 public comments received during the public comment period from September 2021 to March 2022.

USP's Compounding Expert Committee, made up of independent volunteer experts, relied on the previously published chapters as well as input from stakeholders to revise the BUD limits. The revisions to the BUD limits were established based on a risk-based approach since it is difficult to predict the stability and microbial susceptibility for all the different types of nonsterile and sterile preparations (e.g., some preparations may degrade more quickly than others and some preparations may be more susceptible to microbial proliferation than others).

USP Compounding Standards

USP <795> *Pharmaceutical Compounding - Nonsterile Preparations*

USP <797> *Pharmaceutical Compounding - Sterile Preparations*

USP <800> *Hazardous Drugs - Handling in Healthcare Settings*

USP <825> *Radiopharmaceuticals - Preparation, Compounding, Dispensing, and Repackaging*

Updates to BUDs in Compounding Standards

The BUDs in the updated chapters reflect stakeholder feedback, and most of the revisions reflect expanded guidance on stability and sterility considerations for nonsterile and sterile preparations.

BUDs in USP <795> Pharmaceutical Compounding — Nonsterile Preparations

A new concept of "Water Activity" (a_w) was introduced

- The previously published chapter characterized preparations as "nonaqueous" or "water-containing." These characterizations were eliminated to clarify whether a substance containing waters of hydration or vehicles containing a small portion of water are considered "water-containing."
- In the revised chapter, the USP Compounding Expert Committee revised the BUD limit tables and introduced the concept of "water activity" to assess the susceptibility of a nonsterile preparation to microbial contamination and the potential for degradation due to hydrolysis.

What are Beyond-Use Dates?

Beyond-use dates (BUDs) are the date, or hour and the date, after which a compounded sterile preparation (CSP) or compounded nonsterile preparation (CNSP) must not be used, stored, or transported. The date is determined from the date and time the preparation is compounded.

Why are Beyond-Use Dates Necessary?

BUDs help decrease the risks that may be posed to patients. A BUD assigned to a CSP or CNSP identifies the time by which the preparation – once compounded – must be used before it is at increased risk for physical or chemical degradation, microbial contamination and proliferation, and impact on the integrity of the container closure system. In other words, the BUD serves to alert healthcare workers to the time/day after which a CSP or CNSP must not be used.

Comparison of BUD limits

Comparing BUDs between the previously published <795> and the revised <795>

Previous <795>	Revised <795>
Water-containing oral formulations = **14 days**	Nonpreserved aqueous dosage forms ($a_w \geq 0.60$) = **14 days**
Water-containing topical/dermal and mucosal liquids and semisolid formulations = **30 days**	Preserved aqueous dosage forms ($a_w \geq 0.60$) = **35 days**
	Oral liquids (nonaqueous) ($a_w < 0.60$) = **90 days**
Nonaqueous formulations = **6 months**	Other nonaqueous dosage forms ($a_w < 0.60$) = **180 days**

The revised chapter addresses compounded nonsterile preparations (CNSPs) requiring shorter BUDs and BUDs for CNSPs that may be extended (e.g., CNSPs with a *USP-NF* monograph or stability information).

BUDs in USP <797> Pharmaceutical Compounding — Sterile Preparations

New factors for consideration when establishing BUDs

The revised chapter changed the categorization of compounded sterile preparations (CSPs) from microbial contamination risk levels (i.e., low-, medium-, and high-risk level) to Category 1 and Category 2 CSPs. Additionally, Category 3 CSPs were added to describe the requirements a compounding facility must meet at all times for assigning BUDs up to a maximum of 180 days.

- The microbial contamination risk levels were determined based on specific conditions listed for each risk level.
- Category 1 and Category 2 are distinguished primarily based on the conditions under which they are made, the probability for microbial growth, and the time period within which they must be used.
    - Category 1: CSPs must be prepared in an ISO Class 5 or better primary engineering control (PEC) that may be placed in an unclassified segregated compounding area (SCA) and have shorter BUDs.
    - Category 2: CSPs must be prepared in a cleanroom suite and have longer BUDs.
- Category 3 CSPs may be assigned longer BUDs than the limits set for Category 2 CSPs up to a maximum of 180 days when compounded in accordance with all Category 3 CSP requirements. Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequency of environmental monitoring, and stability determination.

The revised <797> includes several factors to be considered when assigning BUDs for Category 2 and Category 3 CSPs. Category 2 CSPs are assigned a BUD based on risk elements including compounding method (e.g., aseptic processing or terminal sterilization), whether sterility testing is performed, the starting ingredients used for compounding (e.g., nonsterile or sterile), and the CSP's storage conditions (e.g., room temperature, refrigeration, or in a freezer). Category 3 CSPs are assigned a BUD based on compounding method and the CSP's storage conditions.

Comparing BUDs between the previously published <797> and the revised <797>

- In general, the storage periods in the previously published chapter are similar and sometimes longer than the BUD limits in the revised chapter.
- Longer BUD limits are permitted in certain specific circumstances based on additional requirements in engineering controls, environmental monitoring, and release testing.
- The table below summarizes and compares the storage periods and the BUDs in the previously published chapter and the revised chapter.

Previous <797>	Revised <797>

• Low-risk in a segregated compounding area
  ◦ 12 hours at CRT*
• Low-risk
  ◦ 48 hours at CRT
  ◦ 14 days in a refrigerator
  ◦ 45 days in a freezer
• Medium-risk
  ◦ 30 hours at CRT
  ◦ 9 days in a refrigerator
  ◦ 45 days in a freezer
• High-risk
  ◦ 24 hours at CRT
  ◦ 3 days in a refrigerator
  ◦ 45 days in a freezer
• BUDs could be assigned up to the duration indicated by appropriate information sources for the same or similar formulations and based on professional experience
 	
**CRT – Controlled Room Temperature*
	• Category 1
	  ◦ ≤ 12 hours at CRT
	  ◦ ≤ 24 hours in a refrigerator
	• Category 2
	  ◦ Aseptically processed, no sterility testing, only sterile starting components
	  4 days at CRT
	  10 days in a refrigerator
	  45 days in a freezer
	  ◦ Aseptically processed, no sterility testing, one or more nonsterile starting component(s)
	  1 day at CRT
	  4 days in a refrigerator
	  45 days in a freezer
	  ◦ Aseptically processed, passed sterility testing
	  30 days at CRT
	  45 days in a refrigerator
	  60 days in a freezer
	  ◦ Terminally sterilized, no sterility testing
	  14 days at CRT
	  28 days in a refrigerator
	  45 days in a freezer
	  ◦ Terminally sterilized, passed sterility testing
	  45 days at CRT
	  60 days in a refrigerator
	  90 days in a freezer
	• Category 3
	  ◦ Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs
	  60 days at CRT
	  90 days in a refrigerator
	  120 days in a freezer
	  ◦ Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs
	  90 days at CRT
	  120 days in a refrigerator
	  180 days in a freezer

Stay informed on USP Compounding Standards by signing-up for USP updates.
Explore USP Education to better understand the new and revised compounding standards at www.usp.org/compounding.
For any technical questions, email CompoundingSL@USP.org to access USP's Healthcare Quality and Safety team.