USP Compounding Standards and Beyond-Use Dates (BUDs)

On June 1, 2019, USP published updates to the USP General Chapters on compounding nonsterile and sterile preparations alongside new standards for compounding radiopharmaceutical drugs.

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 8,000 public comments received during the public comment process.

USP's Compounding Expert Committee, made up of independent volunteer experts, relied on the previously published chapters as well as input from the public and FDA, to revise the BUDs. The revisions to the BUDs were established 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*

What are Beyond-Use Dates?

Beyond-use dates (BUDs) are the date or time after which a compounded sterile preparation (CSP) or compounded nonsterile preparation (CNSP) may not be stored or transported and are calculated from the date or time of compounding.

Why are Beyond-Use Dates Necessary?

BUDs help decrease the risks that may be posed to patients. A CSP's or CNSP's BUD identifies the time by which the preparation – once mixed – must be used before it is at 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.

Updates to BUDs in Compounding Standards

The BUDs in the updated chapters were not significantly revised from the official chapters of <795> (last revised in 2014) and <797> (last revised 2008), 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" was introduced

- The official 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 tables and introduced the concept of "water activity" to assess the susceptibility of a nonsterile preparation to microbial contamination and the potential for

USP Compounding Standards and Beyond-Use Dates (BUDs)

Comparing BUDs between the official <795> and the revised <795>

Official <795> (last revised in 2014)	Revised <795> (published June 1, 2019)
▸ Water containing oral formulations = **14 days**	▸ Non-preserved aqueous = **14 days**
▸ Water-containing topical/dermal and mucosal liquids and semisolid = **30 days**	▸ Preserved aqueous = **35 days**
▸ Nonaqueous formulations = **6 months**	▸ Nonaqueous dosage forms = **90 days**
	▸ Solid dosage forms = **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).

- One type of formulation that has been impacted by the new BUD table is fixed oil suspensions, which previously had an 180 day BUD. In the revised chapter, fixed oil suspensions have a 90 day BUD.
- The USP Compounding Expert Committee made this change based on their experience in performing stability studies, as some oil formulations are susceptible to degradation before 180 days. Additionally, several commenters noted that oil formulations may not always be clinically appropriate.

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.

- 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 are typically prepared in an unclassified Segregated Compounding Area (SCA) and have shorter BUDs.
    - Category 2: CSPs are prepared in a cleanroom suite and have longer BUDs.

The revised <797> includes several factors to be considered when establishing BUDs for Category 2 CSPs, including aseptic processing and sterilization method, starting components, sterility testing, and storage conditions.

Comparing BUDs between the official <797> and the revised <797>

- In general, the storage periods in the official chapter are similar and sometimes longer than the BUDs in the revised chapter.
- Longer BUDs are permitted in certain specific circumstances based on additional requirements in engineering controls, environmental monitoring, and release testing.

USP Compounding Standards and Beyond-Use Dates (BUDs)

- The table below summarizes and compares the storage periods and the BUDs in the official chapter and the revised chapter.

Official <797> (last revised in 2008)	Revised <797> (published June 1, 2019)
▸ Low-risk in 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 CRT • 3 days refrigerator • 45 days frozen	▸ Category 1 • ≤ 12 hours at CRT • ≤ 24 hours in a refrigerator ▸ Category 2 • Aseptically processed, no sterility, only sterile starting components • 4 days at CRT • 10 days in a refrigerator • 45 days in a freezer • Aseptically processed, no sterility, one or more nonsterile starting component(s) • 1 day at CRT • 4 days in a refrigerator • 45 days in a freezer

**CRT (controlled room temperature)*

One of the most significant changes to the chapter is the inability to extend BUDs beyond those in Table 10 and Table 11 for Category 1 and Category 2 CSPs, respectively.

- During the public comment period, USP received numerous comments on extending BUDs. The revised chapters do not have provisions for extending BUDs because of the additional considerations (e.g., validated stability-indicating assays, release testing for sterility, endotoxins, container-closure integrity, particulate matter, and additionally personnel and environmental monitoring) that need to be in place to help ensure quality compounded sterile preparations.
- The 2020-2025 USP Compounding Expert Committee will be discussing this topic further, including developing additional resources on these considerations. We welcome stakeholder involvement in the standard setting process through the 2020-2025 Call for Candidates.

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.

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