How USP's Proposed <795> and <797> Changes May Complicate Patient Care

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A Briefing for Providers • January 20, 2022

Background

The United States Pharmacopeia is the agency that sets standards for drug substances, including for compounded medications. USP is not a regulatory agency; it's a standard-setting body. But FDA and most state Boards of Pharmacy adopt and enforce USP standards in federal and state regulation, and so USP standards in effect serve as the foundational regulatory framework for pharmacy compounding across America.

On September 1 , 2021, USP published revised proposed Chapters 795 and 797, which deal specifically with non-sterile and sterile compounding, respectively.

An earlier release of those revised chapters had been remanded back to USP's Compounding Expert Committee in 2020 as a result of appeals from APC and others. The appeals were largely based on concerns about process and the beyond-use-date limits we'll discuss here today.

APC's Beyond-Use Date Task Force, which included representation from NCPA, provided substantive input to the Compounded Expert Committee to assist CEC's effort to reconsider its earlier proposed limits on beyond-use dates. In its revised proposal the committee accepted some of our recommendations, but on certain substantive matters, the committee chose not to implement APC's recommendations..

As a result, we continue to have grave concerns about the impact of certain aspects of USP's proposals on prescribers' and compounding pharmacists' ability to treat patients with compounded medications. *Because you will almost certainly be affected by USP's actions, we wanted to familiarize you with the proposals and ask that as a prescriber you offer input to USP before the public comment period ends March 17.*

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What is a 'beyond-use date'?

It's the date beyond which a compounded preparation must not be used and must be discarded.

A B-U–D is different from the expiration date on a manufactured drug.

- An expiration date reflects the stability of a product as prepared by a manufacturer and approved by FDA.
- A beyond-use date is the last date that a compounded product can be safely used. Historically it has been based on:
  - Manufacturer recommendations
  - Published clinical literature
  - Limits set by USP

Given the time required in testing compounded medications, the beyond-use date affects how frequently the pharmacy must create a new compound as well as how frequently a patient needs a refill and the cost of that refill.

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USP Chapters <795> vs <797>

USP <795> sets standards for non-sterile compounding. These products are not required to be sterile in their final dosage form.

- Capsules
- Creams/ointments/gels
- Ear drops
- Lozenges/troches/sublingual drops
- Suppositories

USP <797> sets standards for sterile compounding. Compounded sterile products (CSPs) are required to be sterile if they are injectable, ophthalmics, or intended to be used inside of a body cavity

- IV, SQ or IM injections
- Intrathecals
- Eye drops
- Bladder instillations
- Wound irrigations

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Proposed Changes to <795> (Non-Sterile Compounding)

Training

- Defined core competencies
- Requires documentation of training and demonstration of knowledge and ability

Cleaning and sanitizing

- Defines minimum cleaning and sanitizing schedules

Beyond-Use Dates

- Introduces concept of water activity in determining BUD
- Increased focus on container closure

Designated Person

- New role created: Person(s) responsible for performance and operation of the facility and personnel in the preparation of non-sterile products

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How Water Activity Impacts the Assignment of Non-Sterile BUDs

Water activity is a measurement of how much water is in a substance that is free to react or attach itself to a material

Range is 0.03-1.0; a product with a water activity of less than 0.6 is considered anhydrous and can be given longer a BUD

Aqueous (hydrous) examples: water-containing suspensions, solutions, creams, lotions

Non-aqueous (anhydrous) examples: capsules, lozenges, troches, powders, ointments, oil suspensions

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BUDs – Non-Sterile

Type of Preparation	BUD (days)	Storage Temperature
Aqueous Dosage Forms (oral solutions, topical creams/gels)		
Non-preserved aqueous	14	Refrigerated
Preserved aqueous	35	Room Temp or Refrigerated
Nonaqueous Dosage Forms (oil based liquids, capsules, tablets, powders)		
Oral liquids (non aqueous)	90	Room Temp or Refrigerated
Other nonaqueous	180	Room Temp or Refrigerated

Most significant: BUDs for oil-based liquids decrease from 180 to 90 days

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Potential Impact to Non-Sterile Compounds

The BUD standards proposed in the revised <795> would impact non-sterile compounded preparations in the following ways:

- To provide an aqueous non-sterile compound such as metronidazole oral liquid with a BUD of >35 days, or a nonaqueous oral liquid such as calcitriol oral oil with a BUD of >90 days, *compounders will be required to perform costly tests (roughly $30,000 per active ingredient), meaning the price of these medications will drastically increase*.
- Under USP's proposal, no non-sterile compound can be assigned a BUD of >180 days, even if stability study data demonstrates stability beyond 180 days.

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Proposed Changes to <797> (sterile)

Beyond-Use Dates

- Creation of a Category 3 for CSPs (compounded sterile products)
- Category 3 Compounds have a longer BUD compared to Categories 1 and 2 with additional requirements

Endotoxin Testing

- Defines which products require endotoxin testing

Garbing Practices

- Defines changes in garbing requirements for type of CSP

Environmental Monitoring

- Defines personnel and environmental monitoring for pharmacies that make products with extended BUDs

Cleaning and Sanitizing

- Different cleaning/sanitizing practices for pharmacies making different types of CSPs

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The 3 Categories of Sterile Compounds

Low-, Medium- and High-Risk categories were changed to Category 1, 2 and 3

Categories 1 and 2 are distinguished by the facility in which the CSP is made and the length of time that it is stored

- **Category 1:** compounded under least controlled environment, shortest BUDs
- **Category 2:** more environmental controls and testing, longer BUDs
- **Category 3**: CSPs with an extended BUD after performing a stability indicating study, container closure study, sterility testing, more environmental and personnel testing, and more

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Current <797> (published 2008)	**Proposed New <797>**
Low Risk in SCA - 12 hours RT	Category 1 - <12 hours RT, <24 hours refrigerated
Low Risk - 48 hours RT, 14 days refrigerated, 45 days frozen	Category 2 (aseptically processed, no sterility testing, only sterile starting components) - 4 days RT, 10 days refrigerated, 45 days frozen
Medium Risk - 30 hours RT, 9 days refrigerated, 45 days frozen	Category 2 (aseptically processed, no sterility testing done, one or more non-sterile starting components - 1 day RT, 4 days refrigerated, 45 days frozen
	Category 2 (aseptically processed, sterility testing performed) - 30 days RT, 45 days refrigerated, 60 days frozen
High Risk, no sterility testing - 24 hours RT, 3 days refrigerated, 45 days frozen	Category 3 (aseptically processed, sterility tested, passed all applicable tests) - 60 days RT, 90 days refrigerated, 120 days frozen
High Risk with appropriate sterility/endotoxin testing – **extended up to study/literature references (typically 180 days RT)**	Category 3 (terminally sterilized, sterility tested, passed all applicable tests) - 90 days RT, 120 days refrigerated, 180 days frozen

Proposed Category 2 BUDs

Category 2	
Aseptically Produced	
Room Temp	30 days
Refrigerated	45 days
Frozen	60 days
Terminally Sterilized	
Room Temp	45 days
Refrigerated	60 days
Frozen	90 days

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Maximum Usable Shelf Life

Category 2	
Aseptically Produced	
Room Temp	16 days
Refrigerated	31 days
Frozen	46 days
Terminally Sterilized	
Room Temp	31 days
Refrigerated	46 days
Frozen	76 days

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Proposed Category 3 BUDs

Category 3	
Aseptically Produced	
Room Temp	60 days
Refrigerated	90 days
Frozen	120 days
Terminally Sterilized	
Room Temp	90 days
Refrigerated	120 days
Frozen	180 days

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Maximum Usable Shelf Life

Category 3	
Aseptically Produced	
Room Temp	46 days
Refrigerated	76 days
Frozen	106 days
Terminally Sterilized	
Room Temp	76 days
Refrigerated	106 days
Frozen	166 days

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Other Considerations in Extending BUDs

Previously, pharmacies could extend CSPs up to 180 day BUDs (at room temperature storage, with sterility testing) using published or unpublished stability studies, or performing potency over time testing

New maximum proposed batch size is 250 units

Not all drug products are eligible or appropriate for frozen storage or terminal sterilization

Must consider chemical and physical stability of the product, compatibility of the container closure system

BUDs are based primarily on achievement and maintenance of **sterility**

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How Would a Compounder Provide a Patient with a 30-Day Supply of a Sterile Compound?

Under the proposed BUD limitations in <797>, to realistically provide a patient with a sterile compound that has a 30 day usable shelf life, a compounder would need to:

- Store the sterile preparation frozen;
- Terminally sterilize and store the preparation in the refrigerator, or;
- Perform a $30,000+ stability study on the preparation.

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What Do These Options Mean in Terms of Patient Access and Medication Quality?

Colder storage temperatures could present quality and/or administration problems

- Crystallization/precipitation formation in sterile solutions
- Adverse patient reactions to the administration of cold injectables and ophthalmics

Terminal sterilization may not be possible for drugs or packaging that are heat sensitive

Stability study expense may be cost prohibitive for some compounders to even perform, and will drive up medication costs for compounds that do undergo stability testing.

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How Do The Proposed Changes to Sterile Item BUDs and Batch Size Improve Patient Safety?

USP has provided no valid rationale or scientific evidence for how these proposed BUD and batch size limitations will improve product quality.

Instead, USP continues to provide flawed rationale in support of their position that the only way to improve patient safety is to create standards that limit compounders' ability to provide sterile compounds.

This position calls into question:

- USP's commitment to creating standards that ensure both product quality AND patient access - is USP keeping patient care in mind?
- The value of even issuing a chapter on sterile compounding standards, if USP itself feels the standards in <797> are not sufficient to ensure a high level of quality.

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Next Steps

Make comments to USP before the March 17, 2022, deadline here:

- 795: https://usp.az1.qualtrics.com/jfe/form/SV_3OBK7VUbvver6zs
- 797: https://usp.az1.qualtrics.com/jfe/form/SV_81VZpnzjwcQJlZA

Include patient access examples – how overly short BUDs will unnecessarily complicate how you care for certain patients on certain therapies.

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Important Links

USP Compounding General Chapters Available for Public Comment: Comments should be submitted directly to the <795> and <797> proposals

- September 1, 2021: Proposed Revisions to <795> Pharmaceutical Compounding – Nonsterile Preparations
- September 1, 2021: Proposed Revisions to <797> Pharmaceutical Compounding – Sterile Preparations

Supplemental Documents: Not for Public Comment

Stability Study Reference Document for the 2021 Proposed Revisions to <795> and <797

- December 13, 2021 (Updated): Stability Study Reference Document for the 2021 Proposed Revisions to <795> and <797>

USP General Chapter <795> Informational Documents

- September 1, 2021: BUD Scientific Rationale for the 2021 Proposed Revisions to <795>
- September 1, 2021: BUD Reference for the 2021 Proposed Revisions to <795>
- September 1, 2021: Compounding Expert Committee Responses to Stakeholder Engagement Themes for the 2021 Proposed Revisions to <795>

USP General Chapter <797> Informational Documents

- September 1, 2021: BUD Scientific Rationale for the 2021 Proposed Revisions to <797>
- September 1, 2021: BUD Reference for the 2021 Proposed Revisions to <797>
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THE CAMPAIGN TO SAVE COMPOUNDED HORMONE THERAPY

Compounded bioidentical hormones (cBHT OR cBHRT) are an essential medical therapy for millions of women who suffer the debilitating effects of hormone imbalance. For these patients, compounded hormones aren't an alternative to manufactured hormones, they are the only available option. And now there is a significant threat to patient access of this important therapy.

The FDA has signaled that it may consider new regulations that, if implemented, will deny access to a critically important, life-changing medical therapy to millions of people.

The FDA has said it will base its decisions on a deeply flawed report that it commissioned from the National Academies of Science, Engineering and Medicine. The report is neither a complete nor accurate representation of compounded hormones and is tainted by demonstrable bias, conflicts of interest, and bad science.

To learn more, visit compounding.com

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