BEYOND THE BUD: STRATEGIES FOR EXTENDING BEYOND-USE-DATES OF COMPOUNDED PREPARATIONS

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Disclosure Statement

- Disclosure: Dr. Backiel has no relevant financial relationship(s) with ineligible companies to disclose

Pharmacist & Technician Learning Objectives

- At the completion of this activity, participants will be able to:
  - Describe the regulatory foundations of beyond-use-date (BUD) assignment, including key requirements from USP <795>, <797>, and <800>
  - Differentiate between beyond-use-dates and expiration dates, and explain how stability and sterility influence BUD determination
  - Evaluate the scientific evidence used to justify extended BUDs, including stability-indicating assays, literature data, and compatibility studies
  - Identify common pitfalls and safety considerations related to extending BUDs, including environmental controls, compounding technique, and documentation requirements.
  - Develop strategies to implement extended BUDs in practice, such as standard operating procedures (SOPs), staff training, and quality assurance monitoring.

Background

- Drug waste can increase costs for a healthcare system
- Disposal of compounded medications that have exceeded their BUD is a common source of drug waste
- Maximizing the BUD assigned to these products can help to minimize waste

Bekker CL et al., *Pharmacy (Basel)*, 2018
d'Aranda E et al., *Crit Care*, 2025
Ganio M, *AMA J Ethics*, 2024
Carrez L et al. *Am J Health Syst Pharm*, 2008

How to maximize BUD?

- Pharmacy personnel typically use a combination of USP BUD limits and manufacturer prescribing information to assign BUD's

- The BUD can be maximized by:
  - Improving compounding category
  - Sterility Testing
  - Stability Testing
  - Literature Review

USP General Chapter <797> (2023)

Beyond-Use-Date vs Expiration Date

Term	Definition	Applicability
BUD	Either the date, or hour and date, after which a CSP must not be used. The BUD is determined from the date and time that preparation of the CSP is initiated.	Applies to all compounded sterile products (CSP).
Expiration date	The time during which a product can be expected to meet the requirements of the *USP–NF* monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions.	Applies to all conventionally manufactured products, APIs, and added substances.

USP General Chapter <797> (2023)

Polling Question #1

- **True or False:** When assigning a beyond-use-date to a compounded product, you only need to consider the physical and chemical stability of the preparation
  - A) True
  - B) False

Sterility vs Stability

- Sterility- The absence of viable microorganisms
- Stability- The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD
- When assigning a BUD to a compounded product, **BOTH** sterility and stability must be considered.

USP General Chapter <797> (2023)
Pitt R et al., *ASHP*, 2021

"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."

USP Compounding Standards and Beyond-Use Dates (2022)

Why BUD's are necessary?

Parameters to Consider in Establishing a BUD

- Chemical and Physical Stability
- Material composition and compatibility
- Environmental conditions
- Aseptic processing / sterilization
- Sterility of starting components
- Sterility testing
- Storage conditions

USP General Chapter <797> (2023)

Polling Question #2

- According to USP <795>, what is the maximum beyond-use-date for a non-preserved aqueous dosage form?
  - A) 14 days
  - B) 35 days
  - C) 90 days
  - D) 180 days

Non-sterile Compounding USP <795> Beyond-Use-Dates

Revised <795> (published June 1, 2019)

- Non-preserved aqueous = **14 days** (FRIDGE)
- Preserved aqueous = **35 days**
- Nonaqueous dosage forms = **90 days**
- Solid dosage forms = **180 days**

USP Compounding Standards and Beyond-Use Dates (2022)
USP General Chapter <795> (2023)

Sterile Compounding
USP <797> Beyond-Use-Dates

Revised <797> (published June 1, 2019)

- Category 1
  - ≤ 12 hours at CRT (Controlled Room Temperature)
  - ≤ 24 hours in a refrigerator
- Category 2
  - Aseptically processed, no sterility, only sterile starting components
    - 4 days at CRT (Controlled Room Temp)
    - 10 days in a refrigerator
    - 45 days in a freezer

USP Compounding Standards and Beyond-Use Dates (2022)
USP General Chapter <797> (2023)
USP <797> FAQ (2023)

Hazardous Drug Compounding <800> Beyond-Use-Dates

- Follow the BUD's established in chapters <795> and <797>
- Closed-System-Transfer-Devices do not extend beyond-use-date

USP General Chapter <800> (2019)

What we can do to extend: Non-sterile Compounding

- Water Activity (Aw)
- Preservatives
- CNSPs with Stability Information

USP General Chapter <795> (2023)

What we can do to extend: Sterile Compounding

- Improve Compounding Category
- Stability/Compatibility Studies
- Sterilization
- Sterility Testing

USP General Chapter <797> (2023)
Pitt R et al., *ASHP*, 2021

Polling Question #3

- **True or False:** An "Immediate Use" compounded sterile preparation has a maximum beyond-use-date of 4 hours.
  - A) True
  - B) False

Compounding Categories: Immediate Use

- Aseptic technique
- Personnel training and competencies
- Not more than 3 different sterile products
- BUD: 4 hours

USP General Chapter <797> (2023)

Compounding Categories: Category 1

- Hand-Hygiene & Garbing
- Aseptic Manipulation Competency Testing
- ISO Class 5 Primary Engineering Control (PEC)
- Segregated Compounding Area (SCA)
- Microbiological Monitoring
- Cleaning, Disinfecting, and Sporicidal Application

- BUD: 12 hours RT, 24 hours Fridge

USP General Chapter <797> (2023)

Compounding Categories: Category 2

- Category 1 Requirements PLUS:
  - Donn garb in classified area
  - Clean ceilings monthly as well
  - Cleanroom Suite (Secondary Engineering Controls)
    - ISO Class 8 Anteroom
    - ISO Class 7 Buffer-room
  - Air exchange
  - Pressure differentials

Compounding Categories: Category 2 (cont.)

Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20°–25°C)	Refrigerator (2°–8°C)	Freezer (–25° to –10°C)
Aseptically processed CSPs	**No** (using 1+ nonsterile components)	1 day	4 days	45 days
	No (using only sterile components)	4 days	10 days	45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	**No**	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

USP General Chapter <797> (2023)

Compounding Categories: Category 3

- Category 2 Requirements PLUS:
  - More frequent competency testing
  - Enhanced garbing requirements
  - More frequent Microbiological and Environmental Monitoring
  - More frequent cleaning
  - Sterility Testing
  - Stability Requirements

USP General Chapter <797> (2023)

Compounding Categories: Category 3 (cont.)

Compounding Method	**Controlled Room Temperature (20°–25°C)**	**Refrigerator (2°–8°C)**	**Freezer (–25° to –10°C)**
Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs	60 days	90 days	120 days
Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs	90 days	120 days	180 days

USP General Chapter <797> (2023)

Stability/Compatibility Studies

- Published Monographs
  - Trissel's, USP-NF, ASHP Injectable Drug Information

- Stability Studies

USP General Chapter <797> (2023)

Stability/Compatibility: Published Monographs

- Trissel's Stability of Compounded Formulations
- ASHP's Injectable Drug Information
- USP-NF Compounded Preparation Monographs

Stability/Compatibility: Published Studies

- PubMed:

Int J Pharm Compd. 2019 Mar-Apr;23(2):163-166.

Evaluation of the Physicochemical Stability of Amiodarone Hydrochloride in Syringes for the Intensive Care Unit

Benjamin Lardinois [1], Alexandre Dimitriou [1], Charlotte Delcave [2], Jacques Jamart [3], Benoît Bihin [3], Laura Soumoy [4], Jean-Daniel Hecq [5], Laurence M Galanti [6]

Affiliations + expand

PMID: 31085782

Abstract

In some emergency clinical situations, the injection of a more concentrated drug solution in the intensive care units is common. The purpose of this study was to evaluate the physicochemical

Lardinois B et al., *Int J Pharm Compd, 2019*

Sterilization

- Aseptic Processing
  - Sterilization by Filtration
- Terminal Sterilization

USP General Chapter <797> (2023)

Polling Question #4

- Which of the following is considered a method of Terminal Sterilization under USP <1229>?
  - A) Aseptic processing
  - B) Sterilization by filtration
  - C) Dry heat sterilization
  - D) Using only sterile starting ingredients

Sterilization: Aseptic Processing

- Compounding with only sterile ingredients

- Compounding with non-sterile ingredients followed by "sterilization by filtration"

USP General Chapter <797> (2023)

Sterilization: Terminal Sterilization

- USP <1229> - Sterilization of Compendial Articles
  - Steam Heat
  - Dry Heat

USP General Chapter <797> (2023)
USP General Chapter <1229> (2022)
Pitt R et al., *ASHP*, 2021

Sterility Testing

- USP <797>
  - USP <71>
- Membrane Filtration
- Direct Inoculation
- Method Suitability
- Bacterial Endotoxin Testing (BET)

Polling Question #5

- **True or False:** If a sample from a batch of compounded sterile preparations passes a sterility test, it guarantees that the entire batch is completely sterile.
  - A) True
  - B) False

Sterility Testing: USP <797>

Category 2 BUDs

Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20°–25°C)	Refrigerator (2°–8°C)	Freezer (–25° to –10°C)
Aseptically processed CSPs	**No** (using 1+ nonsterile components)	1 day	4 days	45 days
	No (using only sterile components)	4 days	10 days	45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	**No**	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

USP General Chapter <797> (2023)

Sterility Testing: <USP 71>

- USP Chapter dedicated to Sterility Testing

- Number of items to be tested
  - Batch size of 1 to 39 = 10% rounded UP to the nearest whole number
  - Batch size >40 = Follow USP <71>
  - Batch size limited to 250 Final Yield Units per <797>

USP General Chapter <797> (2023)
USP General Chapter <71> (2009)

Sterility Testing: <USP 71>

- Sterility Tests:
  - Membrane Filtration
  - Direct Inoculation

- Method Suitability Testing

- Passing sterility test does NOT mean the entire batch is sterile
  - Passing sterility test means longer BUD permitted

USP General Chapter <797> (2023)
USP General Chapter <71> (2009)

Sterility Testing: Bacterial Endotoxin Testing

- CSPs with Non-sterile Starting components
  - Required for:
    - Category 2 (with sterility testing BUDs)
    - Category 3
- Endotoxin limits - USP <85>

USP General Chapter <797> (2023)
USP General Chapter <85> (2012)

How to Implement?

- Quick Wins
  - Doesn't have to be all or nothing!
- SOP's
- Staff Training
- Re-assess

Pitt R et al., *ASHP*, 2021

Potential Risks/Pitfalls

- Cost-Benefit-Analysis
  - 503b Purchasing
  - Over-batching
  - Time-investment
- Short Stability Examples
  - Phenytoin
- Engineering Failures
  - Risk Assessment

Abbasi G, et al., *Hosp Pharm*, 2017
Pitt R et al., *ASHP*, 2021
Phenytoin Sodium Injection [package insert]. Pfizer Inc; 2011

Conclusion/Wrap-up

- Shorter beyond-use-dates can contribute to drug waste
- Maximizing and extending BUD's while maintaining compliance can potentially mitigate these losses
- Implementation feasibility and benefit can vary from institution to institution

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Thank You!

- Questions?

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