BEYOND-USE DATE BASICS FOR NONSTERILE COMPOUNDING

LIZ FREDERICKSON, PharmD, BCPS

Liz Fredrickson is an Associate Professor of Pharmacy Practice and Pharmaceutical Sciences at the Northeast Ohio Medical University College of Pharmacy. She serves as the Director of Instructional Labs and is the course director for the Basic Pharmaceutics Lab and Parenteral Products and Parenteral Products Lab courses.

Topic Overview

Assigning appropriate beyond-use dates is an important part of the nonsterile compounding process. Using their knowledge of stability and the United States Pharmacopeia (USP) standards, pharmacists can assign beyond-use dates to compounded nonsterile preparations that will ensure product integrity and safety throughout the usage and storage period. This course will assist pharmacy personnel in understanding parameters to consider when determining beyond-use dates for compounded nonsterile preparations and will provide recommendations for assigning appropriate beyond-use dates for these types of preparations. USP General Chapter <795> guidelines will be reviewed.

Accreditation Statement:

RxCe.com, LLC is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

Universal Activity Number (UAN): The ACPE Universal Activity Number assigned to this activity is **0669-0000-22-106-H07-P**.

Credits: 1 hour of continuing education credit

Type of Activity: Knowledge

Media: Internet **Fee Information:** $4.99

Estimated time to complete activity: 1 hour, including Course Test and course evaluation

Release Date: December 21, 2022 **Expiration Date:** December 21, 2025

Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From December 21, 2022, through December 21, 2025, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
2) Study the section entitled "educational activity;" and
3) Complete the Course Test and Evaluation form. The Course Test will be graded automatically. Following successful completion of the Course Test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** factors that can affect the stability of compounded nonsterile preparations
2. **Explain** water activity and its importance in determining beyond-use dates for compounded nonsterile preparations
3. **Assign** appropriate beyond-use dates to compounded nonsterile preparations
4. **Recall** considerations for extending beyond-use dates for compounded nonsterile preparations

Disclosures

The following individuals were involved in the development of this activity: Liz Fredrickson, PharmD, BCPS, and Susan DePasquale, MSN, PMHNP-BC. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Preparing safe, effective, and quality compounded nonsterile preparations requires many essential steps, one of which is assigning an appropriate beyond-use date. This requirement lets patients know when their medication can no longer be safely used. Using their knowledge of stability and United States Pharmacopeia standards, pharmacists can assign beyond-use dates to compounded nonsterile preparations that will ensure product integrity and safety throughout the usage and storage period. This course will assist pharmacy personnel in understanding parameters to consider when determining beyond-use dates for compounded nonsterile preparations and will provide recommendations for assigning appropriate beyond-use dates for these types of preparations. United States Pharmacopeia, General Chapter <795>, will be reviewed in this context.

Beyond-use Date Basics

The term beyond-use date (BUD) refers to the date (or hour and date) after which a compounded nonsterile preparation (CNSP) cannot be used and must be discarded.[1] Guidelines for assigning beyond-use dates are provided by the United States Pharmacopeia (USP).[1] The BUD can be calculated in terms of hours, days, or months.[1] Before learning more about what a BUD is, it can be helpful to understand what it is not. The most important distinction is recognizing the differences between a BUD and an expiration date. These terms are compared in Table 1. An expiration date is defined as the time during which a conventionally manufactured product, active pharmaceutical ingredient (API), or added substance can be expected to meet the requirements of a compendial monograph or maintain expected quality if it is kept under the prescribed storage conditions.[1] An expiration date limits the time during which manufactured products can be dispensed or used.[1] Beyond-use dates are typically much shorter than expiration dates and do not require the extensive testing needed for expiration dating.[1]

Table 1. Comparison of Beyond-use Dates and Expiration Dates[1,2]

	Beyond-use Date	Expiration Date
Definition	The date (or hour and date) after which a CNSP cannot be used	The time during which a conventionally manufactured product, active pharmaceutical ingredient (API), or added substance can be expected to meet the requirements of a compendial monograph or maintain expected quality, if it is kept under the prescribed storage conditions
Assigned by	Assigned by compounding personnel	Assigned by the manufacturer
Determination	Determined using stability data and USP Chapter <795> guidelines	Determined using extensive testing

The Importance of Beyond-Use Dates

Beyond-use dates are important for both compounding personnel and patients. Once the BUD has passed, the product becomes at risk for physical and chemical degradation, reduced integrity of the container-closure system, and microbial contamination.[1] Patient safety should always guide the process of preparing nonsterile compounds, and this includes the assignment of beyond-use dates. However, while choosing a less conservative BUD or extending a BUD may seem convenient or be seen as a method by which to reduce waste, inappropriately assigning BUDs can also lead to potential patient harm. There are some valid methods by which to extend beyond-use dates of CNSPs, and these will be discussed later in this course.

Regulatory Oversight

A BUD can be thought of as a risk assignment determined by using the most current and evidence-based information available.[3] Various regulatory

organizations provide oversight for CNSP beyond-use dating, including the Centers for Medicare and Medicaid Services (CMS) and The Joint Commission (TJC).[3] The American Society of Health-System Pharmacists (ASHP) published "The Pharmacist Guide to Assigning a Beyond-use Date to a Compounded Sterile or Nonsterile Preparation," which includes a useful table detailing stances on beyond-use dating among various organizations (Table 2).[3] Of these organizations, the most influential is the United States Pharmacopeia, and many other organizations refer to these standards.[1,3] For example, the U.S. Food and Drug Administration (FDA) refers to USP recommendations regarding the assignment of BUD.[3]

Table 2. Organizational Stances on Beyond-use Dating[3]

Organization	Relevance of Organization to BUD	Stance on BUD
American Society of Health-System Pharmacists (ASHP)	• ASHP is the largest pharmacy organization in the world	• The ASHP Guidelines on Compounding Sterile Preparations references USP standards
Centers for Medicare and Medicaid Services (CMS)	• CMS is a US federal agency that sets minimum standards of care (for both patients and is intended to set the bar for high quality and value. • Non-compliance with CMS minimum standards would make health systems ineligible for reimbursement and therefore CMS works with other organizations to ensure compliance	• Per general references, "BUD is to be based on information provided by the manufacturer, whenever such information is available."

	with minimum standards.	
Det Norse Veritas (DNV), healthcare sector	• This is a non-profit, independent, non-governmental organization that aligns with CMS standards, but may also exceed federal standards to achieve the highest safety, quality, and value standards.	• Aligned with CMS
Healthcare Facilities Accreditation Program (HFAP)	• A non-profit, independent, non-governmental organization that aligns with CMS standards, but may also exceed federal standards to achieve the highest safety, quality, and value standards. • Recognized as a CMS deeming authority.[a]	• Aligned with CMS
National Association of Boards of Pharmacy (NABP)	• NABP provides a platform for contact information and web links for individual state boards of pharmacy.	• State board of pharmacies vary as to enforcement of BUD requirements and may be more stringent than USP standards.
Joint Commission (JC)	• JC is a non-profit, independent, non-governmental organization that aligns with CMS	• Aligned with CMS. • General reference to USP standards

	standards, but may also exceed federal standards to achieve the highest safety, quality, and value standards.	
United States Food and Drug Administration (FDA)	• FDA is a federal regulatory body that includes medications (both prescription and over the counter) in its oversight.	• Provides compounding-related guidance mainly targeted to outsourcing facilities • Sets expiration date expectations that drug manufacturers must comply with • Defers to USP guidance for BUD assignment

[a]Organizations who meet the standards of this accreditation body automatically qualify for the standards set forth by CMS for reimbursement.

USP standards are divided into chapters. Chapter <795> of the USP, entitled "Pharmaceutical Compounding—Nonsterile Preparations, describes standards to be followed for the preparation of CNSPs for humans and animals.[1] These are considered minimum practice guidelines when compounding nonsterile preparations.[1] Notably, guidance from USP is descriptive rather than prescriptive or exhaustive. Thus, it is up to compounding personnel to implement these measures using the utmost professional judgment.[1,4] The types of CNSPs subject to USP General Chapter <795> requirements include the following:

- Solid oral preparations
- Liquid oral preparations
- Rectal preparations
- Vaginal preparations
- Topical preparations (*i.e.*, creams, gels, and ointments)
- Nasal and sinus preparations intended for local application (*i.e.*, nasal sprays and nasal irrigation)

- Otic preparations (excluding use in perforated eardrums)

The requirements in the chapter must be followed to minimize harm, including death, to human and animal patients that could result from the following:[1]

- Excessive microbial contamination
- Variability from the intended strength of correct ingredients
- Physical and chemical incompatibilities
- Chemical and physical contaminants
- Use of ingredients of inappropriate quality

Previously, USP, Chapter 795, had not been updated since 2014. The following years included rounds of revisions and a public comment period, with the publication of the most recent updates to USP <795> on November 1, 2022,[1] These revised guidelines include stakeholder input and scientific and technological advances and include extensive updates to beyond-use dating.[1,5] United States Pharmacopeia, General Chapter <795>, is considered an enforceable chapter, and such enforcement is the responsibility of state boards of pharmacy, which may choose to require even more stringent beyond-use dating requirements.[1,4] Compounding personnel should always refer to and follow compliance requirements of their specific state board of pharmacy or the board of pharmacy for states in which they are licensed.[1,4]

Factors Impacting Beyond-Use Dates

It is recommended to assign beyond-use dates to CNSPs in a conservative manner; this helps ensure the product will remain safe and effective during use and storage and will minimize the chance of contamination or degradation. In the process of establishing a beyond-use date, there are numerous factors to consider, including the following:[1]

- The chemical and physical stability properties of the active pharmaceutical ingredient (API)

- The chemical and physical stability of any added substances (excipients) in the preparation
- The compatibility of the container closure system with the finished preparation
- The degradation of the container closure system, which can lead to a reduction in the integrity of the CNSP
- The potential for microbial growth in the CNSP
- Any significant deviations from essential compounding steps and procedures, as changes to essential compounding steps may have an impact on the stability of the formulation

Stability Considerations

Compounding personnel cannot assume with certainty that the API within a preparation will maintain its strength and purity solely by following USP 795 guidelines, and thus stability is a key consideration in determining the BUD of a product.[4] Stability is defined as the extent to which a product retains the same properties and characteristics it possessed at the time it was manufactured throughout its time of storage and use.[6,7] United States Pharmacopeia, Chapter <1191> - Stability Considerations in Dispensing Practice, provides useful information on stability considerations for compounding personnel.[7] United States Pharmacopeia recognizes five general types of stability with associated criteria for acceptable levels of stability, including the following:[8]

- Chemical: each API retains its physical and chemical integrity and labeled potency
- Physical: the original physical properties are retained (includes appearance, palatability, uniformity)
- Microbiological: sterility or resistance to microbial growth is retained
- Therapeutic: therapeutic effect remains unchanged
- Toxicological: no significant increase in toxicity occurs

Many factors can affect the stability of a preparation. These include temperature, pH, light, oxygen, moisture, particle size, and changes in formulation ingredients.

Temperature

Temperature has the potential to affect heat-sensitive APIs at many points in the compounding process. Increases in temperature have the ability to increase the speed of chemical reactions.[7] In general, for every 10-degree increase in temperature, the rate of drug degradation will increase exponentially.[7] United States Pharmacopeia, Chapter <1191> includes an example of how the shelf-life of a hydrolyzable drug exposed to a 20-degree increase in temperature could decrease from one-fourth to one-twenty-fifth its shelf life under refrigeration.[7] While this is an extreme example, it highlights the important role of heat in a drug's stability.

pH

pH is another major factor to consider when determining the stability of a product. For any CNSP, personnel should determine the appropriate pH to maintain stability.[7] As the pH of a solution is decreased or increased over a specific range of pH values, the degradation of many drugs will either accelerate or decelerate exponentially. pH buffer systems (a weak acid or base and its salt) can be used to keep pH within the desired range and minimize degradation.[7]

Light

Light can affect CNSP stability by causing photodegradation via photo-oxidation and photolysis.[6] In cases where light-sensitive APIs are used, packaging should be light-resistant.[7] Interestingly, some medications are light-sensitive under different conditions but not others. For example, a drug may be light-sensitive when in water but not when generally exposed to light.[6]

Oxygen

Oxygen can cause product degradation via oxidation.[7] Compounds that are likely to oxidize include those with conjugated dienes, heterocyclic aromatic rings, nitrite derivatives, and aldehydes (for example, flavorings).[7] Products that result from oxidation typically lack therapeutic activity.[7] Oxidation can be noted when the product elicits an unpleasant smell or taste, becomes discolored, or precipitates.[6] There may be instances when compounding personnel are unaware oxidation has occurred. To minimize the risk of oxidation, headspace within a container should be decreased as much as possible.[6] Compounding personnel can also add antioxidants to certain CNSPs to minimize or slow the oxidative process that may occur when the API or excipients are exposed to oxygen.[6] Which antioxidant is best will depend on factors such as solubility, compatibility, and chemical and physical stability.[6] Another technique is to decrease the amount of air entrapped within the preparation.[6] To do this, personnel should be cautious not to foam or whip products during mixing.[6]

Moisture

Moisture or humidity can cause hydrolysis reactions.[6,7] Beta-lactams and esters are types of chemical bonds that are likely to hydrolyze when in the presence of water.[7] Compounding personnel should be aware of medications that contain these types of bonds (such as aspirin) and work to mitigate the impact of hydrolysis.[7] Helpful strategies include keeping the environment dry and packaging products with desiccant packets to assist with minimizing the risk of moisture accumulation.[6]

Particle Size

Particle size can also play a role in instability.[6] In general, the smaller the particle size, the greater the chance the product may react.[6] To mitigate this problem, compounding personnel can try to use a larger particle size when compounding powders and capsules.[6]

Formulation Changes

Formulation changes may alter the stability of a preparation, and any change in ingredients will generally warrant a new stability study or the obtainment of new stability information.[4] For example, if compounding personnel reference a study that used a specific base with the active pharmaceutical ingredient and they wish to change the API, the stability of that compound can no longer be assumed.[4] Interactions between new or added ingredients within a formula can change the stability of a preparation and may warrant assigning a new BUD.[4]

Container Closure Systems

Selecting the right type of container is important to ensure the stability of a CNSP. Compounding personnel should check to see if the drug is compatible with the anticipated container. Not every drug will be stable in every type of container.[6] In general, glass tends to be the most inert and stable container material. However, plastic is commonly used and presents concerns related to stability.[6]

Signs of Instability

It is important for compounding personnel to observe CNSPs periodically for signs of instability. Fortunately, pharmacists and pharmacy technicians are often able to recognize signs of instability for many different dosage forms visibly. Table 3 describes signs of instability.[6]

Table 3. Signs of CNSP Instability[6]

Dosage Form	Signs of Instability
Capsules	● Hardening or softening of capsule shell ● Discoloration or expansion of shell
Solutions, elixirs, syrups	● Caking

	• Discoloration • Release of pressure on opening container
Emulsions	• Breaking or creaming of emulsion
Suspension	• Inability to resuspend by shaking • Caking • Crystal growth
Creams	• Emulsion breakage • Crystal growth • Shrinkage
Ointments	• Change in consistency • Liquid separation • Grittiness
Suppositories	• Excess softening • Brittleness • Changes in melting point

Assigning Beyond-use Dates to CNSPs

The ultimate responsibility for assigning beyond-use dates falls to compounding personnel, with oversight from the designated person or persons.[1] The concept of a designated person is new within the revised guidelines. These individuals are deemed responsible by their institution and must use professional judgment when determining beyond-use dates.[1] Ideally, each institution should utilize a standardized, guideline-driven approach and have established policies and procedures for assigning beyond-use dates. BUD recommendations within USP <795> assume the product is packaged in a light-resistant, tight container (unless other conditions apply).[1]

Beyond-use dating guidelines have undergone significant revisions since the 2014 publication. Prior to the released revisions, the two categories that distinguished BUD were called "nonaqueous" and "water-containing."[8] However, these terms were found to be confusing because it was unclear how to determine whether a substance or vehicle contained a small amount of water under certain scenarios.[8] Table 4 provides the previous beyond-use dating guidelines for comparison.

Table 4. Previous Beyond-use Dating Guidelines[9]

Formulation Type	Beyond-use Date
Nonaqueous formulations	6 months or the time remaining until the earliest expiration of any API
Water-containing oral formulation	Not later than 14 days at controlled cold temperatures
Water-containing topical and dermal and mucosal liquid semisolid formulations	Not later than 30 days

Water Activity

Water makes up the greatest percent of any ingredient within compounded preparations and before discussing the new guidelines, an understanding of the terms *water content* and *water activity* and their relationship to CNSPs is needed. Water content is defined as the total amount of water present in a product, including bound and free water.[10] Water activity (a_w) is a measure of water available to react with or attach itself to other materials and is free water.[10] Information on water activity is detailed in Chapter <1112> Application of water activity determination to nonsterile pharmaceutical products.[11] The USP defines water activity as the ratio of vapor pressure of H2O in product (P) to vapor pressure of pure H2O (Po) at the same temperature.[11] Numerically, it is equal to 1/100 of the relative humidity (RH) generated by the product in a closed system.[11] RH can be calculated from direct measurements of partial vapor pressure or dew point or indirect

measurement by sensors whose physical or electric characteristics are altered by the RH to which they are exposed.[11]

The relationship between aW and equilibrium relative humidity (ERH) is represented by the following equations:

$$aW = P/Po \text{ and } ERH(\%) = aW \times 100$$[11]

Water activity is a good indicator of microbial growth potential, and there are minimal levels of water required for the growth of mold, bacteria, and other organisms in a preparation.[10] Table 5 lists the water activity levels for the growth of different organisms. In general, water activity levels under 0.60 will not support microbial proliferation.[10] Substances with higher water activity levels will typically support more microorganisms.[10] It is necessary to recognize that even though some nonsterile products such as ointments are not ingested orally, they can still support the growth of organisms that could harm patients.[11] When water is present in a CNSP, compounding personnel can lower the a_w by changing the concentration of ingredients such as sodium chloride to make it self-preserving, or add a preservative to protect against microbial growth and patient harm.[10]

Table 5. Water activity values[10]

Organism	**Minimum Water Activity**
Listeria monocytogenes	0.92
Staphylococci and micrococci	0.87
Molds	0.80
Yeast	0.65

Looking at the big picture, it becomes clear why compounding personnel should take water activity into account when assigning a beyond-use date. In general, the lower the water activity level, the longer the BUD that may be assigned. Understanding and determining the water activity of nonsterile dosage forms is helpful for compounding personnel. This information can help with the following decision:[11]

- Optimizing product formulations to improve antimicrobial effectiveness of preservative systems
- Reducing the degradation of active pharmaceutical ingredients within product formulations susceptible to chemical hydrolysis,
- Reducing the susceptibility of formulations (especially liquids, ointments, lotions, and creams) to microbial contamination, and
- Providing a tool for the rationale for reducing the frequency of microbial limit testing and screening for objectionable microorganisms for product release and stability testing

For reference, Table 6 details the water activity of numerous dosage forms.[1]

Table 6. Water Activity of Common Compounded Nonsterile Dosage Forms[1]

Nonaqueous Dosage Forms: $a_w < 0.6$			**Aqueous Dosage Forms: $a_w \geq 0.6$**		
Dosage Form	**Description**	**a_w**	**Dosage Form**	**Description**	**a_w**
Animal treat	Animal treat (oil flavor)	0.507	Animal treat	Animal treat with 15%–18% aqueous flavor	0.716
Capsule (oil filled)	Olive oil encapsulated	0.468	Cream	Cream vehicle (oil in water emulsion, petrolatum free)	0.968
Capsule (powder filled)	Powder base encapsulated	0.435	Cream	Emollient cream (petrolatum and mineral oil)	0.984
Gel (glycol based)	Propylene glycol, ethoxy diglycol, hydroxypropyl cellulose gel	0.056	Cream	Cream (oil in water emulsion with natural oils)	0.989

Nonaqueous Dosage Forms: $a_w < 0.6$			Aqueous Dosage Forms: $a_w \geq 0.6$		
Dosage Form	**Description**	a_w	**Dosage Form**	**Description**	a_w
Lollipop (sorbitol based)	Sorbitol-based lollipop	0.460	Foam	Foaming surfactant solution	0.983
Ointment	Hydrophilic petrolatum	0.396	Gel (water based)	Alcohol-free aqueous gel	0.990
Ointment	Polyethylene and mineral oil gel base	0.459	Gel (water based)	Hydroxypropyl methylcellulose (HPMC) gel	1.000
Oral solution (glycol based)	20% Polyethylene glycol and 80% propylene glycol	0.009	Lotion	Lotion (oil in water emulsion)	0.986
Oral solution (oil based)	Medium chain triglycerides oil	0.338	Nasal spray	Nasal spray	0.991
Oral suspension (fixed oil)	Fixed oil with thickener	0.403	Oral solution (water based)	Low-sucrose syrup vehicle	0.906
Powder for inhalation	Encapsulated powder for inhalation	0.402	Oral solution (water based)	90% Water and 10% glycerin	0.958
Stick	Lip balm	0.181	Oral suspension (water based)	Oral suspension base	0.992
Suppository	Polyethylene glycol base	0.374	Rinse	Polymer gel with 30% water	0.960
Suppository	Fatty acid base	0.385	Shampoo	Shampoo	0.976
Tablet (compressed)	Compressed tablet	0.465	Simple syrup	Simple syrup	0.831
Tablet (triturate)	Tablet triturate	0.427	—	—	—

Nonaqueous Dosage Forms: a_w < 0.6			Aqueous Dosage Forms: $a_w \geq 0.6$		
Dosage Form	**Description**	a_w	**Dosage Form**	**Description**	a_w
	(lactose and/or sucrose)				
Troche or lozenge (gelatin based)	Gelatin troche or lozenge with NMT 3% aqueous flavor	0.332	—	—	—
Troche or lozenge (glycol based)	Polyethylene glycol troche or lozenge with NMT 3% aqueous flavor	0.571	—	—	—

New Guidelines

Table 7 provides the most recent beyond-use dating recommendations from USP <795>, including the type of preparation, its associated BUD, and recommended storage temperature. In terms of temperature, controlled room temperature (CRT) is defined as 25^0C, and refrigerated temperature is between 2^0C and 8^0C.[1]

When preparing CNSPs, personnel should note that materials and equipment contribute to the microbial growth risk of the final preparation.[1] Per USP 795, CNSPs with an aw ≥ 0.6 and a BUD within the limits of Table 7 should contain appropriate antimicrobial agents to protect against the growth of bacteria, yeast, and mold that may be inadvertently introduced anytime during the compounding process or throughout the BUD under appropriate handling and storage conditions.[1] In choosing a preservative, consideration should be given as to its effectiveness in preventing microbial growth and maintaining the stability of the preparation.[1] When antimicrobial preservatives are contraindicated in a CNSP, storage of the preparation in a refrigerator is

required if such storage does not change the physical or chemical properties of the CNSP (*i.e.*, precipitation).[1]

Table 7. New BUD Recommendations[1]

Type of preparation	BUD	Storage Temp
Aqueous dosage forms with water activity ≥ 0.60		
Non-preserved aqueous dosage form	14	Refrigerator
Preserved aqueous dosage form	35	CRT or refrigerator
Nonaqueous dosage forms with water activity <0.60		
Oral liquids (nonaqueous)	90	CRT or refrigerator
Other nonaqueous dosage forms	180	CRT or refrigerator

CNSPs that Require Shorter BUD

The beyond-use dating requirements in USP 795 provide recommendations without considering the potential impact of stability.[1] However, the designated person is still responsible for determining if relevant stability data exists that may require a shorter beyond-use date.[1] Per USP 795, the BUD of the CNSP must not exceed the shortest remaining expiration date of any of the commercially available starting components. This includes both the active ingredients and any excipients used.[1] For example, if a product would normally be assigned a beyond-use date of 180 days per the guidelines but an API is used that expires within the next two months, a BUD of two months would be assigned to the preparation instead. Similarly, CNSPs that are prepared from one or more compounded components should be assigned BUDs that do not exceed the shortest BUD of any individual compounded component.[1]

There may be instances in which it is acceptable to assign a BUD to the final CNSP that exceeds the BUD assigned to compounded components (for example, pH-altering solutions).[1] If the assigned BUD of the final CNSP

exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CNSP must not be negatively impacted.[2] The designated person should ensure this is done appropriately and according to institutional standard operating procedures (SOP).[1]

CNSPs with Extended BUDs

Compounding personnel may wish to extend the BUD of a CNSP, and there are certain cases in which this is permissible. Before doing so, compounders need to thoroughly understand the formulation and evaluate pertinent data using professional judgment.[4] In general, a BUD cannot be extended when a USP-NF monograph is used to compound the preparation.[1] If compounding personnel wish to extend the BUD, they must have appropriate stability studies using stability-indicating analytical methods for the API, CNSP formulation, and material composition of the container-closure system.[1,4] A stability-indicating method is defined as a validated analytical procedure that accurately and precisely measures the active ingredients free from process impurities, excipients, and degradation products, and it must be validated for specific formulation testing.[12] The BUD could then be extended beyond USP recommendations, up to a maximum of 180 days.[1]

By performing a stability study, compounding personnel can benefit from the reduced waste of the drug and increased efficiency.[12] Stability studies should be conducted via a verified third-party testing lab, which can be costly for facilities. Data could also be obtained from published literature, ensuring all study information matches the intended CNSP, including its container and storage conditions.[4] When completing stability-indicating assays, there are many important points to keep in mind. First, compounding personnel should recognize the stability of a product in studies may be formulation-specific, and thus if they elect to change an ingredient, a new stability study should be completed.[12] Even changing one excipient could result in a large change in stability.[4] With regard to degradation limits, the assay of the product should remain within 90% to 110% of the label claim at a minimum.[12] Personnel can determine result trends by testing at least three lots at many different time points.[12]

If a decision is made to extend the BUD, the product must be tested for antimicrobial effectiveness.[1] Information regarding this testing can be found in Chapter 51 – Antimicrobial Effectiveness Testing within USP.[13] Within this chapter, it is noted antimicrobial preservatives should not be used as a way to substitute for good manufacturing practices or to reduce the viable microbial population of a nonsterile product solely.[13] If there is available peer-reviewed literature that matches the CNSP formulation and container closure system, that data could be used in lieu of testing. Designated persons could also opt to rely on tests from an FDA-registered facility.[1] Choosing to extend a BUD requires strict documentation, and all relevant information, including supporting references, should be included on an institution's MFR for the product in accordance with the SOP.[1]

Beyond-use Date Labeling and Documentation

Labeling

Compounded nonsterile preparation labeling must comply with laws and regulations pertinent to the applicable regulatory jurisdiction. Per USP, the term "label" designates the part of the labeling that is on the immediate container.[1] The BUD is considered a minimum requirement of the CNSP label and should be displayed both prominently and legibly.[1] Beyond-use dates should be listed on CNSP labels as the date or hour and date beyond which the product should not be used.[1] Related storage conditions should also be listed, except for products stored at controlled room temperature.[1] BUDs can be noted on labels using the following phrases:

- "Do not use after: _____"
- "Discard after: _____"
- "Use before: _____"

Documentation

The process of preparing CNSPs requires stringent documentation, including the completion of the compounding record.[1] United States

Pharmacopeia <795> guidelines state that such a record must be created for all CNSPs. This documentation must comply with relevant laws and regulations within applicable regulatory jurisdictions, and the required CR must be retrievable for at least 2 years (or as required by regulatory jurisdiction laws). The beyond-use date (with related storage requirements) is a requirement of compounding records.[1]

Further, designated persons should ensure a standardized format for formulations. Beyond-use dates should be included with appropriate references.[1] As an example, in one study, a health system created a standardized formulation record system, developed a computerized system so all pharmacists could access these records, and improved the quality control process for extemporaneously compounded nonsterile formulations.[14]

CNSP Beyond-use Dates: Dos and Don'ts

Do

- Assign the more conservative date when there is conflicting information between regulatory agencies
- Maintain written policies and procedures to ensure standard BUD assignment for each CNSP
- Keep patient safety at the forefront of BUD assignment

Don’ts

- Establish a BUD without considering stability implications
- Exceed the manufacturer expiration date of any ingredient in the CNSP
- Trade patient safety for convenience

Beyond-Use Dating Resources

Pharmacists and pharmacy technicians looking for additional resources related to beyond-use dating have several good options.[6] These include the following:

- Trissel’s Stability of Compounded Formulations
- www.compoundingtoday.com
- AHFS Drug Information monographs
- International Journal of Pharmaceutical Compounding
- American Journal of Health-System Pharmacy
- Hospital Pharmacy
- Other primary literature

Summary

Compounding personnel should recognize the importance of and be knowledgeable regarding the assignment of appropriate beyond-use dates to compounded nonsterile preparations. Numerous factors must be considered when assigning a beyond-use date, with the stability of the preparation requiring specific consideration. A variety of factors have the potential to impact the stability of CNSPs, and compounding personnel should understand these factors and their ramifications. Pharmacists and pharmacy technicians should adhere to USP, Chapter <795> guidelines, including recommendations for extending beyond-use dates. All compounding personnel should refer to their state boards of pharmacy for guidance regarding beyond-use dating.

Course Test

1. **Which of the following is true regarding factors that may impact the stability of a compounded nonsterile preparation (CNSP)?**

    a. For every 10-degree increase in temperature, the rate of drug degradation will decrease exponentially
    b. To minimize the risk of oxidation, container headspace should be increased as much as possible
    c. Oxidation can be prevented by decreasing the amount of air entrapped within a preparation
    d. Moisture and humidity can lead to oxidative reactions

2. **True or False: Changing an excipient within a formulation will not impact its stability.**

    a. True
    b. False

3. **Which of the following is true regarding water activity?**

    a. Water activity is defined as the total amount of water present in a product
    b. Water activity includes free and bound water
    c. Water activity is a good indicator of microbial growth potential
    d. Water activity values under 0.80 will not support microbial growth

4. **Which of the following dosage forms has a water activity value of <0.60?**

    a. Cream
    b. Foam
    c. Ointment
    d. Gel (water based)

5. **Which of the following water activity values would be unlikely to support microbial growth?**

    a. 0.50
    b. 0.70
    c. 0.80
    d. 0.90

6. **Per USP <795>, which of the following beyond-use dates would be assigned to a non-preserved aqueous dosage form with water activity ≥0.60 stored in the refrigerator?**

    a. 14 days
    b. 35 days
    c. 90 days
    d. 180 days

7. **Per USP <795>, which of the following beyond-use dates would be assigned to a preserved aqueous dosage form with water activity ≥0.60 stored at controlled room temperature?**

    a. 14 days
    b. 35 days
    c. 90 days
    d. 180 days

8. **Per USP <795>, which of the following beyond-use dates would be assigned to a nonaqueous dosage form with water activity <0.60 stored in the refrigerator?**

    a. 14 days
    b. 35 days
    c. 90 days
    d. 180 days

9. **What is the maximum beyond-use date a CNSP can be assigned?**

    a. 180 days
    b. 240 days
    c. 360 days
    d. There is no limit

10. **Which USP Chapter contains information on antimicrobial effectiveness testing?**

    a. Chapter 15
    b. Chapter 51
    c. Chapter 1121
    d. Chapter 1190

References

1. General Chapter: USP. Pharmaceutical Compounding-Nonsterile Preparations <795>. In: USP-NF. Rockville, MD: USP; September 2022.
2. General Chapter: USP. Labeling<7>. In: USP-NF. Rockville, MD: USP; May 2020.
3. Pitt R, et al. The Pharmacist Guide to Assigning a Beyond-use Date to a Compounded Sterile or Nonsterile Preparation. ASHP (American Society of Health System Pharmacists). https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/compounding/docs/The-Pharmacist-Guide-to-Assigning-a-Beyond-Use-Date-_final.pdf. Accessed September 30, 2022.
4. Thomson CM, Savji T. Standards of practice, professional judgment, and scientific evidence to establish and extend a beyond-use date. *Int J Pharm Compd.* 2014;18(6):456-460.
5. Open Forum - Beyond Use Date (BUD) Provisions in General Chapters <795> & <797 >. USP. 2020. https://www.usp.org/get-involved/stakeholder-forums/hqs/bud-provisions-gc. Accessed September 30, 2022.
6. Lloyd A. The art, science, and technology of pharmaceutical compounding. 6th edition. American Pharmacists Association. 2020.
7. General Chapter: USP. Stability Considerations in Dispensing Practice <1191>. In: USP-NF. Rockville, MD: USP; May 2018.
8. USP <795> and <797> Beyond-use date updates. US Pharmacist. November 18, 2022. https://www.uspharmacist.com/article/usp-and--beyonduse-date-updates. Accessed September 30, 2022.
9. General Chapter: USP. Pharmaceutical Compounding-Nonsterile Preparations <795>. In: USP-NF. Rockville, MD: USP; September 2020.
10. Allen LV Jr. Quality Control: Water Activity Considerations for Beyond-use Dates. *Int J Pharm Compd*. 2018;22(4):288-293.
11. General Chapter: USP. Application of water activity determination to nonsterile pharmaceutical products <1112>. In: USP-NF. Rockville, MD: USP; 2013.
12. Extended beyond-use dating for compounded preparations presentation webinar Q & A. ARL Bio Pharma. https://www.arlok.com/sites/default/files/Extending%20Beyond%20Use%20Dating%20Q%26A_1.pdf. Accessed September 30, 2022.
13. General Chapter: USP. Antimicrobial effectiveness testing <51>. In: USP-NF. Rockville, MD: USP; September 2022.
14. Evans A, Haile M, Anderson K. Development of a standardized intranet database for formulation records of nonsterile compounding, part 1. *IJPC.* 2010;14(5).

DISCLAIMER

The information provided in this course is general in nature, and it is *solely designed to provide participants with continuing education credit(s)*. This course and materials are not meant to substitute for the independent, professional judgment of any participant regarding that participant's professional practice, including but not limited to patient assessment, diagnosis, treatment, and/or health management. Medical and pharmacy practices, rules, and laws vary from state to state, and this course does not cover the laws of each state; therefore, participants must consult the laws of their state as they relate to their professional practice.

Healthcare professionals, including pharmacists and pharmacy technicians, must consult with their employer, healthcare facility, hospital, or other organization, for guidelines, protocols, and procedures they are to follow. The information provided in this course does not replace those guidelines, protocols, and procedures but is for academic purposes only, and this course's limited purpose is for the completion of continuing education credits.

Participants are advised and acknowledge that information related to medications, their administration, dosing, contraindications, adverse reactions, interactions, warnings, precautions, or accepted uses are constantly changing, and any person taking this course understands that such person must make an independent review of medication information prior to any patient assessment, diagnosis, treatment and/or health management. Any discussion of off-label use of any medication, device, or procedure is informational only, and such uses are not endorsed hereby.

Nothing contained in this course represents the opinions, views, judgments, or conclusions of RxCe.com LLC. RxCe.com LLC is not liable or responsible to any person for any inaccuracy, error, or omission with respect to this course, or course material.