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The Pharmacist Guide to **Assigning a Beyond-Use Date** to a Compounded Sterile or Nonsterile Preparation

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Introduction

A beyond-use date (BUD) is the date or time after which a compounded sterile preparation (CSP) or compounded nonsterile preparation (CNSP) must not be used. The BUD helps mitigate risks to patients by specifying the timeframe within which the preparation must be used to avoid chemical degradation, physical degradation, or microbial contamination.[1-7]

A BUD is assigned from the first manipulation in the compounding process. The responsibility for assigning the BUD is the compounding personnel, which in most cases equates to pharmacy staff involved in compounding. The BUD is calculated from the date or time of compounding and often requires the professional judgment of a pharmacist. This judgment is based on available scientific evidence and must comply with existing regulatory requirements.[3,7] The purpose of this article is to guide pharmacists in choosing the most appropriate BUD for a compounded product.

To appropriately assign a BUD, it is important to first understand the relevant terminology (**Table 1**). For example, a BUD is *not* the same as an expiration date, and the two terms should *not* be used interchangeably[3,4,8]:

- **Expiration dates** apply to commercially manufactured products and indicate the final date a product can be used.
- **BUDs**, on the other hand, apply to CSPs and CNSPs, as defined by USP <797> and <795>.[1,2] A product should not be used past its BUD, excluding the time required for administration.

Notably, a BUD is valid until the earlier of either the assigned BUD or the start of administration. A key distinction between an expiration date versus a BUD is the consideration of the sterility component that goes into assigning a BUD.[6]

Overall, the pharmacist is expected to assess multiple variables in order to appropriately assign a BUD, which is best accomplished using a systematic approach (**Table 2**). The pharmacist will need to exercise judgment to arrive at the most appropriate BUD, where the *most conservative BUD* option should be applied.

Table 1. Defined Terminology

TERM	DERIVATION OF TERM	ASSIGNED BY	PRIMARY USERS	FOUND ON	DEFINITION	NOTES
Beyond-use date	USP <795> and USP <797>[1-3,8]	Compounders of a CSP or CNSP[8]	Compounders and personnel that store or administer the product[3,8]	The label for the CSP or CNSP, designated by the compounders at the organization.[a]	The date or time (could be in terms of hours, days, or months) after which a CSP or CNSP may not be used and should therefore be discarded.[1,2] A BUD applies to a CSP or CNSP up to the point the BUD is reached or to the start of administration, whichever is earlier.[62]	A BUD is typically more conservative than an expiration date because it does not undergo the same rigorous testing that a manufacturer might use to establish an expiration date under cGMP. A BUD can apply to intermediate products used to prepare a CSP or CNSP (e.g., medication vial) or can apply to a finalized CSP or CNSP. Regardless, a BUD no longer applies once a CSP or CNSP reaches the administration stage.[3,8]
Expiration date	FDA[8-10]	Manufacturers of medications or APIs[8-10]	Compounders and personnel that store or administer the product	Manufacturer product[10] Notably, the expiration date is usually listed on both external packaging (e.g., the carton) and on the product itself (e.g., the vial).	The date after which a manufactured product may not be used and should therefore be discarded. After expiry, a product is not guaranteed of its purity, quality, or strength.[9] A drug or API is expected to maintain quality up until the expiration date, pending the product is stored according to manufacturer-specified storage conditions.[2]	An expiration date is established by the manufacturer and derived from the sterility, stability, and analytical chemical studies the manufacturer performs on their products within controlled conditions (e.g., regulated temperatures).[1-6,9] Unless extenuating circumstances authorize otherwise, products should not be used past their expiration dates.[b]

TERM	DERIVATION OF TERM	ASSIGNED BY	PRIMARY USERS	FOUND ON	DEFINITION	NOTES
Administration time (sometimes referred to as "infusion time" or "hang time," although more generic terms like "administration time" are favored to encompass other routes of administration beyond an infusion[18])	FDA and manufacturers, or otherwise health systems	If administration time is not clearly defined by the manufacturer, then health systems often default to their established standardized administration or infusion times as written in their organizational policy and procedures.[3,5,7,11-13] Health systems may use CDC[21,43] and INS[22] for guidance on developing their policy and procedures.	Personnel that administer the product (primarily nursing)[8]	The label for the CSP or CNSP, typically designed by the compounders at the organization.[c,d]	Administration time of the drug to a patient.[3,19] The time during which the CSP or drug product is administered and before tubing or medication must be changed.[20]	The administration or infusion time is outside the scope of USP,[20] but the CDC[21,43] and INS[22] have general guidance on infusion time.[23] A BUD is not intended to impede or limit hang time.[20] Examples of medications whose manufacturer labeling specifies limitations which influence administration time are: ustekinumab states the infusion must be completed within 8 hours of preparing the CSP;[24] cefiderocol recommends a 3-hour IV infusion time;[25] azacitidine directs to administer the drug within 1 hour after reconstitution;[26] vancomycin states to administer within 4 hours to 14 days, dependent on how prepared and stored.[31]

TERM	DERIVATION OF TERM	ASSIGNED BY	PRIMARY USERS	FOUND ON	DEFINITION	NOTES
In-use time	FDA and manufacturers[8]	FDA and manufacturers[8]	Compounders of a CSP or CNSP	Manufacturer labeling (package insert)[8]	In-use time starts when a product is opened (e.g., a vial is punctured[e]) and lasts until the product is discarded.[3] The FDA describes in-use time as the maximum time that can "… elapse between penetration of a container-closure system containing a sterile drug product, or after a lyophilized drug product has been reconstituted, and before patient administration."[27] Hence, this definition can be interpreted to mean that in-use time is specific to the commercially manufactured sterile drug product sealed in a validated container-closure system. In other words, in-use time will address the question of, "How long is this commercial product able to be used after punctured,[e] regardless of whether the product was already in solution, or it was a powder that required reconstitution?" Differentiating in-use time from a CSP with an assigned BUD[f] or administration time[g] is important to understanding the terminology.	In-use time is relevant when a compounder prepares a product precisely according to package insert instructions (i.e., without any deviation from the manufacturer-provided instructions), *and* the package insert provides guidance for a product once punctured or reconstituted (e.g., time parameters for how soon the product needs to be used after reconstitution).[e] For example, zoster vaccine manufacturer labeling (package insert) states the product may be stored refrigerated up to 6 hours after reconstitution, or otherwise it must be discarded.[72] Hence, zoster has a 6-hour in-use time.[h] Experts caution in-use time is subject to context because it could encompass the period of entering and reconstituting a commercial product only, but it could also refer to the period of both compounding through completion of administration.[8,62] Check manufacturer labeling to determine in-use time on a case-by-case basis.

AKA = also known as; **API** = active pharmaceutical ingredient; **BUD** = beyond-use date; CDC = United States Centers for Disease Control and Prevention; **cGMP** = current good manufacturing practice; **CSP** = compounded sterile product; **CNSP** = compounded nonsterile product; **FDA** = United States Food and Drug Administration; **INS** = Infusion Nurses Society; **IV** = intravenous; **USP** = United States Pharmacopeial Convention.

[a] Pro Tip! The term "beyond-use date" or "BUD" terminology can be used on the medication label. However, persons outside of pharmacy may not fully appreciate the meaning of the terminology. For example, a common mistake is to interpret the term "expiration date" as identical to "beyond-use date." Because of this confusion, many health systems elect to omit these terms from the label and instead opt to use more universally understood word choices (e.g., start by). See superscript d below for additional suggestions.

[b] Some circumstances (e.g., drug shortages) justify selective use of products past their expiration date. The FDA has further guidance to ensure this practice is done safely and within legal bounds.[28-30]

[c] Compounders of a CSP or CNSP should verify that any administration time listed on the label for a CSP or CNSP is appropriate in context of the known stability and sterility of the medication.

[d] Pro Tip! To prevent nurses from prematurely discarding CSPs that are still safe to administer, the BUD should clearly be distinguished from the administration (AKA infusion or hang time).[8] Experts recommend clarifying verbiage on the CSP label, such as the following examples:

- discard by[14]
- do not hang after[15-17]
- infusion must be completed by[16]
- start by[14,18]

[e] The term "punctured" may be used interchangeably with "entered," "accessed," or "manipulated" in this case.[18]

[f] Once a product is prepared as a CSP, in-use time no longer applies because a CSP has been created. Instead, the CSP is then governed by USP <797> which justifies assigning a BUD. However, the in-use time by manufacturer labeling could *influence* an appropriate BUD assignment. If strictly sticking to the manufacturer labeling (package insert) rather than compounding, there must be sufficient information in the manufacturer labeling (package insert) to bypass the definition of compounding.[2] In many (if not most) cases, the manufacturer labeling (package insert) does *not* contain sufficient details to bypass the definition of compounding, meaning many products end up abiding by USP <797>.[2] When an FDA-approved manufacturer labeling (package insert) provides an in-use time, the BUD is typically chosen to align with the in-use time or USP standards, whichever is shorter.

[g] Similar to in-use time, administration time may or may not be defined by the manufacturer labeling (package inserts). Regardless, in-use time differs from administration time because in-use time encompasses the preparation time of the CSP or CNSP,[27] and may or may not also include administration time.[62]

[h] If in-use time is *not* defined by the manufacturer labeling (package insert), which is often the case, the product would be considered "compounded" once manipulated in which case USP <797> defines standardized limits for how long an ampule, a single-dose, or multiple-dose CSP container may be used.[2]

Table 2. Systematic Approach for Assigning a Beyond-Use Date

STEP	WHAT	WHERE	WHY
1	Expiration date	The expiration date is typically on the product itself (e.g., vial or prefilled syringe) or on the product box.	Before use, the expiration date of all medications or ingredients used to compound must be checked to ensure they have not expired.
2	Manufacturer product labeling (package insert)	The manufacturer labeling (package insert) should be checked for in-use time or other guidance that may influence BUD assignment. Package inserts are not all created equal, and therefore, it is possible to encounter a package insert that lacks guiding parameters.	Generally, in-use time guidance is more conservative when compared with USP standards. However, in-use time does not always limit BUD assignment, as in the case of pharmacy bulk packages. Any conflicting information needs to be assessed when making a final BUD determination. There may be case-by-case considerations based on the specific medication.
3	Administration time	The FDA-approved labeling should be checked to see if there is administration time guidance that would influence BUD assignment. Prior to finalizing the BUD, the compounder must consider whether there are any implications to consider for administration time, sometimes referred to as "infusion time" or "hang time." In most cases this can be a quick thought assessment where the drug stability and anticipated administration time are considered in context of each other.	In many cases, administration time is not of concern because the medication might be infused quickly (e.g., 30 minutes to 1 hour) or is anticipated to be hung well before the BUD. However, other cases (e.g., continuous infusion) might require more scrutiny when assigning a BUD. For example, in a case where the drug has short stability (e.g., cefiderocol is stable for only up to 6 hours at room temperature[25]), not only should a short BUD be assigned, but the pharmacist may need to coordinate with nursing to ensure administration time is started in a timely manner to avoid the administration time surpassing the time the drug is considered stable.
4	Environment in which compound is prepared Enact minimum standards as outlined in USP <795> and <797> to your organization,[1,2] which will provide parameters that influence the BUD assignment.		Most healthcare organizations that are hospitals (not industry) prepare CSPs in a category 2 environment without further sterility testing, as defined in USP <797>. As such, the category 2 parameters (or whichever category applies to your organization) limit the BUD assignment.
5	Beyond-use date	Assess any limitations you identified for steps 1 to 4 and apply the *most conservative* BUD you can based on the aforementioned. Refer to the *Frequently Encountered BUD Examples* section near the end of this resource if using a USP CPM as that may enable an extended BUD pending the CPM is exactly followed.[3,32]	It is typical for an expiration date to be generous (e.g., 6 months to 1 year). If in-use time exists in the package insert, it might be conservative (e.g., a few hours to days). This would need to be compared with the limits based on the environment and USP parameters. The most conservative dating should be chosen for the finalized BUD of the CSP or CNSP.

BUD = beyond-use date; **CPM** = compounded preparation monograph; **FDA** = United States Food and Drug Administration; **USP** = United States Pharmacopeial Convention.

Regulatory Oversight

There are several authorities and organizations involved in the regulatory oversight or guidance of BUDs (**Table 3**). The most influential in regard to BUDs is United States Pharmacopeial Convention (USP), which is a nonprofit, independent, non-governmental organization that sets quality, purity, strength, and identity *standards* for medicines, food ingredients, and dietary supplements.[3,4,33] USP minimum standards for BUDs are found in nonsterile compounding (USP Chapter <795>) and sterile compounding (USP Chapter <797>) chapters.[1,2]

Regulatory authorities refer to the USP Compounding Compendia as the standard for BUD assignment:

The U.S. Food and Drug Administration (FDA) is a federal regulatory body that affirms their direct oversight of expiration dates,[9] but defers to the latest USP compounding chapters with regard to standards for CSPs and CNSPs.[34] Ultimately the FDA implies that BUD assignment is out of their scope, pointing to USP as the authority.[34,35]

Another federal regulatory body, Centers for Medicare and Medicaid Services (CMS), similarly defers to USP as the authority on pharmaceutical compounding for CSPs and CNSPs, just like the FDA. CMS states that organizations are expected to adopt USP minimum standards, or more stringent, within their pharmacy compounding practice.[11] CMS also states, "The BUD is to be based on information provided by the manufacturer, whenever such information is available."[11] This suggests CMS also recognizes manufacturer labeling (package insert) guidance as influential to BUD assignment.

Multiple state boards of pharmacies adopt USP <795> and <797> into their pharmacy law. However, it is important to recognize state boards of pharmacies may vary as to enforcement of BUD requirements and may even be more stringent than USP standards,[4,12,36] which is relevant in circumstances where the manufacturer labeling (package insert) is being precisely followed.[62] Refer to your specific state board of pharmacy website via the National Association of Boards of Pharmacy for individual state requirements.[37,38]

There are multiple non-governmental organizations that serve as healthcare accreditation bodies, including Accreditation Commission for Health Care (ACHC), Center for Improvement in Healthcare Quality (CIHQ), Det Norske Veritas (DNV) Healthcare, and The Joint Commission (TJC). The goal of these accrediting organizations is to set standards that ensure consistent high-quality care and patient safety as they audit practice of healthcare organizations. All of the aforementioned accreditation organizations serve as CMS-deeming authorities, meaning that healthcare organizations will need to meet or exceed CMS standards and regulations when certified by any of these organizations, which therefore qualifies the healthcare organization for federal reimbursement from CMS.[39]

Aligned with regulatory authorities, the accreditation organizations also refer to the USP Compounding Compendia as the authority for BUD assignment:

Similar to CMS, accrediting bodies such as The Joint Commission (TJC) require storage practices and conditions to be in accordance with the original product manufacturer's instructions whenever possible. Specifically, TJC references USP standards and state boards of pharmacy for determining BUD assignments.[40] All of the identified accrediting bodies (i.e., ACHC, CIHQ, DNV, TJC) are aligned with CMS regarding BUD expectations.

As healthcare organizations prepare for accreditation body surveys, it is recommended they develop and maintain policies and procedures on how they assign BUDs. Their internal guidance should include the expectations personnel should follow when assigning a BUD when information is not

available from the manufacturer.[11] If the manufacturer labeling (package insert) is not sufficient to determine an appropriate BUD, the pharmacist will be responsible to determine the BUD assignment of the CSP or CNSP based on available resources and supporting literature.[3,5,11]

It is important to note that while published literature may provide alternative stability data other than that outlined by the manufacturer, tests used in even peer-reviewed publications do not necessarily meet U.S. FDA standards and thus may not be acceptable to justify an extended BUD assignment.[41] Furthermore, the conditions used in a publication may not match the conditions within your individual practice site, which is another reason to use caution in extrapolating data. There may be a concern for safety if misapplied literature were to be used to justify an inappropriate BUD that does not match a realistic BUD based on actual stability of the medication.

Overall, regulatory authorities and accreditation organizations recognize that professional judgment for BUDs may be required in specific circumstances and tend to encourage the most conservative dating possible for the sake of patient safety. This is aligned with USP which states that BUDs "...should be established conservatively to ensure the drug maintains its required characteristics (i.e., stability and sterility) until its BUD."[2] See an overview of various organizations' stance on BUD below (**Table 3**).

Table 3. Regulatory or Accreditation Organizations' Stance on Beyond-Use Dates

ORGANIZATION	RELEVANCE OF ORGANIZATION TO BUD	ORGANIZATION STANCE ON BUD
Organizations that Provide BUD Standards or Supporting Guidance on Best Practices		
ASHP	One of the largest pharmacy organizations in the U.S. and the world that specializes to health-system pharmacy practice. A section advisory group exists to address compounding practice.	ASHP Guidelines on Compounding Sterile Preparations references USP standards.[5]
CDC	The CDC provides guidance related to administration or infusion times and infection prevention practices.[35,42-44]	Does not directly address BUD but does provide guidance on infection prevention best practices that may influence an appropriate BUD assignment.[35,42-44]
USP	Nonprofit, independent, non-governmental organization that sets quality, purity, strength, and identity standards for medicines.[1-4,33] The information within USP is recognized as the universal standard on how the sterility component contributes toward BUD assignment. USP standards are routinely cited by authoritative organizations.	Provides minimal standards for BUD assignment (primarily based on the sterility component) which is intended to be used in the absence of other scientific data (e.g., direct stability and sterility testing).[1,2]
Regulatory Authorities		
CMS	A federal regulatory body that establishes and enforces minimum health and safety standards that healthcare providers must meet to participate in the Medicare and Medicaid programs. These standards are designed to promote high-quality, value-based care. CMS also functions as a third-party payer, reimbursing healthcare facilities for services provided to eligible Medicare and Medicaid beneficiaries. Providers that fail to comply with CMS standards risk losing their eligibility for reimbursement. To ensure compliance, CMS collaborates with state survey agencies and accrediting organizations.[11,39]	"The BUD is to be based on information provided by the manufacturer, whenever such information is available. The hospital must maintain and implement policies and procedures that provide clear and consistent direction to pharmacy staff regarding how to determine a BUD when complete BUD information is not available from the manufacturer. The policies and procedures must be based on accepted professional principles."[11]
FDA	A federal regulatory body that includes medications, both prescription and over-the-counter, in its oversight.	Provides compounding-related guidance (much of it targeted at outsourcing facilities).[36,45] Sets expiration date expectations that drug manufacturers must comply with.[9] Defers to USP standards for BUD assignment.[34,35]
NABP	Provides a platform for contact information and web links for individual state boards of pharmacy which have regulatory authority.[37]	State board of pharmacies vary as to enforcement of BUD requirements and may be more stringent than USP standards.[4,12,36,38]

ORGANIZATION	RELEVANCE OF ORGANIZATION TO BUD	ORGANIZATION STANCE ON BUD
Accreditation Organizations		
ACHC	Nonprofit, 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] In recent years HFAP merged with ACHC.[46]	Aligned with CMS.
CIHQ	Nonprofit, 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.
CMS	Both a regulatory authority and an accreditation organization.[47,48]	See details of CMS in Regulatory Authority section above.
DNV	Nonprofit, independent, non-governmental organization that aligns with CMS standards in their healthcare sector 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.
TJC	Nonprofit, 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. General reference to USP standards.[40]

ACHC = Accreditation Commission for Health Care; **ASHP** = American Society of Health-System Pharmacists; **BUD** = beyond-use date; **CDC** = U.S. Centers for Disease Control and Prevention; **CIHQ** = Center for Improvement in Healthcare Quality; **CMS** = U.S. Centers for Medicare and Medicaid Services; **CSP** = compounded sterile product; **DNV** = Det Norske Veritas; **FDA** = U.S. Food and Drug Administration; **HFAP** = Healthcare Facilities Accreditation Program; **NABP** = National Association of Boards of Pharmacy; **TJC** = The Joint Commission; **U.S.** = United States; **USP** = United States Pharmacopeial Convention.

[a] Organizations who meet the standards of this accreditation body automatically qualify for the standards set forth by CMS for reimbursement.[39]

Establishing an Appropriate BUD

When preparing a product in accordance with manufacturer labeling (package insert) instructions, the storage and stability information from the manufacturer would dictate the assigned BUD as this falls outside the scope of USP.[1] According to expert opinion and many regulatory agencies (including some state boards of pharmacy), preparation per approved labeling does not constitute compounding,[3] pending the FDA approved manufacturer labeling includes sufficient information (i.e., diluent, resultant strength, container closure system, storage time).[2] If the manufacturer labeling lacks sufficient information or batch compounding[12] is being performed (i.e., more than a single dose is being prepared at a time[2]), then this falls under the definition of compounding.[2]

When preparing a CSP, *both* sterility and stability must be considered; CNSPs have similar considerations, except they need not be sterile as some contamination may be present within acceptable levels (**Table 4**, **Table 5**):

Sterility, which is perhaps the most difficult-to-control variable, constitutes the absence of microbial contamination,[38] with different goals for a CNSP versus a CSP[1,2]:

- For a CNSP, USP <795> focuses on minimizing "microbial growth" or "microbial proliferation" rather than maintaining strict sterility.[1]
- For a CSP, USP Chapter <797> designates category 1, category 2, and category 3 compounding which is primarily based on the state of environmental control under which CSPs are compounded, the probability for microbial growth during storage, and the time period the CSP must be used.[2,38] Sterility is heavily influenced by the environment in which the CSP is compounded, aseptic technique of the compounder, whether the starting ingredients are sterile or nonsterile to being with, and storage conditions of the final product.[2]

Determining the stability of a drug is critical to assigning an appropriate BUD.[3-5,7,38] Stability constitutes the "drug, diluent, container, closure."[3] Stability can be impacted by a wide variety of factors, including temperature, light, and the material of the storage container.[4] Medication-specific stability is not addressed by USP and therefore must be a separate consideration for the pharmacist when assigning a BUD. Stability of a medication is typically determined by assessing the package insert and peer-reviewed literature.[1,2,7,38,49] Alternatively, USP does have compounding monographs which offer medication-specific stability information.

The BUD is ultimately a risk assessment based on best compounding practices and available information.[3,6] The BUD must be chosen in context of patient safety[7] as well as legal and regulatory considerations.[7,38] Other considerations of assigning a BUD include an assessment of many variables that ultimately relate back to either sterility or stability, with examples listed below (**Table 4**).

Table 4. Considerations of a Beyond-Use Date Related to Sterility or Stability

Sterility	Stability
▪ Batch size[12,38] ▪ Environment in which the compounded product is being manipulated[3,12,38] ▪ Microbiologic risk level[4,12,38] ▪ Starting ingredients (sterile or ≥ 1 nonsterile)[2,3,7,12] ▪ Storage temperature[3,4,7,12,38] ▪ Type of manipulation (e.g., aseptic addition to bag, autoclave)[3,12] ▪ USP standards (which primarily focuses on sterility)[2,3,5,7,12,38,49]	▪ Chemical stability[1-5,7,12,38] ▪ Physical stability[1-5,7,12,38] ▪ Compatibility[4,12] ▪ Concentration[4,12] ▪ Container closure system[1-4,12] ▪ Storage temperature[3,4,7,12,38] ▪ USP standards[1,2]

USP = United States Pharmacopeial Convention.

The pharmacist ultimately assigns a BUD that must neither exceed the standards set forth by USP nor exceed the manufacturer constraints, including in-use time or the expiration of any single ingredient in the compound. Pharmacists may choose to be more conservative than the manufacturer labeling (package insert) or USP standards.

Sometimes the package insert indicates stricter time constraints compared with USP standards, in which case it is safest to assign the most conservative BUD assignment between the package insert versus USP.[3] Alternatively, the package insert may recommend longer dating than USP standards. Though this latter situation is less frequently encountered, the safest action is again to default to the most conservative BUD.

Likewise, if conflicting information exists regarding BUD assignment among different regulatory agencies with oversight for a particular compounding pharmacy, the actual BUD assigned should be the most conservative of the collective regulatory group. It is important to maintain written policies and procedures to ensure standard, consistent BUD assignment for each product.[3,5,7,11-13]

Overall, the USP standards provide short-term dating generalizations based on microbial contamination risk or sterility, whereas existing studies of the drug provide more medication-specific data, including stability.[7] Current USP standards are based exclusively on considering the sterility of a product, not the chemical, physical, therapeutic, or toxicological stability of a product.[1,2,7,38,49]

If a pharmacist wishes to assign a longer BUD, category 3 within USP <797> standards outline use of a stability test (to affirm the container and closure system used) and a sterility test (to affirm microbial contamination is not occurring) that justify a longer BUD assignment than could otherwise be assigned.[3] The sterility testing must be in accordance with USP Chapter <71>.[2,7,38,49,50]

Although stability and sterility testing can be outsourced,[3,6] some health systems forego it due to cost and time constraints. Hence, in the absence of stability and sterility testing, best practice would be for the pharmacist to default to the most conservative dating between the package insert versus USP standards in context of any medication-specific stability considerations that were identified.

Summary

Key concepts for the pharmacist to consider when establishing a BUD assignment are:

- Be familiar with pertinent state, federal, and accreditation organization standards to understand the constraints and opportunities.[3,4,7,36]
- Both the manufacturer package insert of the drug(s) and compounding literature should be utilized to assess known characteristics the drug(s), with stability being especially important to determining appropriate BUD assignment.[3-5,7,38]
- USP primarily addresses sterility. Hence, stability information must be sought out in the package insert and other compounding literature.[2,3,5,7,12,38,49]
- USP standards for categories 1 and 2 provide the longest BUD that can be assigned if a sterility test is not performed on *every* batch, assuming operational standards are met.[1-3,38] Category 3 compounding requires additional sterility (on *every* batch) and stability testing to justify an extension of the BUD.[2,3]
- Using literature to extend a BUD is an extrapolation since exact conditions are difficult to replicate. Assumptions based on clinical judgment remain a liability.[7]
- Patient safety should always supersede convenience when assigning a BUD.[7] Assigning the most conservative dating generally minimizes risk to patients.[3,5,7,38]
- Maintain written policies and procedures to ensure standard, consistent BUD assignments.[3,5,7,11-13]

Table 5. Sterility and Stability Considerations of Beyond-Use Date Assignments

Consideration	Sterile Compounding	Nonsterile Compounding
Sterility	Environment controls can be graded and lend towards the degree of sterility of the final CSP. In the context of USP <797>, the environment controls become more stringent with progressively higher-numbered categories (i.e., category 1 is less stringent than category 3). For instance, the garbing worn for category 3 compounding is more comprehensive compared with lesser categories. Additionally, sterility tests would be performed on *every* batch in category 3, which lends an additional confirmation of sterility and may justify a longer BUD.[2] **Key point**: USP <797> focuses on behaviors and controls that can influence sterility of the environment.	With nonsterile compounding, the expectation is not for the final product to be sterile; however, it is still important to minimize microbial growth to the extent possible. Generally, the nonsterile formulation of the compounding recipe, including ingredients and base solution, are considered for likelihood of microbial growth. For example, a formulation with preservatives is less prone to microbial growth compared with a non-preserved formulation. Furthermore, a nonaqueous formulation is less likely to foster microbial growth compared with an aqueous formulation due to the difference in water activity between the two.[1] **Key point**: USP <795> outlines likelihood of microbial growth based on general characteristics of the nonsterile formulation.
Stability	The manufacturer labeling (package insert) should always be reviewed for instruction regarding in-use time and expiration that could influence BUD assignment.[11,12] In addition, other resources can be solicited for available medication-specific stability information. Examples of tertiary resources that may be helpful in identifying stability data include[a,b]: ▪ ASHP® Injectable Drug Information™[51,52] ▪ King® Guide to Parenteral Admixtures®[12,53] ▪ Elsevier's Intravenous Medications[54] ▪ Extended Stability for Parenteral Drugs[4,12] ▪ Pediatric Injectable Drugs: The Teddy Bear Book[55] ▪ Trissel's™ Clinical Pharmaceutics Database[56] ▪ Primary literature may also be used, although the stability tests should be scrutinized for appropriateness.[12,41] **Key point**: The manufacturer labeling (package insert) and other primary and tertiary literature can provide insights into the stability of the medication.	The manufacturer labeling (package insert) should always be reviewed for instruction on in-use time and expiration that could influence BUD assignment. In addition, other resources can be solicited for any available medication-specific stability information. Examples of tertiary resources that may be helpful in identifying stability data include[a]: ▪ Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients[57] ▪ Handbook of Pharmaceutical Excipients[58] ▪ International Journal of Pharmaceutical Compounding (IJPC)[59] ▪ Pediatric Drug Formulations[60] ▪ Professional Compounding Centers of America (PCCA)[61] **Key point**: Each specific formulation should be approached as having unique stability properties. Hence, if literature is used, the recipe must match exactly to confirm stability.

BUD = beyond-use date; **CSP** = compounded sterile product; **USP** = United States Pharmacopeia.

[a] This list is not intended to be exhaustive, and the authors declare no affiliations with the referenced materials. Although some of the cited resources are published by ASHP and the authors are affiliated with ASHP, the authors have not received, and will not receive, any financial or other compensation for their inclusion.

[b] Some experts recommend designating a specific stability reference to streamline decision-making. For instance, some organizations have adopted standard operating procedures that designate a resource as their primary source for stability data: "...designates the ASHP Injectable Drug Information resource as our primary source stability information. Because ASHP vets the stability references according to specified criteria prior to including them in the guide, this removes the need for our team members to assess analytical methods, study bias, and other details of individual studies."[52]

Frequently Asked BUD Questions

Because of the broad range of possible variables when compounding, the pharmacist is faced with a multitude of often complex scenarios when assigning a BUD to a compounded product. Below are some more common examples the compounding pharmacist is likely to encounter. Pharmacists should be mindful of variables that could change outcomes based on their individual circumstances.

1. What is a USP CPM and what role does it play in BUD assignment?

There are over 170 compounded preparation monographs (CPMs) published in the USP Compounding Compendium or the USP National Formulary, accessible through a subscription via USP. A USP CPM can exist for any CSP or CNSP that lacks a commercially-available equivalent.[32,63]

Each CPM serves as an official documentary standard for a specific formulation, detailing ingredients, quantities, compounding procedures, and a BUD. These BUDs often provide a significant advantage to health systems, as the BUDs are longer compared with those assigned based solely on USP chapters. This BUD extension is possible because USP CPMs are supported by stability-indicating studies. However, to apply the extended BUD, the CPM must be followed exactly—including ingredients, quantities, packaging, storage, labeling, and any required testing (e.g., sterility or bacterial endotoxin testing). Any deviation from the CPM invalidates the extended BUD.[3,32]

As of this writing, only one sterile-to-sterile USP CPM exists for a CSP. Therefore, most current opportunities lie in CNSPs. However, this is expected to change as more CSP-focused CPMs are under development.[18]

Another function of USP CPMs is they can serve as the source of truth for acceptable concentration range of API in a CSP or CNSP. This is relevant when conducting original research or interpreting a stability-indicating study published as primary literature.[64]

2. What should the assigned BUD be for a SDV?

A single-dose vial (SDV), as defined by USP <659>, is a container-closure system intended for use with a single patient for a single injection or infusion and does not contain antimicrobial preservatives.[73] Once a SDV is punctured, the contents must not be stored for future use or used for more than one patient.[74,75]

Per CDC guidance, SDVs should be discarded after a single entry unless accessed in a sterile compounding environment.[74,75] Specifically, if a SDV is accessed in a...

- ...non-International Organization for Standardization (ISO) class 5 environment (e.g., bedside, clinic, or procedure area), the SDV must be used immediately and discarded after the procedure. Importantly, there is no storage provision for the vial itself.[70,74,75] The immediate-use BUD as found in USP <797> applies only to the CSP drawn from the vial, rather than the vial itself.[2,70,74] The CSP prepared from the SDV must be administered within 4 hours,[2] unless shorter stability data or manufacturer guidance suggests a shorter time must be used as the BUD.
- ...ISO class 5 or cleaner environment, and the preparation meets USP <797> standards for category 1 CSPs, then the contents of the SDV may be used for up to 12 hours, provided the manufacturer information does not warrant a more conservative BUD.[2,3]

3. What should the assigned BUD be for a MDV?

Unless the manufacturer information would lead to more conservative dating, multiple-dose vials (MDVs) can be opened and maintained for 28 days, regardless of whether the vial is opened and maintained in an ISO class 5 environment or less clean air. MDVs typically contain antimicrobial preservatives within the formulation to allow for longer dating compared with SDVs.[2,3,22,75]

4. What BUD should be assigned to a vial or conventionally-manufactured bag that has been spiked by a dispensing pin?

Dispensing pins, sometimes informally referred to as "spikes," are not addressed in USP <797>.[2,20] It is advised to verify the FDA registration of the dispensing pin device and pay close attention to the manufacturer labeling because many dispensing pins are only intended for single use, whereas others may be supported as multiple use.[62]

If a dispensing pin is intended for single-use only, no storage condition may be appropriate for the "spiked" product because the entry of the dispensing pin provides an entry pathway to the container which could lead to antimicrobial contamination. Therefore, best practice is to use the dispensing pin for the compounding activity (which may include multiple withdrawals using the dispensing pin), and then discard the dispensing pin and the "spiked" container (e.g., bag, vial) immediately thereafter.[62] Other expert opinion suggests a "spiked" product be treated as immediate use (i.e., within 4 hours of entry), especially if the product is preservative free.[3]

5. Can a CSTD be used to extend the BUD of a SDV or a MDV?

The pharmacist should refer to the FDA approved labeling for the closed-system transfer device (CSTD) being used. CSTDs are not currently approved by the FDA for use in extending medication dating. Accreditation organizations generally will follow the FDA stance that CSTDs are not a sufficient means to allow for extended BUDs,[41,65,70] despite some published literature suggesting otherwise.[62,76-78]

USP <797> does not explicitly permit or prohibit the use of CSTDs for extending BUDs,[2] which has led to some ambiguity in practice. This has given rise to the concept of drug vial optimization (DVO), where compounders use microbial ingress data to justify extended use.[62,76-78] However, until USP publishes more definitive guidance, the safest and most compliant approach is to follow FDA labeling, which do not support BUD extension based solely on the use of a CSTD.[70]

6. What should the assigned BUD be for a compounded stock solution?

Stock solutions, whether the final container is in a bag, vial, or syringe—is subject to a 12-hour BUD once accessed.[2] A more detailed explanation follows:

> A compounded stock solution (commonly referred to as a "stock solution," or "stock bag" if prepared in a bag) is a CSP used as a base solution to prepare additional CSPs, usually at a later time. The compounded stock solution must only be prepared in an ISO class 5 or cleaner environment. An initial BUD is assigned to the compounded stock solution based on USP standards and pharmacist judgment.
>
> However, once the compounded stock solution is entered, accessed, or punctured to create other CSPs from it, a 12-hour BUD then applies to the

compounded stock solution, pending the manufacturer information does not dictate more conservative dating. Note that entry to the compounded stock solution must occur prior to expiration of the initial BUD assignment to the compounded stock solution.

The CSPs created from the compounded stock solution can then be stored in accordance with USP Chapter <797> BUDs (i.e., aligned with the BUD of the stock bag prior to entry).[1,3]

Be aware that a compounded stock solution may also be prepared in a syringe (e.g., small volumes for pediatrics) rather than a bag. Just as if prepared in a bag, a compounded stock solution prepared in syringes would be assigned a 12-hour BUD once accessed or a dose is expelled from the syringe as the compounded stock solution.[18]

USP has a helpful example that helps illustrate the concept of assigning a BUD to a compounded stock solution and their subsequent CSPs in their FAQ resource.[20]

7. Does the in-use time of a pharmacy bulk package influence the beyond-use date of a compounded sterile product?

A pharmacy bulk package (PBP) is a special type of container that contains several sterile single doses for parenteral use.[2] A PBP should only be opened in ISO class 5 air quality and is intended to be used in a pharmacy admixture program,[2] with a common example being a PBP being used to prepare parenteral nutrition (PN).

The in-use time of a PBP—typically 4 hours—is determined by the manufacturer labeling (package insert) and reflects the maximum time the container may be used once opened.[3] This in-use time is critical for ensuring sterility and minimizing contamination risk, especially given the potential for multiple accesses.

When a CSP is prepared using a PBP, the BUD of the final CSP is not inherently limited by the PBP's in-use time, provided the CSP is prepared in accordance with USP <797> minimum standards and assigned based on sterility, stability, and risk level.[2,70]

However, if a PBP is repackaged—for example, aliquoted into syringes or smaller containers for later use—then the FDA guidance (see Section 8.a.i of the FDA Guidance[66]) states the BUD of the repackaged product cannot exceed the in-use time of the original PBP. This is a key distinction from CSP preparation and reflects the FDA's concern about contamination risk during repackaging.

It may be helpful to think of a PBP as similar to a MDV *without* preservatives, where repeated access increases the risk of contamination.[62] USP <797> assigns BUDs conservatively, incorporating risk management principles.[2] Keep in mind the risk of contaminating a PBP could affect multiple patients.[62] In summary:

- CSPs prepared from PBPs: BUD is based on USP <797> standards and is not limited by the PBP's in-use time.[2]
- Repackaged PBPs: BUD must not exceed the manufacturer's in-use time (typically 4 hours), per FDA guidance.[66]

8. What BUD do I assign to a repackaged product?

A repackaged product is considered compounding for CSPs,[2] but is *not* considered compounding for CNSPs.[1] In either case, assigning a BUD may be justified. Readers are referred to FDA's Repackaging Guidance,[66] USP Chapter <1178>,[67] or the ASHP Repackaging Beyond-Use Date (BUD) Decision Workflow for further guidance on repackaged products.[68]

9. What is a common scenario a pharmacist might encounter where available data might limit the BUD that can be assigned to a CSP?

The scenario is this: A pharmacist is planning to batch a frequently used antibiotic to support efficient delivery of medications throughout their hospital using category 2 per USP <797>.[2] The manufacturer labeling (package insert) instructions for compounding this antibiotic will be followed. The hope is that the batched CSPs can be stored in the refrigerator and be used during low-staffing times. The pharmacist determines that this compound will be prepared per category 2 conditions according to USP Chapter <797> and therefore would like to assign a 10-day refrigerated BUD. However, the package insert instructions state the antibiotic is only stable for 96 hours. The pharmacist identifies peer-reviewed literature suggesting this antibiotic is stable for longer periods of time around 30 to 60 days and therefore wonders if the USP 10-day refrigerated BUD can still be justified. What is the most appropriate BUD to assign?

In many circumstances, if the package insert is being followed, then the BUD should be aligned with the package insert. However, in this case, compounding is occurring per USP Chapter <797> standards because the pharmacist is batching, and therefore this product would be considered a category 2 CSP.[2] The safest option is to assign the most conservative dating to minimize risk to patients.[3,5,7,38] In this case, the most conservative dating would be to align the BUD with the in-use time of 96 hours per package insert, because it is the more conservative threshold compared with USP Chapter <797>.

The package insert rarely, if ever, defines the environment for which the CSP is prepared. Therefore, the pharmacist should always be consulting both the package insert and USP standards in tandem when determining a BUD. Although not common, it is possible that pharmacists encounter a package insert that is longer than USP Chapter <797> standards. As stated previously, USP standards are based on highly conservative predictions of microbiologic risk.[2,38]

If the pharmacist felt justified in assigning a longer BUD by extrapolating the information identified in the compounding literature, then best practice would be to pursue stability and sterility testing to objectively confirm a longer BUD assignment is appropriate.[3] Without pursuing direct stability or sterility testing on the CSP, the pharmacist should recognize they are making assumptions which pose liability risk. Patient safety should always supersede convenience when assigning a BUD.

It is also worth noting that regulations from CMS and other regulatory or accreditation organizations often drive pharmacy practice in assigning BUDs (**Table 3**). This presents challenges, as the Institute for Safe Medication Practices (ISMP) pointed out when they published results of a survey in 2012.[69] Such challenges include the inability to apply the latest known evidence (e.g., stability assurance) toward justification for an appropriate BUD of the drug without fear of regulatory citations.

In summary, pharmacists must be judicious when assigning a BUD, which is a responsibility within the purview of the pharmacist to decide based on the available information. USP states that "peer-reviewed literature" sources may be used,[1,2] but it is up to the pharmacist to interpret and determine which

literature is actually appropriate.[70] Therefore, pharmacists should recognize the liability they are taking on individually and on behalf of their organization when extrapolating data.[3,7] Ultimately, expectations from regulatory organizations, such as boards of pharmacy and accrediting bodies (e.g., TJC) also play a major role in what the pharmacist feels empowered to do.[70] Overall, pharmacists should always make patient safety the priority.

10. If a CSP was assigned a BUD of 12 hours per USP Chapter <797>, is it acceptable to start the infusion within 12 hours, or must the infusion be completed within 12 hours?

In order to answer this question, an understanding of the following terminology should exist (**Table 1**):

- **BUD:** Assigned by the compounder and described as the time after which a CSP should not be used.[1,2]
- **In-use time:** Starts when a product is opened (e.g., a vial is punctured) and lasts until the product is discarded.[3]
- **Administration time:** The administration time of the drug to a patient, sometimes referred to as "infusion time" or "hang time."[3,19]

Unfortunately, there is no "one-size-fits all" answer to this question. Essentially, the answer would depend on the sterility and stability of the specific drug being used. In general, a pharmacist would need to consider whether the drug's stability would be expected to last beyond the 12-hour assigned BUD throughout the duration of the infusion. If the answer to that is yes (i.e., the drug is considered stable), then the administration time ("infusion time") can usually extend beyond the BUD.[19] In rare cases, a medication would not be expected to be stable for the duration of the infusion, in which case special planning for that circumstance would need to occur (e.g., communication with the nurse).[71]

It is understandable why people may get confused on this question since the definition of a BUD is the time at which a compounded preparation should not be used.[1-7] To some, this definition (understandably) implies that the administration to the patient should be completed before the BUD. For example, one might challenge by stating, "If you allow a drug to be infused past the assigned BUD, then you in essence risk violation of either the sterility or stability being compromised." However, it is helpful to understand that BUD does not encompass administration or infusion time and therefore should be considered as a separate matter.[3] A case-by-case assessment of the individual drug properties should be considered for BUD assignment. Both sterility and stability should be considered, as well as the duration of the administration time to assess whether any potential issues might occur with the anticipated administration time.

The generalization that will fit most circumstances is: the infusion time of most medications is of a short enough duration that if the drug is anticipated to stay stable throughout the infusion time, then the sterility of the drug is less of a concern pending best practice standards were used to compound the drug in a sterile environment. However, it may also be helpful to think of the BUD as a storage time,[71] which ends when administration of the product begins. Thinking of BUD as a *storage time* helps better differentiate the BUD definition from the *administration time* definition.

It may also help to remember that the standards in USP Chapter <797> primarily focus on the *sterility* component,[2,3,5,7,12,38,49] which is intended to help the pharmacist choose an appropriate BUD. However, the pharmacist needs to also independently assess the *stability* of the drug (typically via package insert and peer-reviewed studies) as an additional consideration when assigning the BUD. Ultimately the assigned BUD should default to the more conservative dating after an assessment of sterility and stability. The point being: the BUD is an assignment that requires *judgment* on the part of the pharmacist. Likewise, the pharmacist can use their *judgment* as to whether the drug will still be safe and effective throughout the administration time of the drug and plan accordingly.

Another consideration to this question is that nursing personnel, and even some pharmacy staff, are unaware of the nuances of the terminology commonly used and therefore may erroneously think that a BUD is synonymous with administration time or expiration date. Hence, it is recommended that pharmacists thoughtfully educate and design labels for clarity for both nursing and pharmacy colleagues. For example, some have proposed using language such as, "Do Not Hang After" on the drug label for clarity[15-17] (**Table 1**), though local state requirements may need to be considered.[12]

Finally, just as it is important to maintain written policies and procedures for BUDs,[3,5,7,11-13] it is also important to maintain written policies and procedures for administration times.[3,71] Administration time is outside the scope of USP,[20] but the CDC[21,43] and Infusion Nurses Society[22] have some guidance on administration or infusion time.[23]

11. What should the assigned BUD be when a sterile injectable medication derived from a SDV is used to prepare a CNSP as an oral nonsterile compound?

If it is deemed appropriate to default to standards in USP Chapter <795>, the BUD would be 14 days refrigerated for non-preserved aqueous solutions and 35 days refrigerated or controlled room temperature for a preserved aqueous dosage form.[1] Pharmacists are advised to also search for compounding literature that can be used to assess the appropriateness of a BUD assignment.

12. Should I dispense a CSP for inhalation in a nonsterile syringe?

There are safety considerations to consider regardless, but the recommendation of these authors is no because CSPs for inhalation are required to be sterile by the minimum standards in USP <797>.[2] Subjecting a sterile inhalation to a nonsterile container closure would possibly contaminate the inhalation with bacteria, fungi, spores, or viruses. There is a misconception that one could employ the USP <797> "immediate-use provision" and assign a 4-hour BUD. However, the 4-hour BUD is based on aseptic processing of sterile components with minimal contact of nonsterile surfaces and is not applicable to knowingly subjecting the sterile inhalation to a nonsterile container closure. The viable particulate load in the nonsterile container closure could introduce a bioburden directly into the respiratory system.

An alternative suggestion is to dispense the medication in a sterile IV syringe with an appropriate BUD based on compounding category with plans for the respiratory therapist to transfer the contents of the sterile syringe to the nonsterile inhalation device immediately prior to administration. It would be prudent to take additional safeguards to prevent inadvertent IV administration (e.g., cautionary stickers that warn 'not for IV use' when stored in the sterile IV syringe).

Abbreviations

ACHC = Accreditation Commission for Health Care
API = active pharmaceutical ingredient
ASHP = American Society of Health-System Pharmacists
BUD = beyond-use date
CDC = U.S. Centers for Disease Control and Prevention
CIHQ = Center for Improvement in Healthcare Quality
CMS = U.S. Centers for Medicare and Medicaid Services
CNSP = compounded nonsterile preparation
CPM = compounded preparation monograph
CSP = compounded sterile preparation
CSTD = closed-system transfer device
DNV = Det Norske Veritas Healthcare, Inc.
FAQ = frequently asked questions
FDA = U.S. Food and Drug Administration
INS = Infusion Nurses Society
ISO = International Organization for Standardization
IV = intravenous
NABP = National Association of Boards of Pharmacy
MDV = multiple-dose vial
PBP = pharmacy bulk package
SDV = single-dose vial
TJC = The Joint Commission
USP = United States Pharmacopeial Convention

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Acknowledgements

The authors gratefully acknowledge the following individuals for reviewing this article (review does not imply endorsement):

Version 1: Michael Ganio, PharmD, MS, FASHP; Kevin N. Hansen, PharmD, MS, BCPS, BCSCP; Jason Bergsbaken, PharmD, BCOP; James T. Lund, PharmD, MS, BCSCP; and Erika L. Thomas, BSPharm, MBA.

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Last Reviewed February 2026