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Assigning Beyond-Use Dates for Compounded Sterile Preparations: **Evaluating Stability Data**

Assigning beyond-use dates (BUDs) to compounded sterile preparations (CSPs) is a complex process, fraught with responsibility and risk. To mitigate this risk and provide the highest quality preparations to patients, one must fully understand the risk of non-sterility and then identify and carefully interpret available resources on chemical stability.

USP defines an expiration date as the date placed by the manufacturer on the container and label of a drug product designating the time frame a product is expected to remain within the approved specifications of its identity, strength, quality, and purity, if stored under the conditions defined on the package insert.[1] The BUD is defined in USP <797> as the date and time after which a preparation must not be used or transported. It is important to note that as long as administration of the preparation to the patient began prior to the BUD, the preparation can be used. BUD, in the context of USP General Chapter <797>, is a pre-administration consideration.

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Clearly, the terms "beyond-use date," and "expiration date" are not interchangeable. Expiration dates—given in years—are required on commercially manufactured products and are determined after extensive study of the product's stability. Beyond-use dates for compounded preparations, however, are generally expressed in hours or days, and are far more unique.

You may have noted that the USP <797> section covering the determination of BUDs falls between the sections on Sterility & Pyrogen (endotoxin) Testing, and Monitoring Controlled Storage Areas & Maintaining Sterility, Purity, and Stability of Dispensed And Distributed CSPs. This location reinforces the reality that all of these concepts are fundamentally intertwined.

Know the Basics

The primary objective of USP <797> is to prevent harm, including death, to patients from five key areas during the compounding of sterile preparations:

1) Microbial contamination (non-sterility)
2) Excessive bacterial endotoxins (pyrogens)
3) Variability in the intended strength of the correct ingredients (outside compendial limits)
4) Unintended chemical and physical contaminants
5) Ingredients of inappropriate quality in CSPs

BUDs for compounded preparations must be assigned with all these variables in mind. Although this concept is straightforward, instituting an effective process can be challenging.

Understand the Risks

USP General Chapter <797> indicates that BUDs for compounded preparations are to be assigned on the basis of the compounder's professional experience, starting with the CSPs risk level (low, medium, high) and including a careful interpretation of appropriate sources for the same or similar formulations (consistent with the stability criteria and beyond-use dating information included within USP General Chapter <795>).[2] These data should be reviewed and fully understood before determining a BUD for any preparation. The most common sources for such data are:

- The package insert
- The United States Pharmacopeia (USP/NF)
- USP dispensing information
- Remington's Pharmaceutical Sciences (current edition)
- The Journal of Pharmaceutical Sciences
- AHFS Drug Information
- American Journal of the Health-System Pharmacy
- The International Journal of Pharmaceutical Compounding
- Trissel's 2 Clinical Pharmaceutics Database (electronic form - continually updated)
- Handbook on Injectable Drugs by Lawrence A. Trissel (current edition)
- King Guide to Parenteral Admixtures (current edition)
- Extended Stability for Parenteral Drugs edited by Caryn Bing (current edition)

BUDs are rarely based on preparation-specific chemical stability studies, and as the majority of CSPs are aqueous solutions, hydrolysis of the dissolved ingredients is the most common chemical degradation reaction. The extent of hydrolysis, and other heat-catalyzed degradation reactions at any particular time in the life

of a CSP, represents the sum of exposures, temperatures, and durations. Such "life time" stability exposures may be represented in the mean kinetic calculation described in USP Chapter <1160>—Pharmaceutical Calculations in Prescription Compounding. Drug hydrolysis rates increase exponentially with temperature increases and vary by the individual drug entity. Personnel who prepare, dispense, and administer CSPs must store them in accordance with their labeling. When CSPs have known exposure to temperatures warmer than the warmest labeled limit, or to temperatures exceeding 40° Celsius for more than four hours, such CSPs should be discarded unless direct assay data or appropriate documentation confirms continued stability.[2]

Stability Data Evaluation

It should be noted that only product-specific experimental studies produce valid evidence of stability for predicting beyond-use dating of CSPs. Thin-layer chromatography (TLC) and other semi-quantitative procedures may be acceptable for many CSPs. However, quantitative, stability-indicating assays, such as high-performance liquid chromatographic (HPLC) assays, would be more appropriate for certain CSPs, such as those with a narrow therapeutic index, or products where close monitoring or dose titration is required to ensure therapeutic effectiveness or to avoid toxicity. In addition, any product-specific study should be designed to ensure consistent practices; the compounder should have written policies and procedures governing the determination of BUDs for all compounded preparations. In short, every preparation should be considered a unique system that has its own physical and chemical properties and stability characteristics that differ from its individual components.

Compounded preparation-specific, experimentally determined stability data evaluation protocols are always preferable to published stability information. Consult USP General Information Chapter <1150>—Pharmaceutical Stability, for the appropriate stability parameters when initi-

ating or evaluating a preparation-specific stability study.

In cases where published stability data is used, careful interpretation of the available data in relation to the actual compounded formulation, and conditions for storage and use, must be established. Predictions based upon indirect evidence, such as publications, charts, and tables, result in "theoretically predicted" BUDs. Theoretically predicted BUDs introduce varying degrees of assumptions, and therefore increase the likelihood of error, or at least inaccuracy. Because of the risk involved with theoretically predicted BUDs, and because BUDs determined by direct, product-specific scientific data are more reliable, the latter approach is encouraged by USP <797> to support dating periods exceeding 30 days.[3]

It is clearly the responsibility of compounding personnel to assure that any data used to determine BUDs of preparations is applied consistently and is sufficiently conservative to protect the patient receiving the preparation. Therefore, when CSPs are to be dispensed to residential locations other than health care facilities, the effect of potentially uncontrolled and unmonitored excursions from ideal conditions should also be considered when assigning BUDs. Finally, in cases where compounding personnel have chosen to outsource the preparation of some or all of their CSPs to a third party, review of the contracted compounder's data, methods, cold-chain packaging, and procedures is in order to assure compliance with prevailing statutes, rules, and regulations.

Standard Operating Procedures

Compounders who assign BUDs to CSPs in the absence of direct chemical assay information must critically evaluate and interpret the most valid and appropriate sources available to determine a conservative and safe BUD. Your organization's standard operating procedure (SOP) manual should contain specific CSP formula records describing the general processes employed in the assignment of BUDs and the corresponding storage conditions.

The steps for assigning BUDs and storage conditions should be clearly defined and consistently applied throughout the organization. These SOPs should not be arranged simply to accommodate the organization's drug distribution model, to minimize drug waste, or to maximize redispensing of CSPs. SOPs for assignment of BUDs and labeling of CSPs should also include clear general guidelines for preparations compounded in the absence of sterility testing as prescribed by USP General Chapter <71>—Sterility Tests. Any SOPs created for the assignment of BUDs for CSPs compounded within your organization must be adapted directly from USP General Chapter <797> (See Figure 1).

Figure 1. BUD Matrix

	Controlled Room Temperature (15-30° C)	Cold Temperature (2-8° C)	Frozen (solid state) (-25 to -10° C)
Low Risk	< 48 hrs	<14 days	<45 days
Low Risk (with 12 hr or less BUD)	< 12 hrs	n/a	n/a
Medium Risk	< 30 hrs	< 9 days	< 45 days
High Risk	< 24 hrs	< 3 days	< 45 days

Adapted from USP General Chapter <797>

While not perfect, the BUD Matrix shown in Figure 1 provides a good general guideline for the assignment of reasonable BUDs. The responsibility for applying this information rests with the compounding personnel who should always strive to interpret this information as conservatively as possible to avoid risking patient safety. Keep in mind that Figure 1 assumes microbiological and environmental testing are being performed and that the compounding area meets all the requirements of USP <797>.

Conclusion

Consistent assignment of BUDs to compounded preparations requires a complex balance of chemistry, sterility, and scientific analysis. Understanding the risk of non-sterility and careful interpretation of available resources on chemical stability are paramount in the BUD decision process. Equally important is certainty that the information you are consulting is applicable and appropriate for the specific preparation you are attempting to compound. When considering any extrapolation of data in the determination of BUDs for CSPs, be sure the data is both valid and suitable to your CSPs. ■

References:

1. USP 32 NF 27 (US Pharmacopeial Convention) www.USP.org

2. USP General Chapter <797> www.USP.org

3. USP General Chapter <797> www.USP.org (pg. 40-41)

Additional Suggested Reading:

Trissel, LA. Editorial. Avoiding common flaws in stability and compatibility studies of injectable drugs. *Am J Hosp Pharm*. 1983; 40:1159-1160.

Trissel, LA and Flora, KP. Stability studies: five years later. *Am J Hosp Pharm*. 1988; 45:1569-71.

Trissel LA. Quality-control analytical methods: Overview of beyond-use dating for compounded sterile preparations. *Int J Pharmaceut Compound*. 2008; 12: 524-28.

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