

Baxa Corporation

Expiration Dating, BUD and USP <797>

Technical Paper

An explanation of the concepts of expiration dating and beyond-use dating in the context of USP <797> requirements

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Executive Summary

With the release of the United States Pharmacopeia (USP) Chapter <797> a new 'language' was created for pharmacy pertaining to sterile compounding and the requirements for testing and labeling compounded sterile products (CSPs). This paper reviews the differences between *expiration* dates and *beyond-use* dates for health-system pharmacies in the context of the revised USP <797> requirements.

An *expiration date* is the date beyond which ideally stored medications in the unopened manufacturer's storage container – or in most circumstances – the opened, intact manufacturer's storage container should not be used.

A *beyond-use date* (BUD) is the date beyond which medications that have been manipulated and/or repackaged and stored or dispensed in a container other than the original manufacturer's storage container should not be used.

Overview: the Terms and Their Practical Use

The expiration date and beyond use date (BUD) are two very different things. USP defines the expiration date as "the time during which the article may be expected to meet the requirements of the pharmacopeial monograph provided it is kept under the prescribed conditions."¹ The expiration date, which limits the time during which the article may be dispensed or used, is based on scientifically sound stability studies carried out by the manufacturer and is usually expressed in terms of a month and year as stated on the labeling on the manufacturer's container. This means that the product can be used or dispensed until the last day of the stated month and year, if any indicated storage and handling requirements have been met.

Within the health-system pharmacy, pharmacists are required to affix beyond-use dates – not expiration dates – to prescriptions and repackaged vials that are handled and/or compounded and sent to the patient for administration. Beyond-use dates account for the fact that the manufacturer's original container has been opened in the aseptic manipulation process, thereby exposing the pharmaceutical article to ambient atmospheric conditions and touch contamination. This exposure, and the fact that containers into which dosage forms are repackaged may not have the integrity of the original package, necessitates a shortening of the expiration period from that originally set by the manufacturer. The appropriate terminology to be used on these "repackaged" drug prescription labels is "Beyond-Use Date." The use of the term "expiration date" for a dispensed prescription is not correct.

Application of the beyond-use date is essential for dose safety, because it defines an appropriate period of time during which a prescription drug may be administered to a patient by a healthcare worker [inpatient scenario] or retained by a patient after it is dispensed [outpatient scenario]. This beyond-use date takes into account various factors, such as the nature of the drug being dispensed (i.e., chemical stability, if preservatives are present and concentrations of preservative if present), type of storage containers, microbiological limits, environmental storage conditions (i.e., room, refrigerated, freezing temperatures as well as moisture conditions, and especially the frequent opening of the package. These factors provide the rationale for requiring a limited beyond-use date.

There are, however, exceptions to these specific limits, including medications that are reconstituted before use; medications that have special beyond-use dates from the manufacturer (i.e., the manufacturer tested the stability of the medication after initial entry into the container); medications with special concerns that require limited beyond-use dates from the manufacturer; or when proper, sound and scientific “post-marketing” stability studies have been conducted.

Application of BUD in Pharmacy Practice

USP <797> sets forth clear guidelines for the maximum BUDs for doses that are high, medium and low risk compounding activities.²

Risk Category	Room Temp	Refrigerator	Freezer
Immediate Use	1 hour	1 hour	N/A
Low	48 hours	14 days	45 days
Low w/12-hr BUD	12 hours or less	12 hours or less	N/A
Medium	30 hours	9 days	45 days
High	24 hours	3 days	45 days

Frequently, pharmacies have questions regarding the practical usage of BUDs on specific compounding and sterile fill applications within their practice. Others question the application of Baxa products as related to BUDs. A few of these frequently asked questions are reviewed below.

Sterile filling of saline flushes. As a medium-risk activity, flushes would have a maximum refrigerated BUD of 9 days (under the revised Chapter <797>). If, in their professional opinion, pharmacists determine that the process of filling saline flushes is a low-risk activity, that dating is extended to 14 days as a refrigerated dose. This decision is subject to professional debate and can be argued either way. USP <797> is not prescriptive for these decisions, but rather leaves the interpretation to the judgment of pharmacy professionals.

Cefazolin. Again, compounding one-gram doses of cefazolin can be categorized as either low risk or medium risk. In this case, there is less debate because of the reconstitution step required. For a single dose preparation, the maximum refrigerated BUD is 14 days, if the other factors (e.g., drug stability, etc.) support such a designation. Batch-prepared cefazolin doses use multiple vials, clearly a medium-risk activity. Once again though, these USP 797 guidelines are for maximum BUD’s within activity levels and not absolutes.

End-product sterility testing. It’s possible to expand beyond-use dates through a scientifically proven and valid protocol with a particular product and process to determine that the product remains stable and sterile for periods exceeding the “maximum” default BUD times for the process categories (outlined above). However, the process mandated under USP <797> can be onerous for individual pharmacies, and even for manufacturers. Few pharmacies have the internal resources to meet such a high standard for protocol development and validation testing, or the resources to outsource these activities.

Baxa automation. Baxa products are not critical factors in setting product BUD. The Rapid-Fill™ Automated Syringe Filler (ASF) offers a means to reduce the opportunity for touch contamination in sterile compounding and may be rationalized as providing a low-risk means for batch sterile saline flushes and antibiotics. However, end-product testing is recommended to verify process capability and product sterility. To justify extending beyond-use dating with the Baxa Rapid-Fill ASF would require undertaking the testing mandated under USP <797> for end-product sterility testing.

Guidelines for setting BUD

There is no simple answer or “ultimate source” for guidelines in setting BUD. To investigate the possibility of extending the BUD guidelines set forth under USP <797>, one place to start is with the scientific information provided in Trissel’s *Handbook on Injectable Drugs*³, then consider any intangibles related to your sterile compounding process, environment and personnel. While the USP <797> guidelines for extending BUDs represent a body of work for validation, a well-run pharmacy service can manage the process with time and resources without significant investment.

Summary

As with other guidelines under USP <797>, the intent is to provide a means for addressing issues with sterile compounding, and to provide an appropriate means for addressing identified safety issues.

For CSP’s, the beyond-use date is intended to identify the interval from the time of preparation (mixing) to the time where the preparation can be safely used – that is, before it is at risk for chemical degradation, contamination and/or packaging permeability. Beyond-use dates notify pharmacists and caregivers of the date after which a CSP should not be administered.

References

1. USP Chapter <797>. 2008 August.
2. E. Kastango, STAR Center presentation, USP Chapter <797> Pharmaceutical Compounding-Sterile Preparations, January 2008.
3. Trissel, Lawrence A. *Handbook on Injectable Drugs*. 14 Rev Ed. American Society of Health-System Pharmacists. 2006.