STANDARDS OF PRACTICE, PROFESSIONAL JUDGMENT, AND SCIENTIFIC EVIDENCE TO

Establish and Extend a Beyond-use Date

Abstract The establishment of both a beyond-use date and the extension of a beyond-use date need to be scientifically based. What is accepted as scientific evidence is at times misleading. The pharmacist may have the right to utilize some degree of professional judgment in both establishing and extending a beyond-use date, after a review of appropriate scientific literature. Notwithstanding this scientific review, it is the concept of professional judgment that seemingly needs to be better defined. A new-found appreciation for professional judgment will bring us to the understanding that a validated stability-indicating assay is the correct manner in which to extend a beyond-use date. This article addresses and discusses the recommendations and rigor required to establish and extend a beyond-use date. The perspectives of the pharmacist and physician are explored, as well as the impact of an extended beyond-use date, or lack thereof, are discussed. The application of a set of fundamental principles will be revealed, which will lead to finite conclusions as to the necessary methodology to establish as well as extend a beyond-use date.

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Beyond-use Dating

Much of the compounding community adheres to the United States Pharmacopeia (USP) as their standard of practice. Some States and Provinces, in the U.S and Canada, respectively, apply their own standards, which are at times written into law. It is written in the USP that a compounding pharmacist may apply their professional judgment in specific instances and within the context of a compounding practice (USP 37-National Formulary 32). The USP currently defines a beyond-use date (BUD) as the date after which a compounded preparation cannot be used, administered, stored, or transported.1 What needs to be carefully addressed now is what constitutes professional judgment. Concrete scientific evidence needs to be the basis upon which any decision is made to not only establish a BUD but also to extend it. Well-founded scientific evidence need become synonymous with professional judgment. Patient safety should be the pivotal point upon which decisions are made as they relate to BUDs. Secondary to patient safety is their practicality and convenience, or lack thereof, as it relates to the time from which a prescription is received to the time a compounded medication can be dispensed and consumed.

Pharmacist’s Perspective

Knowledge that a formulation remains consistent in strength and composition is critical in delivering a safe and effective treatment. Under current standards of practice, the default BUDs are based on generalized properties for stability, which can be limiting and may not be suitable for all formulations (Table 1).1 Due to these generalizations, one cannot say with certainty that the active pharmaceutical ingredient (API) has maintained its compounded strength even when deferring to USP criteria. Therefore, using direct stability data for a compounded preparation is an important step in ensuring safety of the patient. The appropriate means by which conclusive data can be obtained need to be clear and consistent. There needs to be an alignment in the standard of practice requirement, and the scientific justification, in both establishing a safe BUD as well as extending a BUD for a compounded preparation.

The ability to extend a BUD needs to be based on a thorough understanding of the formulation and evaluation of data obtained from properly designed and validated stability-indicating assays. It is also recommended that available data be used to establish and justify a suitable BUD, and is defined as the length of time that a formulation is proven to possess the same strength and stability as it did at the time of its preparation.2

In addition to complying with standards of practice, pharmacists need to be aware of the scientific data required to make evidence-based decisions when assigning a BUD. Table 2 describes the different types of stability that must be maintained in a formulation.2,3

Our focus is chemical stability, which is one type of stability and encompasses drug strength and degradation products. From a chemical standpoint, there are several pathways whereby an API can be degraded.
and lose its strength (Table 3). In order for an API to be effective, a minimal concentration must be available in the body. If a drug loses significant strength, the minimal concentration might not be reached, and the therapeutic effect of the drug will be lost. Another consideration is that the degradation products of an API can also lead to toxicity or the alteration of an intended therapeutic effect, as is the case with some antibiotics.

When sufficient scientific evidence from validated stability-indicating assays is unavailable, professionals currently defer to USP criteria to establish a BUD. The necessity of having to assign a BUD that doesn’t allow enough time for an intended course of treatment may seem unreasonable, and this raises the question, based on what scientific evidence have these default BUDs been determined?

Take for example oral aqueous formulations which have shorter BUDs (14 days) than oral non-aqueous formulations, or topical aqueous formulations. This can be justified by the fact that water catalyzes degradation reactions such as hydrolysis and oxidation (dependent on pH) and promotes microbial growth, which can be dangerous when ingested. Studies on the stability of oral aqueous formulations show that while the likelihood of losing stability at 14 days is low, seldom do drugs lose their stability before 10 days due to oxidation. However, due to the unique chemical interactions between the base, the API, the container closure, and storage conditions, each formulation is different, therefore, the stability could also be different. This can be particularly dangerous in neonates, infants, the elderly, and immunocompromised patients; patients within this group happen to be the most likely cohorts to receive therapeutics in the form of oral aqueous suspensions. Therefore, the USP guidelines currently provide general estimations of the short-term stability of a compounded preparation in the absence of supporting scientific data. However, the reality is that these estimates are not based on direct scientific testing on each drug and excipient combination, therefore, the safety of a compounded preparation is not guaranteed. It is with this in mind that it is suggested that, in the interim, USP guidelines be used to fall back on, and that stability tests generated by an accredited research facility on the formulation(s) in question be used not only to extend a BUD but to establish one.

Evidently, stability testing is integral in assigning a BUD. Professional judgment rooted in direct stability data should be used to assign a BUD. This involves performing your own stability-indicating assays through a validated third-party testing lab, or, when available, obtaining results from published BUD studies that have been previously generated by a supplier or fellow pharmacist. Stability-related information must be carefully interpreted to assure the safety of a formulation at the time of its administration. In order to correctly interpret a study, one must take into account the assay method, type of formulation, the nature of the API and its degradation mechanisms, the API concentration, its excipients, solvents, dispensing containers (e.g., PP syringe, PET, glass bottle), and storage conditions (refrigerated vs room-temperature). Using available data that doesn’t entirely match the formulation in question is an extrapolation and can lead to erroneous conclusions. While this data could support the temporary use of default BUDs, it cannot be used to extend a BUD.

One might be tempted to conclude that two formulations containing identical excipients and different APIs that belong to the same chemical class known to be subject to degradation by the same mechanism should have similar stability, but any conclusion remains an assumption. The same argument stands when changing an excipient in a formulation. In some instances, changing an ingredient may alter the degradation of a drug resulting in a risky extrapolation.

### Table 2. Types of Stability Described in United States Pharmacopeia Chapter <1191>.³

<table>
<thead>
<tr>
<th>TYPE OF STABILITY</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>Maintaining appearance and uniformity</td>
</tr>
<tr>
<td>Chemical</td>
<td>Concentration of active pharmaceutical agent vs degradation products</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Maintaining therapeutic effect</td>
</tr>
<tr>
<td>Toxicological</td>
<td>No adverse change in toxicity to patient</td>
</tr>
</tbody>
</table>

### Table 3. Common Degradation Pathways.³

<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epimerization</td>
<td>Occurs rapidly when the dissolved drug is exposed to a pH of intermediate range.</td>
</tr>
<tr>
<td>Hydrolysis</td>
<td>Esters and amide bonds are the chemical bonds most likely to hydrolyze in the presence of water.</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Hydroxyl groups directly bonded to a phenyl group, and aldehydes are most likely to oxidize. Oxidation is catalyzed by pH values that are higher than optimum, and exposure to oxygen and UV illumination.</td>
</tr>
<tr>
<td>pH</td>
<td>The degradation of many drugs in solution accelerates or decelerates exponentially as the pH is decreased or increased.</td>
</tr>
<tr>
<td>Temperature</td>
<td>In general, the rate of a chemical reaction doubles for each 10°C increase in temperature for nearly all hydrolysis and some drug-oxidation reactions.</td>
</tr>
</tbody>
</table>

While assumptions are convenient, they introduce uncertainty and risk to the decision-making process, and are a source of liability. Direct scientific evidence must support any conclusion being made, and published stability studies should be carefully reviewed before using professional judgment to extend a BUD. When extending a BUD, in the absence of pre-existing data that provide direct evidence supporting the decision, a proper stability study using a stability-indicating assay is required.

Industry trends in the methods being employed to perform stability studies are highly variable. Table 4 shows a comparison of the different types of stability studies and the types of data that they generate. In the past, many compounding pharmacists relied on “strength-over-time” studies, which are often erroneously referred to as “potency-over-time” studies. Not only are these studies not stability-indicating, but they do not measure potency. Potency is a measure of the amount of drug required to produce a desired effect. This is a pharmacological measure, which depends on all molecules in a compound, and can only
be determined by biological assays. Strength refers to the absolute concentration of a given API at a given point in time, which is not identical to the biological potency of the API or its degradants. In the past, subjecting a formulation to extreme conditions for a limited amount of time has been used as an alternative to real-time studies, which requires leaving a formulation over an extended period of time to predict BUDs. This is a practice that should be avoided for studies that don’t require years to complete, as the false conditions do not accurately reflect the degradation of the formulation at the controlled temperature conditions under which it would be stored.

Validated Stability-indicating Assay

This leads to the question: What is a validated stability-indicating assay? A stability-indicating method is mandatory to determine stability of a compounded preparation, and it must consist of method development and validation. There are multiple methodologies that can be used to assess stability, however, high-performance liquid chromatography (HPLC) is one of the most common, as it easily leads to stability-indicating assay techniques. It is important to note that not all HPLC methods are stability indicating. In order for a method to be validated as stability indicating, forced degradation studies must be carried out to separate the analyte (substance being identified and quantified) from its possible degradants (substance present after an API has been degraded) to be sure that the HPLC methodology can resolve both peaks on the chromatogram. If degradation of the compound is not performed, then the method is testing the strength of the compound not the stability. The reason for this is that when analyzing the chromatogram to determine the amount of the drug in question, one has to ensure that no excipients or degradants co-eluted with the analyte. This would lead to unresolved peaks, and could result in the inaccurate interpretation of concentration of the analyte. During the validation process, degrading the compound forcefully with an acid, base, heat, peroxide, or sodium hypochlorite separates the drug from its degradants. Therefore, when visualizing the results, one can be sure that the analyte and the degradation products are fully resolved. Having completed this validation procedure, a stability-indicating assay is performed at various time points following extended storage of the formulation. In order to extend a BUD, the compounding pharmacist needs to review data from appropriately validated stability-indicating assays.

Clinical Perspective

From a clinical point of view, physicians are faced with the dilemma of complying with BUDs impractical to the prescribed therapeutic regimen as established by pharmacists, without always understanding the reasons for these imposed limitations. In some cases, the BUD may have a direct conflict with the timeline required for administering the medication and could impede
patient compliance. The course of treatment of a formulation may easily exceed its corresponding BUD as established by the USP. Additionally, time constraints surrounding preparing, shipping, receiving, and administering a formulation may add to the difficulty in respecting a BUD, thus the necessity to extend the BUD using scientifically based professional judgment.

Patient safety needs to be at the forefront of the treatment goal. It is imperative to ensure that the compounded preparation has maintained its integrity. A BUD determined from a validated stability-indicating assay confirms the durability and quality of the final preparation, ensuring the success of the patient’s treatment plan.17 Although it is important not to restrict patient access to needed compounded medications, the extension of a BUD without a validated study poses significant risk to the patient.4,15 This fact confirms the importance of using validated scientific data to establish a BUD and/or extend a BUD. A collaborative practice involving both the physician and the pharmacist is recommended to optimally balance safety-related factors involving what is practical for both formulations and clinical considerations.

**Conclusion**

The determinants of chemical stability exist as a means of securing the integrity of a dosage form when both establishing and extending a BUD for a compounded formulation. Peer-reviewed literature regarding the stability of a given preparation needs to be compared and contrasted, with and against, the formulation in question. If the preparatory procedure between a published peer-reviewed stability study and a compounding pharmacy’s Master Formulation Record is not the same, then the use of that peer-reviewed study is in question. In this case, it is necessary to perform a validated stability-indicating assay. The significance and importance of equating scientific data with professional judgment can now be well appreciated.

**TABLE 4. Comparison of Different Types of Stability Studies and their Respective Outcome Measures.**

<table>
<thead>
<tr>
<th>TEST OPTIONS</th>
<th>CONTAINER ADSORPTION</th>
<th>STRENGTH OF API</th>
<th>DEGRADATION PATHWAYS</th>
<th>EFFECT OF STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength-over-time</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Forced Degradation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stability-indicating Assay with Method Validation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

API = active pharmaceutical ingredient

**References**


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