How Proposed Beyond-Use Date Limits Relate to Compounded Parenteral Nutrition

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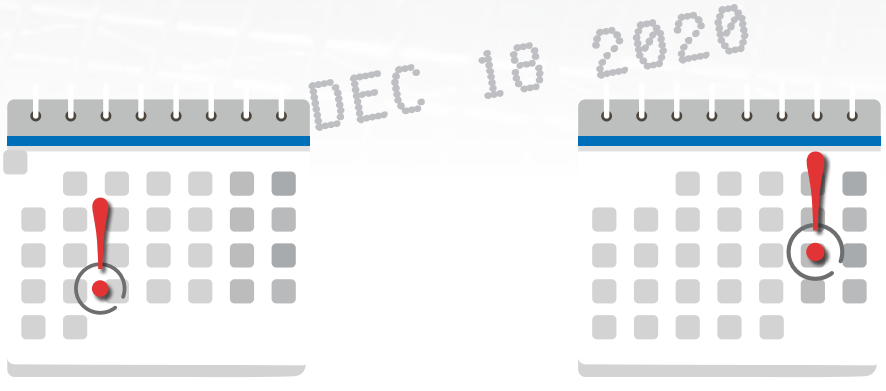
If we were writing a story about how pharmacy compounding has evolved over the last decade, the 2012 meningitis outbreak would drive the narrative. Our tale would then divide into two different chapters called 503A and 503B, each filled with reams of new regulations and guidance documents. Then, we'd introduce a plot twist as the long-awaited revisions to Chapter <797>, "Pharmaceutical Compounding - Sterile Preparations," are delayed due to an appeals process prompted by challenges made to the tighter limits on beyond use dates (BUDs).

USP <797> sets default limits for BUDs on compounded sterile preparations (CSPs). A story about BUD is always bound to be a page turner because these limits on "shelf life" influence how often pharmacies compound, how frequent patients refill, and the amount of waste generated. BUDs affect patients who rely on a steady, safe supply of IV drug therapy, both in their homes and when they travel.

Although the <797> revisions are currently awaiting an appeals decision, this article discusses the underlying process for assigning BUDs to CSPs and how the proposed changes will relate to parenteral nutrition (PN) compounded by home infusion pharmacies.



How the new framework for assigning BUDs relates to compounded PN

The term, beyond use date, is defined in the 2008 <797> compounding standards as "the date or time after which a compounded sterile preparation shall not be stored or transported."[1] The definition proposed in the 2019 revision reads, "the date, or the hour and date, beyond which the preparation must not be used and must be discarded."[2]

In the clinical setting, agreement about the meaning of the definition of BUD has not always been easy. In simple terms, BUDs determine shelf life for compounded or prepared products, while expiration dates describe the shelf life for manufactured products. However, BUDs differ from manufacturers' expiration dates, which are based on rigorous testing and refer to the time during which a conventionally manufactured product can be expected to maintain expected quality, provided it is kept under the specified storage conditions.

Determining default BUD limits is more challenging because these time periods are not based on direct evidence. Instead, the limit on BUD represents the longest amount of time we feel comfortable with when leaving our freshly compounded medications on the shelf, prior to administration. The risk from microbial contamination is of particular concern, and the longer a CSP is stored, the higher the risk of microbial growth.

In any discussion about establishing BUDs for PN, it is important to understand the microbial risk level associated with its compounding process. Producing one bag of compounded PN often requires more packages of sterile ingredients, more compounding supplies, more equipment, and more manipulations than most batches of other types of compounded injectable drugs. With this concept in mind, the 2008 <797> standards classify PN as a medium-risk compound with shorter BUD limits than low-risk compounds. PN prepared on an automated compounding device (ACD) is the quintessential medium-risk compound and, in fact, is the first example listed in <797>.

The proposed USP revisions do away with risk levels. CSPs will instead be divided into two categories. CSPs that are compounded in segregated compounding areas (SCAs) will be classified as category one with shorter BUDs, and CSPs prepared in cleanrooms will be classified as category two with longer BUD limits.

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Proposed Beyond-Use Dates and Parenteral Nutrition

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As long as the appropriate BUD limit is applied, there is nothing in the revisions that prevents individuals from compounding PN in a primary engineering control (IV hood) that is located in an SCA, which is a designated area with regular room air instead of cleanroom air. Although some may feel this opens the door for compounding PN outside of a cleanroom, the very tight 24-hour BUD limit for category one compounding does not make it a practical therapy for home infusion pharmacies.

Category two CSPs, on the other hand, allow for longer BUDs. If the CSPs are terminally sterilized or stored frozen, the BUD limits get even longer, but these practices have no application to PN. As a result, some compounders may be concerned that PN has been left out in the cold by the new BUD limits because they will allow only one extra day of storage for bags that are kept in a refrigerator.

Is sterility testing a practical option for extending the BUDs for compounded PNs?

Although both the 2008 standards and the proposed revisions allow longer BUDs if the CSP first passes a sterility test, this is a less-than-ideal solution for home infusion pharmacies. First, it is important to realize that it is not possible to perform a true sterility test on the actual bag that will be administered to the patient. <797> will require minimum sample volumes for these tests, which are described in USP <71>, the chapter on sterility testing. After a true sterility test, no more than 80% of the original PN would be available for infusion into the patient.[3]

Instead, sterility tests are performed on a number of sample bags, which are meant to represent the larger batch of doses that will be dispensed. In order to better represent the batch, <71> also requires a minimum number of sample bags. But it is unclear what would constitute a batch when compounding patient-specific PN in a home infusion pharmacy because each patient will have a unique formulation. Pharmacies would have to devote additional time and resources to make extra bags for testing.

There are also strict methods in <71> for how sterility tests must be performed. Direct inoculation is not preferred. Using this method might also be a red flag during a pharmacy inspection. An additional concern is that inoculating growth media with a PN formulation containing fat emulsion could obscure the test results.

Membrane filtration is the preferred sterility test according to USP <71>. In this method, samples are run through membrane filters; the filters are treated with rinse solutions; and the filters are introduced into two types of growth media to capture aerobic bacteria, anaerobic bacteria, and fungi. Conducting the test could involve more risk of contamination than the actual compounding process.

Perhaps a greater obstacle for establishing a sterility testing program is the requirement to conduct method suitability on the compounded formulations. Method suitability ensures that the CSPs do not contain any properties that could interfere with a sterility test. It requires the formulations to be standardized and validated ahead of time. But, because daily nutritional requirements change frequently, standardization may not be compatible with the needs of home infusion patients.

Even when pharmacies invest the time and resources to develop the preferred method, produce the extra bags, and validate all the formulations, the sterility tests described in USP <71> will still require 14 days of incubation-time before the final result. By then, a bag from a different "batch" may be infusing into the patient.

How chemical and physical stability relate to BUD

There are other options in <797> for assigning longer BUDs. The revisions allow up to 60 days for frozen CSPs and up to 90 days for frozen CSPs that were first terminally sterilized (e.g., high-pressure steam). But no matter how beneficial these extra days are, compounding pharmacies will not subject PN to a deep freeze or a dose of steam heat because of concerns about the impact on chemical and physical stability.

When multiple drugs are combined into a compounded solution, there can be risks of reactions between the drugs, which could result in a chemical or physical change. For example, certain combinations can lead to the formation of insoluble precipitates. Temperature and storage time also factor into the chances for these interactions to occur.

When it comes to assigning BUD, chemical and physical stability should not be overlooked. BUD is not just about microbial risk. A sterile bag of PN can still precipitate out of solution or break down chemically while being stored in the refrigerator.
Another important factor is the CSP's administration time. Although <797> excludes administration time from the definition of BUD, unstable formulations are still capable of harm, whether they break down

during storage or during IV infusion. Pharmacists must always have assurance that a formula will remain stable throughout both storage and administration.

Without direct testing by the pharmacy, where does this assurance derive from? More often, from published stability studies performed by someone else. To help pharmacists use sound judgement, the 2008 standards contain a separate section in <797> about using published stability data. Here, important concepts are discussed, such as drug composition, extrapolation, valid evidence, drug concentration, and stability-indicating assays. Although the 2019 <797> revision will still require compounders to consider the chemical and physical properties that could affect stability, the section about using published stability studies was not included in the revision.

PN stability and the home infusion patient

There are at least two reasons why home infusion pharmacists would appreciate more clarity about PN stability. The first has to do with the complexity

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of the PN formulations. According to the American Society for Parenteral and Enteral Nutrition, some of the indications for PN include "short bowel syndrome, GI fistulas, bowel obstruction, critically ill patients, and severe acute pancreatitis."[4] Such versatility requires many ingredients in multiple combinations. The opportunities for unwanted chemical or physical interactions can be numerous.

The fewer ingredients, the easier it is to keep track of all the possible interactions. Even a relatively unstable drug like injectable ampicillin has much of the information about stability contained in its package insert. To maximize stability, the package insert tells us to combine injectable ampicillin with Normal Saline, in a final concentration up to 20mg per mL. [5]

The Instructions for compounding PN are not as straightforward. According to *Extended Stability for Parenteral Drugs,* "amino acid products alone are formulated to contain about 15 different nutrients,

and most multiple vitamin products contain 12 or 13 vitamins plus excipients." Therefore, all "the possible permutations and combinations are too numerous to test for stability and compatibility."[6] There are, however, published studies that show the stability of typical PN formulations. These references can also be used to support pharmacists during interventions with prescribers.

Another reason why access to practical information about PN stability is important is that home infusion pharmacists are consistently on the front line, dealing with real issues about BUDs. Often, an on-call pharmacist is the last line of defense preventing the administration of a questionable bag of PN that may have been handled improperly or is past its date for allowable use.

The entire team (e.g., patient, nurse, dietitian, and pharmacist) is usually aware of the risks when there is a breakdown with the PN's transport, storage, handling, and dose scheduling. Home infusion pharmacists will most likely get a phone call if bags break, are left out of the refrigerator, or arrive after the expected delivery time. Deciding the next step is clearly role of the pharmacist – the individual who must have the most knowledge about PN stability.

Home infusion pharmacists might not always get a phone call, however, when bags feel warm, look slightly discolored, or the alarm on the infusion pump acts up. These are more subtle indicators of possible risks. During an off hour, some caregivers might be tempted to make a judgement call, instead of a phone call. Others may not know when to ask.

In the 2008 USP standards, 9 days in the refrigerator is the longest time for storing PN. In the proposed revisions it is 10. Those are days when the product is not under a pharmacist's supervision. Patients, and anyone else handling PN, must recognize conditions that can lead to problems. They must also be encouraged to contact the home infusion pharmacy when something doesn't seem right. Sometimes, the most dangerous question is the one that isn't asked.

Recap

A recap of how the BUD revisions fit in with compounded PN is as follows:

1. When using the new criteria for assigning BUD, only compound patient-specific PN as a category two CSP.
2. The new, longer (10-day) BUD allowed for PN should be sufficient for most home infusion compounders. Compounders should prioritize patient safety over longer storage.
3. By meeting patients' nutritional needs, PN is more complex than many other types of CSPs. Applying stability data to an individual formula will almost always require some level of extrapolation from studies using standard ranges for concentrations of primary components (i.e. amino acids and dextrose).
4. The home infusion pharmacist must always be ready to meet additional patient needs based on individual circumstances.

Next Steps

When a coalition of pharmacy compounders appealed the <797> revisions, two concerns expressed were: shortening the BUDs was not based on science and shorter BUDs will have a profoundly negative impact on patient safety due to lack of compounded drug availability.[7] The next step in the continuing saga to update chapter <797> is for the USP compounding expert committee to engage with stakeholders to address the concerns.

USP has stated that the expert committee will follow a plan when seeking this engagement.[8] The focus will be on the framework for establishing BUDs and possible BUD extensions beyond the default limits that were in the remanded chapters. USP has also obtained an independent party to conduct engagement sessions, which will include smaller roundtable discussions with invited participants. Home infusion pharmacists, who are often on the front lines, must lead the line of participants providing critical stakeholder input.

Some time ago, <797> sprung from a chapter removed from USP called <1206> - "Sterile Products for Home Use." When it evolved into <797>, <1206> went from being an informational chapter aimed at the home care setting to enforceable standards applicable to all sterile compounding.[9] With the latest revisions, <797> continues to evolve. Now, the requirements are more focused on underlying quality systems.

These are monumental advances for patient safety. We applaud the compounding expert committee for including more rigorous standards for cleanrooms, training, cleaning, and environmental monitoring. On the other hand, we wonder if the chapter's

application to compounded PN will be lost when the subject matter is streamlined in the proposed changes. A few of us who work in cleanrooms may miss medium-risk compounding when we become category two compounders.

Perhaps a look back can help us move forward. Although <797> outgrew the home use chapter on which that it was based, the time may be right for other informational chapters about sterile compounding, with one that focuses on best practices for compounding PN. It might also remind other stakeholders why 503A pharmacies, who compound for individual patients, are so different from 503B facilities.

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