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School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists and pharmacy technicians will be able to

- Describe recent changes to USP <795>
- Identify the designated person's responsibilities
- Recognize areas of nonsterile compounding that could be improved

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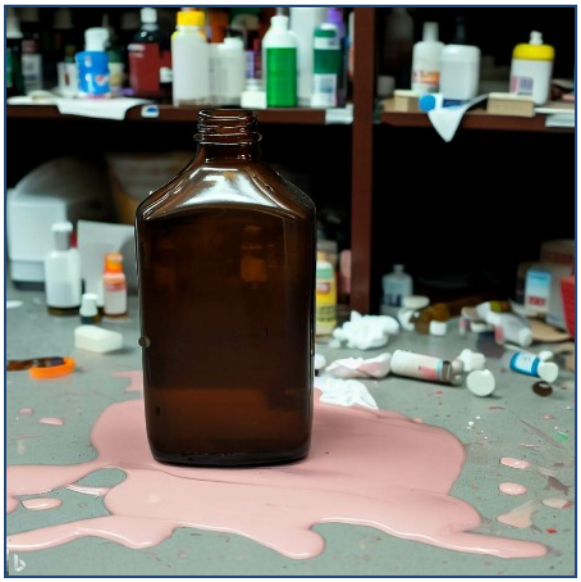

The revised USP 795 becomes official in November 2023. What's new?

TARGET AUDIENCE: Pharmacists and pharmacy technicians who engage in compounding

ABSTRACT: Compounding of drug preparations requires training and knowledge in the science underlying pharmaceutical compounding. Altering the original drug product can change the drug's stability and clinical efficacy. The United States Pharmacopeia (USP) is an independent non-profit organization of knowledgeable volunteers who set the standards for pharmaceutical compounding to ensure patient safety. State regulating bodies oversee and enforce these standards at compounding pharmacies to ensure compounded preparations are up to quality and purity standards. Since the field of pharmaceutical compounding is constantly changing, USP revises its standards regularly. The USP recently revised *General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations* with revisions enforceable on November 1, 2023. To make this transition easier, this continuing education activity outlines the most significant changes made to USP <795>. USP changed *General Chapter <795> Pharmaceutical Compounding - Nonsterile preparations* to mimic those of *USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations*. Overall, the revision elevates nonsterile compounding's quality and sanitary standards to improve patient safety by reducing common safety errors seen across the United States.

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FACULTY DISCLOSURE: The faculty has no financial relationships with an ineligible company.

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INTRODUCTION

The original "little blue pill" was created in the 1860s and was a popular cure for everything from toothache to tuberculosis.[1] Pharmacists compounded "blue mass syrup" and "blue pills" based on their own recipes or on one of several

widespread recipes. Its name probably derives from the use of blue dye or blue chalk (used as a buffer) in some formulations. Blue mass's ingredients varied, as each pharmacist prepared it himself, but they all included elemental mercury. One recipe for blue mass syrup consisted of[1]

- 33% mercury (measured by weight)
- 5% licorice
- 25% *Althaea* (a root extract, possibly from hollyhock or marshmallow)
- 3% glycerol
- 34% rose honey

Pharmacist-compounders produced blue pills by substituting milk sugar or chalk for the glycerol and rose oil for the rose honey. Each pill contained one grain (64.8 milligrams) of mercury and was prescribed two to three times a day, which today we know causes heavy metal poisoning, since the dose is more than 100 times more than the limit set by the Environmental Protection Agency.[1] Products were made without fancy definitions or regard to cleanliness. Times have changed.

Pharmaceutical compounding is the act of manipulating a drug product to create a new drug formulation.[2] Pharmacists and pharmacy technicians still compound drug preparations for a specific patient or group of patients when no drug product exists on the market, or as seen more recently, when the drug product is backordered with no therapeutic alternative(s). It is also interesting to note what the United States Pharmacopeia (USP; described below) does NOT consider to be compounding. Preparing a powdered antibiotic bottle with distilled water per manufacturer's directions is not considered compounding. Splitting tablets and repackaging is also not considered compounding, nor is preparing a single dose for a single patient to be used within four hours. In other words, making one dose of blue mass syrup and giving it directly to a patient is not compounding. (OK, maybe no one makes blue mass syrup anymore, but crushing a tablet and placing it in a liquid for immediate use is still not a compounded preparation.)

Pharmaceutical compounding has two categories: sterile compounding and nonsterile compounding.[2]

- Sterile compounding is creating a new drug preparation that must be sterile (completely free of pathologic microorganisms) and includes preparations that are primarily infusions, injections, eye drops, and many irrigations.
- Non-sterile compounding is creating a new drug product that is not required to be sterile (although these products should be as "clean" as possible) and are mostly used for oral or topical administration. Non-sterile compounding is often employed for pediatric and veterinary preparations where patients need very small or very large doses. Some examples are medicated creams for neuropathic pain, and anesthetic mouthwashes for oral sores and pains.

The USP is an independent non-profit organization of knowledgeable volunteers who set the standards for pharmaceutical compounding to ensure patient safety.[3] The USP also distinguishes guidelines for hazardous and non-hazardous compounding. Both sterile and nonsterile compounding can involve manipulation of hazardous drugs. This continuing education activity focuses on non-hazardous nonsterile compounding. More information on hazardous compounding can be found in *General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings*. Access to the USP Compounding Compendium costs $250.00 for a 12-month membership. There are also various plans for multiple users. Many institutions have a contract with USP. (Readers should check with their designated person or supervisor, as they may already have access to this service.)

The origin of nonsterile pharmaceutical compounding in the U.S. cannot be pinned down to one exact date, but historically, the 1800s saw immense growth in not only population but also in disease states as people traveled and settled to new areas. Between 1840 and 1850, it is estimated that more than 1.5 million persons immigrated to the United States. Backyard herbalists became highly regarded apothecaries seemingly overnight.[4]

Unfortunately, there were no established compounding standards until 1820 when a small group of physicians raised concerns about the high prevalence of poor-quality medicine across America and the USP was formed. By 1863, during the height of the Civil War, the USP had become the most trusted source for information about medicines.[3.]

The USP continuously strives to improve the quality of drugs, including compounded preparations. Today we know that the quality of a compounded preparation depends as much on handwashing, gloving and cleaning, as checking the pH of the product itself. These steps are necessary to safeguard the preparation that a pharmacist or pharmacy technician compounds, and ultimately, safeguard the patient.

The USP sets standards for pharmaceutical compounding but has no regulatory authority, so it does not enforce the standards it sets. Each state is responsible for regulating pharmaceutical compounding, but the Food and Drug Administration (FDA) is also authorized to regulate all aspects of drugs, including compounding. Both state regulating bodies and the FDA can inspect compounding in pharmacies and take legal action and can amass fines if compounders do not uphold USP standards. However, this action only applies to states that write USP standards into their laws. Depending on the situation's severity, legal action could result in a loss of license for the pharmacy or pharmacist.

The USP sets standards for sterile and nonsterile compounding through *General Chapter <797>* and *General Chapter <795>*, respectively. (Here's a PRO TIP: chapters numbered from 1 to 1000 are enforceable by state and federal agencies). More recently,

the FDA has been inspecting compounding pharmacies to ensure they meet *General Chapter <797> standards*, but it is only a matter of time before these agencies turn their attention to *General Chapter <795>.*

In November 2022, the USP published a revised *General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations*. Going forward, we will call these standards the newly revised standards. This revision now includes a designated person (the individual assigned to be accountable and responsible for the compounding facility's operation, performance, and personnel) requirement to mimic *General Chapter <797>*. With the implementation of a designated person for nonsterile compounding under proposed *General Chapter <795>*, when the facility is not up to code, State boards of Pharmacy and the FDA hold the designated person responsible, creating a risk of loss of license. The revised standards will be official in November 2023. Major changes include

- garbing
- cleaning
- training
- beyond-use dating and
- a designated person requirement

The focus here is on how to implement the major changes made to the currently enforceable *General Chapter <795>*, which was revised and reissued in 2020. Going forward, we will call these standards the current standards. Once readers are familiar with this summary of the major changes in the newly revised standards, they are encouraged to review the full text of the proposed chapter <795> to address additional minor changes.

So, to repeat, the standards that were revised and reissued in 2020 and are currently enforceable will be called the current standards. The revision that will be adopted in November 2023 will be called the newly revised standards.

Garbing

The newly revised standards put greater emphasis on garbing procedures for nonsterile compounding than the current standards do. Pharmacy personnel who compound sterile preparations are well acquainted with garbing, however, garbing is a foreign concept to many who prepare nonsterile preparations. Think back to the past. How often did you go to the back of the store, push some items on the counter aside, and start mixing a magic mouth wash? You probably made it wearing a shirt and tie or more formal dress, while possibly wearing a lab coat, unless it was a really hot day. You might even have washed your hands if you just came back from lunch. Conversely, many hospital pharmacies mix magic mouthwash in so much garb, that you might think that it is a toxic preparation. The **SIDEBAR** explores this topic in greater detail.

TECH TALK SIDE BAR[5]

Have you noticed that many pharmacists and pharmacy technicians no longer wear white lab coats? Physicians began to wear white coats in the late 1800s as doctors started to recognize the color white's effectiveness. It is easier to see dirt and soil that prompts the wearer to launder it, and frequent laundering helps reduce pathogens. Soon all medical professionals adopted the practice. White coats were worn not only to protect one's clothing, but they were seen as a sign of prestige and respect.

Today, white coats are rarely used, because according to Dennis Miller, "White coats cause white coat syndrome" (hypertension) and they "increase the distance between the pharmacist and the customer." Few states regulate pharmacy technician attire. Many institutions and most large retail chains require pharmacy technicians to wear uniform "scrubs." Restricting white coats to professional staff may reduce some customer confusion, but in certain situations, scrubs might imply the wearer is a nurse or other hospital professional, which is also confusing. One of this CE's authors says, "I can't even tell you how many patients and families would ask if I was a nurse."

Recently, some hospitals have banned pharmacy technicians from wearing scrubs, forcing them to wear civilian clothing. Unfortunately, that makes technicians look like pharmacists again. Of course, some pharmacists like to wear scrubs to work; are they secretly wishing they were technicians? Doubtful. Business attire has certainly gone downhill lately. So, if we can't wear a white coat and we can't wear scrubs, what are we to wear?

THE ANSWER (which is required by law in many states): A name tag that indicates your position!

The current standards state that personnel involved in compounding should garb "as needed for personal protection and to prevent contamination" of the compounded nonsterile product (CNSP) prior to preparation.[6] For example, compounding staff don two pairs of gloves for personal protection when preparing cytotoxic CNSPs for their own safety. More information on hazardous compounding can be found in *General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings*. The current standards also state compounding personnel are responsible for maintaining good hand hygiene and wearing appropriate clothing to prevent contamination of the CNSP.[6] These statements give compounding personnel some latitude when they make decisions. For example, currently, some compounders don gloves to make magic mouthwash, while many others prepare it with ungloved hands in their practice. Non- sterile gloves will become mandatory on November first.

The newly revised standards now specify hand washing and garbing procedures and provide guidance on personnel who should NOT prepare a CNSP. Compounding personnel are to remove all

"garments that cannot be easily cleaned" before entering the designated compounding area. So compounding personnel must now remove personal outer garments (such as jackets, sweaters, hats, and scarves), hand and wrist jewelry, anything that might hinder the use of gloves, and headphones must be removed before compounding something as simple as magic mouthwash. Compounding personnel must wash their hands for at least 30 seconds and dry with one-time use paper towels before compounding as well. After handwashing, personnel must don non-sterile gloves and inspect the gloves for holes, rips, or tears. Compounding personnel should wipe or replace gloves in between different preparations and must remove these gloves before leaving the designated compounding area.[6] These proposed standards are analogous to the procedures required for sterile compounding. In fact, the format of and definitions within the revised <795> aligns with the revised <797> for sterile products much more closely than in the past.

The current standards still require personnel to be in good health and fit for compounding, but the revisions are considerably more specific. Personnel who have new tattoos, oozing sores, open wounds, conjunctivitis, rashes, or active respiratory infections are not considered fit to compound due to risk of contamination of the CNSP. The newly revised standards hold the designated person responsible for deciding if personnel are fit for compounding or not.[6]

Cleaning the Designated Compounding Area

Do I need to create an area for compounding? Yes. The newly revised standards describe a designated compounding area in detail. Some readers are thinking, "My pharmacy is small. Can I use the area for tasks other than compounding?" The designated compounding area is a space with a marked perimeter that is required to be clean, orderly, sanitary, well-lit, and have low foot traffic, and no other activities can occur in this space simultaneously. You may perform other duties there if there is no compounding going on as long as someone cleans the area before compounding again. The newly revised standards suggest the designated compounding area be uncarpeted for easier cleaning, which in one of this CE's author's opinion should be changed to a must, since carpets tend to harbor dust and dander, and can be very difficult to clean. (Have you ever dropped and broken a bottle on the carpet in your pharmacy? It's not pretty.)

The compounding area must be used in a manner that prevents cross contamination of CNSPs from other areas of the pharmacy. For compounding to be completed in the most efficient manner possible, all equipment in the designated compounding area must be arranged in a way that prevents errors. Last, the facility's standard operating procedures (SOPs) must always include this information and be available to staff.

The current standards simply state that compounding equipment "shall be clean, properly maintained and used appropriately."[6] This statement allowed compounding personnel to decide on their own standard of clean when preparing a CNSP and their own definition of when or if they should clean. The newly revised guidelines strengthen the minimum requirements for cleaning the designated CNSP compounding area. The USP dedicates an entire section to cleaning procedures, representing a major change in the standards. The new standards indicate that personnel must clean the perimeters—walls and ceilings—when visibly soiled, after spills, and when surface contamination occurs.[6] Readers will see that visible soil, spills, and surface contamination form a frequent theme in the newly revised standards!

The new standards also establish a routine cleaning schedule. The section, "Cleaning and Sanitizing" states pharmacy personnel must clean work surfaces at the beginning and end of each shift at a minimum, between each CNSP, and again if spills or surface contamination occurs. The standards add that personnel must clean floors daily on days when compounding occurs, and again if spills or surface contamination occurs.[6.] Personnel must clean storage shelves every three months, after spills, and when surface contamination occurs. Personnel qualified to clean can be defined as any staff member who has been properly trained and observed in a facilities cleaning procedures. That means that pharmacy staff can train housekeeping staff to complete the cleaning.

Personnel need to clean and sanitize, and if two separate products are used—one to clean and one to sanitize—cleaning is done first, followed by sanitizing second. Selecting appropriate cleaning products requires careful attention. They should be (1) compatible, (2) effective, and (3) leave minimal residue. Finally, daily documentation is essential on days when compounding occurs.[6] An old adage applies here: cleaning is not truly done unless it is documented. High tech organizations commonly complete this documentation using an online platform integrated with other daily documentation requirements such as daily temperature monitoring, but a simple sign off sheet is also acceptable. A best practice is to include any cleaning and its documentation into the compounder's daily workflow, so it is not forgotten. Daily and or weekly task charts can be created to include all activities that need to be performed.

PAUSE AND PONDER: How were you originally trained to compound? Were you told to watch how it was done and then you were on your own?

Training

Another major area of change is the training of compounding personnel. The current standards state that compounders must be "proficient in compounding" and suggest that compounders should pursue knowledge by attending seminars or studying literature related to compounding. It also states that compounders must be conversant on *General Chapter <795>* and familiar with *General Chapter <797>*. With standards this vague, and no re-

quired number of CE credits on this subject, how often do you think compounding personnel previously searched for compounding topics? Also, the current standards simply require at a minimum compounding personnel to be trained and capable of the compounding duties assigned to them, and for someone to document the training. Compounding duties include verifying critical processes like weighing and mixing that occur frequently during compounding.

The newly revised standards will require a more structured training program for compounding personnel. All compounding personnel must complete this training program initially before being allowed to compound and every 12 months thereafter. The newly revised standards require compounding personnel to repeat compounding procedures "independently while under the supervision of the designated person or assigned trainer for completion of the training program."[6] The organization's designated person will be responsible for designing the training program, which must include

- the required training, meaning a detailed description of the training
- the frequency of training, and
- the process used to evaluate competency.

Table 1 lists the training program's required topics. It is interesting to note that pharmacists who do not compound but complete in-process checks, verification, or dispensing also must complete the CNSP training program before completing checks, verification, or dispensing. A training program may include an online portion of reading or videos teaching concepts with quizzes to evaluate understanding, and a physical portion to evaluate measuring, mixing, and overall compounding. The designated person or assigned trainers can train personnel, and of course, they must document the completion of the training program.[6] It is important to note this table only lists the minimum requirements, additional requirements may be necessary according to each facility's needs.

The Designated Person

The necessity to designate a person who has oversight and full responsibility for compounding practices now in *General Chapter <800>* is included in proposed *General Chapter <795>* and *<797>*. The current standards again broadly describe the requirements. The chapter states that compounding personnel are responsible for adhering to the general principles of compounding outlined in the current standards. It specifies several responsibilities, which include training, selecting ingredients for compounding, labeling, and cleaning. However, since the compounding process may include many people, the ultimate accountability is unclear.

To clarify accountability, the proposed *General Chapter <795>* requires each organization to designate one or more persons to be responsible and accountable for nonsterile compounding. The designated person's responsibilities include ensuring the organization develops written formal quality control and quality assurance procedures and reviews them annually. The designated person must monitor and observe compounding, identify areas of error, and take corrective action if needed. The designated person has several other responsibilities. These include[6]

- establishing, documenting, and monitoring SOPs within the CNSP compounding area to include component handling and storage
- ensuring that all staff members follow all SOPs
- reviewing complaints
- determining if potential issues are likely with CNSPs
- selecting components to be used in compounding

Table 1. Proposed *General Chapter <795>* Required Topics for Training[6]

Training programs must teach compounding personnel the following:

- cleaning and sanitizing
- documentation such as Master Formulation Records and Compounding Records
- hand hygiene and garbing
- handling and transporting CNSPs and their components
- measuring and mixing
- proper use of compounding equipment and devices
- understanding *General Chapter <795>*
- understanding safety data sheets
- understanding procedures to complete compounding duties

Beyond Use Dates

The final major difference is the establishment of beyond-use dates (BUD) for CNSPs. The current standards hold compounders responsible for establishing BUDs based on their observation of the drug during compounding. Compounders (not a designated person) are held responsible for noticing signs of instability and using their education and experience to assign a BUD to the final preparation.[6] The current standards also recommend assigning BUDs based on three categories: non-aqueous, water-containing oral, or water-containing topical. The new guidelines are based on the activity of water (a_w) in each product.

Table 2 (next page) compares the current and proposed BUD recommendations.[6]

Table 2. A Comparison of BUD Requirements[6,7]		
Description	**Minimum BUD requirement**	
	Current USP<795>	Proposed USP<795>
Aqueous non-preserved	14 days in refrigerator	14 days in refrigerator
Aqueous preserved	14 days in refrigerator	35 days controlled room temp or refrigerator
Aqueous topical (Cream, lotion, shampoo, nasal spray, gel, rinse, foam, etc.)	30 days	35 days if preserved 14 days if non-preserved See activity of water chart
Nonaqueous oral (Oil or powder filled capsule, glycol or oil based oral solution, compressed tablet, powder for inhalation, troche, lollipop, etc.)	6 months	90 days
Nonaqueous (Medicated stick, ointment, suppository, etc.)	6 months	180 days (6 months)

Proposed General Chapter <795> determines BUDs based on a preparation's water activity (a_w, see **SIDEBAR**), which is more clearly defined as aqueous and non-aqueous by the following distinction:

- CNSPs with an a_w ≥0.6, considered aqueous dosage forms
- CNSPs with an a_w <0.6, considered non-aqueous dosage forms

The newly revised standards recommend adding antimicrobial agents to any CNSP with an a_w at or exceeding 0.6 when assigning a BUD of 35 days. Even components as simple as ascorbic acid can help extend the BUD. As always, careful research must be done to determine suitable preservatives for each product and if an extended BUD date is assigned, the preparation must be tested for antimicrobial effectiveness. Consider one formula for magic mouthwash, which might have an a_w of 0.73 and contains no preservatives. With no USP monograph, one would refer to **Table 3** (next page) to determine that the BUD should be limited to 14 days when stored in the refrigerator. We are sure that pharmacists compounding blue mass syrup could have cared less about the activity of water in their concoctions. We wonder if they would have viewed mercury as a preservative.

Compounders can assign non-aqueous dosage forms with an a_w less than 0.6 a maximum BUD of 90 days for an oral liquid and 180 days for alternative routes.

While the newly revised standards provide strong guidance on determining a CNSP's BUD, compounders should only use its tables if no other stability information is available. The designated person is responsible for searching for stability information for each CNSP and determining if a CNSP can have a BUD beyond that specified in **Table 2** (previous page). If the designated person finds an extended BUD appropriate, compounding staff must test it for antimicrobial effectiveness. However, if compounding staff is following a United States Pharmacopeia- National Formulary (USP-NF) monograph for CNSP preparations, the BUD must not exceed that which is indicated in the monograph. Last, the

SIDEBAR: ACTIVITY OF WATER[7-10]

The water in a preparation can "participate in chemical, biochemical, or physicochemical reactions." However, it is not the water content (such as % water in the CNSP), but rather the activity of water that determines the water's availability to participate in degradation reactions and allow microbial growth. Therefore, compounders must determine a BUD by considering the preparation's water *activity* and not the preparation's water *content*.

Water activity is roughly equivalent to relative humidity, except that relative humidity is expressed in terms of percent and water activity is expressed as a fraction. So, a water activity of 0.6 is roughly equivalent to 60% relative humidity. If the dosage form with a water activity of 0.6 were to be sealed in a package, any surrounding space would eventually have a relative humidity of 60%. Compounders can measure water activity for a specific preparation by the procedures outlined in *General Chapter <922> Water Activity*. However, the proposed *General Chapter <795>* provides an easy classification system (see **Table 3**).

The a_w cut-off of 0.6 established in USP comes from various studies showing no microbial growth of any kind in foods below this value. Although the water activity determination was constructed using food, it is also the basis of *USP<1112> Water Activity Determination* and is the foundation for the BUD rationale in the proposed <795>. A product with an a_w greater than or equal to 0.6 has been shown to have increased bacterial, fungal, and other microbial growth. However, in products with an a_w below the threshold of 0.6, no microbial growth was found.

Table 3. Proposed *General Chapter <795>* classification of commonly compounded dosage forms as non-aqueous or aqueous partial list.	
Nonaqueous Dosage Forms a_w <0.6	**Aqueous Dosage Forms a_w ≥0.6**
• Animal treat, oil based • Capsule: oil filled or powder filled • Oral solution: glycol based or oil based. • Glycol based gel • Stick or lip balm • Tablet compressed or triturate • Sorbitol based lollipop • Ointment: hydrophilic petrolatum polyethylene and mineral oil based • Oral suspension: fixed oil • Powder for inhalation • Suppository: polyethylene glycol base or fatty acid base • Troche or lozenge: gelatin based or glycol based	• Animal treat • Foam • Shampoo • Cream: oil in water emulsion, emollient cream, petrolatum, and mineral oil gel: alcohol free aqueous or hydroxypropyl methylcellulose gel • Lotion • Nasal spray • Rinse • Oral solution: water based, low sucrose syrup vehicle • Oral suspension

CNSP's components should drive the overall expiration date, which is not a change from the current standards.

CONCLUSION

Compounders face many of the same challenges today as they did in the 1800s. They were faced with a limited drug list, similar to a closed formulary in today's world. They searched for alternative therapies, and they did, as we still do, face many drug shortages. The main difference is that we have advanced knowledge to make better products to keep patients safer.

The time has come to designate your area, designate your person, and train your staff, including pharmacists who may not actually be compounding! Keep the designated area clear for compounding use only, if possible, and remove any unnecessary items before entering. Set up a cleaning routine for the entire space, including floors, walls, and shelving, and incorporate the routine into the daily workflow so it is never forgotten. Train your staff well to the new standards and reevaluate every 12 months. Look into the literature to determine the best BUD for each CNSP and when information is not available, use USP guidance for assigning a BUD date. Choose a designated person wisely, as they need to be responsible and organized with taking responsibility and accountability for all nonsterile compounding occurring in the facility.

Remember, improvements in nonsterile compounding standards will make for higher quality and safer compounded nonsterile products for our patients and are enforceable come November 1, 2023.

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