USP <797>

Immediate-Use CSPs

Small Changes, Big Impact

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The revised USP <797>, which will be official on November 1, 2023, clarifies the provisions for immediate-use compounding, including changes in the number of components used, the beyond-use date (BUD), and expectations for training and competency. Prior to updating organizational policies or standard operating procedures (SOPs) for immediate-use compounding, compounders need a holistic understanding of these changes and their implications to practice, especially for departments beyond pharmacy (see **FIGURE 1**).

Rationale

Given the changes to the immediate-use CSP requirements, it is prudent to review available literature and analyze the evidence surrounding these changes; this information can then be incorporated into the training components.

Microbiology Based BUD

Currently, the USP <797> immediate-use CSP provision allows for administration to begin within 1 hour following the start of the preparation.[1] In the revised chapter, this BUD was expanded to a maximum of 4 hours to help balance the need for ensuring CSP quality and timely medication access in a variety of healthcare settings.[2] The USP compounding expert committee has noted that this revision to the maximum allowable BUD for immediate-use CSPs was based on the observed lag phase of microbial growth.[3] Allen et al illustrate a "batch culture" growth experiment where a small number of bacteria are inoculated into a well-shaken container filled with a liquid nutrient medium.[4] During the measurement time period, the density of bacteria is measured, and the results are plotted as a function of time. Bacterial growth is characterized by an initial period in which no growth is detected, known as the lag phase. This is followed by a period of exponential growth, known as

the exponential phase, which is followed by a slowing down and eventual cessation of net growth, known as the stationary phase. In general, it is believed that the lag phase occurs because the bacteria need time to adjust to the liquid medium after having been stored under different conditions. Similarly, it is thought that the stationary phase occurs when the population exhausts its nutrient supply or builds up waste products.[4]

Based on recent microbiological studies evaluating the growth kinetics of bacteria in food, there is evidence supporting a 4 to 6 hour lag phase of microbial growth. In the lag phase, potential bacterial cells are adjusting to their environment, undergoing very little change, and they do not immediately begin to reproduce. Therefore, during compounding, if bacterial cells are inadvertently introduced into a CSP, immediate replication is unlikely and there is a window of time in which a CSP can be safely held prior to administration.[5-8]

Aseptic Technique

According to the Centers for Disease Control and Prevention (CDC), aseptic technique refers to the manner of handling, preparing, and storing medications and injection equipment or supplies to prevent microbial contamination and infection.[9] Utilizing proper aseptic technique minimizes direct contact contamination of critical sites. A critical site is a location that includes any component or fluid pathway surfaces (eg, vial septa, injection ports, and beakers) or openings (eg, opened ampules, needle hubs) that are exposed and at risk of direct contact with air (eg, ambient room, HEPA filtered), moisture (eg, oral and mucosal secretions), or touch contamination.[2]

Currently, USP <797> requires that aseptic technique is followed; however, the new revision specifies that "aseptic techniques, processes, and procedures are followed, and written SOPs are in place to minimize potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products."[2] When proper aseptic technique is utilized by compounding personnel, there should be limited and controlled amounts of bacteria present in a sterile compounding environment. In contrast, immediate-use CSPs do not need to be compounded in an ISO Class 5 environment and garbing and gowning are not required.[10] Thus, there is an inherently higher risk for potential contamination due to the environmental conditions present. While aseptic technique must be used in immediate-use compounding to prevent microbial contamination, it is also prudent to address the concern for potential non-microbial contamination, which can also cause patient harm if present.

Non-Microbial Contamination

According to ISMP, practitioners may not be aware that the manufacturer's pop-off vial caps are considered dust covers and are not intended to maintain sterility of the vial diaphragm or access point. Aseptic technique should include the disinfection of the medication access diaphragm on a vial or the neck of an ampule prior to accessing the medication or solution.[10] According to the Association for Professional in Infection Control and Epidemiology (APIC) Safe Injection, Infusion, and Medical Vial Practices in Health Care, practitioners should disinfect vials by cleansing the access diaphragm using friction and a sterile 70% isopropyl alcohol (IPA), ethyl alcohol, iodophor, or other approved antiseptic swab.[11] Each facility should follow organizational standards for which disinfectant to use. When using an antiseptic swab to disinfect a vial or ampule, it is critical to wipe in a single direction to physically remove particle contamination from the access diaphragm or ampule neck.[10] After applying the antiseptic, it is also important to wait at least 10 seconds to allow the site to dry before inserting any device into the vial or ampule or accessing the medication.[11] In addition to promoting proper disinfection, adequate drying time also helps to prevent inadvertent introduction of the antiseptic into the compound.

Vial Coring

Coring occurs when a small piece of a vial's rubber stopper breaks off and contaminates the contents of a sterile vial.[12] The cored piece can be observed floating on the top of or inside the medication or stuck to the inside wall of the vial. Due to its small size, the cored piece may go unnoticed if compounding personnel are not on the lookout for this or if visualization is blocked by a label, a matching background, or a colored vial. If unnoticed, this small foreign body can then be aspirated and injected into a patient. There is evidence to demonstrate that when drawing up medication through a rubber vial top, coring or aspiration of unintended particles is a concern.[12,13] Given these potential safety hazards, consider the following recommendations:

- The needle should be inserted at a 45° to 60° angle with the bevel facing up and away from the stopper. This method of angled puncture has been shown to reduce the possibility of coring by approximately 50%.
- To prevent vacuum formation, a small amount of positive pressure can be applied to the syringe plunger at the point of entry into the stopper. For example, when reconstituting a powdered drug, withdraw a volume of air equal to the amount of diluent to be added. This will prevent positive pressure from developing inside the vial.
- If a rubber stopper is penetrated more than once in a multi-dose vial, the prior puncture site should be avoided.
- Rather than blunt needles, the use of sharp needles is preferred, as their use is associated with a lower incidence of coring.
- Smaller gauge needles may reduce the risk of coring, but this may make the cored piece more difficult to see should coring occur.
- The medication-filled syringe and the vial from which the medication was drawn should be closely inspected for any signs of coring, small flecks, or pieces of the rubber stopper.

Practitioners may not be aware that the manufacturer's pop-off vial caps are considered dust covers and are not intended to maintain sterility.

Glass Ampules

When manipulating drugs from glass ampules, there is potential for glass particle contamination of the contents that can occur upon opening.[14] These glass particles can inadvertently be aspirated into the syringe and injected into a patient, thereby causing potential harm. To prevent this from occurring, consider the following recommendations:

- Prior to breaking the ampule open, the neck of the ampule should be disinfected with 70% IPA and allowed to dry. Using an alcohol swab or gauze to open the ampule can help to reduce the aspiration of glass particles from the ampule into the syringe.

FIGURE 1

Immediate-Use Gap Analysis

At a quick glance, these changes may appear minor, but a full understanding of what is less restrictive, what is more restrictive, and what remains the same, will clarify the significant impact these changes may have throughout various practice settings.

	CURRENT (2008)	REVISED (2023)
< LESS Strict Changes		
Scope	Intended only for emergency situations or immediate patient administration	The emergency situation requirement has been removed
Compounding Complexity	Only low-risk level CSPs (no medium-risk or high-risk level); simple transfers only	The type or complexity of compounding is not specifically addressed
Batch Compounding	Not intended for storage for anticipated needs or batch compounding	Batching allowed for multiple doses and/or multiple patients if all conditions are met
# of Components	≤ 3 sterile packages	≤3 different sterile products
# of Manipulations	≤ 2 entries into any container/package	Entries into container not defined or addressed
Compounding Process	Compounding is a continuous process not to exceed 1 hour	Not addressed directly
Maximum BUD	1 hour	4 hours
Risk Level	Medium-risk and high-risk level CSPs shall not be prepared as immediate-use CSPs	Requirements for Category 1, Category 2, and Category 3 do not apply to immediate-use if all conditions are met
> MORE Strict Changes		
Hazardous Drugs	Antineoplastic shall not be prepared as immediate-use. Only nonhazardous products shall be used	Must comply with USP <800> requirements
Aseptic Technique	Aseptic technique is followed	Aseptic techniques, processes, and procedures are followed, and written SOPs are in place
Personnel Training	Not addressed	Personnel must be trained and demonstrate competency according to facility SOPs
SOPs	Not addressed	Facility SOPs required: (1) methods to minimize CSP contamination and mix-up errors, (2) personnel training, competency, and assigned tasks for those who prepare immediate-use CSPs
CSP Evidence	Not addressed	Preparation is performed in accordance with evidence-based information for physical/chemical compatibility of the drugs (eg, approved labeling, stability/compatibility studies)
Single-Dose Containers	Not addressed	Any unused starting component from a single-dose container must be discarded; single-dose containers must not be used for more than one patient
Compounding Documentation	Not addressed	A compounding record (CR) is required when preparing immediate-use CSPs for more than one patient
= NO Changes		
Labeling	Unless directly administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the BUD time period within which administration must begin	
Component Use	Only sterile starting ingredients and packages	
Unused CSP	If administration has not begun by the listed BUD, the CSP must be promptly, appropriately, and safely discarded	

- To minimize glass particle contamination, 5-micron filter straws or filter needles should be used when withdrawing contents of ampules. One should refer to the drug labeling for manufacturer's recommendations concerning filtration.
- After withdrawing the contents of the ampule, the filter needle or filter straw should be removed and discarded after use and replaced with the needle one would use to inject into the final solution. Filter needles and filter straws should only be used in one direction to prevent potential reintroduction of glass particles that were originally filtered.
- Ampules should not be reused or saved at any time during the compounding process.

Flush Syringe Use

The US Food and Drug Administration (FDA) regulates commercially available prefilled syringes of saline and heparin as medical devices, not as medications.[10] These devices have been approved for the flushing of vascular devices; however, they have not been approved for the reconstitution, dilution, and/or subsequent administration of IV push medications. Following such practices would be considered off label and not how manufacturers intended for these products to be used, as prefilled flush syringes have not been tested for product safety when used in this manner. When prefilled syringes are used in an off-label manner, the practitioner and employer bear legal liability for any adverse events that may result from this practice.

According to the Institute for Safe Medication Practices (ISMP), one should not dilute or reconstitute IV push medications by drawing up the contents in a commercially available, prefilled flush syringe of 0.9% sodium chloride.[10] However, when reviewing current practices with IV injectable medications, it was noted that 54% of ISMP survey respondents reported that they use a commercially available prefilled "flush" syringe to dilute medications. This practice frequently results in a mislabeled syringe, as the labeled flush (0.9% sodium chloride) also contained the diluted medication. When this mislabeling occurs and medications are added to a prefilled syringe without the application of a secondary label, this creates a significant risk for errors. In most cases, the manufacturer's label is permanently affixed to the syringe barrel and contains important information regarding the product, including product codes, bar code, and specific information about the fluid and its volume. Additionally, when another medication is added to this prefilled syringe, there is no appropriate method for amending the manufacturer's label without covering the current information. As a result, the prefilled syringe frequently remains labeled as 0.9% sodium chloride, when it also contained the diluted or reconstitution medication. Given the significant risk for errors, ISMP recommends that this off-label, unsafe practice be eliminated to prevent potential harm.[10]

Practice Implications

After reviewing the standards and understanding the rationale behind the revisions and safe medication practices,

FIGURE 2

Sample Batch Production of Immediate-Use CSP for Multiple Patients

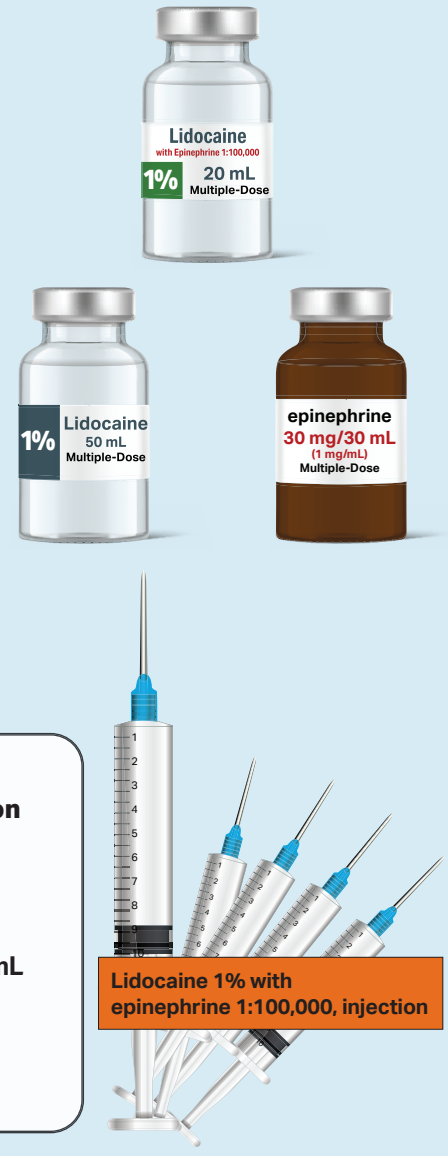
Situation
There is a shortage of conventionally manufactured "Lidocaine 1% with epinephrine 1:100,000 injection, 20 mL multiple-dose vials" that are routinely used for infiltration and nerve block.

Available Ingredients
Pharmacy stocks multiple-dose vials of Lidocaine 1% (50 mL) and multiple-dose vials of Epinephrine 1 mg/mL (30 mL).

Immediate-Use Compounding
Clinics use available ingredients to compound 5 x 10 mL syringes for use in multiple patients over a 4-hour period and label appropriately.

Documentation
Since the prepared doses are intended for multiple patients, the clinic documents a compounding record.

COMPOUNDING RECORD
Lidocaine 1% with epinephrine 1:100,000, injection
(for infiltration or nerve block only)
Prep on: 12/24/2022 @ 9:30AM
BUD: 12/24/2022 @ 1:30PM
Lot #: 12242022KH
+Lidocaine 1% inj – Pfizer – ABC123-Mar/2025 – **49.5 mL**
+Epinephrine 1 mg/mL inj – PAR Pharma – ABC456 – Feb/2024 - **0.5 mL**
Total prepared: **5x10 mL syringes**
QC: Clear solution free of particles



assess what aspects of the compounding program need revision, as well as which staff will need to be included in these new requirements.

Policies and Procedures

USP <797> requires written SOPs to ensure aseptic processes are followed and to minimize contamination in areas that may be different than typical pharmacy compounding environments. SOPs should include the scope of immediate-use compounding, training requirements related to compounding settings and techniques, appropriate selection of components, and BUD and labeling requirements (see **FIGURE 1**). Consider developing an SOP specific to immediate-use compounding to clearly define requirements and communicate with other stakeholders, as the information may prove overwhelming if it is simply included in broader compounding policies.

Compounding Records

A new provision in the revised USP <797> allows for preparation of multiple immediate-use doses for more than one patient if all conditions are met, including creation of a compounding record (CR). While the pharmacy may rely on the EHR or other software tools to document CRs, these may not be easily accessible to non-pharmacy compounders. In this case, standard CR forms may need to be developed to ensure consistent compliance with this expectation. Review all the requirements of a CR and include this important documentation in policy, training and quality assurance requirements (see **FIGURE 2** for an example of an immediate-use batch prepared for multiple patients).

Training and Competency

The chapter describes a new requirement for training and competency for those performing immediate-use compounding. Per USP <797>, "Personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs." This includes both didactic education and demonstration of know-ledge through simulated performance of the skill. Even if many of these training elements are foundational to safe medication handling practices, a review of the why behind these principles (as described above) is always beneficial. Demonstration of competency may be more difficult to implement. USP <797> does not establish a frequency for training and competency so be sure to define this in your SOP; annual is a best practice.

Training should include many of the same core competencies defined in USP <797> such as hand hygiene and garbing, cleaning and disinfection, measuring and mixing, aseptic technique and labeling, as well as BUD and compounding procedures. While microbial contamination is certainly a focus for training/competency, nonmicrobial contamination such as vial coring could also be incorporated into the competency evaluation process via proper needle technique. Competency assessment involves demonstration of skill and documentation of competency. There is no indication that media fill or gloved fingertip testing is required for immediate-use compounders and it may result in limited utility or benefit. However, a simulated aseptic manipulation with visual observation that mimics a typical immediate-use preparation utilizing empty vials, syringes, saline or water, would adequately assess the skill of the compounder, without the need for incubation steps. Leverage the assigned trainer role in USP <797> as the Designated Person may delegate observation responsibilities. Consider utilizing residents, technicians, or light-duty nurses (see **FIGURE 3** for a sample competency form).

Areas and Personnel Impacted

Start by identifying where medications are prepared throughout your organization (eg, acute care, ambulatory clinics, and procedural areas) and who handles them. This may involve some scavenger hunts throughout the organization or additional observation during routine unit inspections. For clinics and procedural areas, review purchasing history to flag medications that may require manipulation. For acute care areas, review par levels for pharmacy

FIGURE 3

Immediate-Use Compounding: Competency Assessment

Competency	Yes	No
Hand Hygiene		
1. Removes all jewelry on hands and wrists (eg, rings, watches) to prevent contamination.		
2. Performs hand washing with warm soap and water for at least 30 seconds to mechanically remove inordinate particulate matter.		
3. Dries excess water off hands with a clean, dry paper towel.		
4. Applies alcohol-based hand sanitizer to hands and allows to air dry to kill microbial organisms.		
Note: If a sink is unavailable, at a minimum, perform hand hygiene with alcohol-based hand sanitizer.		
Garbing		
1. Dons garb for immediate-use compounding as defined in facility SOP to provide protection for personnel and minimize contamination.		
2. Disinfects gloves by applying alcohol-based hand sanitizer or disinfecting agent onto gloves and allows to dry to reduce risk of contamination from gloves.		
Dose Preparation (simulation)		
1. Disinfects compounding space by applying facility approved agent onto compounding tray to minimize potential contact with nonsterile surfaces.		
2. Selects components and arranges compounding supplies in a manner that will allow for quick and efficient use (eg, only supplies needed for compounding are present).		
3. Disinfects vials by performing unidirectional swiping motion using single-use sterile 70% isopropyl alcohol swabs to remove dust or debris.		
4. Uses air displacement to maintain vial pressure to avoid leaks or sprays.		
5. Punctures vial at 45-degree angle with bevel of needle facing upward to avoid vial coring.		
6. Avoids critical sites (eg, septum, needle) while withdrawing SWFI by holding top of vial and lower half of syringe to prevent contamination.		
7. Simulated vial reconstitution (volume transfer) performed with correct volume transfer (eg, 3 mL as requested by observer) of SWFI retrieved from vial and transferred into empty vial.		
8. Performs safe needle technique (uses safety needle mechanism appropriately) to protect from needle-stick injury.		
9. Disposes of waste appropriately by placing needle into red sharps container to prevent improper contact with needles.		
10. Disposes of any unused starting component from single dose vials in appropriate waste bin.		
11. Visually inspects final CSP to ensure it is free of particulates and meets expected appearance and quality.		
Labeling and Documentation		
1. Demonstrates proper labeling by writing names and total volumes of all active ingredients, preparer's initials, and patient identifier onto "Medication Added" label to prevent mix-up of medication.		
2. Applies correct 4 hour BUD to label by writing applicable date and time to "Medication Added" label to prevent administration of outdated, unsafe, and potentially less effective medication to patient.		
3. Completes compounding record that includes all the required elements and can verbally indicate when a compounding record is required for immediate-use compounding.		
Successfully completed evaluation? (circle one)	**YES**	**NO**
Notes		

compounded medications. If these are out of stock, staff may prepare these at the bedside without pharmacy's knowledge, which may qualify as immediate-use compounding. As practices are identified, refer to the definition of compounding to determine what areas or personnel truly require training and competency under the immediate-use provision (see the **SIDEBAR**). As a best practice, consider including additional education for all staff who prepare medications. A review of the central practices of aseptic technique applies to any medication preparation, even if it does not meet the definition of immediate-use compounding.

Product Selection

While assessing medication preparation throughout the organization, take note of the components being used. It is not uncommon to see clinical staff using prefilled saline syringes to draw up or dilute medications. Consider ready-to-administer or ready-to-use alternatives that may require less manipulation, thereby saving time and decreasing the risk for contamination.[10] Proprietary bag-and-vial systems, when docked immediately prior to administration, are not considered compounding and are outside the scope of USP <797>.[2] Implementing ready-to-administer syringes in the OR and other procedural areas as described in previous articles, may provide some efficiencies and decrease drug waste; however, the operational impact of such a conversion should not be taken lightly.[15]

Implementation

A cautious approach should be taken when implementing the revised USP <797> practices for immediate-use compounding. With the coming November 2023 deadline, there may be pressure to early adopt only the less restrictive elements of immediate-use compounding (eg, maximum 4 hour BUDs). This approach should be discouraged, as it does not account for the more restrictive requirements for immediate-use that underpin this practice (eg, training and competency evaluations). Rather, all the requirements and practice changes should be applied simultaneously, or at least start with the most restrictive changes.

The training and competency plan is an area where pharmacy, nursing and clinical educators can collaborate. Given their expertise in aseptic technique, pharmacy can advise other disciplines on best practices for medication preparation and help assess immediate-use preparation areas. Nursing and other clinicians can provide perspectives based on

SIDEBAR

What is Compounding?

USP <797> defines sterile compounding as "*combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation…*" and refers to all persons who prepare CSPs in all practice settings.[1] Immediate-use CSPs are intended for direct and immediate administration, and when certain conditions are met, they are not subject to the requirements for Category 1, 2, or 3 CSPs. USP <797> also describes other practices that would not be considered compounding if performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. Further, if a sterile product or preparation is applied to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form, this is considered "administration" and not within the scope of USP <797>.

workflow and existing practice standards. Clinical educators can review existing training and recommend areas that may need to be enhanced to meet the standards. Together the team can determine who needs to be trained, how competency will be assessed and documented, and who owns the responsibility for demonstrating compliance.

While immediate-use compounding may typically be conducted by nonpharmacy personnel (eg, nursing, anesthesia), it is prudent to review immediate-use compounding conducted by pharmacy personnel, particularly in the emergency department. Some products may be considered "preparation per approved labeling," yet the facility's SOPs may call for immediate-use compounding training, particularly if the package insert requires use of aseptic technique. This is a common situation with tissue plasminogen activator (tPA) used for ischemic stroke.

Conclusion

Meeting the new USP requirements for immediate-use CSPs may necessitate significant practice changes. A firm understanding of the rationale behind these updates is key to successful implementation, which may require updates to policies and procedures, workflows, and product selection. Lean into these changes to implement practices that improve the care and safety of patients. ■

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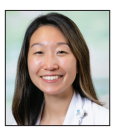

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