You Asked for It! CE

©Can Stock Photo/Zametalov

The Upcoming USP<797> Changes: Impact on Immediate Use Medications

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

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

- Point out an immediate use medication
- Recognize locations where immediate use medications may be compounded
- Investigate the designated person's responsibilities
- Identify core competencies required for immediate use compounding

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.15 CEU (1.5 contact hours) for completing the activity, passing the post-test with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

ACPE UAN: 0009-0000-23-031-H07-P
0009-0000-23-031-H07-T

Grant funding: None
Cost: Pharmacists $5
Technicians: $2

INITIAL RELEASE DATE: September 1, 2023
EXPIRATION DATE: September 1, 2026

To obtain CPE credit, visit the UConn Online CE Center https://pharmacyce.uconn.edu/login.php. Use your NABP E-profile ID and the **session code**

23YC31-ABC28 for pharmacists or
23YC31-BCA82 for pharmacy technicians
to access the online quiz and evaluation. First-time users must pre-register in the Online CE Center. Test results will be displayed immediately and your participation will be recorded with CPE Monitor within 72 hours of completing the requirements.

For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

TO RECEIVE CREDIT FOR THIS CE,
go to
https://pharmacyce.uconn.edu/login.php

TARGET AUDIENCE: Pharmacists and pharmacy technicians seeking to stay abreast of the change since compounding guideline updates.

ABSTRACT: The United States Pharmacopeia (USP) recently published updated guidelines on sterile compounding that become effective on November 1, 2023. These guidelines affect not only sterile medications compounded in pharmacy clean rooms, but also injectable medications that may be compounded in healthcare institutions, medical and surgical treatment sites, infusion facilities, pharmacies, and physician and veterinarian practice sites. This affects personnel such as chiropractors, dentists, naturopaths, nurses, pharmacists, pharmacy technicians, physicians, veterinarians, and any other medical professional who compounds sterile products. The USP made these changes to minimize harm, including death, to human and animal patients. By reviewing these updates, and by making changes, medical professionals will be able to comply with state and federal regulations and prevent harm to their patients.

FACULTY: Laura Nolan, CSPHT, CSPT, Lab Coordinator, at the University of Connecticut School of Pharmacy in Storrs, CT.

FACULTY DISCLOSURE: Ms. Nolan has no financial relationships with an ineligible company.

DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

In 1905, a person in excruciating pain in a dentist's office would have been thrilled to receive an injection of procaine (Novocain) delivered in a reusable glass hypodermic syringe. Besides the dentist's white coat, it's likely nothing else used in the procedure was clean or remotely sterile. Today, given what we know about sterile products, an educated patient would have turned and run in the opposite direction.

PAUSE and PONDER: What kinds of facilities do you think state officials visit and why?

Yet, according to the U.S. Food and Drug Administration (FDA), the number of trendy med spas and intravenous (IV) hydration clinics, some mobile, that treat patients with medications such as injectable vitamin infusions, have exploded. Many operate under the FDA's radar. The FDA may not be aware of which compounders are making such drugs, and some states may have insufficient resources to adequately oversee them. The FDA has recently documented varying offenses from personnel wearing street clothing and not wearing gloves while preparing injections to using toaster ovens for sterilization.[2]

Human drug compounding is a practice in which ingredients are combined, mixed, or altered to create a medication tailored to an individual patient's medical needs. The Federal Food, Drug and Cosmetic Act (FD&C Act) governs human compounding. Section 503A describes the conditions under which compounded human drug products are exempt from its regulations[2]:

- Section 505 concerning approval prior to marketing
- Section 501(a)(2)(B) concerning current good manufacturing practice (CGMP) requirements
- Section 502(f)(1) concerning labeling with adequate directions for use

The FDA act exempts one condition—compounds are exempt when a licensed pharmacist or physician prepares the medication in a licensed facility based on a valid patient specific prescription. An explosion of naturopathic clinics, which often use unapproved nutritional, herbal, and homeopathic products and administer them by injection, have become a growing concern for the FDA. A brief Internet search revealed that nurses run many clinics with a physician consulting offsite. The FDA has become increasingly aware of drug products compounded at medical offices and clinics that may be prepared under unsanitary conditions. The FDA has also become aware of business models, such as IV hydration clinics, medical spas, and mobile IV infusion services, that are compounding drugs that may not meet the conditions of the FD&C Act's section 503A or comply with state regulations.[2]

Unsanitary conditions are more common than one would think. The FDA cites a recent example (February 2021) wherein a 50-year-old patient was hospitalized and treated for suspected septic shock with multi-organ failure after receiving an IV vitamin infusion in her home.[2] The patient's blood cultures grew *Pseudomonas fluorescens,* which is a gram-negative bacterium of emerging concern.[3] A California medical clinic that specialized in services including IV therapies and vitamin injectables, sexual health products, hormone replacement therapy, weight loss/management products, and diagnostic laboratory assays prepared and dispensed the contaminated bag.[2]

When state and federal agents inspected the facility, they observed several deficiencies[2]:

- Lack of an International Organization for Standardization (ISO) air quality classification of ISO-5; in other words, a clean room which is certified to contain a particle count of less than 3,520 particles per cubic meter in the air, required for sterile compounding.
- Contamination in compounding areas including peeling paint, stained work surfaces, visibly dirty equipment, and air vents with dust and grime.
- Difficult-to-clean equipment and surfaces (e.g., carpeting in the IV storage and mixing room).
- Standing water in a refrigerated storage area used to store sterile vials.
- Use of expired active pharmaceutical ingredients to prepare drug products intended to be sterile.

The full extent of this nationwide problem is unknown since many practitioners operating in medical offices or clinics do not register with the FDA. The FDA encourages all patients who experience adverse effects to report them to the FDA MedWatch Adverse Event Reporting program (www.fda.gov/medwatch/report.htm).[2]

Defining Immediate Use Medication

According to the proposed *USP <797> Pharmaceutical Compounding-Sterile Preparations*, sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation. Compounding personnel must follow aseptic techniques, processes, and procedures for preparing any sterile medication.[1]

© Can Stock Photo/AntonPrado

Within a hospital setting, urgent situations may arise where compounding cannot occur in a USP<797> compliant area. Often, acute care situations require STAT (meaning with no delay; at once) doses for critical patients, or medication for an unanticipated procedure.[4] Compounders do not necessarily need to comply with all requirements detailed in USP<797> to make these *immediate use medications*. These frequently asked questions can help clarify when an immediate use medication may be needed and who can compound it.[1,4]

- *Can nurses mix compounded sterile preparations (CSPs) for immediate use?* Yes. Any qualified health professional can prepare an immediate use preparation as long as (1) it is within their scope of practice, (2) the facility's policies allow it, and (3) the designated person (defined and discussed below) has documented the health care professional's competency.
- *Is docking a vial onto a proprietary bag system considered an immediate use medication?* Yes and no. Docking a vial onto a proprietary bag for future activation and use is considered compounding and must be performed in an ISO class 5 environment. However, docking a vial onto a proprietary bag according to manufacturer's instructions for immediate administration to a single patient is considered an immediate use medication and is not considered compounding.
- *Can a nurse prepare an immunoglobulin (IGG) solution in a home care setting, by reconstituting the powder vial with the sterile water supplied by the manufacturer in a kit?* Yes. This is an example of preparation that is compliant with FDA-approved labeling. Preparing a sterile product in accordance with the manufacturer's approved labeling is not considered compounding as long as
    - the product is prepared as a single dose for a single patient
    - the approved labeling includes the following information: the diluent, the final strength, the container closure system, and storage time
- *If a nurse reconstitutes an antibiotic vial and adds it to a piggyback bag, is this considered immediate use?* If the pharmacy is open, this should be done in a sterile clean room. If it is a STAT dose or the pharmacy is closed, then this could be considered immediate use. The nurse mixing the medication needs to have documented competency and the compound should not involve more than three products. One vial of drug, one vial of diluent, and one piggyback bag are three products, which is allowed.

In 2020, the American Society of Health Systems Pharmacists conducted a study among professionals who compounded outside of the pharmacy setting. Of the 444 respondents, 77% were nurses, and the rest were primarily anesthesia providers and decentralized pharmacists. Eighty-one percent performed compounding in a acute care settings; other locations included ambulatory surgery centers, infusion centers, physicians' practices, and long-term care.[5]

The most frequently prepared items were[5]

- IV pushes drawn directly from vials into syringes. (i.e., antibiotics, antiemetics, opioids, proton pump inhibitors)
- Intermittent infusions, all of which were proprietary vial and bag systems.
- Intramuscular injections including vaccines, antipsychotics, and antibiotics

Personnel and Settings Affected by USP<797>

All personnel who prepare CSPs are required to comply with USP<797> guidelines. This includes but is not limited to chiropractors, dentists, naturopaths, nurses, pharmacists, technicians, physicians, and veterinarians.[1]

All sites including but not limited to hospitals, infusion facilities, medical and surgical patient treatment sites, pharmacies, physician or veterinarian sites, and other healthcare institutions must meet at least the minimum requirements in USP<797>.[1]
The compounding facility must designate one or more individuals to be responsible and accountable for the facility's performance, operation, and personnel in the preparation of CSPs and for performing other functions described in USP<797>.[1] The facility's standard operating procedures (SOPs) must identify the person deemed "the designated person." All designated persons now have immense jobs; failure to meet the USP's expectations comes with considerable consequences.

The Designated Person

The USP mentions the designated person more than 50 times in section <797> alone and several other chapters also refer to the designated person. Below is a list of some, but not all tasks required of a designated person, which will become effective on November 1, 2023. Many states, such as Connecticut and Texas, have already embraced the designated person. The designated person or persons must be identified in the facilities SOPs and registered with the state. In Texas and Connecticut, pharmacists must also complete 30 hours of sterile compounding training to become a designated person. Duties include[1]

- Overseeing a training program to ensure competency of personnel involved in compounding, handling, and preparing CNSPs
- Selecting components
- Monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Ensuring that SOPs are fully implemented. The designated person(s) must ensure that follow-up is carried out if problems, deviations, or errors are identified
- Establishing, monitoring, and documenting procedures for the handling and storage of CNSPs and/or components of CNSPs.

The **SIDEBAR** (next page) discusses an issue of emerging importance.

SIDEBAR: Who Inspects Physicians' Offices? [6]

In 2016, the Pew Charitable Trust conducted a study and asked boards of pharmacy in all 50 states and the District of Columbia to respond to several compounding questions. Of the 51 states, 43 responded to the questionnaire. Although the survey consisted of pages of questions, three of them were forward thinking.

1. Does your state have a mechanism to track which in-state physicians' offices or clinics perform sterile compounding? The answer: 2 % yes, 74% no, 24% don't know.
2. Does the state require physicians' offices or clinics to be held to the same quality standards as pharmacies? The answer: 17% yes, 38% no, 45% don't know.
3. How do states provide oversight of physician's offices or clinics that perform sterile compounding to ensure compliance with applicable standards? The answer: 7 by the state board of medicine, 1 by the board of pharmacy (way to go, IDAHO!), 24 reported no oversight system to ensure compliance and 11 states chose not to respond to this question.

Who knew Idaho would be so revolutionary? Keep in mind that this study took place in 2016, four years after the New England Compounding mishap of 2012. The Pew study reported, "The Drug Quality and Security Act of 2013, among other reforms, added a new category of compounders called outsourcing facilities that can compound supplies of drugs without obtaining prescriptions."

The new category—outsourcing facilities—was intended to reduce the number of medications made in offices. However, it is obvious that state policies are not uniform. Some states are still working to advance change, and others have yet to act. The Pew report concluded that we are still in a state of transition and that "The variations in sterile compounding policy across states suggest that an opportunity exists to review state oversight systems for potential weaknesses, and consequently to advance regulatory practices to better protect patients."

PAUSE and PONDER: In what areas of your facility could people possibly be compounding without your designated person's knowledge?

Gap Analysis

In some states, as in the state of Connecticut, the designated person must be a pharmacist. That means that the designated person or persons are responsible for the oversight of all compounding within an institution including the operating room, emergency room, clinics, and nursing station medication rooms.

A gap analysis compares the current situation with a future state. Creating a gap analysis could help identify areas where compounding is done without the designated person's knowledge. A gap analysis is performed in three steps[7]:

1. Identify objectives and goals. Most designated persons will create a sheet with three columns: current state, future state, and actions. They will need to identify who, what, where and when immediate use compounding occurs. Using a team approach and including nurses and physicians is a good place to start.
2. Analyze the current state. Gather data. One critical area to examine is medications in short supply or backordered. (Aren't there always a few of these lately!?!) Checking purchasing records and delivery slips to see where medications are being used can be eye-opening. Facilities that substitute vials because the premixed bag is backordered will find that this is a target area.
3. Determine how to bridge the gap. Collaborating with the team to create policies and procedures for compounding and writing them into standard operating procedures is critical. Facilities should create a designated compounding area in each unit and establish a cleaning routine. They should also create a training document for nurses and other professionals who compound and set date that each person should complete training as a goal.

Table 1. Less Strict Changes to USP<797> [1,8,9]

Subject	Current	Proposed
Compounding process and number of components	Only low risk level NMT 3 sterile packages	NMT 3 sterile products
Situation	Emergency use or immediate administration	No emergency stipulation
Number of manipulations	NMT 2 entries into any container/bag	Not defined
Maximum BUD	1 hour	4 hours
Aseptic technique	Aseptic technique is followed	Aseptic technique, processes, and procedures followed per written SOPs
Risk level	Medium and high risk not prepared as immediate use	Category 1, 2, and 3 requirements do not apply
Hazardous drugs	Only non-hazardous drugs may be used	Must follow USP<800>

ABBREVIATIONS: BUD = beyond use date; NMT = Not More Than

Immediate Use Gap Analysis

All facilities that compound need to compare the current (2008) *USP<797> Pharmaceutical Compounding-Sterile Preparations* guidelines with the proposed (2022) USP<797> guidelines. In short, the proposed changes are few in number but may cause significant impact throughout the facility.[8] **Table 1** (previous page) compares a few minor changes.

A quick glance at the table shows that compounders can now assign a beyond use date (BUD) of four hours for immediate use products. Hurray! This prompts the question, "Is that all I need to implement, and can I do it right now?" Not so fast! These are changes to existing subjects within <797> guidelines, but the proposed guidelines also include many new stipulations, so let's dig deeper. The following requirements have now been added which pertain to immediate use medications[1,8]:

- Written SOPs must be in place and compounding personnel must follow aseptic technique, processes, and procedures.
- Personnel must be trained and demonstrate competency according to the facility SOPs.
- SOPs must include methods to minimize contamination and decrease mix-up errors.
- The product must be compounded in accordance with evidence-based information for physical and chemical compatibility, per labeling or stability studies.
- Any unused starting component from a single use container must be discarded.
- Single dose containers must not be used for more than one patient.
- A compounding record is required when preparing immediate use medications for more than one patient.

Training and Evaluation

Training is the elephant in the room. Many nurses and other health professionals have mixed or prepared single use medications for ages, so it might be difficult to teach an old dog new tricks. Demonstration of competency can be difficult and perhaps this is where the nursing team can shine. Luckily, immediate use compounders need not perform fingertip and thumb sampling, or media fill tests as is required for sterile clean room staff.

All personnel who compound must now be initially trained and qualified by demonstrating their knowledge and competency of sterile compounding before they can perform their job independently. The designated person(s) is responsible for creating and implementing a training program but may assign training to other qualified personnel. The training procedure for immediate use CSPs must be written into the facilities SOPs.[1] One interesting note, the proposed USP<797> states that personnel who are compounding in a clean room, or who have direct oversight of those personnel, must complete training initially, and at least every 12 months. However, immediate use compounders only need to complete training as required by the facilities SOPs.[1] A best practice would be to evaluate yearly.

Normal Saline Flush Prefilled Syringes[7,10]

The Institute for Safe Medical Practices (ISMP) released the results of a 2018 immediate use compounding survey. Of the 977 practitioners who responded to the survey, almost all were nurses. ISMP discovered that 81% of the respondents used premixed 5 mL and 10 mL normal saline flushes to dilute medications. The FDA considers a premixed normal saline flush as a medical device and they are "not approved for dilution and administration of IV push medications."

Some clever (but forbidden) uses of prefilled syringes include

- Using prefilled syringes as vials: withdrawing and or adding part of a prefilled syringe into another prefilled syringe for administration (Example: adding 5 mL from one syringe to another 5 mL syringe to make a 10 mL syringe).
- Using a prefilled syringe to reconstitute a powder vial, then drawing the dose back into the same syringe. (Example, using a 10 mL flush, adding 5 mL from the flush, reconstituting, and withdrawing the 5 mL back into the syringe to create a 10 mL dose.)

Using prefilled syringes in these ways is dangerous, since most of the time the health care professional conducting these "procedures" fail to relabel these syringes, so the syringes still have a bright yellow or white label and can be easily picked up by another person and administered in error.

Why would prefilled flushes be used for compounding? First, among the many recent drug shortages, normal saline topped the list for a very long time. Second, they are quick and easy to use, and third, healthcare professionals cling to many misconceptions. Some professionals believe that a syringe does not need to be labeled. There is also a myth that a 10 mL syringe must be used to administer IV push medications. Perhaps it is due to "telephone tag" teaching, where one procedure is passed from one to another.

So, how do we fix this? Clear procedures need to be established for compounding each medication. Staff training is a must, and a simple roll of blank labels in the compounding area can go a long way to avoiding errors.

Skills may vary from one location to another, but at a minimum, healthcare professionals who will perform immediate use compounding must demonstrate the following core skills[8]:

- Hand hygiene and proper gloving
- Calculations, measuring and mixing
- Aseptic technique and compounding procedures

Required skills will depend on the clinic's location; for example, an oncology clinic will need to follow *USP<800> Standards for Hazardous Drugs*, along with USP<797>. Other skills may include cleaning, garbing, documentation, and labeling and should align with the immediate use procedures in the facilities SOPs.

Competency assessment must be based on the aseptic processes that are related to the tasks being performed, which can be difficult to recreate. Demonstration of a simulated manipulation may be acceptable in most cases. A simulated aseptic manipulation using empty vials, syringes, sterile water, or saline could consist of the three maximum products allowed, with no need to incubate the sample.[7] Using a convenient checklist, like the one in **Table 2** (right), helps trainers evaluate staff and document consistently.

The **SIDEBAR** (previous page) highlights one practice that needs to end immediately.

CONCLUSION

Whether you are the designated pharmacist or just a team member, it is important for you to recognize immediate use medications and locations where they may be compounded. With the implementation of USP<797> commencing on November 1, 2023, now is the time to look at the pharmacy clean room and all areas in your facility where compounding may be occurring. Huge changes in workflow as well and policies and procedures may need to be adopted. Create a well-balanced team of professionals and get to work!

Figure 1 (next page) summarizes key points.

Table 2. Sample Immediate Use Compounding Evaluation

	Name of person assessed: *Jonathan the Husky Dog*	Location: Husky Clinic
	Evaluation of Handwashing, Garbing, Gloving and Aseptic technique: In left-hand boxes, indicate for each activity ✓ = acceptable completion of the described activity in the correct order, X = the order is incorrect or the activity is performed incorrectly or N/O = the activity was not observed.	Notes/comments on any activities
	Removes all jewelry and outer garments	
	Uses nail pick under running water	
	Washes hands with soap and water for 30 seconds	
	Dries hands with approved wipe	
	Dons required garb	
	Applies alcohol-based hand sanitizer, allows to air dry	
	Selects the correct pair of gloves	
	Correctly dons sterile gloves	
	Applies sterile alcohol to gloves, allows to air dry	
	Disinfects compounding area with facility approved agent	
	Selects proper components	
	Disinfects critical sites with 70% alcohol wipe	
	Punctures vial at a 45-degree angle to avoid coring	
	Withdraws the correct amount of fluid from vial	
	Disposes waste in proper container	
	Visually inspects final product	
	Demonstrates proper labeling	
	Applies correct 4- hour BUD	
	Name of evaluator and date	Pass / Fail

Figure 1. Implementing the Immediate Use Guidelines

Best

❶ **Be COMMUNITY CHAMPIONS** and encourage discussion among all pharmacy staff and departments where immediate use compounding is practiced

❷ **Create buy-in** using small prizes or recognition for perfect compliance

❸ **Create training in ways that address different types of learners (aural, visual, and by-doing learners)** so everyone "gets it"!

Better

❶ **Update standard operating procedures now** and start implementing the changes

❷ **Form a team that will establish a training schedule** and stick to it

❸ **Talk, talk, talk about the upcoming changes** and make sure every employee knows what to do

Good

❶ **Keep November 1, 2023 in mind**; that's when the new USP<797> goes into effect

❷ **Start training now** so you needn't burn the midnight oil on Halloween 2023!

❸ **Monitor constantly** looking for areas where you could improve

REFERENCES

1. United States Pharmacopeia (USP). General Chapter, <797> Pharmaceutical Compounding—Sterile Preparations. (2023) USP-NF. Rockville, MD: United States Pharmacopeia. Accessed June 19, 2023.

2. FDA highlights concerns with compounding of drug products by medical offices and clinics under insanitary conditions. Oct. 25,2021. https://www.fda.gov/drugs/human-drug-compounding/fda-highlights-concerns-compounding-drug-products-medical-offices-and-clinics-under-insanitary

3. Scales BS, Dickson RP, LiPuma JJ, Huffnagle GB. Microbiology, genomics, and clinical significance of the Pseudomonas fluorescens species complex, an unappreciated colonizer of humans. Clin Microbiol Rev. 2014 Oct;27(4):927-48. doi: 10.1128/CMR.00044-14. PMID: 25278578; PMCID: PMC4187640.

4. ASHP, The sterile compounding answer book. Chapter 8, Immediate use and preparation for administration. page 33-34

5. Pedersen CA, Schneider PJ, Ganio MC, Scheckelhoff DJ. ASHP National survey of pharmacy practice in hospital settings: Dispensing and administration- 2020. *Am J Health Syst Pharm.* 2021;78(12):1074–93.

6. National Assessment of State Oversight of Sterile Drug Compounding. The Pew Charitable Trust. Februsry 2016. Accessed August 7, 2023. https://www.pewtrusts.org/~/media/assets/2016/02/national_assessment_of_state_oversight_of_sterile_drug_compounding.pdf

7. Mind Tools, Gap Analysis. Accessed Jun18,2023. https://www.mindtools.com/afv9hac/gap-analysis

8. Pharmacy Purchasing & Products Magazine, USP <797> Immediate-Use CSPs: Small Changes, Big Impact. Feb.2023 Vol.20 No.2, page 10. Kevin N. Hansen, PharmD, MS, BCPS, BCSCP Amanda M. Choi, PharmD, MBA Annie Lambert, PharmD, BCSCP February 2023 - Vol.20 No. 2

9. United States Pharmacopeia (USP). General Chapter, <797> Pharmaceutical Compounding—Sterile Preparations. (2008) USP-NF. Rockville, MD: United States Pharmacopeia. Accessed June 20, 2023.

10. Institute of Safe Medical Practices. Part II Survey results suggest action is needed to improve safety with adult IV push medications. Dec. 2018, Vol.16, Issue 12. Accessed June 22, 2023.https://www.ismp.org/sites/default/files/attachments/201812/NurseAdviseERR201812.pdf