The Revised USP 
Sterile Compounding Standards

Implications for 
Home Infusion and Alternate Site Providers

By Connie Sullivan, BSPharm

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Learning Objectives:

1. Summarize the major changes between the current standard and the final revision to Chapter <797> Pharmaceutical Compounding-Sterile Preparations.

2. Explain how and when to apply the standards in Chapter <797> when preparing compounded sterile products used in home infusion and other alternate infusion settings.

3. Discuss the implementation timeframe and method of enforcement for USP general chapters <797> and <800>.

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AUTHOR DISCLOSURE STATEMENT

The author declares no conflicts of interest or financial interest in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria. Sullivan is presenting this information solely as a representative of NHIA and is not speaking on behalf of USP or the USP Compounding Expert Committee.

On June 1, the United States Pharmacopeia (USP) released the long-awaited final revisions to General Chapters <797> Pharmaceutical Compounding - Sterile Preparations, and <795> Pharmaceutical Compounding - Nonsterile Preparations. USP also released a newly developed Chapter <825> regarding the preparation, compounding, dispensing, and repackaging of radiopharmaceuticals.

While standards are living documents subject to further modification, this release aligned several chapters, including Chapter <800> Hazardous Drugs—Handling in Health Care Settings, with an effective date of December 1, 2019. To reach this point, the USP Compounding Expert Committee reviewed over 8,000 comments in a revision process that spanned a multi-year timeframe and included two draft revisions to solicit input from a wide range of stakeholders.

Meeting or exceeding USP <797>—it is designed to be a minimum standard—is a key component in ensuring patient safety and a significant step toward compliance with state and federal regulations, accreditation standards, and other requirements for legal and ethical pharmacy operations. All providers are encouraged to download and familiarize themselves with the new standards and begin modifying their practices.
All providers are encouraged to download and familiarize themselves with the new standards and begin modifying their practices to come into compliance.

to come into compliance (see Box, right, for more). This article will summarize the major changes between the current standard and the final revision and explain how and when to apply the standards in Chapter <797> when preparing compounded sterile products (CSPs) used in home infusion and other alternate infusion settings. Compounding personnel and persons who are responsible for the operation of a compounding facility are highly encouraged to read the chapter in its entirety as this article does not capture every aspect of the standard, rather it focuses on areas most applicable to home infusion.

**Scope**
The intention of USP <797> is to minimize harm from microbial contamination, excessive bacterial endotoxins, variability from intended strength of correct ingredients, and use of ingredients of poor quality. For that reason, the scope of the standard covers all CSPs, all persons who prepare CSPs, and all places where CSPs are prepared for human patients. According to USP, “This includes, but is not limited to, pharmacists, technicians, nurses, physicians, dentists, naturopaths, and chiropractors in all places including, but not limited to, hospitals and other health care institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physicians’ practice sites.” (Important note: While USP chapters numbered under 1000 are compendially applicable, it is up to state agencies or other regulatory authorities to provide enforcement. USP does not have any direct role in enforcement of sterile compounding regulations or standards.)

**EXHIBIT 1: Compounding Exemptions from USP <797>**

<table>
<thead>
<tr>
<th>EXEMPTION</th>
<th>CRITERIA</th>
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| Immediate and direct administration           | • Evidence supporting chemical and physical compatibility is available  
• No more than three different sterile products (components, not containers) are used  
• CSPs prepared for immediate use are used for a single patient (not prepared in batches)  
• Administration begins within four hours of the start of preparation  
• Un-used drug from single-dose containers is discarded after compounding is complete  
• The CSP is labeled with the names and amounts of all active ingredients, the name of the preparer and exact four-hour time within which administration must begin, unless administration is performed or witnessed by the person who compounded the CSP |
| Preparing a CSP according to package insert    | • Mixing, reconstitution, or other such acts occur in accordance with the preparation instructions as described in the FDA-approved labeling.  
• The labeling information includes specific information regarding:  
  » Diluent to be used  
  » Final strength  
  » Storage time  
  » Container closure system  
• The starting components are conventionally manufactured sterile products.  
• Prepared as a single dose for an individual patient |
| Docking and activation of proprietary vial systems | • In accordance with labeling  
• For immediate administration to an individual patient |

Download the Standards  
www.usp.org/compounding/general-chapter-797

Read the FAQs  
www.usp.org/frequently-asked-questions/pharmaceutical-compounding-sterile-preparations
Administration of CSPs, which is defined as the direct application of a sterile medication to a single patient by injecting, infusing, or otherwise providing a sterile medication in its final form, continues to lie outside the scope of USP <797>, as are sterile radiopharmaceuticals, the standards for which were moved to Chapter <825>. For administration, the U.S. Centers for Disease Control and Prevention (CDC)'s standard precautions for patient care and safe injection practices should apply. It should be noted that these CDC standards focus on the prevention of infection between patients and health care workers, not on maintaining sterile product quality.

In addition to the exemption for administration, the chapter provides allowances for some compounding to occur outside of a controlled environment to ensure access to certain compounded medications where the risk of harm is low, or when the preparation is guided by instructions and information provided in the product’s approved labeling (see Exhibit 1). Compounding for “Immediate Use” allows the compounding to mix up to three unique components outside of a primary engineering control (PEC) as long as there is evidence supporting the physical and chemical compatibility and administration begins within four hours of the start of compounding. The exemption for immediate-use for direct administration is limited to preparing CSPs for a single patient. If single-dose vials are used during the compounding procedure, any remaining drug must be discarded and may not be used in further compounding. Additional requirements for labeling the product(s) apply depending on who prepares and administers the CSP.

The revised Chapter <797> also delineates compounding from preparing a sterile product according to the manufacturer’s-approved labeling. The uncertainty around when USP <797> applies to preparing an approved product for administration is lifted by the inclusion of a new section (1.4) dedicated to this issue, which is important to home infusion providers due to the need to mix a single dose of medication for a patient in the home setting in some circumstances. When the product labeling is complete with instructions for preparation, diluent, final strength, the container closure, and storage requirements, then a single dose of medication may be compounded outside of the PEC and stored according to the information in the labeling. Only sterile starting components maybe used in the preparation process and aseptic technique must be strictly followed.

Standard Operating Procedures

USP emphasizes standard operating procedures (SOPs) in this revision by pulling them into their own dedicated section (17). Facilities preparing CSPs are required to develop SOPs for the compounding process and other supporting activities. There are 32 references to SOPs throughout the standards, which specify aspects of the operation that require documented SOPs (see Exhibit 2). For example, “The order of garbing must be determined by the facility and documented in the facility’s SOP.”

Some of the items calling for SOPs are more flexible in that they can be written to fit the facility’s operations, provided the resulting process complies with the standards. For example, the chapter does not offer a specific order or location for hand hygiene and garbing. The procedure can be developed to fit the facility design, particularly as it pertains to the location of the sink and where space is adequate to minimizing donning and doffing without introducing contamination into the classified environment.

EXHIBIT 2: USP <797> References to SOPs

- Hand hygiene and garbing
- Temperature and humidity monitoring
- Environmental monitoring
- Cleaning and disinfecting procedures
- Equipment
- Release testing
- Labeling
- Sterility testing
- Quality assurance

USP <797> covers all CSPs, all persons who prepare CSPs, and all places where CSPs are prepared for human patients.
areas. SOPs must be written, and reviewed every 12 months, by a designated person. Changes must be documented and communicated to all personnel, who should, in turn, document an acknowledgement of the communication.

The “designated person” also appears throughout the chapter many times—25 to be exact. In a move toward further culpability, USP calls for the identification of one or more individuals responsible and accountable for the performance and operation of the compounding facility. Facilities must determine how to allocate responsibility if there is more than one designated person.

**Risk Categories and Facility Design**

The newest revision will alter the current risk categories for CSPs from low, medium, high, and low with a 12-hour beyond use date (BUD) to Category 1 and Category 2. The distinction is primarily based on the conditions under which the CSP is made, the probability for microbial growth, and the time period within which they must be used.

- **Category 1** - Allows for the PEC to be placed in an unclassified space and assigns the CSP a BUD of 12 hours or less at controlled room temperature or 24 hours or less refrigerated that is compounded in accordance with all applicable requirements under Chapter <797>.

- **Category 2** - Requires the PEC to be placed inside a classified room (clean room suite) and allows the CSP to be assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded in accordance with all applicable requirements under Chapter <797>.

Operationally, this means that both Category 1 and 2 CSPs must be prepared in an ISO Class 5 or better PEC. If a provider is compounding only Category 1 CSPs, the PEC may be placed in an unclassified segregated compounding area (SCA) without an ante-room or buffer room. However, the SCA must be located away from things that could compromise air quality, such as unsealed windows, doors that connect to the outside, restrooms, food preparation areas, and so on. A sink for hand hygiene must be placed outside the visible perimeter, at least 1 meter from the PEC (see Exhibit 3).

If a provider is compounding Category 2 CSPs, the PEC must be located in the buffer room of a clean room suite with an ante-room (minimum of 20 air changes per hour) and a buffer room (minimum air change of 30 air changes per hour). The sink should be hands-free and may be located inside or outside the ante-room (USP provides several diagrams in the Chapter). The ante-room must have a line of demarcation (LOD) separating the clean side from the dirty side—the LOD is based on the facility layout and garbing process. Alternatively, providers could choose to have two ante-rooms: one clean and one dirty.

In general, the new revision says that clean room facilities must have fixed walls and doors, HEPA filters located in the ceiling, and daily monitoring and recording of temperature, humidity, and pressure differential. Clean rooms are also required to have low wall returns, unless there is an absence of stagnant air verified by a smoke study. In addition, tacky mats are prohibited in classified areas.

The revision also makes several recommendations for clean room facilities. Temperatures should be at or below 20°C and relative humidity below 60%, and doors should have hands-free access and there should be no seals and sweeps between the ante and buffer rooms. Overhangs and ledges should be minimized in the clean room so that dust cannot collect.

**Transferring Materials Between Compounding Areas**

In this revision, USP created a new section (8.1-8.3) describing the transfer of materials and equipment between an unclassified area (not required to meet air cleanliness classifications) and classified areas (maintains air quality based on ISO standards) as well as into the PEC. Before
any item is introduced into the clean side of an ante-room, placed into a pass-through, or brought inside the perimeter of the SCA, it must be wiped with a sporicidal agent, disinfectant registered with the U.S. Environmental Protection Agency (EPA), or sterile 70% IPA using low-lint wipers by personnel wearing gloves. Before introducing an item to the PEC, it must be wiped with sterile 70% IPA, unless the item is in a sealed container designed to maintain sterility.

If an EPA-registered disinfectant or sporicidal agent is used, the agent must be allowed to dwell for the minimum contact time specified by the manufacturer. It is important that providers know and adhere to dwell times, as well as document this step in their SOPs. If sterile 70% IPA is used, it must be allowed to dry. The wiping procedure must not render the product label unreadable.

**Personnel Qualification and Garbing**
The revised standards clarify, and in some cases, tighten the competency testing and documentation requirements for sterile compounding personnel (see Exhibit 4). The requirements for core competency testing remain the same. However, the requirements for visual observation of hand hygiene and garbing as well as gloved fingertip (and thumb) testing (GFT) have changed.

According to USP, “Before being allowed to independently compound, all compounders must successfully complete an initial competency evaluation, including visual observation and gloved fingertip and thumb sampling on both hands, no fewer than three separate times. Each fingertip and thumb evaluation must occur after performing a separate and complete hand hygiene and full garbing procedure. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling at least every six months after completing the media-fill test.” That means that new employees should perform gloved fingertip and thumb testing no less than four times with their initial competency program.

Initial GFT sampling must be performed on donned sterile gloves in a classified area or SCA (successful completion = 0 zero colony-forming units, or CFU). Subsequent sampling must be performed inside of an ISO Class 5 PEC. If conducting gloved fingertip and thumb sampling in a compounding aseptic isolator (CAI), compounding aseptic containment isolator (CACI), or a pharmaceutical isolator, samples must be taken from the sterile gloves placed over the gloves attached to the restricted-access barrier system (RABS) sleeves. Successful completion of subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤3 CFU (total from both hands).

Garbing requirements apply when preparing both Category 1 and Category 2 CSPs. The order of garbing is not specified in the new revision but is left up to the facility as documented in its SOPs. All personnel entering the compounding area must, at minimum, wear the following:

- Gown or coveralls (low-linting)
- Shoe covers (low-linting)
- Head/hair cover (low-linting)
- Face mask, and facial hair cover, if applicable
- Sterile, powder-free gloves

One important note: donning and doffing should not occur in the ante-room or the SCA at the same time. Unsoiled gowns may be

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**EXHIBIT 4: USP <797> Standards for Personnel Qualification**

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>2019 REVISION</th>
<th>LOCATION OF GFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written/electronic testing of core competencies</td>
<td>Initial and every 12 months</td>
<td>NA</td>
</tr>
<tr>
<td>Visual observation of hand hygiene and garbing</td>
<td>Initial x3 and every 6 months</td>
<td>NA</td>
</tr>
<tr>
<td>Gloved fingertip and thumb testing after completing the hand hygiene and garbing procedure</td>
<td>Initial x3, and then every 6 months post media fill</td>
<td>A classified space (ante-room or buffer room) or within the segregated compounding area.</td>
</tr>
<tr>
<td>Media fill followed by GFT</td>
<td>Initial and every 6 months</td>
<td>Inside the PEC</td>
</tr>
</tbody>
</table>

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re-used during the same shift if stored inside the perimeter of the SCA or in the classified area, although, garb must be replaced immediately if it becomes visibly spoiled or if its integrity is compromised.

The order of hand washing and garbing depends on the placement of the sink. Hands must be sanitized with alcohol-based hand rub (note the requirement for the product to have persistent anti-microbial activity is removed) before donning sterile, powder-free gloves, which must take place in a classified room or SCA. Skin must not be exposed inside the PEC—so no donning and doffing of sterile gloves inside the PEC. Gloves must be disinfected with 70% IPA regularly throughout the compounding process and whenever non-sterile surfaces, such as vials, counter tops, chairs, or carts, are touched.

**Certification and Environmental Monitoring**

PECs where Category 1 and 2 CSPs will be compounded must be certified according to procedures that comply with the Controlled Environment Testing Association (CETA) certification guide. Classified areas, including the PEC, must be certified initially and then again, every six months. These areas also need to be recertified if the facility undergoes construction or redesign; if PEC is repositioned, or if the room is reconfigured in a way that could affect airflow. Certification includes, but is not limited to:

- Airflow testing for velocity, volume, pressure, exchanges
- HEPA filter integrity testing
- Total particle counts
- Dynamic airflow smoke pattern testing

Beyond certification, air particle sampling is a necessary method of measuring the performance of the engineering controls. Likewise, microbiological air and surface monitoring provides information on the environmental quality of the compounding area. Environmental monitoring must be conducted in all classified areas, and the revision calls for more frequent surface monitoring. Viable air sampling must be conducted initially and every six months and surface sampling must be conducted initially and monthly (instead of periodically based on an assessment of risk).

Facilities are also required to develop and implement written procedures for both with an emphasis on the provider being able to paint a picture of what is happening in the environment as well as when and how corrective action will be taken. According to USP <797>, “An effective microbiological air and surface monitoring program identifies environmental quality trends over time, identifies potential routes of contamination, and allows for implementation of corrective actions to minimize the risk of CSP contamination.”

### EXHIBIT 5: Category 2 BUD Default Limits

<table>
<thead>
<tr>
<th>PREPARATION CHARACTERISTICS</th>
<th>STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounding Method</td>
<td>Sterility Testing Passed</td>
</tr>
<tr>
<td>Aseptically Processed CSPs</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Terminally Sterilized CSPs</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Source: USP General Chapter <797> Pharmaceutical Compounding - Sterile Preparations. June 1, 2019

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All procedures, results, and corrective actions must be documented. If action levels are reached, the facility must work with a microbiologist to attempt to identify the microorganism to the genus level. If corrective actions are taken, then data must be collected and reviewed to confirm the corrective actions were effective. Facility SOPs for monitoring must include: a diagram of the sampling locations, sampling procedures, sample size and frequency, a description of compounding activities taking place during testing, and action levels to trigger corrective action.

The revision uses a table (Table 8 in Section 7) to specify minimum frequencies for cleaning and disinfecting as well as applying sporicidal agents. There is no requirement for sterile cleaning supplies for classified areas. Sterile low-lint wipers and “appropriate” cleaning agents (e.g. sterile water) should be used in cleaning the PEC.

### Beyond Use Dates (BUD) and Labeling

USP encourages the conservative establishment of beyond use dates (BUD), to ensure that drugs maintain their stability and sterility. For Category 1, a maximum BUD of 12 hours for room temperature CSPs and 24 hours for refrigerated CSPs may be assigned. For Category 2, assigning a BUD depends on the compounding process, the starting components, sterility testing, and storage conditions (see Exhibit 5). Home infusion providers will benefit from the increases in the default BUDs for Category 2 CSPs (prepared from only sterile starting components) from 9 to 10 days for refrigerated CSPs, and from 30-48 hours to 4 days for those stored at room temperature. The additional day for refrigerated products will allow for thorough chilling of CSPs overnight. Please note that compounders must demonstrate chemical compatibility with the container closure and other components throughout the BUD in all circumstances. Additionally, the BUD does not limit the time for administration, but compounders are encouraged to consider the long infusion times occasionally used in the home infusion setting when assigning BUDs.

### CSPs as Components

Sections 15 and 16 of the new revision change how pharmacies can use conventionally manufactured single-dose vials and stock solutions to make CSPs. Using compounding stock solutions repeatedly, over several days throughout the BUD will no longer be allowed. Once a CSP or compounded stock solution is punctured in the PEC for use in compounding, it must be discarded after 12 hours in order to prevent subsequent CSPs from being assigned a BUD that exceeds that of the parent CSP. The same rule applies to the re-use of single-dose vials. A single-dose vial may be re-used for up to 12 hours as long as it is punctured under ISO 5 conditions and stored according to the product label between uses. This means providers will have a longer timeframe in which to use a single-dose vial for compounding once the chapter becomes official December 1, 2019. Currently providers are limited to 6 hours. See Exhibit 6 for details on how the new standard approaches the use of components in preparing CSPs.

The revised standard also requires more information be communicated in CSP labeling. The current standard requires that the immediate container labeling includes ingredient(s) name and concentration(s) or quantities, volume, route of administration, BUD, and storage information. These standard elements must still be recorded, but the revision also requires immediate container labeling that includes internal identifying information, such as
As with all USP chapters, enforcement ultimately comes down to how regulatory agencies choose to apply the standards.

A barcode or prescription number, a statement that the container is multi-dose (if applicable), and a statement that the container is single-dose (if space allows). CSPs that will be sent outside the facility must also have labeling that includes pharmacy contact information and special handling and storage instructions.

Master formulation records, which describe how the CSP is prepared, must be created for CSPs prepared for more than one patient and for CSPs prepared from non-sterile ingredients. Changes to the master formulation record should be documented according to the facility SOPs. In addition, compounding records must be created for every CSP. The compounding record provides traceability of every ingredient in the event of a recall. Prescription or medication orders and labels may suffice; required information can be stored in electronically (in a workflow management or other system) as long as it can be retrieved.

**USP <800>**

As mentioned earlier, the release of USP <797> was meant to align with Chapter <800> - Hazardous Drugs—Handling in Health Care Settings, so both standards are effective December 1, 2019. Chapter <800> was not changed in this round of revisions and has remained the same since it was introduced in 2016.

Providers may be surprised to learn that because Chapter <800> becomes enforceable through references in <797> and <795>, enforcement is technically limited to activities that fall within the scope of these chapters. While activities exempted from <797> and <795> are also technically exempt from <800>, USP is encouraging compounders who handle hazardous drugs to voluntarily adopt the entire standard. USP released a video explaining the applicability of USP <800> on its website, along with updated FAQ. As with all USP chapters, enforcement ultimately comes down to how regulatory agencies choose to apply the standards. Because chapter <800> is designed to protect health care workers from exposure to HDs, pressure to adopt the standard may also come from the employees themselves.

**Conclusion**

Although this article focused on areas most applicable to home infusion, there are many other important aspects to the newly released standard. We strongly recommend that all compounding personnel and persons who are responsible for the operation of a compounding facility read the chapter in its entirety and become familiar with its contents. Since the chapter’s official release, provider organizations will be digesting the new standards and performing gap analyses to identify any necessary steps toward compliance before the effective date. Accrediting bodies are also evaluating the standards to see what effect they may have on their accredited organizations. Look for more information on USP <797> revisions and accreditation in future issues of INFUSION.