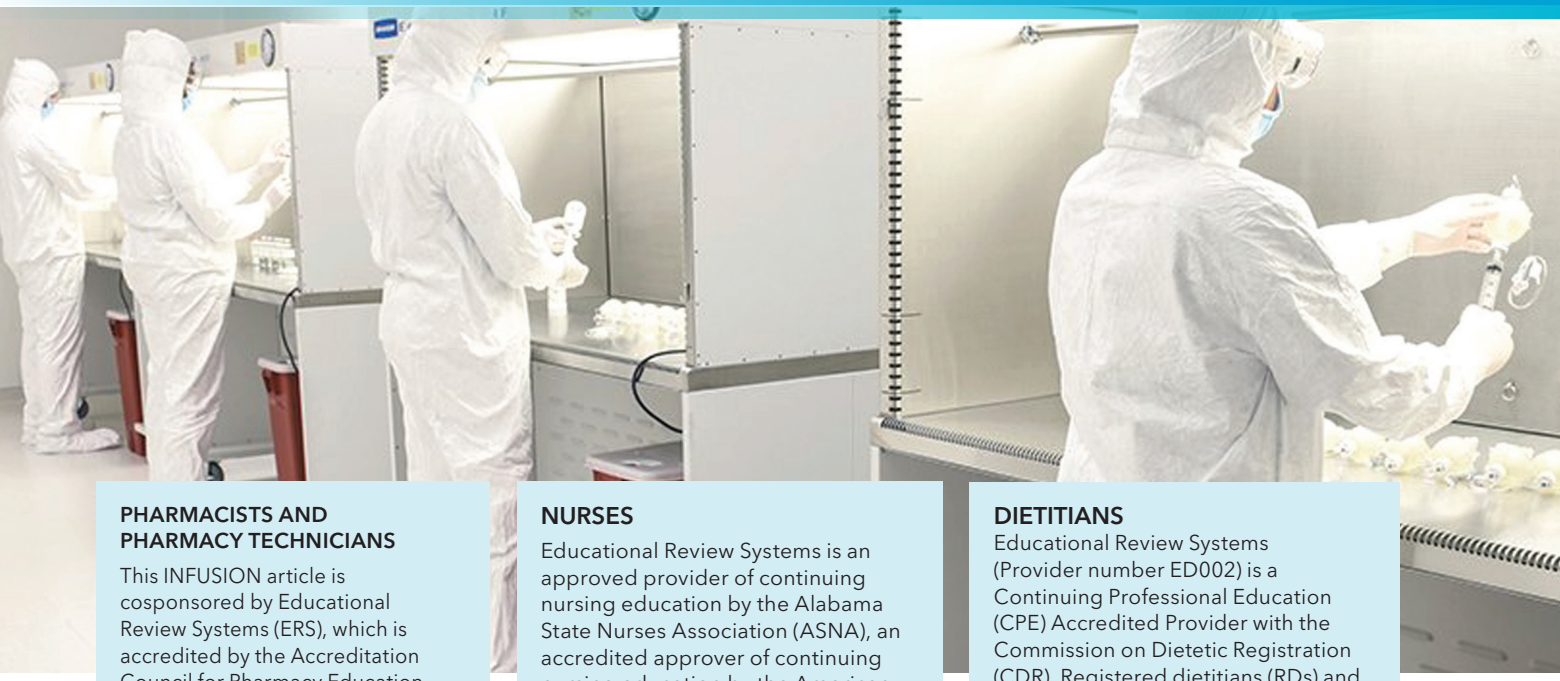
The Home Infusion Compounder's Guide to the Second Proposed Revision to USP <797>

By Connie Sullivan



PHARMACISTS AND PHARMACY TECHNICIANS

This INFUSION article is cosponsored by Educational Review Systems (ERS), which is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. ERS has assigned 1.0 contact hours (0.1 CEU) of continuing education credit to this article. Eligibility to receive continuing education credit for this article begins July 11, 2018 and expires July 11, 2021. The universal activity numbers for this program are: 0761-9999-18-241-H07-P _ and 0761-9999-18-241-H07-T__ Activity Type: Knowledge-Based.

NURSES

Educational Review Systems is an approved provider of continuing nursing education by the Alabama State Nurses Association (ASNA), an accredited approver of continuing nursing education by the American Nurses Credentialing Center (ANCC), Commission on Accreditation. Program #_05-115-18-004. Educational Review Systems is also approved for nursing continuing education by the state of California, the state of Florida, and the District of Columbia. This program is approved for 1.0 hours of continuing nursing education. Eligibility to receive continuing education credit for this article begins July 11, 2018 and expires July 11, 2021.

DIETITIANS

Educational Review Systems (Provider number ED002) is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR). Registered dietitians (RDs) and dietetic technicians, registered (DTRs) will receive 1.0 hour or 0.1 continuing professional education unit (CPEU) for completion of this program/material. Eligibility to receive continuing education credit for this article begins July 11, 2018 and expires July 11, 2021.

Dietitian Knowledge Level: 2

Dietitian Learning Codes:

- 5030 Home care3
- 9010 Data analysis, statistics
- 9060 Research development and design
- 9070 Research instruments and techniques

Approval as a provider refers to recognition of educational activities only and does not imply Accreditation Council for Pharmacy Education, ERS, or ANCC Commission on Accreditation, approval or endorsement of any product. This continuing education activity is intended for pharmacists, pharmacy technicians, nurses, and other alternate-site infusion professionals. In order to receive credit for this program activity, participants must complete the online post-test and subsequent evaluation questions available at www.nhia.org/CE_Infusion. Participants are allowed two attempts to receive a minimum passing score of 70 percent.

Objectives:

1. Compare and contrast the changes between the first and second proposed revisions to USP <797> standard for sterile compounding.
2. List three factors identified in the 2018 proposed revision of USP <797> that may impact the quality of a compounded sterile preparation.
3. Understand how to send comments to USP on the second proposed revision to USP <797>.

AUTHOR BIO:

Connie Sullivan, BSPharm, is NHIA's Vice President of Research and Innovation. Sullivan has over 20 years of home infusion management and clinical practice experience, and is responsible for providing NHIA members with support and education on home infusion pharmacy issues such as sterile compounding regulations, and clinical pharmacy best practices. Sullivan leads NHIA's initiatives to create national quality standards through the implementation of benchmarking programs to describe and quantify the value of home infusion services. In addition to her work for NHIA, Sullivan also oversees the research, leadership development, and education activities sponsored by the National Home Infusion Foundation. Sullivan is the current Vice Chair of the United States Pharmacopeial (USP) Sterile Compounding Expert Committee, and a member of the Parenteral Nutrition Expert Panel. Prior to joining NHIA, Sullivan served 15 years as the National Director of Home Infusion for HCR Manorcare, based in Toledo, Ohio. Sullivan graduated from The Ohio State University College of Pharmacy in 1994.

AUTHOR DISCLOSURE STATEMENT:
The author is presenting this information solely as a representative of NHIA and is not speaking on behalf of USP or the USP Compounding Expert Committee.

Overview

On July 27, 2018, nearly three years after publishing the first proposed revision to *Chapter <797> Pharmaceutical Compounding – Sterile Preparations,* the United States Pharmacopeial Convention (USP) pre-released the second draft of the much-anticipated revision to the chapter. (The official publication date in the *Pharmacopeial Forum (PF)* is September 4, 2018.) USP <797> publishes an enforceable standard for practitioners of compounded sterile preparations in all health care settings. While the goal of USP has not changed—to provide minimum practice and quality standards for compounded sterile preparations (CSPs) of drugs and nutrients based on current scientific information and best aseptic practices—the regulation of pharmacy compounding continues to evolve in response to public demand for safe CSPs. This article will review the most significant changes to the recently published draft revision of USP <797>, and offer insights as to the impact they would have, if adopted, on home infusion and specialty pharmacy providers who engage in sterile compounding.

Background

While the USP Sterile Compounding Expert Committee worked to evaluate over 8000 comments received in response to the first proposed revision released September 2015, the regulations of sterile compounding continued to evolve. The Food and Drug Administration (FDA) was particularly prolific in their publication of several draft and final guidance documents on the topic of 503A compounding; several with relevance to home infusion[4]. (See Exhibit 1.) Meanwhile, accreditation organizations and state Boards of Pharmacy advanced initiatives to broaden enforcement of compounding activities, with some beginning to reference USP <797> for the first time. In the absence of a definitive USP revision for compounding standards many states chose to move ahead with rules that reflect a mixture of current and draft USP standards and FDA guidance documents, leaving compounders with a "foot in each canoe" in terms of old and new thinking. The urgency to update compounding rules was largely a result of a significant incident of contaminated products resulting in patient harm. (See box, below right)

EXHIBIT 1: **List of FDA Draft and Final Guidance Documents Relevant to Home Infusion**

DRAFT GUIDANCES	FINAL GUIDANCES
Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of ____ and the U.S. Food and Drug Administration (2/2015)	Prescription Requirement Under Section 503A of the Food, Drug, and Cosmetic Act (12/2016)
Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act (4/2016)	Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities (1/2017)
Insanitary Conditions at Compounding Facilities (8/2016)	Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (1/2018)
	Mixing, Diluting, or Repackaging Biological Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (1/2018)

Source: FDA website

Confidence in pharmacy compounding was shaken by the tragic multi-state outbreak of fungal meningitis among patients who received contaminated injections of preservative-free methylprednisolone acetate distributed by the New England Compounding Center (NECC). The 793 cases of infection—which included 64 deaths—associated with the 2012 event caused patients and regulators to question their trust in pharmacy compounding[5]. The incident at NECC serves as an example of the professional accountability and liability for pharmacists who are responsible for the oversight of compounding operations. In January 2018, the pharmacist supervisor at the center of the NECC incident was sentenced to eight years in prison and two years of supervised release, after being convicted by a federal jury in Boston of 77 counts, including racketeering, racketeering conspiracy, mail fraud and introduction of misbranded drugs into interstate commerce with the intent to defraud and mislead[5].

The safety of sterile compounding relies upon the expertise and compliance with industry standards by each individual operator. Over the past several years, the education and qualifications of professionals engaged in sterile compounding have gained attention. Organizations such as the Board of Pharmacy Specialties (BPS) and the Pharmacy Technician Certification Board (PTCB) have recognized the need to validate practitioner competency. BPS will offer a pharmacist certification for sterile compounding beginning in September of 2019[6]. In 2018, PTCB began certifying technicians who demonstrate competency in compounding principals[7]. Pharmacists and technicians working in home and specialty infusion settings have come to rely upon USP <797> to guide their operations and ultimately protect patients from receiving contaminated sterile products. The need to assign oversight of compounding operations to a "designated person," responsible for compliance with the standard, is referenced in the 2018 proposed revision. Should the proposed revision become official in December 2019, the new certification programs mentioned above will be well-timed to meet the need of ensuring compounding operations are entrusted to qualified individuals.

The goal of USP <797> is to provide minimum standards of practice for the preparation of CSPs by all entities to prevent harm to patients from contamination, inaccurate ingredients, and poor quality[3]. The new proposed revision maintains the approach of categorizing CSPs according to factors that may contribute to contamination of the product. The shift away from low, medium and high-risk designations, to Categories 1 and 2 endures in this most recent revision. Both draft proposed revisions reference the compounding environment, time between compounding and administration, sterility (or not) of the starting ingredients, and sterility testing as important variables in assessing a CSP's likelihood for contamination. Readers will note the newer version places less emphasis on batch size, the inherent nature of the drug being compounded, and the complexity of the compounding process when assessing risk.

Introduction and Scope

A summary of the major changes from the 2015 proposed revision is shown in Exhibit 2. Some of the most significant and useful changes come right at the start of the chapter in the Introduction and Scope sections. A proposed definition outlines precisely what qualifies as sterile compounding and includes actions such as, *"combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug to create a sterile product"*[1]. The 2015 proposed revision only described what is "not" considered compounding and included an exemption when *"reconstituting and diluting a conventionally manufactured sterile product with no intervening steps strictly in accordance with the manufacturer's labeling*[3]*"* that left the door open for exempting a large number of CSPs. The proposed revision deals with this situation by offering a new exemption that mostly aligns with the FDA's definition of compounding. USP proposes a limit between compounding and administration of one hour in situations where the package insert is being followed to compound a sterile, non-hazardous, conventionally manufactured drug outside of ISO 5 conditions to facilitate administration to a single patient. Redrawing the lines in this way eliminates the need for the "urgent-use" exemption offered by the 2015 version. Additionally, USP attempts to define the act of administration and points to the Centers for Disease Control and Prevention (CDC) for guidance in this area while reiterating that administration falls outside the scope of the chapter.

USP <797> applies to all settings where CSPs are made, and to all personnel involved in preparing CSPs[1]. In the proposed revision, the list of practitioners who must comply has been expanded to include, but is not limited to, chiropractors, dentists, and naturopaths. In the same section however, the chapter is careful to note that USP has no enforcement role in applying the standard.

EXHIBIT 2

SUMMARY OF MAJOR CHANGES FROM THE 2015 PROPOSED REVISION

- Expanded "Introduction and Scope" describing when to apply the chapter
- Elimination of "urgent-use" terminology
- Elimination of "in-use" time terminology
- Changes to required frequencies for personnel qualifications and environmental monitoring
- New section specific to allergen extracts
- Removal of radiopharmaceuticals to *Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging*

Personnel Qualification

In this section, there are several wording changes that bring clarity to how practitioners should apply the standard. More detailed instructions for conducting required testing are outlined, and the requirements reference what an employee must do to compound "independently". The proposed revision adds calculations back to the list of required elements of a training program and also expands the training requirements to any person who enters the cleanroom, e.g., cleaning and certification personnel must be trained and garbed appropriately.

Other changes include reducing the frequency of requalification of personnel from quarterly to every six months for visual observation of hand hygiene and garbing, gloved fingertip and thumb sampling, and media fill. Exhibit 4 summarizes the changes in personnel qualification frequency between the current standard, and the first and second proposed revisions. Employees who fail any portion of competency testing must have one successful re-test rather than the three successive tests as proposed in 2015. Finally, for employees who compound infrequently, the requalification timeframe is increased to six months from the originally proposed three months.

The 2018 proposed revision outlines more clearly where and how to conduct gloved fingertip testing and media fill procedures. The new draft requires that initial gloved fingertip testing be conducted in the ISO 7 buffer area or segregated compounding area, and subsequent testing must occur in the primary engineering control (PEC) after media fill is complete. The media fill procedures are unchanged in the second proposed revision except for incubation procedures and new documentation requirements for testing results. (See Exhibit 3.)

EXHIBIT 4: **Minimum Standards for Personnel Requalification for Category 1 and 2 CSPs**

	CURRENT STANDARD	2015 PROPOSED REVISION	2018 PROPOSED REVISION
Visual observation of hand hygiene and garbing	Annual	Quarterly	6 Months
Gloved fingertip and thumb testing	Annual (low and medium risk)	Quarterly	6 Months
Media fill	Annual (low and medium risk)	Quarterly	6 Months

Source: United States Pharmacopeial Convention

EXHIBIT 3

RECORD KEEPING REQUIREMENTS FOR MEDIA FILL COMPETENCY TESTING

- Name of employee
- Date/time of test
- Media lot and expiration dates
- Results
- Signatures of person completing the evaluation

Source: USP. Proposed revisions to Chapter <797>, July 2018.

Facilities and Engineering Controls

Many of the proposed changes to the facilities section from the 2015 proposed revision are carried over to the most recent draft. Requirements for fixed walls and doors between the ante-room and buffer room, temperature and humidity monitoring, and higher room air quality requirements for compounding Category 2 CSPs in isolators are unchanged. This section now goes a bit further and mentions placement considerations for robotic compounders and specifications for integrated vertical laminar flow zone (IVLFZ) designs. New terminology referring to the ante-room plus buffer room model as a "cleanroom suite" is introduced, and additional validation of air patterns via smoke studies will cause compounders to think carefully about their work station designs to avoid having to frequently re-certify the sterile compounding area. A significant addition for those engaged in compounding from non-sterile components is to conduct pre-sterilization procedures in a containment ventilated enclosure (CVE) located in the ISO 8 area. Requirements for a minimum number of air exchanges and HEPA filter placement in the ceiling apply to both the ISO 7 and ISO 8 areas, and the room certification requirements are more stringent for the classified areas than in the prior version.

The 2018 proposed revision also dedicates an entire section (4.4) to water sources and reiterates that sinks "should" be hands-free, and placement "may" be either inside or outside the ante-room (never in the buffer area), and "must" be outside the perimeter of the segregated compounding area (SCA) at least one meter away from the PEC. The chapter is more specific regarding cleaning that must be done for materials and

equipment that enter the classified areas, and prohibits corrugated cardboard in the ante-room.

Environmental Monitoring

Improvements made to the organization of the chapter are most evident in the sections outlining monitoring procedures in the compounding environment. Changes to this section compared to the 2015 version include moving the nonviable testing out of environmental monitoring and into the certification section and reducing the frequency for viable air (referred to as microbiological air) testing to every six months, allowing for the option to combine this testing with recertification. The surface sampling frequency remains unchanged from the 2015 proposed revision as a monthly requirement. Additional changes are made to the incubation instructions, and requirements are also more prescriptive with regard to the sampling methods, such as requiring a certificate of analysis (COA) for commercially acquired sterile growth media.

EXHIBIT 5: **BUDs Comparison for a Category 2 CSP**

	CURRENT STANDARD	2015 PROPOSED REVISION	2018 PROPOSED REVISION
Aseptically prepared from one or more non-sterile starting components, no sterility testing	24 hrs (RT) 3 days (REF) 45 days (FZ)	4 days (RT) 7 days (REF) 45 days (FZ)	1 day (RT) 4 days (REF) 45 days (FZ)
Aseptically prepared from only sterile starting components, no sterility testing	30-48 hrs (RT)* 9-14 days (REF)* 45 days (FZ)	6 days (RT) 9 days (REF) 45 days (FZ)	4 days (RT) 9 days (REF) 45 days (FZ)
Aseptically prepared and successful sterility testing	Based on sterility test results.	28 days (RT) 42 days (REF) 45 days (FZ)	30 days (RT) 45 days (REF) 60 days (FZ)
Terminally sterilized, successful sterility testing**	Based on sterility test results.	28 days (RT) 42 days (REF) 45 days (FZ)	45 days (RT) 60 days (REF) 90 days (FZ)

Source: United States Pharmacopeial Convention

*Low risk CSPs are 48 hours RT and 14 days REF, medium risk CSPs are 30 hours RT and 9 days REF.

**Assumes no preservative present for comparison to the 2015 proposed revision BUDs.

Sterile compounders have been vocal about the need for additional guidance on how to respond to action level excursions; thus, suggested actions are provided in the text to help compounders conduct appropriate investigations, which must include identifying microorganisms to the genus level when colony forming units exceed the levels for any ISO area. The proposed revision eliminates the requirement to assign Category 1 BUDs until an action level excursion is resolved in an ISO 7 or ISO 8 area, which was a deterrent to encouraging more frequent monitoring over and above what the standard requires. Action level thresholds for viable air revert back to the current standard; surface sampling, and surface action levels are condensed to a single table rather than differentiating between work and non-work surfaces. Finally, the most notable changes regarding the cleaning and disinfection section include reducing the frequency of sporicidal use from weekly to monthly, and eliminating the requirement for sterile cleaning tools. Providers will likely find the new table summarizing the cleaning and disinfecting frequencies easier to follow.

Beyond Use Dates

Determining an appropriate beyond-use date (BUD) for a CSP involves evaluating the drug's physical and chemical properties, the compounding environment, preparation methods used, and the storage conditions to which the CSP will be exposed[2]. Clinicians must consider whether the CSP will retain chemical and physical stability and sterility throughout the BUD. While the BUD does not extend to the administration time, it is worth considering that CSPs in home infusion are often administered using novel delivery systems, and over longer infusion times not contemplated by the drug labeling. Shorter BUDs than those proposed in USP <797> may be warranted in some cases for this reason. Under the current USP standard, the maximum BUD allowed for CSPs where sterility testing is not performed is associated with the assigned risk level (low, medium, high). Both proposed revisions to USP <797> employ a tiered approach to determining the BUD, based on various characteristics of

the compounding process and environment. The proposed revision maintains the limits on Category 1 CSP BUDs as ≤ twelve hours at room temperature, and ≤ twenty-four hours under refrigeration. The maximum BUD for a Category 2 CSP depends on the preparation process, starting ingredients, whether the product is sterility tested, and the storage conditions. The presence of a preservative as a justification for a longer BUD has been removed from the 2018 proposed revision.

The new proposed revision suggests several changes to the BUD limits for Category 2 CSPs. (See Exhibit 5.) The BUDs for aseptically prepared CSPs made from non-sterile starting ingredients that are not sterility tested were shortened by three days from the previous draft, to one day for room temperature storage, and four days when refrigerated. Likewise, the BUD for aseptically prepared CSPs stored at room temperature that are prepared from only sterile starting components dropped from six to four days. The maximum BUD for refrigerated CSPs prepared aseptically from sterile starting ingredients remained the same at nine days. The chapter still imposes a maximum BUD for terminally sterilized, sterility tested CSPs. However, the limits are increased to forty-five days if stored at room temperature, sixty days under refrigeration, and ninety days when frozen. Sterilization by filtration is considered an aseptic method for purposes of assigning BUDs in this draft.

In order to access the longer BUDs for sterility tested CSPs, compounders must conduct method suitability testing and follow either; 1) USP Chapter <71> Sterility Tests, or 2) Show the alternative method is validated and is not inferior to <71> testing according to Chapter <1223> Validation of Alternative Microbial Methods. While language is absent from the 2018 revision that explicitly allows compounders to utilize USP monographs to extend BUDs beyond those provided in Table 12 in the Chapter, compounders can still rely on monographs for guidance in assigning BUDs because USP monographs supersede chapters in terms of the USP hierarchy.

BUDs for Allergenic Extracts

The newly proposed revision shifts toward the current standard, which gives allergenic extracts special consideration, and proposes a maximum BUD of one year, or the shortest expiration date of any single ingredient in the CSP. Lesser environmental requirements and personnel qualification frequencies are also proposed for allergen extracts, which are typically compounded by the physician practices administering these therapies. (See Exhibit 6.)

EXHIBIT 6: **Summary of CSP Compounding Requirements and BUDs in the 2018 USP <797> Proposed Revision**

	CATEGORY 1- SEGREGATED COMPOUNDING AREA (SCA)	CATEGORY 2 – CLEANROOM SUITE (ANTE-ROOM PLUS BUFFER ROOM)	ALLERGENIC EXTRACTS – PEC OR AECA
Visual observation of hand hygiene and garb competency	6 Months	6 Months	Annual
Gloved fingertip and thumb sampling	6 Months	6 Months	Annual
Media fill testing	6 Months	6 Months	Annual
PEC certification	6 Months	6 Months	Annual
Secondary engineering control certification	Not required	6 Months	6 Months*
Microbiological (viable) air sampling	6 Months	6 Months	Not required
Surface sampling	Monthly	Monthly	Not required
Maximum BUD under refrigeration for a CSP prepared aseptically from sterile starting ingredients, not sterility tested	24 hours	9 days	1 year, or the earliest expiration date of any ingredient

Source: USP. Proposed revisions to Chapter <797>, July 2018.

*A PEC is optional for compounding allergenic extracts.

Use of Conventionally Manufactured Products and CSPs in Compounding

The concept of limiting the time for which a conventionally manufactured product or CSP may be used once opened or punctured is not new to USP <797>. However, the "in-use time" terminology proposed in 2015 is eliminated and replaced by several new sections that outline the limits for how long a component may be used during sterile compounding before it must be discarded. Section 13 in the 2018 proposed revision refers to limits for conventionally manufactured single-dose, multi-dose, and pharmacy bulk packages; Section 14 discusses how CSPs (including stock solutions) may be used during compounding. Aside from the changes in organization and terminology, the timeframes for use are not materially changed from the current standard or the 2015 proposed revision.

Summary

The proposed revision to USP <797> published in 2015 introduced several substantial changes to how compounded preparations are assessed and categorized. By contrast, the 2018 draft delves deeper into the finer details of how environmental controls and compounding procedures impact CSP quality. The new proposed revision attempts to balance the necessary requirements for ensuring a sterile CSP with the need to allow patient access in a wide variety of settings. The goal of any USP standard is to establish minimum quality standards that reflect current science, and when followed, sufficiently protect the public from harm. With the publication of this second draft revision USP is one step closer to updating this important standard to guide practitioners in their quest to compound safe CSPs, and ultimately deliver products of the highest quality to patients who require compounded medications.

Public Comment Period Open

USP is currently accepting public comment until November 30, 2018, on the second proposed revision to Chapter <797>. NHIA will be preparing comments for submission to USP on behalf of the home and specialty infusion provider community. NHIA members can submit their comments directly to USP via their website (link to: http://www.usp.org/compounding/general-chapter-797), or through NHIA by emailing Connie Sullivan at connie.sullivan@nhia.org. The date of publication of the final revision is scheduled for June 1, 2019, with an effective date of December 1, 2019, to coincide with the effective date of *USP <800> Hazardous Drugs – Handling in Healthcare Settings*.

References

1. USP. Proposed revisions to Chapter <797>, July 2018. Available at: http://www.usp.org/compounding/general-chapter-797 (accessed July 27, 2018)
2. United States Pharmacopeial Convention, Inc. Chapter <797>. *United States Pharmacopeia 39 –National Formulary* 34. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2016.
3. USP. Proposed revisions to Chapter <797>, September 2015. Available at: www.usp.org/sites/default/files/ usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf (accessed July 28, 2018).
4. FDA. https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm166743.htm (accessed July 28, 2018).
5. FDA. https://www.fda.gov/ICECI/CriminalInvestigations/ucm594800.htm (accessed July 28, 2018).
6. Board of Pharmacy Speciallties. https://www.bpsweb.org/2018/02/27/new-specialty-compounded-sterile-preparations/ (accessed July 28, 2018).
7. Pharmacy Technician Certification Board. http://www.ptcb.org/about-ptcb/news-room/news-landing/2018/01/29/ptcb-launches-new-certification-program-in-compounded-sterile-preparation#.W135sC2ZNPM (accessed July 28, 2018).