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USP Chapter <797>: Understanding the Revisions

Technical Paper

A review of the key revisions to the original USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations

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Abstract

USP Chapter <797> became official on January 1, 2004. The first major revision was released on December 3, 2007, following years of soliciting feedback and the review of hundreds of responses by the USP Sterile Compounding Committee. June 1, 2008 is the effective date for the new standards. This paper summarizes the most important changes to USP <797>.

Introduction

The USP (US Pharmacopoeia) General Chapter <797> Pharmaceutical Compounding – Sterile Preparations¹ became official on January 1, 2004 as the first *enforceable* standards for sterile compounding. Many articles have been written about the history behind the Chapter and the reasons why it was necessary. The short answer to “*Why 797?*” is that years of voluntary recommendations and professional guidelines for US pharmacy IV compounding practices did not consistently provide accurate and safe products. Far too many patients were harmed and killed by non-sterile and inaccurately prepared compounded sterile preparations (CSPs).

All USP documents evolve and change through a scientifically rigorous review process. The USP Sterile Compounding Committee (SCC) released the first major revision to USP Chapter <797> on December 3, 2007², after years of soliciting feedback and hundreds of responses. More than 1,000 pages of feedback and suggestions came from about 500 sources representing every significant area associated with IV pharmacy practice³. The result is a comprehensive overhaul and review of the Chapter. June 1, 2008 is the effective date for the new standards, which can be found at <http://www.usp.org/USPNF/pf/generalChapter797.html>.

For an excellent historical framework in understanding how USP <797> came about, an article titled “USP Chapter 797: Establishing a practice standard for compounding sterile preparations in pharmacy”⁴ was published in the September 15, 2004 issue of the *American Journal of Health-System Pharmacists*. The article also summarizes the original Chapter’s major topics and offers 38 references to complete the story. Another good reference for background is the article, “Patient Safety and Peak Performance,” published in *Pharmaceutical Formulation & Quality*.⁵ Article copies and many other resource and reference materials are available at the American Society for Health-System Pharmacists’ (ASHP) Web site⁶ at http://www.ashp.org/s_ashp/index.asp.

Major Changes: Overview

There are many changes in the revised USP <797>, but one of the most important is the greater emphasis on personnel in the compounding process. It is not surprising that human error, aseptic actions and other personnel-related issues have the most potential to cause patient harm. Still, there is nothing in this summary document or the actual Chapter that is headlined as

“personnel changes,” or something similar. Since personnel interact with virtually every system in the compounding process, these changes are dispersed throughout the following text accordingly.

While engineering issues for particulate control are important, science has demonstrated also that people are the primary source of contamination. This is only common sense, which the framers of USP <797> hope will be an overriding value when implementing the many changes required by 797.

The revised USP <797> principles clearly shift the emphasis to human factors and consequently diminishes the mandates for primary engineering controls. On a practical note, the Chapter indicates that new technological advances can supercede the written requirements of the Chapter, *if* such advances can be shown to produce equivalent, or better, results than the ideas in Chapter <797>. The focus of 797 is that the exact process is secondary to the desired goal of improved outcomes.

The words “shall” and “should” are also consistently and extensively used throughout the new document. “Shall” denotes activities that are mandatory, or must be done to comply with the intent of the Chapter. “Should” includes the activities that would be expected, or could be advised as a more desirable activity, but it is short of being required.

Appendix 1 is at the end of the revised Chapter, but may be the best place to start reading the revision to get a quick overview of the most important changes incorporated in the document. Dozens of bulleted statements are provided in the Appendix that cover each of the Chapter sections on the competencies, conditions and practices required. The text makes a notation before each bulleted summary to differentiate between the “shalls” and “shoulds.” The Appendix and introduction also define dozens of important terms in the context of how they will be used throughout the Chapter to aid in the reader’s interpretation and implementation of USP <797>. An important global intent of the revised document is to enhance the clarity of the communication throughout.

Risk Levels

One of the biggest changes to USP <797> is the addition of a new risk level category of “immediate use” to the previous categories of low, medium and high risk. While not the intent of the immediate-use category, the committee did recognize that low-risk compounded sterile products (CSPs) are in fact low risk, and thus became more open to creating this category. An immediate-use CSP is defined as a compound prepared with no more than three sterile, commercially supplied non-hazardous drugs; using commercial, sterile devices; for an infusion that will start within one hour of preparation and be completed within 12 hours. It should be emphasized here that this does not include any chemotherapeutic or other hazardous drug preparations.

Risk Category	Room Temp	Refrigerator	Freezer
Immediate Use	1 hour	1 hour	N/A
Low	48 hours	14 days	45 days
Low w/ 12-hr BUD	12 hours or less	12 hours or less	N/A
Medium	30 hours	9 days	45 days
High	24 hours	3 days	45 days

Source: Kastango, STAR Center presentation, USP Chapter <797> Pharmaceutical Compounding-Sterile Preparations, January 2008.

The revision also specifies that this immediate-use classification is NOT meant to be a category inappropriately used to circumvent the intent of USP <797>. Immediate-use compounds can never be stored for later use. The intent of this change is to address real-world situations such as handling unstable drugs, emergency situations and operating room satellite pharmacies where the only real engineering controls are an ISO Category 5 hood.

This change, allowing sterile compounding in satellite pharmacy hoods, is one of the most significant practical revisions in the new Chapter for many pharmacies. Removing the requirement for an ISO 7 buffer area basically eliminates the engineering control mandates that caused so much concern in the pharmacy compounding community for what many argued were simple and low-risk compounding activities. It's important to remember, however, that while many engineering controls, gowns, gloves, covers etc. are required for aseptic processing, good hand hygiene remains absolutely critical when preparing even immediate-use CSPs.

Beyond-Use Dating, Vials and Sterilization Procedures

Under the USP <797> revisions, beyond-use dating (BUD, sometimes referred to as "expiration dating") for CSPs has been increased for medium-risk compounding to a maximum of 9 days refrigerated, from the prior 7 days. This is an important change for alternate-site pharmacies to allow the shipment of a week's worth of in-date IVs, such as TPNs and antibiotics. While economics was the primary motivation for the change, versus the more common clinical considerations, the committee felt comfortable that the science supports the extended time.

Multi-dose vials (MDV) now have specific maximum beyond-use dates of 28 days. The only exception to this guideline would be where individual drug manufacturers have specific company studies supporting longer expiration

times. Regardless of the USP <797> guidelines, pharmacies should refer to the drug manufacturers' references to determine best practice for compounding and beyond-use dating.

Under the revised Chapter, single-dose vials (SDV) have new guidelines that restrict beyond-use dating, supported by a history of well-documented SDV problems. <797> now only allows a maximum BUD of 6 hours after the initial needle puncture for SDVs if the aseptic manipulation was conducted in ISO Class 5 (typical laminar flow hood) quality air. In air worse than ISO 5, the BUD drops to just one hour and the remaining contents of the SDV must be discarded immediately. Open ampoules are not to be stored for any period of time. This change is a common-sense clinical approach for the real world. Misuse of SDVs has been a significant patient risk for a long time.⁷

Sterility testing was confusing for many readers after the release of the original USP <797> document. The revised version contains many definitions for the verification of compounding accuracy and sterility. The definitions clarify what is meant by sterility testing, with a particular focus on using filters with high-risk compounding. Misuse of filters in high-risk procedures has caused severe compounding related injuries and deaths. Anyone conducting high-risk compounding activities should read this section carefully.

Maintenance of the sterility and purity of dispensed CSPs also got a rewrite with this new document. It's important to not just compound the products correctly and then ignore what happens after they leave the compounding area. CSPs must have adequate controls from preparation until the time of the administration to be compliant with USP <797>.

Specialty Applications

A number of specialty applications are addressed in more detail than in the prior version of the Chapter. For example, hazardous drug compounding is covered in the revision in far more detail than the original document. Overall, the <797> standards are now somewhat more rigorous than in the NIOSH Guidelines published in 2004.⁸ Compounding personnel who handle these hazardous agents should read the entire new section to familiarize themselves with the updates.

Some of the new USP <797> mandates and definitions around safe handling include the provision of different storage areas, negative pressure rooms and the use of appropriate ISO Class 5 devices acceptable for preparing hazardous drugs. One note that had caused some previous confusion is that mixing on table tops with closed systems outside of an ISO Class 5 hood is now specifically contraindicated.

Allergen-extract CSPs are now specifically exempted from <797> due to the substantial amount of preservatives in the concentrated solutions and studies that demonstrate the unique safety of these formulations. This exemption is

valid only if simple processes are being used that include basic aseptic technique principles such as good hand hygiene.

Radiopharmaceuticals are another pharmacy niche area that now is included specifically in the revised <797> document. This section obviously should be reviewed in detail by those individuals with responsibilities that pertain to those compounds.

Engineering and Facility Design

The reduced focus on engineering controls has been mentioned previously, but it's important to understand that engineering controls are still very important to safe compounding. A cleanroom is still a requirement for low-, medium- and of course high-risk CSPs. Specifically, this means an ISO Class 7 cleanroom (aka buffer area) and ISO Class 7 anteroom for negative pressure systems to surround and complement the ISO Class 5 mixing area/hood. The anteroom still needs to be ISO Class 7 for positive or negative pressure systems.

The revised USP <797> provides a different conceptual depiction of facility design, using new schematic models. The intent of the revision is to provide a more practical approach to cleanroom system design. There is a significant amount of discussion, definition and clarification of ISO Class 5 air sources included in the updated document as well. The sample room floor plans for low- and medium-risk compounding are much improved over the original document. These "target" depictions can be applied conceptually to the compounding area inside a hood and to the cleanroom itself.

On an even more micro level, the document provides guidance on environmental quality assurance for room segregation, use of positive and negative pressures and placement of devices and objects like printers, refrigerators and other devices. Compounding practitioners had many questions about such issues when they tried to implement the initial 797 guidelines. The goal for the revision was to fill these gaps in understanding.

Environmental Sampling

The environmental sampling (ES) sections of the Chapter also received a huge rewrite in the two major areas of facility-related issues and personnel-related metrics. The original <797> ES section caused tremendous debate within the pharmacy profession and even substantial disagreement between agencies such as the Federal Drug Administration and the Centers for Disease Control and the American Society for Microbiology (ASM).

Numerous facility issues are covered in the revised ES guidelines, with sampling as a big one. Air sampling is now required only monthly for low- and medium-risk certified compounding areas and weekly for high-risk. Volumetric "active" air sampling is now required and gravimetric methods such as passive agar plates, or paddles, are no longer permitted.

Another component of the changes is that surface sampling requirements have changed. This was a contentious issue and said to be too expensive for many compounding centers. Mandatory surface sampling is being replaced with personnel-related metrics such as media fills etc. for competency testing that have a greater expectation of predicting outcome enhancement.

Required ES for mixing surfaces is now simply referred to as “surface cleaning.” Any further sampling would be done primarily to evaluate the effectiveness of the cleaning and disinfection procedures. There are many additional minor ES cleaning changes to <797> that should be read by those charged with this responsibility.

Clarification of garbing order was another important change in the revised <797> that is clearly related to environmental maintenance and important to minimizing the personnel-related risks. Under the revision, garbing order is more clearly defined to focus on moving from dirtiest to cleanest in the process. It makes sense to start with a hair net, beard mask, gown and finish with a gown, gloves, shoe covers and finish with a 70% isopropyl alcohol (IPA) glove washing.

Other ES activities related to personnel are the further definition and continuation of the didactic training requirements. Examples include written tests, skills assessment and of course the complete media fills testing programs. A new-employee ES test has been added because simple touch contamination is still the most likely cause of a sterility problem. This is the gloved fingertip sampling test during media fill testing. It is to be performed at least annually for personnel involved in low- and medium-risk compounding and semi annually for those certified for high-risk compounding.

The fingertip test is simple. Personnel being tested touch their fingertips to growth plates immediately after leaving the ISO Class 5 hood area. Obviously, washing with 70% IPA is contraindicated for the test. The revised Chapter 797 even includes a suggested algorithm for action levels depending on the fingertip test results.

In the final analysis, environmental monitoring requirements have been reduced in the revised <797>. The new focus is on people first, and most importantly to activities that will achieve the best compounding outcomes.

Conclusion

Every individual with management responsibilities that involve sterile compounding activities should read the entire revised chapter. This paper only briefly highlights some of the most important changes to the Chapter. Further questions can be answered by going back to the full document to gain a more complete understanding of the meaning and specific requirements for any given topic.

A tremendous amount of feedback was solicited to guide the revision of USP Chapter <797>. The intention of the process was to make the Chapter a better means of ensuring the outcome that everyone agrees is the ultimate goal. That is that no patients are harmed by non-sterile and inaccurately prepared compounded sterile preparations.

USP <797> is still long, relatively complicated and very different from the historical standards used by most US institutional pharmacies for sterile compounding practice. This updated version of the guidelines is an attempt to become more practical and better define and describe what constitutes safe practice. As a result of the concerns raised following the initial publication of USP <797>, the revision features an increased focus on personnel issues, and a decreased focus on the more contentious engineering and system requirements from the original document. The intent is still to provide guidance for the procedural and practical requirements for safe compounding of sterile preparations.

References

1. *USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations*. United States Pharmacopeia. 2004.
<http://www.usp.org/USPNF/pf/generalChapter797.html>
2. *Revision Bulletin. <797> Pharmaceutical Compounding – Sterile Preparations*. The United States Pharmacopeial Convention. 2007.
3. Kastango E. “USP <797> Shalls and Shoulds,” Pharmacy OneSource Webinar, December 18, 2007.
<http://www.pharmacyonesource.com/images/ShallsandShoulds.pdf>
4. Kastango E. and B. Bradshaw. “USP Chapter 797: Establishing a practice standard for compounding sterile preparations in pharmacy,” *American Journal of Health-System Pharmacy*. Volume 61, Number 18. September 15, 2004.
5. Campanella P. and M. Robinson. “Patient Safety and Peak Performance,” *Pharmaceutical Formulation & Quality*. August 2006.
6. The ASHP Compounding Resource Center,
<http://www.ashp.org/SterileCpd/>
7. Kastango E. “Brutal Facts” from *Overview USP <797> and Control of Contamination* presentation, Compliance Tools and Aseptic Certification for USP <797>. STAR Center Training. 2007.
8. NIOSH Alert - “Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Health Care Settings”, March 25, 2004.
www.cdc.gov/niosh/docs/2004-165/