U.S. Pharmacopeia Chapters <797> and <800>

Overview

The U.S. Pharmacopeia (USP) is a compendium of drug information and standards for the safe preparation of drugs, including standards for compounded sterile preparations (CSPs). Although the U.S. Pharmacopeial Convention is a private organization with no actual legal or regulatory authority, many states have adopted pertinent USP standards into their requirements for pharmacies and other regulated entities. Depending on state law, these standards may apply to all persons who prepare CSPs or otherwise handle hazardous drugs, and all settings in which CSPs are prepared (e.g., hospital pharmacies, physicians' offices). This Questions & Answers document addresses questions related to relevant USP chapters.

I. Background

Q. What is the USP?

A. USP is a compendium of drug information and standards published by a nonprofit scientific organization that develops and disseminates public quality standards for medicines and other articles.

II. USP Chapter <797>

Q. What is USP <797>?

A. Chapter <797> of the USP, ***Pharmaceutical Compounding – Sterile Preparation***, provides guidelines, procedures, and compliance standards for compounded sterile preparations (CSPs), and establishes standards for the settings in which CSPs are prepared. The 2019 revision to USP <797> establishes requirements based on two risk classifications, Category 1 and Category 2, which are based primarily on the beyond-use date (BUD) assigned to the CSP, and the corresponding conditions under which each CSP should be prepared.

Q. What is the current version of USP <797>?

A. USP issued the current official version of Chapter <797> in 2008. USP published a revised Chapter <797> on June 1, 2019, which will become the official version on December 1, 2019.[1]
Unless otherwise specified, this Questions & Answers document refers to the 2019 revision of USP <797>. [For more information on the 2008 version of USP <797>, consult the Questions & Answers document from December 2018, document number cp-70398v1.]

[1] U.S. Pharmacopeia, *General Chapter <797> Pharmaceutical Compounding – Sterile Preparations*, SECOND SUPPLEMENT TO USP 42–NF 37, *available at* http://www.usp.org/compounding/general-chapter-797. Date Accessed, June 2, 2019 [hereinafter "USP <797>"].

Q. To whom does USP <797> apply?

A. USP intends for the standards set forth in Chapter <797> to apply to all persons who prepare CSPs and to all places where CSPs are prepared (e.g., hospital pharmacies, physicians' offices).[2] However, state regulators may choose to apply the USP standards only to certain professionals or to specified entities.

Q. Does USP define CSPs?

A. Yes, USP <797> defines sterile compounding broadly to include "combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication."[3] However, USP has narrowed the definition to exclude preparation of a drug in accordance with directions contained in approved labeling, provided certain conditions are satisfied. Under the current official Chapter <797>, which is in effect through November 30, 2019, drug manipulations prepared according to labeled instructions constitute the preparation of a CSP.

Q. Is preparation in accordance with approved drug labeling "compounding?"

A. In most cases, preparation of a drug or biologic according to labeled instructions will not constitute compounding under the 2019 revisions to USP <797>. Diluting, reconstituting, and repackaging are generally deemed to be "sterile compounding" under the revised Chapter, as is docking bag and vial systems (e.g., AddEASE™, ADD-Vantage™) for future, rather than immediate, administration.[4] However, the revised USP definition of compounding excludes mixing, diluting, reconstituting, and other manipulations performed in accordance with manufacturer's directions, provided that:

(1) The product is prepared as a single dose for an individual patient; and

(2) The labeled directions include information regarding the diluent, the resultant strength, the container closure system (e.g., syringe), and storage time.[5]

Q. Are there any other exceptions to preparing approved drugs in conformance with USP <797>?

A. Yes. Even if a drug or biologic is not prepared in accordance with approved labeling, or the manufacturer's directions do not provide the specificity required for the exemption from the definition of compounding, there is a separate exception for "immediate use." Under the 2019 revised Chapter <797>,

[2] USP <797> at 3.

[3] *Id*. at 2.

[4] *Id*. at 4.

[5] *Id*.

Immediate Use CSPs are considered compounded drug products, but need not adhere to <797> standards provided the following conditions are met:

- Written procedures are in place to minimize the potential for contamination and mix-ups, and aseptic processes are followed;
- Preparation is consistent with evidence-based information for physical and chemical compatibility (e.g., FDA-approved labeling);
- Preparation involves no more than three different sterile products;
- Any unused component from a single-dose container is discarded;
- Administration begins within four hours following the start of preparation; and
- The CSP is labeled with the amounts of all active ingredients and the exact four-hour time period, unless it administered by or in the presence of the individual who prepared it.[6]

Q. How does USP categorize the preparation of CSPs?

A. The current official Chapter <797>, which remains in effect through November 30, 2019, categorizes the preparation of CSPs according to three risk levels: low-; medium-; and high-risk CSPs, based on the potential for microbial, chemical, and physical contamination. The 2019 revision to Chapter <797> replaces the existing framework with a two-tier classification: Category 1 and Category 2.

- Category 1 CSPs are assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less when refrigerated.
- Category 2 CSPs may be assigned longer BUDs if they are prepared in accordance with additional safeguards. All CSPs must be compounded in a controlled workspace (e.g., hood), but only for Category 2 CSPs must the workspace be housed within a cleanroom.[7]

Q. How does USP regulate the preparation of CSPs?

A. Under USP <797>, all CSP preparation must occur in a workspace with positive air pressure certified to ISO 5. ISO classifications relate to the control of airflow and the amount of particulate matter in the air, and ISO 5 equates to less than 3,520 particulates per cubic meter.[8] Achieving this standard typically requires use of a laminar air-flow workbench (LAFW), or hood. The ISO 5 workspace must be housed in a "segregated compounding area," but only for Category 2 CSPs must this area feature a cleanroom, ISO 7 buffer room, and ISO 8 ante-room that segregates it from all unclassified areas.[9] In addition to providing standards for the physical environment, USP <797> specifies standards relating to personnel training, hygiene and garbing, cleaning and disinfecting, environmental monitoring, equipment and component certification, product sterilization, and release testing, among other aspects of compounding.

---

[6] *Id*.

[7] *Id*. at 8.

[8] *Id*.

[9] *Id*. at 8-9.

Q. What are key differences between Category 1 and Category 2 CSPs?

A. Category 1 CSPs may be assigned a BUD of no longer than 12 hours (at room temperature; 24 hours refrigerated). Category 2 CSPs may be assigned longer BUDs, up to 90 days in certain circumstances. Multi-dose products must be prepared as Category 2 CSPs. Many standards in the 2019 revision to Chapter <797> apply to all CSPs, such as personnel training, hygiene and garbing, cleaning and disinfecting, environmental monitoring, and product labeling, among other criteria. Several standards differ, however, including:

- Category 2 CSPs generally must pass a sterility test compliant with USP Chapter <71>; and
- Category 2 CSPs must pass an endotoxin test with limits established under USP Chapter <85>.

<797> Standards by CSP Category: A Sample‡		
Topic	**Category 1 CSP**	**Category 2 CSP**
BUD (room temp)	≤ 12 hours	≤ 45 days*
BUD (refrigerated)	≤ 24 hours	≤ 60 days*
BUD (frozen)	N/A	≤ 90 days*
Preparation site	ISO 5 classified workspace (e.g., LAFW)	
Placement of workspace	Unclassified segregated area	ISO classified area (e.g., clean, buffer, and ante rooms)
Sterility testing	Not required	USP <71> compliant sterility test
Endotoxin testing	Not required	USP <85> compliant endotoxin test
Stability testing	Generally not required	
Product labeling	Ingredients, quantity, strength, BUD, storage conditions, use direction	
Personnel training	Recertified annually	
Environmental monitoring	Every 6 months (air)	
Cleaning & disinfecting	Daily schedule	

‡ Not an exhaustive list of USP <797> standards
*Maximum BUDs, which depend on several conditions

III. USP Chapter <800>

Q. What is USP <800>?

A. USP Chapter <800>, ***Hazardous Drugs—Handling in Healthcare Settings***, describes practice and quality standards for receiving, handling, and administering hazardous drugs in clinical and other non-pharmacy settings.[10]

[10] U.S. Pharmacopeia, *General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings,* USP 42—NF 37 at 1, *available at* https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare. Date Accessed, June 2, 2019 [hereinafter "USP <800>"].

Q. What is a hazardous drug?

A. A **hazardous drug** is any drug identified as hazardous or potentially hazardous by the National Institute for Occupational Safety and Health (NIOSH) on the basis of six criteria:

- Carcinogenicity;
- Teratogenicity or developmental toxicity;
- Reproductive toxicity in humans;
- Organ toxicity at low doses in humans or animals;
- Genotoxicity; or,
- New drugs that mimic existing hazardous drugs in structure or toxicity.[11]

Antineoplastic drugs are considered hazardous, as are dozens of non-antineoplastic drugs that meet one of more of the NIOSH criteria. The current NIOSH list is available here.[12]

Q. What is the status of USP <800>?

A. Chapter <800> was first published on February 1, 2016, with several subsequent revisions, and will become effective on December 1, 2019.[13]

Q. What does USP <800> generally require for health care settings including physician offices?

A. In general, USP <800> specifies safeguards for all health care personnel handling hazardous drugs in all health care settings, which are either required or recommended. These protocols relate to facility and engineering controls, receiving and storage, personnel protective equipment and bodily coverage, personnel training, dispensing and administration, cleaning and disinfecting, deactivating and decontaminating, and documentation, among others.[14]

Q. Is medical surveillance of employees required by USP <800>?

A. No, **medical surveillance** is recommended but not required under USP <800>. USP <800> recommends that personnel who handle hazardous drugs be enrolled in a medical surveillance program that involves documentation of symptom complaints, physical assessment, and laboratory confirmation. Additional features of the program should include initial baseline assessment, medical record surveillance, periodic

[11] *Id*. at 1-2, 14.

[12] Dep't of Health & Human Servs., Nat'l Inst. for Occupational Safety and Health List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016, https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf. Date Accessed, June 21, 2019.

[13] U.S. Pharmacopeia, FAQs: <800> Hazardous Drugs—Handling in Healthcare Settings, https://www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings. Last Updated, May 31, 2019 [hereinafter "USP <800> FAQs"].

[14] *See generally* USP <800>.

screening, and an exit examination.[15] In order to safeguard employees' personal medical information, health care providers may choose to contract with an external service provider to perform these surveillance functions.[16]

IV. Application of USP Chapters to Drug Preparation Activities

Q. Are USP chapters legally binding?

A. USP standards are not self-executing and the USP has no role in enforcement. However, USP standards are incorporated into many state and federal statutes and regulations. Most states have adopted applicable USP chapters on the preparation of CSPs, including Chapters <797> and <800>, in whole or in part.

Q. Who enforces USP chapters?

A. State law governs the practice of pharmacy, and state governments determine whether to require compliance with USP standards. Some states may only require compliance with certain aspects of USP chapters, under limited circumstances, or in specified settings. States that have adopted applicable USP chapters typically direct their board of pharmacy to enforce compliance with those chapters. In states in which the board of pharmacy lacks jurisdiction over health care providers, other regulatory bodies, such as the board of medical examiners, may separately enforce compliance with USP. Penalties for violating state rules mandating compliance with USP chapters vary by state, but can include forfeiture of license, closure of facilities, and/or other fines and penalties.

In addition to state oversight, all compounded drugs are considered "new drugs" under the federal Food, Drug, and Cosmetic Act (FDCA) and are subject to oversight by the U.S. Food and Drug Administration (FDA).[17] In guidance, FDA states that compounded preparations made by a licensed pharmacist or physician qualify for an exemption from the new drug requirements only if they are compounded in compliance with the USP chapters on pharmacy compounding.[18]

Q. What is the status of state adoption of the USP chapters on compounding?

A. Most states have adopted part or all of USP <797>.[19] In some instances, such as Tennessee and Iowa, state laws or regulations incorporate USP <797> by cross-reference. In other states, such as New Jersey, excerpts from the Chapter are copied into the regulatory code, sometimes with modifications.

---

[15] *Id*. at 12.

[16] *See* USP <800> FAQs.

[17] *See* 21 U.S.C. § 353a.

[18] Food & Drug Admin., Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry, at 3 (Jun. 2016, rev. 2), *available at* https://www.fda.gov/media/94393/download.

[19] Pew Charitable Trusts, State Oversight of Drug Compounding (Feb. 2018), *available at* https://www.pewtrusts.org/en/research-and-analysis/reports/2018/02/state-oversight-of-drug-compounding.

Because USP <800> does not take effect until December 1, 2019, states have not adopted the Chapter by cross-reference. However, several states, such as Massachusetts and New Mexico, adopt all "required" compendial USP Chapters by cross-reference. In these states, USP <800> might therefore be considered mandatory beginning December 1, 2019. Several other states, such as California, have adopted or begun developing regulations modeled partly or entirely on USP <800> to regulate the safe handling of hazardous drugs in health care settings.

Q. Who decides what drug preparation activities are considered "compounding?"

A. Even if a state has adopted the USP chapters on compounding in their entirety, it does not necessarily mean that the state applies USP's definition of what constitutes a CSP. Many state pharmacy codes or board of pharmacy regulations provide their own definition of compounding. In some instances, these states exclude certain activities from the definition of compounding, such as the preparation of drugs in accordance with a manufacturer's approved labeling.[20] In other cases, the opposite may be true. In general, the USP compounding standards apply to whatever activities the state defines as compounding.

Q. Will states immediately implement the 2019 revision of USP <797> and new definition of compounding?

A. Not necessarily in all cases. In states with laws or regulations that cross-reference USP <797> or all applicable compendial chapters, the presumption is that these jurisdictions will follow whichever version is official. Thus, these states' requirements will incorporate the 2019 revision of USP <797> on December 1, 2019. In states that have manually incorporated USP standards into their regulations, such as by integrating part or all of the text of the current Chapter <797>, the presumption is that these regulations will not incorporate the new official USP <797> unless or until there is an affirmative act by the state to do so.

V. Resources

Q. Where can additional information be found?

A. All compendial chapters on drug compounding are available from the U.S. Pharmacopeial Convention for free (with registration) here.

[20] *E.g.,* N.H. Rev. Stat. Ann. § 318:1-III-a.