Virginia Board of Pharmacy

COMPLIANCE WITH USP STANDARDS FOR COMPOUNDING

§54.1-3410.2 of the Code of Virginia and Regulation 18VAC110-20-321 requires pharmacies performing sterile or non-sterile compounding to comply with USP Standards. USP standards for sterile and non-sterile compounding may be found in the current editions of the USP-NF. In accordance with 18VAC110-20-170, the Board requires a pharmacy to maintain references consistent with the pharmacy's scope of practice and with public safety.

USP Chapter 795 lists the requirements for non-sterile compounding including information about the compounding environment, equipment, stability criteria and beyond-use dating and records. USP Chapter 797 lists requirements for policies and procedures, training and evaluation of personnel performing sterile compounding, determining risk levels and the physical standards for the sterile compounding area. The Board expects that the requirements of Chapters 795 and 797 will be found in compliance at time of inspection. USP Chapter 800 describes practice and quality standards for handling hazardous drugs to promote patient safety, worker safety, and environmental protection. USP first published Chapter 800 in 2014. It was first published as an official standard in February 2016 with a delayed implementation date of July 1, 2018. On September 27, 2017, USP published a notification of intent to revise the effective date of chapter <800> to December 1, 2019. While full compliance with Chapter 800 is encouraged, only those requirements related to compounding are legally required.

The terms "annually" and "semiannually" as used in USP Chapters 795 and 797 are defined to mean every 12 months and every 6 months, respectively. Records associated with annual and semiannual requirements shall be maintained in accordance with USP standards. Such records may be maintained as an electronic image that provides an exact image of the document that is clearly legible provided such electronic image is retrievable and made available at the time of inspection or audit by the Board or an authorized agent.

1. ***Where may information regarding USP-NF standards for compounding be located?***

   A subscription to the current version of "USP on Compounding: A Guide for the Compounding Practitioner" may be purchased at http://www.usp.org/store/products-services/usp-compounding This guide provides access to all compounding-related General Chapters from the USP-NF and is updated with the release of each new USP-NF edition and supplement.

2. ***Does the law require compliance only with Chapter <797>?***

   No, the law requires compliance with all applicable chapters within USP-NF. Regarding sterile compounding, pharmacists should pay particularly close attention to General Chapters: <1>

Injections, <71> Sterility Testing, <85> Bacterial Endotoxin Testing, and <797> Pharmaceutical Compounding- Sterile Preparations.

3. ***Are there specific educational and training requirements regarding personnel?***

Yes. In USP chapter <797>, compounding personnel are required to be adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties: perform aseptic hand cleansing and disinfection of nonsterile compounding surfaces; select and apropriately don protective garb; maintain or achieve sterility of compounded sterile products in ISO class 5 environments; identify, weigh, and measure ingredients; manipulate sterile products aseptically; sterilize high-risk level compounded sterile products and label; and, inspect the quality of compounded sterile products. Personnel must also sucessfully complete a site-specific training program as required in Regulation 18VAC110-20-111.

3. In the absence of sterility testing, what beyond use dates (BUDs) must be used?

When sterility testing has not been performed, the assigned BUD must not exceed the following allowances:

	Controlled Room Temperature	Refrigerator	Freezer
Low-risk	48 hours	14 days	45 days
Medium-risk	30 hours	9 days	45 days
High-risk	24 hours	3 days	45 days

4. ***What BUD must be assigned to a single dose vial used in preparing a compounded sterile product?***

- If the single dose vial is punctured outside of an ISO Class 5 environment, the assigned BUD shall not exceed 1 hour, unless specified otherwise by the manufacturer;
- If the single dose vial is puntured within and stored within an ISO Class 5 environment, the assigned BUD shall not exceed 6 hours;
- A puntured single dose vial that is removed from the ISO Class 5 environment such as for final verification purposes shall not exceed 1 hour from being removed from the ISO Class 5 environment or the originally assigned BUD of 6 hours within the ISO Class 5 environment, whichever is shorter (reference the Center For Disease Control (CDC) and USP Appendix);
- A closed system transfer device (CSTD) should not be used to extend the BUD of a single-dose vial to exceed the 1 hour BUD when punctured outside of an ISO Class 5 environment or the 6 hour BUD when punctured within and not removed from an ISO Class 5 environment.

5. ***Is it appropriate to assign a BUD of 90 days in the absence of sterility testing if there is literature indicating the stability of the drug is assured for 90 days?***

No, it is inappropriate and a violation of law to assign a BUD which exceeds the USP default BUDs in the absence of sterility testing. Drug stability should not be confused with drug sterility.

6. How may stability information be taken into consideration when assigning a BUD?

Stability information for multiple drugs may be considered when combining the drugs in a compound, assuming the shortest BUD is used to assign stability to the compound. Peer-review or reference source literature shall be consulted and the professional judgement of the pharmacist exercised when assigning the BUD of a compound containing multiple drugs. Any extended BUD must also comply with the applicable USP Chapter <795> or <797>.

7. What concepts, at a minimum, should be taken into consideration when determining drug stability?

Pharmacists should use professional judgment to determine appropriate references of chemical stability information and note that sterile and non-sterile drug stability is formulation specific. Existing stability information may only be used when the compound has been prepared using the same formulation (USP-NF equivalent ingredients) as used in either at least one peer-reviewed article or other reliable reference source. The process used by the pharmacist to determine drug stability should be well-documented and maintained for inspector review.

Additionally, stability may be estimated for an aqueous or non-aqueous compound under the following conditions:

- Stability information exists in peer-reviewed articles or reference sources indicating stability at a low concentration and high concentration and therefore, stability for concentrations in-between could be estimated;
- Stability of the drug is not concentration-dependent; and,
- The drug is compounded using the same formulation (USP-NF equivalent ingredients) as used in the peer-reviewed articles or reference sources.

8. *What is skip lot testing and may skip lot testing be used to perform sterility testing of compounded sterile products?*

Skip lot testing is a process that only tests a fraction of the drugs compounded. It is NOT appropriate for sterility testing. It may only be used for ensuring consistency and drug strength (potency). Because skip lot testing is complex and requires a robust program, it may not be possible for a pharmacy to properly implement. Information regarding skip lot testing may be accessed at http://www.itl.nist.gov/div898/handbook/pmc/section2/pmc27.htm

9. How may a hospital pharmacy "batch-producing" limited quantity of CSPs for IN-HOUSE use extend the BUD past the default dating in Chapter <797>?

EACH BATCH must undergo sterility testing in accordance with USP Chapter <71> in order to extend the BUD past the default dating in Chapter <797> and the appropriate documentation to support an extended BUD must be kept on file for presentation upon inspection.

10. Do batches less than 25 require sterility testing to be performed?

No, however, the batches may not be assigned a BUD which exceeds the default BUDs in USP Chapter <797>. The chapter requires sterility testing according to USP <71> before CSPs are dispensed or administered when:

- high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampuls, bags, syringes, vials) or
- in multiple-dose vials (MDVs) for administration to multiple patients or
- CSPs that are exposed longer than 12 hours at 2 to 8 C and longer than 6 hours at warmer than 8 C before they are sterilized.

11. How often must the primary engineering control, e.g., laminar airflow workbench and secondary engineering control, e.g., ante and buffer rooms be certified?

Certification of the primary and secondary engineering controls shall be performed no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. The certification must be performed no later than *the last day of the sixth month*, following the previous certification.
*****Note-** this guidance reflects a change to Major Deficiencies 22 and 23 in Guidance Document 110-9 which was amended at the March 2013 full board meeting.

12. Must compounding personnel who work in multiple pharmacies, to include pharmacy interns on rotations, pass a media-fill test at each pharmacy where they will prepare CSPs?

Yes, all compounding personnel working in multiple pharmacies, to include pharmacy interns on rotations, must pass a media-fill test at each pharmacy prior to performing sterile compounding.

13. How often must media-fill testing be performed?

Media-fill testing of all compounding personnel shall be performed initially prior to beginning sterile compounding and at least annually thereafter for low and medium-risk compounding, and semiannually for high-risk level compounding. *****Note -** the terms "annually" and "semi-annually" are defined within this guidance document to mean every 12 months and every 6 months, respectively. Annual media-fill testing must be performed no later than the last day of the twelfth month from the date the previous media-fill test was initiated. Semiannual media-fill testing must be performed no later than the last day of the sixth month from the date the previous media-fill test was initiated.

14. If compounding personnel fail a media-fill test, may they continue preparing compounded sterile products?

No, compounding personnel who failed a media-fill test may not be allowed to prepare compounded sterile products (low, medium, or high-risk) prior to retraining and receipt of a

passing media-fill test. *****Note-** this guidance reflects a change to Major Deficiency 26a in Guidance Document 110-9 which was amended at the March 2013 full board meeting.

15. Because batches less than 25 do not require sterility testing to be performed, may the CSP which may have been autoclaved be assigned an extended BUD based on stability data?

Per USP, sterility testing is not required for autoclaved CSP prepared in batches less than 25 and if the storage times for high-risk CSPs are not exceeded. If the storage times of high-risk CSPs are exceeded, sterility testing is required. Once sterility testing is successfully completed, a longer BUD may be assigned based on the criteria described in the chapter (e.g., based on stability studies).

16. Does USP-NF address how long a CSP may hang for infusion?

No, USP-NF does not address how long a CSP may hang for infusion. Refer to facility policy on this issue. USP-NF, however, does require the administration of CSPs to begin prior to the assigned BUD.

17. May a pharmacist repackage Avastin for office administration not pursuant to a patient-specific prescription?

No. While pharmacists may repackage a drug product when dispensing a drug pursuant to patient-specific prescription, a pharmacist may not repackage a drug for another entity. The board has historically interpreted the repackaging of a drug for distribution purposes as an act restricted to a manufacturer, defined in Va Code §54.1-3401. This interpretation appears consistent with recent warning letters from the US Food and Drug Administration (FDA). The allowance in Va Code §54.1-3401 for a pharmacist to provide compounded drugs to a physician for office administration does not apply. Repackaging Avastin does not constitute compounding as it does not involve the mixing of two of more substances.

18. May a pharmacist repackage Avastin pursuant to a patient-specific prescription?

Yes, a pharmacist may repackage a drug as part of the dispensing process pursuant to a patient-specific prescription.

19. What concepts, at a minimum, should be taken into consideration when performing sterility testing of CSPs?

- Maintain a written policy and procedure manual clearly identifying sterility testing procedures used by the pharmacy and processes for assigning BUDs.
- Prior to using an outside testing company to perform sterility testing, evaluate the company to determine if it performs testing in full compliance with USP Chapter <71>. This may be done by reviewing 483 reports issued by the FDA to the testing company and which may be available on the FDA website. Alternatively, request copies of the 483 reports directly from the testing company. The observed deficiencies noted on the 483 reports will assist the pharmacist in evaluating the testing company's level of compliance. Also, request written documentation from the testing company which

explains the sterility testing processes used and how it complies with USP Chapter <71> in its totality. This documentation should contain, at a minimum, specific details regarding the method of testing, method suitability associated with each sterility testing process to ensure the drug being tested will not interfere with the test, identification of testing method (membrane filtration is the preferred method of testing), two growth media, and number of days of incubation. Have this documentation readily available for inspector review.

- When performing sterility testing in-house, document in the written policy and procedure manual, at a minimum, specific details regarding the method of testing, method suitability associated with each sterility testing process to ensure the drug being tested will not interfere with the test, identification of two growth media, and number of days of incubation.
- Vendors providing products for in-house testing must describe all conditions and limitations to their testing products. Ensure the appropriate filtration volume and sample size is being tested.
- When determining an appropriate sterility testing process, note that the preferred method per USP is membrane filtration. The Board strongly recommends that written documentation justifying the use of direct inoculation be available for inspection
- Ensure the sterility testing incorporates two media for growth.
- The sample size used for testing must comply with USP Chapter <71>, tables 2 and 3.
- Maintain robust recordkeeping, e.g., chart the dates, temperatures, growth associated with the two media incubations, and employee signatures. Do not simply indicate "no growth" without indicating which growth media was used and the number of days incubated.

20. Must sterility testing be performed on all batches of CSPs?

Sterility testing is not required of low and medium-risk level batched CSPs if the BUDs do not exceed the default BUDs found in USP Chapter <797>. If the low or medium-risk level batched CSP is to be assigned an extended BUD, then sterility testing must be performed. Sterility testing must always be performed of high-risk level CSPs in batches greater than 25. See Response to Q#7

21. What is the definition of a "batch"?

USP does not currently define the term "batch". In 21CFR210.3, FDA defines "batch" to mean a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

22. How should a dilution or stock bag for pediatrics be treated?

USP does not currently address this issue, however, the Board advises that the dilution or stock bag should be treated as a single dose container/vial with the remains being discarded within 6 hours of compounding.

23. What are some important considerations regarding membrane filtration and filter integrity testing, aka bubble point testing?

Membrane filtration may be accomplished using a 0.22 micron filter. It is important to note that sterility testing cannot be accomplished by simply performing membrane filtration. Filter integrity testing, also known as a bubble point test, must be performed to verify that the filter was successful in its application. Smaller disc filters may have filter volume limitations which must be taken into consideration. Because it is known that filtration has not always been successful in preventing the passing through of microorganisms, pharmacists must always build quality processes into their sterile compounding to minimize the risk and the introduction of contamination.

24. What are some best practices for performing required media fill testing and gloved fingertip sampling?

Persons performing high-risk level CSPs must successfully pass media-fill testing prior to initially compounding sterile products and semi-annually (within 6 months of the last testing). Persons performing low or medium-risk level CSPs must successfully pass media-fill testing prior to initially compounding sterile products and annually (within 12 months of the last testing). Persons who fail a media-fill test may not perform sterile compounding prior to retraining and receipt of a passing media-fill test.

Media fill testing should mimic the most challenging sterile compounding activity performed by those persons. Robust documentation regarding the media-fill testing process and individual testing must be maintained which documents, at a minimum, the media growth to include lot and expiration date, number of days in incubator, incubator temperature, name of person being tested, dates testing performed, results of growth. Blanks in the form used to document media fill testing should be evaluated and corrected to ensure an accurate testing process.

Glove finger tip testing verifies the person can properly don gloves without contaminating them and is routinely disinfecting them. To improve compliance with required testing, pharmacists should consider performing media-fill testing and glove finger tip testing around the same time that environments are being certified. Employees who use isolators must also perform gloved fingertip sampling by donning sterile gloves within the ISO Class 5 main chamber and testing those gloves.

25. How often must air and surface sampling be performed?

USP requires air sampling to be performed at least every 6 months. Air sampling shall be conducted using volumetric air sampling equipment and the appropriate media (bacterial sampling for all risk levels and fungi sampling for high-risk level compounding operations). USP requires surface sampling to be performed “periodically”. The Board advises that surface sampling should be performed at least quarterly. It may be performed by pharmacy personnel or outsourced.

26. What minimally should be taken into consideration when having primary and secondary engineering controls certified?

Certification and testing of primary (LAFWs, BSCs, CAIs and CACIs) and secondary engineering controls (buffer and ante areas) shall be performed by a qualified individual no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. Certification procedures such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006) shall be used. Pharmacists shall request written documentation from the certifying company explaining how the company's certifying processes fully comply with these standards. This shall include written acknowledgement that certification testing will be performed under dynamic conditions. Certifications issued shall specifically indicate the ISO standard for each primary and secondary engineering control and not simply indicate "passed".

27. What minimally should be taken into consideration when compounding multidose vials?

Currently USP Chapter <797> does not contain specific requirements for compounding multiple-dose containers, such as the need for a preservative, nor requirements for testing, labeling, and container closures for compounded multiple-dose containers. Chapter <797> references Chapter <51> for informational purposes as the source of the 28-day BUD after initially entering or opening a multiple-dose container, unless otherwise specified by the manufacturer.

28. What BUDs are recommended for non-sterile compounded products?

USP Chapter <795> makes the following recommendations for assigned BUDs of non-sterile compounded products:

Nonaqueous formulations - The BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
Water-Containing Oral Formulations - The BUD is not later than 14 days when stored at controlled cold temperatures.
Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations – The BUD is not later than 30 days.

These maximum BUDs are recommended for nonsterile compounded drug preparations in the absence of stability information that is applicable to a specific drug or preparation. The BUD shall not be later than the expiration date on the container of any component.

29. May a non-sterile compounded product be assigned an extended BUD beyond the recommendations in USP Chapter <795>?

The Board advises that non-sterile compounded products should not be assigned an extended BUD unless the pharmacist maintains full documentation to justify the appropriateness of the extended BUD.

30. Under what conditions may a glove box be used to perform sterile compounding?

The glove box, referred to as an isolator (CAI/CACI) in Chapter <797>, must be placed in an ISO 7 buffer area UNLESS it meets all of the following conditions listed in USP Chapter 797:

- The isolator shall provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
- Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO Class 5 levels during compounding operations.
- Not more than 3520 particles (0.5 µm and larger) per m^3 shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.[8]

It is incumbent upon the compounding personnel to obtain documentation from the manufacturer that the CAI/CACI will meet this standard when located in environments where the background particle counts exceed ISO Class 8 for 0.5-µm and larger particles. When isolators are used for sterile compounding, the recovery time to achieve ISO Class 5 air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.

If the primary engineering control (PEC) is a CAI or CACI that does not meet the requirements above or is a LAFW or BSC that cannot be located within an ISO Class 7 buffer area, then only low-risk level nonhazardous and radiopharmaceutical CSPs pursuant to a physician order for a specific patient may be prepared, and administration of the CSP shall commence within 12 hours of preparation or as recommended in the manufacturer's package insert, whichever is less.

The weighing of chemicals must occur in at least ISO Class 8 conditions. An isolator used to compound hazardous drugs (with exception of "low volume") must be located in a separate negative pressure room and exhausted outside.

31. May hazardous sterile products be compounded in the same hood as non-hazardous sterile drugs?

No. Hazardous sterile products may not be compounded in the same hood as non-hazardous CSPs.

32. Under what conditions may hazardous drugs be compounded in a cleanroom with positive air pressure?

USP allows a "low volume" of hazardous CSPs to be compounded in a cleanroom with positive air pressure, however, USP does not currently define the term "low volume". The "low volume" hazardous CSPs must be compounded under two tiers of containment, the isolator or biologic safety cabinet and closed system transfer device.

33. Must a compounding pharmacy using Schedule II powders comply with the perpetual inventory requirements of Regulation 18VAC110-20-240?

Yes.

34. Must bladder irrigation fluids and irrigations for wounds be prepared in a sterile manner in compliance with USP-NF requirements?

Yes.

35. In addition to bladder irrigation and irrigations for wounds, what other types of drugs must be prepared in a sterile manner in compliance with USP-NF requirements?

USP Chapter <797> states that for the purposes of the chapter, a compounded sterile product includes any of the following: compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations for the lungs, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants. Note: Nasal sprays and irrigations for the nasal passages may be prepared as non-sterile compounds.

36. May a pharmacist provide a compounded drug to another pharmacy or veterinarian who will then dispense the drug to his client?

No. Va Code §54.1-3410.2 indicates pharmacists shall not distribute compounded drug products for subsequent distribution or sale to other persons or to commercial entities, including distribution to pharmacies or other entities under common ownership or control with the facility in which such compounding takes place.

VA Code §54.1-3410.2 does authorize pharmacists to provide compounded drug to practitioners of medicine, osteopathy, podiatry, dentistry, or veterinary medicine to administer to their patients in the course of their professional practice, either personally or under their direct and immediate supervision. The compounded drug must be labeled with (i) the statement "For Administering in Prescriber Practice Location Only"; (ii) the name and strength of the compounded medication or list of the active ingredients and strengths; (iii) the facility's control number; (iv) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; and (v) quantity.

37. May a prescriber or patient obtain a compounded sterile product from an out-of-state pharmacy that is not registered by the Virginia Board of Pharmacy as a nonresident pharmacy?

No, only nonresident pharmacies registered by the Virginia Board of Pharmacy may ship compounded sterile products into Virginia. Verification of registration may be determined at https://secure01.virginiainteractive.org/dhp/cgi-bin/search_publicdb.cgi by searching the business name and choosing the occupation of “non-resident pharmacy”.

38. What risk-level is associated with repackaging an undiluted multi-dose vial?

The repackaging of an undiluted multi-dose vial, e.g., insulin, into multiple syringes is a medium-risk level manipulation when puncturing the vial more than 3 times. Note: this guidance addresses repackaging, not administration.

39. May a microbiological method alternative to compendial methods be used?

Regarding sterility testing, USP Chapter <797> states, "The *Membrane Filtration* method is the method of choice where feasible (e.g., components are compatible with the membrane). A method not described in the *USP* may be used if verification results demonstrate that the alternative is at least as effective and reliable as the *USP Membrane Filtration* method or the *USP Direct Inoculation of the Culture Medium* method where the *Membrane Filtration* method is not feasible." Additionally, USP General Chapter <1223> "provides guidance on the selection, evaluation, and use of microbiological methods as alternatives to compendial methods. To properly implement alternative methods, one must consider a number of important issues before selecting the analytical technology and qualifying that method with the actual product. These issues include, but are not limited to, identification of suitable alternative methodology, development of user specifications for equipment selection, demonstration of the applicability of the method as a replacement for a standard compendial method, and qualification of the method in the laboratory…..*General Notices and Requirements* in the *USP* states, "Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances." General Chapter <1223> also makes reference to 21 CFR Part 211.194 stating, "This subsection of the regulations also recognizes the legal basis of *USP* and the *National Formulary (NF)* standards and makes it clear that it is the responsibility of the user to validate methods or procedures that differ from those standardized in the compendia." Refer to *USP* for additional guidance.

40. What is the status of the General Chapter <800> and when will General Chapter <800> become official?

USP announced the **intent to postpone** the official date of General Chapter <800> *Hazardous Drugs – Handling in Healthcare Settings*. Per USP, the intent of this postponement is to align the official date of General Chapter <800> with the official date of the next revision of General Chapter <797> *Pharmaceutical Compounding — Sterile Preparations,* to provide a unified approach to quality compounding. The next revision to General Chapter <797> is anticipated to be published in the *Pharmacopeial Forum* 44(5) September/October 2018 for a second round of public comment. Both USP General Chapter <797> and USP General Chapter <800> are anticipated to become official on December 1, 2019. Sections of the revised <797> may have longer implementation dates that will allow time for adoption of the standard.

41. What does 'official date' mean?

Per USP, the USP "official date" indicates the date by which affected users are expected to meet the requirements of a particular standard. Ensuring compliance with the requirements of these

standards is the responsibility of regulators such as the FDA, states, and other government authorities. USP has no role in enforcement.

42. Other than the change to the official date, are there other expected substantive changes to USP General Chapter?

Per USP, no. The only part of USP General Chapter <800> that is expected to change is the official date, which is expected to be changed to December 1, 2019.

43. Is <800> enforceable in Virginia?

Section §54.1-3410.2 (E) of the Drug Control Act requires compliance with USP-NF standards for compounding. When the chapters become official in December 2019, the law will require compliance with the requirements in Chapter 800 that relate to compounding. Standards within Chapter 800 that do not relate to compounding will not be required under current law.

44. Does the December 1, 2019 official date of <800> impact my current or early adoption of the general chapter?

Per USP, no. USP encourages adoption and implementation of General Chapter <800> to help ensure a quality environment and protection of healthcare workers and patients when hazardous drugs are handled.

45. How do I adopt USP General Chapter <800> if sections are not harmonized with USP General Chapter <797>?

Per USP, two sections that are not harmonized between the two chapters are: Segregated Compounding Area and 'Low volume' hazardous drug compounding. Below please find guidance on how to adopt USP <800> until the revised USP <797> is published.

Segregated Compounding Area (SCA)

- USP <797> only allows low-risk level nonhazardous and radiopharmaceutical Compounded Sterile Preparations (CSPs) with 12 hour or less beyond-use date (BUD) to be prepared in an unclassified segregated compounding area (SCA).
- USP <800> allows low and medium risk level hazardous drug CSPs to be prepared in an unclassified containment segregated compounding area (C-SCA). The C-SCA is required to have fixed walls, be externally vented with 30 ACPH and have a negative pressure between 0.01 and 0.03 inches of water column relative to the adjacent areas.
- Note the differences in terminology and requirements in the SCA in USP <797> and C-SCA in <800>.
    - For early adoption of <800>, low- and medium- risk level HDs may be prepared in a C-SCA provided it meets the requirements in the chapter and the CSP is assigned a BUD of 12 hours or less.
    - For facilities that have not yet adopted <800>, the standards in USP <797> would apply. Only low-risk level nonhazardous and radiopharmaceutical CSPs with 12 hour or less BUD may be prepared in a SCA.

"Low volume" hazardous drug compounding

- USP <797> allows facilities that prepare a "low volume" of HDs to compound these drugs in a non-negative pressure room if "two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room)" are used.
- USP <800> requires facilities that prepare HDs to have a containment secondary engineering control (C-SEC) that is externally vented, physically separated, have appropriate air exchange, and have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas.
- For early adoption of <800>, HDs must be prepared in a C-SEC meeting the requirements in the chapter.
- For facilities that have not yet adopted <800>, the standards in <797> would apply. Facilities preparing a low volume of HDs may continue to compound these CSPs outside a negative pressure room if two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room)" are used.

46. What are the hazardous drugs (HD) that USP Chapter <800> oversees?

Refer to the most current National Institute for Occupational Safety and Health (NIOSH) list at www.cdc.gov. Note: Chapter <800> defines HDs are those on the NIOSH list, not the EPA hazardous materials list. Some drugs on the Environmental Protection Agency (EPA) list may not be on the NIOSH list, e.g., epinephrine.

47. In general, how are drugs grouped within the NIOSH list?

Hazardous drugs are categorized into three tables:

- Antineoplastic drugs, e.g., cisplatin, methotrexate
- Non-antineoplastic drugs, e.g., carbamazepine, estrogen/progesterone combinations
- Non-antineoplastic drugs that have adverse reproductive effects, e.g., temazepam, warfarin

48. What drugs MUST comply with all USP Chapter <800> containment requirements?

Drugs on the NIOSH list that will be involved in compounding must follow the requirements in this chapter include:

- Any HD active pharmaceutical ingredient (API) on any of the three tables, and
- Any antineoplastic requiring manipulation other than counting or repackaging.

49. What drugs do NOT have to comply with all the USP Chapter <800> containment requirements?

Drugs on the NIOSH list that do not have to follow all the containment requirements of this chapter if an assessment of risk is performed and implemented include:

- Final dosage forms of compounded HD preparations and conventionally manufactured HD products, including antineoplastic dosage forms, that do not require any further manipulation other than counting or repackaging (unless required by the manufacturer)

50. How should a pharmacist determine how to comply with 800?

Pharmacists should ask themselves the following questions, at a minimum:

- What drugs do I receive, store, dispense that are deemed hazardous pursuant to the NIOSH list and are used in compounding products?
- Must those drugs comply with all containment requirements or do some qualify for performing an assessment of risk?
- What changes will I need to make to my facility in order to comply with Chapter <800>?
- What personnel training is needed to meet compliance?
- What cleaning processes must be implemented or changed to meet compliance?
- What activities do I perform with these hazardous drugs, e.g., compounding, administration, etc.?

51. If it is determined that the pharmacy stocks HDs, what options exist for the pharmacy?

The pharmacy may treat all dosage forms of all HDs that are used in compounding products the same and follow all containment requirements in Chapter <800> or it may perform an assessment of risk to identify and use alternative containment strategies and/or work practices for specific dosage forms of HDs that are not antineoplastic agents or not API.

52. What hazardous drugs may be considered during an assessment of risk?

- Antineoplastics that only need to be counted or packaged
- Non-antineoplastics
- Reproductive-only hazards

53. What should be considered, at a minimum, during an assessment of risk?

- Type of HD, dosage form, risk of exposure, packaging, manipulation to be performed
- Alternative containment strategies and/or work practices should be documented
- The assessment of risk shall be reviewed every 12 months and documented.

54. What minimal questions and/or information will an inspector for the Board of Pharmacy be asking during an inspection? Note: Refer to page 1 regarding enforcement of Chapter <800>.

- Does the pharmacy perform sterile or non-sterile compounding?
- Does the pharmacy stock HDs that are used in compounding products? The list of HDs that are used in compounding products that the pharmacy stocks must be provided for inspector review.

- Are all HDs that are used in compounding products contained in a manner consistent with USP Chapter <800> or was an assessment of risk performed to identify and use alternative containment strategies and/or work practices for specific dosage forms of HDs that are not antineoplastic agents or not API. The assessment of risk must be provided for inspector review.
- Who is the 'designated person' for the pharmacy who is responsible for the continuing to evaluate the fundamental practices and precautions for handling HDs?
- Documentation of required training.
- Appropriate personnel equipment.
- Appropriate engineering controls.
- Standard operating procedures for safe handling of HDs that are used in compounding products for all situations in which the HDs are used throughout the facility.

55. What does USP Chapter <800> list as the general engineering control requirements for performing non-sterile HD compounding?

Table 2. Engineering Controls for Nonsterile HD Compounding

Containment Primary Engineering Control (C-PEC)	Containment Secondary Engineering Control (C-SEC)
• Externally vented (preferred) or redundant–HEPA filtered in series • Examples: CVE, Class I or II BSC, CACI	• Externally vented • 12 air changes per hour (ACPH) • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas • Fixed walls

56. What does USP Chapter <800> list as the general engineering control requirements for performing sterile HD compounding?

Table 3. Engineering Controls for Sterile HD Compounding

Configuration	C-PEC	C-SEC	Maximum BUD
ISO Class 7 buffer room with an ISO Class 7 ante-room	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 30 air changes per hour-ACPH • Negative pressure between 0.01 and 0.03 inches of water colum relative to adjacent areas	As described in ‹797
Unclassified C-SCA	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches of water column relative to adjacent areas	As described in ‹797› for CSPs prepared in a segregated compounding area

57. Where may a list of recommended personal protective equipment by type of drug formulation and engineering controls for working with HDs in a healthcare setting be found?

Table 5 of the NIOSH list.

58. Regarding the Segregated Compounding Area (SCA) definition, Chapter <797> states an SCA may be a designated space, room or demarcated area. Chapter <800> states SCA requires fixed walls and removes the "space or demarcated area". Please clarify the Board's expectations on this issue.

Per USP, please note the differences in terminology in <797> and <800>. General Chapter <800> specifies that this is a containment segregated compounding area (C-SCA). For hazardous drug compounding, the C-SCA must have fixed walls. For nonhazardous drug sterile compounding, the SCA may be in an unclassified area (and not necessarily have fixed walls). For the C-SCA, fixed are also necessary to maintain negative pressure.

59. ***Regarding low-risk level compounding with 12 hour or less beyond use dating (hood within a non-ISO Class 7 area), Chapter <797> states that this configuration does not allow hazardous compounding. Chapter <800> states that it is allowed, but only low and medium risk HDs may be prepared and beyond use dating (BUD) that cannot exceed <797> for being prepared in a SCA. Please clarify the Board's understanding on this issue.***

Per USP, the intent of <800> is to apply a 12-hour or less BUD to low- and medium- risk level compounded sterile products prepared in a containment segregated compounding area (C-SCA). USP is aware of the conflict and is in the process of revising <797> to align with the requirements in <800>.

60. Chapter <797> also allows for placement of an isolator outside of an ISO Class 7 buffer room with meeting of specification requirements and allowance of full BUD. Chapter <800> states if the containment primary engineering control (C-PEC) is placed in a containment segregated compounding area (C-SCA), then the BUD of all compounded sterile products must be limited as described in <797>. Again, Chapter <797> states that this configuration does not allow hazardous compounding. Please clarify the Board's understanding on this issue.

Per USP, the intent of <800> is to apply a 12-hour or less BUD to low- and medium- risk level compounded sterile products prepared in a C-SCA. USP is aware of the conflict and is in the process of revising <797> to align with the requirements in <800>.

61. With the implementation of Chapter <800>, will USP continue to allow compounding aseptic isolators (CAI) placed outside of a classified area to be used to compound sterile products and assigned a full BUD as authorized in <797>?

Yes, Chapter <797> still allows for a compounding aseptic isolator (CAI) placed outside of a classified area to be used to compound sterile products and assigned the full storage period BUD provided the conditions specified in the chapter are met. Note, for compounding sterile hazardous drugs, the compounding aseptic containment isolator (CACI) must be placed in a negative pressure containment secondary engineering control (C-SEC) with adequate air changes per hour (ACPH).

62. Does Chapter <800> recommend wipe sampling and medical surveillance?

Yes, Chapter <800> states that "environmental wipe sampling for HD surface residue should be performed routinely." Medical surveillance is also a recommendation of the chapter. The chapter states that "healthcare workers who handle HDs as a regular part of their job assignment should be enrolled in a medical surveillance program." Note, both of these issues are recommendations of Chapter <800> and not a requirement.

63. USP <797> and USP <800> recommend the use of closed-system drug-transfer devices (CSTD). Is there guidance on the proper evaluation of the available technologies?

USP currently recommends the use of CSTDs for compounding HDs. Per USP, it is not a requirement as there is no published universal performance standard for evaluation of CSTD containment. NIOSH is currently working on developing such a protocol.

64. Is a line of demarcation for doffing personal protective equipment (PPE) required for all hazardous containment secondary engineering controls?

USP <800> *requires* a doffing area if the negative-pressure hazardous drug (HD) buffer room is entered through the positive-pressure non-hazardous drug buffer room. Additionally, it states a designated doffing area *should* be indicated within all containment secondary engineering controls (C-SEC). Other than the line of demarcation mentioned in section 5.3.2, General Chapter <800> does not specify where doffing should occur. However, this is entity dependent and should additionally follow garbing requirements in <797>.

65. USP <800>, within Section 5.3, indicates that an eyewash station and/or other emergency or safety precautions that meet applicable laws and regulations must be readily available. Are there applicable laws and regulations in Virginia regarding eyewash stations and/or other emergency or safety precautions?

The Board is not currently aware of laws and regulations in Virginia related to use of eyewash stations or other safety precautions related to this issue.

66. May a laminar airflow workbench (LAFW) or a compounding aseptic isolator (CAI) be used for compounding with an antineoplastic hazardous drug (HD)?

No.

67. Is it required to compound all sterile hazardous drugs within an externally vented containment primary engineering control (biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI))?

No, dosage forms of non-antineoplastic and reproductive risk hazardous drugs may be handled and compounded under an assessment of risk. If, however, bulk active pharmaceutical ingredients (API) of these drugs are used as starting ingredients, all of the containment requirements in <800> would apply. Refer to Box 1 within USP Chapter <800>.

68. What are the specifications required of a pass through chamber? Is it required be interlocking and HEPA filtered purged? Between what areas may these chambers be utilized?

General Chapter <800> defines a pass-through as "an enclosure with interlocking doors that is positioned between two spaces for the purpose of reducing particulate transfer while moving materials from one space to another. A pass-through serving negative-pressure rooms needs to be equipped with sealed doors. The chapter does not require the pass-through to be HEPA filter purged and does not limit where these pass-throughs may be placed. General Chapter <800> additionally states that refrigerator pass-throughs must not be used.

69. Chapter <800> states sterile and nonsterile HDs may be stored together, but HDs used for nonsterile compounding should not be stored in areas designated for sterile compounding to minimize traffic into the sterile compounding area. What is the intent of this statement?

The intent of prohibiting the storage of nonsterile compounding materials in sterile compounding areas is to minimize traffic flow into the sterile classified areas.

70. May bulk active pharmaceutical ingredients (API) used for sterile compounding be stored in the negative pressure C-SEC?

Yes. Refer also to USP's frequently asked question #16 found at http://www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings

71. Where must manipulation of non-sterile, non-antineoplastic and reproductive risk hazardous drugs (that are not bulk active pharmaceutical ingredients (API)) occur?

The location where manipulation occurs should follow an assessment of risk for non-antineoplastic and reproductive risk hazardous drugs (that are not bulk APIs). Facilities should determine their own strategies based on its assessment of risk.

72. Does Chapter <800> address whether scrubs that are worn within the hazardous compounding/storage area may be allowed to be taken home?

No. General Chapter <800> does not specify best practices for clothing under the gown. However, section 7.2 does require gowns to be disposable and shown to resist permeability by HDs.

73. What is the best practice for receiving hazardous drugs (HD)?

USP <800>, within Section 5.1, states antineoplastic HDs and all HD active pharmaceutical ingredients (API) must be unpacked (i.e., removal from external shipping containers) in an area that is neutral/normal or negative pressure relative to the surrounding areas. HDs must not be unpacked from their external shipping containers in sterile compounding areas or in positive pressure areas. Best practice is to unpack the hazardous drugs from the delivery tote, and leave packaged in a zip-locked plastic bag. From there, the unopened plastic bags should be moved to HD storage room, where the HDs can be removed from the bags and received into inventory. HDs should never be withdrawn from the plastic transport bags in any room other than the HD storage room.

74. If the C-PEC vents externally and the room is able to maintain appropriate negative pressure and air exchanges, does the C-SEC need to be vented?

No.

For more information regarding USP Chapter <800>, an extensive list of frequently asked questions published by USP may be accessed at http://www.usp.org/frequently-asked-questions/hazardous-drugs-handling-healthcare-settings.