Virginia Board of Pharmacy

COMPLIANCE WITH USP STANDARDS FOR COMPOUNDING

§54.1-3410.2 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.

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. The latest edition, USP 36- NF 31, published on November 1, 2012 becomes official May 1, 2013.

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?

Yes, sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units. The board would expect to see that biological indicators are used with each autoclave batch and that the cycle time and temperature were recorded on a log or printer tape directly from the autoclave.

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.