

<797> FAQs

Updated: November 1, 2023

General

1. Where can I find FAQs and other information on USP Compounding Standards?

For FAQs on USP Compounding Standards, please see below:

- [General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations](#)
- [General Chapter <797> Pharmaceutical Compounding—Sterile Preparations](#)
- [General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings](#)
- [General Chapter <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging](#)
- [Compounded Preparation Monographs \(CPMs\)](#)

2. Where can I find information about how to interpret and apply General Chapters?

The *General Notices and Requirements* describe the basic assumptions, definitions, and default conditions for the interpretation and application of USP–NF content. For example, Section 2.30. *Legal Recognition* describes the legal recognition of USP and NF. Section 3.10.30 *Applicability of Standards to the Practice of Compounding* describes when USP compounding practice standards are or are not applicable.

Introduction and Scope

3. What is the definition of sterile compounding?

For purposes of General Chapter <797>, sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile medication. However, administration and preparation per the manufacturer's approved labeling are out of the scope of the chapter as described in 1.2 *Administration* and 1.4 *Preparation Per Approved Labeling*, respectively.

4. To whom do the standards in General Chapter <797> apply?

This chapter applies to all persons who prepare compounded sterile preparations (CSPs) and all places where CSPs are prepared for human and animal patients. This includes, but is not limited to, pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including, but not limited to, hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physicians' or veterinarian practice sites. Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in 3. *Personal Hygiene and Garbing*.

Please note, compounding of sterile hazardous drugs (HDs) must additionally comply with General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*.

5. What is considered a compounding facility? Are there requirements that have to be met in order to be considered a compounding facility?

The requirements of the chapter apply to all places where CSPs are prepared for human and animal patients. Additionally, there may be local or federal requirements that must be met.

6. How do I know what are requirements versus recommendations in the chapter?

Generally, requirements in a General Chapter are conveyed by use of the term “must”. Recommendations are conveyed by use of the terms “should” and “may”.

7. What does “official date” mean?

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 the applicable regulatory jurisdiction. USP has no role in enforcement. All text in the United States Pharmacopeia (USP) or National Formulary (NF) that has reached its official date is “official text.” Although all text of the *USP–NF* that has reached its official date is “official text,” not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

8. When do the revisions to General Chapter <797> become official?

The revision of <797> published on November 1, 2022, became “official” on November 1, 2023. The “official date” indicates the date by which affected users are expected to meet the requirements of a particular standard. However, ensuring compliance with the requirements of these standards is the responsibility of the applicable regulatory jurisdiction. Regulatory bodies such as state boards of pharmacy may have a different official date. USP has no role in enforcement.

9. Are the temperatures in the chapter expressed in degrees Fahrenheit or Celsius?

Unless otherwise specified, all temperatures in the *USP–NF* are expressed in degrees centigrade (Celsius) (see also *General Notices 8.180 Temperatures*).

10. Who can be the designated person(s)?

The designated person is one or more individuals assigned by the facility to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of compounded sterile preparations (CSPs). Facilities must determine whether they have one or more designated person(s), select the designated person(s), and determine how to allocate responsibility if there is more than one designated person. The designated person(s) can delegate activities to an assigned trainer provided that is described in the organization’s policies.

11. Why were the categories of low-risk, medium-risk, and high-risk CSPs renamed?

In the 2015 proposed revision of *USP <797>*, it was first introduced to change the compounded sterile preparation (CSP) categories from a three-termed format of low-risk, medium-risk, and high-risk to a two-termed format of Category 1 and Category 2. This change was to avoid inaccurately conferring a level of risk to a particular CSP without consideration for all factors that influence the quality of that CSP. Renaming the CSP categories as Category 1 and Category 2, distinguished primarily by the conditions under which they are made and the time within which they are used, is intended to be a neutral designation. The 2021 proposed revision of *USP <797>* added Category 3 which allows compounders who are willing to add additional quality assurance requirements, the ability to assign BUDs longer than Category 2 BUDs.

12. What are Category 3 CSPs?

Category 3 describes CSPs made in a compounding facility that meets additional quality assurance requirements. Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs in *<797>*. Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequencies for environmental monitoring, and determining stability.

13. Does docking and activation of a proprietary bag and vial system for immediate administration in accordance with the manufacturer's labeling instructions have to occur under ISO 5 conditions?

No. Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for *immediate* administration to an individual patient is not considered compounding and may be performed outside of an ISO Class 5 environment.

14. When does the chapter apply for docking a proprietary bag and vial system?

Docking of the proprietary bag and vial systems for *future activation* and administration is considered compounding and must be performed in an ISO Class 5 environment in accordance with *<797>*, with the exception of *14. Establishing Beyond-Use Dates*. BUDs for proprietary bag and vial systems must not be longer than those specified in the manufacturer's labeling.

15. Am I required to keep proprietary bags and vials which have been docked for future activation in a classified cleanroom?

The chapter does not address storage of the docked proprietary bag and vial system, nor does the chapter require it to be stored in a cleanroom suite. The chapter states that docking of the proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in accordance with this chapter, with the exception of *14. Establishing Beyond-Use Dates*. Users should refer to the manufacturer's labeling for storage recommendations.

16. Does the chapter apply for repackaging of a conventionally manufactured sterile product?

Yes, repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter.

17. Is administration out of the scope of the chapter?

Yes. The intent of the chapter is to establish minimum standards for practitioners when compounding sterile products in order to minimize harm, including death, to human and animal patients. The scope of the chapter is intended to ensure a CSP maintains its integrity up until the time when administration begins. Standard precautions such as the Centers for Disease Control and Prevention's (CDC's) safe injection practices apply to administration (see 1.2 *Administration*).

18. Does a conventionally manufactured sterile product prepared for administration to a single patient in accordance with manufacturer's approved labeling outside of ISO Class 5 conditions have to be administered within 4 hours of reconstitution or mixing if it meets all the conditions in 1.4 *Preparation Per Approved Labeling*?

No. When all of the conditions in 1.4 *Preparation Per Approved Labeling* are met, the storage information in the manufacturer's approved labeling may be followed.

19. What is the appropriate BUD to assign when preparing a conventionally manufactured sterile product for administration?

Preparation of a single dose of a conventionally manufactured sterile product in accordance with the approved labeling that includes information about the diluent to be used, the resultant strength, storage time, and container closure system is not considered compounding and these preparations are not subject to the BUD limits in the chapter. The BUD provided in the approved labeling may be assigned to these preparations when the labeling contains the required information mentioned above. (See 1.4 *Preparation per Approved Labeling*).

20. Is withdrawing a dose from a container of a conventionally manufactured sterile product or spiking an IV bag, without any further manipulation, for immediate administration to a patient considered compounding?

No, withdrawing a dose from a container or spiking an IV bag of a conventionally manufactured sterile product without any further manipulation is considered administration rather than compounding and is out of the scope of <797>. If the dose is further mixed with another product, it would be considered compounding and subject to the requirements of <797>.

21. Is spiking IV fluids (taking IV spikes and putting them into a bag; putting a set into an IV bag) considered compounding?

No, a facility's policies and procedures regarding spiking IV fluids is outside the scope of the chapter.

22. When compounding immediate-use CSPs, may more than three individual containers of a sterile products be used?

The immediate-use CSPs provision states that the preparation must not involve more than 3 different sterile products. Two or more of the same sterile components (product) may be used as long as there are not more than three different sterile components (products). For example, two vials of the same component (drug product) are reconstituted using two vials of *Sterile Water for Injection* (component products) and added to a single component product intravenous diluent bag such as NS or D5W. As another example, when the CSP requires combining 4 vials of the same component (drug product) into a single component product intravenous bag of diluent, only 2 different sterile components (products) are used to prepare the CSP. Both examples may be considered immediate-use as long as the criteria listed in 1.3 *Immediate-Use CSPs* are met.

23. Are COVID-19 vaccines limited by the 4-hour immediate-use BUD or can the BUD from the manufacturer be used?

As long as the approved labeling or supplemental materials provided by the product's manufacturer includes information for the diluent, the resultant strength, the container closure system, and storage time, then this would be considered 1.4 *Preparation Per Approved Labeling* and is not considered compounding.

24. Can a single-dose container be used to prepare doses for more than one patient when compounding an immediate-use CSP?

No. One of the conditions of the immediate-use CSP provision specifies that any unused starting components from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient when used for preparing immediate-use CSPs.

25. Why does the immediate-use CSP provision allow for administration to begin within 4 hours following the start of the preparation?

The immediate-use CSP provision was revised to allow up to 4 hours for beginning administration to balance the need for ensuring CSP quality with timely access to medication in a variety of healthcare settings. The allowance of up to 4 hours was based on the 4-to-6-hour lag phase of microbial growth, during which potential bacterial cells are adjusting to their environment and change very little, and they do not immediately start reproducing.¹ In the event bacterial cells were inadvertently introduced into a CSP during compounding, replication is unlikely and therefore there is a window of time in which a CSP can be held prior to administration.

¹References:

- Daquigan N et al. Early recovery of *Salmonella* from food using a 6-hour non-selective pre-enrichment and reformulation of tetrathionate broth. *Front Microbiol.* 2016;7:2103.
- Jarvis, Basil. *Statistical Aspects of the Microbiological Examination of Foods, Third Edition.* Academic Press, 2016.
- Ryan, Kenneth et al. *Sherrie Medical Microbiology, Sixth Edition.* McGraw-Hill Education, 2014.
- Wang J et al. A novel approach to predict the growth of *Staphylococcus aureus* on rice cake. *Front Microbiol.* 2017;8:1140.

26. Is it considered compounding if the steps used to prepare a single dose of a conventionally manufactured product are different from the directions contained in the manufacturer's approved labeling?

Yes. Any compounding (e.g., mixing, reconstituting) that is not performed according to the manufacturer's approved labeling is considered sterile compounding and is subject to the requirements in the chapter.

27. What information is needed to meet the requirements of Section 1.4 Preparation Per Approved Labeling?

The approved labeling or supplemental materials provided by the product's manufacturer, including information for the diluent, the resultant strength, the container closure system, and storage time.

28. Does the chapter address compounded radiopharmaceutical dosage forms?

No. Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in General Chapter <825> *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging*.

29. Do pharmaceutical manufacturers have to comply with <797>?

No. Manufacturers must comply with FDA's current good manufacturing practices (CGMP) and/or laws and regulations of the applicable regulatory jurisdiction.

30. What is the difference between compounding and what is described in 1.4 Preparation Per Approved Labeling?

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer if the product is prepared as a single dose for an individual patient and the approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

31. Where may Category 1 CSPs be prepared?

Category 1 CSPs must be prepared in a primary engineering control (PEC) that may be placed in an unclassified segregated compounding area (SCA) or a cleanroom suite.

32. What qualifications must a designated person have?

This must be determined by the facility's SOPs. Some states and accreditation organizations have more specific guidance.

33. Is the use of technology other than what is listed in the chapter allowed?

The introduction and scope section outlines the use of technologies, techniques, materials, and procedures not specifically covered by the chapter, as it would be impossible for this chapter to address all of the current technology on the market and potential for new technology coming to market in upcoming years after release of the finalized chapter. It is important that the technology that is being used as indicated in the manufacturer's approval documentation or if it is being used for a different intended purpose that it is validated for that purpose. This ensures that any use of technology does not bypass any safety requirements within the chapter itself and meets or exceeds those requirements. *USP* chapters <1223> and <1225> can assist compounders in this validation process.

34. What is USP's position on drug vial optimization (DVO)?

USP <797> does not address drug vial optimization (DVO). The organization would need to determine if the process used is noninferior to the requirements of the chapter.

35. Will there be any future USP guidance on the use of technology in compounding?

The Compounding Expert Committee will consider the development of future resources or a standard related to the use of technology in compounding. The introduction and scope section of <797> outlines the use of technologies, techniques, materials, and procedures not specifically covered by the chapter, as it would be impossible for this chapter to address all of the current technology on the market and potential for new technology coming to market in upcoming years after release of the finalized chapter. It is important that the technology that is being used as indicated in the manufacturers approval documentation or if it is being used for a different intended purpose that it is validated for that purpose. This ensures that any use of technology does not bypass any safety requirements within the chapter itself and meets or exceeds those requirements. *USP* chapters <1223> and <1225> can assist compounders in this validation process.

36. If a device (e.g., a repeater pump) has undergone validation by the FDA, is the compounder required to verify the volumetric accuracy each day of use?

Yes. Before using automated compounding devices or other similar equipment, compounding personnel must conduct an accuracy assessment before the first use and again each day the equipment is used to compound CSPs.

37. Are albumin, IVIG, etc., included as part of "blood-derived and other biological materials" in Section 1.1.2?

No. These commercial products have been processed by the manufacturer to be sterile. Blood or biological materials derived directly from a patient are not sterile.

38. Do facilities have to change their standard operating procedures (SOPs) and practices for immediate-use from 1 h to 4 h?

No, facilities may choose to maintain the 1-hour limit for administration of immediate-use CSPs, however increasing the time to 4 hours would be considered acceptable.

39. Can immediate-use CSPs be made in a batch for more than one patient?

Compounders can prepare multiple doses of immediate-use CSPs intended for use in one or more patients in a single batch as long as the conditions in Section 1.3 are met.

40. What does “directly administered” mean in 1.3 Immediate-Use CSPs?

“Directly administered” refers to the dose being prepared and then immediately administered by the person who prepared it, or administration is witnessed by the person who prepared it. In a situation where a CSP may be prepared for direct and immediate administration there is risk involved if a CSP is unlabeled and the person who compounded it is not administering or present for the administration.

41. What are the training and competency assessment requirements for personnel who only prepare immediate-use CSPs?

Training and competency assessment requirements are determined by the specific tasks performed and the facility’s SOPs, and must include aseptic processes to minimize the potential for contact with nonsterile surface surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.

42. How often does the training and competency of personnel who perform immediate-use products need to be performed?

Section 1.3 *Immediate-Use CSPs* requires that personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility’s SOPs. No specific frequency is identified for training and competency of personnel who perform compounding of immediate-use CSPs.

43. Is the use of dispensing pins allowed per <797>?

The chapter does not address the use of specific disposable supply items other than to say supplies in direct contact with the CSP must be sterile and depyrogenated. It is the responsibility of the facility to determine the appropriateness of specific items, including dispensing pins.

Personnel Training and Evaluation

44. Section 2.1 Demonstrating Knowledge and Competency of Core Skills states that personnel must complete training and be able to demonstrate knowledge of principles initially and at least every 12 months. Does this mean that each person needs written or electronic testing on each of the listed topics in addition to competency testing?

The written training program must describe the required training and the process for evaluating the performance of personnel, but personnel must both demonstrate knowledge of principles and competency of skill for performing sterile manipulations and achieving and maintaining appropriate environmental conditions as applicable to their assigned job functions.

45. Must cleaning staff or personnel who restock the cleanroom undergo the same training as compounders?

Personnel who only perform restocking or cleaning and disinfecting duties outside of the primary engineering control (PEC) must be initially trained and demonstrate competency in maintaining the quality of the environment in which they are performing their assigned task. At a minimum, these personnel must meet the requirements for personal hygiene and garbing that are described in 3. *Personal Hygiene and Garbing*. Facility SOPs must outline what initial and ongoing training is required.

46. Must vendors and certifiers be trained before entering the cleanroom?

Section 1.1.3 specifies that any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in 3. *Personal Hygiene and Garbing*. Facility SOPs must outline specific requirements.

47. Do supervising pharmacists that do not compound have to undergo training and evaluation?

Yes. The following must be included:

1. **Core skills:** <797> requires that personnel who do not compound, but supervise compounding personnel, have to be trained and demonstrate competency initially and at least every 12 months as outlined in Section 2.1 *Demonstrating Knowledge and Competency of Core Skills*.
2. **Garbing Competency:** Initially and at least every 12 months.
3. **Aseptic Manipulation Competency:** Personnel who have direct oversight of compounding must complete an aseptic manipulation competency evaluation at least every 12 months. The evaluation should correspond to the type of activities of the personnel they oversee but does not require the same quantities.

48. If a compounder floats between pharmacies under the same healthcare system, do media fills have to be repeated at each location?

This must be determined by the designated person(s) and specified in the facility's SOPs. Sites might differ in facilities and engineering controls, so media fills must capture the most difficult and challenging conditions and simulate the conditions and procedures encountered by the compounder and meet the requirements of Section 2.3.

The designated person(s) must develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of individuals who compound, have direct oversight of compounding personnel, perform in-process checks, final verification, and dispensing of CSPs.

49. Compounding independently is mentioned multiple times. Does that mean someone can compound for patients before passing testing as long as they are observed? Is this left entirely to SOPs?

Before beginning any compounding (independently or with supervision), personnel must successfully complete the initial garbing competency. Additionally, all personnel entering a compounding area must abide by 3. *Personal Hygiene and Garbing*. The process of developing competency requires practice. Each compounding facility must develop a written training program that outlines what is permitted.

50. How many gloved fingertip and thumb sampling tests and media-fill tests must be done initially and subsequently?

In the revised chapter gloved fingertip and thumb samplings are taken during both the aseptic manipulation competency (i.e., immediately after media-fills) and the garbing competency evaluation (i.e., after garbing and gloving). The complete garbing competency evaluation, including gloved fingertip and thumb sampling, must be successfully completed no fewer than 3 separate times initially, and only 1 time on subsequent evaluations. All aseptic manipulation competency evaluations, including media-fill and gloved fingertip and thumb sampling after media-fill, must be successfully completed 1 time for the initial and 1 time for all subsequent evaluations.

51. What is the purpose of the increased frequency of the garbing competency?

Personal hygiene and garbing are essential to maintain microbial control of the environment. Most microorganisms detected in cleanrooms are transferred from individuals. Preparation of compounded sterile preparations by personnel who lack proper training and competency may result in increased contamination risk and potentially poor outcomes for patients. Preventing contamination by ensuring personnel are trained and competent is more impactful than detecting contamination through sampling methods.

52. Is documentation of gloved fingertip and thumb sampling and media-fill testing only required when results exceed action levels?

No. All results of the evaluations must be documented and maintained to provide a record and long-term assessment of personnel competency. Documentation must at a minimum include the name of the person evaluated, evaluation date/time, media and components used including the manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

53. If compounding personnel fail media-fill testing or gloved fingertip and thumb sampling, are they required to stop compounding until corrective action and reevaluation have been completed?

General Chapter <797> chapter does not require compounding personnel to cease compounding, however, the facility must evaluate the cause of failure and determine appropriate corrective actions. The results of the evaluation and corrective action must be documented, and the documentation must be maintained to provide a record and long-term assessment of personnel competency. General Chapter <797> describes gloved fingertip and thumb sampling and media-fill testing in Sections 2.2 *Demonstrating Competency in Garbing and Hand Hygiene* and 2.3 *Competency Testing in Aseptic Manipulation*, and required documentation in 20. *Documentation*.

54. Why are incubation conditions different for media-fill testing, gloved fingertip and thumb sampling, and environmental air and surface sampling?

Environmental air and surface samples and gloved fingertip and thumb samples are incubated at a high temperature 30°–35° for no less than 48 h and then a low temperature 20°–25° for no less than 5 additional days. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans. The incubation conditions are consistent with General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*. Media-fill test samples are incubated for a longer period, 7 days each at two temperatures, 20°–25° and 30°–35° to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs.

55. Why must a higher incubation temperature be used first for gloved fingertip and thumb sampling, and environmental air and surface sampling?

Incubating gloved fingertip and thumb samples, and environmental air and surface samples at a higher incubation temperature first helps recover bacteria first. Incubation at a lower temperature first may compromise recovery of Gram-positive cocci which are often associated with humans.

56. If the controlled room temperature is 20-25°, can the samples be incubated without an incubator?

No. Samples must be incubated in an incubator.

57. Do the three initial gloved fingertip tests need to be done on the same day?

Not necessarily. The organization can determine the interval for the three initial gloved fingertip tests. In any case, these need to be three separate instances of hand hygiene, garbing, and the gloved fingertip test. Garbing once and completing three sets of gloved fingertip tests does not meet the requirement for the initial testing. The 3 successful completions must be in succession—failure of any of the 3 initial garbing competency evaluations requires repeat testing until personnel successfully complete 3 evaluations in a row.

58. Are personnel who only prepare immediate-use CSPs required to perform media-fill testing?

No, but the facility's SOPs must determine how their competency will be evaluated. When specific conditions in <797> are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs. Personnel must be trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs. The competency should include appropriate preparation (e.g., hand washing, cleaning the area that will be used) and technique that is evaluated and approved by a qualified individual.

59. Can gloved fingertip testing be done more frequently than what is in the chapter?

The chapter provides minimum compounding standards. Compounders can implement more frequent sampling if they deem it appropriate for their facility.

60. The media used for the media-fill test doesn't filter easily and personnel may need to use additional filters for the media-fill test than used for the actual batch. Is this acceptable?

Yes. Additional filters may be used as necessary for the media-fill test. Using a pre-filter may help maximize the volume of the sterilizing filter. A filter integrity test (e.g., bubble point test) must be performed on all sterilizing filters used during media-fill testing.

61. Does the ongoing garbing competency include gloved fingertip and thumb sampling (GFT) after the visual observation of garbing?

Yes. Performing GFT after the visual observation of garbing ensures personnel can don sterile gloves without contaminating them.

62. Are the staff that are currently competent according to the <797> 2008 chapter required to repeat the initial GFT (three times) with the new incubation temperatures on November 1, 2023?

No. The initial requirement applies to personnel who are beginning to compound, not those who are currently competent according to the <797> 2008 chapter.

63. Describe how to appropriately handle and store samples for media-fill testing, including the right temperature.

All samples must be incubated for 7 days each at two temperatures, 20°–25° and 30°–35°, to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs. If sending samples to the laboratory for incubation, samples must be sent as soon as possible (e.g., within 24 h) for the most accurate results. Samples must be protected from damage as well as temperature and humidity extremes during transit. Refer to <117> *Microbiological Best Laboratory Practices* for additional information.

64. Does the media-fill need to include multiple dosage forms that are compounded?

No. When performing a media-fill test, simulate the most difficult and challenging aseptic compounding procedures encountered by the person replacing all the components used in the CSPs with soybean-casein digest media. Only one dosage form needs to be represented, but it must meet the requirements of Section 2.3 that require the elements that affect the sterility of the CSP be captured, including the complexity of manipulations that may be associated with dosage forms.

65. How many personnel are allowed in the buffer room or SCA during media-fill testing?

Media-fill testing must simulate the most difficult and challenging aseptic compounding procedures encountered by the person, and it must capture all elements that could potentially affect the sterility of the CSP. The chapter does not specify the exact number of personnel in the buffer room or SCA, but it must simulate the conditions encountered by the compounder.

Personal Hygiene and Garbing

66. What is the order and location of garbing?

General Chapter <797> does not specify the order and location of garbing. The order and location of donning and doffing each article of required garb would depend on the type of garb used (e.g., sterile gowns) and the placement of the sink (e.g., if the sink is located inside or outside of the anteroom). The garbing order, location, and donning/doffing each article of required garb must be determined by the facility and documented in the facility's SOP. For example, if a sink is located outside of the anteroom, a facility's garbing policies and procedures may indicate that certain garb would be donned outside of the anteroom to more easily transition into hand hygiene procedures. Garb must be donned and doffed in an order that reduces the risk of contamination. Please note, sterile gloves must be donned in a classified room or SCA. Skin must not be exposed inside the ISO Class 5 PEC (e.g., gloves must not be donned or doffed inside the ISO Class 5 PEC exposing bare hands).

67. Can donning and doffing activities by different personnel occur in the same room at the same time?

The chapter recommends (but does not require) that donning and doffing not occur in the anteroom or the segregated compounding area (SCA) at the same time. Personnel must be aware of activity in the room to ensure that the integrity of garb is not compromised. For example, if one person is performing hand hygiene while another is donning a gown, personnel must consider the risk of contaminating the gown (e.g., from potential splashing).

68. What are examples of methods to cover jewelry that cannot be removed?

Examples of jewelry that cannot be removed are dermal piercings (also known as a microdermal piercing), which is a piercing that is held in place with a dermal anchor that is installed underneath the skin. Facilities must determine the appropriate method for covering dermal piercings to minimize the risk of contaminating the CSP and the environment. For example, depending on the location of the piercing, an adhesive bandage or head cover may be used to cover the jewelry.

69. Are wedding rings permitted to be worn under sterile gloves?

The chapter requires removing all hand jewelry that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination of the CSP. Wedding rings may potentially compromise the integrity of the glove (e.g., tearing) and prevent adequate hand hygiene.

70. Are eyelash extensions allowed in the cleanroom?

No. Cosmetics are not permitted.

71. What accommodations can the designated person allow with regards to garbing in the cleanroom?

The designated person(s) may permit accommodations to personnel preparation as long as the quality of the CSP and environment will not be affected. Accommodations must be documented.

72. Must the accommodation to personnel preparation be documented each time or just once?

The accommodation must be documented per the facility's SOPs and 20. *Documentation*.

73. Are 3 pairs of gloves required for using a compounding aseptic isolator (CAI) or compounding aseptic containment isolator (CACI)?

No, if using a CAI or CACI, the chapter recommends disposable gloves to be worn inside gloves attached to the restricted-access barrier system (RABS) sleeves. However, the chapter requires sterile gloves to be worn over the gloves attached to the RABS sleeves. The use of disposable gloves inside of gloves attached to the RABS sleeve is intended to maintain the cleanliness of the gloves attached to the RABS sleeve which may collect sweat or other touch contaminants. Sterile gloves outside of the gauntlet gloves help minimize the risk of contamination to the environment and the CSP.

74. If I am compounding Category 1 CSPs in an SCA, do I have to wear the same garb as when compounding Category 2 CSPs in a cleanroom suite?

Yes. Minimum garbing requirements are not stratified based on facility design. The chapter lists the minimum garbing requirements to protect the CSP and the environment. Sterile gloves are required for preparing CSPs inside an ISO Class 5 PEC.

75. Can gowns be re-used?

Yes. If compounding Category 1 and Category 2 CSPs, gowns used for nonhazardous compounding may be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the SCA in a manner that prevents contamination. Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. Additionally, gowns and other garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing).

76. Regarding Section 3.1, gum-chewing and mints are considered food. Why can't compounders have anything in their mouths or put anything in their mouths while in the cleanroom suite?

It is too easy to want to blow bubbles or move gum and candy around in the mouth that could spew additional wet into the mask and contaminate it. The candy or gum can also fall out of the mouth, out of the mask and onto a hood counter or floor and contaminate the area.

77. Why is the use of brushes not allowed for hand hygiene?

The practice of using a brush to scrub hands in hand-antiseptic can damage skin of personnel and result in an increase of bacteria shed from the hands. The CDC recommended discontinuing the use of the brushes and the brush side of scrub/sponge brushes in 2002. See the CDC Guideline for Hand Hygiene in Health-Care Settings, Morbidity and Mortality Weekly Report, October 25, 2002, 51(RR16); 1-44.

78. Where should I garb when preparing Category 1 CSPs in an SCA?

Sections 3.2 and 3.3 outline the requirements for hand hygiene and garbing for Category 1. The order of hand washing and garbing depends on the placement of the sink, is determined by the facility, and is documented in the facility's SOPs.

An example garbing procedure in a facility that has a sink in the SCA is as follows:

1. The compounder enters the SCA and dons head, face, and shoe covers in an order determined by the facility and documented in the facility's SOPs.
2. The compounder washes their hands then dons a gown.
3. The compounder applies alcohol-based hand rub to all surfaces of hands and fingers and allows hands to dry thoroughly then dons sterile gloves.

79. When sterile garb is required, does the equipment, such as goggles or PAPRs, need to be sterile as well?

No. Sterile garb is limited to powder-free gloves when compounding Category 1, 2, and 3 CSPs, and low-lint garb when compounding Category 3 CSPs. Facilities must have an SOP describing the disinfection procedures for reusable equipment.

80. For which categories must the facility's SOPs describe disinfection procedures for reusing goggles, respirators, and other reusable equipment?

For Category 1, 2, and 3 CSPs, the facility's SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

81. When must laundering be performed with a validated cycle?

For facilities that compound Category 3 CSPs, laundered sterile garb must not be reused without being laundered and resterilized with a validated cycle. The facility's SOPs must describe this process.

82. When should I apply sterile 70% IPA to gloves?

Application of sterile 70% IPA to gloves must occur immediately before compounding (e.g., before entering the ISO Class 5 PEC) and regularly throughout the compounding process.

83. Do conditions such as dandruff, eczema, or psoriasis exclude someone from compounding CSPs?

These are all conditions that could cause someone to be at higher risk for contaminating a CSP or the environment so they must be reported to the designated person(s). The designated person(s) is responsible for evaluating the situation and making a decision on whether the affected person must be excluded from working in compounding areas until the condition is resolved.

Facilities and Engineering Controls

84. Why must the HEPA filter be located in the ceiling of the buffer and anterooms?

Placement of HEPA filters in the ceiling eliminates the potential for post-filtration contamination of the air stream. Air distribution systems with duct-mounted HEPA filters are susceptible to introduction of unfiltered air into the airstream after the air is filtered. HEPA filter placement in the ventilation duct is difficult to leak test and susceptible to contamination, especially in the event of water leakage or other breaches. Ceiling mounted filters help facilitate testing and servicing.

85. Why are CAIs and CACIs required to be placed in an ISO Class 7 buffer room with an ISO Class 8 anteroom for preparing Category 2 CSPs?

The PEC must be located in a controlled environment for preparing Category 2 CSPs to minimize the risk of contamination. Movement of materials in and out of the RABS (e.g., CAI or CACI) in unclassified air carries a higher risk of contamination. Placement of the RABS in a classified area mitigates the risk of inadvertent contamination of CSPs with the longer BUDs that are permitted for Category 2 CSPs.

86. Does the integrated vertical laminar flow zone (IVLFZ) require 100% HEPA filter coverage in the ceiling? Can returns be under the worktable?

In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the worktables and by effective placement of air returns. Strategic location of air returns in addition to full coverage of HEPA filters above the work surface is required. Specific location of the air returns is not specified. Both static and dynamic smoke studies verifying a continuous flow of HEPA-filtered air void of turbulence, dead air zones, and refluxing from the HEPA filters to and across the entire work area and to the air returns must be documented (e.g., with video). [Note—Dynamic airflow smoke pattern tests have shown that it is difficult to achieve this type of design and also achieve and maintain unidirectional airflow under dynamic operating conditions.]

87. Can a containment ventilated enclosure (CVE) be used for presterilization procedures (e.g., weighing, mixing nonsterile components)?

Presterilization procedures must be performed in a single-use containment glove bag, CVI, BSC, or CACI to minimize the risk of airborne contamination.

88. When pass-through chambers are used, do the doors have to be interlocking?

The chapter recommends that pass-through doors be interlocking. However, if a pass-through is used, both doors must never be opened at the same time.

89. How often are visual smoke studies performed (e.g., in rooms where air returns are not located low on the wall)?

Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow. This smoke study along with environmental monitoring must be repeated whenever a change is made to the placement of equipment within the room or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units). A visual smoke study uses a visible source of smoke, which is neutrally buoyant, to verify an absence of stagnant airflow where particulates can accumulate in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow.

90. What is the difference between a pharmaceutical isolator and a RABS (i.e., a CAI or CACI)?

Unlike RABS, pharmaceutical isolators are different in that they contain 4 major elements: controlled workspace, transfer device, access device, and a decontamination system. A pharmaceutical isolator is equipped with a generator that distributes a sporicidal disinfectant throughout the chamber. If the isolator is used to prepare Category 2 CSPs, it must be placed in an ISO Class 8 or better positive-pressure room. In contrast, if a CAI or CACI is used to prepare Category 2 CSPs, the CAI or CACI must be placed in a cleanroom suite with an ISO Class 7 or better positive-pressure buffer room with an ISO Class 8 or better positive-pressure anteroom.

91. Can analog pressure gauges be used for monitoring pressure differentials?

Yes, analog pressure gauges may be used to monitor pressure. The quantitative results from the pressure monitoring device must be reviewed and documented at least daily on the days when compounding is occurring. Some analog pressure gauges do not warn or alert personnel to events where there is a loss of pressure whereas there are other pressure monitoring systems that may have audible or visible alarms.

92. Why are sinks allowed to be placed outside of the anteroom? Does the sink placement in <797> contradict the sink placement requirements in <800>?

In facilities with cleanroom suites, the sink used for hand hygiene may be placed either inside or outside of the anteroom. If the sink is located outside of the anteroom, it must be located in a clean space to minimize the risk of bringing in contaminants into the anteroom. Sinks are permitted outside of the anteroom to offer more flexibility to the cleanroom design and help minimize the risk of contamination from water sources to the classified areas. In facilities preparing hazardous drugs (HDs) in a cleanroom suite, General Chapter <800> requires the sink to be placed in the anteroom at least 1 meter away from the entrance of the HD buffer room to avoid contamination migration into the negative-pressure HD buffer room. There are no conflicts for the sink placement in <797> and <800>. Facilities compounding sterile HDs must meet the requirements in both <797> and <800>.

93. Is an SCA required to be in an enclosed room (i.e., walls and doors)?

No. An SCA is defined as a designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of only Category 1 CSPs.

94. Why do I need a line of demarcation in the anteroom?

The line of demarcation serves to create visible separation between the clean and dirty sides of the anteroom. Distinguishing the “dirty” side of the anteroom from the “clean” side ensures all personnel abide by the garbing and material transfer procedures defined by the sterile compounding organization’s SOPs. The line of demarcation signifies the locations where specific contamination control principles are implemented to aid in decreasing the number of particles introduced into the buffer room. The facility may choose where the line of demarcation is located. Please note, the anteroom is entered through the dirty side, and the clean side is the area closest to the buffer room (see Section 4.2 *Facility Design and Environmental Controls*). Facilities may also utilize a design with two physically separate anterooms, one clean and one dirty.

95. Can presterilization procedures (e.g., weighing) be performed in an unclassified environment?

Yes. Presterilization procedures can be performed in unclassified environments for Category 1 CSPs. For Category 2 and Category 3 CSPs, presterilization procedures must be completed in an ISO Class 8 or better environment (e.g., anteroom or buffer room) wherein the compounder uses a containment device (e.g., single-use containment glove bags, containment ventilated enclosure (CVE), BSC, or CACI) to minimize the risk of airborne contamination.

96. In an SCA, can the sink be in the same area or room?

The sink needs to be accessible to the compounding area. It can be inside the area defined as the SCA but cannot be closer than 1 meter to the PEC. That distance is intended to ensure that splashes do not reach the PEC.

97. How can the garbing location be in a classified area with a sink outside the anteroom?

The order of garbing must be determined by the facility and documented in the facility’s SOPs. If hand hygiene is completed outside of a classified area, alcohol-based hand rub must be used prior to donning garb. Hands must also be sanitized with alcohol-based hand rub before donning sterile gloves.

An example garbing procedure in a facility that has a sink outside the anteroom is as follows:

1. The compounder washes their hands in the sink located outside of the anteroom.
2. The compounder enters the anteroom and applies alcohol-based hand rub to all surfaces of hands and fingers and allows hands to dry thoroughly.
3. The compounder dons garb in an order determined by the facility and documented in the facility’s SOPs.
4. Before donning sterile gloves, hands are re-sanitized with alcohol-based hand rub and allowed to dry thoroughly.

98. What types of biological safety cabinets (BSCs) are appropriate for compounding?

A BSC is a ventilated cabinet that is typically used for compounding hazardous sterile and nonsterile preparations but may be used to compound nonhazardous sterile and nonsterile preparations as well. BSCs are divided into three general classes (Class I, Class II, and Class III). Class II and Class III BSCs provide an ISO Class 5 environment so are suitable for sterile compounding. Class II BSCs are further divided into types (Type A1, Type A2, Type B1, Type B2, and Type C1). Class I BSCs are suitable for nonsterile compounding only. A BSC used for hazardous drugs must exhaust to the outdoors.

Nonsterile Non-HD	Nonsterile HD	Sterile Non-HD	Sterile HD
Class I, II, or III	Class I, II, III Must exhaust to outdoors	Class II, III	Class II, III Must exhaust to outdoors

99. What are the requirements for temperature and humidity for an SCA?

There are no specific requirements for temperature or humidity in an SCA, but it is reasonable to use the requirements for a cleanroom suite as guidance. However, if drugs or supplies are stored in the SCA, there may be other USP, FDA, or manufacturer/supplier requirements. See *USP <659>* for additional information on storage requirements for drugs.

100. May personnel reach across the perimeter of the SCA to access supplies without actually stepping over the perimeter?

The chapter requires that when personnel exit the compounding area, garb, except for gowns, cannot be reused. At minimum, this would require changing the affected garb (e.g., gloves).

101. May an anteroom be shared between a Category 2 and Category 3 buffer room?

Yes.

102. May an anteroom be shared between an HD and non-HD buffer room?

Yes.

Certification and Recertification

103. Is certification of the compounding area required to be performed using the current Controlled Environment Testing Association (CETA) Certification Guide for Sterile Compounding Facilities?

Before a compounding area is used to compound either Category 1, Category 2, or Category 3 CSPs, it must be independently certified using the requirements in this chapter and when applicable, manufacturer specifications. Facilities must determine the appropriate certification guide to use for certifying their compounding area.

104. What is ASHRAE?

The American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) is a professional organization that provides certification (including healthcare facility design) and professional development for engineers in this field.

105. What is CETA?

The Controlled Environment Testing Association is a professional organization for controlled environment certification personnel that provides certification (including Registered Certification Professional – Sterile Compounding Facilities), education, and resources for certification personnel.

106. A facility may have several cleanrooms under the same corporate structure (e.g., within a healthcare system) but state law requirements may require separate licenses for each compounding area. Are personnel that float between the different cleanrooms required to complete training and competency at each location if they are working in the same type of primary and secondary engineering controls?

This is in the purview of the state board of pharmacy and outside the scope of <797>. The chapter requires that each compounding facility develop a written training program that describes the required training, the frequency of training, and the process for evaluating performance. This program must equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks. The facility's SOPs should specify the training required for such tasks, and training and evaluation of personnel must be documented.

107. Regarding 'dynamic operating conditions', what does "the largest number of personnel and highest complexity" mean as it relates to certification of ISO-classified areas?

This refers to testing in a particular ISO-classified area (e.g., ISO Class 5 PEC, ISO Class 7 buffer room). The highest number of personnel that would be expected to work in a PEC and/or SEC should be present and performing the highest complexity of compounding expected including use of compounding equipment and performance of particle-generating activities (e.g., pre-sterilization activities such as weighing and mixing powders). Testing under dynamic operating conditions is required for particle testing of ISO-classified areas, air changes per hour (ACPH) of ISO-classified rooms, and some types of smoke studies.

Microbiological Air and Surface Monitoring

108. Why has the frequency of surface sampling changed?

Surface sampling was previously required "periodically", which was interpreted differently by users (e.g., monthly, quarterly, or biannually). The change requiring minimum frequencies based on the category of CSP the facility compounds is intended to provide an additional measure of control and monitoring in between viable air monitoring and certification requirements. Regular surface sampling provides additional data for trending and allows for monitoring of contamination risks.

109. How many microbiological air and surface samples are required based on the size of classified areas?

Microbiological air and surface testing must be conducted in all classified areas to confirm that the required environment quality is maintained. The microbiological air and surface sampling must be facility-specific and must be described in the facility's SOPs. The chapter does not specify a minimum number of air or surface samples based on the size of the room, however, the International Organization for Standards (ISO) 14644-1:2015(E) Table A.1 – 'Sampling locations related to cleanroom area' states the area of a cleanroom (m²) and the minimum number of sampling locations to be tested (N_L) that are necessary for certification. Facilities must determine the appropriate number of locations and select the locations of sampling based on their relationship to the activities performed in the area.

110. What is the appropriate method for cleaning the hood after surface sampling?

After sampling, the sampled area must be thoroughly cleaned and disinfected using a cleaning agent followed by a disinfecting agent or by using a one-step disinfectant cleaner. Additionally, in a PEC, sterile 70% IPA must be applied after cleaning and disinfecting.

111. Do microorganisms need to be identified to the genus level regardless of action level?

No. An attempt must be made to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter.

112. What is the rationale for only requiring an attempt to identify any microorganisms recovered to the genus level if the levels measured during sampling exceed the action levels in the chapter?

In some instances, microorganisms cannot be identified to the genus level because the microorganism is no longer viable, or if a mold, it may not be producing the reproductive structures necessary for identification. In these instances, the genus may not be identified, but the chapter does require that an attempt be made to identify the microorganism to the genus level.

113. Is changing HEPA filters considered "servicing facilities or equipment" for the purposes of requiring microbiological air and surface monitoring?

Yes, changing HEPA filters in the ceiling would require microbiological air and surface sampling because there is potential for unclassified air to enter the cleanroom. Changing HEPA filters in the ISO Class 5 PEC would also require microbiological air and surface sampling to ensure the PEC is operating as expected. Changing prefilters for the ISO-classified rooms and PECs usually would not require additional sampling because the downstream HEPA filter remains intact.

114. If two media samples are collected at a single location, how are the colony-forming units (CFU) counted?

If a facility were to choose to utilize two different media devices for sampling, they would sample each location according to their sampling map using both devices (e.g., TSA and MEA). If each device at one location demonstrates growth, the CFU are counted separately. For example, if a TSA plate grows 5 CFU and the MEA plate at the same location grows 3 CFU, the CFU would be recorded separately as 5 CFU and 3 CFU for the respective plates. The count would NOT be recorded as 8 CFU.

115. Is a self-enclosed robotic device different than a “closed RABS” as used in <1211>? When should surface sampling occur in a self-enclosed robotic device?

This verbiage “self-enclosed robotic device” was specifically used in <797> as there are robotic enclosures on the market that do not meet the definition of a closed-RABS, whereas some would meet this definition. For self-enclosed robotic devices that meet the definition of closed-RABS, it would be detrimental to the air quality inside the device to surface sample at the completion of each batch. Therefore, the requirement for these specific devices is to be conducted at least once daily at the end of compounding operations. This is generally when the device is opened for cleaning and disinfecting.

116. May settle plates be used in place of an impaction air sampler for viable air sampling?

No. An impaction air sampler must be used to collect 1 cubic meter or 1000 L of air from each classified area.

117. When should samples be submitted by certifiers to the laboratory after collection?

If the certifier is sending samples to the laboratory for incubation and identification, samples must be sent as soon as possible (e.g., within 24 h) for the most accurate results. Samples must be protected from damage as well as temperature and humidity extremes during transit. Refer to <1117> *Microbiological Best Laboratory Practices* for additional information.

118. Describe the process and action levels associated with testing of pass-through chambers.

For entities compounding Category 1 and Category 2 CSPs, each pass-through chamber must have surface sampling performed monthly (see <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*). For entities compounding Category 3 CSPs, each pass-through chamber must have surface sampling completed prior to assigning a BUD longer than the limits established in *Table 13*, and at least weekly (see <1116>) on a regularly scheduled basis regardless of the frequency of compounding of Category 3 CSPs.

Neither General Chapter <797> nor <1116> states which ISO classification to correlate with. The facility’s SOPs should describe how growth bacteria will be defined. For example, if a pass-through chamber goes between an ISO 7 and an ISO 8 area, the surface sampling growth criteria could be based on either the ISO 7 or ISO 8 limits.

Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA

119. What is the difference between cleaning and disinfecting?

Cleaning is the process of removing substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products. Disinfecting is the process of destroying fungi, viruses, and bacteria on inanimate surfaces and objects.

Sporicidal disinfectants are also indicated in the chapter. A sporicidal disinfectant destroys bacterial and fungal spores and is expected to kill all vegetative microorganisms.

120. What is a one-step disinfectant cleaner?

A one-step disinfectant cleaner is a product with an EPA-registered (or equivalent) claim that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

It is important to note that sterile isopropyl alcohol (IPA) is not a one-step disinfectant cleaner. Sterile IPA is a sanitizing agent which, when used on inanimate surfaces and objects, reduces the number of all forms of microbial life including fungi, viruses, and bacteria.

121. Where can I find examples or sources of EPA-registered one-step disinfectant cleaners?

USP cannot endorse particular products. Users may research one-step disinfectant cleaners or contact cleaning/disinfecting agent manufacturers to get more information on available products.

122. Does Table 10. Minimum Frequency for Cleaning and Disinfecting Surfaces and Applying Sporocidal Disinfectants in Classified Areas and in the SCA apply to all surfaces in the SCA?

The minimum frequencies in *Table 10* apply to all surfaces within the perimeter of the SCA except the ceiling. Ceilings of the SCA are required to be cleaned, disinfected, and applied with sporicidal disinfectant only when visibly soiled and when surface contamination is known or suspected.

123. Does the equipment inside a PEC need to be cleaned?

Yes, the chapter requires equipment inside of the PEC to be cleaned, disinfected, and a sporicidal disinfectant applied (see *Table 10*).

124. Are cleaning supplies required to be sterile?

Cleaning and disinfecting supplies used in the PEC must be sterile with the exception of tool handles and holders, which must be cleaned and disinfected prior to use in a PEC. The chapter states that all cleaning supplies (e.g., wipers, sponges, and mop heads) with the exception of tool handles and holders must be low lint.

Further, the chapter recommends that wipers, sponges, and mop heads be disposable.

125. Are cleaning agents required to be sterile?

Cleaning, disinfecting, and sporicidal disinfectants used within the PEC must be sterile. In classified areas outside of the PEC, sterile cleaning and disinfecting agents should be used.

126. Where can I find information about the minimum contact time for the cleaning, disinfecting, and sporicidal disinfectants used?

Refer to the manufacturer's directions or published data for the minimum contact time for the agent used. The minimum contact time may differ depending on the agent used and on the intended purpose. For example, an agent may have a 1-minute contact time to be bactericidal and a 3-minute contact time to be sporicidal.

127. Does the chapter require a separate cleaning and disinfecting step in addition to applying a sporicidal disinfectant?

The chapter requires cleaning and disinfecting of the compounding areas. These steps can be combined if an EPA-registered one-step disinfectant is used. One-step disinfectants have been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Sporicidal disinfectants must be used at least monthly. Some EPA-registered disinfectant cleaners may also have sporicidal properties. If the sporicidal disinfectant is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.

128. Is an EPA-registered disinfectant required if the compounding process is over 30 minutes? <797> states "During the compounding process sterile 70% IPA must be applied to the horizontal work surface, including any removable work trays, of the PEC at least every 30 min if the compounding process takes 30 min or less. If the compounding process takes more than 30 min, compounding must not be disrupted, and the work surface of the PEC must be disinfected immediately after compounding."

No. As with compounding that takes 30 minutes or less, sterile 70% IPA must be used when the compounding process is over 30 minutes, and must be applied immediately after compounding.

129. Is a biological safety cabinet the only PEC that has a removable work surface tray?

No. CAIs, CACIs, and some laminar airflow workbenches (LAFWs) have removable work trays.

130. Do cleaners and disinfectants have to be EPA-registered?

In the U.S., yes. Disinfectants are registered with the EPA in the USA, and depending on the international location, registered with entities with an equivalent jurisdiction in that nation.

131. Can containers of sterile supplies (such as bottles of sterile alcohol and containers of sterile saturated wipers) be used for more than one compounding session?

Yes, as long as they remain in the intended area once opened. This needs to be defined by the organization's policies, based on information provided by the manufacturer/supplier. Sterile solutions and supplies are used to avoid introducing spores or other contamination into the cleanroom. For example, a packet of saturated sterile alcohol wipers opened in the ISO 5 PEC can remain in the PEC until depleted, unless the packet is contaminated. A bottle of sterile alcohol can remain open and used in the ISO 7 cleanroom until depleted, unless contaminated.

132. Once opened, how long may a cleaning and disinfecting agent or package of sterile wipers be used?

Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs.

133. Are personnel that only clean and disinfect ISO 7 and ISO 8 areas, but not ISO 5 areas, required to wear sterile gloves?

Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must be properly garbed including sterile gloves.

134. If an IV bag has tubing attached in one hood and compounding is done in a second hood, does the IV bag need to be wiped with sterile 70% IPA before bringing into the second hood?

Yes. Just before any item is introduced into the PEC, it must be wiped with sterile 70% IPA using sterile low-lint wipers and allowed to dry before use.

135. Do personnel have to wipe gloves with sterile 70% IPA every time their hands enter the ISO Class 5 PEC even if not touching contaminated surfaces (e.g., throwing out trash without touching trash can or grabbing a supply that was disinfected for them prior to touching)?

Application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process. The facility SOPs should describe this process. For example, gloves might be wiped with sterile 70% alcohol before beginning to stage items into the hood then re-wiped before beginning compounding, after handling trash, when retrieving items outside the hood, etc. Handling trash or retrieving a supply item outside the hood could contaminate gloves so they should be re-wiped with sterile 70% alcohol after performing these tasks.

Equipment, Supplies, and Components

136. Why are active pharmaceutical ingredients (APIs) required to be obtained from an FDA-registered facility and components other than APIs only recommended to be obtained from an FDA-registered facility?

The Federal Food, Drug, and Cosmetic Act requires compounded preparations to be prepared from bulk drug substances that are obtained from FDA-registered facilities. The Expert Committee recognizes that there may be some components other than APIs that cannot be obtained from an FDA-registered facility, thus, it is a recommendation that these components be obtained from an FDA-registered facility.

137. How often do I need to calibrate my temperature monitoring equipment or verify its accuracy?

Section 9.3.4 *Component handling and storage* states that all monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer. For example, if the manufacturer specifies to calibrate every 2 years, then that would be the correct interval. If a manufacturer does not specify the calibration interval, then it must occur at least every 12 months.

138. Does API refer to conventionally manufactured drug products?

The term “API” refers to any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body. Also referred to as *Bulk drug substance*. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

139. If a CSP is stored outside of the pharmacy, do we need to monitor and document temperature readings for nursing unit floor refrigerators or remote-access Pyxis refrigerators?

Once a CSP is dispensed, you should handle this as you would any other medication (manufactured or compounded). Temperature storage conditions in healthcare facilities such as hospitals have requirements from other regulators and accreditors concerning maintaining and documenting temperatures of medication storage areas. Generally, this requires at least daily monitoring and documentation.

140. “All monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.” Does this statement apply to humidity sensors, pressure monitors, and thermostats?

Yes. Those are examples of monitoring equipment.

141. Do we need a certificate of quality for each lot of sterile empty bags we use? <797> states “Each lot of commercially available sterile, depyrogenated containers and container closure systems must be accompanied by a COA or other documentation showing conformance with established specifications (i.e., sterility and depyrogenation requirements).”

Sterile empty bags obtained from suppliers are described as such in the product labeling. The lot number is traceable back to the manufacturer/supplier if any concerns would be identified.

Sterilization and Depyrogenation

142. What is the difference between aseptic processing and terminal sterilization?

USP General Chapter <1229> *Sterilization of Compendial Articles* summarizes the common requirements for sterilization process: design, development, validation, and process control. USP <1229.4> *Sterilizing Filtration of Liquids* states, “Sterilization processes are divided broadly into two categories: destruction of microorganisms, and their physical removal from the material to be sterilized. Terminal sterilization (e.g., autoclaving) is an example of the former, and sterilizing filtration is an example of the latter.”

Aseptic processing includes either 1) compounding with only sterile starting ingredient(s), or 2) compounding with nonsterile ingredient(s) followed by sterilization by filtration. Filtration sterilization is not terminal sterilization because it is not a lethal process of microbial destruction.

Terminal sterilization includes compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization with a lethal process intended to achieve a probability of a nonsterile unit (PNSU) of 10^{-6} (e.g., steam, dry heat, irradiation).

143. Can stoppered and crimped empty vials be sterilized using steam heat?

Sealed containers must be able to generate steam internally to be sterilized by steam heat. Stoppered and crimped empty vials must contain a small amount of sterile water to generate steam (see also <1229> *Sterilization of Compendial Articles*).

144. Does a sterile filter with a pore size of 0.2 μm meet the requirement of the chapter (“0.22 μm or smaller”)?

Yes. For the purposes of <797> and USP–NF compounded preparation monographs, 0.2 μm and 0.22 μm filters are interchangeable, as they pass the same performance criteria.

145. Why is a prefiltration step with a filter of a pore size of 1.2 μm required before sterilization procedures?

A prefiltration step with a filter of a pore size of 1.2 μm removes particulate matter in the solution before sterilization. This is only required if CSPs are known to contain excessive particulate matter, which may also be an indication that the formulation may be problematic and therefore the formulation and the process should be assessed and modified if necessary.

146. What is the PNSU for CSPs sterilized by filtration?

A PNSU value cannot be applied to CSPs that are sterilized by filtration because sterilization by filtration is not terminal sterilization.

147. Is a biological indicator required for each sterilization cycle using steam or dry heat?

Yes, the effectiveness of the steam and dry heat sterilization method must be verified and documented with each run or load using an appropriate biological indicator.

148. Why does the chapter continue to exclude terminal filtration container systems from its definition of terminal sterilization?

Filtration-based methods of sterilization are not considered to be a method of terminal sterilization because they are not a lethal process of microbial destruction.

Each method of sterilization must take into consideration the container closure system that holds the compounded preparation. Since there are many container closure systems and methods of terminal sterilization, it becomes a complex matrix that is specific to the container closure system and the method of sterilization. The permutations are too numerous to include in the chapter.

149. What is depyrogenation?

Pyrogens are organic compounds that are soluble in water and not removed by filtration or steam sterilization. They are endotoxins; lipo-polysaccharides produced by Gram-negative bacteria. Depyrogenation is the destruction or elimination of endotoxins (i.e., pyrogens). There are several methods that can be used to accomplish depyrogenation.

Master Formulation and Compounding Records

150. Do I need a master formulation record (MFR) for repackaged conventionally manufactured components?

Repackaging conventionally manufactured components is within the scope of the chapter. General Chapter <797> requires a master formulation record for CSPs created for more than 1 patient and for CSPs prepared from nonsterile ingredients. If the CSP is created for more than 1 patient, such as repackaging several units, a master formulation record is required.

151. Are master formulation records required for patient-specific CSPs?

A master formulation record must be created for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s). If the CSP is only for a single patient and does not contain nonsterile ingredients, a master formulation record is not required.

152. When is a compounding record needed for immediate-use CSPs?

If the immediate-use CSPs are prepared in a batch and are intended for use in more than one patient, then a compounding record as described in Section 11.2 *Creating Compounding Records* is required.

153. Does a change in any of the information listed as MFR requirements in Box 9 when compounding the same drug require an entirely new MFR, or can an MFR be created to contain the differences?

Any change to the process, ingredients, or packaging specified in an MFR are to be noted on a compounding record. The MFR is not changed.

If a preparation is made repeatedly that has differences in process, ingredients, or packaging, consideration should be given to creating a new MFR for that version of the preparation. Otherwise, all changes are to be noted on a compounding record.

154. Where does the documentation of compounding occur (in process, in the buffer room, outside of classified areas)?

The master formulation record would be established prior to compounding a CSP, usually outside of the cleanroom suite. The compounding record should be initiated before the components of the CSP are assembled. When documented on paper, this is usually performed outside of the cleanroom suite. Depending on your work practices, final sign-off on the CR would be done in the most appropriate area. While labels need to be available for placement on the completed CSP in the buffer room, exposure of paper records should be minimized in the buffer room. Those organizations with workflow technology that supports completion of the CR in the buffer room will likely have a different process than those with only manual records.

Release Inspections and Testing

155. What is required to be documented for the visual inspection of the CSP and the container closure system?

All CSPs must be visually inspected to determine whether the physical appearance of the CSP is as expected. The master formulation record must list specific requirements for a particular CSP. Examples of visible quality characteristics might include discoloration, visible particulates, or cloudiness. Examples of visual inspection of the container closure system might include checking for leakage, cracks in the container, or improper seals.

156. Why should CSPs administered epidurally have the same endotoxin limit as that of intrathecally administered CSPs?

CSPs delivered by implanted pumps may be administered over a long period of time and may be compounded from nonsterile components. Bacterial endotoxin testing helps ensure that CSPs do not contain excessive bacterial endotoxins. Although <797> refers to General Chapter <85> *Bacterial Endotoxins Test* for calculating endotoxin limits for the appropriate route of administration, <85> does not address products administered epidurally or administered directly into the central nervous system. Compounders should be aware that endotoxin testing is also important for CSPs administered epidurally due to the close proximity of the epidural and intrathecal spaces.

157. Do all Category 2 CSPs need to undergo bacterial endotoxins testing?

No. General Chapter <797> Section 12.3 *Bacterial Endotoxins Testing* requires Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing per Table 13 to undergo bacterial endotoxins testing. For example, ophthalmic compounded preparations are not required to undergo bacterial endotoxins testing because they are not Category 2 injectable CSPs. Category 2 injectable CSPs made from one or more nonsterile component(s) and assigned a BUD that does not require sterility testing are recommended to be tested for bacterial endotoxins.

158. How is the endotoxin limit of CSPs for non-human species determined?

Endotoxin limits for non-human species are calculated as described in USP <85> based on the largest recommended dose and weight (or average weight for more than a single animal) of the target animal species unless a different limit is scientifically supported. The formula to calculate endotoxin limit is: K/M where K = the threshold pyrogenic limit for the dosage form (expressed as EU or endotoxin units), and where M = the largest dose/patient or per species average weight in kg per hour. K has been defined by route of administration as follows: injections = 5 EU/kg, radiopharmaceutical injections = 175 EU/dose, intrathecal injections = 0.2 EU/kg, and radiopharmaceutical intrathecal injections = 14 EU/dose. To calculate the endotoxin limit for compounded morphine sulfate 50 mg/ml injection in a 5 kg cat, the following calculations are performed. The maximum dose of morphine sulfate in cats is 0.25 mg/kg. $K = 5 \text{ EU/kg/hr}$ (as defined for injections) $M = 0.25 \text{ mg} \times 5 \text{ kg} \times 1 \text{ hr} = 1.25 \text{ mg/kg/hr}$ $K/M = 5 \text{ EU/kg/hr} / 1.25 \text{ mg/kg/hr} = 4 \text{ EU/mg}$.

The average representative weights for non-human species can be found here:

<https://www.fda.gov/media/102469/download>.

159. Why is there a maximum batch size of 250 units for CSPs requiring sterility testing?

Sterile compounding within 503A facilities is largely a manual process. The chapter sets a minimum standard for quality assurance that encompasses a wide variety of practice sites. These quality assurance parameters are not intended for outsourcing facilities or pharmaceutical manufacturers, as they were created to accommodate the equipment and processes normally performed by 503A facilities. The risk of contaminating a CSP is likely to increase as the batch size increases, especially for a manual process. For example, equipment limitations (such as the size of a PEC) may only permit a portion of a large batch to be packaged in one continuous process. If 25 units are packaged in one continuous process, a batch of 250 units would require repeating this process 10 times. A batch of 1000 units would require repeating this process 40 times.

Smaller batches reduce the potential for operator error due to fatigue. To help ensure sterility assurance, batch size is limited to 250 final dosage units for CSPs that require sterility testing. Sterility testing does not guarantee that an entire batch is sterile, only the units tested. The possibility of detecting a contaminated preparation is about 10% for batch sizes between 10 and 100 but drops to about 4% for a batch size of 250 and only 2% for a batch size of 500.

160. Why is there not a batch size limit in <71> Sterility Tests?

USP General Chapter <71> Sterility Tests falls under the Microbiology Expert Committee and was created for facilities that follow current good manufacturing practices (CGMP). Following CGMP requires a level of quality assurance significantly higher than what is required by 503A facilities who follow <797>. Modifications have been made in <797> to require a fewer number of test samples with batch sizes 1 to 39 units and to limit batch size to 250 final dosage units. Other aspects of <71>, including method suitability, number of units to be tested (for batch sizes 40 to 250), and quantity per unit tested, are required.

161. How many additional units of CSPs must be compounded to perform sterility testing if there are less than 40 units, and does this apply to ophthalmics, large volume parenteral (LVP) solutions, etc.?

If 1–39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number. This applies when the number of CSPs to be compounded in a single batch is less than the number of CSPs needed for testing as specified in <71>, Table 3. Table 3 requires testing 5% or a minimum of 2 ophthalmic preparations, whichever is greater, so this would apply to ophthalmic preparation batch sizes of 1 or 2 units. If compounding more than 2 units of ophthalmic preparation, use the numbers in <71>, Table 3.

162. Do I have to wait for the results of the sterility tests before releasing the CSP?

Sterility testing is not required for Category 1 CSPs. Category 2 and Category 3 CSPs that require sterility testing may be administered or dispensed prior to receiving the results of release testing (including sterility testing).

In order to do this, the facility must have procedures in place to:

- Immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., sterility, strength, purity, bacterial endotoxin, or other quality attributes)
- Recall any unused dispensed CSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of out-of-specification dispensed CSPs must contain:

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CSP, including the date and quantity of distribution
- Procedures to identify patients who have received the CSP
- Procedures for disposal and documentation of the recalled CSP
- Procedures to investigate and document the reason for failure

163. <797> states, “When a CSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CSP does not exhibit any defects such as precipitation, cloudiness, or leakage, which could develop during storage.” Would this prohibit stocking CSPs on the floors in automated dispensing cabinets (i.e., Pyxis) to no more than a 24-hour supply?

No, releasing a CSP to the floor is similar to dispensing to a patient so a second check is not required by a pharmacist. Nurses should be educated to check all types of sterile preparations – manufactured, from a registered outsourcer, prepared by pharmacy, or those that they activate or mix – prior to administration to a patient.

164. After a CSP has been verified by a pharmacist and placed in an area to be picked up for a specific patient in a specified timeframe, does the CSP need to be re-checked by a pharmacist before going out to a patient?

<797> requires that “at the completion of compounding, before release and dispensing, the CSP must be visually inspected to determine whether the physical appearance of the CSP is as expected”. If the pharmacist has performed the release check and dispensed the CSP, and it is only awaiting pick-up or delivery, a re-check is not required.

165. Why is bacterial endotoxin testing required for Category 2 injectable CSPs compounded from one or more nonsterile component(s) and assigned a BUD that requires sterility testing and Category 3 injectable CSPs compounded from one or more nonsterile component(s)?

The purpose of the bacterial endotoxins test is to ensure the source material does not contain excessive endotoxins and ensure any mitigation steps that were performed are adequate. Bacterial endotoxins entering patients' bloodstreams in sufficient concentrations can cause harmful effects such as fever and septic shock and can be fatal in the most severe cases.

Establishing Beyond-Use Dates

166. What is the difference between the beyond-use date (BUD) and “hang time” (e.g., administration time, infusion time)?

The BUD is the date, or the hour and date, after which the CSP must not be used. BUDs apply to CSPs and are not intended to limit the time during which a CSP is administered (e.g., infused). “Hang time” is often used to refer to the amount of time during which a CSP or conventionally manufactured product (e.g., pre-mix, large volume parenteral solution) may be infused before which either the tubing or the medication must be changed. General Chapter <797> does not address administration time (e.g., hang time).

167. Can a CSP be administered beyond the assigned BUD?

Administration cannot begin past the assigned BUD; however, it is not intended to limit administration that began before the BUD lapsed (see 14.1 Terminology). For example:

- An intravenous preparation begins 1 hour before the BUD lapses; however, it is scheduled to continue infusing for a total of 2 hours. The BUD is not intended to limit the dose from being completed.
- An ophthalmic preparation is scheduled to be given once daily for 14 days; however, the BUD will lapse in 10 days. The medication can continue to be administered up until the assigned BUD in 10 days, beyond which the preparation must not be used and must be discarded.

168. After the CSP has begun to infuse, does it need to be taken down and discarded after the BUD is met?

No. Administration must begin before the BUD. The administration process is outside the scope of <797>. Standard precautions such as the Centers for Disease Control and Prevention (CDC) safe injection practices apply to administration. See <800> for additional recommendations for the administration of hazardous drugs.

169. How does the storage condition affect the BUD of a CSP? What is the relationship between storage temperature and BUDs?

Generally, longer BUDs are permitted for CSPs stored in colder conditions than for CSPs stored at controlled room temperature as colder temperatures have been shown to slow the growth of most microorganisms.

Temperature affects chemical reaction rates; thus, storage at higher temperatures will accelerate degradation and reduce a BUD. The accepted rule of thumb is reaction rates increase two-fold for every 10 degree increase in temperature. This means that 1 year storage at 30 °C is equivalent to approximately 6 months at 40 °C and approximately 3 months at 50 °C. Correlating this concept to a refrigerated product (stored at 5 °C) estimates the BUD to be one-fourth at room temperature (25 °C). The exact mechanism of degradation and rate of reaction will determine the actual difference, which can only be determined through a stability evaluation over time.

170. Are BUDs cumulative?

No, BUDs must not be additive. The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition.

For example, a CSP that is assigned a BUD based on storage at room temperature cannot subsequently be refrigerated or frozen in order to extend the original BUD assigned. Likewise, the BUD of a frozen CSP must not be extended based on storage at room temperature when it is thawed.

171. Can the BUDs of Category 2 CSPs be extended beyond those in Table 13. BUD Limits for Category 2 CSPs?

The chapter states that BUDs for Category 2 CSPs must be established in accordance with *Table 13*. However, if there is a compounded preparation monograph for a particular CSP formulation, that BUD may be assigned if the CSP is prepared according to the monograph and all monograph requirements are met (e.g., Specific Tests). *General Notices 3.10* states that where the requirements of a monograph differ from the requirements in an applicable general chapter, the monograph requirements apply and supersede the general chapter.

Category 3 CSPs may be assigned longer BUDs than those set for Category 2 CSPs but not exceeding the limits in *Table 14*, if compounded in accordance with all applicable requirements for Category 3 CSPs.

BUDs must be assigned conservatively and must take into account factors such as validated stability-indicating analytical methods and testing for sterility, endotoxins, container closure integrity, and particulate matter.

172. Why is the BUD for aseptically prepared Category 2 CSPs using only sterile ingredients 4 days when stored at controlled room temperature?

The previous version of <797> specified a storage time of 48 hours and 30 hours at controlled room temperature for low- and medium-risk level CSPs, respectively. The longer BUD in the revised chapter is based on a risk-based approach to balance the need for quality CSPs and to facilitate patient access. Further, the revised chapter contains additional requirements (e.g., facility and engineering controls and surface sampling) to help mitigate risks of inadvertent contamination.

173. Is mixing MVI vial 1 and vial 2 compounding? What is the BUD?

No. Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. Refer to the approved labeling for use of MVI once mixed.

174. If the compounding facility meets the requirements for compounding Category 3 CSPs, can a CSP still be given a Category 2 BUD to avoid sterility testing that particular CSP?

Yes. The chapter does not prohibit a compounder from assigning a shorter BUD than is specified in the BUD Limits tables (Table 14 for Category 3 CSPs). As these are BUD limits, they are the date and time after which a CSP must not be used, stored, or transported, and a BUD shorter than the limit may be assigned to a CSP.

175. What is an example of a CSP requiring a shorter BUD based on stability and sterility?

Shorter BUDs must be assigned when the CSP's stability and/or sterility is less than the hours or days established in BUD limits for each CSP Category. For example, per guidelines, parenteral nutrition compounded as a total nutrient admixture (TNA) at a final concentration of amino acid > 4%, monohydrated dextrose > 10%, and lipid injectable emulsion > 2% are more likely to remain stable for up to 30 hours at room temperature or for 9 days refrigerated followed by 24 hours at room temperature.

176. Are there special considerations for CSPs that contain lipid emulsions?

Manufacturer recommendations regarding administration times and filtering must be followed for CSPs containing lipid emulsions. Some lipid-containing products should not exceed an administration hang time exceeding 12 hours and many require the use of a 1.2-micron filter.

177. Do Category 3 CSP BUDs have to be based on published stability studies?

The USP Compounding Expert Committee has compiled the Formulation and Stability Reference Document for Pharmaceutical Compounding posted [here](#) to help compounders understand when a stability study is suitable for assigning Category 3 BUDs to CSPs. While every CSP must meet release testing requirements for each batch to ensure sterility, evidence to prove the physicochemical stability of a CSP may be obtained from any stability-indicating assay method study, either published or unpublished, and does not have to be repeated for each batch as long as the formula, procedures, and container closure systems in the study are exactly the same for the CSP being prepared.

178. Describe when <51> testing is necessary.

An aqueous multiple-dose CSP must pass antimicrobial effectiveness testing in accordance with <51> *Antimicrobial Effectiveness Testing*.

179. Is <51> testing required for stock solutions?

No. When a CSP stock solution is used as a component to compound additional CSPs, the original CSP stock solution must be entered or punctured in ISO Class 5 or cleaner air and must be stored under the conditions upon which its BUD is based (e.g., refrigerator or controlled room temperature). The CSP stock solution may be used for sterile compounding for up to 12 h or its assigned BUD, whichever is shorter, and any remainder must be discarded.

180. Must antimicrobial effectiveness testing results be provided by an FDA-registered facility?

The compounder may rely on antimicrobial effectiveness testing 1) conducted (or contracted for) once for each formulation in the particular container closure system in which it will be packaged or 2) results from an FDA-registered facility or published in peer-reviewed literature sources, provided that the CSP formulation (including any preservative) and container closure system are exactly the same as those tested, unless a bracketing study is performed. Outside of the United States, facilities must comply with the laws and regulations of the applicable regulatory jurisdiction.

181. The conversion from high, medium, and low-risk compounding to Category 1 and Category 2 CSPs means that CSPs previously categorized as low-risk (48 hours at room temperature; 14 days refrigerated), now categorized as Category 2 (4 days room temperature; 10 days refrigerated) would increase the BUD at room temperature but decrease the BUD if refrigerated. Why is that?

The Compounding Expert Committee replaced risk levels with categories based on criteria other than just starting ingredients and number of manipulations. In addition to starting ingredients, BUDs are also based on environmental quality, personnel hygiene and garbing, physicochemical stability, and requirements for release testing.

182. If I only compound Category 3 CSPs occasionally, do I still have to follow the Category 3 requirements at all times?

Yes, if a compounder desires to assign a BUD longer than those allowed in *Tables 12 and 13*, then the requirements outlined in *Section 14.4 Additional Requirements for Category 3 CSPs* must be met at all times.

183. What BUD should we use if there is no stability data available for the exact concentration of a CSP?

In this case, the maximum allowable BUD limits in <797> must not be exceeded.

184. May a plastic luer lock vial be stored after access?

No. The container closure system must remain intact in order to store a single-dose container after opening. Opened plastic luer lock vials are treated like ampules and must not be stored for any time period.

185. May a vial that has the septum or metal septum ring removed be stored after access?

No. The container closure system must remain intact in order to store a single-dose container after opening. Vials that have the septum or metal septum ring removed are treated like ampules and must not be stored for any time period.

Use of Conventionally Manufactured Products as Components

186. Is a conventionally manufactured single-dose container required to be stored in an ISO Class 5 PEC in order for it to be allowed to be used for up to 12 hours?

No, opened or punctured conventionally manufactured single-dose containers may be stored outside of an ISO Class 5 PEC. However, the chapter does require that the conventionally manufactured single-dose container be entered or punctured inside of an ISO Class 5 PEC. These containers may be used up to 12 hours after initial entry or puncture provided that the storage requirements (e.g., controlled room temperature, cold temperature) are maintained. Opened single-dose ampules must not be stored for any period of time.

187. When determining the BUD for a single-dose vial after puncture, how long can the single-dose vial be stored if the package insert states “use immediately”?

Compounding does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer. When preparing a product per approved labeling, the labeling must be followed.

When compounding a CSP, if a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained and based on sterility assurance.

Package inserts are often based on stability assurance and lack sterility data, so if this is the case and the package insert states “use immediately”, the same microbiological principles of a 4-hour immediate-use time may apply. Contact the manufacturer for stability information.

188. Are conventionally manufactured sterile topical ophthalmic products considered multiple-dose containers?

No, <659> *Packaging and Storage Requirements* defines multiple-dose containers as a container closure system that holds a sterile medication for parenteral administration (injection or infusion) that has met antimicrobial effectiveness testing requirements, or is excluded from such testing requirements by FDA regulation. Therefore, the requirement that multiple-dose containers not be used for more than 28 days unless otherwise specified on the labeling does not apply to conventionally manufactured sterile topical products.

189. If the approved labeling of a pharmacy bulk package describes a long storage time (e.g., 14 days), can the pharmacy bulk package be stored and used for that period of time?

Users should carefully review the manufacturer's approved labeling for pharmacy bulk packages. Some approved labeling may provide a storage time based on stability (e.g., 14 days) as well as a shorter time (e.g., 4 hours) based on the risk of microbial contamination. Users must use the shorter storage time specified in the manufacturer's approved labeling. The pharmacy bulk package must be used according to the manufacturer's approved labeling.

Use of CSPs as Components

190. How is the BUD of a CSP affected by pH-modifiers or other stock solutions that are used as components?

For CSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CSP must not be negatively impacted.

191. What is an example of assigning a BUD to compounded stock solutions and their subsequent CSPs?

A compounder wants to reconstitute a conventionally manufactured sterile product and further dilute it to prepare a subsequent CSP (see *16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions*).

- Day 1: a 2-gram single-dose conventionally manufactured container of powder for solution is reconstituted with 8 mL of a conventionally manufactured diluent, yielding 10 mL of 200 mg/mL of drug (**CSP-A**, original CSP). **CSP-A** is assigned a BUD of 10 days because it is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator (see *Table 13*).
- Day 3: **CSP-A** is entered or punctured in an ISO Class 5 PEC, where 10 mL of **CSP-A** solution is further diluted with 40 mL of diluent, yielding 50 mL solution of 40 mg/mL of drug (**CSP-B**, a finished CSP). **CSP-B** is aseptically processed, has not passed sterility testing, was prepared from only sterile starting components, and will be stored in a refrigerator. The BUD of a CSP prepared from one or more compounded components may not exceed the shortest BUD of any of the individual starting components. Therefore, the assigned BUD for **CSP-B** will be 7 days (10 days minus the 3 lapsed days of **CSP-A**), because that is the shortest BUD of all of its individual components.
- Additionally, **CSP-A** must be used within 12 hours of initial entry/puncture or its originally assigned BUD, whichever is shorter, and the remainder must be discarded.

192. What BUD must be assigned to Category 2 or Category 3 CSPs made using a CSP stock solution?

The BUD assigned to a CSP, whether compounded from conventionally manufactured components or from compounded stock solutions, follows the same standards in Section 14. *Establishing Beyond-Use Dates*. The one difference found in Section 14.3 *Establishing a BUD for a CSP*, is that the BUD of CSPs made from compounded components may, at times, exceed the BUD of compounded components. For example, if a compounded pH-altering solution with a short BUD is used to compound a CSP, the resulting CSP would likely have greater stability, and thus a longer BUD than the pH-altering solution. Another example would be a Category 2 CSP that was not sterility tested and used to make a Category 3 CSP that will be sterilized and sterility tested. If the physical, chemical, and microbiological stability is not negatively impacted, the BUD of the resulting CSP may exceed that of the component. This exception does not exist for commercially available components. It is important to note that the BUD of the final CSP should not be further restricted by the time limits for entering or puncturing components found in Sections 15 and 16.

193. Once punctured, can a CSP or conventionally manufactured product still be used for the length of its BUD?

Compounders may utilize both conventionally manufactured and compounded components. The chapter specifies the time in which each of these components can be stored and used after first entered. This is often called in-use time, although this term is not used in the chapter. The BUD is not the same as in-use time. A multiple-dose vial may have a BUD of 60 days but must still be discarded no later 28 days after first puncture.

194. The chapter states, “After a multiple-dose CSP is initially entered or punctured, the multiple-dose CSP must not be used for longer than the assigned BUD or 28 days, whichever is shorter. This time limit for entering or puncturing is not intended to restrict the BUD of the final CSP.” Can you clarify what the last sentence means?

Each component, whether conventionally manufactured or compounded, must have a time limit for entering or puncturing after first use. For example, a conventionally manufactured multiple-dose vial may not be used after 28 days of first puncture. This 28-day time limit for use is not the same as the BUD of the component and is not intended to restrict the BUD of the resulting CSP. If a CSP is prepared from a multiple-dose vial either 1 day or 10 days after first puncture, the BUD of the resulting CSP would remain the same. For example, let’s assume a conventionally manufactured multiple-dose vial with a one-year expiration date is used to compound a CSP with a 60-day BUD. The multiple-dose vial component may be punctured on day 1 to make the CSP and a BUD of 60 days would be given. Now, 27 days later the same multiple-dose vial component is punctured to make the CSP, and still, a 60-day BUD is assigned. In this instance, the time limit for entering or puncturing the MDV component does not further restrict the CSP being compounded.

195. Please explain the requirements as to the appropriate BUD for a reconstituted single-dose vial. For example, a reconstituted vial of daptomycin is stable for 2 days in the refrigerator. Can this vial be saved and reused for multiple preparations if kept in the refrigerator?

See Section 15 of <797>, which describes the different types of components that could be part of a CSP. When using a single-dose vial, <797> says: “If a single-dose vial is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained.”

The vial of daptomycin mentioned in this example may be used for multiple preparations up to 12 hours after initial entry or puncture provided that the storage requirements (e.g., controlled room temperature, cold temperature) are maintained. If reconstituted in advance as a *single dose for a single patient*, then the daptomycin reconstituted solution may be stored per the approved labeling.

Quality Assurance and Quality Control

196. What does “the overall QA and QC program” entail?

A quality assurance program is guided by written procedures that define responsibilities and practices that ensure compounded preparations are produced with quality attributes appropriate to meet the needs of patients and healthcare professionals. The authority and responsibility for the quality assurance program should be clearly defined and implemented and should include at least the following nine separate but integrated components: (1) training; (2) standard operating procedures (SOPs); (3) documentation; (4) verification; (5) testing; (6) cleaning, disinfecting, and safety; (7) containers, packaging, repackaging, labeling, and storage; (8) outsourcing, if used; and (9) responsible personnel.

CSP Handling, Storage, Packaging, Shipping, and Transport

197. <797> states that the temperature in the storage area must be monitored each day, either manually or by a continuous recording device. (“The results of the temperature readings must be documented in a temperature log per facility SOPs or stored in the continuous temperature recording device and must be retrievable.”) Does this mean that it would be acceptable to record temperatures on Monday if closed on weekends?

Yes.

198. Do all personnel who “touch” a CSP need to have training?

Yes, but not all personnel require the same training. <797> is specific about training for compounding, but leaves requirements for other personnel up to the organization. Personnel who receive sterile products and preparations, enter orders but do not compound or check CSP preparation, clean compounding areas, transport CSPs, or other activities must have documented competence as defined by the organization.

See related question in [Personnel Training and Evaluation](#).

Compounding Allergenic Extracts

199. What are allergenic extracts?

Allergenic extracts are biological substances used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy. Allergenic extract prescription sets are combinations of licensed allergenic extracts which would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved biological license application (BLA) for the licensed biological products.

200. Does 21. *Compounding Allergenic Extracts* apply to physician and pharmacy settings?

Yes, the provisions in 21. *Compounding Allergenic Extracts* apply regardless of where the allergenic extract is compounded when:

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances, and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

201. Why are the BUDs for compounded allergenic extracts longer than those required for Category 1 and Category 2 CSPs?

Because of certain characteristics of allergenic extracts and allergy practice (e.g., preservative systems and risk of anaphylaxis), preparation of allergenic extract for individual patient prescription sets is not subject to the requirements in this chapter that are applicable to other sterile CSPs. Further, FDA provides additional information for preparation of allergenic extracts in the FDA Guidance for Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.

202. Does gloved fingertip and thumb sampling need to occur after media-fill testing for personnel who compound allergenic extracts?

No. Unlike personnel training for other CSPs, the goal of gloved fingertip and thumb sampling for personnel who compound allergenic extracts is to evaluate hand hygiene and garbing but not aseptic technique, due to the nature of the CSPs they compound. Therefore, personnel perform gloved fingertip and thumb sampling three times initially before compounding; thereafter gloved fingertip and thumb sampling is performed immediately after donning gloves at least once every 12 months. The action level for these samples is anything greater than 0 CFU per each hand.

203. Can allergenic extracts be prepared for immediate-use?

Yes.

204. Can this section apply for vials that are made for multiple patients?

No. Compounding allergenic extracts is per individual patient prescription set only.

- 3) Procedures for the maintenance and testing of the written plan for recovery; and
- 4) A procedure to notify the Board, each organization which has contracted with the pharmacy, each patient of the pharmacy, and other appropriate agencies, of a disaster and the date on which the pharmacy expects to recommence the provision of service.

13:39-10.8 WRITTEN PROGRAM FOR PREVENTATIVE MAINTENANCE OF AUTOMATED MEDICATION SYSTEM

A pharmacy which uses an automated medication system to fill prescriptions or medication orders shall maintain a written program for preventative maintenance of the system.

SUBCHAPTER 11. COMPOUNDING STERILE PREPARATIONS IN RETAIL AND INSTITUTIONAL PHARMACIES

13:39-11.1 PURPOSE AND SCOPE

The rules in this subchapter regulate the practice of sterile compounding and shall apply to all retail and institutional pharmacies that compound and dispense sterile preparations. This subchapter establishes standards for the quality and control of processes, components, and environments associated with compounded sterile preparations and for the skill and knowledge of pharmacy personnel who prepare compounded sterile preparations.

13:39-11.2 DEFINITIONS

The following words and terms, when used in this subchapter, shall have the following meanings:

“Ante area” means an ISO class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, labeling, and other high-particulate-generating activities are performed. The “ante area” is also a transition area that:

- 1) Provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas; and

2) Reduces the need for the heating, ventilating, and air-conditioning (HVAC) control system to respond to large disturbances.

“Biological safety cabinet” means a ventilated cabinet for compounded sterile preparations that has an open front with inward airflow for personnel protection, downward high-efficiency particulate air (HEPA)-filtered laminar airflow for product protection, and HEPA-filtered exhaust air for environmental protection.

“Buffer area” means an ISO class 7 area where the primary engineering control is physically located and where the preparation and staging of components and supplies used in compounding sterile preparations occurs.

“Cleanroom” means a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness (ISO) class. Microorganisms in the environment are monitored, so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class. A “cleanroom” includes a buffer area or room and an ante area or room.

“Compounding” means the preparation, mixing, assembling, packaging, or labeling of a drug or device as the result of a practitioner's prescription or medication order or initiative based on the relationship of the practitioner or the patient with the pharmacist in the course of professional practice, or for the purpose of, or incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs or devices in anticipation of prescriptions or medication orders based on routine, regularly-observed prescribing patterns. Compounding includes mixing, reconstituting, or assembling a drug according to the product's labeling or to the manufacturer's directions.

“Compounding aseptic containment isolator” means a compounding aseptic isolator designed to provide worker protection from exposure to undesirable levels of airborne hazardous drugs throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (high-efficiency particulate air (HEPA) minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded.

“Compounding aseptic isolator” means a form of isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer process. Air exchanges into the isolator from the surrounding environment should not occur unless the air has first passed through a microbially retentive filter (high-efficiency particulate air (HEPA) minimum).

“Immediate use compounded sterile preparations” means preparations intended for emergency patient care and involve only simple aseptic measuring and transfer manipulations of no more than three sterile non-hazardous commercial drug and diagnostic radiopharmaceutical drug products, including an infusion or diluent solution. Unless required for the preparation, the compounding process occurs continuously without delays or interruptions and does not exceed one hour. Administration of immediate use compounded sterile preparations shall begin within one hour of preparation or the compounded sterile preparations shall be discarded. Immediate use compounded sterile preparations shall not be compounded and stored for anticipated needs and shall not be compounded as batch preparations. At no time during the compounding process, nor prior to administration, are critical sites and ingredients of the compounded sterile preparation directly exposed to contact contamination, such as human touch, cosmetic flakes, or particulates, blood, human body substances, and non-sterile inanimate sources.

“ISO class 5 air quality conditions” means conditions in which the air particle count is no greater than a total of 3,520 particles of 0.5 micrometers and larger per cubic meter of air (100 particles per cubic foot) that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

“ISO class 7 air quality conditions” means conditions in which the air particle count is no greater than a total of 352,000 particles of 0.5 micrometers and larger per cubic meter of air (10,000 particles per cubic foot) that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

“ISO class 8 air quality conditions” means conditions in which the air particle count is no greater than a total of 3,520,000 particles of 0.5 micrometers and larger per cubic meter of air (100,000 particles per cubic foot) that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

“Negative pressure room” means a room that is at a lower pressure than the adjacent spaces and, therefore, the net airflow is into the room.

“Positive pressure room” means a room that is at a higher pressure than the adjacent spaces and, therefore, the net airflow is out of the room.

“Primary engineering control” means a device or room that provides an ISO class 5 environment for the exposure of critical sites when compounding sterile preparations. Such devices include laminar airflow workbenches, biological safety cabinets, compounding aseptic isolators, and compounding aseptic containment isolators.

“Risk levels for compounded sterile preparations” means the established classification for compounded sterile preparations based on the potential for microbial, chemical, and physical contamination of the preparations and are defined as follows:

1) “Low-risk level compounded sterile preparations” means preparations compounded with aseptic manipulations entirely within ISO class 5 or better air quality using only sterile ingredients, products, components, and devices. The compounding process involves only assembling, transferring, measuring, and mixing, using no more than three commercially manufactured sterile products, and not more than two entries into one sterile container or package to make the compounded sterile preparations. The compounding process is limited to aseptically opening ampules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.

2) “Medium-risk level compounded sterile preparations” means preparations compounded under low-risk level conditions but which require multiple individual or small doses of sterile products to be combined or pooled to prepare compounded sterile preparations that will be administered either to multiple patients or to one patient on multiple occasions. The compounding process includes complex aseptic manipulations other than single volume transfer, and requires an unusually long duration, such as that required to complete dissolution or homogeneous mixing.

3) “High-risk level compounded sterile preparations” means preparations compounded from non-sterile ingredients or from ingredients that are incorporated using non-sterile equipment

before terminal sterilization, or from commercially manufactured sterile products that lack effective antimicrobial preservatives and whose preparation, transfer, sterilization, and packaging is performed in air quality worse than ISO class 5 for more than one hour. Water-containing preparations that are stored for more than six hours before terminal sterilization are also classified as high-risk level compounded sterile preparations.

13:39-11.3 APPLICATION AND PRE-APPROVAL REQUIREMENTS FOR COMPOUNDING STERILE PREPARATIONS

- a) An applicant for a new pharmacy who wishes to compound sterile preparations shall satisfy all pharmacy permit application requirements set forth in N.J.A.C. 13:39-4.1. As part of the permit application, the applicant shall submit plans detailing the physical arrangements necessary to ensure compliance with the requirements in this subchapter. An applicant for a pharmacy permit shall not compound sterile preparations at the site until receiving written approval from the Board to engage in such activities. Prior to issuing the written approval, the Board shall conduct an inspection of the pharmacy to ensure compliance with the requirements in this subchapter.
- b) The holder of an existing pharmacy permit who wishes to compound sterile preparations shall submit an amended pharmacy permit application to the Board. The amended permit application shall contain plans detailing the physical arrangements necessary to ensure compliance with the requirements in this subchapter. The holder of an existing pharmacy permit shall not compound sterile preparations at the site until receiving written approval from the Board to engage in such activities. Prior to issuing the written approval, the Board shall conduct an inspection of the pharmacy to ensure compliance with the requirements in this subchapter.
- c) A pharmacy permit holder who is approved to compound sterile preparations shall notify the Board at least 60 days in advance of any remodeling, change of location, or change in size of the pharmacy cleanroom, consistent with the requirements of N.J.A.C. 13:39-4.7 and 4.8. Such notification shall include the pharmacy's remodeling or relocation plans, as appropriate, the pharmacy's interim plans for the continuation of sterile compounding operations, which the Board shall review and approve, and the anticipated date of completion. The pharmacy permit holder and the pharmacist-in-charge shall ensure compliance with all requirements set forth in this subchapter while compounding operations continue during the remodeling or relocation process. The pharmacy permit holder shall notify the Board upon completion of the remodeling or relocation process, at which time the Board shall inspect the premises.
- d) A pharmacy holding an institutional permit that is approved to compound sterile preparations and that intends to compound sterile preparations using a laminar airflow workbench not located in a buffer area, as provided in N.J.A.C. 13:39-11.10, shall notify

the Board at least 60 days in advance of its intention and of all locations where such equipment will be installed. The pharmacy permit holder shall notify the Board upon completion of such installation, at which time the Board shall inspect the equipment. The pharmacy shall not utilize such equipment to compound sterile preparations until receiving Board approval.

- e) A pharmacy permit holder who is approved to compound sterile preparations and who intends to utilize compounding aseptic isolators or compounding aseptic containment isolators not located in a buffer area, as provided in N.J.A.C. 13:39-11.8, shall notify the Board at least 60 days in advance of its intention and of all locations where such equipment will be installed. The pharmacy permit holder shall notify the Board upon completion of such installation, at which time the Board shall inspect the equipment. The pharmacy shall not utilize such equipment to compound sterile preparations until receiving Board approval.
- f) Notwithstanding the requirements of (a) through (e) above, a pharmacy permit holder or pharmacy applicant may compound sterile preparations for the sole purposes of process, equipment, personnel, and environmental testing. Any sterile preparations compounded for these purposes shall be destroyed.
- g) Approval by the Board to dispense compounded sterile preparations shall be contingent upon demonstration that, as is related to maintaining a sterile compounding environment, all environmental control and processes have been tested and validated, and all equipment has been certified, tested, and validated.

13:39-11.4 CLEANROOM: USE, ACCESS, LOCATION; TEMPERATURE; AIR PRESSURE

- a) The pharmacy shall have a designated area for sterile preparation compounding, known as the "cleanroom." A cleanroom shall be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites. Critical sites are locations that include any component or fluid pathway surfaces (for example, vial septa, injection ports, beakers), openings (for example, opened ampules, needle hubs), exposed and at risk of direct contact with air (for example, ambient room or HEPA-filtered), moisture (for example, oral and mucosal secretions), or touch contamination. A cleanroom shall include a buffer area and an ante area. The buffer area shall contain an ISO class 5 or better primary engineering control, such as a laminar airflow workbench, biological safety cabinet, compounding aseptic isolator, and/or compounding aseptic containment isolator, unless the buffer area has ISO class 5 or better air quality.
- b) All sterile compounding shall take place within the confines of the buffer area, except for the following:

- 1) Compounding in a compounding aseptic isolator or a compounding aseptic containment isolator pursuant to N.J.A.C. 13:39-11.8;
 - 2) Compounding in a laminar airflow workbench in an institutional pharmacy pursuant to N.J.A.C. 13:39-11.10; and
 - 3) Compounding immediate use compounded sterile preparations in an institutional pharmacy pursuant to N.J.A.C. 13:39-11.11.
- c) A cleanroom shall be:
- 1) Accessible only to designated personnel;
 - 2) Used only for the compounding of sterile preparations or such other tasks that require a cleanroom;
 - 3) Structurally isolated from other areas within the pharmacy by means of restricted entry or access; and
 - 4) Air conditioned to maintain a temperature of 59 to 77 degrees Fahrenheit with an ideal temperature of 66 degrees Fahrenheit.
- d) A pressure indicator or air velocity meter shall be installed that can be readily monitored for correct room pressurization or air velocity, respectively, consistent with the following:
- 1) For compounding of non-hazardous drugs, if the buffer area and the ante area are physically separated through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02 inch to 0.05 inch water column shall be required. For buffer areas not physically separated from the ante area, the principle of displacement airflow shall be employed. Using displacement airflow, an air velocity of 40 feet per minute or more from the buffer area across the line of demarcation into the ante area is required.
 - 2) For compounding of antineoplastic agents and other hazardous substances, the standards set forth in N.J.A.C. 13:39-11B.
- e) No chewing gum, drinks, candy, or food items shall be brought into the cleanroom.

13:39-11.5 CLEANROOM REQUIREMENTS

- a) The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the cleanroom shall be smooth, impervious, free from cracks and crevices, and nonshedding,

thereby minimizing spaces in which microorganisms and other contaminants may accumulate.

- b) Work surfaces shall be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that the work surfaces may be readily cleaned and sanitized. All work surfaces shall be resistant to damage from cleaning and sanitizing agents.
- c) Junctures where ceilings meet walls shall be covered, caulked, or sealed to avoid cracks and crevices in which microorganisms and other contaminants can accumulate. All areas in ceilings and walls where the surface has been penetrated shall be sealed.
- d) Ceilings that consist of inlaid panels shall be impregnated with a polymer to render them impervious and hydrophobic and shall either be caulked or weighted and clipped.
- e) Walls shall be constructed of flexible material (for example, heavy gauge polymer), panels locked together and sealed, or of epoxy-coated gypsum board.
- f) Floors shall have a covering that shall be seamless or have heat-welded seams and coving to the sidewall. There shall be no floor drains.
- g) There shall be no dust-collection overhangs (such as ceiling utility pipes) and ledges (such as window sills) shall be avoided. All sprinkler heads shall be flush with the ceiling.
- h) Ceiling lighting fixtures shall have exterior lens surfaces which are smooth, mounted flush, and air tight.
- i) Carts shall be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility.
- j) Refrigerators shall be within, or reasonably accessible to, the cleanroom in order to ensure the integrity of the compounded sterile preparations, consistent with the requirements of N.J.A.C. 13:39-11.12(b)3.

13:39-11.6 ANTE AREA REQUIREMENTS

- a) The ante area shall have appropriate environmental control devices capable of maintaining ISO class 8 air quality conditions for non-hazardous drug compounding activities.
- b) The ante area shall contain the following equipment:

- 1) A sink with hot and cold running water with an integrated and closed plumbing system;
 - 2) Waste containers for all personal protective equipment;
 - 3) An eyewash station; and
 - 4) A hazardous waste spill kit.
- c) The ante room shall continuously maintain ISO Class 8 air quality under dynamic conditions.

13:39-11.7 BUFFER AREA REQUIREMENTS

- a) The buffer area shall have appropriate environmental control devices capable of maintaining ISO class 7 air quality conditions during normal activity consistent with the requirements of N.J.A.C. 13:39-11.4(d).
- b) The buffer area shall contain only the following:
 - 1) Items such as furniture, equipment, supplies, and other materials that are required for the tasks to be performed there;
 - 2) Items that are nonpermeable, nonshedding, cleanable, and resistant to damage from disinfectants; and
 - 3) Items that have been cleaned and disinfected immediately prior to their being placed in the buffer area.
- c) Equipment and other items used in the buffer area shall not be taken from these areas except for calibration, servicing, or other activities associated with the proper maintenance of the item.
- d) The buffer area shall be kept clean and arranged in an orderly fashion. All required equipment shall be maintained in good operating condition.
- e) The buffer area shall not be used for bulk storage, warehousing, or clerical and secretarial functions.
- f) The buffer area shall not contain any sinks.

- g) The buffer area shall be a minimum of 100 square feet in size and shall continuously maintain ISO Class 7 air quality under dynamic conditions.
- h) The buffer area shall contain waste containers in compliance with Occupational Safety and Health Administration (OSHA) standards for disposal of used needles and syringes set forth in 29 CFR 1910.1030 and for disposal of chemotherapy waste set forth at 29 CFR 1910.1200, incorporated herein by reference, and available at www.osha.gov.

13:39-11.8 USE OF COMPOUNDING ASEPTIC ISOLATORS AND COMPOUNDING ASEPTIC CONTAINMENT ISOLATORS LOCATED OUTSIDE OF A CLEANROOM

A pharmacy may utilize compounding aseptic isolators and compounding aseptic containment isolators not located in a cleanroom to prepare compounded sterile preparations, provided the compounding aseptic isolators and compounding aseptic containment isolators can provide isolation from the room and maintain ISO class 5 air quality during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of compounded sterile preparations. Particle counts sampled approximately six to 12 inches upstream of the critical exposure site must maintain ISO class 5 air quality levels during compounding operations. Compounding personnel shall obtain documentation from the manufacturer that the compounding aseptic isolator or compounding aseptic containment isolator will meet this standard when located in worse than ISO class 7 environments. A compounding aseptic isolator and compounding aseptic containment isolator not located in a buffer area shall be located in an area that is maintained under sanitary conditions and such area shall only be traveled by persons engaging in the compounding of sterile preparations.

13:39-11.9 (RESERVED)

13:39-11.10 INSTITUTIONAL PHARMACY USE OF AIRFLOW WORKBENCHES NOT IN A BUFFER AREA FOR LOW-RISK LEVEL COMPOUNDED STERILE PREPARATIONS

A pharmacy holding an institutional pharmacy permit may utilize ISO class 5 laminar airflow workbenches not located in a buffer area to prepare low-risk level compounded sterile preparations provided that the administration of such preparations commences within 12 hours of the preparation or as recommended by the manufacturer, whichever is less. Such workbenches shall be located in an area which is maintained under sanitary conditions and which is traveled only by persons engaging in the compounding of sterile preparations. Such workbenches shall not be in a location that has unsealed windows or doors that connect to the

outdoors or high traffic flow, or that is adjacent to areas including, but not limited to, construction sites, warehouses, or food preparation. Sinks may not be located adjacent to the ISO class 5 workbench environments and must be separated from the immediate area of ISO class 5 workbenches. Personnel engaged in sterile compounding in such areas shall follow the procedures relating to cleansing and garbing set forth in N.J.A.C. 13:39-11.14.

13:39-11.11 COMPOUNDING IMMEDIATE USE COMPOUNDED STERILE PREPARATIONS IN AN INSTITUTIONAL PHARMACY

A pharmacy holding an institutional pharmacy permit may prepare non-hazardous immediate use compounded sterile preparations outside of an ISO class 5 laminar airflow workbench when the delay resulting from the use of the workbench would harm the patient, including situations in which the patient experiences a sudden change in clinical status.

13:39-11.12 PHARMACIST-IN-CHARGE RESPONSIBILITIES

- a) The pharmacist-in-charge shall supervise all sterile compounding performed by pharmacy personnel. The pharmacist-in-charge shall be trained in aseptic manipulation skills.
- b) The pharmacist-in-charge shall be responsible for, at a minimum, the following:
 - 1) Determining the procedural, environmental, and quality control practices that are necessary for the risk levels he or she assigns to specific compounded sterile preparations;
 - 2) Ensuring that the selected sterilization method both sterilizes and maintains the strength, purity, quality, and packaging integrity of the compounded sterile preparations;
 - 3) Ensuring the placement in buffer areas and ante areas of equipment (for example, refrigerators), devices (for example, computers and printers) and objects (for example, carts and cabinets) that are not essential to compounding is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which shall be verified by monitoring;
 - 4) Storage of all materials pertinent to the compounding of sterile preparations, including drugs, chemicals, and biologicals, and the establishment of specific procedures for procurement of the materials in accordance with State and Federal laws and regulations;

- 5) Ensuring that all packaging and labeling of all compounded sterile preparations in the pharmacy are performed under the immediate personal supervision of a pharmacist;
- 6) Ensuring that preparation and compounding of sterile preparations is performed only by pharmacists who have been trained in aseptic manipulation skills, or by pharmacy technicians, pharmacy interns or pharmacy externs who have been trained in aseptic manipulation skills working under the immediate personal supervision of a pharmacist trained in aseptic manipulation skills;
- 7) Recording all transactions of the pharmacy as may be necessary under applicable State, Federal, and local laws and rules, to maintain accurate control over, and accountability for, all pharmaceutical materials, and ensuring that policies and procedures exist with respect to the maintenance of the audit trail required pursuant to N.J.A.C. 13:39-11.20;
- 8) Ensuring that all pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs who compound sterile preparations are trained and evaluated consistent with the requirements of N.J.A.C. 13:39-11.16;
- 9) Establishing procedures for maintaining the integrity of the product and the manufacturer's control identity when repackaging sterile products. A pharmacist shall check all repackaging and shall initial the repackaging records;
- 10) Disposal of all unused drugs and materials used in compounding sterile preparations, including antineoplastic agents and other hazardous substances, in accordance with accepted professional standards, and the Medical Waste Act, N.J.S.A. 13:1E-48.1 et seq., so as not to endanger the public health;
- 11) Ensuring that the compounding area and its contents and other areas where compounded sterile preparations are present are secured, so as to prevent access by unauthorized personnel;
- 12) Ensuring that the pharmacy contains, in addition to the minimum reference library mandated in N.J.A.C. 13:39-5.8(a)1, the most recent edition of references pertinent to compounding sterile preparations;
- 13) Ensuring that records are maintained that document, at least twice daily, that appropriate controlled cold (refrigerator), controlled freezer, if applicable, and controlled room temperatures, as these terms are defined in United States Pharmacopeia 797, are maintained. Such records shall be maintained for no less than five years and shall be made available to the Board for inspection upon request;

- 14) Ensuring that all information required to be maintained as part of a pharmacy's patient profile record system pursuant to N.J.A.C. 13:39-7.19 or 9.19 is maintained for all compounded sterile preparations;
- 15) Ensuring that initial and ongoing multidisciplinary clinical monitoring and comprehensive care plans are maintained and readily available; and
- 16) Maintaining a policy and procedures manual detailing the pharmacy's standard operating procedures with regard to compounded sterile preparations, consistent with the requirements of N.J.A.C. 13:39-11.23, ensuring compliance with such policies and procedures, and maintaining a written quality assurance program, consistent with the requirements of N.J.A.C. 13:39-11.24.

13:39-11.13 PHARMACY TECHNICIANS, PHARMACY INTERNS, AND PHARMACY EXTERNS; REQUIRED SUPERVISION

- a) Pharmacists shall provide immediate personal supervision to pharmacy technicians, pharmacy interns, or pharmacy externs who are performing sterile compounding. The ratio of pharmacists to pharmacy technicians shall not exceed 1:2 at any given time unless all of the requirements of N.J.A.C. 13:39-6.15 are met.
 - 1) Supervision shall include, but is not limited to, the checking of each ingredient used, the quantity of each ingredient whether weighed, measured or counted, and the finished label.
- b) The pharmacist may delegate to pharmacy technicians, pharmacy interns, or pharmacy externs only the following tasks: recording of the prescription, selection of the drugs, container, and diluent, labeling, and compounding of preparations. The pharmacist shall ensure that each task has been performed correctly.

13:39-11.14 PERSONNEL CLEANSING AND GARBING REQUIREMENTS

- a) All personnel who engage in compounding sterile preparations shall comply with the following requirements before entering the buffer area:
 - 1) Personnel shall remove personal outer garments (for example, bandanas, coats, hats, jackets, scarves, sweaters, vests), all cosmetics, and hand, wrist, and other visible jewelry or piercings (for example, earrings, or lip or eyebrow piercings);
 - 2) The wearing of artificial nails or extenders is prohibited while working in the compounding area. Natural nails shall be kept neat and trimmed;
 - 3) Personnel protective equipment shall be donned in the following order:

- i) Dedicated shoes or shoe covers;
 - ii) Head and facial hair covers (for example, beard covers in addition to face masks);
 - iii) Face masks; and
 - iv) Eye shields, if required;
- 4) A hand and forearm cleansing procedure shall be performed. Personnel shall remove debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing for at least 30 seconds. Hands and forearms to the elbows shall be completely dried using either lint-free disposable towels or an electric hand dryer; and
- 5) Personnel shall wear non-shedding gowns with sleeves that fit snugly around the wrists and enclosed at the neck, that are designed for buffer area use.
- b) Following the completion of all steps in (a) above, and once inside the buffer area, personnel shall perform antiseptic hand cleansing, using a waterless alcohol-based surgical hand scrub with persistent activity following manufacturers' recommendations. Once hands are dried thoroughly, personnel shall don sterile gloves. Gloves shall be routinely inspected for holes, punctures, or tears, and shall be replaced immediately if any are detected.
- 1) Gloves become contaminated when they make contact with non-sterile surfaces during compounding activities. Disinfection of contaminated gloved hands may be accomplished by wiping or rubbing sterile 70 percent Isopropyl Alcohol (IPA) on all contact surface areas of the gloves and letting the gloved hands dry thoroughly. Routine application of sterile 70 percent IPA shall occur throughout the compounding process and whenever non-sterile surfaces (for example, vials, counter tops, chairs, and carts) are touched.
- c) When compounding personnel exit the cleanroom during a work shift, the exterior gown may be removed and retained in the cleanroom if not visibly soiled, and may be re-donned during that same work shift only. Shoe covers, hair and facial hair covers, face masks/eye shields, and gloves, however, shall be replaced with new ones before re-entering the buffer area, and proper hand hygiene shall be performed, consistent with (a) and (b) above.

13:39-11.15 CLEANING AND DISINFECTION REQUIREMENTS FOR CLEANROOM, BUFFER AREA, AND ANTE AREA

- a) The cleanroom, buffer area, and ante area shall be cleaned and disinfected consistent with the following requirements:
- 1) All surfaces in laminar airflow workbenches, biological safety cabinets, compounding aseptic isolators, and compounding aseptic containment isolators shall be cleaned and disinfected at the beginning of each work shift, before each batch preparation is started, after spills, and when surface contamination is known or suspected;
 - 2) All counters, work surfaces, and floors shall be cleaned and disinfected daily; and
 - 3) All walls, ceilings, and storage shelving shall be cleaned monthly.
- b) All cleaning and disinfection shall be performed consistent with the standards established in USP 797 Appendix II, which is incorporated herein by reference, as amended and supplemented, and which is available for purchase at the United States Pharmacopeia website, www.usp.org.

13:39-11.16 TRAINING AND EVALUATION REQUIREMENTS

- a) The pharmacist-in-charge and all pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs involved in compounding sterile preparations shall have didactic and practical training in sterile preparation compounding, including proper personnel cleansing and garbing, and cleaning and disinfecting the sterile compounding areas, cleanroom technology, laminar flow technology, isolator technology, if applicable, and quality assurance techniques. Such training shall be documented for each person before that individual begins to compound sterile preparations and annually thereafter for all pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs who compound sterile preparations. That documentation shall be maintained by the permitholder for five years and made available to the Board upon request.
- b) The pharmacist-in-charge shall be responsible for ensuring that, prior to compounding sterile preparations and annually thereafter, all pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs shall have passed a written test that demonstrates competency in all areas set forth in (a) above, and in the pharmacy's standard operating procedures with regard to compounding sterile preparations as set forth in the policy and procedure manual required to be maintained pursuant to N.J.A.C. 13:39-11.23.
- c) The pharmacist-in-charge shall be responsible for testing of the aseptic technique of all pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs involved in

compounding sterile preparations consistent with the methods set forth in USP 797 concerning "Aseptic Manipulation Competency Evaluation," incorporated herein by reference, as amended and supplemented, and which is available for purchase at the United States Pharmacopeia website, www.usp.org, prior to compounding sterile preparations. Aseptic technique retesting shall be conducted annually for all personnel engaged in compounding low- and medium-risk level preparations and semi-annually for all personnel engaged in compounding high-risk level preparations.

- d) All pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs engaging in the compounding of sterile preparations shall successfully complete an initial gloved fingertip/thumb sampling procedure prior to compounding sterile preparations. Gloved fingertip/thumb sampling shall be conducted annually for all personnel engaged in compounding low- and medium-risk level preparations and semi-annually for all personnel engaged in compounding high-risk level preparations. All initial and subsequent gloved fingertip/thumb sampling procedures shall be consistent with the standards established in USP 797, which is incorporated herein by reference, as amended and supplemented, and which is available for purchase at the United States Pharmacopeia website, www.usp.org.
- e) Individuals who fail the written test and/or the test of aseptic technique shall be prohibited from compounding sterile preparations until passing both tests.
- f) All test results shall be maintained by the permit holder for five years and shall be made available to the Board for inspection upon request.

13:39-11.17 BATCH PREPARATION

- a) Pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs, consistent with N.J.A.C. 13:39-11.13, may compound sterile preparations in a quantity that is supported by prior valid prescriptions or medication orders before receiving a valid written prescription or medication order, provided the pharmacist:
 - 1) Documents a history of valid prescriptions or medication orders subsequently received, within the beyond-use dating time of each product, which have been generated solely within an established professional prescriber-patient-pharmacist relationship;
 - 2) Maintains the prescription or medication order on file for all such products dispensed at the pharmacy;
 - 3) Documents the batch preparation process, including selection of the drugs, containers, and diluents, lot numbers and expiration dates of the drugs, containers

and diluents, if any, and verification that the compounded sterile preparation has been visually inspected to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling. Each batch shall be given a unique batch number to identify the specific batch; and

- 4) Ensures that the labeling requirements set forth at N.J.A.C. 13:39-11.21(a)1, 5, 7, 9, and 10 are satisfied.
- b) Pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs shall not batch prepare compounded sterile preparations for human use without a prescription for a licensed prescriber to use in his or her practice, except to the extent permitted by Federal law. Anyone batch preparing compounds for non-human use without a prescription pursuant to this section shall comply with all requirements of N.J.A.C. 13:39-11.18 and the documentation requirements of N.J.A.C. 13:39-11.20(c).

13:39-11.18 COMPOUNDED STERILE PREPARATIONS FOR PRESCRIBER PRACTICE USE

In the absence of a valid patient-specific prescription or medication order, pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs shall not prepare compounded sterile preparations for human use for a licensed prescriber to use in his or her practice, except to the extent permitted by Federal law. A pharmacy may prepare compounded sterile preparations for a licensed prescriber for non-human use in the prescriber's practice without a prescription consistent with State and Federal laws pertinent to the prescriber's health care practice.

13:39-11.19 STABILITY AND STERILITY CRITERIA AND BEYOND-USE DATING

- a) For purposes of this section, stability means the extent to which a preparation retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding.
- b) In the absence of supporting valid scientific sterility testing and stability information that is directly applicable to specific preparations, the following dates and times for storage and initiation of administration of the compounded sterile preparations shall apply, according to the assigned risk level of the preparation, unless the manufacturer's package indicates a different stability time:

- 1) For low-risk level compounded sterile preparations, in the absence of passing a sterility test:
 - i) Administration shall begin within 48 hours when the preparation is stored at controlled room temperature (20 degrees Celsius to 25 degrees Celsius);
 - ii) Administration shall begin within 14 days when the preparation is stored at cold temperatures (two degrees Celsius to eight degrees Celsius);
 - iii) Administration shall begin within 45 days when the preparation is stored in a solid frozen state (-20 degrees Celsius); and
 - iv) For products prepared in an airflow workbench not located in a buffer area in accordance with N.J.A.C. 13:39-11.10, administration shall begin within 12 hours or less of preparation;
- 2) For medium-risk level compounded sterile preparations, in the absence of passing a sterility test:
 - i) Administration shall begin within 30 hours when the preparation is stored at controlled room temperature (20 degrees Celsius to 25 degrees Celsius);
 - ii) Administration shall begin within nine days when the preparation is stored at cold temperatures (two degrees Celsius to eight degrees Celsius); and
 - iii) Administration shall begin within 45 days when the preparation is stored in a solid frozen state (-20 degrees Celsius);
- 3) For high-risk level compounded sterile preparations, in the absence of passing a sterility test:
 - i) Administration shall begin within 24 hours when the preparation is stored at controlled room temperature (20 degrees Celsius to 25 degrees Celsius);
 - ii) Administration shall begin within three days when the preparation is stored at cold temperatures (two degrees Celsius to eight degrees Celsius); and
 - iii) Administration shall begin within 45 days when the preparation is stored in a solid frozen state (-20 degrees Celsius); and

- 4) For immediate use compounded sterile preparations, administration shall begin no less than one hour following the start of preparing the compounded sterile preparation.
- c) The administration dates and times established in (b) above shall not be exceeded or extended for compounded sterile preparations without verifiable supporting valid scientific sterility and stability information that is directly applicable to the specific preparation or compound.
- d) A pharmacist shall determine the beyond-use date for a compounded sterile preparation consistent with (b) above and assign an appropriate discard-after date for the compounded sterile preparation. The discard-after date shall appear on the label consistent with the requirements of N.J.A.C. 13:39-11.21.
- e) Opened or needle-punctured single-dose containers of sterile products (for example, bags, bottles, syringes, and vials) used in the compounding of sterile preparations for immediate use in an institutional pharmacy pursuant to N.J.A.C. 13:39-11.11, shall be used within one hour if opened in worse than ISO Class 5 air quality, and any remaining contents shall be discarded.
- f) Single-dose vials used in the compounding of sterile preparations exposed to ISO Class 5 or cleaner air quality may be used up to six hours after initial puncture.
- g) Opened single-dose ampules used in the compounding of sterile preparations shall not be stored for any period of time.
- h) Opened or needle-punctured multiple-dose vials used in the compounding of sterile preparations shall be used within 28 days after initially entering the vial, unless otherwise specified by the manufacturer.

13:39-11.20 DOCUMENTATION; AUDIT TRAIL

- a) The pharmacist shall ensure that compounded sterile preparations have been properly prepared, consistent with the assigned risk level of the preparation, labeled, controlled, stored, dispensed, and distributed in accordance with the provisions of this subchapter. The pharmacist shall be responsible for the accuracy and appropriateness of the compounded prescription. When more than one pharmacist is involved in the steps of the compounding process, the pharmacist shall be responsible for the accuracy and appropriateness of each step he or she performed or he or she approved and reviewed, and his or her unique and secure user identifier(s) shall be recorded in the audit trail.

- b) A pharmacy shall maintain an audit trail for all compounded sterile preparations consistent with the requirements of N.J.A.C. 13:39-7.6.
- c) A pharmacy shall maintain a compounding record for each compounded sterile preparation that contains the following information:
 - 1) Selection of the drugs, container, and diluent prior to their being compounded, including documentation of lot numbers and expiration dates of the drugs, containers, and diluents, if applicable;
 - 2) Verification that ingredients comply with the prescription or medication order;
 - 3) Verification that the prescription or medication order label complies with the requirements of N.J.A.C. 13:39-11.21;
 - 4) Verification that the compounded sterile preparation has been visually inspected to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling; and
 - 5) Verification that the prescription or medication order is complete and ready to be dispensed, including any necessary ancillary supplies.

13:39-11.21 INFORMATION REQUIRED TO APPEAR ON PRESCRIPTION LABEL

- a) The dispensed container for any compounded sterile preparation shall bear a permanently affixed label with at least the following information:
 - 1) The date and the time prepared;
 - 2) In the retail pharmacy only, the name of the prescriber;
 - 3) The name of the patient;
 - 4) Directions for use;
 - 5) The name and strength or quantity of all active ingredients, and the name and volume of the diluent, vehicle, and base solution(s), if applicable;
 - 6) The name, address, and telephone number of the pharmacy;

- 7) The phrase “use by” followed by the preparation’s use by date and time (if no time is stated, it is presumed to be 11:59 P.M. of the stated use by date).
 - 8) Any ancillary and cautionary instructions as needed;
 - 9) As pertinent, a warning consistent with applicable Federal and State law, that antineoplastic agents and other hazardous substances products are biohazardous;
 - 10) As pertinent, the requirements for proper storage; and
 - 11) In a retail pharmacy, for those medications not dispensed pursuant to the requirements of N.J.A.C. 13:39-9, the prescription number.
- b) For immediate use compounded sterile preparations, when the preparation is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the compounded sterile preparation shall be labeled consistent with the requirements of (a) above and shall also include the name or identifier of the person who prepared the compounded sterile preparation.

13:39-11.22 HANDLING, PACKAGING, AND DELIVERY

- a) The pharmacy shall be responsible for the proper handling and packaging of compounded sterile preparations for delivery from the pharmacy to the patient in order to assure and maintain the integrity, efficacy, stability, and sterility of these preparations. The pharmacist-in-charge shall ensure that:
- 1) Tamper-evident packaging is utilized;
 - 2) Delivery is made from the pharmacy to the patient or patient care location within a reasonable time; and
 - 3) Proper in-transit storage is provided consistent with product labeling.

13:39-11.23 POLICY AND PROCEDURES MANUAL

- a) The pharmacy’s policy and procedures manual shall set forth in detail the pharmacy’s standard operating procedures with regard to compounded sterile preparations.
- b) The policy and procedures manual shall include policies and procedures governing the following:

- 1) A risk-management program, including, but not limited to, documentation of incidents, adverse drug reactions, and product contamination.
 - i) The risk-management program shall require that the pharmacist-in-charge report all confirmed incidents of product contamination to the New Jersey Board of Pharmacy within 48 hours of becoming aware of such incidents;
- 2) Security measures ensuring that the premises where compounded sterile drugs are present are secured, so as to prevent access by unauthorized personnel;
- 3) Equipment;
 - i) Procedures for use; and
 - ii) Documentation of appropriate certifications;
- 4) Cleaning and disinfecting standards and procedures, consistent with the requirements of N.J.A.C. 13:39-11.15;
- 5) Reference materials as set out in N.J.A.C. 13:39-5.8 and 11.12(b)12;
- 6) Information concerning drug:
 - i) Preparation;
 - ii) Storage and handling;
 - iii) Dispensing;
 - iv) Labeling;
 - v) Delivery; and
 - vi) Destruction, recalls and returns;
- 7) Patient recordkeeping as set forth in N.J.A.C. 13:39-11.12(b)14;
- 8) Handling, dispensing and documentation of investigational new drugs;

- 9) A quality assurance program as set forth in N.J.A.C. 13:39-11.24;
 - 10) Verification of training and competency guidelines as set forth in N.J.A.C. 13:39-11.16;
 - 11) Compounding process validation;
 - 12) Documentation as set forth in N.J.A.C. 13:39-11.20;
 - 13) Description of appropriate garb and garbing procedures, consistent with the requirements of N.J.A.C. 13:39-11.14;
 - 14) Conduct guidelines for personnel in the cleanroom;
 - 15) Personnel responsibilities;
 - 16) Patient education;
 - 17) Protocol and procedures to maintain the integrity of the interior work area of the laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators, and biological safety cabinets; and
 - 18) Written procedures in compliance with the Occupational Safety and Health Administration standards for handling small and large spills of antineoplastic agents and other hazardous substances.
- c) The policy and procedures manual shall be reviewed, at a minimum, once every 24 months and shall be updated, on a continuous basis, to reflect current practice. Documentation of the review shall be made available to the Board upon request.

13:39-11.24 QUALITY ASSURANCE PROGRAM

- a) The pharmacy's quality assurance program shall require, at a minimum, that:
 - 1) A reasonable effort shall be made by the pharmacist to assure that compounded sterile preparations shall be kept under appropriate controlled conditions at the location of use by providing adequate labeling and verbal or written instructions regarding proper storage and administration as set forth by the product manufacturer, with each compounded sterile preparation dispensed;

- 2) The quality assurance program encompasses all phases of sterile compounding for each unique type of compounded sterile preparation dispensed;
- 3) After the preparation of every admixture, the contents of the container are thoroughly mixed and then visually inspected to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, or any other defects, and the accuracy and thoroughness of labeling;
- 4) All pharmacists, pharmacy technicians, pharmacy interns, and pharmacy externs involved in compounding sterile preparations shall have their aseptic technique tested consistent with the requirements of N.J.A.C. 13:39-11.16;
- 5) All high-risk level compounded sterile preparations that are prepared in groups of more than 25 identical individual single-dose packages (for example, ampules, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or that are exposed longer than 12 hours at two degrees to eight degrees Celsius and longer than six hours at warmer than eight degrees Celsius before they are sterilized, and all compounded sterile preparations whose beyond-use date has been exceeded, shall be tested to ensure that they are sterile before they are dispensed or administered. The USP membrane filtration method shall be used where feasible. Another method may be used if verification results demonstrate that the alternative is at least as effective and reliable as the membrane filtration method or the USP direct inoculation of the culture medium method, consistent with the standards set forth in USP 797 concerning "Sterility Testing," 2012 edition, incorporated herein by reference, as amended and supplemented, and available for purchase at the United States Pharmacopeia website, www.usp.org.
 - i. When high-risk level compounded sterile preparations are dispensed before receiving the results of the sterility tests set forth in (a)5 above, the written quality assurance procedure shall require daily observation of the incubating test specimens and immediate recall of the dispensed compounded sterile preparations when there is any evidence of microbial growth in the test specimens. The patient and the physician of the patient to whom a potentially contaminated compounded sterile preparation was administered shall be notified immediately of the potential risk. Positive sterility tests shall require rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls in order to identify sources of contamination and to take corrective action.
 - ii. All high-risk level compounded sterile preparations, except those for inhalation and ophthalmic administration, shall be tested to ensure that they do not contain excessive bacterial endotoxins;

- 6) Air and surface sampling for microbial organisms in ISO class 5 primary engineering controls, such as laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators, and biological safety cabinets, and in all other ISO classified areas shall be certified by an independent certification company once every six months and at any time when microbial contamination is suspected;
- 7) Pressure differential monitoring shall be conducted consistent with the requirements of N.J.A.C. 13:39-11.4(d). A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante area and between the ante area and the general environment outside the cleanroom. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device;
- 8) Laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators, and biological safety cabinets shall be certified every six months, and every time they are moved, by an independent certification company to ensure that these primary engineering controls meet appropriate ISO classifications;
- 9) A cleanroom shall be certified by an independent certification company every six months and whenever the room or a primary engineering control in the room is relocated or altered, or whenever major service to the facility is performed, to ensure that the cleanroom meets appropriate ISO classifications. Such certifications shall be performed consistent with procedures outlined in the Controlled Environment Testing Association (CETA) Certification Guide for Sterile Compounding Facilities (CAG-003-2006) (revised December 8, 2008), incorporated herein by reference, as amended and supplemented, and which may be found at the CETA website, www.cetainternational.org, specifically, www.cetainternational.org/reference/CETAasepticCompoundingCertificationGuide.pdf; and
- 10) Whenever test results indicate that the cleanroom or any primary engineering controls do not meet the standards established in this section, the pharmacy shall immediately cease using the cleanroom or primary engineering control that is out of compliance until such time that the cleanroom and/or the primary engineering control meets the requisite standards. The pharmacy shall notify the Board in writing within 48 hours of any air and/or surface sampling test results that are out of compliance. Test results indicating non-compliance with the requisite standards shall require re-evaluation of all procedures associated with the production of compounded sterile preparations in the impacted cleanroom or primary engineering control and documentation with respect to the period of time that the cleanroom and/or primary engineering control was out of compliance.

13:39-11.25 PROHIBITED COMPOUNDING

- a) A pharmacist shall not compound preparations that contain drug products that appear on the Federal Food and Drug Administration's List of Drug Products Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness, codified at 21 CFR 216.24.
- b) A pharmacist shall not compound any commercially available drug products unless:
 - 1) The commercially available product is modified to produce a significant difference, in the professional judgment of the prescriber, between the compounded product for the patient and the comparable commercially available product; or
 - 2) The commercially available product is not available from normal distribution channels in a timely manner to meet the patient's needs, and the dispensing of the compounded product has been approved by the prescriber and the patient.
- c) A pharmacist who compounds a commercially available product consistent with the requirements of (b) above shall maintain documentation of the reason for such compounding.

13:39-11.26 (RESERVED)**13:29-11.27 (RESERVED)**

**SUBCHAPTER 11A. COMPOUNDING NON-STERILE PREPARATIONS IN
RETAIL AND INSTITUTIONAL PHARMACIES**

13:39-11A.1 PURPOSE AND SCOPE

The rules in this subchapter regulate the practice of non-sterile compounding and shall apply to all retail and institutional pharmacies that compound and dispense non-sterile preparations. This subchapter establishes standards for the quality and control of processes, components, and environments associated with compounded non-sterile preparations, and for the skill and knowledge of pharmacy personnel who prepare compounded non-sterile preparations. The requirements in this subchapter establish minimum good compounding practices that will enhance a pharmacist's ability to compound non-sterile preparations that are of acceptable strength, quality, and purity.