USP General Chapter <797> Frequently Asked Questions

Revised January 12, 2010

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General

1. We are a privately owned physician’s office. We do not have a pharmacy license or pharmacist. We have 2 RN’s trained and certified to mix and give chemo in our outpatient infusion center. We follow the NIOSH guidelines. Do we have to follow the USP 797 guidelines?

The USP Chapter <797> standards are not limited in their application to any specific profession or to any specific type(s) of sterile compounding site. USP Chapter <797> standard applies to sterile compounding without regard to the location or profession of the compounding personnel. This is because no patient should have to give up their right to an accurate, safe, sterile dose no matter where that dose is prepared or who prepares it.

2. Does the spiking of an IV bag, such as Normal Saline, constitute sterile compounding?

Spiked IV bags containing no added drugs, one added drug, or two added drugs would be either Immediate-Use, Low-Risk Level with 12-Hour Beyond-Use Date, or Low-Risk Level CSPs, depending on the environmental quality and personnel cleansing and garbing.

Microbial Contamination Risk Level Categories

3. What types of sterile compounds can nurses prepare on the floor? Can they draw up IV push medications?

Only Immediate-Use CSPs (Compounded Sterile Preparations) may be prepared in worse (dirtier) than ISO Class 5 environments, such as in clinical patient care areas. Refer to the Immediate Use CSPs section for the six specific criteria.

4. Nurses in our practice currently mix Infliximab in the home just prior to infusion. If we receive an order for 600 mg in 6 vials of 100 mg each admixed in a 250 mL bag of Normal Saline, would this fall outside the Immediate Use CSP as defined in <797>?

Assuming the bag entry is limited to two, this would fall outside the immediate use CSP as defined in <797>.

The standards for Medium-Risk Level CSPs apply, because more than three containers of sterile ingredients are used. When there are more than two entries into one sterile container, this also qualifies as Medium-Risk Level. Increasing quantities of sterile ingredients and manipulations of them increase the risk of dosage and ingredient errors, and microbial contamination.

5. Can nurses draw up IVP medications on the nursing unit? Can they keep the left over drug in a syringe in the patient’s medication drawer for future dosing?

Intravenous medications prepared in worse (dirtier) than ISO Class 5 environments are subject to the standards for Immediate-Use CSPs. Immediate-Use CSPs cannot be stored.

6. Is there a limit of how many times a vial can be entered by a nurse using a single dose vial on a nursing unit within 24 hours?

This practice qualifies as an Immediate-Use CSP. A maximum of two stopper entries is permitted within one hour from when the preparation began for administration to the same patient.

7. Continuous infusion pumps and other devices that are filled with a single ingredient that may require multiple vials and where a Luer lock extension tubing is used to fill the catheter, can this medication be prepared in the operating room in the sterile field?

Also can this preparation be administered over several days?

The requirements for Immediate-Use CSPs apply to medications prepared in worse (dirtier) than ISO Class 5 environments. Chapter <797> does not apply to clinical administration practices and conditions; however, the Immediate-Use CSPs section states a warning regarding potential harm to patients from extended administration durations of contaminated CSPs.

8. Can a product be considered immediate use risk level if product/device is administered over multiple days (continuous infusion pumps, insulin pumps, etc.)?

The Immediate-Use CSPs category does not limit the duration of clinical administration of the CSP. Please refer to the answer to question 5.

9. Which risk level would apply to vials with the stopper removed to compound for patient who are allergic to latex? They might be prepared in ISO Class 5 or outside ISO Class 5.

The stopper must be removed by contacting only sterile surfaces; e.g., sterile forceps. If stopper and content removal occur within an ISO Class 5 environment, and if the vial is one of three or fewer sterile ingredients, then this qualifies as either a Low-Risk Level CSP or a Low-Risk Level CSPs with 12-hour or Less BUD, depending on whether or not the primary engineering control, PEC or ISO Class 5 source is located in an ISO Class 7 buffer area. If the vial is one of more than three sterile ingredients, then this requires compliance with Medium-Risk Level CSP standards. If the stopper is removed by contacting only sterile surfaces in worse (dirtier) than an ISO Class 5 environment, then this qualifies as an Immediate-Use CSP.

10. Can you define the risk level for white blood cell labeling?

http://www.usp.org/audiences/pharmacist/797FAQs.html 1/21/2011
11. If you prepare a large batch of drug and submit a portion of the batch for sterility testing, as dictated in Chapter <71>, and the batch passes, does this validate the process for subsequent batches allowing use of chemical stability BUD?
No. Sterility testing is required for each batch in order to extend BUD to chemical stability.

12. When compounding a high risk CSP that is at a concentration that may not remain in solution below body temperature, i.e., intrathecal medications, be stored in an incubator at body temperature ~37°C?
This is permissible when there is direct testing evidence to verify sterility is maintained, and when there is either direct testing or reliable literature evidence of chemical stability. Chemical stability of drug products and preparations is generally defined as a loss of potency of not more than 10% for a given period of time. Provided that the stability testing data is appropriately validated.

13. A compounding pharmacy compounds stock solutions to be used in the compounding of TPNs, Cardioprotection solutions, etc. These stock solutions are compounded using non-sterile ingredients and sterilized by filtration and therefore are high-risk level CSPs. Each lot or batch of these stock solutions undergoes testing and meets the requirements of the Sterility Test <71> and the Bacterial Endotoxins Test <85>. The concentration of each stock solution is determined to ensure the concentration is within plus or minus 10% of the label claim. Since each lot of stock solution is tested to ensure it meets the requirement of the Sterility Test <71>, the pharmacy bases the Beyond-Use Date (BUD) on the chemical stability of each formulation not microbial stability. The pharmacy uses these stock solutions to compound other CSPs which have the compounding complexity of either low or medium risk level based on the manipulations involved. Are these resulting CSPs, compounded using a stock solution, classified as low or medium risk level based upon the complexity of the CSP or as a high risk level CSP because the stock solution used is itself a high risk level CSP?

According to USP <797> low-risk level CSPs are compounded with aseptic manipulations entirely within ISO Class 5 or better air quality using only sterile ingredients, products (see definition in this Chapter), components, and devices. The compounding involves only transfer, measuring and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package of sterile product. A medium-risk level CSP is compounded aseptically under low-risk conditions but involves complex aseptic manipulations, pooling of sterile products for administration to multiple patients or to a single patient multiple times, or the compounding process requires an unusually long duration. A product that has been evaluated for safety and efficacy by the FDA, and is not expressly prohibited as Immediate-Use CSPs, intrathecal injections, and extended sterility storage times require sterility testing evidence.

A high-risk level CSP, which has met the requirements of the Sterility Test <71> remains a high-risk level CSP. Therefore, anything compounded from this stock solution would be considered a high-risk level product and must meet the BUD of a high-risk level CSP unless the requirements of the Sterility Test <71> are met for each compounded lot of CSP. The BUD for a low, medium or high-risk CSP that has met the requirements of the Sterility Test <71> may be based on the chemical stability of the CSP instead of the microbial stability.

14. If compounding outside of the manufacturer's instructions, it is understood that stability and purity must be verified. Is this also the case for sterility and pyrogen testing if beyond-use-date (BUD) is less than 48 hours?
The 48 hour BUD at controlled room temperature (see the General Notices and Requirements) is required for Low-Risk Level CSPs in the absence of sterility testing data. Testing for sterility and pyrogens or bacterial endotoxins is required only for High-Risk Level CSPs administered by specific routes, which are delineated in that section.

15. In a code situation with the pharmacist preparing the drugs, what kind of labeling will be necessary?
This will usually be an Immediate-Use CSP for which labeling requirements are described in that section.

16. When risk levels are assigned, what is meant by “In absence of passing sterility test”?
When there are no sterility testing results to establish a statistical probability that each unit of CSP is sterile, i.e., sterility is assumed based on personnel practices and compliance with standards for quality of air environments and surfaces.

17. Is there a standard for preparing intrathecal CSPs?
Standards for compounding intrathecal CSPs are according to the particular microbial contamination risk level. The standards for Low-Risk Level CSPs are, prudenty, the least that should be applied to intrathecal CSPs. While not expressly prohibited as Immediate-Use CSPs, intrathecal injections pose the greatest risk of harm and death to patients if contaminated with microorganism and bacterial endotoxins, which is most likely to occur under Immediate-Use CSP conditions.

18. If you perform a large volume of medium risk compounding is it necessary to perform low risk media fills?
No, because the Medium-Risk Level CSP medial fill testing is more rigorous than that for Low-Risk Level CSPs.

19. If media fills are incubated for an extended period is that sufficient to extend the BUD?
No. BUD applies to chemical and physical stability. Extended incubation of media fill test specimens is irrelevant to extending BUD and sterility storage times for a particular CSP microbial contamination risk level. Extended BUDs require evidence from stability-indicating chemical assays, and extended sterility storage times require sterility testing evidence.

20. If single use containers can remain open in ISO Class 5 for 6 hours does this apply to solutions hanging on a TPN compounding that are spiked (closed system)?
Yes, except for Pharmacy Bulk Packages, which bear a manufacturer's specific BUD, which is usually 4 hours after initial puncture of the closure.

21. Under what risk categories are parenteral nutrition preparations prepared?
Parenteral Nutrition preparations in almost all circumstances fall into the category of medium-risk level CSPs no matter if fat emulsion is present or not.

In the absence of passing a sterility test, the storage conditions cannot exceed 30 hours at controlled room temperature or 9 days at a cold temperature. Parenteral Nutrition preparations shall not be frozen.

About the only instance where low-risk level compounding would be applicable would be using a dual-chamber container system and only making two injections into the container. In the absence of a sterility test, the storage conditions cannot exceed 14 days at a cold temperature. Parenteral Nutrition preparations may also be high-risk level compounding if one of the ingredients is compounded under high-risk conditions such as from a non-sterile bulk powder. In the absence of a sterility test, storage conditions cannot exceed 3 days at a cold temperature.

22. How would a bladder irrigation be categorized, such as a product for immediate use that uses non-sterile ingredients (alum)?
If the product labeling indicates it is permitted to be administered unsterile, then <797> does not apply. If it is supposed to be sterile before administration, e.g., the <797> Introduction states that irrigations for body cavities are required to be sterile, and then this is a High-Risk Level CSP, which must be sterilized before administration.
Beyond-Use Date (BUD)

23. What is the reasoning behind not allowing a longer beyond use date, especially when there is dependable literature which shows a chemical/physical stability for perhaps several weeks or even months? Does it make a difference if the final container is sealed?

The same data that confirm long term chemical and physical stability give no assurance regarding sterility and lack or acceptable level of bacterial endotoxins.

24. Immediate use CSPs must be administered within one hour following preparation. Must administration be completed within that same hour? With low-risk level CSPs with 12 hour BUD, must administration be completed within those 12 hours?

Administration of Immediate-Use CSPs must begin within 1 hour from the start of their preparation; there is no requirement for the duration of administration. For Low-Risk Level CSPs with 12-Hour or Less BUD, there must be maintenance of the CSP within 12 hours from the start of compounding, but there is no administration duration requirement.

25. If a pharmacy prepares an epidural bag of bupivacaine in 100 mL normal saline, can an anesthesiologist add fentanyl to that same bag on the floor? If so, what would the BUD be?

If fentanyl is added in worse (dirtier) than an ISO Class 5 environment, then this becomes an Immediate-Use CSP, for which there is no administration duration requirement. The Immediate-Use CSP section states a warning regarding potential harm to patients from extended administration durations of contaminated CSPs.

26. Does the 28 day expiration on multi-dose vials apply to their use in additional compounding, or does it apply to only administration of that preparation?

28 days is the USP chapter <51> testing requirement for Multiple-Dose Containers to be used under any conditions. The BUD on some products may be labeled more or less than 28 days, at the discretion of the manufacturer.

27. The Chapter only mentions the expiration dates for single-dose and multi-dose vials. What is the appropriate expiration date for eye drops and for multi-dose vials of oral solutions if commercially made?

For ophthalmics, the expiration date is labeled by the manufacturer. Multi-dose vials of oral solutions are not required to be sterile; thus, <797> does not apply thereto.

28. Nursing is known to mix IVPB way ahead of time for administration. What is the BUD?

The BUD for intravenous piggyback (IVPB) infusions depends on the conditions under which they were prepared. For example, when prepared under conditions of Immediate-Use CSPs, infusions must start within 1 hour of starting to prepare the CSP with no time limit to finish the infusion; when prepared under conditions of Low-Risk Level CSPs with 12-Hour or Less BUD, infusion must start within 12 hours of preparing the CSP with no time limit to finish the infusion; when prepared under conditions of Low-Risk Level CSPs, BUD is 48 hours at controlled room temperature (see USP General Notices and Requirements), 14 days at cold temperature (see USP General Notices and Requirements), and 45 days in solid frozen state between -25° and -10°, in the absence of direct sterility testing evidence that supports longer BUDs.

29. Are there any criteria that specifies BUD if sterility testing is done?

Sterility storage durations specified at the particular temperature ranges for Low-Risk Level, Medium-Risk Level, and High-Risk Level CSPs may be exceeded when evidence of sterility based on proper testing can be documented. The particular BUD of longer sterility storage times based on testing evidence shall be the judgment of appropriate compounding personnel, and it shall assure chemical and physical stability of the CSPs.

30. What type of expiration dating do you give to devices such as continuous infusion pumps?

Refer to USP General Notices and Requirements to differentiate expiration date from beyond-use date. The BUD of such preparations in this question depends on the microbial contamination risk level of the compounding process, i.e., whether for Immediate-Use CSPs, Low-Risk Level CSPs with 12-Hour or Less BUD, Low-Risk Level CSPs, or Medium-Risk Level CSPs.

31. What is the BUD for extemporaneously compounded eye drops for both inpatient and outpatient use?

The BUD of ophthalmic CSPs depends on the microbial contamination risk level of the compounding process, i.e., whether that for Immediate-Use CSPs, Low-Risk Level CSPs with 12-Hour or Less BUD, Low-Risk Level CSPs, Medium-Risk Level CSPs, or High-Risk Level CSPs.

32. If a commercially available IV fluid (i.e., Lactated Ringers or Normal Saline) is spiked in anticipation of emergent administration, for example in an ambulance, trauma emergency bay or a trauma OR room, does the 1 hour expiration time apply to this situation?

Yes. Since the spiking of an IV bag is considered sterile compounding, administration within the one hour time limit would be applicable. The individual performing this task should use appropriate aseptic technique and should perform (if possible) a thorough hand sanitation.

Cleaning and Disinfecting the Compounding Area

33. Can vials be cleaned with alcohol swabs or 70% IPA wetted gauze pads?

Alcohol swabs must be sterile. Sterile 70% IPA wetted gauze pads or other particle generating material shall not be used to disinfect the sterile entry points of packages and devices (see Cleaning and Disinfecting the Compounding Area).

34. Can nonsterile 70% IPA be used to disinfect surfaces other than those in the DCA of the primary engineering controls in the ISO Class 5, 7, and 8 areas?

Yes. The chapter requires that surfaces be cleaned with sterile water for irrigation or injection to remove any soluble residues with low-shedding wipes. This is followed by wiping with a residue-free disinfecting agent (such as sterile 70% IPA), which is allowed to dry before compounding begins. However, the Chapter does not require that the residue-free disinfecting agent be sterile.

35. Do supplies need to be decontaminated when they are put on the shelf (taken out of shipping carton) if pharmacy is going to wipe them before they are introduced into the buffer area?

If the supplies are going to be put on a shelf in a general pharmacy area they do not need to be wiped until being introduced into the buffer area.

36. How soon before going into the BSC do supplies need to be sprayed with sterile IPA?

If supplies are sprayed immediately before being introduced to the BSC the operator minimizes the risk of touch contamination that may occur if supplies are sprayed in advance.
37. We currently store syringes and needles in bins in the buffer area. Can we wipe every syringe down the day before and restock bins to get ready for the next shift or do we need to remove them from the buffer area? Can we re-spray with sterile IPA in the buffer area?

Removing supplies from the buffer area on a daily basis is not required. If supplies are disinfected prior to use it minimizes the risk of touch contamination. Re-spraying with sterile IPA in the buffer area is acceptable.

38. Do you recommend spraying sterile IPA and wiping with something dry (like Texwipe) or using a pre-moistened sterile wipe? Does it matter?

Pre-moistened sterile IPA wipes are acceptable. Water-soluble residues can be removed with sterile water and low-shedding wipes. This is followed by wiping with a residue-free agent such as sterile 70% IPA which is allowed to dry.

39. How does one clean the hood every 30 minutes during continuous compounding if the compounding process takes more than 30 minutes?

Clean the hood after completing the compounding process that takes more than 30 minutes.

40. Can bleach be used as appropriate cleaning agent and can diluted bleach be used exclusively as a disinfectant?

Bleach can be effective as a disinfectant but is inactivated by proteins. Bleach is not appropriate for disinfecting critical sites. Bleach is appropriate if followed by sterile 70% IPA wipe (see question #34) Consideration for the selection of cleaning agents should be given to the effect on surfaces and potential respiratory, skin, and eye irritation to the operator.

41. If practicing in a certified green building with limits on the types of cleaners that can be used, are there any Green alternatives for cleaning floors?

Vendors should be consulted for Green alternatives.

42. Are instant hand sanitizers adequate for use in the cleanroom?

Products for use in the clean room must be classified as a waterless, surgical hand antiseptic.

43. Individual alcohol wipes are used to swab the top of vials which involves opening multiple individual swabs. Can you describe a better process for this?

No

44. Are floor fatigue mats allowed and what is the cleaning process for them?

Floor fatigue mats have the potential to collect grit and grime. If fatigue mats are used they must be thoroughly cleaned on a daily basis which means picking them up and cleaning all surfaces.

45. It has been stated that other procedures can be used if proven better than <797> standards. Is this true for sterile IPA? If it can be proved that the disinfectant we use is better than sterile IPA, can we use our disinfectant?

Yes. However the operator needs to consider the effect on surfaces, material compatibility, and the operator. The disinfectant must not leave a residue.

46. Are we required to use sterile IPA for everything, including cleaning carts before bringing them into the clean room or just for the actual compounding activities?

Sterile 70% IPA is required for critical sites. Other disinfectants may be appropriate for carts and other surfaces. Consider the effect on surfaces, material compatibility and the operator.

47. We are seeing resistance to the use of sterile gloves and sterile IPA. Can you direct us to scientific support for the benefits of using sterile alcohol and sterile gloves over non-sterile?

Sterile gloves and alcohol have a lower bioburden.

48. In a facility that uses CACI/CAI would using sterile gloves and sterile alcohol be needed outside the isolators?

Yes, unless documented by the equipment manufacturer that this is not required.

49. May cleaning wipes be used for cleaning in the buffer area as long as they are lint free?

Low-shedding wipes shall be used.

50. In autoclaving, in order to reach a temperature of 121°C, should the pressure be raised higher than one atmosphere?

Steam sterilization is accomplished at 121°C at 1 atmosphere.

51. What concentration of sodium hydrochloric solution should be used? Why are solutions of NaDCC not listed under chlorine since they are more efficient, pH neutral, and more stable?

The chapter does not prohibit other agents. However, agents that may be used need to be evaluated based on microbial inactivation as well as chemical and physical properties.

52. When a secondary set and syringe/needle is attached to a bulk bottle for withdrawal of drug, how long can the set be kept before you need to change the set?

Pharmacy bulk packages are labeled as to the time period they can be used after initial puncture.

Personnel Cleansing and Garbing

53. What garbing is appropriate for a pharmacist that is checking but not manipulating CSPs in the buffer area? What if the pharmacist is entering to check the pump setting and lyte pool and calculation prior to mixing?

All individuals who enter the buffer area or clean room shall be fully garbed with appropriate personal protective equipment.
54. Is nail polish allowed? The Chapter refers to natural nails being kept short and neat but does not refer to polish. Is it allowed under gloves?
No. Nail polish should be removed under all circumstances as chipped nail polish has been shown to harbor microorganisms.

55. What garb is required for a CAI operator?
If the CAI is located in an ISO Class 7 environment, typical clean room garb (i.e. shoe covers, gown, hair cover, and mask) is required. If the CAI is not located in an ISO Class 7 environment, and it meets the requirements as stated in the Chapter to allow such placement, no additional garbing is required.

56. Are eye glasses required to be sterilized before entering the clean room?
No.

57. Do healthcare practitioners preparing immediate use parenteral products need to gown up, including gloves and mask?
No. Immediate use compounding is exempt from all requirements of the Chapter. That does not preclude the process of performing scrupulous hand hygiene and adhering to appropriate proper aseptic compounding technique.

58. Is gowning required even in an isolator? Should the isolator be located in a specific cleanroom?
See question 52. If the isolator does not meet the requirements set forth in the Chapter for maintenance of ISO Class 5 conditions during dynamic use, then yes, it must be placed in an ISO Class 7 environment (i.e. clean room) and gowning is required.

59. What do you consider sterile gloves? Do they have to be individually wrapped or can they be those that come with multiple gloves in a box?
As a rule, individually packaged gloves are considered sterile, single use and labeled as such. Multiple gloves in a box are generally not considered sterile once opened for use.

60. Are face covers required only for beards or do all personnel male and female need to cover their mouth and nose?
Face masks (that adequately cover the mouth and nose) are required for ALL compounding personnel.

61. If a glove is torn during compounding, do you have to wash your hands again before re-gloving?
It is not necessary to do a hand cleansing with soap and water within 30 seconds, but the hands should be re-sanitized using the alcohol-based (waterless) surgical hand antiseptic agent.

62. Do we need to garb before cleaning the ante-area?
The need to garb before cleaning the ante-area is dependent on the organization's policies and procedures. One should consider requiring full garbing and gowning if the period of time spent in the ante-area is of a longer duration (i.e. cleaning, stocking, etc.).

63. Can the gown be left in the ante area?
Yes.

64. Are we required to sterilize the lint free clothing?
No.

65. Are sterile chemotherapy gloves available?
Sterile chemotherapy gloves are commercially available.

66. If a vertical BSC (which is half-covered with glass in the front) is used, do we have to use full mask and face shields?
The wearing of a face mask is required if the BSC is located in one's clean room. A face shield is not required.

67. Must any headgear (including religious headgear) be totally covered by a cap in the clean room?
Yes.

68. Are masks required in the ante-area? If was our understanding that masks were only required in the clean room and buffer area.
The need to wear masks in the ante-area is dependent on the organization’s policies and procedures. One should consider requiring full garbing and gowning if the period of time spent in the ante-area is of a longer duration (i.e. cleaning, stocking, etc.).

69. During cleaning of our biological safety cabinets our operators wear N95 masks. Should other personnel in the clean room also take exposure precautions?
Yes, if compounding is occurring during the cleaning of the BSC. Optimally, cleaning of the BSC should occur when no other activity is occurring in the clean room.

70. If humans are the greatest risk in the compounding of IVs, why not consider secondary gowning requirements?
While the individual compounding is the greatest source of contamination, the environment does contribute to a certain degree. Appropriate use of PEC’s along with the appropriate use of sterile gloves, routine disinfection of those gloves and technique should result or maintain a sterile CSP.

71. Please speak to the need for further verification/validation of automated compounding devices when the manufacturer states that calibration is the only necessary step?
Periodic additional verification/validation of the automated compounding device ensures that the calibration and use process result in the stated product (volume, contents, etc.) being prepared.
Hazardous Drugs as CSPs

72. If hazardous drugs are non-sterile does the requirement to use an ISO Class 7 ante-area apply?

Hazardous non-sterile drugs used to compound non-sterile dosage forms such as oral capsules or liquids and topical ointments (among others) should also be handled in a manner to prevent contamination of healthcare workers and others. Personnel protective equipment (PPE) such as gloves should be worn when handling hazardous drugs. Compounding hazardous drugs that are in powder form may require the use of a device to control and contain powder that could become airborne; a fume hood or similar device vented to the outside may be satisfactory. An ISO Class 7 ante area is not required for preparing non-sterile compounded preparations.

73. Can CACI that meets the negative pressure requirement be used if it is placed in a regular room or does the negative pressure CACI need to be placed in a separate negative pressure room?

The CACI shall be placed in a separate negative pressure room. The ISO Class 5 (see Pharmacists’ Pharmacopeia, Table 1, page 797) BSC or CACI shall be placed in an ISO Class 7 (see Table 1 above) area that is physically separated (i.e., a different area from other preparation areas) and optimally has not less than 0.01-inch water column negative pressure to adjacent positive pressure ISO Class 7 (see Table 1 above) or better ante-areas, thus providing inward airflow to contain any airborne drug. However, in facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (example: closed-system vial-transfer device within a BSC or CACI that is located in a non-negative pressure room) is acceptable.

74. Do hazardous drugs need to be stored in a separate room to meet the air changes standard?

Hazardous drugs may be stored in the same negative pressure room as the CACI or BSC.

75. Does the storage standard apply to all hazardous drugs or just the chemo agents?

It applies to all hazardous drugs. If documented information becomes available as to the safety of storage and handling of specific drugs, it may be possible to store them in standard storage areas.

76. Should the room be negative pressure if you have a room with a horizontal flow hood and a vertical flow hood for hazardous drugs?

As stated in chapter <797>, hazardous drugs shall be prepared in a negative pressure room. All hoods and procedures used in the room should be designed for proper operation in the negative pressure environment unless the situation allows for the low volume exception in the chapter. A second-tier of containment (e.g., CSTD) would be required when a BSC is located in a positive-pressure ISO Class 7 buffer area.

77. In a satellite pharmacy that compounds hazardous medications, is an ante-area necessary if compounding is done in a CACI that is vented to the outside located in a negative pressure room?

Ideally, yes. The reasoning here is that under most cases patients being treated with these hazardous drugs are immune-compromised and the extra sterility precaution is needed for their protection. However, in facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (example: closed-system vial-transfer device within a BSC or CACI that is located in a non-negative pressure room) without the use of an ante-area or buffer room is also permitted in Chapter <797>.

78. If the CACI does not exchange air with the room that it is placed in, does it have to be vented?

The issue with a CACI that does not vent to the outside is that volatile substances (hazardous drugs) can build up inside the CACI and contaminate the outside of IV bags, etc. thus increasing the potential to bring contamination outside the CACI. All BSC’s and CACI’s should be vented.

79. Can you explain what a “closed-system vial transfer device (CSTD)” is?

A Closed System Vial Transfer Device is a generic term used to describe a device that does not allow any substance to escape outside the vial or bag during the transfer process. This will include vapors, liquids, powders, etc. The system should be totally closed. An air vent is not considered a closed system even if the vent includes a 0.22 micron filter.

80. How do you certify staff compounding cytotoxic agents? Are there any guidelines?

There are many commercial certification programs available, but a self-designed program may also be sufficient as long as all criteria are met and personnel are continually evaluated. There are test kits available to verify technique using fluorescein as a marker which may be a method of annual evaluation of personnel.

81. If a pharmacy does a very limited number of chemos using CSTD, why do they have to store drugs in (-) pressure?

No matter how few the doses prepared, the drugs are still hazardous and should be stored properly to protect personnel working in the area. However, USP <797> states "Thus storage is preferably within a containment area such as a negative pressure room".

82. Does USP 797 require that hospitals maintain separate ante-area/clean room environments for chemotherapy preparations and non-chemotherapy preparations? In other words, for a hospital that makes both types of therapies, do they need to have two production environments that are independently certified?

Hazardous drugs should be prepared in an ISO class 5 BSC or CACI that is placed in an ISO class 7 area that is physically separated (i.e., a different area from other preparation areas). Separate areas are needed for non-hazardous compounding and hazardous compounding. The exception being for facilities in which hazardous compounding is low-volume.

Radiopharmaceuticals as CSPs

83. If a nuclear medicine tech prepares a kit from a Tc99m standard preparation sent from a radiopharmacy, would this be considered Immediate Use if it is a single dose? If multiple doses is it considered Low Risk? 12 hr. BUD

The classification of a radiopharmaceutical kit prepared by a technologist using Technetium 99m Sodium Pertechnetate sent from a radiopharmacy depends upon the environment that is used for its preparation. The kit can be prepared for a single dose or within one hour of its preparation. In this case, the technologist must comply with the six conditions specified in the Immediate-Use CSPs category. Also, the prepared radiopharmaceutical kit should not be stored for any anticipated needs.

The kit may be used for multiple doses if it is prepared as a Low-Risk Level CSP with 12-Hour or Less BUD in a segregated compounding area or better environment by a technologist that is properly prepped and garbed.

84. For radiopharmaceuticals, should the bubble point test be performed before and after filtration or just after?

The bubble point test should be performed after the filtration of radiopharmaceuticals. Precautions to control radioactive contamination and to maintain radiation exposures to As Low As Reasonably Achievable (ALARA) must be in place.

85. Under what circumstances can radiopharmaceuticals be used beyond 12 hours?
The determination of beyond-use times and beyond-use dates (BUDs) for radiopharmaceuticals as CSPs are reviewed in USP 32 NF 27 General Chapter <797> under the heading Determining Beyond-use-Dates. It reads that “when CSPs deviate from conditions in the approved labeling of manufactured products contained in CSPs, compounding personnel may consult the manufacturer of particular products for advice on assigning BUDs based on chemical and physical stability parameters.” It continues with “compounding personnel may refer to applicable publications to obtain relevant stability, compatibility, and degradation information regarding the drug or its congeners. When assigning a beyond-use-date, compounding personnel should consult and apply drug specific and general stability documentation and literature where available, and they should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions and the intended duration of therapy.” This section also describes the limitations of theoretical BUDs of CSPs based on predictions derived from other evidence such as publications, charts and tables. The section also explains that “truly valid evidence of stability for predicting BUDs can be obtained only through product-specific experimental studies … such as thin-layer chromatography.”

The Determining Beyond-use-Dates section also states that “the compounding facility shall have written policies and procedures governing the determination of the BUDs for all compounded products.” It requires that “The SOP manual of the compounding facility and each specific CSP formula record shall describe the general basis used to assign the BUD and storage conditions.”

A BUD can be established by following the methods described in the Determining Beyond-use-Dates section of General Chapter <797>. An experimental study method for establishing the stability of the radiopharmaceutical would require the compounding facility to verify the CSPs quality and purity under its preparation and storage conditions that are routinely used. For Radiopharmaceuticals as CSPs, compounding personnel must consider verifying at a minimum: the conditions of preparation that go beyond approved labeling of the product, packaging used, storage conditions, and that the CSP maintains sterility, the appropriate limit for pathogens for its route of administration, its radiopharmaceutical purity, and its radionuclidic purity. (Refer to page 338 USP 32 NF 27 General Chapter <797>)

86. When using high risk non-nuclear components in synthesis of PET preparations the components are prepared in a clean room adjacent to the synthesis area. Does the chapter apply to the clean room specifications and to the preparation of the non-nuclear component preparations?

General Chapter <797> is superseded by USP 32 NF 27 General Chapter Radiopharmaceuticals for Positron Emission Tomography – Compounding <823>. The PET chapter contains a section titled - Control of Components, Materials and Supplies, which indicates that “a designated person shall be responsible for ensuring that activities are carried out and completed properly.” It further requires that such person “determine that each batch of components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals are in compliance with established written specifications.” If the written SOPs of the facility references General Chapter <797>, it would apply. If a clean room is designated as the area of preparation in the written SOPs of the facility it would have to meet the definition of a Clean Room in General Chapter <797> and general information chapter Microbiological Evaluation of Clean Rooms <1116>. In any case, professional judgment for patient safety in regard to the compounding environment for components used in a PET radiopharmaceutical preparation must be used.

87. Are radionuclide white blood cells medium or high risk?

It is difficult to categorize CSPs that are radiolabeled blood components as medium or high risk-level CSPs. The blood component could be considered a nonsterile ingredient. If considered so, the labeling process would be a high-risk condition and guides for that category would be used (e.g. OSHA regulation 29 CFR 1910.1030 Bloodborne pathogens).

Environmental Quality and Control

88. How long may sterile plastic caps, syringes, or devices be stored in a class 5 environment after being opened?

These supplies and devices should only be opened just prior to use. Any opened packages need to be protected from touch contamination and must be stored in “first-air” and within the ISO Class 5 air at all times. The USP Chapter does not stipulate this time and it is responsibility of the compounding facility to ensure the sterility of any supply or device used when compounding CSPs.

89. How often does the endotoxin challenge test need to be performed?

The effectiveness of EACH dry-heat depyrogenation cycle needs to be verified with an endotoxin challenge test.

90. Can you incubate a plate too long?

Yes.

91. Are fingertip sampling and surface sampling required in CAIs and CACIs?

Yes. Sampling should be incorporated into an overall Quality Improvement Program that measures the competency of the worker and the effectiveness of the cleaning and disinfection process.

92. For initial sampling, 3 samples with 0 CFU are required but the table for Microbiological Action Levels sets the action level as >3. Can you clarify the requirements for glove finger tip sampling?

The initial sampling is to demonstrate the training and garbing competency of personnel training prior to compounding. Compounding personnel must be able to don sterile gloves without contaminating them. The action level of 3 is the maximum allowable CFUs on gloves during actual compounding activities.

93. A pressure gauge is required to monitor the pressure between the buffer area and the ante-area, and also between the ante-area and the main pharmacy room. Does this mean that we need two pressure gauges for the IV room?

Yes.

94. Is there a requirement to use a third party for particle count sampling or can we do it ourselves?

The particle counting can be done by the pharmacy staff or by someone brought in from the outside so long as they are deemed competent to operate such equipment.

95. What additional filter integrity testing methods exist?

The appropriate HEPA filter integrity testing method is to use an aerosol photometer with an appropriate oil-based challenge such as PAO.

96. Are there USP Action Levels for non-viable counts?

See Pharmacists’ Pharmacopeia Table 1, page 797.

97. Can we use the USP recommended action levels instead of using historical data, if the USP levels are stricter?

If historical data are higher than USP levels, a qualified microbiologist should be consulted to investigate the differential between USP levels versus actual levels. Changes in cleaning agents or frequency may be required to decrease the microbial bioburden in the area being tested.

98. Are random glove finger tip cultures recommended or mandatory? Could they be incorporated into the media fill procedures?

Glove finger tip cultures are required as a measurement of operator competency, and incorporating them into the media fill procedure would be an excellent aseptic technique proficiency test.
99. Are there specific recommendations for air samplers in terms of sampler size, air volume, etc.?

Specific recommendations are not provided. The impaction air sampler should be able to collect a sufficient volume (e.g., 1000 liters) within a reasonable amount of time.

100. Should all positive cultures be sent for microbial identification?

Yes. The chapter states: "Regardless of the number of cfu identified in the compounding facility, further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial isolates cultured as a cfu from an impact air sampler. Highly pathogenic microorganisms (e.g., Gram-negative rods, coagulase positive staphylococci, molds and yeasts) can be potentially fatal to patients receiving CSPs and shall be immediately remedied, regardless of cfu count, with the assistance of a competent microbiologist, infection control professional or industrial hygienist."

101. How do we demonstrate competency of personnel performing environmental testing if we are performing our own environmental testing using our own purchased equipment?

There are vendors who sell training programs and there are commercial environmental microbiology labs that can be contacted for assistance in validating the competency of personnel.

102. Our facility uses an automix compounder for macro ingredients when compounding TPNs. This compounder is gravimetrically validated the competency of personnel.

You contact the manufacturer and ask them how to verify the device's volume accuracy. USP Chapter <797> states: "The intermediate precision of the ACD can be determined on the basis of the day-to-day variations in performance of the accuracy measures. Thus, compounding personnel shall keep a daily record of the above-described accuracy assessments and review the results over time. This review shall occur at least weekly to avoid potentially clinically significant cumulative errors over time. This is especially true for additives with a narrow therapeutic index, such as potassium chloride."

103. Is end product testing required for low and medium risk preparations?

No.

104. If using manufactured single use filters for high risk compounding do we need to test each filter before use? Do you test the lot of filters purchased?

USP Chapter <797> states: "Filter units used to sterilize CSPs shall also be subjected to manufacturers' recommended integrity test, such as the bubble point test."

105. Should bubble-point testing be done for every high risk CSP that is sterilized by filtration?

Yes, see the answer above for Question #103.

106. When monitoring temperatures and humidity in rooms, what are the humidity ranges we need to be looking for?

Temperatures below 20°C (68°F). Specific guidance is not provided in USP Chapter <797> for humidity but general practice is to maintain the humidity between 35% and 60%.

107. If a hood certifying company would perform every six month electronic air sampling, what would the facility need to do? Alert humidity between 35% and 60%.

This must be agreed upon between the certification company and the pharmacy. It is the pharmacy's responsibility to assure a plan is in place that properly accomplishes the required tasks.

108. Do positive and negative isolators need to be in separate rooms and what defines separation?

Positive isolators are appropriate for non-hazardous compounding and must be in a separate room from the negative pressure isolator used for hazardous compounding unless the low-volume exception applies. Separation is physical separation such as a separate room.

109. What do you do if action levels are exceeded in environmental monitoring?

You use the data to assist in identification of the source of contamination and then develop and execute a remediation plan.

110. What is the proper disposal of culture media after exposure and incubation?

Culture media should be autoclaved or discarded as hazardous medical waste after exposure and incubation.

111. In a low volume (5-6 products per day) operation we want to use one biologics hood. Can we move from hazardous to nonhazardous when compounding these preparations?

USP <797> does not require nor forbid such a practice. The decision is left up to each compounding site. However, whatever procedures and practices are used, they should be designed to keep personnel safe from exposure to drug contamination and keep the dose safe from inadvertent microbial contamination. In addition, care must be taken to prevent cross contamination from hazardous to nonhazardous such as through cleaning of the hood, etc. Documentation such as wipe studies can be conducted to make sure the hazardous drugs are being contained.

112. How do we read the temperature listed in USP 797?

All temperatures in the USP and NF that lack a temperature system abbreviation are degrees Celsius or Centigrade. When Fahrenheit temperatures are used, they are in parentheses after Celsius or Centigrade temperatures, and include the F designation. For example, from the General Notices and Requirements, Cold – between 2° and 8° (36° and 46°F).

113. We have recently purchased barrier isolators. These hoods have an ISO Class 100 environment. Per the newest revisions what is the maximum sterility/stability time for chemotherapeutic agents compounded in this way?

The sterility storage durations for all CSPs depends on the conditions under which they were prepared. The answer to follow assumes that chemotherapeutic agents mean Hazardous Drugs by NIOSH definition. Hazardous Drugs as CSPs are not permitted under the conditions of Immediate-Use CSPs and Low-Risk Level CSPs with 12-Hour or Less BUUs. The sterility storage durations for Hazardous Drug compounded according to the conditions for Low-Risk Level CSPs are 48 hours at controlled room temperature (see USP General Notices and Requirements), 14 days at cold temperature (see USP General Notices and Requirements), and 45 days in solid frozen state between -25° and -10° in the absence of direct sterility testing evidence that supports longer BUUs.

114. We compound all 3 risk levels of products. If we compound high-risk products, are we required to do viable air sampling monthly using an impaction device? I was under the impression that 797 requires this sampling every 6 months.

USP requires minimum sampling every 6 months. You should evaluate your facility and trend your data to assure every 6 months is adequate.
115. What physical objects are allowed to be in the clean room, such as floor mats, printers, pens, markers, shelving, etc.? Does alcohol have to be 70% IPA to disinfect the technician's gloves?

There is no prohibition to particular objects, devices, and materials in clean rooms or buffer areas. The presence of such items must be verified according to the Environmental Testing and Surface Sampling standards to maintain the air and surface quality required for these compounding areas. All 70% IPA used to disinfect the gloves of compounding personnel and critical sites, such as vial stoppers and ampul necks, must be sterile.

116. Commercial sterile empty vials are used by compounders to be the packaging for sterile products. The practice is to inject the sterile drug into the empty sterile vials. This results in a vial with a punctured stopper and is usually sealed with a foil seal and given a BUD in accordance with the 4 limits of low, medium, or high risk compounding. Once a commercial sterile vial is punctured is it considered a single use vial or can the defaults for low, medium, and high risk BUD be used in absence of stability and sterility data?

The general notices section of USP 32 defines a multiple-dose container as "a multiple-unit container for articles intended for parenteral administration only." According to the same section, "a multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion." Since stability and sterility data are not available, it should be considered a single-dose container.

117. Does the Chapter address air-tight pass-through devices from the ISO 7 clean/buffer room directly into the unclassified areas of the pharmacy for IV checking?

No. The chapter does not address the use or placement of air-tight pass-through devices.

118. Are pass-through refrigerators allowed from the ISO 7 clean/buffer room directly into the unclassified pharmacy? Or do they need to pass through to the ante-room only?

Pass-through refrigerators are allowed and should be installed in a manner that will have no negative impact on the environmental controls.

119. Does the anteroom and segregated compounding area need to have the same finishes as the buffer rooms? Since this is cleaned on the same rotation as the buffer room it would seem so, but please clarify.

Yes, the ante area and segregated compounding area need to have the same finishes as the buffer area.

120. Where is the best location for the low air return in a negative pressure chemo mixing room in relation to the hood to cause the least disruption of air and assure that the chemo hood will vent correctly?

Ideally, air is exhausted and not returned back into a negative-pressure hazardous drug buffer area. Total airflow volume will dictate exhaust volume rate. In some cases, all exhaust air is pulled from the PEC.

121. We have seen some pharmacies that requested that the walls to be coved to each other vertically as well as the walls coved to the ceiling. Is this necessary? Is just caulking gyp board to gyp board and painting with epoxy sufficient? Is that just a cleaning issue--being easier if coved?

Coving is not necessary. It does aid cleaning.

122. Must there be a separate room for the mixing of IVs (low and medium risk) or can it be an area of the main pharmacy as long as ISO 8 ante and ISO 7 buffer areas are maintained and it is out of the path of travel?

The sterile compounding area must be a separate area defined by walls and doors. The chapter provides details for fit and finish, room segregation, as well as HEPA filtration of the air. Sterile compounding is a very specialized critical operation and should not be carried out in the main pharmacy, except in the rare case of Immediate-Use CSPs.

123. Where is the line of demarcation to be located...at the entrance to the Buffer area or within the ante-room where garbing of foot covers occurs? Does this need to be a built-in line such as a different color of sheet vinyl?

The line of demarcation is a visible line on the floor that separates the room into areas for different purposes. For example, in the ante area the line separates the cleaner and less clean sides of the room. "When the line of demarcation separates two different ISO classification areas, it must be accompanied by a minimum air velocity of 40 fpm from the cleaner area to the less clean area." The line can be built into the floor or it can be tape on the floor. If tape is used, over time the tape may become damaged, collect dirt (which makes cleaning more difficult), and peel up from the floor causing a tripping hazard, therefore should be monitored. The exact location of the line will be dictated by the process and the facility design.

124. When using polymer wall panels in the buffer room, what is the recommended way to apply and finish them? In other words, do you recommend using the trim pieces or just caulking the joints and leaving as flush as possible?

USP does not recommend specific processes. The chapter requires the finished product to be smooth and imperious to facilitate cleaning.

125. Since the mops used in the buffer area cannot be used elsewhere, do you recommend a housekeeping closet in the ante-area?

USP does not recommend how this is facilitated. A housekeeping closet can accomplish the task.

126. Is a large ante-room required, or would a small vestibule for hand washing and donning of protective garb be sufficient? In other words, could there be an IV work room that is unclassified where the computer input, unboxing and storage of IVs takes place outside of an ante-room to reduce the square footage of space required to be ISO 7 or 8? The IVs would still pass into the buffer area through the vestibule that is the ante-room.

USP does not define the process flow requirements. A small ante room that simply facilitates hand hygiene and gowning is adequate.

127. Does the exhaust from the room air returns as well as the exhaust from the hood need to be HEPA filtered and exhausted 100% outside in negative pressure hazardous drug buffer rooms?

No. The exhaust from the BSC must be HEPA filtered. Class II BSCs and CACI's are equipped with HEPA filters in the exhaust. Additional HEPA filtration typically is not required.

Education and Training

128. Is a written examination required for personnel training or would a verbal exam be enough?

Yes, a written competence assessment is required. <797> states "Compounding personnel shall complete didactic training, pass written competence assessments, undergo skill assessment using observational audit tools, and media-fill testing).

129. If dispensing to patients, who then have the CSP administered by a visiting nurse, is the pharmacy required to provide formal education to the nurse or to the patient?
The patient and the nurse must both be educated. A formal training program is provided as a means to ensure understanding and compliance with the many special and complex responsibilities placed on the patient or caregiver for the storage, handling, and administration of CSPs. There are 12 instructional objectives given in the chapter and at the conclusion of the training the patient or caregiver should, correctly and consistently be able to perform them all. The compounding facility, in conjunction with nursing or medical personnel, is responsible for ensuring initially and on an ongoing basis that the patient or caregiver understands, has mastered, and is capable of and willing to comply with all of these home care responsibilities.

130. What protocol is recommended for compounding during room certification? Should the technicians be working on actual preparations?

When room certification is going on you have extra equipment in the room and extra people. It would not be appropriate to work on actual preparations but instead you may use that time to perform a media fill which would be the very worst case scenario, or work using expired drugs which are then destroyed. As long as it is a dynamic situation with your people in the room going about normal tasks it is fine.