

**Additional Commentary to USP 31-NF 26 Second Supplement**  
**General Chapter <797>Pharmaceutical Compounding—Sterile Preparations**  
Revised July 31, 2008

*Note: This commentary document applies exclusively to public comments relating to General Chapter <797> Pharmaceutical Compounding – Sterile Preparations, which was published in USP 31-NF 26 Second Supplement.*

In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, revision proposals can advance to official status with modifications without further public review, unless the Expert Committee determines that additional review is needed due to the nature or significance of the comments received or the changes made. When no additional review is needed, a summary of comments received and the appropriate Expert Committee's responses are published in the *Commentary* section of the USP website at the time the revision becomes official. For those proposals that require further revision and republication in *Pharmacopeial Forum*, a summary of the comments and the Expert Committee's responses will be included in the briefing that accompanies each article.

The *Commentary* section is not part of the official text of the General Chapter and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee's response to public comments. If there is a difference between the contents of the *Commentary* section and the official monograph, the text of the official monograph prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary* section, shall prevail.

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**Expert Committee:** Sterile Compounding (SCC)  
**Number of Commenters:** 500+

Comments and responses are grouped according to sections and topics in the proposed version of the chapter, and do not necessarily correspond to the final version of the revised chapter.

## ***INTRODUCTION***

**Comment:** Most of the comments about this section involved the purpose of the chapter, and the perceived costs of implementing the proposed changes. Some commenters wanted more clarification as to the intent of the chapter, and its limitation to only pre-clinical administration compounding activities. Many commenters stated that clinical administration information is included in the chapter, even though the Sterile

Compounding Committee (SCC) insists that the chapter does not describe conditions for clinical administration. Some commenters wanted the SCC to remove any reference to clinical administration.

**Response:** The SCC has no comment in relation to the cost of implementing changes in chapter <797>. The SCC asserts that the purpose of the chapter is clearly stated, and that <797> clearly states that it pertains to preparation, storage, and handling of the compounded sterile preparations (CSPs) up to the point before administration to patients. The SCC maintains that any process during or after administration is not covered by chapter <797>. SCC maintains that the chapter only pertains to pre-clinical compounding, storage, and transportation activities except in cases where there is no break in practice, such as handling and disposal of hazardous drugs, etc. Thus, the SCC maintains that the chapter does not pertain to clinical administration, and therefore no change was made regarding that matter. However, the SCC modified this section slightly to emphasize that the avoidance of contamination from direct contact is paramount, and that this is a critical consideration in maintaining sterility.

**Comment:** Comments asked to whom the chapter applies, and what is covered by the definition of “compounded sterile preparation” (CSP). Others questioned whether USP Chapter <797> applies to sterile compounding of veterinary preparations, and if it does, whether that should be explicitly stated.

**Response:** The SCC asserts that the definition of CSP is clearly stated. The SCC used the word “patients” and purposely omitted categorizing them as humans or animals. The intention is that the chapter apply to CSPs for humans and animals.

**Comment:** The environment surrounding isolators is different for three different applications of isolators described in the chapter: (1) No restrictions or pressurization or surrounding air quality, (2) ISO Class 8, or (3) Negative pressure with either ISO Class 7 or no restriction on surrounding air quality. Commenters recommend omitting these references if the isolator manufacturer can provide validation that the isolator maintains ISO Class 5, is gas tight for both airlock and primary chamber.

**Response:** The SCC has clearly described the conditions of requirement for placement of primary engineering controls where hazardous drugs, nonhazardous drugs, and radiopharmaceuticals are prepared as CSPs. The SCC agrees that the isolator manufacturer must provide validation information proving through objective testing that the isolator can maintain an ISO Class 5 air quality in the area in which critical sites are exposed, including entry and egress of essential materials, when the isolator is located in either an ISO Class 7 or 8 controlled environment or any uncontrolled, unclassified environment. The revised chapter states the conditions that must be met if the isolator is located in an uncontrolled environment and only low-risk level nonhazardous and radiopharmaceutical CSPs pursuant to a physician’s order for a specific patient are prepared.

## **GENERAL COMMENTS**

**Comment:** A commenter suggests that this chapter is not ready for implementation. It should be moved to an informational chapter and given a number above 1000 until it can be determined if the content should be enforceable.

**Response:** The SCC has heard the comment, and notes that the precursor chapter to <797>, chapter <1206>, was numbered above 1000 but was, in fact, more stringent than this current chapter. That chapter, however, was not implemented by a large number of practitioners. The SCC has simplified the requirements in some sections such as environmental monitoring, and added or revised new sections and subsections such as “Immediate Use” and “Low-Risk Level CSPs with 12 hour or less BUD.”

**Comment:** Many changes were recommended that were editorial in nature.

**Response:** The editorial changes suggested by commenters were considered and incorporated.

**Comment:** The chapter emphasizes the need for high standards but continues to recommend non-sterile alcohol as a disinfectant without discussion or reference to the efficacy of alcohol. One commenter recommends requiring the use of sterile alcohol, requiring all disinfectants to be sterile, identifying a number of examples of disinfectants, and listing FDA recommendations. Another commenter questions whether sterile alcohol must be used, and whether it presents a significant advantage to the use of regular 70% isopropyl alcohol (IPA). Use of sterile 70% IPA is not cost effective for the healthcare facility and patients. Another commenter suggested that sterile alcohol must be used in order to disinfect a suitable environment for compounding a sterile preparation, and that the use of non-sterile disinfectant should not be considered.

**Response:** The SCC adopted the use of sterile 70% IPA in the chapter after considering published data and recommendations from multiple commenters including the advisory panel formed to review the section. Sterile 70% IPA must be used to disinfect sterile gloves intermittently, vial stoppers, ampul necks, and injection ports on containers. The SCC felt that since a sterile glove is required to minimize bio-burden, the use of sterile 70% IPA will help enhance the bio-burden reduction effort. SCC discussed the use of sporicidal agents, but decided against them because of their drying time of one or more hours, deposition of residues, and chemical reactivity were strong disadvantages.

**Comment:** A commenter questioned why the SCC requires sterile gloves.

**Response:** The SCC adopted the use of sterile gloves in the chapter after considering published data and recommendations from multiple commenters, and the advisory panel formed to review the section in addition to the existence of evidenced-based science in community standard of practice. The greatest risk of contamination is from touch, so by using sterile gloves this bio-burden is minimized.

**Comment:** One commenter suggested reformatting the chapter to (1) state the legal requirements and (2) include a “non binding” section that includes examples, illustrations and details of ways to comply with the requirements. The commenter argued that this approach would allow for innovation and more freedom to apply sound principles for the preparation of compounded sterile products.

**Response:** Although the chapter has not been reformatted exactly as the commenter suggested, the revised chapter includes a statement regarding new and non-included technologies. In addition, an Appendix differentiates, section by section, the practices and standards that are requirements from those that are recommendations only.

## **DEFINITIONS**

**Comment:** One commenter suggested that the definition of ante area should include written procedures to address how materials are to be introduced into the ante area, and then to the buffer area. Other commenters felt that the SCC has not defined the term “ante-area” before using it interchangeably with ante-room. This interchanging of ante-area and ante-room causes confusion.

**Response:** The SCC judges the definition of ante-area to be adequately broad to allow each compounding facility to create its best practice environment. The suggested standard operating procedure section of the chapter has some minimum practice process in place. This could be extrapolated to accommodate requirements in handling materials from the ante area into the buffer area. Based on the other comments, the SCC has changed the term ante-room to ante-area throughout the document.

**Comment:** The definition of buffer area should be distinct from cleanroom to avoid confusion. Too many different names were used to describe the buffer room/area. Choose one term to use throughout the document to avoid confusion.

**Response:** Only one term is used for the buffer area and the SCC has defined the buffer area and clean room separately. Please see the definitions section of the chapter.

**Comment:** Include the concept of sterilization in the definition of an isolator.

**Response:** Sterilization is described in the chapter for working in ISO class 5 environments.

**Comment:** Direct and Contiguous Compounding Area (DCCAs) should be defined.

**Response:** A definition for direct compounding area (DCA) now is provided and moved to the definitions section. The term DCA replaces DCCA; thus, no definition for DCCA was provided.

**Comment:** A commenter suggests adding a definition for Compounding Aseptic Containment Isolator (CACI). The CAI definition is not precise enough.

**Response:** The Committee has reviewed the definition of CAI and slightly revised it. The Committee then added the new term “compounding aseptic containment isolator” (CACI), and a definition for it.

**Comment:** A commenter suggests that the Committee totally misses the primary function of the anteroom for antiseptic preparation of sterile products. One commenter recommends inclusion of appropriate disinfectant in the definition of ante area. Another commenter suggested that the definition of disinfectant should be modified and expanded to include references such as FDA, etc.

**Response:** Regarding disinfectants, the SCC made no change. The section on Cleaning and Disinfecting the Compounding Areas in <797> refers to USP chapter <1072>, and a new Appendix II was developed with additional information regarding selection, use, and properties of disinfectants.

**Comment:** Commenters suggested defining “expiration date” and “beyond-use date” (BUD).

**Response:** These terms are defined in the *USP* General Notices.

**Comment:** Commenters suggested defining the following terms: “Hazardous drugs” (should be defined using the NIOSH definition), “garb,” “clinical administration” (and

clarify whether it is different from administration), “compounding,” “sterile compounding” (to reflect FDA’s definition), “dispensing,” and “sheddable cosmetics.”

**Response:** The SCC clarified many and added several definitions including, for example, critical sites, First Air, and Segregated Compounding Area. It also clarified the term Sterilizing Grade Membrane. However, the SCC also determined that the definition section should contain a limited number of definitions that apply primarily to multiple sections in the chapter. Generally, a term used only in one section is defined only in the section it is used.

**Comment:** A commenter suggested that negative pressure rooms have no place in the chapter.

**Response:** The SCC asserts that negative pressure rooms are pertinent to compounding of hazardous drugs, and; therefore, did not delete this reference. The SCC sees the need to define the terms used in some section(s) of the chapter, e.g., the hazardous drugs section, and establish standards to protect compounding personnel from exposure to toxic substances. Negative pressure is recommended, but not required, for ISO class 5 primary engineering controls (e.g., CACIs or biological safety cabinets (BSCs)) in ISO Class 7 buffer areas. In such cases, there is only a small possibility of airborne contamination, which is less likely than the contamination potential from direct contact. The majority of the air that enters a negative pressure room comes from an ISO Class 7 buffer area; thus, the amount of contamination that could come through wall penetrations is insignificant.

**Comment:** Commenter suggests expanding Reference number 1 (footnote in the definition of Anteroom referencing ASHRAE) to include a more appropriate facility design definition such as ISO 146644-1.

**Response:** The SCC acknowledges the comment but disagrees with the contention that other design definitions are “more appropriate;” thus, did not make a change. One objective of the chapter is to provide minimum practice and quality for CSPs of drugs and nutrients based on current scientific information and best sterile compounding practices.

**Comment:** Regarding reference number 2 (footnote citation of CETA in the definition of CAI), the commenter suggests that CETA is not a recognized source for definitions of technical engineering control devices. Commenter suggests removing the CETA reference because, in the commenter’s view, the reference adds no value to the document and detracts from its credibility.

**Response:** The SCC made no change based on the preponderance of information provided at the April 13, 2007 meeting of representatives of isolator manufacturers and experts at which almost all attendees acknowledged and recognized the appropriateness of CETA guidelines as a valid performance testing document.

## ***RESPONSIBILITY OF COMPOUNDING PERSONNEL***

**Comment:** A commenter asked whether a compounding supervisor is required to be a pharmacist or other licensed person.

**Response:** A compounding supervisor is a licensed healthcare professional or other person who is skilled, educated, or well trained to safely and correctly supervise the activities of sterile compounding.

**Comment:** Commenters requested clarification of the term “qualified licensed healthcare professional.”

**Response:** The SCC made no changes, as it believes that the term “qualified licensed healthcare professional” speaks for itself.

**Comment:** Commenters requested that the Committee add “stability and sterility” between the words “direct testing” under “beyond use date.”

**Response:** The SCC did not add the words “stability and sterility” because they are already indicated for BUD testing.

**Comment:** Commenters also asked the Committee to clarify whether the CSP must be time stamped to ensure that 6 hours has not passed since the initial time of preparation.

**Response:** <797> does not include a requirement for time-stamping, as this is a personnel training or standard operating procedure (SOP) issue.

## ***CSP MICROBIAL CONTAMINATION RISK LEVELS***

**Comment:** Commenters suggest that the CSP microbial contamination risk levels should be modified to address issues specific to radiopharmaceuticals. They suggest creating a new category of CSPs specific to radiopharmaceuticals within the chapter, consistent with that described in USP chapter <1075> Good Compounding Practices.

**Response:** The SCC made no changes. The proposed section titled Radiopharmaceuticals as CSPs appeared in the 2006 In-Process Revision as a result of public requests received at some of the five public workshops and one compounding stakeholder forum that featured chapter <797> that were held by USP in 2004-2006.

### ***Low-Risk Level CSPs***

**Comment:** Commenters request clarification of the requirement for low-risk level. Would three vials of a liquid medication placed into one IV bag for a single patient be considered a low- or medium-risk level CSP? Can one use three products plus a diluent and consider that low-risk? Is it correct to say that mixing 2 additives to a liter bag is low-risk, but mixing 3 additives to a liter bag is medium-risk? Can the proof entry of an infusion bag be punctured no more than 3 times within the requirement for low-risk?

**Response:** The SCC made no change. SCC asserts that the description of low-risk level conditions is clear: “no more than three commercially manufactured sterile products, and no more than three entries into one container package (e.g., IV bag or vial) of the sterile products to make the CSP.” Any difference in the required number of products for manipulation will disqualify the preparation as low-risk level.

**Comment:** Commenters ask whether storage temperature value is Celsius or Fahrenheit.

**Response:** All temperatures in *USP-NF* are in Celsius, as defined in the *USP* General Notices.

**Comment:** Commenter asks whether a simpler version of USP <71> sterility test can be devised for all three risk levels at the pharmacy level for batches up to 24 identical dosage units to yield a dating equal to or greater than 30 days. They also inquire whether rapid testing methods (e.g. by Pall) can be solution to this test.

**Response:** USP chapter <71> Sterility Tests cannot be simplified with present technology; however, there are expert consultants and businesses that specialize in sterility testing, which may be of help in performing batch related tests.

**Comment:** For the storage period, there is no limit specified for the storage of drugs that cannot be refrigerated after compounding. The commenter asks whether there is a reason for this omission.

**Response:** Data to support the information requested needs to be gathered through published research, which currently is lacking. Such research is outside the capability of the Committee.

### ***Medium-Risk Level CSPs***

**Comment:** A commenter asks why the statement in the official chapter, “The CSPs do not contain broad-spectrum bacteriostatic substances ...” was removed in the proposed revision. Together with the definition of multiple dose containers, this original statement makes medium-risk conditions more clear, in the commenter’s view. For condition #2, a commenter suggests that an example of “complex aseptic manipulations” would be helpful. Why is “controlled room temperature” used for room temperature and “controlled cold temperature” is not used for cold temperature? Should total parenteral nutrition (TPN) be considered a medium-risk and not a low-risk level CSP?

**Response:** The SCC made no change. The SCC asserts that the requirements of the medium-risk level category are clear.

**Comment:** Can product simulation sterility testing in lieu of testing the actual product be used for low- and medium-risk level CSPs?

**Response:** Product simulation sterility testing in lieu of testing actual CSPs was considered by the Committee, but the Committee declined to add it. Instead, the chapter includes greater emphasis in personnel aseptic work practices to prevent microbial contamination of CSPs.

**Comment:** Commenters ask, with regards to the change of storage time from 7 to 9 days, whether scientific evidence supports this change, and, if so, whether the committee can provide references. Is there scientific evidence to support a higher risk to patients at 10-12 days? One commenter asserts that the BUD of 9 days for medium-risk CSPs is arbitrary and should not be any less than the low-risk CSPs BUD of 14 days.

**Response:** The change from 7 to 9 days was due to the practical issues of compounding TPNs, including transportation (especially interstate shipping) times by home-care practices. ***High-Risk Level CSPs***

**Comment:** Commenter asked the Committee to clarify whether ISO Class 7 or 8 environments are required for high-risk level procedures.

**Response:** The SCC made no change. The ISO class for this risk level is delineated in this section.

**Comment:** Commenter suggests that the BUD for high-risk CSPs is arbitrary and far too short to provide patients with needed medications in a timely manner, and would result in an additional cost to patients.

**Response:** The SCC made no change because of the absence of information to support the safe use of a different BUD. The BUD provided is to be used in the absence of data supporting a longer time period. If the compounder has research data to support longer time period, then that can take precedence.

### ***IMMEDIATE-USE CSPs***

**General statement:** This section was included in the 2006 In-Process Revision based on (a) requests from attendees at the five public workshops on compounding that featured chapter <797>, which were held by USP in 2004 and 2005; and (b) the reality that preparation of some urgently medically necessary CSPs according to the conditions stated in the chapter for low-risk level CSPs would consume too much time to provide therapy for some acutely ill and severely suffering patients.

**Comment:** A commenter asks for clarification about the relationship between “Immediate Use” and the statement “complying with low-risk level standards.” Are they not separate issues?

**Response:** Immediate-Use CSPs is a separate section that is not covered by the CSP Microbial Contamination Risk Levels section. The Immediate-Use section applies only to the simple aseptic transfers that otherwise would be considered low-risk level CSPs, but that are not compounded under the conditions required of low-risk level and are intended for immediate use rather than for prolonged storage. The SCC has revised this section to clarify its intended purpose and compounding conditions to indicate that it includes only simple aseptic transfers of not more than three commercial sterile drugs, as is also the case for low-risk level CSPs. Immediate Use also excludes Hazardous Drugs, to protect compounding personnel from unwarranted exposure.

**Comment:** A commenter suggested that the Immediate-Use category would not allow the use of TPN therapy, IV fluid additives, and IV Pump medications to be drawn up in syringes for patients to administer or add to their IV bags at home. Another commenter asks whether TPNs to which caregivers must add additional ingredients prior to infusing at homes are exempt from the Immediate Use CSP rules.

**Response:** TPN therapy usually consists of more than three sterile ingredients; therefore, it is usually medium-risk level and does not qualify for the Immediate-Use category.

**Comment:** Commenters asked about the scientific justification for the one hour expiration. A commenter suggests that the one hour expiration is too strict unless scientific support exists. Another suggests that the choice of one hour appears arbitrary, and that 12 hours would be just as appropriate. A commenter suggests that no scientific evidence indicates that mixing sterile solutions under otherwise sterile conditions, except for air quality less than ISO Class 5 results either in contamination after a maximum of one hour or has been shown to pose a risk to patients after one hour.

**Response:** One hour is a judgment expected to minimize the opportunity for microbial contamination and colonization based on the expected growth rates of microbes that might be accidentally introduced during compounding, and to fulfill the purpose of “Immediate Use.”

**Comment:** Another commenter inquires whether the one hour expiration could be expanded for certain locations, e.g., satellite pharmacies with hoods.

**Response:** If compounding of all sterile ingredients is performed by properly trained and garbed personnel with critical sites being exposed in ISO Class 5 sources, then those CSPs are either low- or medium-risk level, subject to the longer time limits in those sections.

**Comment:** A commenter asks whether certain unstable 4-ingredient admixtures may be prepared by competent staff in a surgical environment, as approved by the facility.

**Response:** Under <797>, these admixtures cannot be prepared as Immediate-Use CSPs. This example describes a medium-risk level CSP.

**Comment:** If an IV is mixed without utilizing a Laminar Air Flow (LAFW) hood and hung within one hour and does not hang for longer than 12 hours, would this qualify as an Immediate-Use CSP?

**Response:** The Immediate-Use category of CSPs is only concerned with preparation and storage time prior to initiation of clinical administration. The chapter does not include limits on times or durations of clinical administration of CSPs although it does note that these properly remain professional concerns of health care personnel for the safety of patients.

**Comment:** The commenter points out that institutions with LAFW hoods located in satellites that are not ISO Class 7 environments prepare low-risk level CSPs with 24 hour BUD, but cannot guarantee that the product is used in one hour. The commenter inquires whether these preparations can be considered Immediate-Use CSPs.

**Response:** To address this concern, the SCC added a subsection on “Low-Risk Level CSPs with 12 Hour or Less BUD” in the “Low-Risk Level CSPs” section.

**Comment:** The proposed chapter states that drugs on the NIOSH list may not be prepared as Immediate-Use CSPs. A number of the drugs on the list are required to be prepared at the patient’s bedside. An example is Pitocin (Oxytocin). The commenter recommends removing the reference to hazardous drugs from the chapter, as the inclusion of this text does nothing to increase patient safety, which is the intent of chapter <797>.

**Response:** The SCC maintains that hazardous drugs should be prepared in a safe and controlled environment. Safety of compounding personnel is as important in this chapter as is patient safety; thus, the requirements of the Immediate-Use category and the Hazardous Drugs as CSPs section have been modified and retained. Oxytocin is not required to be prepared at the patient’s bedside, although that has been done in practice for convenience. Diluted oxytocin is often supplied by the central pharmacies in hospitals and by outsourcing compounding pharmacies. The SCC does not have authority to revise the NIOSH list of hazardous drugs. Stability studies have been published to demonstrate the extended chemical stability of diluted oxytocin, which allows compounding to occur in the pharmacy under appropriate environmental conditions while using proper personnel protective equipment (PPE).

## ***SINGLE- DOSE AND MULTIPLE-DOSE CONTAINERS***

**Comment:** Several commenters were opposed to the 28 day limit for multi-dose vials. Two suggested that the limit should be 30 days or monthly, rather than 28, because implementation of the 28 day process is extremely cumbersome. The hospital culture is accustomed to a 30 day month. This would also ease the dating of vials in the work setting. Commenters ask whether studies have proven that an anti-microbial is only good for 28 days after entry. Since sterility testing was carried out for only 28 days, they suggest that it is highly likely that the multiple-dose vials would have been sterile longer. They suggest that the test be repeated and extended to a real end point before the 28 day limit is established. They point out that the limit for medium-risk compounds has been extended from 7 to 9 days for ease of home delivery of TPN, and inquire why the limit for multi-dose vials cannot be similarly extended. They also point out that FDA had directed to use the manufacturer's expiration date and the Joint Commission had previously defined 30 days. They ask whether those entities are now supportive of the 28 day limit.

**Response:** The selection of 28 days instead of 30 days is based on the testing performed under USP General Chapter <51> Antimicrobial Effectiveness Testing that is conducted on multi-dose products for a period of 28 days. The SCC added a notation that permits use for longer time periods after initial entry if the manufacturer allows for a longer period in the product labeling.

**Comment:** Commenters requested several other changes to the time limits for usage. For multi-dose solutions, a commenter requests inclusion of a statement that when solutions containing preservatives are mixed and stored under sterile conditions, without meeting ISO Class 5 air quality, the time limit for usage can be up to 12 hours. A commenter asked the Committee to consider the use of single-dose vials in the operating room for a longer period of time, such as 8 hours. Another commenter requests scientific evidence to support the 1 hour and 6 hour time limits.

**Response:** The requirements for both single- and multi-dose containers have been clearly delineated in this section, and after careful consideration, the SCC made no other changes to the existing text.

## ***HAZARDOUS DRUGS AS CSPs***

**Comment:** Several commenters suggested deleting this section. Some commented that it does not meet the objectives of USP chapter <797>. A commenter suggested that USP should focus on General Chapter <797> on patient treatment and leave issues of employee safety to the experts at OSHA and NIOSH.

**Response:** This section appeared in the 2006 In-Process Revision as a result of public requests, including at least one from a state board of pharmacy, received at some of the five public workshops that featured chapter <797> that were held by USP in 2004 and 2005. Based on the preponderance of pre-2006 public comments that support including such a section in the chapter, the SCC disagrees with the recommendation to remove this section entirely. The SCC disagrees that the chapter's primary purpose of

protecting patients treated with CSPs expressly excludes protecting compounding personnel from hazardous drugs. The SCC thoroughly revisited this proposed new section and made several changes. The new revision has changed many of the proposed requirements to recommendations only.

**Comment:** Commenter suggests that footnote number 6 and recommendation are inappropriate for storage of parenteral products. A negative pressure room would increase to some extent the level of nuisance dust in the room that could lead to an additional bio burden on the outside of containers. Commenter recommends removing the sentence beginning with “The storage area...any airborne contaminants.”

**Response:** The SCC disagrees and made no change. While the main focus of <797> is on sterile and accurate CSPs being provided to patients, this does not obviate the need to protect compounding personnel from hazardous drugs. The negative pressure condition protects personnel outside the compounding area from hazardous drug exposure at a minimal risk of ingress of airborne contamination. The reference in footnote 6 allows compounding practitioners to identify and maintain the best practice environment free of airborne contamination. Also, see response to comment in the definitions section.

**Comment:** Several commenters objected to the recommendation for a negative pressure storage area for hazardous drugs with a minimum of 12 air exchanges per hour. One commenter suggested that the recommendation is in direct conflict with FDA recommendations and standard practice for areas used in the preparation of sterile products. The commenter suggested that the referenced “Laboratory Design Guide” has nothing to do with sterile facilities. The commenter asserted that contamination of facilities comes from two sources: improper primary engineering controls and touch transfers by personnel working in the area. If the engineering control is validated to control to a defined level, then only limited amounts of contaminant will be present in the surrounding area. Thus, proper engineering controls, personnel protective equipment, personnel training supported by monitoring, and procedures for decontamination when leaving the area will provide a safe environment. Another suggested removing the section on hazardous drugs entirely, and requiring only primary engineering controls that are validated for hazardous drugs. The controls need to be validated in dynamic conditions and for the intended use. Another commenter states that no evidence in the literature shows that the negative pressure area would have any effect on exposure to employees or others.

**Response:** The SCC maintains that while the main focus of <797> is on sterile and accurate CSPs being provided to patients, that does not preclude the necessity of protecting compounding personnel from hazardous drugs. The negative pressure condition protects personnel outside the compounding area from hazardous drug exposure at a minimal risk of ingress of airborne contamination. The hazardous drug section will help to maintain the best practice environment free of airborne contamination.

**Comment:** Several commenters suggest that NIOSH guidelines should not be written into USP chapter <797> because this will make them enforceable. One commenter suggested that recommendations contained in the NIOSH alert are currently recommendations and if incorporated into the chapter would become regulations.

**Response:** Chapter <797> presents sterile compounding practice standards that are enforceable by regulatory authorities, but are not regulations. The SCC asserts that the chapter is correct in providing practice standards for the safety of persons who both prepare and are treated with CSPs.

**Comment:** Commenters suggested that the need for negative pressure storage areas and negative pressure room for the BSC external venting are excessive and expensive, and should be deleted. The requirement for a separate ISO 7 anteroom for the negative pressure hazardous drugs will be prohibitive for most hospitals, as well as for freestanding clinics, and may overwhelm low-volume hospitals. In fact, imposing this standard may encourage more outpatient preparation of these materials under less rigorous standards. Another commenter pointed out that the statement, “If a compounding isolator ... quality” indicates that an isolator can be used outside a cleanroom but must be located in a negative pressure room with the entrance to the negative pressure room being an ISO class 7 ante-room. This effectively requires a cleanroom to be built to support the negative pressure room.

**Response:** The Committee feels there is need for negative pressure storage. The negative pressure condition protects personnel outside the compounding area from hazardous drug exposure at a minimal risk of ingress of airborne contamination. There is no requirement for a separate ante-room for the negative pressure room. The same ante-room can be used for both the non hazardous and hazardous compounding rooms. The difference in cost of making the ante-room ISO class 7 instead of ISO class 8 is minimal. For example, using a relatively large ante-room size of 10' x 10' with an 8' ceiling (total volume of 800ft<sup>3</sup>) the difference to go from 20 air changes per hour (ACPH) (266 cubic feet per minute (CFM)) as appropriate for an ISO class 8 room to a minimum of 30 ACPH (399 CFM) for an ISO class 7 space only requires 133CFM. In either case, all of the supply air can be delivered through one HEPA filter. Additionally, there is no need for an additional negative pressure room for hazardous drug storage. Smaller volume hazardous compounding facilities can simply store the hazardous drugs in the chemo prep room, which should already meet the minimum criteria for drug storage. The NIOSH alert requires the use of engineering controls that do not recirculate either within the device or back into the room (i.e., they must be externally vented). Chapter <797> is consistent with NIOSH in requiring external venting of the primary engineering control. Since the primary engineering control must be externally vented, the requirement for a negative pressure room becomes easy to accomplish. The act of externally venting the primary engineering control will typically remove enough air from the room to create the necessary negative pressure.

**Comment:** Several commenters suggested that the volume of preparation of hazardous drugs varies between hospitals. Although the chapter allows an exception for chemo in the small hospital if they use a compounding aseptic isolator and a system like Phaseal, this exception is limited to less than 5 compounded chemo doses per week. One commenter recommends that there be no quantitative restrictions for the number of chemo preps prepared using a CAI and a closed system vial transfer device (CSTD) system like Phaseal, while another suggests that “a reasonable number” of preparations (greater than 5/week) or an average number should be allowed. An alternative would be to avoid defining specific number and allow the institute to determine what is appropriate. The commenters urge that an allowance must be made

for the sterile compounding of hazardous, chemotoxic, or radioactive products utilizing negative pressure in order to protect personnel and the environment from contamination with hazardous products.

**Response:** The use of CSTDs is a recommendation and not a requirement. It is preferable or desirable as a best practice to protect patients and personnel from aerosolized hazardous drugs and prevent venting or exposure of the hazardous substance to the environment. The use of CSTDs does not preclude the need for a properly operating primary engineering control designed for sterile hazardous drug preparations.

**Comment:** Some commenters objected to the language allowing the use of a CSTD for low volumes of hazardous drugs and the language that “Containment of the finished hazardous product shall be maintained throughout the administration/disposal phase.” The commenters suggested that only validated primary engineering controls should be used for hazardous drugs, and that these controls need to be validated in dynamic conditions and for their intended use.

**Response:** The use of CSTDs is a recommendation and not a requirement. It is preferable or desirable as a best practice to protect patients and personnel from aerosolized hazardous drugs and prevent venting or exposure of the hazardous substance to the environment. The use of CSTDs does not preclude the need for a properly operating primary engineering control designed for sterile hazardous drug preparations.

**Comment:** The NIOSH guidance document referenced in the chapter does not apply to radiopharmaceuticals or their preparations. The commenter recommends that USP specifically state in this section and in the proposed “hazardous drug” definition that radiopharmaceuticals are not classified as hazardous drugs.

**Response:** Radiopharmaceuticals are excluded from the Hazardous Drugs as CSPs section. The revised chapter includes a specific section titled Radiopharmaceuticals as CSPs.

**Comment:** Several commenters questioned the requirement for 12 air changes per hour (ACPH). One questioned the need for and the expense of ensuring that the storage area for hazardous drugs has 12 ACPH unless this is the normal number of air exchanges in an air conditioned controlled room temperature area. Another suggested reducing the requirement to 10.

**Response:** The engineering factor that gives an area the ability to maintain the desired classification is primarily the amount of HEPA filtered air delivered to the room. The FDA guidance value for aseptic manufacturing is a minimum of 20 ACPH for an ISO class 8 room. Various clean room guidances suggest ACPH between 10 and 25.

**Comment:** The proposed changes to the chapter would require venting of all primary engineering controls. A commenter asks whether USP has data to support this requirement for all primary engineering controls. The commenter further asks whether a manufacturer of a primary engineering control may be exempt from the requirement if they have validated data to support that venting is not required and, if so, whether this exemption will be stated in the regulation. If not, the commenter asks about the justification for this prescriptive action that, in the commenter’s view, could limit innovation.

**Response:** The Committee defers to scientific evidence whenever it is available. The SCC cannot assume that primary engineering control devices from all manufacturers meet and maintain the ISO Class 5 air quality during preparation and transfer of CSPs in all secondary engineering control environments. It is the responsibility of each engineering control device manufacturer to provide validation data and information that support this requirement. Nearly all representatives of CAI and CACI manufacturers at the April 13, 2007 isolators meeting at USP headquarters noted that their products are externally vented. The Committee would consider data and information submitted to support exceptions to this requirement. The SCC believes that this requirement encourages innovation while providing a best practice environment for patient and personnel safety.

### ***RADIOPHARMACEUTICALS AS CSPs***

**Comment:** One commenter suggested deleting this section, as it does not meet the objective of chapter <797>.

**Response:** The SCC formed an Ad Hoc Advisory Panel of radiopharmaceutical pharmacists and scientists to review the section. The Panel recommended keeping this section, and its recommendation was approved by the Committee.

**Comment:** One commenter asserted that glove fingertip sampling should not apply to nuclear pharmacy practice because it is too prescriptive.

**Response:** The SCC feels that since contact is a great way of introducing contaminants to sterile preparations, no exemptions to glove fingertip sampling are appropriate, and glove competency evaluation is required for all personnel as indicated in the section.

**Comment:** Two commenters asked that the SCC eliminate the requirement for storing and eluting technetium-99/molybdenum-99 generator systems in an ISO Class 8 or cleaner environment. The commenters recommend that the chapter require a limited access room and individual site verification of compounded sterile product quality through ongoing environmental, product, and personnel monitoring methods, as described in the proposed “same-day radiopharmaceutical CSPs” new category.

**Response:** The Panel recommended, and the Committee approved, that the storage recommendations are provided, but that the manufacturer’s recommendations should prevail in the event of a difference.

### ***VERIFICATION OF COMPOUNDING ACCURACY AND STERILITY***

**Comment:** Commenter suggested that it may be useful to explain what a bubble test is or how to appropriately conduct one

**Response:** The SCC made no change. Bubble test procedures are provided in relevant textbooks, internet sites, and by sterilizing filter manufacturers.

**Comment:** Commenters suggested that it may be useful to clarify the steam and dry heat sterilization section.

**Response:** The sterilization section has been improved to clarify the effectiveness of steam and dry heat sterilization. Additionally, the SCC added text to differentiate between the use of dry heat for sterilization and depyrogenation.

## ***ALLERGY THERAPY***

**Comment:** Commenters suggested that the requirements presented are excessive for the practice of allergy therapy. They suggested that allergy treatment is a unique process that needs proper consideration if it is to be a part of <797>.

**Response:** The SCC added the new section titled “Allergenic Extracts as CSPs” after publication of the 2006 In-Process Revision based on evidence that 27,000 immunotherapy injections, which were not prepared in ISO classified controlled environments by personnel gloved and garbed according to standards specified in the chapter for low- and medium-risk level CSPs, were not associated with any infections (Lin SY, et al, May 2007 issue *Otolaryngology-Head and Neck Surgery*). Dr. Lin provided this information to the SCC as a representative of The American Academic of Otolaryngic Allergy (AAOA) and Joint Council of Allergy & Immunology (JCAAI). The SCC established practice standards in the Allergenic Extracts as CSPs section that are deemed appropriate to protect patients treated with allergen extract CSPs administered by intradermal or subcutaneous injection. These CSPs require less rigorous conditions than those established for low-, medium-, and high-risk level CSPs, which are often given intravenously or intrathecally.

## ***ENVIRONMENTAL QUALITY AND CONTROL***

### ***Facility Design and Environmental Controls***

**Comment:** Commenter requested the insertion of a floor plan for use with CAIs.

**Response:** The SCC revised the current sample floor plans to conceptually or simplistically represent functional zones of ISO Classes 5, 7, and 8 as a series of concentric circles. Because CAIs are ISO Class 5 primary engineering controls, CAIs would be included in the general ISO Class 5 zone depicted in the new diagram.

**Comment:** A commenter suggested that USP should reconsider the method used to calculate the environmental air flows. At the very least, USP should provide more time for engineers to evaluate the calculation rationale used to derive the particle counts and air changes. Further, tests should be done to determine if there is any impact from the buffer area air quality on the air in a properly-located ISO 5 cabinet.

**Response:** The SCC reviewed the comment, but did not see cause to make a change.

**Comment:** Commenters suggest that the following proposed engineering controls will increase design, construction, and operational costs:

- Increasing the performance requirements for the buffer area from an ISO 8 to an ISO 7 level;
- Provide an ISO 8 level of performance for the anteroom;
- Requiring HEPA filtration for supply air to the buffer area;

- Creating a pressure differential of .02 to .05 inches water column between the buffer area and anteroom if there is a wall present; and
- Providing displacement airflow of 40 fpm or more across the line of demarcation from the buffer area to the ante-area.

The commenters point out that three authoritative sources (FDA's GMPs, ASHRAE, and USP <1116>) fail to justify the need to dramatically increase the air purity requirements. Another commenter recommends adding the following text: "Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended cleanroom design and control parameters. The principle of slow, careful movement should be followed throughout the cleanroom."

**Response:** The SCC maintained the ISO Class 7 proposal for buffer areas (clean rooms). The SCC believes that nearly all facilities will not require major reconstruction to meet ISO Class 7 as long as the buffer area is supplied with HEPA-filtered air from the ceiling, return air vents are located low on the walls, and ISO Class 5 primary engineering controls contribute to the buffer area air environment. These three factors along with basic sound design should allow for meeting the limit of 40 fpm airflow and 0.02 inches water column pressure between the buffer area and ante-area if there is a wall present.

#### ***Placement of Primary Engineering Controls Within ISO Class 7 Buffer Areas***

**Comment:** One commenter notes that the location for testing is indicated as 6 to 12 inches "upstream" of the critical exposures site, which is different from the location recommended by the FDA. The commenter suggests that the "upstream" location will not give any indication of particulate generation during the dynamic activity of compounding but simply will measure clean air direct from the HEPA filter. The commenter recommends changing the statement to identify the testing locations as "downstream" or "most critical locations during compounding."

**Response:** The Committee maintained the proposed language and made no change based on the scientific information provided at the April 13, 2007 meeting of representatives of isolator manufacturers and experts at the USP headquarters.

#### ***Cleaning and Disinfecting the Sterile Compounding Areas***

**General Statement:** The SCC substantively revised this section based on the recommendations of the Disinfectant and Cleaning Advisory Panel.

**Comment:** The commenters recommended that in the title "Cleaning and Disinfecting the Sterile Compounding Areas," SCC should change "sterile" to "aseptic."

**Response:** After reviewing this section, the SCC changed the title of the section to "Cleaning and Disinfecting the Compounding Areas."

**Comment:** A commenter asked whether isopropyl alcohol pad packets should be sprayed with alcohol before entering the buffer zone.

**Response:** The SCC feels that this issue should be addressed through SOPs. The commenter may wish to review the suggested SOP section of the chapter.

**Comment:** A commenter inquired about the rotation and disinfecting of cleaning agents, and about the appropriate types of cleaning agents.

**Response:** The SCC received objective scientific information that argued against the need to rotate disinfectants. The SCC decided against the use of sporicidal agents to disinfect critical sites, because those agents require extensive time (e.g., minutes to hours) to exert their effect, leave physical residues, are chemically reactive with some compounding component materials, and toxic to personnel. The revised chapter includes an appendix summarizing the usage and properties of several disinfectant chemicals.

### ***Personnel Cleansing and Garbing***

**Comment:** A commenter asks whether scientific evidence supports donning of sterile gloves. The commenter points out that as soon as any object is touched, the gloves are no longer considered sterile.

**Response:** <797> requires the use of sterile gloves instead of non-sterile gloves to reduce the initial microbial bio burden in ISO Class 5 areas where critical sites are exposed. It also requires the routine inspection of those gloves for defects, and routine re-disinfection with sterile 70% IPA.

## ***ENVIRONMENTAL MONITORING***

**General Statement:** The SCC considered the many comments regarding this section, and the recommendations of an Ad Hoc Advisory Panel on Disinfectants and Cleaning. Following extensive deliberation, this section was replaced with the following two new sections: Viable and Nonviable Environmental Air Sampling (ES) Testing, and Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices, and Cleaning/Disinfection Procedures. These new sections are deemed by the SCC, as recommended by the Panel, to represent reasonably achievable practices that ensure the maintenance of an appropriate aseptic compounding environment and suitable aseptic practices by compounding personnel. The SCC developed the following three performance evaluations (check lists) that are Appendices III-V in the chapter: Sample Form for Assessing Hand Hygiene and Garbing, Sample Form for Assessing Aseptic Technique and Related Practices for Compounding Personnel, and Sample Form for Assessing Cleaning and Disinfection Procedures.

**Comment:** Several commenters raised questions or issues about the proposed environmental monitoring section generally. One commenter points out that air and surface sampling only verify that a proper process is in effect, and that weekly monitoring is excessive and costly. Another commenter points out that many institutions have policies that prohibit routine, undirected sampling for microbial contamination. Others suggest that sampling should only be done if a problem is suspected, because random sampling will not help identify problems, but only will provide a considerable amount of data that is labor-intensive to collect but effectively meaningless. Because no consistent results can be obtained, the whole section should

be a recommendation only. Another commenter supported both air and surface sampling.

**Response:** The SCC had a prolonged deliberation on this section based on the comments received and on comments from the Panel that was formed to review this section. The SCC feels that surface sampling is an important component of the maintenance of a suitable microbially controlled environment for compounding CSPs, especially since transfer of microbial contamination from improperly disinfected work surfaces via inadvertent touch contact by compounding personnel can be a potential source of contamination into CSPs. Surface sampling is useful for evaluating facility and work surface cleaning and disinfecting procedures and employee competency in work practices such as disinfection of component/vial surface cleaning. Surface sampling shall be performed in all ISO classified areas on a periodic basis.

**Comment:** One commenter asks how environmental monitoring programs are to promptly identify “potential sources” of contamination, and asks whether this refers to air, surface or gloves, or identification of microbes. If the latter, the commenter points out that nothing in the environmental monitoring program is designed to identify contaminating species of microorganisms.

**Response:** The SCC considers sampling programs important in evaluating the competency of compounding personnel work practices, maintaining suitable microbially controlled environments, and designing and implementing corrective actions on an ongoing basis. The SCC has reorganized the environmental monitoring section to reflect these important facts.

**Comment:** If the purpose of surface and glove tip sampling is to demonstrate individual instances in which compounding personnel may contaminate surfaces and glove fingertips, several commenters suggest performing this testing at the time of media-fill competency to demonstrate any problems with sterile technique that an individual compounding technician or pharmacist may have. Media-fill testing is on a different, much less frequent, schedule from the Environmental Monitoring Sampling Schedule.

**Response:** The SCC has considered this comment and has made changes in the section Environmental and Quality Control in the revised chapter. The Committee did not link the frequency of surface and fingertip sampling to the frequency of media-fill testing.

**Comment:** A commenter points out that any facility preparing compounded sterile medications would be expected to follow the guidance put forth in <797>. However, the Healthcare Infection Control Practices Advisory Committee (HICPAC) of the CDC has published an evidenced-based guideline that specifically addresses the issue of routine microbiologic sampling of the environment in healthcare facilities. The evidenced-based CDC guidelines recommend against routine microbial sampling of both operating room equipment and the staff performing surgery as there is no data to support such a recommendation. The commenters are concerned that the proposed revision to chapter <797> would create a double standard for environmental monitoring in healthcare facilities and would likely lead to confusion. The commenters suggest that, consistent with the CDC guidance, environmental sampling should be optional, and should be recommended only in four specific situations: outbreak investigations, research, monitoring of a potentially hazardous condition (e.g. a suspected bio-terrorism event) and to assess changes in infection control practices or the function of specific equipment or systems.

Another commenter pointed out that the CDC Guideline for Environmental Infection Control in Health-Care Facilities (2003) referenced in footnote 13 is not consistent with FDA environmental monitoring recommendations. The commenter recommends removing the CDC reference and replacing it with FDA recommendations.

**Response:** The SCC considered the CDC guidelines, FDA recommendations, and comments, and has made changes in sampling procedures in the finalized chapter.

**Comment:** A commenter inquires whether satellite compounding areas that are only used for compounding stat items (i.e., Immediate Use) could be exempt from environmental monitoring requirements.

**Response:** <797> includes no exemptions from the sampling program.

**Comment:** Given the added focus on worker exposures, the environmental monitoring term will have different meanings to different audiences. A commenter suggests that adding "...for Asepsis" will clarify the intent of this section.

**Response:** The title of one of the sections replacing the proposed Environmental Monitoring section includes the term "aseptic," to increase clarity.

**Comment:** For environmental sampling, weekly for low-, medium-, and high-risk compounding is far too frequent and restrictive. Every six months would be more appropriate but every 3 months might be satisfactory.

**Response:** The SCC has clarified the frequency of environmental sampling in the revised chapter.

### ***Growth Media***

**Comment:** One commenter suggests that the use of MEA agar and the requirement of two media are not needed. TSA is commonly used in sterile pharmaceutical manufacturing and is quite capable of supporting fungal growth when incubated at the proper temperature, typically 20-25° C.

**Response:** The SCC has noted the comments, and made changes that are reflected in the new subsection on Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices, and Cleaning/Disinfection Procedures. Appropriate growth media are described in the sections for sampling programs.

### ***Air Sampling***

**Comment:** One commenter suggests that air sampling should be optional, rather than required, if all other monitoring is done for the anteroom and buffer room area. Another asks why the particle count is required monthly and not daily, since air sampling correlates with colony counts. Another suggests that the air sampling in buffer and ante areas has no proven benefit in low- and medium-risk compounding, and should be recommended for high-risk compounding only.

**Response:** The chapter now requires that nonviable air sampling shall be performed at least every 6 months as part of the recertification of facilities and equipments for the area where primary engineering controls are located.

**Comment:** Several commenters suggested the use of "active" air samplers rather than "electronic" air samplers. One commenter points out that this would give facilities more choice in matching the best test method to the particular environment. Active electronic

sampling validates the process, anything else is excessive. Another commenter points out that electronic air sampling would be a large expense to hospitals, especially 100 bed hospitals. Electronic samplers can move 100 liters of air per minute. Another commenter suggests the use of hand held electronic samplers. The commenter suggested that this would help keep the cost down and would recognize possible breaches in procedure to allow for quicker intervention. Another suggests that if electronic sampling is required, the frequency should be decreased.

**Response:** <797> requires the use of electric air samplers that actively collect volumes of air for evaluation. Volumetric air samplers are also recommended. Commenters may refer to USP chapter <1116> for recommendation on samplers.

**Comment:** One commenter suggests changing “settling plates” to “active air sampling counts” or “contact plate counts.”

**Response:** The SCC agrees with the commenter and eliminated the term “settling plates.” The revised section requires the use of electric air samplers when sampling air for viable particles.

### ***Surface Sampling***

**Comment:** Several commenters had input on surface sampling. One commenter does not agree with doing disburden testing on primary environmental control surfaces and asks for the justification for this section. One commenter expressed appreciation that surface sampling is only recommended. Another points out that no useful information is gained from routine surface sampling if a SOP for cleaning is followed, as it provides information for a single point in time. Another suggested that surface sampling has little or no value for low- and medium-risk compounding, and should be recommended for high-risk compounding only.

**Response:** The SCC disagrees with the commenters regarding the value of bio-burden testing. The requirements of <797> now are less stringent than in the proposed revisions. The chapter requires that surface sampling be performed on a periodic basis. This can be accomplished using contact plates and/or swabs as part of employee-related activities.

**Comment:** If this section is included, a commenter suggests that the chapter provide recommendations on appropriate surface sampling media (rather than “desired nutrient agar”) and devices (swab, strip, dip stick etc.). Another commenter requests guidance on testing using sterile swabs. One commenter recommended that the swab be used on a defined surface area and the results be based on the area that is swabbed.

**Response:** The SCC has made changes regarding the appropriate surface sampling media and specific requirements for surface area and CFU results for each respective area.

### ***Glove Fingertips Sampling***

**Comment:** Many commenters weighed in on the proposed requirement for weekly glove fingertip sampling. Several asked the committee to reconsider the requirement for glove fingertips sampling. Some suggested that it is too expensive and/or redundant and therefore a waste of resources, in light of the other testing and cleaning required of

compounding personnel, especially as it only verifies the quality of the system. Others suggested that microbes cultured from gloves have no clinical significance regarding patient safety, and that competency, testing, and monitoring of aseptic technique are virtually the only proven practical meaningful methods to assure CSPs are prepared appropriately. Others suggested that better value will come from frequent IPA disinfecting instead of weekly culturing of fingertips. Another commenter asks for the justification for glove fingertip sampling.

Some suggested that glove fingertip sampling be required only monthly, or made optional, for those preparing only low- or medium-risk CSPs. Another suggested that glove fingertip sampling should be recommended but not required. Another suggested that if all other samplings and monitoring are done, and staff passes media fill testing semi-annually, glove fingertip sampling should be an option in the event that the counts of colony-forming units (CFUs) increase or other monitoring exceeds baseline. Another commenter suggests that sampling should first be used during training and competency testing.

Some commenters suggest that glove sampling of one or 10% of staff does not seem an adequate number due to variability in individual technique and the fact that infrequent compounders might contaminate a higher rate of critical sites.

**Response:** The SCC maintains that all compounding personnel must successfully complete an initial competency evaluation and a gloved fingertip/thumb sampling procedure showing zero CFU no less than three times before initially being allowed to compound CSPs for human use. Since the greatest risk of CSP contamination is from operator touch contamination, fingertip sampling is intended to heighten personnel awareness of touch contamination and emphasize proper cleaning and disinfection of component surfaces.

**Comment:** Some commenters asked for clarification on the performance of glove fingertip sampling. Should four fingers be sampled, or four fingers and thumb be sampled? Another commenter asks whether each compounder requires a weekly glove fingertip testing, or whether one glove fingertip test per pharmacy per week is acceptable.

**Response:** The SCC has clarified the requirements for fingertip sampling in the revised chapter.

**Comment:** How is glove fingertip sampling performed in a CAI since the glove cannot be removed?

**Response:** The method of sampling gloves will need to be determined by the manufacturer and the user of the isolator, since these gloves are removable. The SCC believes that the information can be supplied by the isolator manufacturer. There have been a number of reported cases worldwide of microbial contamination of CSPs prepared in isolators. Regardless of the engineering control used, compounding personnel must be vigilant to ensure that gloved hands are routinely disinfected.

### ***Air and Surface Sampling Frequencies***

**Comment:** One commenter suggests that surface sampling for high-risk level CSPs should be conducted weekly rather than daily. Another suggests that low-risk level facilities should not have to conduct air sampling monthly.

**Response:** The revised version of <797> reduces the frequency of environmental sampling.

### ***Sampling Plate Incubation Period***

**Comment:** One commenter suggests harmonizing the temperature ranges and durations with those in chapter <1116>, which says to use Soybean-Casein Digest Medium and Soybean-Casein Digest Agar and incubate “in the 22.5° ± 2.5 and 32.5° ± 2.5 ranges ... with an incubation time of 72 and 48 hours, respectively.” The In-Process Revision of that chapter <1116> says “Typically for general microbiological growth media such as SCDM, incubation temperatures in the 22.5° ± 2.5 and 32.5° ± 2.5 ranges have been used with an incubation time not less than 72 hours.” Another commenter suggests that the SCC consider incubating the TSA at 20-25° for approximately 3-4 days and then transferring the samples to 30-35° for 2-3 days, which is common practice.

**Response:** The SCC agrees. The incubation section is harmonized with USP chapter <1116> and the SCC has clarified the temperature and duration of media incubation in the revised chapter.

### ***Action Limits, Documentation, and Data Evaluation***

**Comment:** Environmental sampling / culturing can be a very tricky monitoring process due to the lack of well accepted standards in interpreting results e.g. in Table 4, where microbial CFU is greater than 3, it triggers action to be taken. How was that number derived?

**Response:** The CFU counts in the revised chapter are only guidelines. Two principle documents that have recommended levels of CFUs are referenced in the revised chapter.

### ***Pressure Differential Monitoring***

**Comment:** One commenter is concerned with cost of air samplers and the necessity of pressure monitors. Another asks whether a pressure gauge or velocity meter, to be monitored daily, is really necessary with all of the other monitoring in effect.

**Response:** The SCC believes that the critical operating parameter of a properly functioning controlled environment is the maintenance of pressure differential. The cost of installing a simple magnehelic gauge or similar device is not cost prohibitive and integral to verifying the performance of the controlled environment.