

## Grifols Guide to USP <797> – Question of the Week

Answers by Lawrence A. Trissel and Eric Kastango



With the recent publication of the revisions to USP Chapter <797> many questions have arisen related to compliance with the new provisions. This issue of Grifols Guide to USP <797> includes answers to the question of the week through **September 29, 2009**. The answers to each question are provided by pharmacy experts & authors, Lawrence A. Trissel and Eric Kastango.

Answers by Lawrence A. Trissel

**Q:** Assuming physical stability, can I apply extended dating to a CSP that is mixed in a class 5 hood inside a class 7 clean room under the new USP <797> chapter guidelines?

**A:** USP Chapter <797> provides for surpassing the Microbiological Beyond Use date limits when a batch of a manually-compounded sterile preparation is subjected to the official USP Chapter <71> sterility test and passes that test. Then the Microbiological Beyond Use limits do not need to be applied. In addition, the Chapter provides for the use of alternative technologies to manual preparation as long as those technologies have been validated to be equivalent or, preferably, superior, to standard manual compounding. If the compounded sterile preparation is prepared using automated or robotic devices that have been validated to a 95% confidence level to prepare the compounded sterile preparations with less than 0.1% contamination occurring, and the device(s) are being maintained and used correctly, then extended dating can be applicable.

**Q:** In the introduction, the revised chapter says that "The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein." What does one demonstrate and how is it done with statistical significance? Can you give an example?

**A:** USP Chapter <797> used the language that is cited above for the specific purpose of not standing in the way of new and improved technologies that have been and are being developed. The Chapter describes the most common sterile compounding situation at present; that is, manual preparation by human compounding personnel. But automation and robotics are beginning to change the way sterile drugs are prepared. The Grifill® system, IntelliFill, RIVA, and CytoCare are already here. Other automation technologies are in development.

No matter how clean we believe we are, all of us humans are laden with microbes and can shed particles carrying these microbes at a rate in the millions per hour. This makes humans the largest source of contamination in the sterile compounding environment. The use of automation and robotics has the

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opportunity to reduce human contact in the compounding environment and, therefore, the chance that contamination finds its way into a patient's dose.

However, USP Chapter <797> states that before alternative technologies are considered suitable for use, they must be proven with statistical significance to be equivalent to or (hopefully) superior to manual preparation of sterile doses. This is typically the responsibility of the manufacturer of the technology, and is performed during the development process using microbial growth medium to simulate the automated sterile drug preparation process but with the ability to detect microbial contamination in every unit prepared.

To be statistically significant a minimum of 3000 media fill samples must be prepared with no contamination events occurring to be able to demonstrate a contamination rate less than 0.1% with 95% statistical confidence. This media fill testing should be conducted as the manufacturer proposes the device to be used in the clinical setting. Let's look at the Gri-fill® system media-fill verification testing as an example. The manufacturer indicates that the Gri-fill® system may be used outside of a ISO Class 5 primary engineering control, Therefore, the media-fill verification testing of over 3000 media fill samples by the Gri-fill® system was performed in such an environment to demonstrate that the contamination rate is no worse than that found with manual sterile compounding in an ISO Class 5 primary engineering control inside of an ISO Class 7 buffer area. Since the media-fill verification testing performed on the Gri-fill® system found no contamination occurred among this 3000+ unit cadre of growth medium samples, then statistical significance has been met, and the device would be considered acceptable under the USP Chapter <797> standards.

It is the responsibility of sterile compounding personnel to become educated consumers and be able to evaluate manufacturer's information to make sure the manufacturer's verification testing supports the intended use of the technology by the compounding organization.

Q:

**Who will inspect for and enforce the new USP <797> guidelines?**

A:

The United States Pharmacopeia provides drug standards for the United States. However, it does not enforce any of its standards. That function is performed by others.

In the case of USP Chapter <797>, this national quality standard that provides for an increased level of safety for patients, should be a professional aspiration of all of those involved in sterile drug preparation. It sets a level of quality and safety that patients deserve and have a right to expect.

Holding sterile drug compounding facilities and personnel to the standards of Chapter <797> is increasingly being performed by numerous state boards of pharmacy around the country. As these standards become more widely adopted, a transformation that is occurring at an increasing pace, additional states will undoubtedly begin enforcement. Furthermore, much of the content of Chapter <797> is consistent with the requirements of JCAHO. JACHO enforces its own rules, of course, including those consistent with <797>. Additionally, failing to adhere to Chapter <797>, a U.S. national safety standard, will increase the potential for legal judgments in the event of morbidity or mortality associated with flawed sterile drug preparation.

It can be expected that more payers and insurers, hospital infection control departments, and risk management departments will require compliance to minimize the risks (to patients, compounding personnel, and institutions) that are created by sterile drug compounding. For example, the Federal Government will no longer reimburse hospitals for hospital-acquired infections. That should be a financial motivator and important driver for improving the quality of sterile compounding.

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**Q: Can Barrier Isolators be used in lieu of re-modeling / or adding a clean room for compounding?**

**A:** Compounding aseptic isolators (CAIs) are a more recent technology in the United States having pluses and minuses compared to more traditional unidirectional airflow work benches. USP Chapter <797> states that CAIs are to be used in an ISO Class 7 clean room unless that isolator has been validated by the manufacturer to completely isolate the compounding area from the outside environment, maintaining the ISO Class 5 environment at all times, including during material transfer in and out as well as during all compounding manipulations. Although this makes simple common sense, not all CAIs can achieve this.

Typically CAIs that can perform in this way successfully will have unidirectional airflow in the material transfer chamber as well as throughout the compounding chamber and have airflow pressures balanced for the compounding chamber, material transfer, and the outside environment so as to prevent ingress of outside air. Each CAI will have a recovery time when materials are transferred into the compounding chamber. The good ones will recover back to an ISO Class 5 environment in seconds. Others can take many minutes.

The manufacturer must validate that the CAI can perform acceptably in its own facilities as well as it must document its performance at each use site as it is placed and used. In addition, certification of the CAI at the use site must be performed to Controlled Environment Testing Association (CETA) standards during dynamic working conditions (that is, with drugs going in and out and drugs being compounded), and must be recertified every six months.

It should be noted that poor personnel work practices can easily overcome the environmental controls created by the CAIs. These are not "magic boxes" that create sterile drugs. Compounding personnel with acceptable work practices create sterile drugs. The CAI can only provide a suitable environment for safe compounding. The work practices are really important in determining whether a successful sterile preparation is actually compounded.

**Q: If we purchase our CSP from an outsourced pharmacy, we transfer the liability to them if there is a contamination or dosing error, right?**

**A:** Actually no. The liability is likely to be shared between the outsource pharmacy and the purchasing pharmacy in the event of contamination or errors. The purchasing pharmacy has an obligation to secure and provide suitable safe and effective drug products for their patients from appropriate sources. The outsource pharmacy has an obligation to compound and prepare CSPs using methods and procedures to insure sterility and accuracy and that conform to all quality standards of USP Chapter <797>, requirements of state boards of pharmacy where the drugs are used, and requirements of accreditation bodies.

It is incumbent on pharmacies that purchase drugs from outsource compounding pharmacies to insure that those compounding pharmacies perform in a manner that meets all of the required standards. Do not just take their word for it; perform thorough and repeated evaluations to make sure that the outsource pharmacy is preparing CSPs correctly and responsibly.

Even then, purchasing pharmacies need to keep in mind that compounded CSPs are not as safe as commercial sterile drug products manufactured under FDA's Good Manufacturing Practices. Purchasing pharmacies should remember that they will always share a portion of any liability and should select drug

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sources that are in their patients' best interests for both the patients' and institution's safety.

**Q:** I work in a physician run clinic. We mix therapy for infusion and administration here at this clinic. Because we are not part of a hospital pharmacy, we don't have to worry about USP <797>, is that correct?

**A:** USP Chapter <797> is a national quality standard for the preparation of sterile drug doses. It applies to all sites and to all individuals without exception for profession or location, including physician run clinics. This national standard applies because no patient should ever have to give up their right to safe, sterile, accurate doses no matter where they are treated or the profession of the people involved in preparing the dose.

**Q:** In a presentation on USP <797> it was quoted that pharmacies should be striving for a less than 0.1% statistical contamination rate. We do all the recommended environmental testing, and media fill tests via a kit, yearly for each of our compounding staff members. Our results show that we don't have a problem. Can we assume that we have accomplished a less than 0.1% contamination rate?

**A:** A benchmark for aseptic processing in commercial drug manufacturing is proving statistically to the 95% confidence level that the contamination rate is less than 0.1% in manufacturing process. To do this, a minimum of 3000 media fill samples must be prepared with no contamination events occurring. Frequently, multiple batches of 3000 are prepared for each manufacturing process. This level of statistical evaluation is most useful for automated or robotic systems where the contamination from microbially-laden, error-prone human compounding personnel are minimized. However, given the human fallibility that we all share plus the microbial load we bring to the compounding environment, it is unlikely, to say the least, that manual compounding will achieve this level of certainty on a regular and ongoing basis, even if each employee was able to prepare the needed 3000 media fills for a test. All it takes is for a compounding person (who performed acceptably during their annual media fill test) to touch a contaminated surface, grab the phone, talk or sneeze, scratch their nose, get in a hurry and fail to wipe their gloved finger tips with sterile 70% isopropanol, etc. to compromise aseptic technique and accidentally contaminate a dose. Expecting humans to perform flawlessly, no matter how well trained, is a doomed strategy.

The goal of striving for a contamination rate of less than 0.1% to the 95% confidence level is a laudable one, but not likely to be achievable on a consistent and ongoing basis using manual compounding. While USP Chapter <797> expects media fill validation of compounding technique for each compounding employee on a regular basis, especially for training and educational purposes, the Chapter limits Beyond Use Dates instead of statistical evaluations to limit the risk to patients of contaminated aseptically prepared doses.

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**Q:** We have always compounded multi-unit containers and assigned 21 days BUD based on the use of aseptic technique and stability data for a CSP that falls under medium risk. Under the new USP <797> guidelines, what do we need to do to our cleanroom, so that we can continue this practice? Is this satisfactory?

**A:** Medium-Risk Level compounding is typically more complex than less risky simpler compounding. It usually involves four or more (sometime a lot more) drug packages being aseptically incorporated into a container, or multiple doses for a patient in the same container. Because of the complexity involved, the chance of contaminating a dose is increased compared to simple Low Risk Level compounding. Under USP Chapter <797>, both the original version and the new revision, Medium Risk Level compounding shall be performed in an ISO Class 5 primary engineering control, such as a unidirectional airflow workbench that is in an ISO Class 7 cleanroom. If all requirements of USP Chapter <797> for equipment and work practices are met, then the Beyond Use Dates in the Chapter can be used in conjunction with the chemical stabilities of the components of the preparation, whichever is less. In the case cited, the maximum Microbiological Limits for a Medium-Risk Level preparation are not longer than 30 hours at controlled room temperature, 9 days under refrigeration, and 45 days frozen at -20 °C.

**Q:** Should pharmacy personnel remove all jewelry and makeup before entering a buffer zone even when covered by masks, gloves, and goggles?

**A:** Absolutely. Jewelry and makeup are great sources of the microbes that each of us sheds continuously, no matter how clean we think we are or try to be. In addition, jewelry can interfere with the way appropriate clean room garb fits, and, therefore, performs. For those reasons, USP Chapter <797> specifies that all jewelry shall be removed before hand an arm scrubbing and donning appropriate garb such as hair covers, sterile gloves, etc. The National Health Service in the United Kingdom has determined that non-essential articles such a ties, white lab coats, and jewelry are a significant sources of pathogens that can get transferred to patients and contributes to nosocomial infections in hospitals. As a consequence, health care workers in the UK are to not wear jewelry, ties, and white lab coats, remaining bare to the elbows and washed and scrubbed.

Makeup should not be worn into a clean room at any time. Neither the drug industry nor the electronics industry permits cleanroom workers to wear makeup while working in a cleanroom because of particulate shedding. Makeup should be removed before garbing and entering a buffer area. Of course, it can be reapplied after exiting the buffer area.

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**Q:** Can a computer, refrigerator, or freezer be located in a clean room?

**A:** USP Chapter <797> does not specifically permit or forbid a computer, refrigerator, or freezer in the buffer area (cleanroom). Instead, the chapter cites performance standards for the buffer area that must be met with whatever equipment, personnel, and sterile compounding activities are performed in the buffer area. The ISO Class 7 buffer area must remain within the specifications for ISO Class 7 (not more than 352,000 particles per cubic meter of air) during dynamic working conditions. That is with all equipment running, personnel working, and sterile compounding activities ongoing. The point of having the buffer area is for it to stay within the ISO Class 7 requirements during actual sterile compounding. The equipment that is in the buffer area must not degrade the environment to a point below the <797> standard.

It should be recognized that the compressors of refrigeration equipment can be problematic and require special design and construction considerations to avoid having them create environmental problems. Computers also have fans for cooling that can blow air around but are also notoriously filthy on their keyboards being a really great place to pick up microbial contamination on fingertips. If contamination-generating equipment must be placed in a cleanroom, consider placement of low-wall air returns behind the equipment to reduce the particle burden that can find its way into the compounding area.

While such devices are not specifically prohibited, it is incumbent compounding personnel to assure that any and all devices placed in the buffer area do not adversely affect the quality of the compounding environment and result in an increased risk of contamination in patients' doses.

**Q:** Environmental testing has been completed in the past by a local testing facility, is there a certification required I should expect from them?

**A:** Compounding personnel should expect to get proper certification of adequacy of performance every six months for the ante-area, buffer area (cleanroom), and ISO Class 5 primary engineering controls such as laminar airflow workbenches (LAFW), biological safety cabinets (BSC), compounding aseptic isolators (CAI), and compounding aseptic containment isolators (CACI). The certification should be performed during dynamic working conditions. That means with all equipment running, personnel working, and sterile compounding activities ongoing, including bringing materials in and finished doses and waste out. The point is to assure that the quality of the environment meets the minimum standards of Chapter <797> in the "real life" setting as the doses are actually being prepared, and not in empty, static, pristine periods when no personnel are in the areas and no work is going on.

Compounding personnel should expect, no make that demand that the testing be performed to the established standards of the Controlled Environment Testing Association (CETA). All qualified certifiers will know about these standards and be able to apply them for the testing methodologies that must be used and the air quality requirements that must be met for airborne particulates. Certifiers that want to use other unconventional methodologies or device manufacturers' home grown testing techniques that differ from the CETA standards are not in compliance with the requirements of USP Chapter <797>. Compounding personnel should insist on certification to CETA standards. If the certification then fails by the CETA standards, this would be a very important fact to find out about your equipment. The CETA standards are designed to provide an objective assessment of the quality of the environment using scientifically-established methodologies. You

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should want the equipment you use to pass the CETA testing standards or get alternative engineering controls that do.

Additionally, the primary and secondary engineering controls in each and every compounding site must also pass viable airborne particle testing standards every six months. USP Chapter <797> sets methodologies and standards for sampling the environmental air for microbes. Using volumetric air sampling devices and microbial growth media, the air is sampled, the growth media is incubated, and the number of viable microorganisms (colony forming units, cfu) counted. The certifier should perform the testing in accordance with USP Chapter <797> during dynamic working conditions and provide the compounding personnel with the results. The cfu results are to be reviewed to determine if the microbial contamination exceeds the action levels set in the chapter and, if so, appropriate action needs to be taken to find the source of the contamination and mitigate it.

The following minimum expectations have been recommended by knowledgeable controlled environment certification professionals:

1. All testing procedures used by the certifier must be clearly explained and detailed in the final certification report or referenced by SOPs that are attached to the report. All certification criteria outlined in CAG-003-2006 should be met.
2. All individual data points collected during any testing must be documented.
3. All test parameters such as HEPA filter testing via aerosol challenge concentrations must be documented.
4. All calculations including intermediary and final values must be documented.
5. Airflow volumes to the buffer and ante areas must be measured with capture hoods.
6. Airflow velocities for all primary engineering controls must be measured with a thermal anemometer.
7. A videotaped smoke study should be performed on all primary engineering controls.
8. All certification test equipment should be calibrated at least annually unless the manufacturer recommends a more frequent recalibration cycle.
9. All equipment calibration documentation must be included in the final report.
10. The certification technician must be NSF accredited and experienced in certification of cleanrooms as used in either cGMP or sterile compounding facilities. The certification technician should also be experienced in airflow visualization studies.

**Q:** Regarding low risk level CSPs with 12 hour or less BUD, can you explain this classification further? Does this include chemotherapy CSPs? What was the thought behind this requirement?

**A:** USP Chapter <797> incorporates a new risk category called Low-Risk Level CSPs with 12-hour or less BUD. This risk category has been included because it was recognized that in some cases (hopefully not very many) a health care institution may be physically unable to have an ISO Class 7 buffer area for the placement of each and every ISO Class 5 primary engineering control, such as a laminar airflow workbench. In such cases, the placement of the primary engineering control may have to be located in a room that does not qualify as an ISO Class 7 buffer area - what is termed an uncontrolled environment. The instance that served as a model is low-volume short-term sterile compounding performed in an ISO Class 5 hood located in a satellite pharmacy. However, it must also be recognized by compounding personnel that aseptic compounding in an uncontrolled environment has a higher potential of producing contaminated doses than if a real cleanroom

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with full cleanroom work practices was utilized.

Because of this higher risk of microbial contamination in doses prepared in an uncontrolled environment, this risk category includes a short time limitation on the acceptable use period. If a small contamination from airborne microorganisms should occur, the utility time limitation not exceeding 12 hours will be short enough not to permit an overgrowth of the microorganisms to hazardous or fatal levels. Even so, use of this kind of compounding environment for a patient population subject to compromised immune systems is probably a bad idea.

USP Chapter <797> places several limitations on the sterile compounding that can be performed under this risk category:

1. The room must be in a segregated compounding area not in a high traffic area with no unsealed windows or doors that connect outdoors.
2. The segregated compounding area cannot be adjacent to food preparation sites, warehouses, or construction sites.
3. The segregated compounding area must meet all of the cleaning and disinfecting requirements in Chapter <797> for a real buffer area.
4. All personnel cleansing and garbing requirements for Low-Risk Level compounding still apply.
5. All quality assurance personnel testing and environmental sampling requirements for Low-Risk Level compounding still apply.
6. No Hazardous Drugs (like chemotherapy doses) are permitted to be compounded because little or no containment for personnel safety is present.
7. Administration must begin within 12 hours or as stated in the package insert, whichever is shorter, so as not to permit an overgrowth of the microorganisms to hazardous or fatal levels.

**Q:** When compounding Hazardous Drugs, the revised chapter states the BSC and CACI "optimally should be 100% vented to the outside air through HEPA filtration". Does this language constitute a requirement? If not, what are the options if the air is NOT vented to the outside?

**A:** USP Chapter <797> uses the words "optimally should" to indicate what may be the best situation for employee safety, but this is not a requirement. In Chapter <797>, a requirement uses the word "shall". A suggestion, best practice, optimal situation or similar practice that is not required uses the word "should". This word usage is deliberate and consistent throughout the Chapter. "Shall" for requirements; "Should" for best practices and optimal situations.

Venting 100% to the outside through a HEPA filter describes a situation where all of the air that is vented from ISO Class 5 containment device is passed through a HEPA filter and then delivered outside to undergo dilution. It should be recognized that not all of the air moving through the ISO Class 5 device is being vented, but all of the air that is vented (100% of it) is vented to the outside through a HEPA filter. This situation would tend to remove as much airborne contamination of hazardous drugs as possible. The other options include using complete recirculation of the air in the ISO Class 5 containment device. Unfortunately, complete recirculation permits a greater amount of the airborne hazardous drugs to find its way into the pharmacy, clinic, hospital, etc., which places employees and patients' families at a somewhat higher risk of exposure to hazardous drugs. Such exposure may lead to adverse health consequences over time, particularly for employees who are repeatedly exposed. However, the Committee recognized that the ideal situation of venting 100% to the outside through a HEPA filter may not always be technically feasible. It is also costly in

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terms of heating/cooling loss. In this situation, the Committee wanted to call attention to a recommended best practice but permit alternatives if necessary.

It needs to be kept in mind that a pharmacy that is preparing hazardous drugs, has an obligation to its workers and patients' families to minimize the amount of hazardous drug exposure that they receive because (unlike the patients) they have no benefit to be derived from such exposure. What I would want for myself, my co-workers, and the patients' friends and relatives is the most robust system that can realistically be obtained.

**Q:** **Is it correct that under the new USP <797> guidelines, if a sterility test is performed, then the BUD can be extended until the physical stability of the components being used? How often must the sterility testing be done? Is it on each batch or is it on the process?**

**A:** The Microbiological Beyond Use limits specified in USP Chapter <797> are applied to compounded sterile preparations that have not been subjected to the official USP Chapter <71> sterile test. This official sterility test is not a media-fill process validation test, but instead is specific to each batch of drug prepared. The test is generally performed once shortly after preparation of a batch of drug. During long-term shelf life testing, it may be performed several times to assure container/closure integrity over time. If a batch of drug passes the official USP Chapter <71> sterility test, Chapter <797> states that the Microbiological Beyond Use limits need not be applied. If a batch of drug exhibits any microbial growth upon sterility testing, the entire batch must be destroyed. If a sterile preparation is not subjected to the sterility test, as is often the case in compounding individual patient doses, then the Microbiological Beyond Use limits along with the chemical and physical stability of the drug(s) involved must be considered, and the shortest beyond use period, whether chemical, physical, or microbiological, must be applied to the drug

**Q:** **What if our operation does not meet with USP <797> by June 2008? What happens?**

**A:** Fortunately for many pharmacies there are no "compounding police" waiting to pounce. But it must also be recognized that the standards described in USP Chapter <797> are similar to the ASHP Guidelines that go back to 1993, the USP Chapter <1206> that appeared in 1995, in addition to the original Chapter <797> in 2004. We have had at least 15 years of "notice" about what facilities, equipment, and work practices and procedures are needed to improve the quality of the sterile compounding operations and reduce the risk of microbial contamination reaching patients. There is really no acceptable excuse for failing to comply with quality and safety standards that have been in existence for such a long time period.

USP Chapter <797> is a national quality standard that provides for an increased level of safety for patients. Compliance with these quality standards should be a professional aspiration of all of those involved in sterile drug preparation. The Chapter sets a level of quality and safety that patients deserve and have a right to expect.

Compounding operations all across the country are currently complying with USP Chapter <797> in its totality, not at some indeterminate point in the future. These pharmacies set the practice standard bar. More and more State Boards of Pharmacy are requiring compliance with the Chapter standards and are training their inspectors to be proficient in the requirements of <797>. And undoubtedly the legal risk for both

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institutions and individuals of not complying with these minimum quality standards is increasing as well.

Perhaps the biggest driver of compliance with USP Chapter <797> may be that the Federal Government will no longer pay hospitals to treat patients for hospital-acquired infections or hospital errors. Can private payers be far behind? This should provide serious financial incentives to reduce all sources of hospital-acquired infections, including those coming from sterile compounding operations.

Q:

**What monitoring in a cleanroom must be done to comply with USP <797>?**

A:

Chapter <797> requires only a small amount of routine environmental monitoring of the ISO Class 5 primary engineering controls (such as a laminar airflow workbench) and ISO Class 7 buffer areas and ISO Class 8 ante-areas. The primary emphasis in the chapter is on personnel education, training, and competence and facility cleaning and disinfection.

Pressure differential for the various classified air environments (e.g. ISO Class 5, 7, or 8) is to be monitored using a pressure gauge or velocity meter to assure that the correct air balance is being maintained. This can be accomplished using a continuous recording device or by manual review and documentation every work shift with a minimum of once daily.

The minimum environmental sampling requirements for both primary and secondary engineering controls are intended to be performed as part of the initial commissioning as well as recertification at least every 6 months of the facilities and equipment to provide a minimum level of assurance that the equipment is performing properly. It would be expected that this semi-annual recertification would typically be performed by controlled environment testing professionals to Controlled Environment Testing Association (CETA) standards. Of course environmental sampling may be performed more frequently if the compounding personnel want a greater degree of assurance of the adequacy of the compounding environment. Indeed, more frequent monitoring may be required in response to identified problems with preparations, patient infections, or improper staff work practices. The environmental monitoring consists of two principal parts: airborne non-viable particles and viable particles (those particles carrying microbes).

Non-viable particle sampling is intended to determine the performance of the engineering controls that create air cleanliness such as an ISO Class 5 laminar airflow workbench or BSC or an ISO Class 7 buffer area (cleanroom). During certification, an electronic air sampler is used to measure the amount of particles of 0.5 microns and larger per cubic meter of air to assure that the engineering controls are working properly.

Viable particle testing is also performed at a minimum every 6 months during recertification. Using an electronic volumetric air sampler that impacts airborne particles on microbial growth media, the amount of airborne microorganisms that can grow and multiply is determined. The number of colony forming units (cfu) are used to determine the approximate amount (if any) of microbial bioburden in the air of the compounding environment. The amounts should be trended over time to see if adverse changes in the air quality are occurring. Increasing cfu counts may mean corrective action is required. As an aid, guideline action levels are indicated in Chapter <797>. Action should be taken to identify the source of the microorganisms and to mitigate it. Identification of the microorganisms to verify no pathogens are present is also important.

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**Q: What BUD can be applied to Single-dose vials? What BUD can be applied to Multi-dose vials?**

**A:** Single-dose containers are designed for a single use and then are to be discarded. However, the definition of a “single use” is subject to interpretation. Such products do not contain a preservative that will kill or inhibit the growth of microorganisms that are likely to be introduced when drawing out drug. To keep patients safe from the potential of microbial growth in such unpreserved single-dose products, USP Chapter <797> states that single-dose containers once opened or needle-punctured shall be used within 1 hour if opened or stopper-penetrated in air that is less clean than ISO Class 5. That would usually mean in buffer areas, ante-areas, and in uncontrolled environments. If single-dose vials are opened or stopper-penetrated and kept in an ISO Class 5 air environment such as a laminar airflow workbench, etc., then the container may be used for up to 6 hours before it must be discarded.

A special case is made for single-dose glass ampules, which may not be stored for any period after opening. They should be discarded immediately after the dose has been removed.

Multiple-dose vials have become the stuff of an “urban legend”. The “urban legend” is that they are can be used until the printed expiration date on the package regardless of how long ago the stopper was first penetrated and the number of subsequent penetrations that have occurred. However, in reality the expiration date on the package is for the drug in the intact container (including a stopper that has not been penetrated) when stored as directed by the manufacturer.

To be classified as a multiple-dose container designed for removal of portions of the drug on multiple occasions, the formulation contains a substance that acts as a preservative that can kill or prevent the growth of microorganisms that are likely to be introduced when entering through the stopper and drawing out drug. To document that this preservative actually works, the multiple-dose drugs are subjected to a challenge test, the USP Chapter <51> Antimicrobial Effectiveness Test. Five species of microorganisms are inoculated into samples of each specific drug formulation and evaluated over 28 days for microbial growth to determine whether the preservative is effective.

In addition to microbial concerns, once the vial stopper is penetrated, the inert gas layer inside the vial is replaced with oxygen-containing air. The manufacturer will have tested the drug to assure that it will also remain chemically stable for at least 28 days after stopper penetration.

Because the Antimicrobial Effectiveness Testing is performed over a period of 28 days, and the drug must be stable for this period after the introduction of air, USP Chapter <797> specifies that a multiple dose vial once the stopper has been punctured shall have a beyond use date of 28 days unless otherwise specified by the manufacturer.

Some manufacturers for some multiple-dose products have documented a different stability period after initial stopper penetration and state it in the labeling. In such cases, the manufacturer’s beyond use date period after stopper penetration may be used.

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(Continued)

**Q:** In a presentation on USP <797> it was quoted that pharmacies should be striving for a less than 0.1% statistical contamination rate. What kind of data do we need to log to demonstrate that we meet or are below this statistical contamination rate? Does this data need to be per individual or for the department?

**A:** A minimum of 3000 media fill samples must be prepared with no contamination events occurring be able to demonstrate a contamination rate less than 0.1% with 95% statistical confidence. However, it is unlikely that manual aseptic compounding can be documented with a contamination rate less than 0.1% to the 95% confidence level for an individual let alone a whole department that would apply on a regular and ongoing basis. This is especially true since a single accidental breach of aseptic technique can invalidate all of the media fill validations that a person has performed. When it comes to all of us error-prone microbe-covered humans, such a low contamination rate with high statistical confidence is not likely to be an achievable goal on a continuing basis. Even so, media fill verification of compounding personnel aseptic technique is a great opportunity for training and education, reminding people of the necessary components of safe aseptic compounding.

However, the use of this statistical benchmark is much more applicable to automated and robotic systems that have the advantage of removing microbe-covered humans from the immediate compounding environment. For these systems, achieving contamination rates near the very low levels of industrial drug manufacturing is a possibility, a possibility that needs to be documented, of course. Furthermore, running the thousands of media fill samples necessary to document a low contamination rate is much less difficult for automated systems than for people. And finally, automated and robotic systems are much less likely to make mistakes that could contaminate a dose than are people.

**Q:** Does immediate use compounding include infusion centers where we compound therapies only after the patient is in the building and receiving the dose immediately after it is mixed?

**A:** The Immediate Use category of compounded sterile preparations is intended as an option for occasions when no delay between preparation and administration occurs. Examples include in emergency rooms, in the back of ambulances, during Code situations, a dose prepared by a nurse at the patient's bedside, and in any other location where there is no delay.

The Immediate Use category states that the doses are exempted from all requirements in USP Chapter <797> only if all of the following requirements are met:

1. Only simple aseptic transfers involving three or fewer drug packages are involved, including an infusion solution.
2. No delays or interruptions during dose preparation.
3. The dose is prepared using good aseptic technique and care is taken to prevent direct contact contamination of the ingredients and critical sites during preparation.
4. No hazardous drugs are involved, since no protection from exposure exists for the compounding personnel.
5. The maximum amount of time from the beginning of compounding to the start of administration is not more than one hour. If more than one hour has elapsed, the dose must be destroyed.

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6. No dose storage beyond one hour from the start of preparation or recycling is permitted.
7. The dose must be fully and completely labeled if not administered by the preparer or the administration is witnessed by the preparer.

If these requirements cannot or are not met, then all of the requirements of USP Chapter <797> must be followed.

Q:

**Does a BSC have to be located in a negative pressure room?**

A:

USP Chapter <797> specifies that a biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI) that meets the requirements of the chapter be used to compound sterile hazardous drugs. The BSC or CACI is required to be in an ISO Class 7 buffer area physically separated (that is by walls or other material barriers) from other sterile compounding. This buffer area is to have not less than 0.01-inch water column negative pressure compared to adjacent positive pressure ISO Class 7 or better ante-areas to provide the necessary personnel protection. Placing the ISO Class 5 containment device in a negative pressure ISO Class 7 buffer room is considered a best practice for the safety of employees and patients' families as well as a requirement of Chapter <797>.

The chapter does make an exception for facilities that compound a low-volume of hazardous drugs since the amount of possible exposure is minimal. The benchmark that was considered as "low-volume" was not more than five doses of hazardous drugs per week on average. Such low-volume facilities may use a BSC or CACI in a non-negative pressure room as long as a second tier of containment such as a closed-system transfer device is also used inside the BSC or CACI.

Compounding sites that prepare more than five doses of hazardous drugs per week on average have a greater need for a negative pressure buffer area to protect personnel while a site that compounds only a small number of hazardous drug doses, such as five doses per week on average, has a smaller risk of hazardous drug exposure to workers and patients' families.

Another exception is the potential placement of a CACI that meets the requirements of the chapter outside of an ISO Class 7 buffer area if the manufacturer has validated that the device can be used safely in such an environment. In this case, the chapter requires that the CACI, if not in an ISO Class 7 area, be placed in a separate compounding area (separated from other activities by walls or other material barriers) that maintains a sufficient negative pressure environment of not less than 0.01-inch water column compared to adjacent areas and must have at least 12 air changes per hour. It needs to be emphasized that it is incumbent on compounding personnel to perform their "due diligence" regarding any such CACI considered for use outside of an ISO Class 7 environment and verify that the device has been rigorously tested according to the Controlled Environment Testing Association (CETA) established standards and not some home grown manufacturer's testing that may have been designed to avoid certification failure.

It should be recognized that if an ISO Class 5 containment device is used outside of a negative pressure ISO Class 7 buffer area greater amounts of the airborne hazardous drugs might find their way into the pharmacy, clinic, hospital, etc. If it does, this places employees and patients' families at higher risk of exposure to hazardous drugs. Such exposure may lead to adverse health consequences over time, particularly for employees who are repeatedly exposed.

It seems to me that compounding facilities and personnel that prepare hazardous drugs have an obligation to

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the workers and patients' families to minimize the amount of hazardous drug exposure that they receive since (unlike the patients) they have no benefit to be derived from such exposure.

**Q: Is good aseptic technique more important than a clean room in preventing microbial contamination?**

**A:** The new revised USP Chapter <797> that goes into effect in June, 2008 states in the Introduction "It is generally acknowledged that direct or physical contact of critical sites of compounded sterile preparations (CSPs) with contaminants, especially microbial sources, poses the greatest probability of risk to patients." While the creation and maintenance of a suitably controlled compounding environment is important, it is what the compounding personnel do that is critical. We must recognize that all of us are human and are covered in microbial contamination at all times that we shed constantly, no matter how clean we think we are. To make matters worse, we are error-prone and can inadvertently touch contaminate items and perhaps not realize it. The ISO Class 7 buffer area and the ISO Class 5 primary engineering control (such as a laminar airflow workbench) do not create sterile preparations. They simply create a suitable environment for compounding sterile preparations. It is well-trained and competent compounding personnel who understand the importance to patients of performing their compounding tasks correctly that create sterile the preparations.

Compounding personnel aseptic technique and work practices along with organizational work practices are the most important factors in consistently creating uncontaminated CSPs. Even the best engineering controls can be overcome by poor work practices resulting in contaminated doses and the potential of patient infections. Because of this, Chapter <797> notes that "compounding personnel must be meticulously conscientious in precluding contact contamination of CSPs".

**Q: Our housekeeping department cleans our ante room, are there guidelines which I can supply the Director of Housekeeping?**

**A:** USP Chapter <797> describes the required cleaning and disinfecting practices for all areas involved in sterile compounding, including ISO Class 5 primary engineering controls, ISO Class 7 buffer areas, and ISO Class 8 ante-areas. Compounding personnel are specified as the individuals responsible for ensuring that the cleaning is performed in accordance with the necessary frequency requirements as well as determining the cleaning and disinfecting products to be used. Obviously, organizational or institutional policies concerning disinfectant selection must be considered.

USP Chapter <797> specifies the following minimum cleaning and disinfecting frequencies for Buffer Areas and Ante-Areas:

1. ISO Class 5 device – At the beginning of each shift; before each batch is prepared; no longer than 30 minutes following the previous disinfection during ongoing compounding; after spills; any time surface contamination is known or suspected.
2. Counters – Daily
3. Floors - Daily
4. Walls – Monthly

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5. Ceilings – Monthly
6. Storage shelving – Monthly

In cases when Housekeeping Department or a Department other than the compounding personnel themselves are to be performing the cleaning and disinfecting, the compounding personnel are nevertheless responsible and must insure that the cleaning and disinfecting is performed appropriately for a sterile compounding environment. You would not want the mop used to mop the floor in the men's room being used to mop the Buffer Area or Ante-Area!

USP Chapter <797> has a section entitled Cleaning and Disinfecting the Compounding Area devoted to this topic. It is too long to cover in this short space. However, one way to conceive of the nature of the cleaning required and communicate this to the Housekeeping Department is to compare the cleaning and disinfecting needed for the sterile compounding area to that of the Operating Room. Housekeeping will have special cleaning procedures in place for cleaning and disinfecting the OR. The sterile compounding area requires no less.

Q:

**How often should a Barrier Isolator be validated?**

A:

The design and configuration of a compounding aseptic isolator (CAI) or a compounding aseptic containment isolator (CACI) is validated by the manufacturer during the design and validation phase of product development. The Controlled Environment Testing Association (CETA) has established an applications guide for such isolators that includes guidance to the industry for the initial performance validation so that the manufacturer can demonstrate and prove that the design of the CAI or CACI actually does what it is intended to do. In addition, the CAI or CACI should be certified to meet the needed performance criteria. The certification to the standards of the CETA applications guide should first be performed by the manufacturer at the factory.

Chapter <797> specifies that CAIs and CACIs, like other ISO Class 5 primary engineering controls, are to be certified initially upon being commissioned and put into service, each time the device is moved, and at least every 6 months during routine use. This is the same schedule as for the buffer and ante areas to be recertified. The initial certification is to ensure that the device is working properly after installation. The recertification after moving a device is to ensure that the device is working properly after the move.

The semi-annual recertification is to provide a minimum level of assurance that the equipment remains performing properly during routine use. USP Chapter <797> requires and compounding personnel should insist that this semi-annual recertification be performed by controlled environment testing professionals to Controlled Environment Testing Association (CETA) applications guide standards. Certifiers that want to use other unconventional methodologies or device manufacturers' home grown testing techniques that differ from the CETA standards are not in compliance with the requirements of USP Chapter <797>.

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**Q:** Do softwall (plastic strips) cleanrooms meet the requirements for USP <797>?

**A:** USP Chapter <797> states that “ The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area shall be smooth, impervious, free from cracks and crevices, and nonshedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate.” The chapter goes on to state “Walls may be constructed of flexible material (e.g. heavy gauge polymer); panels locked together and sealed, or epoxy-coated gypsum board.”

While some commercial flexible plastic (soft wall) cleanroom walls made of continuous panels of soft heavy gauge polymer may be able to meet the requirements, plastic strip type “walls” would appear to pose significant challenges to meeting the performance standards in Chapter <797>. By their very nature there are cracks between each plastic strip, which can influence and interfere with air flow as well as hampering cleanability. Chapter <797> requires that the buffer area be separated from the ante-area and outside environments. Furthermore, that separation must be continuously monitored by airflow or air pressure to assure the suitability of the environment. It would seem that maintaining that separation is much more difficult with plastic strips than with more conventional cleanroom construction. In addition, the chapter requires that buffer area floors have coving up the sidewalls. This is again for cleanability. Coving up plastic strips is not possible. It appears to me that the use of plastic strips as buffer area “walls” could be more challenging in meeting the performance standards of Chapter <797>.

**Q:** In regards to personnel garbing; can an individual wear cosmetics in the compounding area if they also wear a protective face mask?

**A:** No. USP Chapter <797> is quite clear that cosmetics are not permitted in compounding areas. No industry that utilizes cleanrooms, including both pharmaceutical and electronic manufacturing, permits cosmetics to be worn. Neither should sterile compounding operations. The reason is clear. Cosmetics can increase the amount of particles shed by the compounding personnel. Particles shed from personnel, which can number in the millions per hour, are vectors that deliver microorganisms into the compounding environment. This is just not acceptable.

Chapter <797> specifies that before entering a buffer area or segregated compounding area, personnel shall remove outer garments, remove cosmetics (because they shed flakes and particles), and remove all hand, wrist, and other visible jewelry and piercings that can interfere with the effectiveness of personnel protective garb. Artificial nails or extenders are not permitted either. In addition, the personnel must be garbed to reduce the contamination that is naturally shed.

All of these requirements center on one thing: the minimization of contamination coming from personnel in the sterile compounding areas and thereby contaminating patient doses.

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**Q:** USP Chapter <797> says that facilities with low volumes of hazardous drugs may not need to construct a negative pressure room if they employ closed system transfer device (CSTD) within a BSC. However, I am not clear if the laminar flow hood and the BSC can be in the same positive pressure buffer room because the chapter also says that hazardous drugs must be prepared in a "physically separated" area.

**A:** This is a common question because USP Chapter <797> is silent on the issue. For hazardous drug compounding, USP Chapter <797> specifies that a biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI) that meets the requirements of the chapter be used to compound sterile hazardous drugs. The BSC or CACI is required to be in an ISO Class 7 buffer area physically separated (that is by walls or other material barriers) from other sterile compounding. This buffer area is to have not less than 0.01-inch water column negative pressure compared to adjacent positive pressure ISO Class 7 or better ante-areas to provide the necessary personnel protection. Placing the ISO Class 5 containment device in a negative pressure ISO Class 7 buffer room is considered a best practice for the safety of employees and patients' families as well as a requirement of Chapter <797>.

USP Chapter <797> then makes an exception for facilities that compound a low-volume of hazardous drugs since the amount of possible exposure is minimal. The benchmark that was considered as "low-volume" was not more than five doses of hazardous drugs per week on average, although the actual decision is left to the compounding personnel. Such low-volume facilities may use a BSC or CACI in a non-negative pressure room as long as a second tier of containment such as a closed-system transfer device is also used inside the BSC or CACI. USP Chapter <797> is silent on whether low-volume hazardous drug compounding still needs to be in a separate room (though not one with negative pressure). Consequently, most readers have interpreted the intent to be that there is no specific prohibition on other compounding activities being conducted in the same positive pressure room occasionally used for a low-volume of hazardous drug compounding in a BSC or CACI along with a second tier of containment.

**Q:** We have read in articles that it would be acceptable to use a new bottle of regular isopropyl alcohol each day for sanitizing instead of the sterile isopropyl alcohol as stated in <797>. Is this acceptable to use?

**A:** Isopropyl alcohol (IPA) 70% has been a commonly used agent for sanitizing surfaces in primary engineering controls such as laminar airflow hoods. Although other disinfecting agents exist, IPA 70% is effective in killing vegetative forms of microorganisms, does not result in microbial resistance, and is not damaging or toxic to intact human skin upon contact. USP Chapter <797> specifies that when IPA 70% is used for sanitizing critical sites such as vial stoppers and ISO Class 5 work surfaces that it be sterile. Although IPA 70% kills the vegetative forms of microorganisms (a very important function!) it does not kill the spores from spore-forming bacteria. Such spores can survive in IPA 70% indefinitely. If the spores find their way onto critical surfaces (think vial stoppers) during sanitizing and then are pushed into a drug solution by a needle penetration, they can begin to grow. The Microbiological Advisory Committee to the USP Sterile Compounding Committee made a strong case that the IPA 70% used for sanitizing critical sites must be sterile, and this was adopted as the standard. Non-sterile IPA 70%, even in brand new bottles, can contain bacterial spores and does not meet the standard in USP Chapter <797>.

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**Q:** USP <797> requires a negative air pressure environment for the preparation of hazardous drugs. Why? Is it primarily because of environmental contamination due to breakage and spillage? How does a negative pressure protect workers?

**A:** USP Chapter <797> specifies that the preparation of hazardous drugs occur in negative pressure environments to protect workers, patients not receiving the hazardous drugs, patient's family members, and others from exposure to these toxic agents. Of course, the problems of contamination from breakage and spillage are real and need to have specific and vigorously enforced procedures established to deal with such hazard-filled situations. However, even proper preparation of hazardous drugs results in the spread of low level drug contamination through the facilities that prepare them. The containers come with trace contamination by the hazardous drugs on the outside of vials and packages, which easily gets transferred within environments.

Reconstitution and other preparation steps lead to microdroplet aerosolization and contamination, and some hazardous drugs have vapor pressures that allow volatilization at room temperature. These seem to be sources that permit hazardous drugs to get delivered around facilities by personnel and potentially by air handling equipment. In studies in facilities that compound large amounts of hazardous drugs (such as cancer centers), the drugs have been found not only in the compounding area, but also in the Institutions' common areas outside the compounding facilities. Although present technology cannot eliminate the migration of trace contamination of hazardous drugs, the use of properly constructed and operated negative pressure environments can help to minimize the spread of hazardous drug contamination.

Working in a suitable ISO Class 5 primary engineering control, such as a biological safety cabinet vented to the outside that is located in a negative pressure ISO Class 7 buffer area will help direct airborne trace hazardous drug contamination that is inevitably generated during compounding procedures away from the workers reducing the amount that can be inhaled or ingested inadvertently. It will also reduce the amount of contamination that is carried into Institutions' common areas outside the compounding facilities.

**Q:** One of our ambulatory care centers is preparing a significant number of compounded sterile products on a daily basis, but they do not feel that they need to abide by the USP<797> standards. How can we effectively educate and influence their practice?

**A:** The United States Pharmacopeial (USP) Convention is the drug standards setting body for the United States. USP Chapter <797> is a national standard that applies to all aseptic compounding regardless of compounding site or the profession of those performing the compounding. These are not pharmacy standards; these are aseptic compounding standards that apply whenever and wherever the aseptic compounding is performed. This national quality standard provides for an increased level of safety for patients and should be a professional aspiration of all of those involved in sterile drug preparation no matter their work site or profession. It sets a level of quality and safety that patients deserve and have a right to expect. This national standard applies universally because no patient should ever have to give up their right to safe, sterile, accurate doses no matter where they are treated or the profession of the people involved in preparing the dose. The Chapter specifically states that:

“The standards in this chapter are intended to apply to all persons who prepare CSPs (compounded sterile preparations) and all places where CSPs are prepared (e.g. hospitals and other healthcare

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institutions, patient treatment clinics, pharmacies, physicians' practice facilities, and other locations and facilities in which CSPs are prepared, stored, and transported). Persons who perform sterile compounding include pharmacists, nurses, pharmacy technicians, and physicians."

USP Chapter <797> notes that its objective is to describe conditions and practices to prevent harm, including death, to patients. All health care workers of good will should be both willing and able to meet the USP <797> standards as a condition of exercising the privilege of aseptic compounding. Like other patient safety standards, there is a professional duty to do so. The standards described in USP Chapter <797> are not about the convenience or profits of compounding personnel. Although undoubtedly important, these are secondary concerns. Rather, the standards are directed at patient safety, a notable and laudable goal that is expected of all health care workers.

USP Chapter <797> sets forth national standards to protect patients from:

1. Microbial contamination
2. Excessive bacterial endotoxins
3. Incorrect components and component strengths
4. Chemical and physical contaminants
5. Ingredients of inappropriate quality

Health care workers who willfully disregard these established quality standards are placing their patients at unnecessary risk to their health and life, a situation that is indefensible for health care professionals. Health care workers also put their own careers at greater risk because there is simply no acceptable explanation for failure to follow established quality standards if a patient injury or death occurs as a result. Patients, regulators, legal entities, other health care professionals have a right to expect that the standards set forth in USP Chapter <797> will be followed. Intentionally failing to meet the quality standards in USP Chapter <797> for aseptic compounding could be considered reckless disregard for the safety and welfare of patients being administered the compounded preparations.

Health care workers of good will, for the sake of their patients, need to remain mindful of these standards and make every effort to ensure that aseptic compounding is performed in accordance with the national standards and remind others of the necessity of preventing patient injury and death by adopting these quality standards. In time, it is expected that all health care workers will come to recognize their professional duty to their patients and meet the quality standards of USP Chapter <797> when performing aseptic compounding.

**Q:** Can clean room personnel use non-sterile gloves that have been rubbed with alcohol? Are sterile gloves an absolute requirement for meeting <797> standards?

**A:** The Introduction to USP Chapter <797> states "It is generally acknowledged that direct or physical contact of critical sites of CSPs with contaminants, especially microbial sources, poses the greatest probability of risk to patients." Because of this, great emphasis in the Chapter is placed on proper hand cleaning and sanitization. In addition, USP Chapter <797> specifies the use of sterile powder-free gloves for personnel performing aseptic compounding to minimize the amount of contamination present on the parts of the personnel that interacts most closely with the doses being prepared...the hands.

After thoroughly washing hands and arms to the elbows with soap and water, and after application of an

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alcohol-based surgical hand scrub with persistent activity, the Chapter states that sterile powder-free gloves should be donned as the last step in personnel preparation to perform aseptic compounding. Obviously, these sterile gloves should be donned in a manner to avoid contaminating them!

Compounding personnel need to recognize that the sterile gloves do not stay sterile while performing the manipulations necessary for aseptic compounding, but at least they start sterile, a much better starting situation compared to non-sterile gloves. Non-sterile gloves have microbial contamination present and in some cases have even been found to have insect contamination in the polymer matrix. Starting with gloves that have been sterilized by radiation is obviously much better. Because the gloves become contaminated from touching non-sterile items and surfaces during compounding activities, repeated and frequent disinfection of the gloves by wiping or rubbing with sterile 70% isopropyl alcohol (IPA) on all contact surface areas of the gloves is specified by USP Chapter <797>. The gloves should be permitted to dry thoroughly before proceeding. These steps are essential in minimizing the accidental transfer of microorganisms that can wind up in doses intended to be sterile.

The pivotal role played by the hands of compounding personnel was demonstrated in two studies.<sup>1,2</sup> Trissel and co-workers determined the contamination rate for a complicated 10-step Medium-Risk Level manual compounding procedure using microbial growth medium. Initially, no gloves were required, and about 5.2% of the units (or about 1 in 20) were found to be contaminated. When the personnel were required to wear non-sterile gloves that had been wiped with 70% IPA, the contamination rate fell to about 1% (or about 1 in 100), which was better but not great. Finally, the personnel were required to wear sterile powder-free gloves and to wipe the contact surfaces of the gloves, especially the finger tips, with 70% IPA frequently during compounding manipulations. Starting with sterile gloves and repeatedly wiping with 70% IPA during the compounding procedure, the contamination fell further to 0.3%, an order of magnitude decrease!

From these studies, it has become clear that the hands of the compounding personnel were principal vectors that delivered microbial contamination (inadvertently) into the containers. It was also clear that starting with sterile gloves and repeatedly sanitizing them with 70% IPA reduced the rate at which contamination of the units prepared occurred. This one simple and relatively inexpensive change in a single work practice had resulted in a profound improvement in quality assurance and patient safety.

It is incumbent on health care personnel who perform aseptic compounding to take reasonable steps to minimize the chances of microbial contamination being introduced into the doses by the individuals preparing those doses. While a lot of attention has been focused on expensive and technologically challenging environmental engineering controls, simply using sterile powder-free gloves and repeatedly sanitizing them with sterile 70% IPA can have a huge positive impact on patient safety.

**Referentes**

Trissel LA, Gentempo JA, Anderson RW, et al. Using a media fill simulation to evaluate the microbial contamination rate for USP medium risk level compounding. [Am J Health-Syst Pharm](#). 2005;62:285-288.

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**Q: Is batch size a determining factor in risk level?**

**A:** USP Chapter <797> specifies several Risk Categories based on the likelihood that inadvertent contamination may find its way into the final dosage forms. Low-Risk Level compounding is believed to be at lower overall risk of contamination than High-Risk Level compounding.

USP Chapter <797> does not designate batch size as a determining factor. Instead the nature of the compounding procedure, the complexity of the compounding procedure, and the compounding environment and personnel work practices are factors that determine risk category. A final patient dose compounded by simple aseptic transfer of a commercially manufactured sterile drug from one container to another is much less likely to be contaminated than a dose compounded from non-sterile raw ingredients. Even so, a larger batch of compounded units simply has more opportunities to inadvertently contaminate a dose. Compounding personnel may consider this increased risk contamination and assign the preparation to a higher risk category such as going from Low-Risk to Medium-Risk level with its shorter beyond-use date.

Batch size does come into play with High-Risk Level compounding of sterile drugs from non-sterile raw ingredients. USP Chapter <797> states that High-Risk Level compounding of batch sizes of 26 individual single-dose packages or more (e.g. vials, bags, etc.) or multiple-dose vials for administration to multiple patients shall meet the sterility test requirements of USP Chapter <71> before they are dispensed or administered. For smaller batch sizes of 25 units or less, sterility testing is optional.

**Q: The chapter revision states "Once inside the buffer area or segregated compounding area, and prior to donning sterile powder-free gloves, antiseptic hand cleansing shall be performed..." To clarify...hand sanitizing and donning of sterile gloves should occur in the buffer area instead of the ante area where the rest of the garbing is taking place?**

**A:** Minimizing the inadvertent transfer of contaminating microorganisms by the hands of compounding personnel may be the single most important quality assurance step performed in the aseptic compounding. To this end, compounding personnel must be thoroughly trained in hand cleaning and sanitization as well as acting scrupulously to avoid the transfer of microorganisms to the doses that are prepared. Unfortunately, we human beings that compound the doses are the dirtiest thing in the aseptic compounding environment. Worse yet, our hands are typically the dirtiest part of us that interact with the doses being prepared. Consequently, USP Chapter <797> repeatedly notes the importance of hand cleaning and sanitization in various parts of the chapter. In fact, the Introduction to the Chapter states "It is generally acknowledged that direct or physical contact of critical sites of CSPs with contaminants, especially microbial sources, poses the greatest probability of risk to patients." Because of this, great emphasis is placed on proper hand cleaning and sanitization.

Under the section on Additional Personnel Requirements, the Chapter states "Personnel hand hygiene and garbing procedures are also performed in the ante-area, which may contain a sink that enables hands-free use with a closed system of soap dispensing to minimize the risk of extrinsic contamination." The Chapter goes on to say "Adequate provision for performing antiseptic hand cleansing using an alcohol-based surgical hand scrub with persistent activity followed by the donning of sterile gloves should be provided after entry into the buffer area."

Under Personnel Cleansing and Garbing, Chapter <797> this sequence is once again noted. This section describes the how, where, and when of the personnel cleansing and garbing activities. In the ante-area

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removal of outer wear, removal of jewelry and cosmetics, donning of personnel protective equipment such as shoe covers, hair covers, eye shields and face masks, is performed. This is followed by washing hands and arms to the elbows for at least 30 seconds with soap and water while in the ante-area. After hands and arms have been completely dried, a non-shedding gown with snug fitting sleeves and closed at the neck is donned, again in the ante-area.

At this point, the compounding personnel may enter the buffer area or segregated compounding area, being careful to avoid acquiring contamination of the hands by touching non-sterile items and surfaces. Once inside the buffer area or segregated compounding area and before donning sterile powder-free gloves, the personnel perform antiseptic hand cleansing using a waterless alcohol-based surgical hand scrub with persistent activity to further reduce the amount of microorganisms on the hands. Lastly, sterile gloves are donned taking great care not to contaminate the gloves in the process.

Compounding personnel need to recognize that the sterile gloves do not stay sterile, but at least they start sterile, a much better starting situation compared to non-sterile gloves. The gloves do become contaminated from touching non-sterile items during compounding activities. Consequently, repeated and frequent disinfection of the gloves by wiping or rubbing with sterile 70%isopropyl alcohol on all contact surface areas of the gloves and letting the gloves dry thoroughly before proceeding is essential to minimizing the accident transfer of microorganisms that can wind up in supposedly sterile doses.

Q:

### SPECIAL EDITION: Beyond-Use Dating

A:

The United States Pharmacopeia<sup>1</sup> (USP) Chapter <797> (entitled Pharmaceutical Compounding — Sterile Preparations) has established a quality standard for compounding that includes the assigning of beyond-use dates to compounded sterile preparations. The following overview contains the opinions of the author regarding beyond-use dating for compounded sterile preparations including consideration of the standards in this chapter.

#### Beyond-Use Date

“Beyond-use date” is the correct term for the date after which an extemporaneously compounded preparation should not be used. (The term “expiration date” applies to manufactured drugs.) Usually the beyond-use date for a preparation is assigned by the individual compounding the preparation and should be for a conservative period from the date (or time) of compounding that reasonably assures the preparation’s pharmaceutical quality — chemical and physical integrity, sterility, and nonpyrogenicity — is maintained. The intended duration of the therapy also should be included in a beyond-use date assignment.

#### Factors that Must Be Considered in Arriving at a Suitable Beyond-Use Date for a Compounded Sterile Preparation

Chemical and physical integrity are among the principal pharmaceutical quality concerns when assigning a beyond-use date to a compounded sterile preparation as they are for non-parenteral products. These factors are related to the specific drug and formulation. However, additional important factors include the sterility and nonpyrogenicity of the final preparations. These attributes are not related to a specific drug, but instead are dependent on the components, preparation method, adequacy of the compounding environment, and compounding personnel capabilities and performance. Compounding personnel, like all humans, are covered in microbes that are shed constantly. In addition, no one is perfect; we are all are subject to unintentional work performance errors that can directly transfer microbes to compounded sterile preparations. It must

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always be kept in mind that the single most important factor in assuring that manually compounded preparations are, in fact, sterile is the adequacy of personnel work practices.

Sterility, the absence of living microorganisms, is an essential quality for all preparations that are administered by routes that bypass the patient's natural protective systems. Such preparations include injections by the intravascular, intramuscular, subcutaneous, intrathecal, and epidural routes, as well as ophthalmic preparations, inhalation solutions, and topical preparations to be used on broken or abraded skin. Failure to assure sterility has been a cause of much patient morbidity and mortality. For injections to be administered by the intravascular, intrathecal, and epidural routes, the absence of bacterial endotoxins or pyrogens — fever-producing lipopolysaccharides from microorganisms — is also essential. The qualities of sterility and nonpyrogenicity can limit the beyond-use date that should be assigned to a compounded sterile preparation as much as chemical and physical concerns can.

In the final analysis most beyond-use date decisions are for the individual compounding the preparation to answer. The decision for each specific compounded sterile preparation is generally a two-step thinking process: (1) consider the compounded sterile preparation's chemical and physical stability, and (2) consider the microbial risk of the preparation being contaminated during compounding. The beyond-use date that is applied should be the shorter of the two. It should be recognized that there may not always be a single answer in all cases. Knowledgeable compounding personnel with good intent can and do have differences in how they address such decisions.

The USP has provided some examples of compounding that would fall into various risk categories that are noted in Chapter <797>, but the Chapter can not provide all of the answers for the myriad of compounding preparations, practices, and situations that exist, and how each would fall under the risk-level categories. The individual performing the compounding is responsible for deciding what risk category applies in each specific case. These are important decisions that have consequence not only for the beyond-use date (and therefore patient safety) but also may have consequence should a legal or regulatory question arise about the nature of the compounding.

It is important to remember that risk categories and beyond-use dating are not about the convenience or profit of compounding personnel; they are and should always be about patient safety. A good way of thinking about these compounding decisions is as if one's own loved one, maybe a child, spouse, or parent, was to be the recipient. This is known as the "Loved-One Test." What would we want for people for whom we care deeply? If the compounding decisions (including beyond-use dating) are made as if the preparation was going to be administered to a loved one, then we have a better chance of our moral compass pointing correctly. It is also important to think about how one would explain and defend these compounding decisions to a legal or regulatory body should a need arise. If the decisions are made with these moral considerations in mind along with the scientific and technical information, compounding personnel will be on firmer moral and professional ground and can feel more confident about their beyond-use date decisions.

To arrive at a suitable beyond-use date, all of the factors mentioned above must be considered, and the most conservative beyond-use date assigned based on whichever factor results in the shortest time frame.

### **Assigning a Beyond-Use Date to a Compounded Sterile Preparation Using Stability Information**

When assigning a beyond-use date, the compounding personnel should consider both general and drug-specific stability information from reputable sources. The expected type of decomposition mechanism and the storage conditions need to be factored in. The available stability information, especially published articles from peer-reviewed journals when this information is available, should be considered. Drug manufacturers may also be sources of stability information, particularly general information on the known stability behavior

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of a drug. Using education and experience, the person compounding the preparation should consider carefully the available information in relation to the specific preparation composition and should determine a suitable period of use based on chemical and physical integrity of the preparation. The microbiological integrity of the preparation should then be considered. (See below.) The beyond-use date that is assigned should be based on the chemical and physical integrity of the preparation, especially the least stable component, or the microbiological limit based on contamination risk category for the appropriate type of preparation (low-risk level, low-risk level with 12-hour beyond-use date, medium-risk level, high-risk level, immediate use), whichever is shorter.

### **Assigning a Beyond-Use Date to a Compounded Sterile Preparation in the Absence of Stability Information**

In general, compounded sterile preparations have more stability information available than do nonparenteral preparations. Even so, drug-specific stability information that can be applied to a compounded sterile preparation sometimes does not exist. When no published studies have appeared and no reference work provides the needed basis for determining a beyond-use date, USP Chapter <797> refers to the general beyond-use date guidance in USP Chapter <795> for assigning a beyond-use date.<sup>1</sup> Compounding personnel need to be familiar with USP Chapter <795> (entitled Pharmaceutical Compounding - Nonsterile Preparations) as well as Chapter <797>. This general guidance from the USP for physical and chemical stability factors is the same for sterile and non-sterile preparations. In the absence of applicable stability information for water-containing preparations, a chemical stability beyond-use date of not more than 14 days when stored at refrigeration temperatures may be applied. Refer to Chapter <795> for other types of preparations. For compounded sterile preparations the microbiological contamination risk of the preparation must then be considered. (See below.) The beyond-use date that is assigned should be based on the maintenance of the chemical and physical integrity of the preparation from the general guidance or the microbiological limit based on contamination risk category for the type of preparation (low-risk level, low-risk level with 12-hour beyond-use date, medium-risk level, high-risk level, immediate use), whichever is shorter.

### **Assigning a Beyond-Use Date to a Compounded Sterile Preparation on the Basis of Microbiological Contamination Risk Category**

The risk of inadvertent microbiological contamination in a compounded preparation intended to be sterile results from the sterility or contamination of the starting drugs, components, and equipment used during compounding, the complexity of the preparation procedure, adequacy of the compounding environment, and the competency of the personnel who compound the preparation. USP Chapter <797> offers general guidance in assigning a microbiological beyond-use date based on the contamination risk category and storage condition of the compounded sterile preparation when the chemical and physical stability of the compounded sterile preparation permit.

### **Low-Risk Level Compounded Sterile Preparations**

Low-risk level compounded sterile preparations are those that are prepared by simple aseptic transfer of sterile drugs from one container to another using sterile equipment and devices in a suitable controlled air environment meeting ISO Class 5 (Class 100). To be low-risk level, the drugs and components must always be in sealed containers and not exposed to the open compounding environment at any time. Examples would include simple injections, infusions, admixtures, ophthalmic products that are compounded using no more than three commercially manufactured sterile drug containers, commercially manufactured sterile equipment such as needles and syringes, and involving only simple aseptic transfers.

If the low-risk level compounded sterile preparation passes a USP sterility test, then the chemical and physical stability of the preparation can be used to assign the beyond-use date. In the absence of passing a sterility test, the maximum microbiological beyond-use date periods (if chemical and physical stability permit)

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by storage condition are:

Room temperature - 48 hours

Refrigeration - 14 days

Frozen - 45 days

**Low-Risk Level with 12-Hour or Less Beyond-Use Date Compounded Sterile Preparations**

Low-Risk Level compounded sterile preparations with 12-hour or less BUD is a risk category that applies to situations when a compounding site may be physically unable to have an ISO Class 7 buffer area for the placement of each and every ISO Class 5 primary engineering control, such as a laminar airflow workbench. In such cases, the placement of the primary engineering control may have to be located in a room that does not qualify as an ISO Class 7 buffer area — what is termed an uncontrolled environment. However, to qualify for this risk category the space must be a segregated compounding area dedicated solely to compounding sterile preparations. The instance that can serve as a model is low-volume short-term sterile compounding performed in an ISO Class 5 hood located in a segregated space within a satellite pharmacy. However, it must also be recognized by compounding personnel that aseptic compounding in an uncontrolled environment has a higher potential of producing contaminated doses than if a real ISO Class 7 buffer area cleanroom with full cleanroom work practices was utilized.

Because of this higher risk of microbial contamination in doses prepared in an uncontrolled environment, this risk category includes a short time limitation on the acceptable beyond-use period. If a trace contamination from airborne microorganisms should occur, the microbiological beyond-use period limitation not exceeding 12 hours should be short enough not to permit an overgrowth of the microorganisms to hazardous or fatal levels. Even so, use of this kind of compounding environment for a patient population with compromised immune systems is probably a bad idea.

Several limitations are placed on the sterile compounding that can be performed under this risk category:

The ISO Class 5 primary engineering control must be located in a space that is a segregated compounding area not in a high traffic area with no unsealed windows or doors that connect outdoors and that is restricted to preparing low-risk level compounded sterile preparations.

The segregated compounding area cannot be adjacent to food preparation areas, warehouses, construction sites, or other locations that may increase the risk of contamination.

The segregated compounding area must meet all of the cleaning and disinfecting requirements in Chapter <797> for a real ISO Class 7 buffer area.

All personnel cleansing and garbing requirements for low-risk level compounding still apply.

All quality assurance, personnel testing, environmental sampling, and other requirements for low-risk level compounding still apply.

No hazardous drugs (like chemotherapy doses) are permitted to be compounded because little or no containment for personnel safety is present.

Administration must begin within 12 hours of preparation or as stated in the package insert for the drug, whichever is shorter, so as not to permit an overgrowth of the microorganisms to hazardous or fatal levels.

**Medium-Risk Level Compounded Sterile Preparations**

Medium-risk level compounded sterile preparations are those that are prepared in a suitable controlled air environment meeting ISO Class 5 (Class 100) by multiple or complex aseptic transfers of sterile commercial

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drugs from sealed containers using sterile commercial equipment and devices, or are prepared for the use of multiple patients or one patient on numerous occasions over time, or are those for which the compounding process is of an unusually long duration for dissolution or mixing. The commercial drugs and components must always be in sealed containers and not exposed to the open compounding environment at any time. Although only aseptic transfers of commercial drugs are performed, the number and/or complexity of the aseptic manipulations make this category of aseptic compounded preparations at greater risk for contamination. Examples would include parenteral nutrition admixtures, solutions prepared for infusion device reservoirs with multiple components, or multiple individual dosage units subdivided from a pooled reservoir.

If the medium-risk level compounded sterile preparation passes a USP sterility test, then the chemical and physical stability of the preparation can be used to assign the beyond-use date. In the absence of passing a sterility test, the maximum microbiological beyond-use date periods (if chemical and physical stability permit) by storage condition are:

Room temperature - 30 hours

Refrigeration - 9 days

Frozen - 45 days

**High-Risk Level Compounded Sterile Preparations**

High-risk level compounded sterile preparations are at higher risk of being inadvertently contaminated or not adequately sterilized during compounding resulting in patient injury or death. High-risk level sterile compounding should be performed only by personnel with sufficient specialized education, training, and experience in high-risk level compounding to be truly knowledgeable and competent. In addition, high-risk level sterile compounding should be performed only in truly adequate sterile compounding operations with outstanding facilities, work practices, and quality assurance. Even then, high-risk level sterile compounding should be reserved only for those occasions when the patient's medical need can be met in no safer way, such as using commercially manufactured drugs. It must be recognized and kept in mind that manual compounding of sterile preparations can never hope to achieve the quality assurance level of a commercial drug manufactured under FDA Good Manufacturing Practices (GMPs). Examples of high-risk level compounded sterile preparations include those preparations compounded from nonsterile components and/or with nonsterile equipment, or those compounded from sterile components but in an environment inferior to ISO Class 5 (Class 100), including inadvertent touch contamination. All such preparations require terminal sterilization. Autoclaving is the preferred sterilization method when drug stability permits. Filtration through a 0.2-micron filter is a common alternative sterilization technique but is less certain than autoclaving to result in sterility.

If the high-risk level compounded sterile preparation passes a USP sterility test, then the chemical and physical stability of the preparation can be used to assign the beyond-use date. In the absence of passing a sterility test, the maximum microbiological beyond-use date periods (if chemical and physical stability permit) by storage condition are:

Room temperature - 24 hours

Refrigeration - 3 days

Frozen - 45 days

**Immediate-Use Compounded Sterile Preparations**

The Immediate-Use category of compounded sterile preparations is intended for occasions when no delay between sterile drug preparation and administration occurs. Examples include aseptic drug preparation in

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emergency rooms, in the back of ambulances, during Code situations, a dose prepared by a nurse at the patient's bedside, and in any other location where there is no delay between sterile drug preparation and administration.

The Immediate-Use category states that the doses are exempted from all requirements in USP Chapter <797> only if all of the following requirements are met:

1. Only simple aseptic transfers involving three or fewer drug packages are involved, including an infusion solution.
2. No delays or interruptions occur during dose preparation.
3. The dose is prepared using good aseptic technique and care is taken to prevent direct contact contamination of the ingredients and critical sites during preparation.
4. No hazardous drugs are involved, since no protection from exposure exists for the compounding personnel.
5. The maximum amount of time from the beginning of compounding to the start of administration is not more than one hour. If more than one hour has elapsed, the dose must be destroyed.
6. No dose storage beyond one hour from the start of preparation and no recycling of doses is permitted.
7. The dose must be fully and completely labeled if not administered by the preparer or the administration must be witnessed by the preparer.

If these requirements cannot or are not met, then all of the requirements of USP Chapter <797> must be followed.

**Conclusion**

USP Chapter <797> is first and foremost about patient safety. Far too many patients have been injured or killed by unacceptable, poor quality sterile compounding practices. The Chapter has established a meaningful and achievable quality standard for compounding sterile preparations. The standard is being adopted and implemented in the better quality sterile compounding facilities across the United States and around the world. Appropriate beyond-use dating is one critical part of achieving the patient safety goals of this quality standard.

**Reference**

The United States Pharmacopeia, 31<sup>st</sup> ed., Rockville, MD: United States Pharmacopeial Convention, 2008.

**Q:** With the new USP <797> guidelines there is a question about expiration dating on large containers of antibiotics such as Vancomycin 5 gram vials. When reconstituted what expiration date is appropriate?

**A:** USP Chapter <797> provides guidance on safe practices regarding the utility period of containers, including bulk pharmacy vials, after reconstitution. Because vials are not finished sealed doses for patient use, they are specifically addressed separately from the finished compounded sterile preparation risk categories as either single-dose vials or multiple-dose vials.

In the example of pharmacy bulk vials (such as vancomycin hydrochloride 5-g vials), there is usually no antimicrobial preservative present in the formulation. Consequently, these are generally not tested as nor intended to be multiple-dose vials within the meaning of USP and the manufacturers' drug labeling. If no

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antimicrobial preservative is present in the formulation, the container is, strictly speaking, a single-dose container, bulk packages notwithstanding.

USP Chapter <797> states that single-dose vials opened or needle-punctured in ISO Class 5 or cleaner air (such as the air in a laminar airflow workbench, biological safety cabinet, etc.) may be used for up to six (6) hours after the initial entry. Any remaining drug would then need to be discarded. Pharmacy bulk vials would usually fall into this category. The Chapter also states that if the vials are opened or needle-punctured in air quality worse than ISO Class 5, the vial shall be used within one (1) hour with any remaining drug being discarded.

Obviously the concern of USP Chapter <797> is that microbial contamination could find its way into the containers during repeated entry. Antibiotic formulations provide no guarantee that some microorganisms will not grow in the reconstituted products. Minimizing the holding time of reconstituted vials, including pharmacy bulk packages, reduces the chances that any microorganisms that are inadvertently introduced can grow to harmful or fatal levels.

**Q: Do USP <797> standards allow anti-fatigue mats on the floor of the clean room, particularly in front of a laminar airflow hood?**

**A:** USP Chapter <797> does not include a prohibition of anti-fatigue floor mats or most anything else for that matter. Instead, the Chapter establishes performance standards that must be met for patient safety. If the use of anti-fatigue floor mats does not compromise the environmental quality where compounding is performed then they are permitted. Of course the opposite is also true. If the use of a specific kind of anti-fatigue floor mat compromises the environmental quality then it must not be used.

To ensure that the anti-fatigue floor mats are OK for clean room use, one would be well advised to purchase anti-fatigue floor mats specifically designed and manufactured for use in clean rooms. Some mats are very porous, or tend to crumble and leave pieces behind, or would otherwise be problematic. Such mats would be impossible to clean and disinfect effectively. Remember, USP Chapter <797> requires floors (and that includes floor mats) in ISO Class 7 clean room buffer areas to be cleaned and disinfected every day. If you want to use anti-fatigue floor mats, they need to be amenable to easy and frequently repeated cleaning and disinfecting. Such mats should have smooth surfaces all around including on top, on the bottom, and on the edges. Each day compounding personnel or those they supervise need to pick up the mats and clean and disinfect the floor space under them. In addition, all surfaces of the mats themselves need to be cleaned and disinfected daily as well.

If the anti-fatigue floor mats that are selected are of a suitable type and the cleaning and disinfecting can be and is properly performed then the compounding environment will not be compromised and the floor mats would not be prohibited by USP Chapter <797>.

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**Q:** I understand that the administration of immediate use CSPs should be begun within one hour of preparation and preparation should not exceed 1 hour. This section also specifies that the label list the "exact one hour BUD and time". Does this mean that the CSP is only good for 1 hour from the preparation time?

**A:** Health care personnel need to recognize that the quality standards cited in USP Chapter <797> apply to the compounding, transportation, and storage of compounded sterile preparations (CSPs). The quality standards are not aimed at and do not apply to administration of such doses; administration and treatment are outside the scope of USP. Even so, these are clinical care decisions that health care workers, such as nurses, pharmacists, pharmacy technicians, and physicians, must make and make properly to protect the safety of patients who depend on the wisdom of their decisions.

The Immediate Use category states that the doses are exempted from all requirements in USP Chapter <797> only if all of the following requirements are met:

1. Only simple aseptic transfers using three or fewer drug packages are involved, including an infusion solution.
2. No delays or interruptions occur during dose preparation.
3. The dose is prepared using good aseptic technique and care is taken to prevent direct contact contamination of the ingredients and critical sites during preparation.
4. No hazardous drugs are involved, since no protection from exposure exists for the compounding personnel.
5. The maximum amount of time from the beginning of compounding to the start of administration is not more than one hour. If more than one hour has elapsed, the dose must be destroyed.
6. No dose storage beyond one hour from the start of preparation or recycling is permitted.
7. The dose must be fully and completely labeled, including the exact 1-hour beyond-use date and time if not administered by the preparer or the administration is not witnessed by the preparer.

If these requirements cannot or are not met, then all of the requirements of USP Chapter <797> must be followed. If these conditions are met, the Immediate Use doses must begin administration within one hour after the beginning of preparation. The Chapter requires citing the exact one-hour Beyond-Use Date (BUD) and time when the dose is being labeled for administration by someone other than the preparer. This BUD is the time point at which administration of the dose can no longer begin.

The administration period is not addressed by USP Chapter <797>. Nevertheless, it is the responsibility of health care personnel to determine the safety of the time period of administration of such doses keeping in mind the greatly increased chance of microbial contamination that is expected with such doses. Time is the enemy; longer time frames give microbes a chance to grow to higher concentrations, which can cause morbidity and mortality. This is the reason for the short one-hour BUD; trace microbes inadvertently introduced into the container during preparation are unlikely to be able to grow to dangerous or lethal levels in one hour.

Minimizing the time of administration of Immediate Use doses is important for patient safety. And utilizing Immediate Use doses in patients with compromised immune systems is generally a bad idea unless absolutely necessary for emergency treatment. Immediate Use doses should be limited to those cases where emergency or immediate use is needed and administration periods are brief.

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**Q:** Do we have to run a sterility test for lipids syringes prepared in batches in the isolator and given 24 hrs under refrigeration?

**A:** Pre-filling commercial sterile syringes with commercial sterile lipid injections, such as Intralipid for pediatric use, in batches in properly functioning ISO Class 5 primary engineering controls in ISO Class 7 buffer areas and using a commercial sterile tip cap to seal the syringe tip would qualify as Low-Risk Level compounding. In such cases, USP Chapter <797> does not require sterility testing of batches of the pre-filled syringes that are prepared according to USP Chapter <71> although it is certainly permitted.

The only requirement for sterility testing in Chapter <797> is for High-Risk Level compounding, such as from non-sterile raw ingredients, in batches of 26 or more units. In all other batch preparation, the application of sterility testing is optional and the professional responsibility of the compounding personnel to decide.

Lipid injections such as Intralipid are very good at supporting the growth of microorganisms. Restriction of the utility time, such as use within 24 hours and stored under refrigeration as in this questioners practice, is a recognition of and response to that increased risk.

**Q:** Is it acceptable to enter a bag once with a prn adapter, then enter the prn adapter multiple times? An example is when we mix NaBicarb 150 mEq in D5W 1000 ml. We pull 150 ml out of the bag - 3 entries - then inject 150 ml of bicarb into the bag - 3 more entries. As long as we use a prn adapter on the bag, can this still be considered low risk compounding?

**A:** The procedures used in aseptic preparation of Low-Risk Level and Medium-Risk Level compounded doses are fundamentally the same: The use of only commercial sterile dosage forms and the use of commercial sterile devices, such as needles and syringes. The difference is in the complexity and frequency of the procedural steps that are required. The more numerous and complex the manipulations the more opportunities there are for microbial contamination to find its way into the finished dosage forms. Consequently, USP Chapter <797> specifies that at a maximum three individual containers be used and not more than two entries into any one container be made. The type of "entries" is not addressed, but the number of entries is specified.

In the case cited in this question, more than three containers are involved and more than two entries into the bag are made. Consequently, this would be more appropriately considered a Medium-Risk Level compounded sterile preparation. With all of the manipulations involved in its preparation, compounding personnel need to be mindful of its increased risk of becoming contaminated in the compounding process.

Because this is a Medium-Risk Level preparation USP Chapter <797> states that the beyond-use dates that are appropriate are 30 hours at room temperature and 9 days refrigerated considering that the components of the this formulation are themselves chemically stable and the potential for microbial contamination.

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**Q:** I wanted to make sure I understood that for each employee preparing IVs the new revision states that they also should have glove tip dips annually if Low or Medium Risk and q 6 months if High Risk level? Why was this added to the testing, as we are Medium Risk Level at our facility and we already do a Media-Fill Testing annually with Glove Tip Dips done MONTHLY when we have our air sampling done?

**A:** USP Chapter <797> makes a point of calling out the role compounding personnel and especially their hands play in inadvertently contaminating doses during preparation. The Introduction to the Chapter states “It is generally acknowledged that direct or physical contact of critical sites of CSPs with contaminants, especially microbial sources, poses the greatest probability of risk to patients.” Unfortunately, all compounding personnel share the attribute of being a contamination source if they are not sufficiently careful.

Minimizing the inadvertent transfer of contaminating microorganisms by the hands of compounding personnel may be the single most important quality assurance step performed in the aseptic compounding. To this end, Chapter <797> calls for compounding personnel to use sterile gloves and repeatedly and frequently sanitize them during compounding activities using sterile 70% isopropyl alcohol.

As a part of reaching the goal of reducing hand transmitted microbial contamination, the Chapter also emphasizes education, training, and evaluating compounding personnel on a regular basis both as a competency check and as an opportunity to remind, refresh, and educate personnel in necessary work practices to minimize such contamination.

As part of this effort to evaluate personnel and reinforce proper aseptic work practices, USP Chapter <797> calls for gloved finger-tip evaluation (for all ten fingers including the thumbs!) using microbial growth media. Initially, compounding personnel should be able to demonstrate successful (that is no microbial growth) from sterile glove fingertip sampling at least three times for the complete garbing procedure and for an evaluation of aseptic compounding competency. After that initial testing, personnel should be tested at a minimum annually for those who are engaged in Low-Risk and Medium-Risk Level compounding, and semiannually for those who are engaged in High-Risk Level compounding. More frequent testing certainly complies with the minimum frequencies in Chapter <797> and would be considered a better more rigorous evaluation program. The Chapter simply sets a relatively infrequent minimum to ensure that at least some gloved finger tip testing gets performed. Congratulations on exceeding the minimal requirements in Chapter <797>!

**Q:** The new <797> standards address allergenic extracts and exemptions to the required beyond use dating if all mentioned criteria are adhered to. Why would labeling each vial with a patient name exempt the use by date of the multi-dose vial to the manufacturer’s use by date? If doses are withdrawn in an ISO 5 environment, couldn’t the extended use by date be used?

**A:** As noted in the question, USP Chapter <797> has a section that addresses allergen extracts as compounded sterile preparations (CSPs). The section indicates that allergen extracts may not be subject to the standards in the Chapter as long as eleven separate requirements are met. One of these is that a multiple-dose container of allergen extract be labeled for use by a specific patient.

The intention of this specification is that if microbial contamination should have occurred during preparation of that vial, a great number of patients will not risk being harmed by it... “mass casualties” as the FDA has phrased it. Limitation to a single patient limits the exposure to only that patient. If the allergen extract CSPs are a large batch multiple vial compounding operation, then the risk to more members of the public is much

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greater from an inadvertent microbial contamination of the allergen extract.

For an allergen extract that meets all eleven criteria including being labeled for use of a specific patient, USP Chapter <797> states that the beyond-use date that is assigned may be based on the manufacturer's recommendations or on peer-reviewed publications.

**Q:** We have an IV room that does not meet all the engineering controls specified in the USP <797> for a clean room but we will be using isolators and keep one LAFW for stat doses in the same room. We will use LAFW in the satellites. Do we have to provide an annual evaluation for aseptic manipulation skills based on LAFW and another evaluation based on barrier isolators?

**Based on the previous information, do we need to continue using shoe covers?**

**A:** USP Chapter <797> specifies a number of personnel training and evaluation standards for aseptic compounding operations. Media-fill challenge testing requirements are noted under Personnel Training and Evaluation in Aseptic Manipulation Skills. USP Chapter <797> states that personnel performing Low-Risk Level and Medium-Risk Level compounding are to be tested annually. For those compounding High-Risk Level preparations, the testing is to be semi-annual.

The intention is to evaluate the skill of the compounding personnel that prepare compounded sterile preparations (CSPs) under the compounding conditions, protective environments, and compounding work practices that are present in the facility. The media-fill testing should represent the most challenging and stressful conditions actually encountered in real compounding for patients.

To do this effectively (which is the point of course), the testing must incorporate all aspects of the compounding milieu that compounding personnel are going to encounter including differing environmental engineering controls and differing manipulative steps. The media-fill challenge testing that each facility designs should represent the equipment in that facility; for this questioner, that would include both laminar airflow workbenches as well as compounding aseptic isolators. Working with these highly different primary engineering controls requires not only the differing equipment but also differing manipulative skills. All of these factors need to be included in the media-fill testing that is performed annually for Low- and Medium-Risk Level and semi-annually for High-Risk Level compounding personnel.

It should be recognized that to comply with USP Chapter <797> working in a laminar airflow workbench that is in a room that is not an ISO Class 7 buffer room is permitted only as long as it is a segregated compounding area that is separate and apart from all other functions and meets all of the other specified criteria to keep patients safe. (See Low-Risk Level CSPs with 12-Hour or Less BUD in USP Chapter <797>.) The criteria include cleaning and disinfecting that are the same as if the room was a true clean room buffer area and assuring that all of the personnel garbing requirements of a true clean room buffer area are met. There is no exemption for shoe covers. Shoes worn in from the outside are dirty by definition and need to be covered. One alternative is to have dedicated clean room shoes that are hard surface and easily and repeatedly cleaned and disinfected inside and out.

It is also important to recognize that USP Chapter <797> states that if all of these requirements are met, the compounding must only be only simple Low-Risk Level doses (because complexity increases the risk of contamination), and the beyond-use period must be no longer than 12 hours from the start of preparation because of the greater likelihood that the doses will be contaminated in the uncontrolled air environment.

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**Q:** What are labeling requirements for low and medium risk CSPs?

**A:** USP Chapter <797> does not state or imply any differences in the labeling requirements for the different risk levels cited in the chapter. The chapter specifies that the labels of compounded sterile preparations (CSPs) “bear the correct names and amounts or concentrations of ingredients, the total volume, the BUD (beyond use date), the appropriate route(s) of administration, the storage conditions, and other information for safe use.” Of course, compounding personnel also need to comply with the labeling requirements of their state regulatory boards and of accreditation bodies for medications as well.

**Q:** I have just hired an employee of Arabic descent who is inquiring if she may wear a head scarf in our <797> clean room. She is wondering if autoclaving her scarf on a routine basis would be acceptable. We have just developed a separate clean room within our 5 hospital system. I am expecting all employees to wear a cap, gown, sterile gloves, mask and foot booties in our IV compounding area. Thanks for your help in this question.

**A:** The garbing requirements in USP Chapter <797> are very detailed and specific for all personnel working in an ISO Class 7 environment. The goal of donning hair nets, beard covers, masks, gowns and shoe covers is to contain and minimize the release of hundreds of thousands to millions of particles per minute. Bacteria require particles 0.5 micron and larger to move. Minimizing the number of particles reduces the risk of contamination from airborne microbial particles.

Balancing clean room practices with religious or cultural beliefs can be challenging at times. I contacted colleagues I met while in Saudi Arabia this year and here is their response to your question. The Islamic restriction is to cover the hair and neck (covering the face is not a must except in certain sects); this is why a head cover preferably the one that can be tied (she can use two covers above each other if it is transparent) along with a high neck top covered with a mask would be enough. Females working in the OR usually get a brand new clean scarf to be worn below the cap with the edges placed under the scrub suit; otherwise, they do have a cap made by Kimberley-Clarks called “protected surgical hood” (same material and color as scrub suit) as a replacement to the scarf (it is big enough to cover the head and neck at the same time).

**Q:** How long can the following medication that has been opened inside ISO class 5 air quality be kept?

- Multi dose vial
- Reconstituted solution
- Single dose vial

**A:** USP Chapter <797> specifically addresses the beyond-use periods of opened or needle-punctured single-dose and multiple-dose containers. Reconstituted solutions fall into one of those categories.

Single-dose containers opened outside of an ISO Class 5 environment must be used within one hour and any remaining contents must be discarded. If a single-dose container is opened or needle-punctured in an ISO Class 5 environment (or better) such as those provided by properly designed and functioning primary engineering devices (laminar airflow hoods, compounding aseptic isolators, etc.), it may be used for up to six

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hours after the initial entry into the container. Opened ampoules shall not be stored for any time period; they must be discarded immediately after initial opening and entry because there is no barrier to the entry of microbial contamination.

Multiple-dose containers, which are designed for removal of portions of the drug on multiple occasions, contain a substance that acts as a preservative that can kill or prevent the growth of microorganisms that are likely to be introduced when entering through the stopper and drawing out drug. Manufacturers of multiple-dose drugs subject the formulations to a challenge test, the USP Chapter <51> Antimicrobial Effectiveness Test, to prove they kill or prevent the growth of five species of microorganisms. The test is conducted over 28 days to determine whether the preservative is effective.

In addition to microbial concerns, once the vial stopper is penetrated, the inert gas layer inside the vial is replaced with oxygen-containing air. The manufacturer will have tested the drug to assure that it will also remain chemically stable for at least 28 days after stopper penetration.

Because the Antimicrobial Effectiveness Testing is performed over a period of 28 days, and the drug must be stable for this period after the introduction of air, USP Chapter <797> specifies that a multiple dose vial once the stopper has been punctured shall have a beyond use date of 28 days unless specified otherwise by the manufacturer.

Some manufacturers for some multiple-dose products have documented a different stability period after initial stopper penetration and state it in the labeling. In such cases, the manufacturer's beyond use date period after stopper penetration may be used.

### EDITORS NOTE:

As a container is reaching its beyond-use-date, if there is documented chemical stability, it can be safely transferred into a Gri-bag<sup>®</sup> using the Gri-fill<sup>®</sup> System, maintaining the sterility of the solution and used later as a source container for additional doses, which is particularly useful with expensive drugs.

### **USP <797> states the compounding personnel appropriately don protective garb. We are looking into clarification on if protective garb includes hospital provided “scrubs” or is it allowable for staff to wear personal scrubs and use non-shedding gown with sleeves and preferably disposable supplied by the hospital and put over their own scrubs?**

USP Chapter <797> requires that all personnel in an ISO Class 7 buffer area wear appropriate prospective garb to enclose and act as a barrier to the shedding of skin particles and associated microbes that inevitably occur in huge quantities from all people all of the time. Before entering the buffer area or segregated compounding area, personnel are required to remove their outer garments such as hats, coats, jackets, scarves, sweaters, vests, etc. They all also need to remove all jewelry and cosmetics.

The personnel then need to don protective equipment in an order from dirtiest to cleanest, beginning with head and facial hair covers and shoe covers (or change into dedicated clean room shoes). After washing hands and arms to the elbows with soap and water and thoroughly drying. A non-shedding gown with sleeves that fit snugly around the wrists and enclosed at the neck is donned. After entering the buffer area or segregated compounding area, hands are sanitized with an alcohol-based hand scrub with persistent activity. As a last step at enclosing compounding personnel, sterile powder-free gloves are donned in a manner to avoid contaminating them.

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USP Chapter <797> does not require that special hospital-issued scrubs be worn by compounding personnel under their protective non-shedding gowns. Indeed, the chapter is silent on the clothing compounding personnel wear under their protective garb. Having noted that, it must be recognized that clothing worn in from the outside world, including personal scrubs from home, is likely to be more heavily microbe laden capered to freshly-laundered scrubs or other clothing donned once inside the hospital. Furthermore, it would be expected that there would be a great degree of variability among individuals in the frequency of laundering and the frequency of wear between launderings. One study in a hospital setting found that articles of clothing, including neck ties and white lab coats, were carriers of and vectors to deliver MRSA to patients. The National Health Service in the United Kingdom is in the process of banning neckties and white lab coats from patient care areas for this reason.

Whether the wearing of personal clothing of uncertain (but potentially heavy) microbial burden could translate into a higher rate of contamination among compounded sterile doses when using appropriate personnel protective garb with properly functioning primary and secondary environmental engineering controls is not known. USP Chapter <797> has no requirements or suggestions on the clothing worn under the protective garments. Therefore, it falls to the compounding personnel, particularly supervising personnel, to make these decisions for their facilities and personnel and implement and enforce them for the safety of their patients.

**Q:** I have been informed that the Baker EdgeGard hood, because of its high velocity return air slots, obviates the necessity of working 6 inches within the hood and that anywhere within this particular hood is acceptable.

**A:** Each laminar airflow hood (LAFW) is designed and built differently but these primary engineering controls for the most part are very robust devices. The only way to make sure that this situation exists in your particular ISO Class 5 device (please don't assume that this situation exists in your hood just because you heard about it) is to ask your certifier to perform smoke studies during your semi-annual recertification. These smoke studies will identify the areas of unidirectional airflow vs. zones of turbulence. Sterile compounding must be performed in a unidirectional device for the purpose of facilitating aseptic technique using the concept of "first air."

"First air" is the air exiting the HEPA filter in a unidirectional air-stream and is virtually free of particulate contaminants. All aseptic manipulations must be carried out in the unobstructed "first air" zone in the direct path of the HEPA filter discharge. Knowing how your ISO Class 5 engineering control operates and how to best create and maintain first air during compounding activities is best done with smoke studies.

The certifier will know how to perform this study and you should let him know before he visits to certify the hood that you want to do a smoke study (so he can have the equipment needed to perform this test). Also, instruct your certifier to test all of your primary engineering controls (LAFWs, BSCs and isolators) and secondary engineering controls (buffer area and ante area) to the CETA standards that are referenced in USP Chapter <797> and can be found at <http://www.cetainternational.org/reference/isg.php>, document CAG-003-2006, updated in 2008. Most certifiers are aware of these standards and this will ensure that your certifier is doing all of the tests necessary to verify the performance of your hoods and rooms according to USP Chapter <797> facility requirements.

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**Q:** With respect to the garbing procedure recommended in USP chapter <797>, they state that garbing should proceed from the "dirtiest to the cleanest" activity; i.e. shoe covers, then hair covers, masks, etc. However, shouldn't the order be the other way around? If you start with the "dirtiest" procedure, then proceed to "cleaner" activities, aren't you potentially contaminating everything else down the line?

**Why are shoe covers considered good enough to enter the IV Room or buffer area when they're not considered a sterile product?**

**A:** One of the changes made to the revised USP Chapter <797> was the clarification and rewriting of the garbing section. This revised section was harmonized with the CDC Guidelines for Hand Hygiene in Health-Care Settings. In addition to the language on the importance of proper hand hygiene, the garbing order and requirements was addressed relative to garbing a person in order of dirtiest to cleanest. The intent of the committee was not to be prescriptive or literal on the order of garb as published in the chapter but to identify the dirty activities that need to occur PRIOR to performing proper hand hygiene procedures. Mask, head cover and shoe covers (in that order) most certainly would be acceptable. The order of this garbing may be dictated by the location of the sink and the door into the ante area. The sink needs to be on the "clean side" of the line of demarcation and if space is limited, the line of demarcation might have to be at the door going into the ante area. If that is the case, shoe covers should go on first to minimize or eliminate a significant source of soil and other contaminants that is found on shoes.

It is important to stress that the importance of being properly garbed in order to contain the millions of particles that are shed when we work. We are not sterile after garbing and the ante area and buffer area can have up to 100,000 particles and 10,000 particle per cubic foot of air respectively. Since microorganisms need to travel via a particle, the goal is to minimize the opportunity for microorganisms to travel by being properly garbed and having the ante area and buffer area maintain a state of control while we compound. Everything that we bring into the ante area and buffer area (including drug vials, tubing, needles and syringes) is not sterile nor is there a requirement for them to be sterile. Aseptic compounding is all about minimizing and preventing the risk of introducing microorganisms into the CSPs. Garbing is one of several strategies for achieving that goal.

**Q:** Are there any requirements/precautions in compounding monoclonal antibodies and/or anti-necrosis factor agents insofar as USP <797> regulations? Can they be compounded in a clean IV room with other compounded IV's or must they be separated, possibly under a horizontal flow chemo hood?

**A:** Prior to handling, compounding, and transporting drugs, a pharmacist should evaluate the drug in question and consult with the manufacturer regarding any special handling, compounding, or transportation requirements. Most manufacturers categorize their drugs according to the American Hospital Formulary Service (AHFS) nomenclature. ASHP publishes the AHFS which is an excellent resource in determining the pharmacologic-therapeutic classification of drugs. You should also consider looking at the NIOSH Alert, available online at <http://www.cdc.gov/niosh/docs/2004-165>. In Appendix A, you will find a list of drugs that are considered hazardous. Some of the monoclonal antibodies are listed in the appendix and should be considered hazardous drugs. If they are, care and caution should be used and you should handle them as according to the NIOSH Alert and USP

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Chapter &lt;797&gt;.

**Q:** Please advise if we have a room that contains two barrier isolators (Germfree glove boxes) with one vented to outside and using negative pressure for chemo and one using positive pressure for non-chemo I.V. admixtures, will this meet USP <797> standards?

**A:** Glove box is a common term synonymous with isolator. By definition, a glove box is an enclosed workspace equipped with gloved openings that allow manipulation in the interior of box, designed to prevent contamination of the product, the environment, or the worker. The interior space may not be supplied with conditioned (HEPA filtered) air. An isolator is defined in USP Chapter <797> as “a form of isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbially retentive filter (HEPA minimum)”. There are positive-pressure isolators (CAIs) used for the preparation of non-hazardous drugs and negative-pressure containment isolators (CACIs) used for the preparation of hazardous drugs.

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 room) from other preparation areas. Non-hazardous compounding must be separated from hazardous compounding, except for facilities that have a low-volume hazardous compounding operations. The number of hazardous drug CSPs that defines low-volume has not been stipulated in the chapter. In the proposed revisions, the Sterile Compounding Committee suggested 5 hazardous CSPs per week (less than one a day) as low volume but when challenged, could not justify the number. Personally speaking, I believe that low-volume compounding is one hazardous drug CSP per day. The final determination is up to pharmacist since the focus of the "Hazardous Drugs as CSPs" section of the chapter was on the need to protect the personnel handling, compounding and transporting the hazardous drug CSP as well as ensuring sterility of the CSP.

**Q:** For sterile preparations compounded in the OR with air exchange etc., is there longer than a 1 hour BUD? (Referring specifically to the physicians that mix marcaine and lidocaine together and a syringes or irrigation preparations that are made up in the OR prior to the patient's arrival)

**A:** Compounding in air cleanliness conditions less than ISO Class 5 would fall under the "Immediate-Use" provision of the chapter. In order to extend the BUD beyond the 1 hour limit, the preparation of the CSPs described in the question would have to occur within an ISO Class 5 primary engineering control; the air in OR suites is HEPA filtered air but typically cannot meet the performance criteria identified in the USP chapter. Physicians or assistants should prepare these CSPs just prior to use, using aseptic technique in order to minimize the risk of microbial contamination.

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**Q:** Is it necessary that the housekeepers who clean the IV room (compounding and buffer etc) remove their makeup and what about tattoos?

**A:** Since makeup can be a significant source of particles and microbial contamination, all personnel entering the buffer area are required to comply with the hand hygiene and garbing requirements of the chapter. This would include the removal of makeup. When the certifier comes semi-annually to test the facility and engineering controls, they too should be properly garbed. Tattoos involve ink that is imbedded in the skin of the owner. Unless the tattoo is new (i.e. the site of the tattoo is still weeping), I am not aware of any special precaution necessary for tattoos. Many employees have chosen to have eye liner tattooed on their face in lieu of makeup, which does not require any additional precautions.

**Q:** Our hospital does not have a clean room. We use a CAI-Compounding Aseptic Isolator (Glove Box). According to the manufacturer we do not need to do glove tip testing, since the gloved hand does not come in touch with the preparation. Please comment.

**A:** Based on the intent and language in the USP, there is NO language in the chapter that supports the manufacturer's claim that you do not have to do fingertip sampling on the gloves in an isolator. The gloves do come in contact with the critical sites and therefore they must be sterile. Isolators are not the panacea that everyone thinks they are, because you are still required to bring in components and supplies that may have been disinfected but are not sterile. There is still a risk of touch contamination when using an isolator, especially because some of the gloves are thick and cumbersome to work in. In my opinion, the isolator is even more dependent on the sterility of the gloves than the other primary engineering controls because of the exemptions we have given them. The chapter allows compliant isolators to be placed outside of an ISO Class 7 buffer area because of the physical barrier provided by the device and gloves. How can it be said that those very gloves can be less robust than the sterile gloves required in other ISO Class 5 primary engineering controls that do not qualify for cleanroom exemptions? I have spoken with a number of isolator users who use non-sterile gloves mounted on the isolator gauntlet and then don a pair of sterile gloves over the isolator mounted gloves from inside the isolator. This is cumbersome but manageable procedure.

**Q:** I have been hearing a lot of different interpretations on chemo storage of products both before and after admixture and separate chemo ante rooms and refrigerators. What is the latest USP Chapter <797> interpretation on these subjects? I confirmed that the wholesalers are segregating all chemo products in their storage and shipping although I haven't seen any "hazardous substance" labels or totes.

**A:** I strongly encourage you to read the chapter yourself and not depend on the interpretation of this requirement from others. The chapter is very clear on the requirements of hazardous drug storage. The chapter states: "Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure. Many hazardous drugs have sufficient vapor pressures that allow volatilization at room temperature; thus storage is preferably within a containment area such as a negative pressure room. The storage area should have sufficient general exhaust ventilation, at least 12 air changes per hour (ACPH) to dilute and remove any airborne contaminants. Hazardous drugs shall be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking,

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inventorying, preparation for administration, and disposal." Additional practice recommendations can be found the NIOSH Alert-Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings-Worker Employer Recommendations (<http://www.cdc.gov/niosh/docs/2004-165/>) and the ASHP Guidelines on Handling Hazardous Drugs-Am J Health-Sys Pharm. 2006;63:1172-93.

**Q:** **Where is the best place to put a sink? Can the sink used for handwashing also be used for preparation of cleaning solutions for cleaning the classified areas? What about discarding the used cleaning solutions?**

**A:** Personal hand hygiene and garbing procedures, as well as cleaning support operations, will be performed in the ante area. A line of demarcation (LOD) will separate the clean side of the ante area from the dirty side. Since a sink is integral to proper hand hygiene practices, the sink needs to be located on the "clean side" of the ante area. The chapter goes on to state: "The buffer area shall not contain sources of water (sinks) or floor drains." There is nothing in the chapter to prohibit the sink that is used for handwashing to be used for the preparation and disposal of cleaning solutions. The sink should be kept clean and properly maintained. If possible, a mop sink should be available for the preparation and disposal of cleaning solutions. You should consider consulting your environmental services and/or infection control professionals to ensure that the agents being used are appropriate and approved in your facility and are being properly disposed of in accordance with local, state and federal requirements.

**Q:** **USP Chapter <797> requires the use of sterile gloves when compounding sterile products. For the production of chemotherapy, our hospital requires the use of chemotherapy gloves and then the application of sterile gloves. Is this required by USP Chapter <797>? Is the use of sterile gloves sufficient?**

**A:** The use of sterile gloves is required for all types of compounding with all types of ISO Class 5 primary engineering controls (LAFWs, BSCs, CAIs and CACIs). The chapter also states "Appropriate personnel protective equipment (PPE) shall be worn when compounding in a BSC or CACI and when using closed-system transfer device (CSTD) devices. PPE should include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving with sterile chemo-type gloves, and compliance with manufacturers' recommendations when using a CACI." Until recently, sterile "chemo" gloves were not available. Whatever gloves are chosen, they must be appropriate for handling hazardous drugs, since many of the hazardous drugs routinely handled by staff can permeate the glove material over time. When selecting an appropriate glove, request a "spec sheet" or Product Data Sheet from the manufacturer or wholesaler. This document should provide you with critical information on the permeation performance of the glove material (e.g., nitrile or neoprene). Double-gloving is an important work practice since it will protect the employee from exposure to hazardous drugs and provide a mechanism to contain any surface contamination from spreading to areas outside of the primary engineering control.

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**Q:** Some institutions have utilized special procedures for preparing products for intrathecal administration. In discussion with colleagues around the country various procedures exist and some institutions have never used a "special" procedure for these preparations. The idea behind the special procedures was to produce a syringe that is "sterile" on the outside that would be placed on a sterile field during the administration. This was accomplished by one technique which utilizes 2 people in the preparation process- one person is the "clean" person the other is the "dirty" person. This is defined as one person who handles the packages of syringes and other supplies as an assistant to the "clean" person who would only handle the sterile syringe or other sterile supplies wearing sterile gloves. The final product was then placed in a sterile bag and sealed into of the LAFW. With the implementation of USP <797>, are there any comments regarding this practice?

**A:** The chapter does not address the sterility of the outside surfaces of devices, packages or CSPs that will be placed in a sterile field. The goal of the chapter is to ensure the sterility of the fluid and fluid pathway. The procedure you have described is very interesting, but I am not aware of any procedure involving people that would yield a CSP container or package that can be labeled as sterile. The only way that I am aware of and how this could be accomplished would be to terminally sterilize all of the components and devices that were going to be used with ethylene oxide or some other type of agent or method. Whatever method or means used cannot have any detrimental effect on the components or devices prior to use. It would be critical to ensure that your described procedure can yield a package that can be labeled as sterile. Consideration should be given to verifying this aseptic process through the use of growth media (TSB). This verification procedure can be accomplished by preparing a media fill syringe using the same methods as the intrathecal syringe and placing it into a tube of tryptic soy broth (a sufficient quantity to cover all surfaces of the syringe). The syringe in the TSB will be incubated for 14 days. If there is any solution turbidity, then the syringe was not sterile.

**Q:** Does the door swing matter when designing a clean room?

**A:** There is nothing in the chapter that sets out a door swing requirement. Any door swing will need to comply with local architectural, building and fire safety codes. ISO Class 5 primary engineering controls should not be located immediately adjacent to doors since their opening can create disruptive air currents that can affect the performance of these devices. Typically you open the door in the direction of the pressure. The door should be designed in such a way as to facilitate hands-free use.

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**Q:** My question regards the appropriate BUD for unit dose syringes for injection repackaged from a multi-dose vial. An example would be methadone injection which is only available as a multi-dose vial, but for patient safety and accountability our institution repackages these as a unit dose syringe for storage in Pyxis at room temperature. According to USP Chapter <797> on multi-dose products: "The beyond use date after initially entering or opening (e.g., needle-punctured) a multiple-dose container is 28 days unless otherwise specified by the manufacturer." The guidelines for the BUD for the Low-risk category at room temperature is 48 hours. In our situation the multi-dose vial has been manipulated (under aseptic conditions within an ISO Class 5 LAFW within a Class 7 buffer area), so one could ascertain that the Low-risk BUD of 48 hours should apply. However, since the vial has likewise been manipulated and can retain a 28 day BUD, we have been unsure as to which guideline is applicable in this situation. Your assistance and interpretation would be appreciated.

**A:** Your question is a common one and one that is not directly answered by USP Chapter <797>. The definition of a multi-dose vial, which can be found in the General Notices section of the USP-NF is as follows: "A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only. (See also Containers for Injections under Injections <1>). A multi-dose vial is a container designed to prevent contamination or loss of contents. Closures (septa) of multiple-dose containers permit the withdrawal of contents without removal or destruction of the closure. Multiple-dose vials must be validated to ensure package integrity and prevent microbial contamination or loss of product contents under anticipated conditions of multiple entry and use." Preparing a compounded sterile preparation (CSP) from a medication from a multiple-dose vial (assuming that the drug is not diluted) under the conditions you describe could be considered a low-risk level CSP. Once the medication is withdrawn from the vial and its validated container-closure system, the microbial integrity cannot be guaranteed. The methadone syringes your organization is compounding may be sterile, but in order to extend the BUD beyond that associated with low-risk CSP, a sterility test according to USP Chapter <71> would need to be performed.

**Q:** We decontaminate our biologic safety cabinet weekly in addition to routine cleaning. Our decontamination process involves the use of three agents: Dakin's Solution, sterile water for irrigation and sterile isopropyl alcohol. A cleaner with a pH approximating soap is supposed to aid in the removal of cytotoxic agents. Dakin's solution is used as the cleaner. The Dakin's Solution is used initially, followed by sterile water for irrigation then sterile IPA. However, the commercially available Dakin's solution which we purchase is not sterile. Are there recommendations available regarding appropriate cleaning agents which should now be used in the process of decontaminating a BSC?

**A:** If you are using the Dakin's Solution to decontaminate the BSC, there is no requirement that it be sterile, assuming that sterile solutions (as you described) are used AFTER the non-sterile solution. The procedure you have described appears to be appropriate for the task that you are performing. The best way to verify that the use of non-sterile Dakin's Solution is NOT having an impact on your BSC is through surface sampling with TSA plates that contains lecithin and polysorbate 80. These additives will neutralize any disinfectants on the surfaces. If you do not have any CFU growth on the surface of your BSC, then you don't have problem.

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**Q:** Our anteroom and buffer room are one in the same. At this time, IV labels print in this area. The technicians assigned to work in the IV room wear scrubs, don protective gear, etc. However, when short staffed someone may have to move in and out of the room quickly to pull IV labels, or grab a vial from the cabinet. I have read another hospital's policy that stated something to the effect if a person needs to access the buffer zone for a couple of minutes they could come and go without donning hair cover, booties and outer protective garments over their street clothes. In terms of workflow this would be a great relief to off shifts, etc who must constantly gown and regown. Is this acceptable per <797> guidelines?

**A:** The short answer is NO. How do you protect the environment and CSP from contamination when a person who is not properly garbed enters the area? They do not have an aura of sterility around them and can contaminate both the area and any preparations. I would analyze your workflow and figure out a way to minimize any back and forth traffic. Move supplies and drugs to an area that is readily accessible to properly garbed personnel so the need for ungarbed personnel entering is minimized or eliminate. All personnel who enter the ISO Class 7 buffer area needs to have performed hand hygiene and be properly garbed.

**Q:** Regarding growth media used for viable air sampling, the chapter says "... media that support the growth of fungi shall be used in high-risk level compounding environments." Should all designated sampling locations for a compounding environment then be sampled twice - once with soybean-casein digest medium for bacteria and once with fungal medium?

**A:** Assuming that high-risk level sterile compounding is occurring in the area in question, a growth media for bacteria and one that will support the growth of fungi is required. The sampling can occur either simultaneously or concurrently. Some of the volumetric air samplers can be purchased with a dual sampling collection head that would allow two different agar plates to be used simultaneously. It is important to ensure that agar plates be incubated correctly. The TSA plates should be incubated at 30°C to 35°C for 48 to 72 hours. Malt extract agar or other suitable fungal media should be incubated at 26°C to 30°C for 5 to 7 days.

**Q:** Regarding identification of microorganisms recovered during viable microbial air sampling: Under what circumstances is microbial identification recommended? Should it be performed routinely, for every cfu recovered, or is this procedure a suggestion for a course of action in the event an action level has been exceeded?

**A:** 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 bioburden captured as a cfu using an impaction air sampler. Highly pathogenic microorganisms (e.g., Gram-negative rods, coagulase positive staphylococcus, 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."

It is important to understand what type of microbial bioburden is in your sterile compounding area. These environments are designed to minimize the number of particles in the air. Microorganisms need particles to

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travel on so in addition to having a properly designed, certified and functioning environment, employee work practices can have a huge (negative) impact of the microbial bioburden. Garbing and cleaning practices are critical to minimize environmental bioburden. The chapter requires the identification of microorganisms when any CFU is recovered.

**Q:** If a single-dose container is needle-punctured in an ISO Class 5 environment, why would it be able to be used for up to six hours after the initial entry into the container? If it has been needle punctured, and is for single dose only, would it not have to be discarded immediately after the first and only needle puncture permitted under the parameters of single dose only? Is there a device available that would permit penetration into the single dose vial (a needleless system or device that once it punctures the vial stopper would stay in place- no further penetration), attach to the vial and stay there. This would then allow for the single dose vial use for up to six hours within the confines of an ISO Class 5 environment (we have a clean room).

**A:** Technically, a single-dose vial can only be used once, since the solution does not contain a preservative. There has been some recent updated guidance from the CDC on the proper use of single-dose vials. These vials were originally conceived to be used most often in areas with ambient air and thereby increasing the risk of microbial contamination either through poor aseptic technique or airborne contaminants. The official USP definitions germane to this question can be found in the General Notices section of the current USP-NF. They are as follows: A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article. The definition of single-dose container is a single-unit container for articles intended for parenteral administration only and is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled. If possible, please review the information regarding Containers for Injections under USP Chapter <1>- Injections. Neither definition stipulates the quality of the air where these containers will be used. The integrity of the vial can only be maintained through proper aseptic technique in controlled air environments. The USP Sterile Compounding Committee believes that properly garbed individuals working in an ISO Class 5 air cleanliness environment utilizing proper aseptic technique extends the BUD of single-dose vials to 6 hours. The use of devices that limit the number of needle punctures into the vial septum should further minimize the risk of contamination.

Editor's note: Grifols now has the Quickpin available for minimizing the number of needle punctures and allowing for complete drain-ability of the vial for expensive drugs. Use in combination with the Gri-fill® System and Gri-bag® to filter the contents of a vial into a bag to save the remainder of a vial of expensive drug. This assures the sterility while allowing for extended dating. Would you like more information?



Quickpin



Gri-fill® 3.0 System



Gri-bag®

**Grifols Guide to USP <797> – Question of the Week**

Answers by Eric Kastango

(Continued)

**Q:** I have a theoretical question for you about losing power to my clean room. If we lost power to our clean room, like in a thunderstorm or the air handling system was turned off for an extended period of time, and everything in the air handling system closed down appropriately, would our clean room still have "maintained" integrity? No human is in the clean room during the shutdown time. Or would it require a reesterilization in order to restart it up? We have HEPA filters within the ductwork of the supply side and dampers on the return. I'm not sure if this is enough information to answer this, but I was hoping to pick your brain on this possibility.

**A:** My rule of thumb when I ran a cGMP operation for Baxter was for employees to leave the area immediately upon loss of power. If power was restored in less than an hour (i.e. within 59 minutes and 59 seconds) we allowed the room to run for 15 minutes, verified proper pressure relationships between spaces, and wiped down the ISO Class 5 working surfaces. For power loss longer than one hour, the room was broken down, cleaned once (walls, ceilings, floors, everything), allowed to dry and setup new compounding operations. This worked for us: sometimes we were lucky (less than 1 hour) and other times, not so lucky.

**Q:** We have an OR pharmacy that would like to make up syringes to put in the automated dispensing unit. They need ephedrine diluted with saline for OR. Trissel's Handbook of Injectable Drugs says it would be good for 60 days at room temp. But the question comes with Beyond-Use Dating (BUD). We would not likely test these syringes since we would not make up batches of 25 or more. When I read USP it does talk about having literature to back up extended BUD, so what would you recommend? We generally only give syringes a 24 hour expiration.

**A:** You are required to test batches of high-risk level CSPs in quantities greater than 25. There are two elements of BUD: chemical stability and microbial sterility. Trissel has the chemical side of the house covered and if you want to extend BUD past those listed in USP <797> for these syringes (which I would classify as medium-risk level), you need to do sterility testing. If you batch them in an appropriate environment and keep refrigerated in the pharmacy, you could give these syringes 9 days refrigerated and 30 hours at room temperature without any testing.

**Q:** When preparing hazardous drugs, do you absolutely have to be double gloved with sterile chemo gloves? Can you put a non-sterile pair of chemo gloves under a sterile pair of chemo gloves? We have a cancer center where pretty much all they do is compound chemo and it gets extremely expensive to double glove with sterile chemo gloves SEVERAL times each day.

**A:** As long as the outer pair of gloves is sterile, you can use non-sterile gloves underneath.

**Grifols Guide to USP <797> – Question of the Week**

Answers by Eric Kastango

(Continued)

**Q:** The question relates to segregation of hazardous and non-hazardous compounding. In the situation where there is only an anteroom and a cleanroom for preparation and all the patients are oncology patients, is it acceptable to have both hazardous and non-hazardous compounding in the same room? The compounding is done in separate Biosafety Cabinets with the ante room (ISO 7) positive pressure and the compounding room (ISO7) negative pressure.

**A:** The reason for segregating hazardous from non-hazardous compounding is to avoid by environmental and healthcare worker exposure. The literature is replete with evidence that medication vials come from the manufacturer/wholesaler with residual hazardous material on the vial and within the shipping cartons. Containment and exposure control are some of the major objectives behind USP <797>, NIOSH Alert and the ASHP Guidelines on Handling Hazardous Drugs. Both USP <797> and the NIOSH Alert recommend a separate room for the preparation of hazardous drugs from non-hazardous drugs. Minimally, having dedicated and separate primary engineering controls (BSC) for each type of medication (hazardous and non-hazardous) is required. It is my recommendation that all non-hazardous drugs be handled in the same manner as the hazardous drug using the same packaging, labeling and handling precautions used for hazardous drugs. Nurses should wear gloves to prevent exposure to any possible HD residue on the outside of the CSP container. This recommendation is based on consultation with experts at NIOSH and the principle author of ASHP's Guidelines on Handling Hazardous Drugs. It is my professional opinion that this practice will comply with the spirit of the industry guidance documents without presenting any undue risk to patients and employees assuming appropriate work practices and PPE procedures are followed.

**Q:** In the introduction, the revised chapter says that "The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein." What does one demonstrate and how is it done with statistical significance? Can you give an example?

**A:** USP Chapter <797> used the language that is cited above for the specific purpose of not standing in the way of new and improved technologies that have been and are being developed. The Chapter describes the most common sterile compounding situation at present; that is, manual preparation by human compounding personnel. But automation and robotics are beginning to change the way sterile drugs are prepared. The Grifill<sup>®</sup> system, IntelliFill, RIVA, and CytoCare are already here. Other automation technologies are in development.

No matter how clean we believe we are, all of us humans are laden with microbes and can shed particles carrying these microbes at a rate in the millions per hour. This makes humans the largest source of contamination in the sterile compounding environment. The use of automation and robotics has the opportunity to reduce human contact in the compounding environment and, therefore, the chance that contamination finds its way into a patient's dose.

However, USP Chapter <797> states that before alternative technologies are considered suitable for use, they must be proven with statistical significance to be equivalent to or (hopefully) superior to manual preparation of sterile doses. This is typically the responsibility of the manufacturer of the technology, and is performed during the development process using microbial growth medium to simulate the automated sterile drug preparation process but with the ability to detect microbial contamination in every unit prepared.

To be statistically significant a minimum of 3000 media fill samples must be prepared with no contamination events occurring to be able to demonstrate a contamination rate less than 0.1% with 95% statistical

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Answers by Eric Kastango

(Continued)

confidence. This media fill testing should be conducted as the manufacturer proposes the device to be used in the clinical setting. Let's look at the Gri-fill® system media-fill verification testing as an example. The manufacturer indicates that the Gri-fill® system may be used outside of a ISO Class 5 primary engineering control, Therefore, the media-fill verification testing of over 3000 media fill samples by the Gri-fill® system was performed in such an environment to demonstrate that the contamination rate is no worse than that found with manual sterile compounding in an ISO Class 5 primary engineering control inside of an ISO Class 7 buffer area. Since the media-fill verification testing performed on the Gri-fill® system found no contamination occurred among this 3000+ unit cadre of growth medium samples, then statistical significance has been met, and the device would be considered acceptable under the USP Chapter <797> standards. It is the responsibility of sterile compounding personnel to become educated consumers and be able to evaluate manufacturer's information to make sure the manufacturer's verification testing supports the intended use of the technology by the compounding organization.

**Q:** **With all the requirements for construction and environmental monitoring, am I better off to just build an ISO class 5 room without hoods to do compounding? Is it cheaper? I have heard of this in manufacturing environments. Is it feasible for a pharmacy to maintain?**

**A:** An ISO class 5 room is acceptable within the USP <797> guidelines. However, it is not recommended for sterile compounding. The Direct Compounding Area (DCA) is the most critical area within the compounding environment; it must be unidirectional airflow and it must provide an area of "first air" to protect the product from outside and process generated contamination. When the entire room is the unidirectional zone that creates the DCA; the dirtiest component of the process (people) is in the critical area (ISO Class 5 zone). This increases the potential for product contamination. Additionally, gowning requirements are increased when the clean room personnel are in the DCA which will increase cost and decrease operator comfort. A proven alternative to the ISO class 5 room is a hybrid room that incorporates an ISO class 5 space within an ISO class 7 room. HEPA filters are positioned along one wall with a clear shield to separate the unidirectional flow DCA from the operator and the rest of the room. Stainless steel tables are positioned approximately 2 inches from the wall under the VLF HEPA filters. Unidirectional airflow is directed downward across the tables and then out of the curtain area to the returns. Design of this type of system should be left to those with an in-depth understanding of airflow. Certifiers have noted difficulty certifying poorly designed hybrid designs for numerous reasons including the following: Improper placement of or inadequate low-wall return locations, too large of a gap between the HEPA filters or the HEPA filters and the curtain, inadequate space between the work table and the wall. The hybrid clean room design can provide a flexible compounding environment if designed and built properly. An ISO class 5 room is typically too cumbersome and expensive for sterile compounding.

Eric Kastango would like to acknowledge the assistance of Jim Wagner in answering this question. Jim is also a member of the Expert Committee responsible for drafting the current USP Chapter <797>.