



CSI TESTING

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FREQUENTLY ASKED QUESTIONS RELATING TO CONTROLLED ENVIRONMENT FACILITY AND EQUIPMENT REQUIREMENTS OF USP 797.

Background:

On January 1, 2004, United States Pharmacopeia issued Chapter 797, Pharmaceutical Compounding – Sterile Preparations. Based upon feedback from our pharmacy customers, we have developed this information to help guide you through the compliance process.

Question: Who can enforce or audit USP 797 compliance?:

Answer: The Food and Drug Administration (FDA), State Boards of Pharmacy, and Joint Commission on Accreditation of Healthcare Organizations (JCAHO). The Food and Drug Administration (FDA), State Boards of Pharmacy, and Joint Commission on Accreditation of Healthcare Organizations (JCAHO). JCAHO began including this in their audits in July 2004. State Boards vary as to whether they are adopting USP 797 and to what degree they will participate in its enforcement.

Question: Why was USP 797 standard developed?

Answer: The purpose of USP 797 is to reduce or prevent harm to patients that could result from microbial contamination, excessive bacterial endotoxins, large content error, and incorrect ingredients or contamination of compounded sterile products (CSP). The earlier efforts to promote improved practices were disappointing. By setting minimum facility and equipment control standards it was felt that the potential for microbial contamination would be reduced. 797 is an enforceable chapter, where 1206 (the chapter it replaced) was voluntary.

Question: What are the critical compliance dates for JCAHO ?

Answer:

- July 1, 2004 - Should have begun the process of compliance evaluation and formulated an initial action plan.
- January 2005 – Should have conducted a risk assessment (or gap analysis) of their compliance to all provisions of this chapter.
- July 2005 – Should have a renovation plan developed.
- January 2005 Should be certifying all LAFW, Isolators and Buffer rooms every 6 months.

(NOTE: Based on statements made by JCAHO at 8/6/04 USP workshop)

Question: What are the facility requirements of USP 797 ?:

Answer:

Equipment (Primary Controls): A Laminar Airflow Workbench (LAFW) and / or a biological safety cabinet certified to ISO Class 5 for airborne particles are required. These must be located within an ISO Class 8 environment (please note that as of this writing, the current version of USP 797 specifies an ISO Class 8 environment, however, at the August 8th symposium on 797 held by the USP, they indicated that they are considering changing the document to ISO Class 7). An approved alternative is the barrier isolator certified to ISO Class 5 that may be used outside an ISO Class 8 environment (although it is recommended that the barrier isolator also be located in the ISO Class 8 environment).

A common means of achieving an aseptic processing environment is to provide unidirectional airflow through a High Efficiency Particulate Air (HEPA) filter. A properly designed unidirectional airflow system reduces the opportunity for contamination and cross contamination on the work surface. Primary control equipment should utilize unidirectional airflow (versus mixed airflow or dilution airflow) to provide a proper aseptic processing environment. LAFW's and most biological safety cabinets utilize unidirectional airflow. Not all barrier isolators utilize unidirectional airflow.

Room Environment (Secondary Controls): USP 797 requires a controlled environment (the “Buffer Area” or “Buffer Zone”) where particle levels must meet ISO Class 8 requirements, with temperature and humidity controls, and where ceilings, walls, floors, fixtures, and furnishings are constructed of materials that can be easily cleaned using anti-microbial agents. Surfaces should be smooth (not porous or seamed) to avoid microbial growth. An Anteroom adjacent to the Buffer Area is recommended where gowning and hand-washing can occur before entry to the Buffer Area. Sinks should be located in the Ante Room to facilitate hand washing and to minimize microbial growth in the Buffer Area.

- Where Low and Medium Risk CSP’s are prepared, the Ante Room and Buffer Zone may be separated by a visible line or a physical barrier.
- Where High Risk CSP’s are prepared, a physical barrier between the Anteroom and ISO 8 Buffer Zone or Area is required.
- Temperature and humidity controls must be maintained within the Buffer Zone or Area.

Practices: Policies and procedures for maintaining and working in aseptic processing must be prepared, updated, maintained, and implemented by the pharmacy. These procedures are determined by the scope and risk levels of the activities performed in the compounding operation.

Question: Do I need a Cleanroom like those used in a manufacturing environment?

The short answer is Yes, and No: There is a great deal of confusion surrounding whether USP specifically requires a “Cleanroom” as would be used in a pharmaceutical or manufacturing environment, or a “Controlled Environment” where certain environmental controls common to cleanroom design applications are used to provide environmental stability.

It is common to find situations where only the LAFW or biological safety cabinet are supplying all of the filtration for the rooms in which they are located. In many cases, the rooms would meet the particle levels allowed in ISO Class 8. However, these would not provide the control of the environment that is required. Although USP 797 does not specifically call for the use of certain building systems such as HEPA filtered air supply, statements made by the USP Panel of Experts at the May 14-15, 2004, workshop on 797 is that these are required. In order to achieve stable environmental control there must be basic elements that can and should be incorporated into the room, as listed below:

1. Properly installed HEPA filters on the supply air system will provide sub-micron level filtration of the air. Supply air is vulnerable to external contamination and without filtration can actually force contaminants into the room.
2. Positive room air pressurization is used in cleanrooms to help keep ambient airborne contamination from entering the room through open doors, construction joints, wall penetrations, ceiling tiles, and light fixtures. While USP 797 does not give specific values for pressurization, other guidance documents do. For example, the FDA recommends 0.05 inches of water gauge as an acceptable level of room pressure differential. ISO 14644-4:2001 recommends between 0.02 and 0.08 inches of water gauge (5 Pa to 20 Pa) to maintain control.
3. The Buffer Room should be physically segmented from ambient space. It’s very difficult to maintain a stable clean zone within ambient spaces without the use of a physical barrier. This can be achieved using walls and doors, or using cleanroom rated materials such as vinyl wall curtains.
4. Cleanable surfaces should be utilized to facilitate cleaning and maintenance. We recommend using cleanroom rated ceiling tiles that have a non-porous cleanable surface, or the use of a solid ceiling with epoxy paint.
5. Controlling personnel access, limiting particle generating materials (e.g. cardboard and cotton fiber), good gowning practices, and regular cleaning are also important elements in maintaining the controlled environment.
6. Temperature and humidity controls are an essential element of USP 797. Be sure to include this in any room upgrade or remodel. As part of the planning, be sure to include the added heat that may be generated by LAFW and biological safety cabinets.
7. Policies and procedures for maintaining and working in aseptic processing must be prepared, updated, maintained, and implemented by the pharmacy. These procedures are determined by the scope and risk levels of the activities performed in the compounding operation. Strict but understandable gowning, washing, cleaning, and behavior protocols should be developed and adhered to in order to maintain the optimum environment.

Question: How do I know if I meet ISO Class 5 and/or ISO Class 8 requirements?

Answer: USP 797 requires regular environmental monitoring. The LAFW, biological safety cabinet, and/or barrier isolator must be certified for performance and tested to ISO Class 5 particle levels by a qualified operator at least every 6 months, upon installation, or when moved. The ISO Class 8 Buffer or Clean Area and Ante-room areas must also be tested for ISO Class 8 particle levels at least every 6 months or when modified.

Question: What is a barrier isolator?

Answer: There is no universal definition of a barrier isolator and no uniform standard for the construction, operational requirements, or testing of barrier isolators. These vary by manufacturer and have no common performance attributes. USP 797 considers these to be an *emerging alternative technology*. The only criteria is that they be well-designed, have positive pressure, and be supported by adequate procedures for maintenance, monitoring, and control.

Class III Biological Safety Cabinets (gloveboxes) have been used for many years for handling the most dangerous biological pathogens, exotics, certain nuclear materials, and dangerous drugs or chemicals. But barrier isolators are NOT the same as a Class III Biological Safety Cabinet as they have not been manufactured to the same containment specifications.

Question: Will purchasing a barrier isolator help me to avoid having to build a cleanroom and save money?

Answer: NO. The use of barrier isolators can be a cost effective alternative, but there are certain issues that should be considered:

- Barrier isolators are not always less costly than building a controlled environment, especially where you already own the primary equipment. Pricing of barrier isolators varies and does not necessarily correlate to the level of quality or performance you may need.
- You should require the manufacturer to provide you with written test methodology as there is no common test method. There are no national standards listing quantifiable data for testing individual isolators. Once obtained from the manufacturer you should provide this test material to your testing service agent for the semi-annual testing required.
- Barrier isolators in relation to USP 797 are popular because it appears that their use would alleviate the need for a cleanroom or other primary control equipment. This position has mainly been promoted by some barrier isolator manufacturers and is not always accurate. The isolator may or may not provide the aseptic environment required. Isolators that create diluted or mixed air within the chamber can fail to provide airflow to wash away contamination build up. This may result in contamination and cross contamination in processing or when multiple products are produced in this same equipment. For aseptic processing, we recommend the use of unidirectional airflow, whether an isolator or LAFW.
- One complaint we hear from barrier isolator owners is that isolators can be difficult to clean and hard to work in. Be sure that the main chamber can easily be accessed, and that no special tools are needed to clean the unit. We also recommend height adjustments where available.
- As product is manipulated in the transfer chamber leading to the main chamber of the isolator, we recommend that the transfer chamber be HEPA filtered to maintain asepsis in the transfer process.
- There are certain applications where the barrier isolator may be the better choice over a cleanroom environment. For example, smaller pharmacies or those where construction of a room may not be feasible.
- Although 797 does not specifically require a classified space for the isolator, it is recommended. Furthermore, the intent is to voluntarily elevate the compounding profession to the level of FDA regulated facilities. The 2003 draft of the FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Procession – current Good Manufacturing Practice specifically calls for barrier isolators located within an ISO 8 environment.

Question: Can Barrier Isolators be used for processing chemotherapy and other hazardous materials?

Answer: Safety in processing chemotherapy and other hazardous drugs is why biological safety cabinets have been the standard for many years. Barrier isolators are allowed, but only if they provide the worker with safety that is required. USP 797 states only that a positive pressure barrier isolator is approved for use, but this raises safety concerns when used with hazardous drugs. We do not recommend the use of positive pressure barrier isolators when working with hazardous drugs.

The most recent NIOSH publication (dated June 2004) states, *“When aseptic technique is required, the recommended ventilated cabinets include Class II (Type B2 preferred, Type A2 & B1 allowed under certain conditions) and Class III BSC’s as well as isolators intended for asepsis and containment (Aseptic Containment Isolators)” [NSF/ANSI 2002; PDA 2001]. Regardless of type, each ventilated cabinet should be equipped with a continuous monitoring device to allow confirmation of adequate airflow prior to each use. The exhaust from these controls should be HEPA (High Efficiency Particulate Air) filtered and preferably exhausted 100% outside . . . A ventilated cabinet with air recirculation, either within the cabinet or to the room environment, should only be used if the hazardous drug(s) in use will not volatilize during process manipulation or after capture by the HEPA filter.”*

Choose a barrier isolator manufacturer as you would a biological safety cabinet manufacturer. Look for stability, long term history, and ability to support the product post sale. Ask about pricing and availability of replacement parts, filters, gloves, and other items that you will need as time goes on. Also, ask questions about the manufacturing facilities. Do these meet recognized quality standards? Finally, contact us for advice. We serve as a resource for providing you with information you may need to make your best long term purchase decision.

Testing, Certification, and Environment Requirements

Clean Environment Type	USP – Compounded Sterile Preparation – Section 797 (2004)	Test and Certification Frequency by a “qualified operator”
Laminar Airflow Work (LAFW)	ISO Class 5. Certified for proper operation. Must be located within an ISO Class 8 area.	Every 6 months or when moved.
Barrier Isolator	ISO Class 5 Positive Air Pressure May be located outside an ISO Class 8 area.	Every 6 months or when moved
Clean room	ISO Class 5 Clean room if sterile preparation performed without barrier isolator or clean bench. ISO Class 8* Core Area, Buffer Area, Buffer or clean area where clean bench or safety cabinet is located and used for sterile preparation. Where High Risk Preparations are performed, a Class 8 area is to be preceded by an ante-chamber separated by a physical barrier, that provides a clean area for donning gowns, etc. * NOTE: USP also refers to an ISO Class 7 as appropriate.	Every 6 months or when renovated.
Biological Safety Cabinet	ISO Class 5 if used for sterile preparations. Certified for proper operation.	Every 6 months or when moved