"Current Comments on Healthcare IAQ Issues™"

March 1, 2010 (Revised) Volume 8, No. 1.

USP General Chapter <797> 2008 Standard

Medical Air Solutions, LLC. attended and participated in the **USP** Webinars (Web Seminar) held on June 6, 2007, February 21, 2008 and May 15, 2008. The Webinars were hosted by the **United States Pharmacopeia** (**USP**) to provide information and discussion on the final **USP General Chapter <797>** for clarification of various sections of the chapter. This included information, clarification and discussion on the final release that occurred on December 3, 2007. The final issue may be downloaded at the URL below;

http://www.usp.org/pdf/EN/USPNF/generalChapter797.pdf)

There have been some significant changes from what was written in the previously proposed revision documents. Below is the URL to the USP web site's FAQ page answering many "frequently asked questions.

http://www.usp.org/audiences/pharmacist/797FAQs.html

Introduction

For those of you that already have a **MAS** proposal, if you are not performing high risk CSP, **MAS** does not plan to change your present proposal. (For a list of high risk drugs, go to the **NIOSH** web site at www.cdc.gov/niosh/docs/2004-165/). Those of you that perform high risk CSP (identified as "hazardous" on the **NIOSH** web site and also now in the **USP** Standard), you may need a revision to our proposal provided you would like to fully meet the new standard.

The **Joint Commission on Accreditation of Healthcare Organizations** (**JCAHO**) may be surveying the pharmacy for compliance with **USP <797>** but will not be issuing violations according to the Survey Director at **JCAHO**. This may change at a later date. **JCAHO** has been requiring pharmacies to have a "*gap analysis*" as required by **<797>** in some states. Please note that an **MAS** proposal can be utilized to serve as the gap analysis.

The **U. S. Food and Drug Administration** (**FDA**) has deemed **USP <797>** as a "***Standard of Care***" and will expect all state **Boards of Pharmacy** to enforce compliance. To quote the **USP June, 2006, Webinar Guidebook**:

"Thus, while the FDA generally defers to the states to regulate the practice of pharmacy and other health professions, it takes a keen interest in the quality and safety of the compounded preparations that reach patients. The FDA will act with states in investigating allegations of poor quality compounded drugs, but is willing and able under the FFDCA [Federal Food, Drug and Cosmetic Act] to act on its own initiative. The FDA intends to continue to work with states, but if a state is unwilling or unable to join the Agency's efforts, the FDA may choose to act unilaterally to protect the public health from compounded drugs that pose unreasonable risks."

The **USP <797>** committee feels that enforcing the **USP <797>** standard will fall to the states' **Boards of Pharmacy** and that the **FDA** will rely on them only. With regard to the paragraph above,

and with a new administration in Washington, DC, **MAS** feels the **FDA** may take a more proactive stance in having all compounding pharmacies that perform low/, medium and high risk CSP meet this standard.

MAS will continue to provide basic design services and medical-grade equipment that will ensure your pharmacy will meet and/or exceed **USP <797>**. With few exceptions, our designs do very rarely affect the actual structure (building). There are some states and local governments that may require an architect and/or engineer to approve any pharmacy renovation. **MAS** will work with a local contractor, A&E, engineering company and/or pharmacy to gain these approvals and provide assistance to the contractor and or architect during renovation or construction.

MAS has a preferred national contractor that performs many CSP Area upgrades. **American Medical Systems, LLC.**, based on Kansas City, KS, has extensive experience in pharmacy upgrades.

Some of the items presented here will not necessarily be associated with engineering design. We are providing some of the more important information in condensed form for all interested parties. Much of the explanations for the risk types and descriptions of the various elements of **USP <797>** have changed which is why we strongly suggest you download the standard.

We are providing the entire list of definitions that is found in the December 3, 2007, standard. We have added some text to the definitions based on information and clarifications received during the February 21, 2008, and May 15, 2008, Webinars.

If you have any questions regarding the physical upgrade to your pharmacy please feel free to call us at 800-645-1059 or call our engineering direct at 770-377-3884.

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Table 1. ISO Classification of Particulate Matter in Room Air (limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet [former Federal Standard No. 209E, FS 209E])*

Class Name		Particle Count	
ISO Class	U.S. FS 209E	ISO, m^3	FS 209E, ft^3
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

*Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 14644-1 : 1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3,520 particles of 0.5 µm per m^3 or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (Class 100) (1 m^3 = 35.2 ft^3).

Glossary of Definitions

Ante-area / Anteroom — An ISO Class 8 (see *Table 1*) or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities are performed. It is also a transition area that (1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and (2) reduces the need for the heating, ventilating, and air-conditioning (HVAC) control system to respond to large disturbances.

Aseptic Processing (see *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* <1116>) — A mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers–closures or packaging material for medical devices) and the transfer of the product into the container and its closure under at least ISO Class 5 (see *Table 1*) conditions.

Beyond-Use Date (BUD) (see *General Notices and Requirements* and *Pharmaceutical Compounding — Non-sterile Preparations* <795>) — For the purpose of this chapter, the date or time after which a CSP shall not be stored or transported. The date is determined from the date or time the preparation is compounded.

Biological Safety Cabinet (BSC) — A ventilated cabinet for CSPs, personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward high-efficiency particulate air (HEPA) filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

Buffer Area (or Buffer Area/Zone) — An area where the primary engineering control (PEC) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.

Clean Room (**or Cleanroom** - see *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* <1116> and also the definition of *Buffer Area [or Buffer Area/Zone*) — A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

Compounding Aseptic Containment Isolator (CACI) — A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation. The interior of the CACI will always be under a negative pressure environment.

Compounding Aseptic Isolator (CAI) — 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). The interior of the CAI will always be under a positive pressure environment.

Critical Area — An ISO Class 5 (see *Table 1*) environment.

Critical Site — A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampuls, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. The risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

Direct Compounding Area (DCA) — A critical area within the ISO Class 5 (see *Table 1*) primary engineering control (PEC) where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Disinfectant — An agent that frees from infection, usually a chemical agent, but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores. It refers to substances applied to inanimate objects.

First Air — The air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.

Labeling [see *General Notices and Requirements* and 21 USC 321 (k) and (m)] — A term that designates all labels and other written, printed, or graphic matter on an immediate container of an article or preparation or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term “label” designates that part of the labeling on the immediate container.

Media-Fill Test (see *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* <1116>) — A test used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile product without microbial contamination.

During this test, a microbiological growth medium such as Soybean–Casein Digest Medium is substituted for the actual drug product to simulate admixture compounding. The issues to consider in the development of a media-fill test are media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.

Multiple-Dose Container (see *General Notices and Requirements* and *Containers for Injections* under *Injections* <1>) — A multiple-unit container for articles or preparations intended for parenteral administration only and usually containing antimicrobial preservatives. The beyond-use date (BUD) for an opened or entered (e.g., needle-punctured) multiple-dose container with antimicrobial preservatives is 28 days (see *Antimicrobial Effectiveness Testing* <51>), unless otherwise specified by the manufacturer.

Negative Pressure Room — A room that is at a lower pressure than the adjacent spaces (an area that is neutral in pressure) and, therefore, the net flow of air is *into* the room.

Pharmacy Bulk Package (see *Containers for Injections* under *Injections* <1>) — A container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. The pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

Where a container is offered as a pharmacy bulk package, the label shall (a) state prominently “Pharmacy Bulk Package — Not for Direct Infusion,” (b) contain or refer to information on proper techniques to help ensure safe use of the product, and (c) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.

Primary Engineering Control (PEC) — A device or room that provides an ISO Class 5 (see *Table 1*) environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs).

Preparation — A preparation, or a CSP, that is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.

Product — A commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA approved manufacturer's labeling or product package insert.

Positive Pressure Room — A room that is at a higher pressure than the adjacent spaces (considered to be an area that is neutral in pressure) and, therefore, the net airflow is ***out of*** the room.

Single-Dose Container (see *General Notices and Requirements* and *Containers for Injections* under *Injections* <1>) — A single-dose container is a single-unit container for articles (see *General Notices and Requirements*) or preparations intended for parenteral administration only. It is intended for a single use. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Segregated Compounding Area — A designated space, either a demarcated area or room, that is restricted to preparing low-risk level CSPs with 12 hour or less BUD. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 (see *Table 1*) air quality for preparation of CSPs and shall be void of activities and materials that are extraneous to sterile compounding.

Sterilizing Grade Membranes — Membranes that are documented to retain 100% of a culture of 10 microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* per square centimeter of membrane surface under a pressure of not less than 30 psi (2.0 bar). Such filter membranes are nominally at 0.22-µm or 0.2-µm porosity, depending on the manufacturer's practice.

Sterilization by Filtration — Passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent.

Terminal Sterilization — The application of a lethal process (e.g., steam under pressure or autoclaving) to sealed containers for the purpose of achieving a predetermined sterility assurance level of usually less than 10^{-6}, or a probability of less than one in one million of a non-sterile unit.

Unidirectional Flow (see footnote 3) — An airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

Primary and Secondary Engineering Requirements

As stated above, some of the requirements listed here are not necessarily of an engineering nature. We have included these to ensure a more comprehensive presentation.

Immediate Use CSPs

Description: The immediate-use provision is intended only for those situations where there is a need for emergency or immediate patient administration of a CSP. Such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or

critical therapy where the preparation of the CSP under conditions described for *Low-Risk Level CSPs* subjects the patient to additional risk due to delays in therapy. Immediate-use CSPs are not intended for storage for anticipated needs or batch compounding. Preparations that are medium-risk level and high-risk level CSPs shall not be prepared as immediate-use CSPs.

Immediate-use CSPs are exempt from the requirements described for *Low-Risk Level CSPs* only when all of the following criteria are met:

1. The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers' original containers and not more than two entries into any one container or package (e.g., bag, vial) of sterile infusion solution or administration container/device. For example, anti-neoplastics shall not be prepared as immediate-use CSPs because they are hazardous drugs.

2. Unless required for the preparation, the compounding procedure is a continuous process not to exceed 1 hour.

3. During preparation, aseptic technique is followed and, if not immediately administered, the finished CSP is under continuous supervision to minimize the potential for contact with non-sterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other CSPs, and direct contact of outside surfaces.

4. Administration begins not later than 1 hour following the start of the preparation of the CSP.

5. Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the CSP shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour BUD and time. If administration has not begun within 1 hour following the start of preparing the CSP, the CSP shall be promptly, properly, and safely discarded.

MAS Comments: These may not be compounded in an ISO 5 environment so extra caution is required to ensure the immediate use CSP does not come into contact with other contaminated items or surfaces and should be in a non-traffic area.

Hazardous Drug Storage

Description: 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)[4] to dilute and remove any airborne contaminants. The negative pressure Buffer Area/Zone is sufficient for storing these drugs.
MAS Comments: This is an exception to the standard that requires all flat surfaces (including storage racks and/or cabinets) to be removed from the Buffer Area/Area/Zone. Any refrigeration unit should be cleaned on a regular basis to keep microbial growth from forming on any coils.

Placement of Primary Engineering Controls (LAFW, BSC, CAI and CACI)

Description: All Primary Engineering Controls (LAFW, BSC, CAI and CACI) shall be placed in an ISO 7 Buffer Area/Area/Zone for all risk level CSP. Only authorized personnel shall have access to this area when CSP operations are taking place.

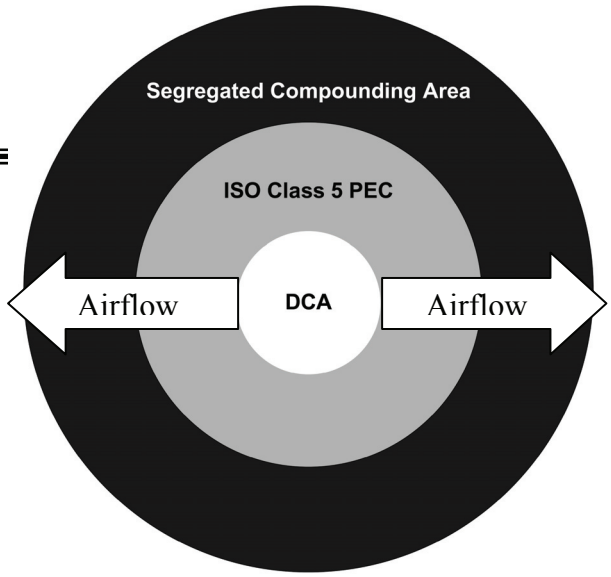
Exceptions: When closed-system vial-transfer devices (CSTDs) (i.e., vial-transfer systems that allow no venting or exposure of hazardous substance to the environment) are used, they shall be used within the ISO Class 5 (see *Table 1*) environment of a BSC or CACI. In facilities that prepare a *low volume of hazardous drugs*, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable. (This includes locating the CACI in the positive pressure Buffer Area/Area/Zone). Also:

CAI's shall be placed in an ISO Class 7 (see *Table 1*) buffer area. CACI's shall be placed in an ISO Class 7 *unless* it meets all of the following conditions:

- The isolator shall provide isolation from the room and maintain ISO Class 5 (see *Table 1*) during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
- Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO Class 5 (see *Table 1*) levels during compounding operations.
- Not more than 3520 particles (0.5 µm and larger) per m^3 shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.
- It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CACI will meet this standard when located in environments where the background particle counts exceed ISO Class 8 (see *Table 1*) for 0.5-µm and larger particles.

MAS Comments: **MAS** has always advocated placing Primary Engineering Control(s) in an ISO 7 Buffer Area/Area/Zone. We also advocate having the entire CSP Areas enclosed with hard walls except where only low volumes of low and medium risk CSP are performed. This has minimal impact on the cost of renovation.

Conceptual representation of USP Chapter <797> facility requirements



The ISO 7 Positive Pressure Buffer Area/Area/Zone

Description: The ISO 7 Buffer Area/Zone shall be segregated from any surrounding unclassified areas and be accessed through an Anteroom/Area. When the Buffer Area/Zone is enclosed by walls it shall maintain a positive pressure of +0.02" - +0.05" W. C. and have a minimum of 30 ACH. Keep in mind this area is virtually identical to the physical design of a standard surgical suite (operating room).

If the Buffer Area/Zone is segregated from an Anteroom/Area by a demarcation line or soft barrier (i.e., plastic strips) then the air movement from the Buffer Area/Zone to the Ante-Anteroom/Area shall be a minimum of 40 feet per minute (FPM – this can be measured by a thermal anemometer).

The minimum 30 ACH shall be delivered either by the Secondary Engineering Control device(s) (usually ceiling mounted laminar airflow units) or a combination of the Primary and Secondary Engineering Controls to achieve the 30 ACH. The air being provided and exchanged via the Primary and Secondary Engineering Controls shall be through a HEPA (High Efficiency Particulate Air) filter

with a minimum starting efficiency of 99.97% at 0.3 microns whose efficiency shall be confirmed on a yearly basis.

The exhaust from these rooms shall be near the floor (under a door or a low HVAC return) of the ISO 7 area if physically possible. Exhausting air via ceiling return should be a second option.

MAS Comments: **MAS** has extensive experience in designing and, via our contractor partners, renovating rooms and areas to achieve both positive and negative pressure, ultra-clean indoor air environments. We currently design the positive pressure ISO 7 Buffer Area/Zone to provide a target of +0.03" W. C. (in an enclosed Buffer Area/Zone) and 35 ACH in any Buffer Area/Zone. We also build in enough excess capacity to achieve 40-60 ACH when possible. The LAFW, BSC, CAI and/or CACI shall have more than sufficient supply of ultra-clean air to pass through the 99.99% HEPA filters in these units. It should be noted that the pressure in the Buffer Area/Zone must always be significantly higher than the Anteroom/Area when there is a hard wall segregating these two areas by at least 0.02" W. C..

In enclosed ISO 7 Buffer Area/Zones, the differential pressure (dP or ΔP) should be continuously monitored via a pressure sensing device. Keep in mind that the differential pressure in the ISO 7 room should be compared to a non-pressurized adjacent area such as the common pharmacy area or a hallway and not the Anteroom/Area. The same applies to monitoring the differential pressure of the Anteroom/Area.

Airflow dynamics (air mixing and air movement) is an integral part of the design of any pressurized room needing an ultra-clean air environment. We design with considerations of where doors, pass-throughs, other CAIs and any other physical barriers that may be present. The primary concern is to evaluate what the airflow patterns will be after the installation of the Secondary Engineering Controls and design so that the LAFW, BSC, CAI and/or CACI is protected from any source of contamination.

The installation of return air grilles near the floor is usually a difficult procedure due to the construction and thickness of an existing wall and may be prohibitively costly. In some cases it may be unavoidable to have return air exiting the room via a ceiling or upper wall return as long as its placement does not allow for the possible contamination of the ISO 5 units. **MAS** will usually have the excess air exit the room under the entrance door to the ISO 7 Buffer Area/Zone into the Anteroom/Area.

The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the Buffer Area/Zone shall be smooth, impervious, free from cracks and crevices, and non-shedding, thereby promoting cleanability and minimizing spaces in which microorganisms / contaminants may accumulate.

The surfaces shall be resistant to damage by disinfectant agents. Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydro phobic, and they shall be caulked around each perimeter to seal them to the support frame. Walls may be constructed of flexible material (e.g., heavy gauge polymer), panels locked together and sealed, or of epoxy-coated gypsum board.

Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust-collecting overhangs, such as ceiling utility pipes, and ledges, such as windowsills, should be avoided.

The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls shall be sealed.

The Buffer Area/Zone shall not contain sources of water (sinks) or floor drains. Work surfaces shall

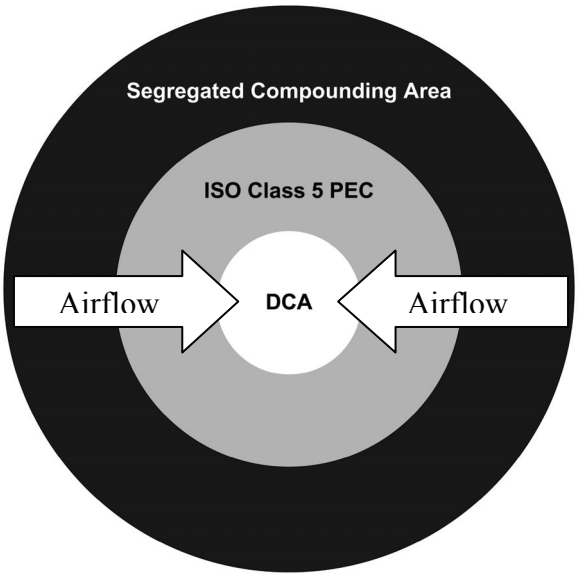
be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected.

Carts should be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility. Storage shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, non-shedding, cleanable, and disinfectable; their number, design, and manner of installation shall promote effective cleaning and disinfection.

The Negative Pressure Buffer Area/Zone

Description: The ISO 7 Buffer Area/Zone that is used for High Risk CSP (Hazardous Drugs) shall be segregated from the Anteroom/Area by a wall and shall be accessed from the Anteroom/Area. The Buffer Area/Zone, enclosed by wall(s), shall maintain a minimum negative pressure of +0.01" W. C. minimum and have a minimum of 12 ACH. Keep in mind this area is virtually identical to the physical design of standard Airborne Infectious Isolation (AII) room.

Conceptual representation of USP Chapter <797> facility requirements



The minimum 12 ACH shall be delivered either by the Secondary Engineering Control device (usually ceiling mounted laminar airflow units) or a combination of the Primary and Secondary Engineering Controls to achieve the minimum 12 ACH. The air being provided and exchanged via the Primary and Secondary Engineering Controls shall be through a HEPA (High Efficiency Particulate Air) filter with a minimum starting efficiency of 99.97% at 0.3 microns whose efficiency shall be confirmed on a yearly basis.

The exhaust from these rooms is usually provided by the Hood/BSC or CAI/CACI. 100% of the exhaust Hood/BSC or CAI/CACI from the Hood/BSC or CAI/CACI should be vented to the outside via a dedicated duct.

Exceptions: In facilities that prepare a *low volume of hazardous drugs*, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable. (This includes locating the CACI in the positive pressure Buffer Area/Zone)

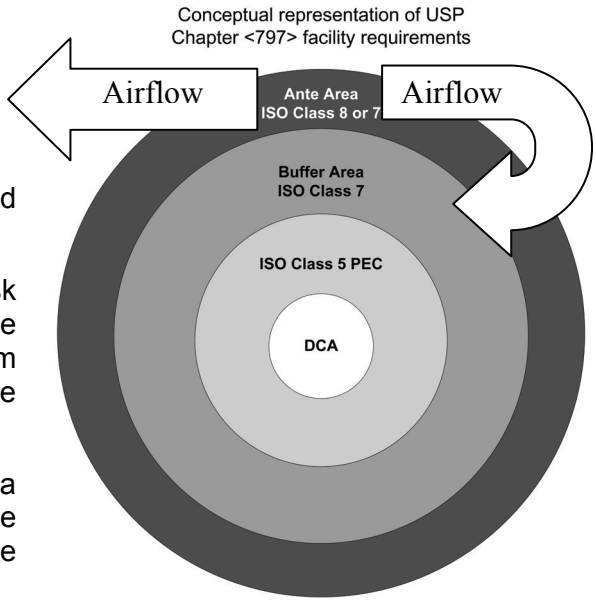
MAS Comments: **MAS** has extensive experience in designing and, via our contractor partners, renovating rooms and areas to achieve both positive and negative pressure, ultra-clean indoor air environments. We currently design the negative pressure ISO 7 Buffer Area/Zone to provide a target of -0.01" W. C. minimum and 35 ACH in any Buffer Area/Zone (i.e., a "clean room" requires 30 ACH minimum). We also build in enough excess capacity to achieve 40+ ACH when possible. The BSC and/or CACI shall have more than sufficient supply of ultra-clean air to pass through the HEPA filters in these units. It should be noted that the pressure in the Buffer Area/Zone is negative and must always be significantly lower than the positive pressure Anteroom/Area. There shall always be a hard wall segregating these two areas for High Risk CSP operations.

In enclosed ISO 7 Buffer Area/Zones the differential pressure (dP) should be continuously monitored via a pressure sensing device. Keep in mind that the differential pressure in the ISO 7 room should be compared to a non-pressurized adjacent area such as the common pharmacy area or a hallway and not the Anteroom/Area.

Airflow dynamics (air mixing and air movement) is an integral part of the design of any pressurized room needing an ultra-clean air environment. We design with considerations of where doors, pass-throughs, other CAIs and any other physical barriers that may be present. The primary concern is to evaluate what the airflow patterns will be after the installation of the Secondary Engineering Controls and design so that the BSC and/or CACI is protected from any source of contamination.

The exhaust air will usually be exhausted to the outside via the BSC and/or CACI to create a negative pressure environment. In some instances additional exhaust air via return grilles near the floor may be required. **MAS** will usually have the make-up air enter the room under the entrance door to the ISO 7 Buffer Area/Zone from the Anteroom/Area. Additional supply APS may be required for a larger Buffer Area/Zone.

The Ante-area or Anteroom



Description: An enclosed Anteroom/Area is defined as a positive pressure area with an ISO Class 8 or better environment maintaining a nominal +0.01" W. C. differential pressure. All Buffer Area/Zones shall have and Ante-area or Anteroom that is segregated from the areas adjacent.

A negative pressure Buffer Area/Zone for High Risk CSP must have an Anteroom/Area. If the negative pressure Buffer Area/Zone has a common Anteroom with a positive pressure Buffer Area/Zone, then the minimum ISO requirement for the Anteroom is ISO 7.

The positive pressure in an enclosed Anteroom/Area plus Buffer Area/Zone (with no intervening wall) shall be continuously monitored in relation to the area(s) outside the room.

An Anteroom/Area that is not enclosed may have a demarcation line between it and the Buffer Area/Zone but the entire area may be segregated from the adjacent areas. The Anteroom/Area may be physically separated from the adjacent areas around it with only a demarcation line to segregate it from any surrounding areas when only a low volume of low and medium risk CSP are performed.

The demarcation line of an Ante-area from a Buffer Area/Zone or an area surrounding the Anteroom/Area itself may be as simple as a line painted on the floor or may be a barrier of plastic strips or another type of soft non-porous barrier.

MAS Comments: Placing the entire CSP unenclosed area (Buffer Area/Zone and an Anteroom/Area) in any location will usually require some type of barrier to segregate the Buffer Area/Zone on at least three sides. **MAS** usually recommends that, for a low volume of Low and Medium Risk CSP, this is acceptable and we always recommend that a barrier of plastic strips be used to separate the Anteroom/Area from the Buffer Area/Zone. It is usually a good engineering practice to separate the Anteroom/Area from the adjacent outside areas with this type barrier.

Although the present USP <797> standard does not adequately address the air changes per hour, **MAS** uses standard cleanroom design criteria and designs for >12 ACH/ACPH with the target at 15.

MAS will design a hard wall for a high volume of Low and Medium Risk CSP to separate the Buffer Area/Zone and Anteroom/Area.

We recommend monitoring the pressure in an enclosed Anteroom/Area /Buffer Area/Zone at the entrance to the Anteroom/Area. This will measure the differential pressure in the entire CSP area only.

For an enclosed Anteroom/Area and an enclosed Buffer Area/Zone we measure the pressure in both areas to ensure that the airflow direction is moving correctly for the CSP area configuration. In some instances where there are both enclosed High Risk and a Low and Medium Risk Buffer Area/Zones, we will measure the differential pressure in both Buffer Area/Zones and the enclosed Anteroom/Area. It is vitally important that airflow from a negative pressure Buffer Area/Zone be moving in the correct direction.

General CSP Area Requirements

1. **General** – 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 non-shedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate. The surfaces shall be resistant to damage by disinfectant agents.

2. **Ceilings** – Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydrophobic, and they shall be caulked around each perimeter to seal them to the support frame. A sealed (gasketed) ceiling system are available and acceptable for use in this area.

3. **Walls and Floors** – Walls may be constructed of flexible material (e.g., heavy gauge polymer), panels locked together and sealed, or of epoxy-coated gypsum board. Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust-collecting overhangs, such as ceiling utility pipes, and ledges, such as windowsills, should be avoided. The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed.

4. **Wall and Ceiling Penetrations** – All penetrations through the ceiling or walls shall be sealed.

5. **Doors** – All primary entrance and egress doors must be sealed on the top and sides. Other doors in the area shall be sealed on all four sides.

6. **Sinks/Drains/Work Surfaces in the Buffer Area/Zone** – The Buffer Area/Zone shall not contain sources of water (sinks) or floor drains. Work surfaces shall be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected.

7. **Pressure Monitoring** – A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 (see Table 1) and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column).

8. **Carts** – Carts should be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility.

9. **Anteroom/Area Storage** – Storage shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, non-shedding, cleanable, and disinfectable; their number, design, and manner of installation shall promote effective cleaning and disinfection.

10. **Engineering Control Performance Verification** – PECs (LAFWs, BSCs, CAIs, and CACIs) and secondary engineering controls (buffer and ante-areas) are essential components of the overall contamination control strategy for aseptic compounding. As such, it is imperative that they perform as designed and that the resulting levels of contamination be within acceptable limits. Certification procedures such as those outlined in 'Certification Guide for Sterile Compounding Facilities' (CAG-003-2006) shall be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated or altered or major service to the facility is performed.

11. **Total Particle Count Analysis** – Certification that each ISO classified area, for example, ISO Class 5, 7, and 8 (see *Table 1*), is within established guidelines shall be performed no less than every six (6) months for low and medium risk areas (ISO 7) and no less than one (1) month for high risk areas (ISO 7) or whenever the LAFW, BSC, CAI, or CACI is relocated or the physical structure of the buffer area or ante-area has been altered. Testing shall be performed by qualified operators using current, state-of-the-art electronic equipment calibrated yearly to NIST traceable standards with results of the following:

    - ISO Class 5: not more than 3520 particles 0.5 µm and larger size per cubic meter (100 particles 0.5 µm and larger size per cubic foot) of air for any LAFW, BSC, CAI, and CACI;
    - ISO Class 7: not more than 352,000 particles of 0.5 µm size and larger per cubic meter (10,000 particles 0.5 µm and larger size per cubic foot) of air for any buffer area;
    - ISO Class 8: not more than 3,520,000 particles or 0.5 µm size and larger per cubic meter (100,000 particles 0.5 µm and larger size per cubic foot) of air for any ante-area.

11. **Sampling Plan** – An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed. Selected sampling sites shall include locations within each ISO Class 5 (see *Table 1*) environment and in the ISO Class 7 and 8 (see *Table 1*) areas and in the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 [see *Table 1*] environment, counters near doors, pass-through boxes). Refer to *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* <1116> and the CDC's 'Guidelines for Environmental Infection Control in Healthcare Facilities, 2003' for more information on sampling methodology. (**MAS'** partner, **MTI,** can provide third party sampling and training of laboratory personnel. Call **MAS** for more information.)

12. **Air Sampling Devices** – The sampling for pathogen testing must be performed no less than every 6 months for low and medium risk areas (ISO 7) and no less than one month for high risk areas (ISO 8) preferably with an active air sampling device. There are a number of manufacturers of electronic active air sampling equipment. It is important that personnel refer to the manufacturer's recommended procedures when using the equipment to perform volumetric air sampling procedures. A sufficient volume of air (400 to 1000 liters) shall be tested at each location in order to maximize sensitivity. The volumetric air sampling devices need to be serviced and calibrated to NIST traceable standards as recommended by the manufacturer. This is preferable to static agar plates placed in the CSP Area.

13. **Cleaning Schedule** – Cleaning and disinfecting surfaces in the LAFWs, BSCs, CAIs, and CACIs are the most critical practices before the preparation of CSPs. Consequently, such surfaces shall be cleaned and disinfected frequently, including at the beginning of each work shift, before each batch preparation is started, every 30 minutes during continuous compounding periods of individual CSPs, when there are spills, and when surface contamination is known or suspected from procedural breaches.

Work surfaces in the ISO Class 7 (see *Table 1*) buffer areas and ISO Class 8 (see *Table 1*) ante-areas as well as segregated compounding areas shall be cleaned and disinfected at least daily, and dust and debris shall be removed when necessary from storage sites for compounding ingredients and supplies using a method that does not degrade the ISO Class 7 or 8 (see *Table 1*) air quality (see *Disinfectants and Antiseptics* <1072>).

Table 3. Minimum Frequency of Cleaning and Disinfecting Compounding Areas

Site	Minimum Frequency
ISO Class 5 (see *Table 1*) Primary Engineering Control (e.g., LAFW, BSC, CAI, CACI)	At the beginning of each shift, before each batch, not longer than 30 minutes following the previous surface disinfection when ongoing compounding activities are occurring, after spills, and when surface contamination is known or suspected
Counters and easily cleanable work surfaces	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage shelving	Monthly

MAS Comments:

As stated above, some of the revisions and changes listed here are not necessarily possible in all pharmacies. Space limitations and the physical layout or geometry of the area where the CSP operations are performed may not always lend itself to a "perfectly designed" CSP area. For the most part, as long as the intent to comply as much as is possible with **USP <797>** is attempted and that the actual air environment of the area where the CSP is taking place is within acceptable parameters, this ***may*** be adequate. You State Board of Pharmacy may have published requirements that will assist in your design decisions.

MAS has worked with many pharmacies to ensure that our designs are economical and meet or exceed the **USP <797>** standard. Our *medical-grade* laminar airflow units deliver ISO 6 or better clean air to both the Anteroom/Area/Anteroom/Area and the Buffer Area/Zone. There is no extra cost for this feature it is inherent in our equipment that this is provided.

It should be noted that having the Primary and Secondary Engineering Controls are not a substitute for proper procedures and protocols for the personnel performing the CSP. The importance of having proper protective equipment (correct gloves, gowns, head coverings, shoe covering, etc.) and abiding by the Standard Operating Procedures (SOP) are paramount. Most all contamination other than cross-contamination of drugs will usually come from the humans performing the CSP operation. As an example, humans without protective garments generate the following:

- A person sitting or standing still generates about 100,000 particles/ft^3.
- The act of sitting down or standing up generates about 2,500,000 particles/ft^3.
- Walking generates about 10,000,000 particles/ft^3.
- Strenuous activity generates about 30,000,000 particles/ft^3.

Current Requirements

The following is taken from the present **USP <797>** standard.

Positive Pressure Buffer Area/Zone (I. V. CSP)

1) >+0.03” W. C. (Water Column) but not more than +0.08"

2) The room should be an ISO 7 environment

3) **MAS** target = >0.05" W. C.

4) >30 ACH (**MAS** target - 35+ ACPH/ACH)

5) Room pressure should be monitored 24/7 in enclosed ISO rated rooms

6) Positive pressure Buffer Area/Zone should be higher in pressure than the Anteroom/Area by a minimum of 0.02" W. C.

Negative Pressure Buffer Area/Zone (Chemo CSP)

1) >-0.01”” W. C. (Water Column) but not more than -0.08

2) The room should be an ISO 7 environment

3) **MAS** target = -0.04“+ W. C. or greater

4) >12 ACH (**MAS** target - 35+ ACPH/ACH)

5) Room pressure should be monitored 24/7 in enclosed ISO rated rooms

6) Negative pressure Buffer Area/Zone should be lower in pressure than the Anteroom/Area by a minimum of 0.02" W. C. with the Anteroom being +0.01 or greater

Positive Pressure Anteroom(s)

1) +0.01” W. C. (Water Column) but not more than +0.15 (**NOTE:** If the pressure in this room is >+0.015” W. C. it must have a difference of 0.02” W. C. which is acceptable)

2) The room should be an ISO 7 environment.

3) **MAS** target = +0.01” W. C.

4) 12 ACH (**MAS** target - 15 ACPH/ACH)

5) Room pressure should be monitored 24/7 in enclosed ISO rated rooms

6) Note that if an Anteroom/Area is common to both a positive and negative Buffer Area/Zone the ISO rating for the room becomes ISO 7 not ISO 8

Laminar Air Flow Workstations (LAFW), Biological Safety Cabinets (BSC) and Compounding Aseptic Isolator (CAI and CACI)

1) Should be placed in the **Buffer Area/Zone**. If they are countertop units, they need to be placed on a plain stainless steel table (no drawers or storage under the table).

2) Positive pressure Primary Engineering Controls will utilize air from the **Buffer Area/Zone** for the horizontal and/or vertical laminar flow air stream.

3) Negative pressure barrier isolators for high risk CSP may import air from the **Buffer Area/Zone** but this air cannot be recirculated back into the room, it should be vented to the outside.

Buffer Area/Zone and Anteroom/Area Laminar Flow Supply Air

1) Must be provided through a minimum 99.97% HEPA filter. (**MAS** = 99.99%)

2) Must be provided from a ceiling laminar airflow diffuser.

3) In virtually all cases the air should be provided by a fan-driven unit. Most facility HVAC systems do not have the capacity to provide the volume of air needed through a HEPA filter for ACH and to maintain a constant positive pressure.

Buffer Area/Zone Exhaust Air

1) Exhaust air should be vented from the room via exhaust grilles that are located near the floor whenever possible. In some cases this may not be practical and the exhaust will be in other areas of the room.

2) Some or all air may be vented under the door into the Anteroom/Area.

3) Air from a negative pressure room or a negative pressure barrier isolator where high risk CSP is being performed must be vented to the outside (usually via the hood/BSC).

Anteroom/Area Exhaust Air

4) Exhaust air should be vented from the room via exhaust grilles that are located near the floor whenever possible. In some cases this may not be practical and the exhaust will be in other areas of the room.

5) Some or all air may be vented under the door into the non-CSP Area.

Supplies

1) Should not be stored in the **Buffer Area/Zone** if at all possible. As many flat surfaces as possible should be removed from the room.

2) All supplies should be stored in the Anteroom/Area or Anteroom/Area. All prep for drugs and personnel should be accomplished in this room.

3) An Anteroom/Area (separated by a curtain or demarcation line) is only acceptable if there is a low volume of low and medium risk CSP performed on an average day.

Horizontal Flat Surfaces

1) All furniture and equipment not essential to the CSP operation should not be in the **Buffer Area/Zone**. It should be removed to outside the area.

2) If there are horizontal flat surfaces that cannot be removed from the area then a procedure should be in place to clean these flat surfaces with biocidal type cleaning agent before each working day to prevent contamination of CSP elements.

3) All surfaces should be able to withstand cleaning with biocidal type cleaning agents. It is advisable that the compounding personnel do the actual cleaning of the CSP are to ensure sterile conditions.

Ceilings

1) Should be a “clean room” type ceiling that is non-porous and gasketed with either “hold down” clips or other retaining devices for the ceiling tiles. In some instances a sealed drywall ceiling can be used provided there are access hatches installed in the ceiling to access overhead laminar flow equipment. Care should be taken to not have a ceiling in place that, under positive pressure, would lift ceiling tiles and allow contaminated air into the CSP area via the Venturi effect.

2) A ceiling specifically designed for positive pressure room applications is recommended for this type room. Simply using glue as a sealant in a standard drop ceiling is not sufficient.

3) All ceiling equipment and fixtures (lighting, sprinkler heads, etc.) should be flush with the ceiling itself and withstand cleaning with a biocidal type cleaning agent.

4) The ceiling, if installed as part of a renovation, must be sealed so that no air movement can occur between the working are and the interstice space above the room.

Walls and Doors

1) Existing walls should have a non-porous surface or coating that can withstand cleaning with biocidal type cleaning agents. (An epoxy coating is ideal but other wall coverings can be used.)

2) Walls that have to be created with wallboard (drywall) or prefabricated walls that can be erected in situ must also meet this requirement.

3) All doors must be sealed on the top and sides with ~ ½" gap on the bottom side of the door. Other doors must be sealed on the bottom also.

Floors

1) Floors should be one contiguous covering with no cracks, crevices or seams where pathogen growth could occur including baseboards.

2) If a tiled floor is existing then it should be removed and a contiguous floor installed or a heat sealed polymeric covering be installed over top of the existing tiled floor.

3) All floor surfaces or coatings must be able to withstand cleaning with biocidal type cleaning agents.

4) All baseboards should be sealed and must be able to withstand cleaning with biocidal type cleaning agents.

Airflow Dynamics (Air Mixing and Unidirectional airflow)

1) The placement of the air purification systems (APS) is critical in ensuring that the air that the LAFW's and/or barrier isolators intake is pure, uncontaminated air, which, after passing through the workstation's filter(s), makes it ultra-pure.

2) Perfect air mixing is only possible when there are no mobile elements in a room (room at rest). A room designed for perfect air mixing will only be so until a person enters the room and disrupts the airflow pattern. **MAS** has added upper room ultraviolet germicidal irradiation (UVGI) devices to ensure that the least risk of pathogen contamination can occur during the compounding operation. This is not mentioned in **USP <797>**, but, it is an **MAS** value added option.

In Conclusion

MAS will include, when appropriate, upper room UVGI as a second line of defense, to de-activate or destroy airborne pathogens in the upper area of the CSP Area.

We will provide the finest state-of-art equipment specification data, design criteria (free at this time) with line drawings and written explanation, and an equipment, budget conscious, quotation for your pharmacy.

If you have any questions you can go to our web site and fill out the feedback form or send an e-mail to us. For more immediate help call our corporate office at 800-645-1059.

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