



CETA Applications Guide for the use of Compounding Aseptic Isolators in Compounding Sterile Preparations in Healthcare facilities CAG-001-2005 Revised December 8, 2008

The introduction of USP Chapter 797¹ in January 2004 (revised in June 2008) along with increased pressure from some State Boards of Pharmacy has led to more robust implementation of environmental controls by facilities involved in the compounding of sterile preparations. In some cases, isolators intended for compounding sterile preparations are used either as an alternative or as an adjunct to traditional methods. Isolator use for sterile compounding is relatively new to the United States. Few isolator standards exist and none of those that are in place have been developed with pharmacy compounding in mind. This guide is intended to provide an overview of isolators and assist individuals considering their use in purchasing, installation and commissioning issues.

Scope

This guide will focus on isolator applications appropriate for use in facilities that compound sterile preparations. We will define compounding isolators, describe isolator types and applications as well as describe minimum performance expectations. The definitive standard for compounding sterile preparations in the United States is USP Chapter 797. This document provides application guidance specifically for compounding sterile preparations as dictated by USP. We address both positive pressure isolators used for sterile compounding and negative pressure containment isolators used for sterile compounding of hazardous drugs.

Overview

Isolators have become an effective option in the effort to develop compliance strategies for compounding facilities. Traditional equipment that is used to provide the critical sterile manufacturing zone (ISO Class 5²) protects the product with a unidirectional flow of particle free (HEPA filtered) air. Compounding Isolators go one-step farther. The use of gloves and view-screens provides a physical barrier between the operator and the product. A well-designed positive pressure isolator, supported by adequate procedures for its use, maintenance, monitoring, and control, may offer tangible advantages over classical aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should not adopt a false sense of security with these systems. There are no uniform industry standards for the manufacture of Compounding isolators and as you will see, there are significant differences in design applications. Furthermore, positive pressure isolators are not appropriate for compounding hazardous drugs and negative pressure isolators designed to contain hazards present some real challenges to sterile compounding (as we describe later in this Guide). Pharmacists should also be aware of the need to establish new procedures addressing issues unique to isolators. We have seen different types of isolators applied to the pharmacy application.

Some are more effective than others. It is critical that you match the proper isolator to the application.

Definition

Compounding Isolator: A class of isolator designed for use during pharmacy sterile drug compounding. Compounding isolators utilize an airtight glove/glove port design that allows the user to perform hands-on tasks inside the isolator without compromising the intended performance of the isolator.

There are two types of compounding isolators, each named according to their design objective: *Compounding Aseptic Isolator*, and *Compounding Aseptic Containment Isolator*. Among other features, the compounding isolator achieves its design objective through the following:

- The full enclosure of the drug compounding process.
- The intentional use of air pressure relationships that define the direction of airflow in/out of the cabinet.
- The use of airflow capture velocities to capture and remove aerosolized drug product near its point of generation.
- The use of high-efficiency filtration system (HEPA minimum) to capture aerosolized drug preparations and particulate contamination.
- The use of external venting to remove vaporized hazardous drugs from work chamber and from the pharmacy.
- The use of material transfer processes that allow material transfer in/out of the compounding isolator without compromising worker exposure to undesirable levels of airborne drug or unwittingly compromising the sterility of the compounding environment.

Compounding Aseptic Isolator: 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 it has first passed through a microbially retentive filter (HEPA minimum).

Compounding Aseptic Containment Isolator:

A compounding aseptic isolator 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 it is first passed through a microbially 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.

Design Characteristics:

1. Prerequisite Features:

- A. A Compounding Isolator is supplied with air through a microbially retentive filtration system (IEST Type C or J HEPA minimum)³.
- B. Compounding Aseptic Isolators may discharge unfiltered air from the isolator venting directly into the room. Compounding Aseptic Containment Isolators may discharge air from the isolator through an exhaust HEPA filter into the room only in the absence of volatile hazardous drugs. Where volatile hazardous drugs are compounded, the isolator design must be a total exhaust (non-recirculating) design where discharge must be passed through an exhaust HEPA filter and properly vented from the building⁴.
- C. Compounding Aseptic Containment isolators must maintain containment of the specific hazard through all aspects of normal operation and material transfer. Containment tests are recommended in the CETA Compounding Isolator Testing Guide⁵.
- D. The cleanliness classification of the Compounding Isolator work zone must meet ISO class 5 at 0.5µm and larger particles under dynamic operating conditions.
- E. The Compounding Isolator must be designed to allow for safe and effective disinfection.
- F. The preparation is never directly exposed to the compounding personnel or the outside environment. Access to the preparation is through gloves.
- G. Ingress and egress of product is through either aseptic connection (Closed system) or specially engineered doors or openings (Open system). Isolators used in sterile compounding are typically open isolators where material is transferred via pass-throughs.

2. Closed system vs. open system:

Closed isolator systems exclude external contaminants from the isolator's critical zone by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations and use only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTPs) for material transfer.

Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g., using continuous overpressure) to exclude the entry of external contamination into the isolator. Typically, pressurized pass-throughs are used to isolate the interior of the isolator from the surrounding atmosphere when material is transported in and out of the isolator.

3. Air Recirculation:

Compounding Isolators vary by design of air recirculation. End user understanding of these design aspects is important as these relate to placement, economy of operation, and the appropriate safety of air removed from the isolator.

Non-recirculating: Compounding Isolators that use a single pass of filtered air that is completely exhausted from the chamber. Compounding Aseptic Isolators may exhaust air to the surrounding space either through HEPA filters or without filtration. Non-recirculating Compounding Aseptic Containment Isolators must exhaust air through a HEPA filter, and where volatile hazardous drugs are prepared, this exhaust air must be properly vented from the building. CETA recommends that only non-recirculating compounding isolators utilizing total exhaust through HEPA filters and connected to a properly designed building exhaust system be used for preparing hazardous drugs that volatilize.

Partial recirculating: Compounding Isolators that are designed to reuse exhaust air by routing a portion of exhaust air back to the supply HEPA filter, expelling the remaining exhaust air from the isolator in a manner consistent with the level and type of hazard. CETA recommends that partial recirculating compounding isolators not be used with hazardous drugs that volatilize.

Full recirculating: Compounding Isolators that are designed to reuse all the exhaust air by routing the exhaust air back to the supply HEPA filter. CETA recommends that full recirculating compounding isolators not be used with hazardous drugs that volatilize.

4. Airflow:

It is critical that the end-user of the Compounding Isolator considers the process and makes an educated decision about the airflow type that best fits their needs. The two fundamental differences in isolator design are in supply airflow utilization and pattern.

Air will be delivered to the process chamber through one of two methods; *Flow Control* (produced by unidirectional airflow) or *Dilution Control* (achieved through turbulent airflow). Aseptic processing is traditionally carried out in unidirectional or laminar flow areas. Non-aseptic processes are more often associated with a turbulent flow environment, such as with the surrounding support areas. **It should be noted that USP Chapter 797 requires unidirectional airflow for all primary engineering controls used in sterile compounding operations.**

Unidirectional Airflow: 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 area⁵.

- A. A flow-controlled Compounding Isolator will provide protection by sweeping HEPA filtered air over the preparation and carrying particulates away from the critical zone to an air return. The FDA guideline for Sterile Drug Products Produced by Aseptic Processing and USP Chapter 797 states “Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations”⁶. Realizing that the ultimate objective of the USP Chapter 797 document is to provide guidance sterile operations, we use this to provide direction to the following recommendations.

The unidirectional airflow velocity should be sufficient to sweep particles away from the compounding area within the isolator work-zone. Traditionally, airflow velocity of unidirectional flow clean-air devices is recommended to be 90 fpm (.45m/s) per IEST-RP- CC002.2⁷. However, application of unidirectional airflow velocity may be higher or lower to achieve specific desired results. It has been demonstrated and validated within the NSF/ANSI 49:2004⁵ standard for Class II Biosafety Cabinetry that lower velocities can provide sufficient sweeping action for aseptic processing.

The unidirectional airflow velocity, at whatever value is used, should be proven by the manufacturer to repeatedly achieve the required particle sweeping action. The demonstration will normally include an airflow velocity profile along with a visual smoke pattern test. The manufacturer-determined unidirectional airflow parameters will be established based on its ability to assure that particle generation from work practices, work product and packaging will not cross-contaminate associated product during and/or after subsequent work practices within the isolator work zone. This process of verification should be repeatable during a field test at the user site under dynamic operating conditions.

The unit shall be designed to achieve a smooth, even flow absent of turbulence and upward reflux. A documented demonstration of flow from the point of filtration across the product exposure area to the returns (front, side, and rear air grilles) should give the user confidence that the unidirectional isolator is well designed for compounding sterile drugs. This is typically demonstrated using an airflow smoke pattern test.

Turbulent Airflow: The process of introducing a supply of filtered air that mixes with and dilutes airborne contaminants, thus reducing the concentration within the environment. Most contaminants are ultimately removed from the environment through the air exhaust system. Contamination removal takes longer to achieve than in a unidirectional isolator because the air turbulence keeps particles suspended and the dilution process is dependent on the volume of air cycling through the space. More chamber volume requires more time or a higher air exchange rate.

- A. A dilution-controlled Compounding Isolator provides a state of control by replacing unconditioned air with HEPA filtered air. An estimate of the effectiveness of the level of control can be determined by calculating the number of times the air within the space is replaced with HEPA filtered air. This is referred to as Air Changes per Hour (ACPH) and in an isolator used for critical operations, greater than 300 ACPH is typical.⁹

The FDA guideline⁶ on aseptic processing states that turbulent flow is normally acceptable within closed isolators. While this is a defensible position, it is important to understand that most pharmacy compounding is performed in *open* isolators meaning materials are generally brought in and out of the isolator through an interchange chamber having sealed doors from the main chamber.

Room air may be allowed to enter the interchange chamber and subsequently pass into the main chamber during the material transfer process. Closed isolators use aseptic Rapid Transfer Ports (RTPs) or direct connection for material transfer to prevent room air from entering the main chamber.

Another factor that would affect the ability of a dilution-controlled isolator to perform in a compounding facility is Recovery Time. Recovery time is how long it takes to return to original base-line particulate levels after an elevation to the particle counts. The number of air changes per hour will have a direct affect on recovery time. Increased air exchange rates should decrease recovery times.

The following variables affect the impact of recovery time:

1. How many different preparations will be compounded in the same isolator and the frequency of these operations? If you plan to compound more than one preparation and are concerned about cross contamination, recovery time is an extremely important factor. The amount of time needed to recover after manipulation of one preparation before introduction of another must be determined. Tests can be conducted to determine this, but the test procedure must be carefully documented.
2. How effective is the pass-through at isolating the inside of the main work chamber from the room? In the event particulate is allowed to enter the main work chamber in the process of product introduction, the recovery time needs to be considered before compounding can begin. Well designed pass-throughs will minimize transferred contamination; Static pass-through systems do not adequately protect the isolator environment during material transfer. Recovery time of the pass-through and the compounding chamber should be considered when determining how long the isolator should be allowed to purge after material transfer before compounding.
3. How clean is the material that is being brought into the Compounding Isolator? Outer packaging for all disposables can create particulate contamination as packages are opened or manipulated. In a dilution-controlled environment, these particles may travel across clean areas, contaminating items thought to be sterile. In a flow-controlled environment, this contamination will be swept away with minimal cross contamination.

5. Pressurization:

Compounding Isolators that bring product in through pass-throughs have a potential for compromise in achieving complete physical separation from the external environment. Compounding Aseptic Isolators use positive air pressure relative to the surrounding space to reduce the ingress of external airborne particles during both product transfer and compounding operations. A positive air pressure differential adequate to achieve this full separation should be employed. Pressure differential will typically maintain a minimum of 0.1" water gauge. The appropriate minimum pressure differential will depend on the system's design. The isolator manufacturer should validate the appropriate positive pressure differential for each unit. As a point of reference, the FDA guideline for

aseptic processing suggests a pressure range between 0.07 and 0.2" w.g.⁶. Additionally the manufacturer should validate that the pressure will not change state from positive to negative or vice versa during glove manipulation or normal operations.

Compounding Aseptic Containment Isolators are either recirculating or total exhaust and use negative air pressure relative to the surrounding space and exhaust airflow to contain the escape of hazards during the compounding process and during a breach of containment (e.g. glove failure) to protect the operator.

6. Venting:

HEPA filters are designed to contain particles and aerosols but not vapors or fumes from volatile substances. Compounding Aseptic Containment Isolators used to prepare hazardous preparations that volatilize must be properly vented through HEPA filtration and then outside the building (not into the surrounding space) in order to protect the worker from harm⁴.

Compounding Isolator exhaust air that is vented to the outside environment should be done so with a building exhaust blower using direct-drive motors, when possible. Belt-driven devices are more susceptible to failure and loss of exhaust volume due to belt slipping, stretching, or breaking.

The exhaust blower should be on the roof (per NSF/ANSI Standard 49 - 2004)⁸ or in a top-floor unoccupied equipment room if it is the final component of the exhaust system prior to discharge from the building to maintain containment (negative air pressure) in the exhaust ductwork. Equipment rooms should have adequate ventilation.

Exhaust air must be 100% exhausted to the outside atmosphere. The exhaust system shall not re-circulate air back into the building. Exhaust stacks should extend at least ten feet above the adjacent roofline to protect maintenance workers from direct exposure to the effluent from the top of the stack. Care must still be taken as this may not be sufficient to guarantee or prevent re-entrainment of isolator exhaust air back into the building or nearby buildings¹⁰ through open doorways, windows, or air intake systems.

An exhaust airflow alarm to alert the operator of an exhaust system failure should be either part of the isolator or the exhaust system. If it exists, its performance must be verified and documented.

Name of Isolator	Type of Isolator	Purpose	Building Exhaust Requirements	Placement
Compounding Aseptic Isolator	Positive Pressure and positive pressure recirculating	Compounding of sterile preparations	None	If located in an uncontrolled room, it should be proven that the isolator prevents transfer of unfiltered room air into the isolator during material transfer or compounding operations
Compounding Aseptic Containment Isolator - Recirculating	Negative Pressure Recirculating	Compounding hazardous drugs that do not volatilize.	Optional	Must be located in an area devoted to hazardous drug handling. If located in an uncontrolled room, it should be proven that the isolator prevents transfer of unfiltered room air into the isolator during material transfer or compounding operations. The room should be a minimum of 0.01" w.c. negative and have a minimum of 12 ACPH.
Compounding Aseptic Containment Isolator – non-recirculating	Negative Pressure Total Exhaust	Compounding hazardous drugs including those that volatilize.	Must be properly connected and vented from building	Must be located in an area devoted to hazardous drug handling. If located in an uncontrolled room, it should be proven that the isolator prevents transfer of unfiltered room air into the isolator during material transfer or compounding operations. The room should be a minimum of 0.01" w.c. negative and have a minimum of 12 ACPH.

7. Decontamination/ Disinfection:

The isolator design should facilitate physical disinfection of all work surfaces. Interior seams should be shaped and sized to facilitate easy cleaning. All interior surfaces should be easily reached through the gloves to accommodate cleaning. If the interior is designed in a manner that does not permit easy physical disinfection of all surfaces, an alternative gaseous decontamination process must be developed and validated.

8. Gloves/Sleeves:

Manipulations within a isolator are conducted through a glove/sleeve (gauntlet) assembly. Two types of glove/sleeve assemblies are available:

- A. *One-Part*: The one-part assembly is where the glove and sleeve are of a single, unbroken unit.
- B. *Two-Part*: The two-part assembly is where the glove and sleeve are separate and are connected at the sleeve (gauntlet) by some type of seal system. The two-part system allows for the relatively simple change-out of gloves.

The type of work conducted in the isolator and the disinfectants that will be used should be taken into consideration in determining the glove material. Commonly used materials include Neoprene®, Nitrile®, Hypalon® and latex. The gloves must have sufficient chemical resistance to stand up to decontaminating chemicals, cleaning agents, and process materials. Special gloves developed for use with Chemotherapy agents may be appropriate for certain applications.

It is common practice to use a double glove system to minimize the possibility of a tear or leak to compromise the environment within the isolator. An ordinary latex glove can be worn underneath the isolator glove and changed as needed. Glove life will be affected by the cleaning agents, solvents, and process materials. A faulty glove will represent a potential route of exposure to the product. Gloves should be inspected daily for pinholes as well as breaches at seams, gaskets and seals. A regular replacement program should be established so gloves are replaced before a breach of integrity occurs.

9. Pass-through considerations:

The transfer of materials into and out of the isolator is one of the greatest potential sources of contamination. There are three basic types of pass-throughs that are employed in the design of an open Compounding Isolator system - Static Air, Dilution Airflow, and Unidirectional Airflow. In all cases, the pass-through must be designed to effectively isolate the interior of the isolator from the room when materials are transported in and out, and where containment is required, isolate the operator and room from the hazardous drugs.

Static Pass-through: In its most basic form, a static pass-through is a box with doors on 2 sides that is sealed to the isolator. Materials are placed into the pass-through from the outside door. After the materials are placed inside, the outside door is closed. The inside door can then be opened and materials passed through to the isolator. The process is reversed for material removal from the isolator.

Static pass-throughs generally are not considered appropriate for sterile compounding applications.

Dilution and Unidirectional Airflow Pass-through: Improvements over the static air pass-through are dilution control and unidirectional pass-throughs because the particulate level in the pass-through can be reduced before opening the door to the main body of the isolator. Airborne particulate levels can be reduced with a dilution-controlled pass-through or virtually eliminated with a unidirectional pass-through.

To prevent direct exposure between the Compounding Isolator main chamber and the room, both pass-through doors should not be open at the same time. The installation of

door interlocks may be used to prevent simultaneous opening, and timers may be used to aid operators. The interior pressure of the Compounding Aseptic Isolator should be sufficient to prevent air movement from the pass-through to the main work chamber and in the case of Compounding Aseptic Containment Isolators; both prevent air movement from the pass-through to the main work chamber and contain the hazardous preparation for operator protection. Manufacturer validation of the appropriate time required and procedures before opening either the exterior or the interior door should be provided.

Regardless of the isolator type, opening and closing the pass-through to the room may allow some room air into the pass through. Additionally, there will be some surface contamination on the material that is brought into the unit via the pass through. A dilution-controlled isolator dilutes out the airborne contamination over time. A unidirectional isolator will flush out the contamination almost immediately with a continuous bath of HEPA filtered air. Any airborne contamination that is brought in through the pass-through with the product is swept away, carried to the return, and removed from the work zone. Note that for both unidirectional and turbulent flow isolators, provisions should be made to address the issue of surface contamination on inbound materials.

Care should be taken to avoid the ingress of any airborne particles from the external environment by induction at product ingress locations such as the pass-through door. This induction can occur from local turbulent flow causing air swirls or backflows into the isolator from the room in both positive and negative pressure isolators. Additionally, negative pressure isolators are more susceptible to drawing room air in to the work chamber, so the operation of the pass-through must incorporate this condition into the overall design of the isolator.

10. Materials of Construction:

Suitable materials should be selected for construction. Considerations include cleanability, durability and functionality. Stainless steel and glass interior surfaces are common materials. High performance plastics have been used for the viewing panels. The use of plastics in the design of the glove panel allows flexibility of design that would be made difficult with glass. The plastics employed should be scratch resistant and compatible with common cleaning materials and work products used within the isolator.

11. Ergonomic Considerations:

Working in an isolator can often involve long periods of time with arms in a relatively still position. Comfortable working conditions are obviously very important. Consideration to worker comfort is recommended as part of any isolator purchase. Most manufacturers have height adjusters available as part of their units. Some form of height adjustment is strongly recommended to provide easy transition from short to tall operators or from sitting to standing working positions. Also, the design should have front view screen and glove ports sized and positioned to allow comfortable and efficient work. It should be noted that height adjusters may not work with units connected to an external exhaust system. Flexible duct connections may help but may limit the length of travel.

Conclusions:

Type of Design

Compounding Isolators are designed to be surface disinfected, not decontaminated in a manner that would penetrate all hidden areas of the isolator. Therefore, contamination may remain and could become airborne during the operation of the compounding isolator. The capability of the compounding isolator to supply and maintain filtered air at the work zone level becomes critical to successful aseptic practices. Because turbulent airflow compounding isolators do not use a continuous fully diffused top to bottom piston of clean air, it is possible that contamination may be harbored in stagnate air zones within the critical work zone space and therefore are not recommended.

Additionally, the frequency of chamber air changes determines the recovery time to acceptable levels in the event particles are drawn into the chamber during a transfer, or through normal operation. Compounding isolators with unidirectional airflow designs remove particles from the work zone more rapidly than do turbulent flow designs and because of lower air change rates, turbulent flow compounding isolators recover more slowly from particle excursion than do unidirectional flow equipment. Unidirectional airflow will more quickly remove particles carried in on preparations during a transfer and reduce opportunity for particle transfer to the critical work zone.

Airborne Particle Level Testing

USP Chapter 797 requires the compounding isolator critical work zone meet ISO Class 5 particle levels and be regularly tested to this requirement. CETA recommends that the classification of all cleanliness levels should be done under dynamic operating conditions to ensure that acceptable particle levels are met during routine operation not just during an "At Rest" state. CETA also recommends that the particles to be counted should be 0.5µm and larger both in the compounding isolator work zone and surrounding cleanroom space. This particle level is consistent with ISO 14644-1 (1999) methodology.

Placement and Clean Zone Classification

USP Chapter 797 requires a minimum cleanliness classification of ISO class 5 (FS209E class 100) for the compounding zone within the isolator. ISO class 5 should be stated as follows; ISO class 5 at 0.5 µm particles under dynamic operating conditions.

Compounding Isolators should be placed in an ISO class 7 cleanroom unless they can meet all of the following conditions:

- a. The isolator shall provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
- b. Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO class 5 levels during compounding operations.
- c. Not more than 3,520 particles per cubic meter shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.⁴

Isolator Testing and Commissioning

Isolator testing to CETA CAG-002-2006 is recommended in USP Chapter 797. The isolator manufacturer should provide specific procedures for testing and use of their product along with acceptance criteria. When choosing a compounding isolator, it is strongly recommended that you verify that the manufacturer has considered field certification and has accommodated that eventuality.

¹ USP28-NF23: United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852

² ISO 14644-1:1999 Cleanrooms and associated controlled environments-Classification of air cleanliness, International Organization for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland

³ IEST-RP-CC001.4: HEPA and ULPA Filters, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008, USA, www.iest.org

⁴ NIOSH Alert for Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings, Department of Health and Human Services, CDC, NIOSH, NIOSH – Publications dissemination, 4676 Columbia Parkway, Cincinnati, OH 45226-1998, www.cdc.gov/niosh

⁵ CAG-002-2006 (*revised 12/08/2008*): CETA Compounding Isolator Testing Guide, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607, www.cetainternational.org.

⁶ USFDA: Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice, September 2004, Centers for Drug Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, MD 20852-1448, www.fda.gov/cber/guidelines.htm

⁷ IEST-RP-CC002.2: Unidirectional Flow Clean-Air Devices, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Rolling Meadows, IL 60008-3841

⁸ NSF/ANSI 49-2004: Class II (laminar flow) Biosafety cabinetry, NSF International, P.O. Box 130140, Ann Arbor, MI 48113-0140

⁹ Design of Barrier Isolators for Aseptic Processing: A GMP Perspective” Pharmaceutical Engineering Volume 18 No. 2 March April 1998

¹⁰ ANSI/AIHA Z9.5-2003: American Industrial Hygiene Association, 2700 Prosperity Ave., Suite 250, Fairfax, VA 22031, www.aiha.org

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