USP 797 Compliance in the Laminar Flow Workstation

Cabinet Design Attributes and Best Practices

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Introduction

Regulatory compliance procedures abound for the pharmaceutical industry, but perhaps one of the best-known in the compounding side of the industry is USP 797, Sterile Pharmaceutical Compounding Procedures. USP 797 compliance focuses on practices that prevent harm or death to patients due to microbial contamination, excessive bacterial endotoxins, variability in the intended strength of correct ingredients, unintended chemical and physical contaminants, or ingredients of inappropriate quality.

Sterile Pharmaceutical Compounding Procedures

USP 797 Sterile Pharmaceutical Compounding Procedures[1] essentially focus on maintaining air quality through the separation of contaminants from compounding materials. In relation to air quality, this typically involves maintaining a Class 5 or better (according to ISO air standards; see Table 1 below) environment in all critical areas of compounding processes.

Table 1. ISO Classification of Particulate Matter in Room Air
*(Limits are in particles of 0.5µm 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).*

Compounding personnel maintain Class 5 sanitation levels through the use of primary engineering controls (PECs), which include laminar flow cabinets (LFCs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs). These PECs are coupled with HEPA filtration to ensure a high level of purification. According to USP 797, one of the most important components of any compounding sanitation system is the ability to provide "first air"—the air exiting the HEPA filter in a unidirectional air stream that is essentially particle-free.

Definitions of Terms

In order to fully understand USP 797, some critical terms first need identified and defined:

1. **Compounded Sterile Preparations (CSPs)**: Any compounded material containing sterile or nonsterile ingredients or components that must be sterilized prior to administration to a patient.
2. **Critical Site**: A location that includes any component or fluid pathway surfaces or openings exposed and at risk of direct contact with air, moisture, or touch contamination.
3. **Direct Compounding Area**: 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.
4. **Primary Engineering Control**: 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 work-benches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs).
5. **Unidirectional Flow**: Airflow in a single direction, drawn across filter media.
6. **First Air**: Air exiting the filter media in a unidirectional flow that is essentially particle-free.
7. **Turbulence**: flow characterized by erratic or violent movement.
8. **Stagnant Air**: having no current or flow and containing particulates as a consequence.

1 "[797] Pharmaceutical Compounding—Sterile Preparations." Revision Bulletin. *The United States Pharmacopeial Convention.* 2008. Print.

Testing Conditions

Manufacturers and third-party testing facilities incorporate a variety of initial tests to ensure HEPA filtration in products designed for pharmaceutical applications conform to industry standards and certifications. These tests include aerosol challenge testing, particle count testing, airflow uniformity testing and airflow pattern visualization testing.

Aerosol Challenge Testing

Aerosol challenge testing has been used since the mid-1950's as a means to measure the effectiveness of HEPA filtration and appears in many different standards throughout the world. Individual test conditions can vary, but the general method involves challenging a HEPA filter with a reference aerosol, testing for initial leaks around the filter frame and gasket, and then measuring the filter media downstream of the filter by using an aerosol photometer. Commonly referred to as DOP testing, the aerosol photometry test method is good for measurements to 0.003% and meets most requirements within the pharmaceutical industry, yet new technology and instrumentation allows testing of 0.0003% to be possible.

The aerosol photometer uses a near forward scattered light chamber and a photomultiplier tube as its detection method. The forward scattered light is directly proportional to the aerosol mass concentration, which makes the instrument a continuous real-time detector and allows an alarm point to be set for easy detection of leaks.

The standard requires that the challenge aerosol is used as the 100% reference for the downstream measurement and must be homogeneously mixed resulting in an even challenge to the filter. The measurement downstream of the filter is measured as percentage penetration with maximum permissible leaks of 0.01%.

Particle Count Testing

Particle count testing is another method of aerosol challenge testing that involves a known recorded concentration of aerosol, an aerosol diluter and a discrete particle counter. This method is newer than DOP testing and uses a discrete particle count (DPC) test method, which is good for measurements to 0.000005% and better. This exceeds the requirements for the pharmaceutical industry and is really good only for cleanrooms ISO Class 4 and lower because the particle counter is a batch measuring device and not designed to make continuous measurements.

The particle counter uses a discrete detector measuring the peak light scattered height of the individual particle passing through the detection chamber, and cannot count two particles in the chamber at a time (known as coincidence counting). A diluter has to be used to measure the upstream aerosol challenge because of the reliance of this method on a low challenge.

Airflow Uniformity

The objective of airflow uniformity testing is to meet the criteria set for airflow velocity and uniformity set in the design specifications of the unit, which should not be exceeded by more than 15% on average. Test methods are relatively straightforward, and involve dividing the environment into a grid, with velocities measured at the center of each square in the grid by a thermal anemometer, vane-type anemometer, or equivalent. Measurement probes should be located at a distance of 15 cm or six inches from the filter face or before the air encounters an obstacle. Readings at work height are taken for informational purposes only and turbulence induced by non-aerodynamically designed objects upstream may impede the proper and accurate measurement.

Airflow Pattern Visualization (Smoke Testing)

Airflow pattern visualization studies (also known as smoke tests) are conducted to confirm unidirectional airflow exiting HEPA and ULPA filters, providing visual evidence of airflow direction rather than quantitative results. Smoke tests are a useful demonstration and diagnostic of unit performance. The basic requirements of a smoke test are:

1. Airflow moves toward potential sources of contamination and away from the product path
2. Air is flowing in a single direction with no turbulence or eddies
3. Air should regain unidirectional flow quickly from movement within the air stream such as attendants manipulating equipment

There are minimal equipment and support requirements for performing a smoke study, which include the fogger, a video camera, and trained personnel to perform the testing. Adhering to good laboratory processes, personnel will set the fogger up to release smoke or fog into the unit while the video camera records the results. Various laboratory procedures will be performed while the unit is fogged to test the ability of airflow to recover from disturbance and the results documented both via video camera and anecdotal note taking. By observing the patterns of the fog or smoke as it follows the airflow, inferences can be made about the airflow patterns and unidirectional flow provided by the unit during normal operating procedures.

IEST Testing

The Institute of Environmental Sciences and Technology develops recommended practices and testing procedures for the scientific and pharmaceutical communities to meet USP 797 standards[2]. First air quality standards are certified based on media-fill testing as outlined by USP 797:

> *This test or an equivalent test is performed at least annually by each person authorized to compound in a low-risk level environment under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of low-risk level CSPs. Once begun, this test is completed without interruption.*

While the media-fill test is utilized to certify air cleanliness and the capabilities of individual techniques to avoid contamination, this is not typically the main test used to certify PECs. The media-fill test is designed to represent the most challenging or stressful conditions encountered by personnel, and when the test simulates high-risk level compounding, the test can verify the capability of the compounding environment to produce a sterile preparation.

Typically, filter challenge testing using aerosol and particle counts are the main tests to perform to certify PECs. The principle of this style of testing involves comparing the number of particles penetrating the filter as it is scanned or challenged to the upstream particle count. The lower the level of downstream particles detected, the greater filter efficiency and increased safety.

Overlap of Standards and Testing

IEST recommendations directly overlap with USP 797 standards and incorporate additional safeguards to ensure testing meets all identified standards. One additional IEST requirement is that when performing velocity testing, airflow velocity test points cannot be placed more than 12 inches apart in order to ensure that such velocity tests take into account any dead spots or areas of stagnant air. Smoke testing is a fast and effective technique that can help identify areas of stagnant or turbulent air in a unit prior to the actual velocity test, allowing personnel to visualize the airflow patterns within the unit and correct any issues caused by products or instruments.

Typical Cabinet Design Features to meet USP 797 and IEST standards

In order to meet USP 797 and IEST standards, most cabinet designs involve unidirectional flow across HEPA filters. Any disruption in the flow pattern of the air through the cabinet can result in stagnant or contaminated air being able to come in contact with critical sites. While there may be a variety of methods to overcome these risks, Air Science laminar flow products incorporate sound design principles to effectively meet USP 797 and IEST testing standards.

2 *IEST Standards and Recommended Practices: Complying with USP 797 Requirements for Cleanrooms and Other Controlled Environments.* The Institute of Environmental Sciences and Technology (IEST), 2015.

Air Science Designs that meet USP 797 and IEST standards

When used according to best practices, the LF Series cabinet encourages compliance with criteria set forth by USP 797 for sterile preparation in pharmaceutical compounding of nonhazardous agents. These include injectables, IV admixtures, pastes and ointments, and irrigating solutions that are protected by a laminar flow of filtered air over the work surface.

The design of the Purair© LF series cabinets incorporate several unique characteristics, such as an ULPA filter pressure gauge to measure filter performance and all-steel construction with exclusive MICROgone™ anti-microbial powder finish. Other design attributes are unique to horizontal or vertical laminar flow orientations, as follows:

Purair Horizontal Laminar Flow (HLF)

- Horizontal flow cabinets are designed with a lip on the rear of the work surface to protect the ULPA filter from spills. This riser does not interfere with unidirectional flow or create turbulence.
- The design of the HLF provides first air across the entire interior width with a high-capacity air handling system that delivers flow velocity of 0.35-0.45 m/s or 70-90 fpm.

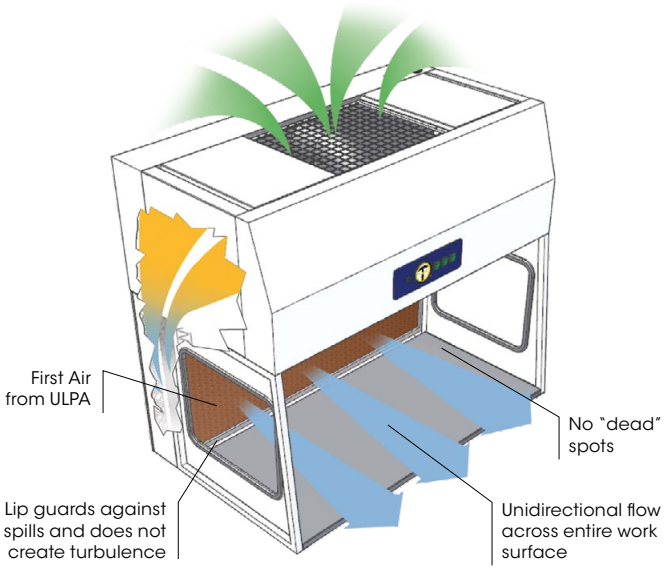
Purair Vertical Laminar Flow (VLF)

- The rear wall is perforated to reduce work surface turbulence by removing some of the airflow to the rear.
- The design of the Purair VLF prevents turbulent or stagnant air through the use of negative pressure around and above the sides of the filter and filter gasket.
- Negative pressure pores around the filter frame prevent contamination to the product and do not interfere with first air or unidirectional flow from the ULPA filter.

Air Science Design Enhancements

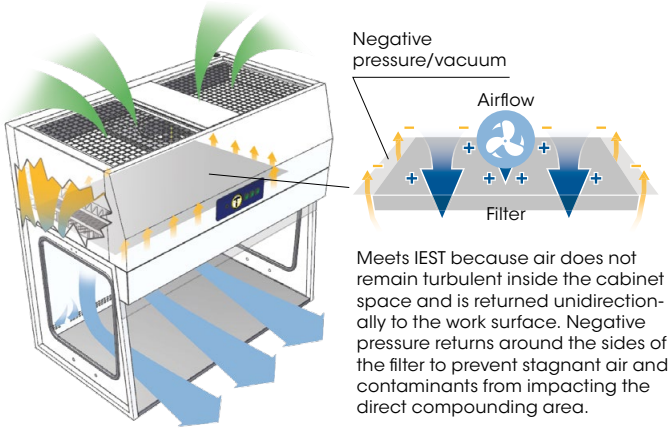
Air Science has incorporated a variety of internal design principles that help their laminar flow products to specifically comply with USP 797 and IEST standards. The ULPA filter supplies particle-free air in a unidirectional stream to the direct compounding area. Additionally, the Critical Area exceeds ISO Class 5 requirements and the air velocity is sufficient to sweep particles away from the compounding area.

Purair HLF Airflow



The Air Science Horizontal Laminar Flow cabinet provides unidirectional airflow directly from the ULPA filter across the entire work surface. Cabinet design ensures no air dead spots to interfere with first air delivery and a rear lip on the work surface guards against contamination from spills.

Purair VLF Airflow



Meets IEST because air does not remain turbulent inside the cabinet space and is returned unidirectionally to the work surface. Negative pressure returns around the sides of the filter to prevent stagnant air and contaminants from impacting the direct compounding area.

In the Air Science Vertical Laminar Flow cabinet, first air contacts the work surface directly as it flows from the ULPA filter. The VLF incorporates a perforated rear panel to combat turbulent or stagnant air in this area of the work zone. Additionally, no stagnant air exists on the ceiling of the unit as perforations in the ceiling panel to the side of the filter gasket help create an area of negative pressure to ensure all air entering the work zone is ULPA-filtered first.

Conclusions

Significant design features have been considered to ensure that airflow and filtration in Air Science cabinets meet the stringent standards required by the pharmaceutical compounding community. Air Science laminar flow products sufficiently meet USP 797 standards when used in accordance with IEST recommended practices.

Suggestions for further testing

Further testing on Air Science products could provide conclusive evidence that would benefit the laboratory products community. Incorporating smoke tests, induction testing, and further media-fill tests on all Purair Laminar Flow models can help to identify potential sources of turbulence or contamination. While Air Science laminar flow products currently meet all stringent compounding standards, testing protocols and standards may change over time. However, Air Science is committed to continuing to meet such necessary standards and guidelines in order to ensure safety, accuracy, and integrity.

About the Author: Andre Chambre

Andy Chambre is the founder and CEO of Air Science, LLC and has been associated with the ductless fume hood industry for more than 25 years. He was formerly the US Vice President for Captair Labx and President of Astec Microflow US. He was named President of Filtco Corporation in 2003 and currently also serves as a Director of Air Science Technologies Ltd. in the UK. Mr. Chambre has written numerous articles on fume hood safety and assisted in the development of safety standards by serving on various committees such as the Canadian Standards Association subcommittee on fume hoods and the SEFA 9 Ductless Enclosures Committee.

Sources

- "[797] Pharmaceutical Compounding—Sterile Preparations." Revision Bulletin. *The United States Pharmacopeial Convention*. 2008. Print.
- *IEST Standards and Recommended Practices: Complying with USP 797 Requirements for Cleanrooms and Other Controlled Environments.* The Institute of Environmental Sciences and Technology (IEST), 2015.

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