CONDUCTING AIRFLOW VISUALIZATION STUDIES: METHODS AND TECHNIQUES

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Abstract:
Airflow Visualization Studies provide a visual representation of the contamination control effect of cleanrooms and clean zones. This information is important for unidirectional, non-unidirectional and mixed flow conditions. These studies can be used to identify adverse airflow and optimize the contamination control effect that is critical to cleanrooms and clean zones of all classes and grades. Airflow Visualization Studies are more than a single set of pass/fail tests that are part of the cleanroom or clean zone qualification, they provide information that can be used to optimize and improve the contamination control effect, assist in risk analysis, identify environmental monitoring locations (for viable and non-viable), and provide operator training. This paper will discuss the various methods and techniques of airflow visualization as well as provide examples such as: Investigative or engineering studies for troubleshooting contamination problems, evaluating the cleanroom design, equipment layout and standing or work positions for personnel prior to implementing the environmental monitoring program; static studies to evaluate the manufacturing environment after optimization (prior to in situ dynamic studies); in situ dynamic studies to evaluate airflow patterns during simulations of manufacturing operations.

INTRODUCTION

For medical product cleanrooms, Airflow Visualization Studies (AKA Smoke Studies) should be considered as more than a definitive pass/fail test. The criticality of these areas demands additional scrutiny that goes beyond the testing outlined in international cleanroom standard ISO 14644-3:2019 Cleanrooms and associated controlled environments Part 3: Test methods. As the ISO 14644 series of standards apply to all industries, additional considerations are required for the control of particulate and microbiological contamination in medical product cleanrooms. Air pattern analysis (airflow visualization with conclusions) is an expectation by regulatory bodies worldwide and an important tool for contamination control.

Suitably conducted, analyzed and utilized, airflow visualization studies allow for:

- Characterization and documentation of airflow patterns in cleanrooms, barrier systems and controlled environments.
- Evaluation of actual airflow direction and air velocity uniformity against design and performance specifications. (ISO 14644-3:2019)
- Identification of any undesirable air patterns that can act as a channel or reservoir for contamination.
- Elimination of undesirable air patterns via optimization of cleanroom and barrier system air patterns or adjustments in operational behavior, prior to conducting environmental monitoring location selection.
- Minimization (when elimination is not possible) of undesirable air patterns via optimization of cleanroom and barrier system air patterns or adjustments in operational behavior, prior to conducting environmental monitoring location selection.
- Identification of adequate locations for testing during cleanroom classification, (in the at rest and operational state) as part of risk assessment with attention on areas where the complete elimination of undesirable air patterns is not possible.
- Identification of adequate locations for monitoring the risk of viable and non-viable particles with attention on areas where the complete elimination of undesirable air patterns is not possible.

AIRFLOW VISUALIZATION APPLICATIONS

In addition to regulatory expectations, airflow visualization is a useful engineering and validation tool that can be used for the following applications:

Cleanroom Qualification (for unidirectional and non-unidirectional flow cleanrooms)

In the qualification of cleanrooms, mapping of Airflow patterns is used for confirming design and performance specifications. Additional benefits include risk assessment purposes, environmental monitoring site selection and operator training.

Equally important is the identification of areas where airflow patterns have a lessor contamination control effect. (e.g., doors, pass-throughs, spaces between HEPA filters and areas with equipment exhaust fans).

- In unidirectional airflow zones, air should create a sweeping action over critical areas across the entire Grade A (ISO Class 5) clean zone. Any adverse air patterns such as excessive turbulence, eddy currents, vortices or refluxing should be identified and addressed in the Risk Assessment and evaluated in the Contamination Control Strategy. When possible, optimization/modification of the cleanroom should occur. If a physical modification is not possible, additional environmental monitoring scrutiny of these areas must be undertaken.

- For non-unidirectional airflow cleanrooms, it should be demonstrated that HEPA filtered air entering the cleanroom effectively mixes with room air and exhausts via suitably placed (low wall air returns). When ceiling mounted air returns or exhausts are present, airflow visualization studies must demonstrate that HEPA filtered air does not "short circuit" into air returns or equipment air inlets and suitable mixing of HEPA filtered air occurs. Important for medical product cleanrooms is the identification of any areas of concern (such as equipment cooling fans, heat sources, pneumatics, product handling robotics or areas with poor mixing or no air movement). These areas once identified, must be addressed in the Risk Assessment and evaluated in the Contamination Control Strategy.

- For non-unidirectional airflow areas that support critical operations, it is important that Airflow patterns from equipment cooling fans, heat sources, pneumatics, product handling robotics do not pose a contamination risk, as a particle source or by washing over operators or components that may enter critical areas or are in close proximity to critical areas.

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Barrier System FAT/SAT Qualification

In the qualification of Barrier Systems (e.g., RABS, Isolators) it is important that unidirectional airflow is specified and demonstrated as part for the FAT/SAT qualification, prior to performing official in situ air pattern analysis. It is important to consider airflow patterns in the planning and specification stage of a project. RABS and Isolators already integrated into a production cleanroom have been unable to provide a suitable environment for aseptic processing due to excessive turbulence and eddy currents caused by design and integration flaws.

- FAT: The demonstration of unidirectional flow and a contamination control effect for all use-case conditions must be performed prior to equipment acceptance. Especially important is the demonstration of open-door conditions for RABS and isolators. The question that must be answered: Is there a suitable outward flow of air to prevent outside air from entering the Grade A zone when the doors are open?

- SAT: The ability of the Barrier system to prevent outside air from entering is critical to establishing a suitable environment for aseptic or sterile operations. Large product contact components such as stopper Bowls and hoppers must be appropriately sterilized and transferred into the filling or processing equipment. As these items are too large to be transferred via product transport ports, it is imperative that during equipment set-up, outside air (Grade B for RABS, Grade C for Isolators) cannot enter the Grade A barrier system's environment.

Pass-through and Air Lock Qualification

Pass-throughs and Air Locks should be designed and used to provide physical separation and to minimize the transfer of microbial and particulate contamination between different areas.

The qualification of pass-throughs and airlocks should utilize airflow visualization as a tool to evaluate these devices ability to act as an air lock. Tracer particles (smoke) should not leak from the pass-through or air lock into the surrounding rooms. Often pass-through gaskets are not integral, damaged or missing. The use of Airflow Visualization Studies provides a useful Pass-Through Leak test that effectively tests the "Air Lock" principle.

Active or Dynamic Pass-Throughs (with Fan Powered HEPA filter modules) can be evaluated for the effectiveness of the air exchange, or how quickly the pass-through flushes itself with clean air. Evaluation of pass-through Airflow patterns should be performed simulating transfer operations with timing and sequence matching normal use-case scenarios.

Optimization of cleanroom and barrier systems integration

Often the overall contamination control effect of sterile or aseptic processing areas is compromised by poor integration of Barrier Systems into cleanrooms. After the Cleanroom and Barrier systems have demonstrated suitable air patterns as part of their individual qualifications, Airflow visualization should be conducted in order to evaluate the Airflow patterns related to the integration of the barrier system within the cleanroom.

- Air patterns inside of barrier systems must not be influenced by external activities such as the opening and closing of cleanroom doors, or the movement of personnel in the surrounding environment.

- Air patterns inside of barrier systems must not be influenced by the connection of mobile HEPA transfer carts, transfer RABS or transfer Isolators.

- The evaluation of Air Patterns and the interface between the cleanroom and barrier system must be evaluated in all possible scenarios, including the opening and closing of doors and during simulations of all inherent and corrective interventions. Important consideration related to the placement HEPA locations, air returns, equipment intake and exhaust impact on air patterns should be evaluated in relationship to contamination risk.

Optimization of operator movements and positions

As operator movements and positions can influence air patterns, characterization of these moments as well as standing positions can be assessed in terms of air pattern analysis. Airflow visualization testing as an engineering tool can help optimize operator movements as well as positions to achieve improved airflow and increased contamination control. These tests may need to be performed multiple times in order to optimize air patterns to provide the best possible overall contamination control effect during simulations of inherent and corrective interventions.

Training Tool

Additionally, videos from air pattern analysis can providing training material as a method of critiquing operator behavior in relationship to airflow patterns, particularly while performing aseptic techniques, inherent and corrective interventions and environmen-

tal monitoring. Care related to operator gowning, movement and attitude during AVS recording is important. It may take several different tests to suitably capture the ideal operator movement for training purposes.

Establishing Risk Based Environmental Monitoring (EM) locations

When establishing environmental monitoring locations and methods, the review of Airflow Visualization studies should assist in the selection of risk based environmental monitoring locations for conducting viable and non-viable particle monitoring. Additionally, this information should be considered when selecting locations for cleanroom classification testing, utilizing the sample selection per ISO 14644-1:2015. From the AVS, air patterns are reviewed and identification of areas where the greatest risk of contamination could occur (from an airflow perspective).

Frequency of Airflow Visualization Testing and Cleanroom Re-Qualification

The frequency of performing airflow visualization studies is dependent upon the type of facility as well as the operations carried out.

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Airflow Visualization studies should be repeated during routine certification/re-qualification of the cleanroom or advanced aseptic processing system and whenever significant changes are made to the operation, such as changes to; personnel flow, equipment operation, material flow, air handling systems or equipment layout. It is important to note that even successfully qualified systems can be compromised by poor operational, maintenance, or personnel practices.

In the Re-qualification of cleanrooms, it is important to compare studies historically to assess any differences from the original airflow visualization study.

Pharmaceutical Manufacturing Airflow Visualization Testing Frequency

The maximum interval for repeating airflow visualization studies for pharmaceutical manufacturing is not defined in regulatory documents however, the first edition of ISO 14644-2: (2000) indicated repeating this test at a maximum interval of 24 months. This was changed in the second edition (ISO 14644-2: 2015) to be based upon risk assessment however many manufacturers are repeating the test between 12 and 24 months.

Pharmaceutical Compounding Airflow Visualization Testing Frequency

The maximum interval for repeating airflow visualization studies for Sterile Pharmaceutical Compounding facilities (per USP 797) is 6 months. The increased frequency is meant to address the high degree of human activity, the fluid nature of compounding as well as the transportable nature of equipment, tables and chairs often utilized in pharmaceutical compounding facilities.

Types of airflow visualization:

Cleanroom Airflow Visualization can be undertaken to characterize airflow patterns with several different objectives.

Investigative Airflow Visualization

Investigative Airflow Visualization studies are used for identifying specific contamination control issues or as part of a cleanroom audit. This type of testing is a useful tool in troubleshooting contamination and cross contamination problems. Investigative smoke studies can detect airflow patterns that could act as a transport mechanism or as a reservoir for contamination. To avoid problems prior to media fills, these studies should be

done prior to conducting formal and documented "Dynamic In situ Air Pattern Analysis" in order to detect and address problems before qualification testing starts.

Engineering Airflow Visualizations

Engineering Airflow Visualization Studies are used as an engineering tool in order to characterize the cleanroom airflows and barrier system integration. Of particular importance is the interface between different clean zones such as between Grade A and Grade B zones in aseptic manufacturing. Additionally Engineering Airflow Visualization is useful as part of a physical risk assessment of the contamination control effectiveness and should be used for establishing environmental monitoring locations within the Contamination Control Strategy. These types of studies should be specified in equipment specifications (URS) and required as part of FAT and SAT testing of any barrier system (Isolators, RABS). Particular attention should be focused on the interface between barrier systems and the external environment. To avoid problems prior to media fills, these studies should be done prior to conducting formal and documented "Dynamic In situ Air Pattern Analysis" to detect and address problems before qualification testing begins.

Static Airflow Visualization Studies

Static Airflow Visualization studies are conducted in the at rest occupational state. These studies are used to characterize the airflow patterns of the entire cleanroom and any associated clean air device, barrier system (RABS, Isolators or HEPA Carts). All doors, pass-throughs, conveyer belts and equipment that can impact air patterns must be evaluated. The spatial relationship of HEPA filter diffusers and air returns must be evaluated in terms of overall contamination control effect of the area being tested. These studies are a pre-requisite of "Dynamic In situ Air Pattern Analysis". Poor airflow under static conditions is a cleanroom design or integration issue and should be addressed prior to attempting Dynamic Airflow Visualization studies simulating operations.

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"Dynamic In situ Air Pattern Analysis" (AKA Dynamic Smoke Studies)

Dynamic In situ Air Pattern Analysis is used to characterize airflow patterns during simulations of operations. Because these studies are focused on the movements of people and equipment, the overall contamination control effect of the cleanroom cannot be evaluated only with dynamic airflow visualization studies. Prior to conducting a "Dynamic In situ Air Pattern Analysis", a static airflow study must be performed that evaluates the entire area. The FDA's expectations are "Dynamic In situ Air-Pattern Analysis" is used to demonstrate unidirectional airflow and a sweeping action over and away from the product under dynamic conditions". Multiple cameras may be used to best reflect and document the airflow. This type of study is often used as evidence of suitable air patterns as recommended by regulatory authorities.

What is "Dynamic In situ Air Pattern Analysis"? As the word in situ implies "in the original, natural position; undisturbed" This is an important consideration when performing airflow visualization studies. Having an additional test person holding a smoke tube over the operator performing an intervention does not represent the natural airflow situation. Manifolds and fixtures should be utilized as much as possible to better provide a more realistic simulation of activities performed during "Dynamic In situ Air Pattern Analysis".

Simulations of Activities During Airflow Visualization:

The most commonly accepted cleanroom norm is the even appropriately attired human beings are the greatest source of microbial and particulate contamination in the cleanroom. This is why the simulation of activities during dynamic airflow visualization is required in order to demonstrate that air patterns do not act as a channel or reservoir for conta-

mination (adverse airflow).

Regulatory expectations include airflow visualization during simulations of: the transfer of materials into the critical area, equipment set-up, assembly, environmental monitoring in addition to all the inherent Interventions (part of the process) and corrective Interventions (problem resolution) that could occur during operations.

Prior to conducting dynamic AVS a list of interventions and activities should be created and attached to the associated protocol and report. Examples of activities are shown in Table 1 below.

Inherent Interventions	Corrective Interventions
Line set-up and Assembly	Stopper jams
Replenishment of components	Fallen vials
Weight / volume checks & adjustments	Broken vials
Environmental monitoring	Defective seals on containers
Removing waste	Liquid leaks and spills
Non-assisted automated operation of equipment (smoke studies while filling and closing operations)	Other mechanical failures requiring manual correction

Table 1 – Examples of Interventions

Preparation for Dynamic Smoke Studies

The importance of understanding how to perform these tests as well as the nature of the dynamic testing in the critical environment cannot be understated. Cleanroom testing professionals may or may not understand the suitable methods for performing a dynamic smoke study for a specific cleanroom and the operations carried out. This is because they may not have a clearly defined list of all personnel movement for all aseptic operations.

Dynamic smoke studies require the simulation of production activates. In order to correctly visualize airflow under dynamic conditions, the cleanroom must be configured to simulate actual operations. The equipment, product containers, vessels and transfer materials must be in place. This also requires the actual personnel ready to perform their operations. This may include support personnel that assist operators working in the critical environment, as they may (due to their proximity to the critical environment) influence air patterns as they support operators in the critical environment.

Setting up a dynamic smoke study with video evidence requires the same complexity as setting up the filming of a small video or movie production. Lighting, camera angles, (multiple camera angles) as well as directing the operating personnel are all important in performing a well-documented AFV/Smoke study.

Prior to performing any dynamic AFV/Smoke study, it is imperative to perform a static AFV/Smoke study. The logic is: if a static AFV/Smoke study reveals turbulence or eddy currents or air moving from a less critical area to a critical area under static conditions then we do not meet the requirements of proper cleanroom airflow. Poor airflow under static conditions equates to poor airflow under dynamic conditions.

Fire and Smoke Detection Systems

It is important to notify security and if required any external fire monitoring agency that AFV/Smoke Studies are being conducted in advance and just prior to commencing the testing. Not all Fire/Smoke Detection Technologies are the same. Different technologies used, have different sensitivities to smoke/fog particle sizes.

Tracer Particle Manifold Position

The position of the smoke manifold is extremely important. Figure 1 shows the correct position of the tracer particles manifold: Just below the HEPA Diffuser. In Figure 1 we have Unidirectional Airflow with First Air Sweeping over the Product Contact Surfaces.

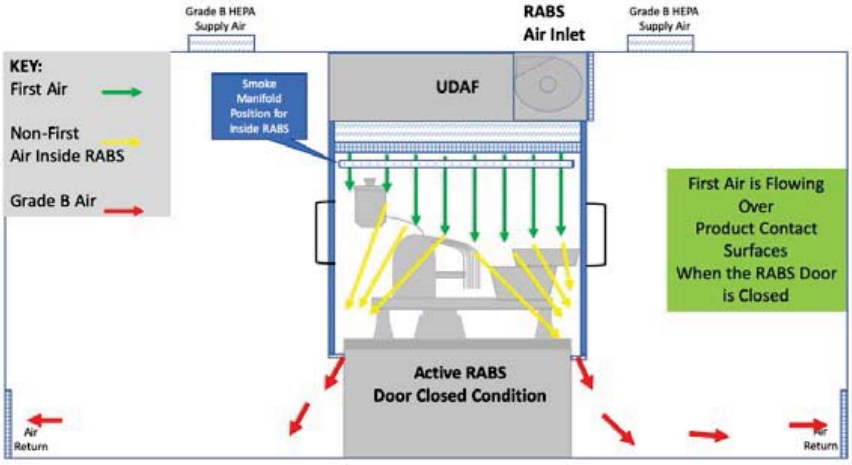

Figure 1 – Illustrates Correct Manifold Position Inside RABS

Figure 2 shows the correct position of the tracer particle manifold: Just below the HEPA Diffuser. In Figure 2 when the RABS door is open, we no longer have unidirectional flow inside the RABS. This is due to the poor integration of the RABS into the cleanroom. This is problematic as there is no longer unidirectional flow inside the RABS and first air is NOT getting to product contact surfaces.

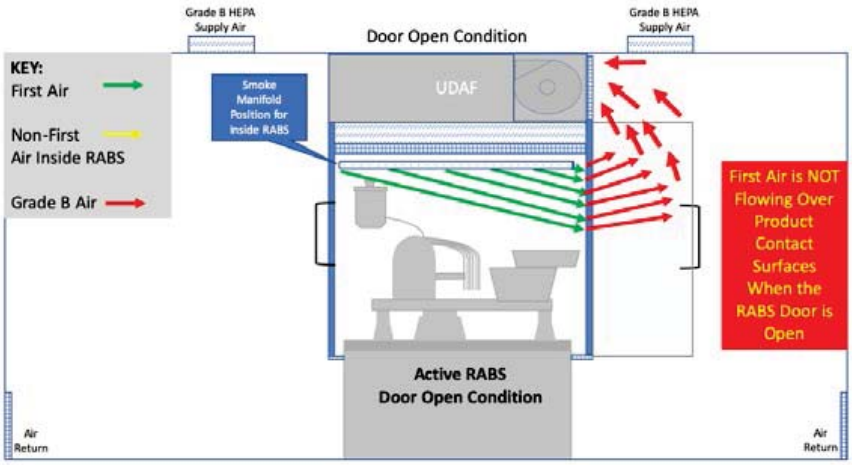

Figure 2 - Illustrates Door Opening Effects On RABS

Figure 3 shows the incorrect position of the tracer particle manifold: The manifold is placed here to hide the effect of the door opening on the RABS internal airflow. Unidirectional airflow is not maintained, and first air is NOT getting to product contact surfaces.

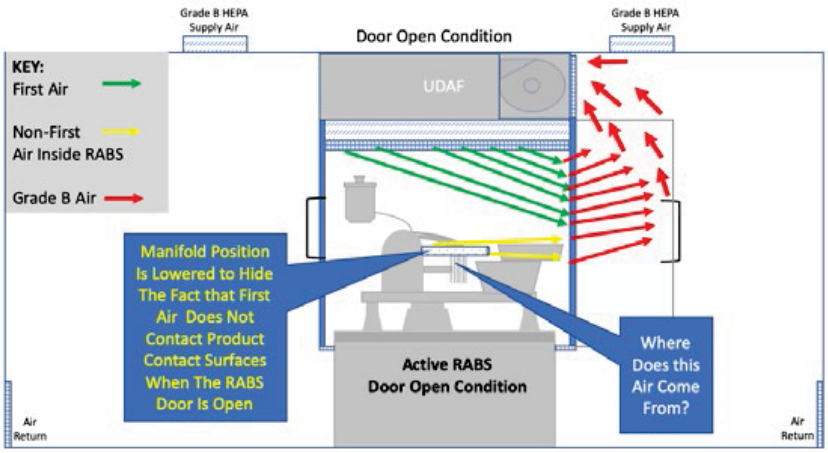

Figure 3 - Illustrates Incorrect Position of Tracer Particle Manifold

Figure 4 shows the position of the tracer particles manifold for testing a Grade B Room. Because the RABS inlet is very close to the RABS inlet a "Short Circuit" is created. This is detrimental to the overall contamination control effect of the facility.

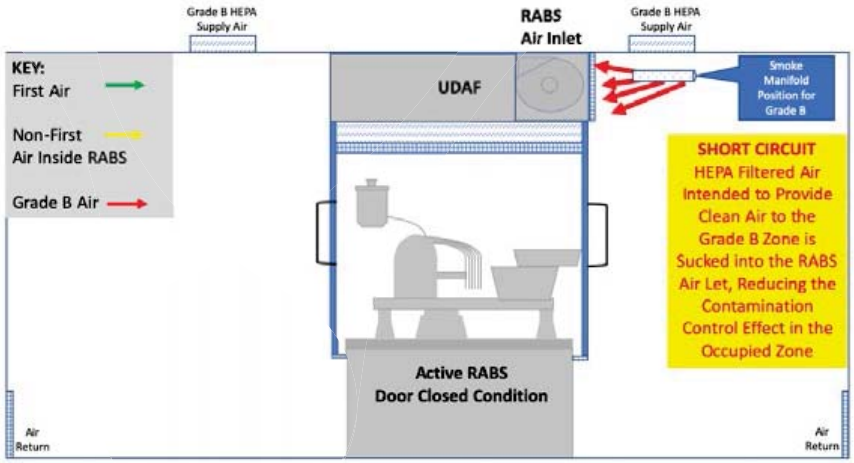

Figure 4 - Illustrates Short Circuit

Common Airflow Visualization Tests and Methods

In newly commissioned facilities it is common to perform extensive engineering investigative smoke studies for reasons outlined previously. In general, any air source or movement that can affect airflow including individual room HEPA filters, air returns, doors, pass throughs, downflow booths and equipment exhausts should be considered for testing during airflow visualization study. The following is a list of tests that are typically performed in a clean room.

1. Static Door Tests. Door pressure differentials are confirmed by generating smoke along the perimeter of the door to confirm pressure differential across the door.

2. Dynamic Door Tests. Typically, a Pillar of Smoke is generated adjacent to the door opening and the door is opened, and an operator walks through the opened door then closes it. Depending on the movement of the door and the operator transfer of air from the low-pressure side to the high-pressure side may occur. Figure 5 is an example of a system for generating a pillar of smoke adjacent to a door.

Figure 5 - System For Generating A Pillar of Smoke Adjacent To A Door

3. Individual HEPA filter Tests. Smoke is generated just below each HEPA filter and the airflow from the HEPA is observed. Individual HEPA filter tests can identify inadequate mixing of the air in non-unidirectional rooms possibly due to inadequate air volume, unstable airflows due to fluctuations in the air handling, HEPA filters that are off, etc. These results can be factored into the development of the EM plan for the facility.

4. Air Return Tests. Ceiling and Wall Air Returns are tested by generating smoke adjacent to the returns and confirming the airflows are adequate.

5. Pass-through Tests. Both Passive and Active Pass-throughs are tested by placing a smoke source inside the Pass-through with the door closed and filling the Pass-through with smoke. Any leaks in the Pass-through are readily identified by observing the door perimeters immediately after filling the pass through with smoke. If the Pass-through is an Active Pass-through the environment should clear in an adequate amount of time. At the end of the test the door on the high-pressure side can be opened to observe any transfer of smoke from the Pass-through to the room. Figure 6 is an example of a system that can be used for testing Pass-throughs.

Figure 6 – System for Testing Pass-throughs

6. Equipment Exhausts. Many machines including incubators, freezers, cell processing equipment, etc., contain fan exhausts and air-cooling inlets that can have a significant impact on airflow. The airflow of these sources should be characterized by generating smoke adjacent to them and observing the air movement. If an unfiltered fan exhaust is located adjacent to an open incubator this can be problematic and may warrant changing the layout of the equipment in the room.

7. BSC Exhausts. These tend to move a large volume of air and if they are located at the top of the machine near a ceiling and adjacent HEPA filter they can have a substantial impact on the airflow in the room and first air coming from the adjacent HEPA filter. In extreme situations substantial turbulence is created and since this is adjacent to operator location at the front of the BSC it can result in air traveling upward over the operator thereby violating the requirement of sweeping downward first air to protect critical operations.

8. BSC Inlets. BSC Inlets can move a large amount of air and can affect mixing in non-unidirectional cleanrooms. When testing individual HEPA filters adjacent to BSC Inlets the airflow effects of the BSC inlets should be fully characterized and accounted for.

9. Downflow Booths. Downflow booths are used locally for powder operations and contain HEPA filtration spanning a large area. These booths should be tested to ensure airflow is sufficiently unidirectional and any gaps between HEPA air inlets do not create excessive turbulence. In addition, consideration should be given to the interaction of these airflows with the airflows created by adjacent door operations to ensure the possibility of cross contamination is minimized.

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