microrite

WHITEPAPER

AIRFLOW VISUALIZATION (SMOKE STUDIES): THE MOST MISUNDERSTOOD AND UNDERAPPRECIATED CLEANROOM TEST

Morgan Polen

Microrite, Inc. San Jose, CA, USA, https://www.microrite.com

ABSTRACT

Airflow Visualization studies (AKA Smoke Studies) are used to evaluate air patterns in medical product cleanrooms and barrier systems (RABS, Isolators, pass-throughs and airlocks) that support aseptically produced, terminally sterilized and low bioburden product manufacturing.) These studies should be considered as more than a definitive pass/fail test. The criticality of adequate airflows in medicinal product manufacturing demand additional scrutiny that goes beyond the testing outlined in international cleanroom standard ISO 14644-3:2019.[1]

AIR PATTERN ANALYSIS

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 expected test by regulatory bodies worldwide and currently appears to be a widely misunderstood test by manufacturers, equipment suppliers, and regulators.

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.[1]
- 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 a focus 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 a focus on areas where the complete elimination of undesirable air patterns is not possible.

Cleanrooms and clean zones operate via the “Contamination Control Effect of HEPA Filtered Air Movement”. How air moves through the cleanroom or clean zone determines its contamination control effectiveness. Because air is transparent it is difficult to determine this contamination control effectiveness. Airflow visualization allows for a visual representation of air movement in both unidirectional and non-unidirectional flow cleanrooms and barrier systems. Additionally, these studies allow for the analysis of the airflow at the interface between unidirectional and non-unidirectional areas. To establish control, it is important to identify any possible sources of air patterns that may act as a channel or reservoir for contamination.[2]

Morgan Polen

Microrite, Inc. San Jose, CA, USA, https://www.microrite.com

AIR PATTERN ANALYSIS (CONTINUED)

Accurate airflow visualization is an essential part in the analysis and characterizing of air patterns in cleanrooms, controlled environments, barrier systems, airlocks and pass-throughs that support aseptic or low bioburden processing.

Complete elimination of undesirable air patterns is impossible in aseptic and low bioburden manufacturing. Turbulence and vortexes exist in even the most well-designed aseptic filling areas. Gaps between HEPA filters, interface between unidirectional and non-unidirectional zones and areas around doors typically have undesirable air patterns. The complexity of operations, process equipment designs, including automation and robotics prevent the complete elimination of undesirable air patterns.

Because of the complexity of operations, airflow visualization is not a definitive pass/fail test. Airflow visualization is a contamination control tool for holistically and visually evaluating the entire cleanroom system's ability to provide adequate airflow for contamination control. It should identify any weakness and provide a means of optimization of the physical characteristics of the cleanroom, RABS, isolators, or mobile equipment locations. Additionally, it allows for the evaluation of personnel standing positions and movements in respect to airflow patterns.

This testing should include the evaluation of the mixing effect in non-unidirectional flow cleanrooms as well as the operation of air returns, air locks and pass-throughs. Important consideration should be given to the interface between critical areas under unidirectional airflow and adjacent areas of non-unidirectional airflow (i.e., Grade A and Grade B or C background environments for aseptic operations).

Possible contamination sources such as equipment cooling fans, air intakes, exhausts from flow hoods or cabinets (even if a filtered exhaust is utilized), heat sources or areas with no airflow (dead spaces) must be identified and considered in the overall contamination control strategy of any operation that uses cleanrooms. The analysis of the airflow visualization data should be used for contamination risk assessment and the selection of sampling locations for viable and non-viable particle monitoring locations.

The simulation of equipment operation, operator activity (equipment set-up, intrinsic and corrective interventions, environmental monitoring) is needed to meet the FDA's[3] dynamic in situ air pattern analysis requirements. Because operator behavior can influence airflow, air pattern analysis should be used for operator training.

Airflow Visualization is a science not unique to pharmaceutical manufacturing. Many high technology industries: electronics, chemical, automobile, aerospace and defense, use airflow visualization as an engineering tool to evaluate and optimize design and performance of mechanical systems. The accuracy of these studies and the conclusions obtained, is dependent upon multiple factors. The methodology, equipment and the material used can impact the accuracy of the airflow visualization studies.

Morgan Polen

Microrite,inc. San Jose, CA, USA, https://www.microrite.com

AIRFLOW VISUALIZATION METHODS

As airflow patterns are invisible to the naked eye; there are a variety of methods for conducting airflow visualization of which the most common is the Tracer Particle Injection Method. This method involves the observation and recording of the behavior of tracer particles that are injected or diffused into the air stream being tested.

The accuracy of the air pattern analysis is dependent upon:

- The tracer particles faithfully following the air patterns
- The tracer particles remaining visible long enough to allow for the analysis of the area being tested
- The location of the tracer particle injection
- The method in which the tracer particles are injected into the air patterns being tested

Various systems and equipment are used for performing airflow visualization and creating the tracer particles with varying levels of accuracy. (Figure 1) For consistent and repeatable results, the following requirements for the generation of tracer particles must be addressed.

REQUIREMENTS FOR TRACER PARTICLES

Neutrally Buoyant Tracer Particles (should not sink without air flow)

Neutrally Buoyant is a term used to describe the behavior of Tracer Particles when they are diffused into an area with no apparent air flow. The cloud of tracer particles should not settle rapidly or rise rapidly after being released into an area with no airflow.

Various conditions (e.g., Tracer Particle Size, Temperature, Composition, Vapor pressure, Gravity) may influence the tracer particles behavior. These conditions cause the tracer particles to deviate from the actual airflow patterns. Tracer particles that are too large or colder than the area being tested will deviate from the actual airflow patterns and settle rapidly. This deviation has led to incorrect conclusions related to airflow patterns in critical areas. These incorrect conclusions have led to failed media fills, failed sterility testing, contaminated products, 483 observations and warning letters.

Stable Tracer Particles (visible long enough to evaluate the area being tested)

In order to accurately observe and record the air patterns by observing tracer particles, these particles must remain visible long enough to visualize the air patterns being tested. Tracer particles that are unstable and evaporate too rapidly cannot accurately characterize the “Contamination Control Effect of HEPA Filtered Air” in cleanrooms and controlled environments.

As stated above, various conditions (e.g., Tracer Particle Size, Temperature, Composition, Vapor pressure) may influence the tracer particles stability. This lack of stability has led to incorrect conclusions related to airflow patterns; these conclusions have the same impact as denoted above.

Morgan Polen

Microrite,inc. San Jose, CA, USA, https://www.microrite.com

FIGURE 1-TRACER PARTICLE GENERATOR TECHNOLOGY

Technology (Equipment)	Tracer Particle	PROS	CONS
Ultrasonic Cleanroom Fogger (water based)	Tracer Particles are approximately 5.0 to 10 µm in size, however due to vapor pressure they expand and increase in size. These particles are not neutrally buoyant and are unstable (evaporate rapidly)	Can utilize WFI, or purified water	1. The cloud of tracer particles is not neutrally buoyant, 2. The tracer particles evaporate rapidly. 3. Condensation of water on surfaces. 4. Cleaning of all cleanroom surfaces required after testing. 5. Not suitable to characterize air patterns in non-unidirectional flow cleanrooms.
Carbon Dioxide Cleanroom Fogger	Tracer Particles approximately 5.0 µm in size, however due to vapor pressure they expand and increase in size. These particles are not neutrally buoyant and are unstable (evaporate rapidly)	No Condensation on surfaces	1. The cloud of tracer particles is not neutrally buoyant 2. The tracer particles evaporate rapidly. 3. Cleaning of all cleanroom surfaces required after testing. 4. Not suitable to characterize air patterns in non-unidirectional flow cleanrooms.
Nitrogen Cleanroom Fogger	Tracer Particles approximately 2.0 µm, however due to vapor pressure they expand and increase in size. These particles are not neutrally buoyant and are unstable (evaporate rapidly)	No Condensation on surfaces	1. The cloud of tracer particles is not neutrally buoyant 2. The tracer particles evaporate rapidly. 3. Cleaning of all cleanroom surfaces required after testing. 4. Not suitable to characterize air patterns in non-unidirectional flow cleanrooms.
Glycol Based Fogger	Tracer Particles are approximately 0.2 to 0.5 µm in size, with a low vapor pressure. These particles are neutrally buoyant and are stable. Suitable to characterize air patterns in unidirectional and non-un directional flow cleanrooms	Neutrally Buoyant Tracer Particles That remain visible in long enough to visualize the air patterns from the HEPA filter to the air return. Suitable to characterize air patterns in unidirectional and non-unidirectional flow cleanrooms	1. Cleaning of all cleanroom surfaces required after testing. 2. Can trigger smoke/fire alarm systems. 3. Particles will be trapped on filters. Excessive studies can impact filter performance (similar to filter integrity testing)
Smoke Sticks	Tracer Particles are a chemical smoke sub-micron (<1.0 micron)	Neutrally Buoyant Tracer Particles That remain visible in long enough to visualize the air patterns from the HEPA filter to the air return.	1. Cannot control output 2. Output is too low 3. Difficult to configure for in situ testing 4. Cleaning of all cleanroom surfaces required after testing.

Morgan Polen

Microrite,inc. San Jose, CA, USA, https://www.microrite.com

REQUIREMENTS FOR TRACER PARTICLES (CONTINED)

Suitably diffused or injected into the air stream

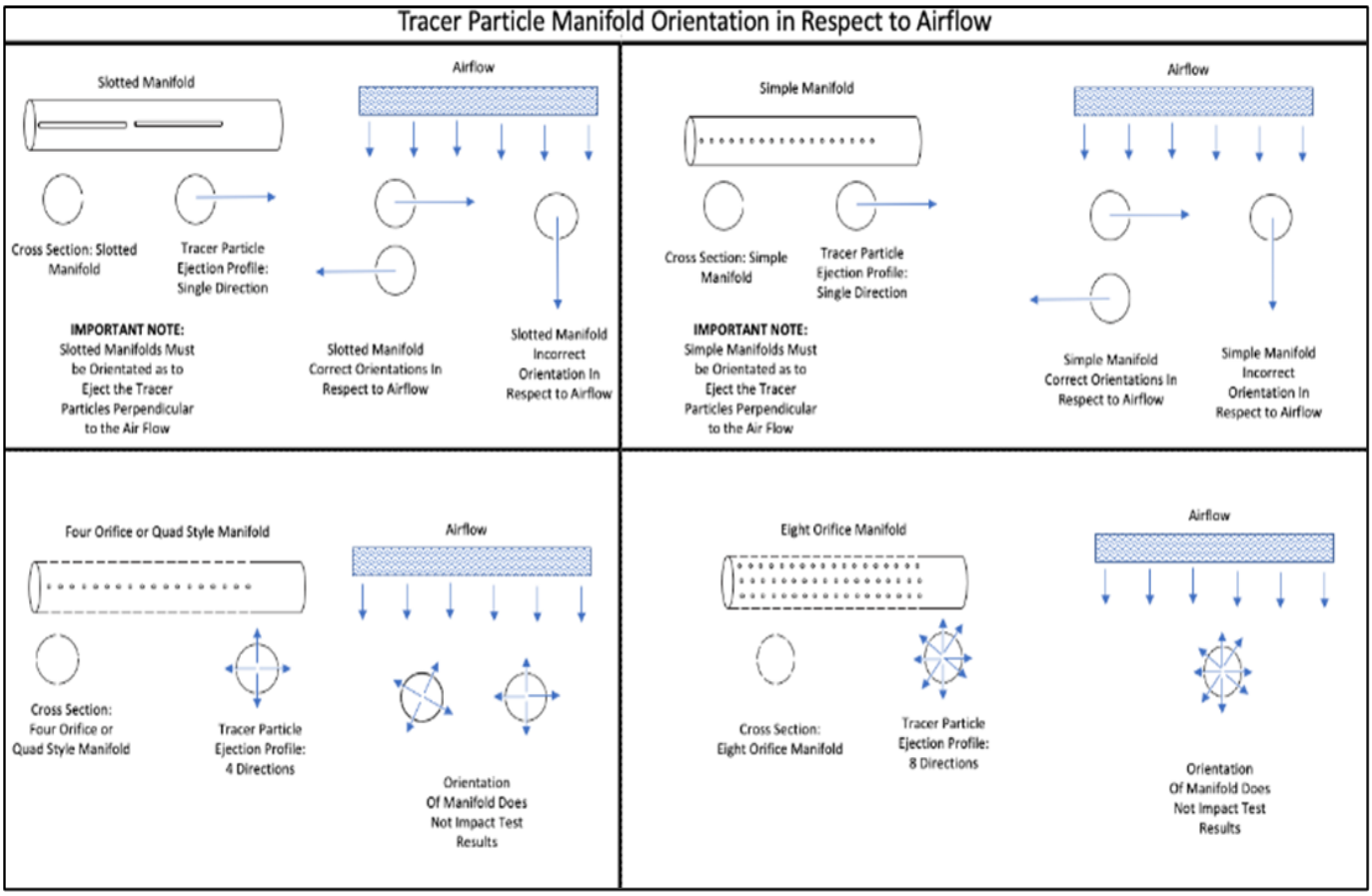
For accurate airflow visualization it is important that the tracer particles be introduced without altering, disturbing or overpowering the air patterns being tested. Per the FDA guidance[3] "In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions." Definition of the word[4] In situ: situated in the original, natural, or existing place or position, undisturbed.

In order to deliver the tracer particles into the critical area the use of; tubing, manifolds, stands, suctions cups, cable ties or tripods may be necessary (Figure 3). Additional test personnel operating a wand or tube to inject the tracer particles through a partially opened door, should be avoided if possible.

The use of a tracer particle dispersion manifold should be considered to best deliver the tracer particles to the critical area being tested. Manifold design and orientation can influence the accuracy of the air flow visualization.

Manifolds with a slotted or single row of orifices along the length of the manifolds (Figure 2) must be orientated so as to not to overpower the air patterns and give the false impression of unidirectional air flow when the air pattern is something different.

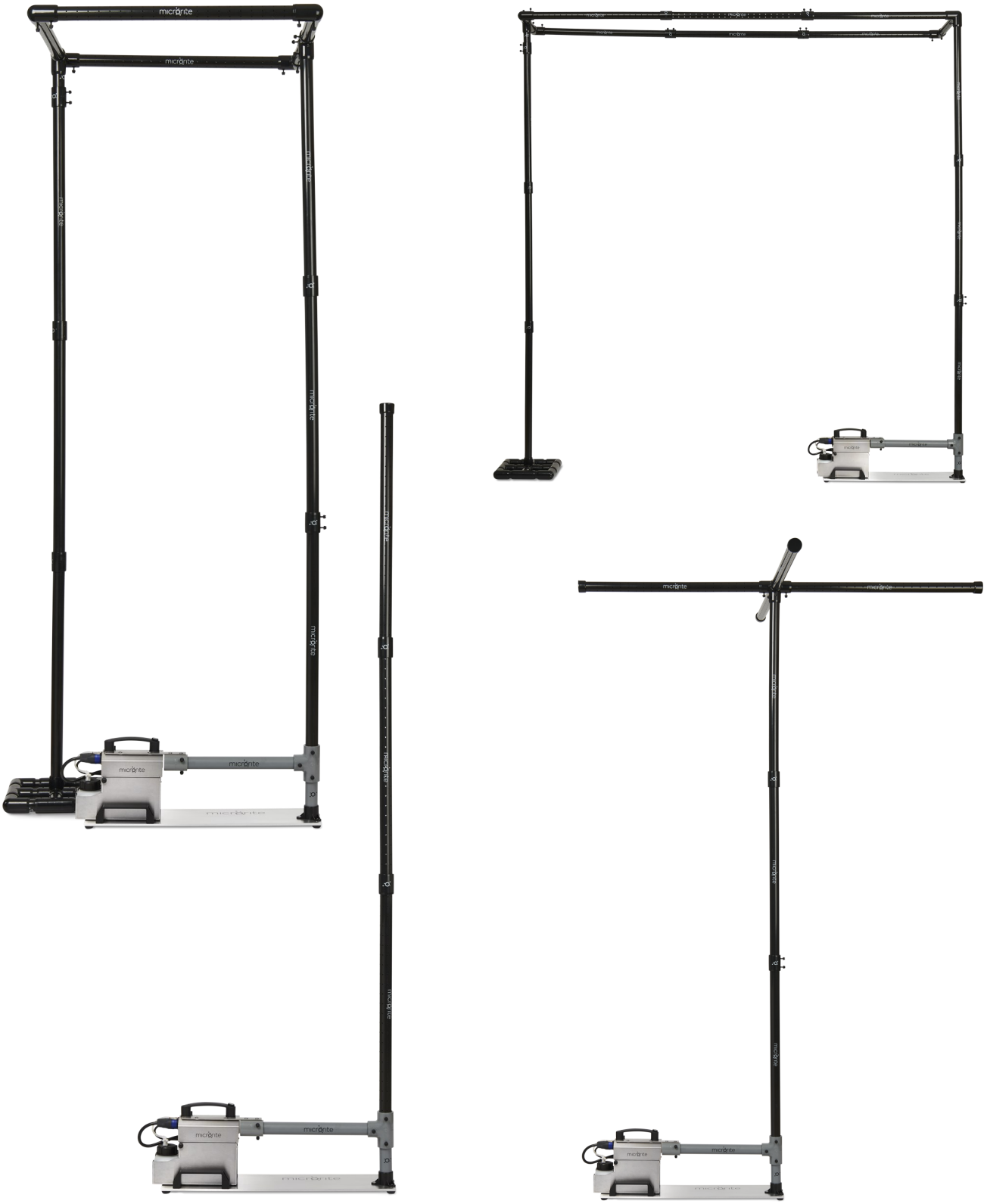
FIGURE 2-TRACER PARTICLE MANIFOLD ORIENTATION



Morgan Polen

Microrite,inc. San Jose, CA, USA, https://www.microrite.com

FIGURE 3-TRACER PARTICLE MANIFOLD CONFIGURATION EXAMPLES



Morgan Polen

Microrite,inc. San Jose, CA, USA, https://www.microrite.com

CONCLUSION

In conclusion, there is nothing clean about a "Smoke Study". Air Flow Visualization studies release a massive number of particles into the cleanroom and clean-air systems, cleaning the cleanroom after is required. The very nature of a Smoke Study exceeds the particle concentration limits of the cleanroom. Additionally, the type of Air Flow Visualization that is required by the FDA and other international regulatory bodies requires smoke studies to be performed in conjunction with the simulation of processing tasks, filling and closing of containers, loading and unloading of freeze dryers, normal and abnormal interventions and aseptic connections. As these simulations mimic actual operations with additional testing personnel, additional equipment (cameras, Tracer Particle Generator, tripods etc.), a deep cleaning inclusive of sanitization, disinfection and sterilization must be undertaken.

ABOUT THE AUTHOR

Morgan Polen has been involved with cleanrooms and contamination control since 1984. Morgan is Microrite's airflow visualization and cleanroom contamination control expert. He has Worked in over 40 countries involved with projects ranging from cleanroom design, construction, validation, monitoring program development, particle counter design and product management for cleanroom related products and systems. He has addressed monitoring and control solutions in a wide variety of clean industries such as pharmaceutical, medical device, semiconductor, data storage, aerospace, defense, automotive, optical and others.

Microrite, Inc. is a USA based consulting and training firm assisting companies globally. Our clients include pharmaceuticals, biotechnology, medical devices, other healthcare related industries and high technology manufacturing facilities. We strive to provide our clients with a comprehensive approach and unparalleled expertise in the areas of facilities, validation, microbiology, quality assurance and quality control.

In 2019 Microrite developed a tracer particle generation system to specifically produce neutrally buoyant tracer particles. To learn more please visit www.tracerparticlegenerator.com.

REFERENCES

1. International Organization for Standardization (ISO) (2019) ISO 14644-3:2019 Cleanrooms and associated controlled environments Part 3: Test methods.
2. USP <1116>, Microbiological Control and Monitoring of Aseptic Processing Environments
3. Food and Drug Administration (FDA) (2004) FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice.
4. In situ. (n.d.). Retrieved March 15, 2021, from https://www.dictionary.com/browse/in-situ

For additional information please contact info@microrite.com , or visit www.microrite.com