Demystifying dynamic smoke pattern tests for sterile compounding pharmacies

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Despite efforts to improve quality and reduce risk in sterile compounding pharmacies over the last 6 years, significant gaps in retail and hospital pharmacy compounding processes remain.[1] Compounding facilities must better utilize known process validation tools that can significantly reduce microbial contamination risk in sterile compounding. One such tool is a dynamic airflow smoke pattern test. Smoke studies have been a requirement of *United States Pharmacopeia (USP)* chapter 797 since 2008.[2] Airflow visualization provides visual confirmation of the suitability of the unidirectional airflow device for sterile compounding (Figure 1). It also demonstrates the optimal layout and proper usage of the unidirectional airflow (first air) during compounding. However, smoke studies may be underutilized as a validation tool by the compounding staff because such studies do not assess true dynamic conditions; this may present inherent risks for sterile compounding processes.

Because dynamic smoke studies are a requirement in both *USP* chapter 797 and the applicable Controlled Environment Testing Association (CETA) applications guide,[3] they are often performed by the certifier. Certifiers are qualified and trained to conduct certification tests of the compounding areas. They are almost certainly more experienced at conducting a smoke study than most pharmacy staff; however, they are not experts in sterile compounding, aseptic technique, and the pharmacy's specific aseptic processes.

The drawback of having the certifier perform the smoke study is that pharmacists become less involved in the planning, performance, and analysis of the study. When the pharmacy staff have little involvement in the study, 4 potential problems arise:

(1) The smoke study does not simulate true dynamic conditions. Certifiers have been known to use their own employees to simulate the dynamic conditions, which is in direct contradiction to the definition of dynamic conditions in the proposed changes to *USP* chapter 797.
(2) There is inadequate time to assess and troubleshoot problematic areas. The certifier is only there for a minimum amount of time and is generally looking to move on to his next customer as quickly as possible.
(3) The final report may not adequately address all critical items of the compounding process. The certifier will only perform what they believe to be the dynamic operations if the pharmacy staff is not involved.
(4) Typically, when the certifier is performing the smoke studies, only 1 pharmacy technician participates, resulting in much of the staff missing an important training opportunity.

Truly dynamic smoke studies are essential because a certified primary engineering control (PEC) is only as efficient as the suitability of the process design and proficiency of the staff. The quality of the International Organization for Standardization (ISO) class 5 cleanroom environment at the critical site is easily compromised by poor and inconsistent practices. Consider the airflow supplied from the high-efficiency particulate air (HEPA) filter in the PEC. Within a laminar airflow workbench (LAFW), the typical airflow velocity 6 inches from the face of the HEPA is approximately 90 feet per minute.[3] This is much slower

Figure 1. Dynamic airflow visualization is performed during a sterile compounding simulation.

than one would estimate. The velocities within a biological safety cabinet (BSC), compounding aseptic isolator (CAI), or containment aseptic compounding isolator (CACI) are usually even lower than 90 feet per minute. If one were to walk 10 feet in 7 seconds, it would seem like a snail's pace, but that is approximately the velocity of unidirectional airflow protecting the direct compounding area (DCA) within an LAFW.

Also, sterile compounding is a manual process that introduces materials and personnel with high bioburden. There is ample opportunity to compromise the quality of the environment during compounding. The risks associated with sterile compounding mandate adequate process validation measures through smoke studies.

Many pharmacies have been cited by the Food and Drug Administration (FDA) for "no or improper smoke studies," as illustrated by an excerpt from an FDA form 483 (issued if an inspection finds potentially violative conditions)[4]: "The smoke study video that we viewed demonstrated an operator standing at the hood making manipulations with one IV bag at the top of the hood. This was not representative of aseptic processing operations observed [during a previous site visit]. We observed your staff aseptically processing on the bench, with components, equipment (such as the [total parenteral nutrition] mixer or the repeater pump), and other items which can affect laminar air flow."

Truly dynamic airflow smoke pattern tests that validate actual working conditions are not easy to perform and document. A compounding operation may have wide variations in compounding processes. There are variations in risk levels, complexity, personnel, equipment, and components. Without proper airflow studies that account for these critical variables, hidden risks to the product may lurk and not be targeted for correction. Pharmacy staff must become heavily involved in the planning, execution, and analysis of smoke studies. Successful completion of a smoke study takes time, careful planning, and attention to detail, not to mention someone who understands the best camera angles for videotaping the smoke study.

This article describes helpful tools that will enable pharmacy staff to reduce risk in their sterile compounding operation with a dynamic airflow visualization study. Regardless of whether the study is performed solely in-house or in conjunction with the certifier, these steps will help the pharmacy staff better understand and validate the aseptic process. Although a smoke study is not the sole means of validation, it is a critical and often overlooked piece that needs to be better understood by compounding pharmacists.

Planning the study. Before an airflow study begins, it is imperative to properly plan and design the study. Studies that are poorly designed or impromptu will probably have deficiencies that hinder efforts to obtain an accurate assessment of dynamic conditions. Instructing a technician to sit in front of the hood and perform simple aseptic transfers is not enough to simulate the process. Instead, the actual workspace configuration and processes normally employed in the cleanroom must be tested.

The purpose of a properly designed study is to demonstrate adequate airflow "to support aseptic operations as required for the intended tasks" utilized in the pharmacy.[3] One of the first planning activities is to precisely identify the process being studied. For the purposes of this article, "sterile compounding process" refers to all specific steps utilized in the compounding of a CSP. For example, one may choose to study simple compounding that involves simple reconstitution of a vial and sterile transfer to an i.v. bag, or the study may focus on complex batch compounding that involves sterile filtration and unit dosing into a vial. The process to be studied should be identified precisely and given a specific name (e.g., "high-risk batch compounding—syringes"). It may be beneficial to keep the process general enough to encompass several formulas and batch sizes. This is acceptable for a compounding pharmacy as long as the processes are similar and the simulation represents worst-case conditions in terms of complexity and final yield. If there are several different processes utilized, then it is highly recommended to perform several smoke studies, one for each PEC, even if only on a rotating basis.

Clarify and standardize specific steps. Once a process to be studied is identified, it is important to understand and define the intricate steps from beginning to end. A useful tool that may be considered is process mapping. A cross-functional team can be formed to assist in outlining and deconstructing the process. This team must include the personnel performing the task on a regular basis. A process map brings clarity to the exact steps being performed. Begin by standardizing the specific steps involved in compounding. Be sure to include at the least the following 6 elements:

(1) Introduction of components into the ISO 5 area
(2) Placement of equipment
(3) Exact location where unwrapping occurs
(4) Placement of components during compounding
(5) Exact location where sterile compounding occurs
(6) Specific aseptic technique used by personnel

The suitability of these decisions will be confirmed and/or further directed by the smoke study itself. Be prepared to make changes to the process during the study, as it is unusual to perform an initial smoke study and find acceptable results. The process mapping should represent the highest volume and most complex conditions. If the typical process is to compound in batches of 5 units but on occasion 20 units are prepared, then process map with 20 units.

Identify critical steps for analysis. After the process map is completed, identify critical compounding steps that may pose contamination risk from an airflow standpoint. These critical steps will be different for every pharmacy, but they should all

Figure 2. The 5 general critical areas analyzed during smoke studies. PEC = primary engineering control, ISO 5 = International Organization for Standardization class 5.

1	Staging of materials in the PEC (especially exposed critical sites)
2	Unwrapping components in proximity to or exposing critical sites
3	Proper placement of trash (wrappers, alcohol wipes, and used materials) inside the PEC
4	Significant movements in proximity to critical sites
5	The handling, puncture, or exposure of critical sites to the ISO 5 environment

focus on risk of contamination at critical sites (e.g., vial stoppers, ampule necks, and i.v. bag septums).

In addition to a static smoke visualization of the entire DCA, the 5 general critical steps that should be analyzed (Figure 2) are as follows:

(1) Placement of materials and equipment in the PEC (especially exposed critical sites)
(2) The handling, puncture, or exposure of critical sites in the ISO 5 environment
(3) Unwrapping components in proximity to or exposing critical sites
(4) Proper placement of trash (wrappers, alcohol wipes, and used materials) within the PEC
(5) Significant movements in proximity to critical sites

With each process mapping, these critical steps are flagged and analyzed during the smoke study. If additional areas of risk are identified during the simulation, such as unplanned interventions, then they should be included in the study.

After a thorough understanding of the specific sterile process of interest and identified areas of risk, one must be clear about what is considered an acceptable outcome. According to *USP* chapter 797 and FDA guidance on aseptic processing, the study must "demonstrate(s) unidirectional airflow and sweeping action over and away from the product under dynamic conditions."[2,5] Additionally, the FDA guidance document states that the workspace should be free from turbulence, stagnant air, and eddy currents. The airflow will be judged by these criteria for each critical step identified. If the acceptance criteria are not met for a particular area of concern, then mitigation steps should be implemented before finalizing the study, as discussed below.

Simulating dynamic conditions. To properly simulate dynamic conditions, conduct a water fill that mimics the exact process being studied. Be sure to pay special attention to the critical steps identified in the planning phase. Actual operating personnel must simulate actual processes. A certifier or other person who is not part of the compounding team is not a suitable substitute.

The staging and setup portion should focus specifically on introduction, placement, and unwrapping of all materials in the PEC. The exact locations in which each of these functions occurs, as well as the potential impact on airflow over the critical site, should be determined. In addition, the placement and configuration of equipment should be determined.

The most critical piece of the simulation will involve all aseptic transfers, aseptic connections, and exposed critical sites. The exact container closure and same aseptic connection actually used should be tested. Testing should include simulating the highest-complexity configuration and the same sequence of events that occur during working conditions.

During aseptic processing, unplanned interventions may arise during the working day, which can impact airflow. It would be best to identify potential unplanned interventions encountered by staff. These mishaps can be studied to identify potential risks posed by the unplanned process; this includes misplaced or dropped container closures and spill cleanups.

There are other, often-overlooked processes that should be considered during the study because they potentially impact airflow. These include placement of discarded materials and filled containers. The manner in which materials are moved within a PEC and ultimately discarded can represent a potential source of risk and should be studied.

Conditions in the surrounding room may also impact the environment within the PEC, so movement within the room (opening and closing of doors, personnel walking briskly next to the compounder) should be simulated. It is important to demonstrate that these worst-case conditions do not impact airflow during compounding. As a side note, smoke studies of the ISO 7 (nonunidirectional) room itself are not needed during certification if compounding is performed within an ISO 5 PEC and environmental monitoring results in the adequate microbial control of the room. There are cases in which a room visual smoke study is required, such as when the room has ceiling-mounted air returns, but that is beyond the scope of this article.

Risk identification and mitigation. Another important aspect of simulations is risk identification and mitigation; staff must allow enough time during the study for these activities, which include analyzing and changing practices that are deficient according to results of the airflow visualization. These identified areas of risk must be mitigated by determining an alternative practice that maintains adequate sweeping action over the critical site throughout the compounding process. For example, if it is revealed during the study that personnel obstruct the airflow of a vial septum during filling (Figure 3), then the work practice must be changed to mitigate the risk. Risk mitigation may be as simple as moving the location of a specific aseptic manipulation within the PEC (Figure 4), or it may require a completely new configuration and workflow process.

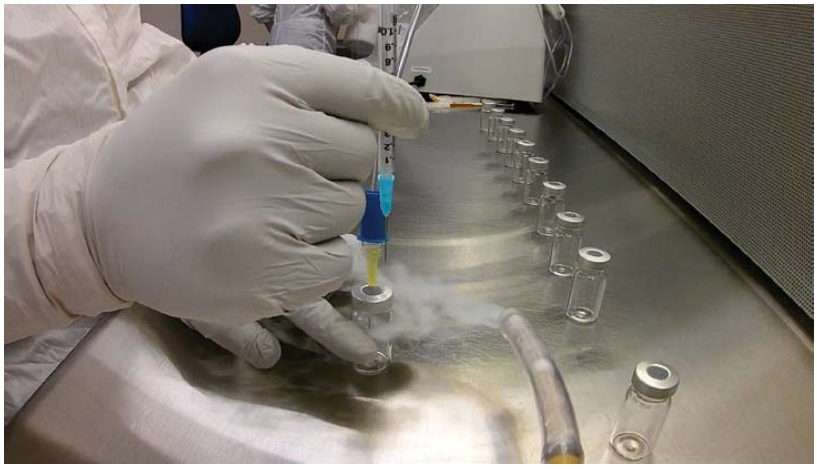
Processes that are modified to mitigate risk are critical and must be followed; this means they must be standardized in a procedure, and staff must be adequately trained. Failure to follow through on properly mitigating risk will pose an even greater risk to your product.

Special considerations for different PECs. When choosing a proper PEC to use for compounding, consideration must be given to airflow direction (vertical versus horizontal airflow), workspace required to perform proper compounding, and the effects these decisions will have on the workflow within the PEC. LAFWs with more than 1 filter often have "dead zones" where the 2 HEPA filters meet, creating a space that must be avoided when compounding. Some horizontal-flow LAFWs are equipped with a "lip" at the rear of the work surface and, therefore, do not have unidirectional airflow (first air) directly at the work surface. If a diffuser screen is not installed to correct this, exposed critical sites cannot be placed directly on the work surface. Regardless of the PEC used, a DCA in which only aseptic compounding processes occur must be established. Sterile materials should be unwrapped on one side of the LAFW, with the DCA established on the opposite side of the work area. The workflow should be from the unwrapping area to the DCA, minimizing the potential for contamination of the DCA by the unwrapping process.

Figure 3. Generated smoke reveals obstructed airflow at critical site by personnel finger placement on the container closure.

Vertical-flow devices such as BSCs, CAIs, and CACIs introduce HEPA-filtered airflow vertically from the top-mounted HEPA filter down to the work zone. Air is pulled to the return grilles positioned at the front and rear of the work surface. Vertical-airflow PECs have a split in the middle of the work surface that creates a "roll," disrupting unidirectional airflow (first air) at the work surface. Because of this split and with the exceptional pull of airflow from the return grilles within the BSC, smoke studies often show that the best place to compound is near the return grilles in the front or rear of the BSC. While acceptable airflow is found at the rear grille, working there may not be practical. Both front and rear grilles must remain unobstructed throughout the compounding process. The smoke study should be used to confirm that air does not escape from the access opening when work is performed towards the front of the work zone. The airflow within a CAI or CACI is similar to that within a BSC except that the airflow velocity is typically much slower than in a BSC, making it difficult to find areas within the work area where unidirectional airflow (first air) can be maintained throughout the compounding process.

Figure 4. After risk mitigation, unidirectional airflow without turbulence sweeps over and away from the critical site.



Execution of dynamic smoke pattern test. The selection of the fog (smoke) generator is critical, as the machine must produce a smoke medium that is adequate to illuminate the airflow. It is imperative that the fogger has the potential to produce enough smoke to be visible on the video but not so much as to mask potential contamination issues. Attachments may need to be fabricated in order to adequately distribute the smoke throughout the PEC without affecting the airflow. The fog source must be neutrally buoyant so that it does not influence the airflow within the PEC. The smoke source should be nontoxic and must be cleanable. Airflow ventilation smoke tubes are a known acceptable source, as are glycol-based fog generators. The fog created must be visible from the entrance plane (i.e., the HEPA filter), across the critical zone within the DCA, and to the exit plane of the PEC. The exit plane can be past the operator in a horizontal-flow LAFW or, in vertical-flow devices, the returns located within the PEC itself. It may be necessary to produce greater amounts of smoke during the static mode to capture the airflow within the entire PEC and lesser amounts of smoke when concentrating on the critical compounding activities within the PEC.

The airflow visualization should be videotaped, and both static and dynamic operations should be included in the video. A digital video camera, a GoPro device (GoPro, Inc., San Mateo,

CA), or even cell phones have adequate quality to produce an acceptable video. The goal is to capture the unidirectional airflow (first air) within the PEC during dynamic conditions; due to the size of some PECs, accomplishing this may require use of 2 cameras or multiple shots of the same process. If use of 2 cameras is not an option, then the process must be recorded from several camera angles to ensure that the entire process is captured in order to prove there is unidirectional airflow (first air) across the critical areas within the DCA.

Analysis and reporting. Airflow visualization testing is a team effort. The total process is best accomplished with a minimum of 3 personnel. The camera operator and the person responsible for positioning the smoke must both have knowledge of aseptic processing techniques and unidirectional airflow (first air). Sometimes the videographer cannot see exactly what is happening at the critical zones and may overlook some adverse airflow conditions, in which case the individual introducing the smoke may catch them. The videos should always be viewed on a larger screen to ensure that results are equivalent to real-time viewing. The third person involved in testing should be the technician who actually compounds in each PEC.

A written summary report in support of the video, outlining any nonunidirectional airflow or any activity that is not commensurate with aseptic processing techniques, should be developed. The language used to describe the airflow within the PEC should be descriptive, using terms such as *sweeping, smooth, steady, flowing, controlled, fluid, turbulent, unidirectional, backward flow,* and *slow or lazy*. Per the aforementioned FDA guidance document,[5] once relevant parameters are established, airflow patterns must be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants (e.g., from an adjoining lower-classified area). 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.

In keeping with the adage "pictures are worth 1,000 words," adding pictures to the report may enhance its clarity when defining questionable zones within the PEC. Ensure that the summary report uses descriptive language, such as "pass" or "fail," when describing the overall performance of the PEC.

Closing notes. Airflow visualization is an effective tool to reduce the risk of microbial contamination within a sterile compounding facility. Although dynamic airflow smoke pattern tests are traditionally seen as a certification tool, they should be heavily relied upon for process validation. Pharmacist involvement in the setup, performance, and analysis of the smoke study is essential to its utility in the pharmacy. Smoke studies that replicate the compounding processes, along with input from the compounding staff, are meaningful in providing a visual tool to demonstrate a proper environment during compounding. Such testing may also be incorporated into technician training assessment requirements. Smoke studies done without input from the compounding team are simply checkoffs on the road to compliance that have little true process improvement value.

Disclosures

The authors have declared no potential conflicts of interest.

References

1. Douglass K, Kastango ES, Cantor P. What prevents excellence in sterile compounding? (October 2017). https://www.pppmag.com/article/2127 (accessed 2019 Sep 15).
2. Pharmaceutical compounding—sterile preparations (general information chapter 797). In: United States pharmacopeia, 31st rev., and the national formulary, 26th ed. Rockville, MD: United States Pharmacopeial Convention.
3. CETA applications guide for sterile compounding facilities CAG-003-2006. Raleigh, NC: Controlled Environment Testing Association; revised 2015 May.
4. Food and Drug Administration. Form 483 report to Coram Healthcare, Crown Point, IN (April 26, 2017). https://www.fda.gov/media/106206/download (accessed 2018 Dec 20).
5. Food and Drug Administration. Guidance for industry: sterile drug products produced by aseptic processing—current good manufacturing practice (2004). https://www.fda.gov/media/71026/download (accessed 2019 Sep 15).