Air Flow Visualization

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Air Flow Visualization

- **Velocity testing must be performed to**
  - Confirm the velocity of air exiting the HEPA filter
  - Uniform velocity from filter to filter
  - Understand the speed that the air is flowing into air returns
  - Consistency of the air balancing/returns in the clean room
    - This is a criteria that most companies do not evaluate

Air Flow Visualization

- **Types of velocity testing equipment**
  - Rotameter
  - Hotwire
  - Velgrid

Air Flow Visualization

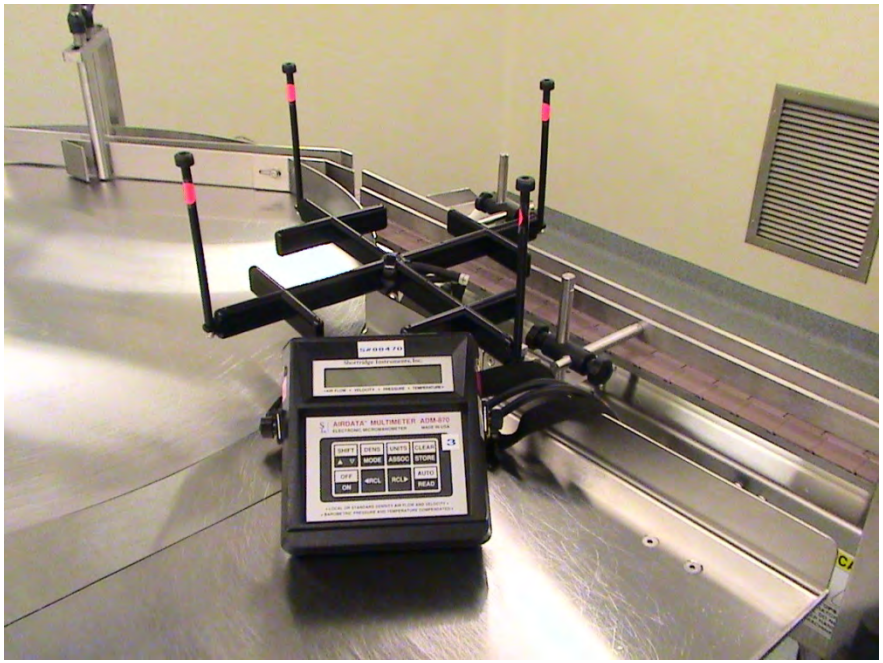
- **Velocity Testing**
  - Rotameter

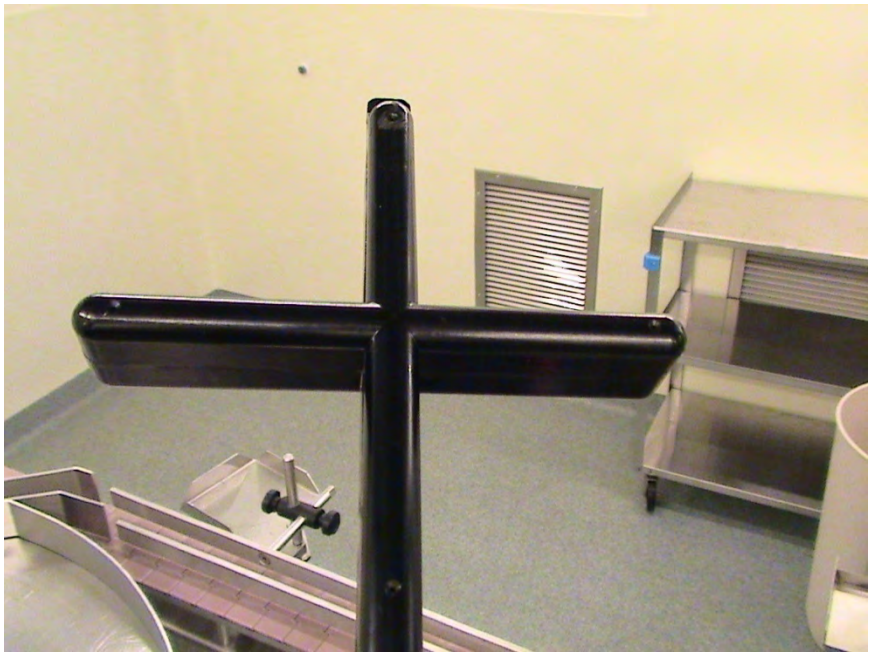
Air Flow Visualization

- **Velocity Testing**
  - Hotwire

Air Flow Visualization

- **Velocity Testing**
  - Velgrid



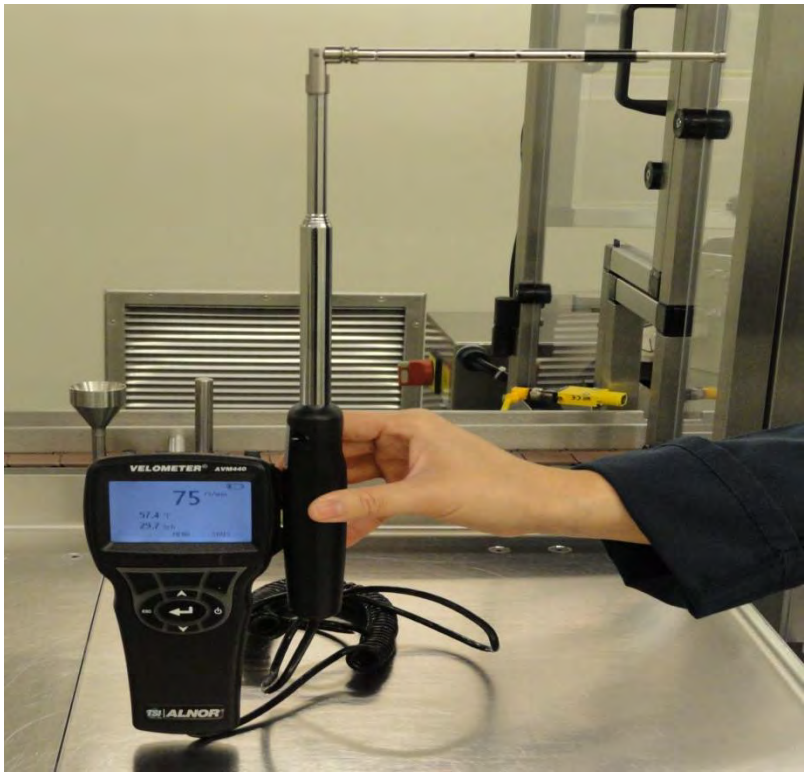


Air Flow Visualization

- **Velocity Testing**
  - Hotwire Filter Face

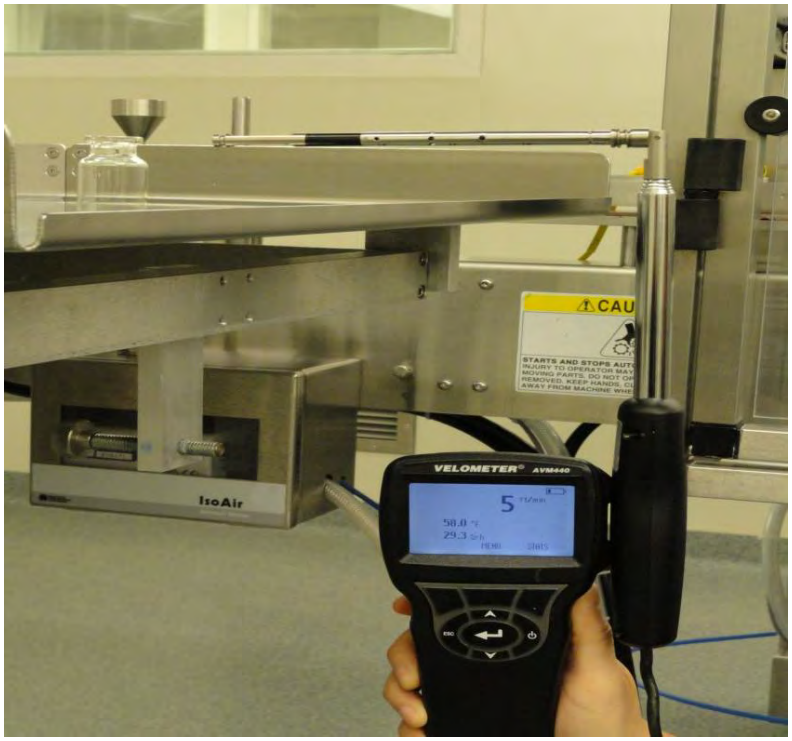
Air Flow Visualization

- **Velocity Testing**
  - Hotwire 18-Inches from work height



Air Flow Visualization

- **Velocity Testing**
  - Work Height, Vertical



Air Flow Visualization

- **Velocity Testing**
  - Work Height, Horizontal

Air Flow Visualization

- **Volume Testing**
  - Take the velocity at filter face
  - Calculate the area of HEPA Filter surface
  - Determine the volume of the room
  - Compute the room air exchanges
    - The number of times the entire room volume exchanges within 1-hour
  - Most companies use a volume-meter to determine room air exchanges

Air Flow Visualization

- **Volume Testing**

Air Flow Visualization

- **Generation Systems**
  - Titanium Tetrachloride
  - Dry Ice, Carbon Dioxide
  - Glycol
  - Ultra Sonic
  - Liquid nitrogen

Air Flow Visualization

Equipment: Titanium Tetrachloride

Smoke Sticks by TEL TRU

Air Flow Visualization

Equipment: Titanium Tetrachloride

T-T Puffer by TEL Tru

Air Flow Visualization

Equipment: Titanium Tetrachloride

Smoke Sticks by Dragger

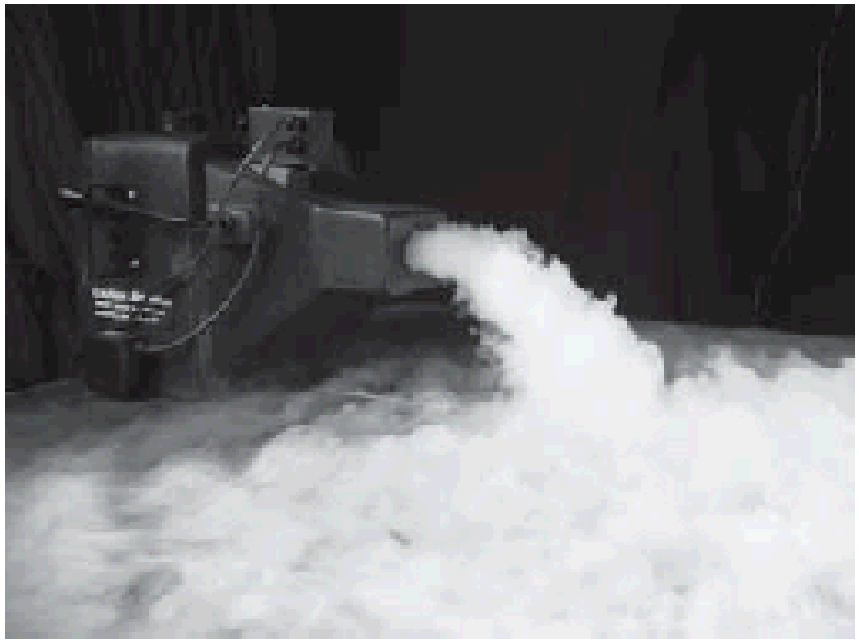
Air Flow Visualization

Equipment: Titanium Tetrachloride

- **Advantages**
  - Small, portable and easy to use
  - Can produce smoke for a maximum or 45 minutes
  - Dragger tubes can be covered and re-used but not stored for a long time
  - Smoke is easily visible
- **Disadvantages**
  - Smoke irritating to eyes and mucous membranes
  - Provides only a single stream of smoke
  - May require multiple tubes to be used at one time
  - Leaves a residue on surfaces
  - Must be shipped by ground

Air Flow Visualization

Equipment: Carbon Dioxide



Pea Souper Machine Model 1800

Air Flow Visualization

Equipment: Carbon Dioxide

Applied Physics Inc. Model 5 CO2

Air Flow Visualization

Equipment: Glycol Based

Portable Generator by Flow-Marker

Air Flow Visualization

Equipment: Glycol Based

Theatrical Stage Fogger & Glycol

Air Flow Visualization

Equipment: Glycol Based

Theatrical Fogger by Battle

Air Flow Visualization

Equipment: Ultra-Sonic

Utility Fogger by Applied Physics Inc.

Air Flow Visualization

Equipment: Ultra-Sonic

Clean-Air Trakker by Clean Air Solutions

Air Flow Visualization

Equipment: Ultra-Sonic

SISTEMA-MK

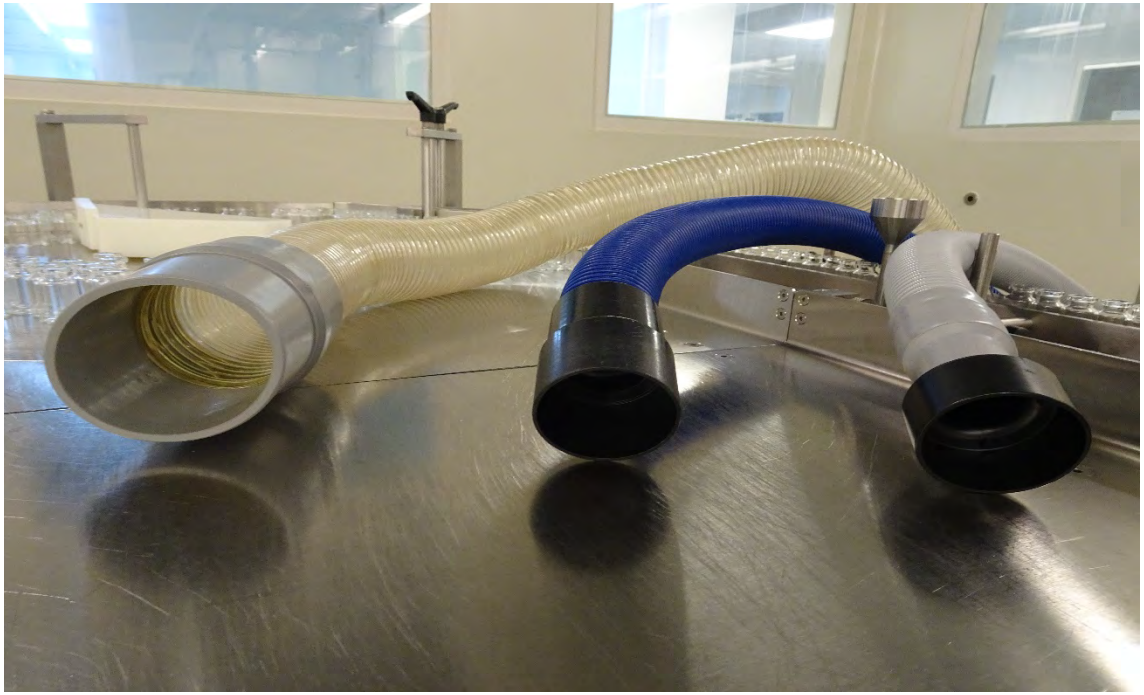
Air Flow Visualization

Equipment: Liquid Nitrogen

MSP Model 2001

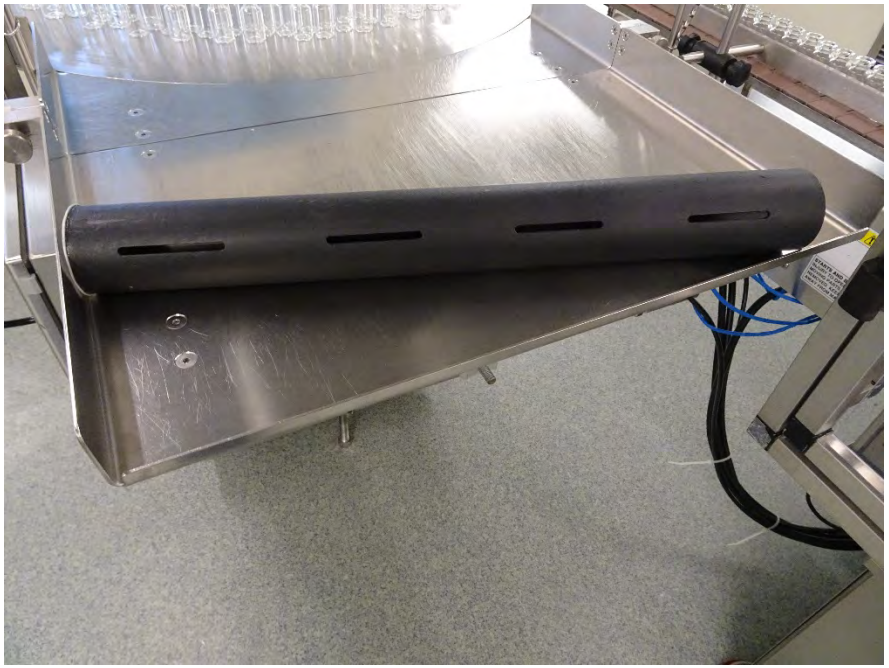
Air Flow Visualization

- **Equipment**
  - Smoke comes directly from hose



Air Flow Visualization

- **Equipment**
  - Smoke delivered through wand



Air Flow Visualization

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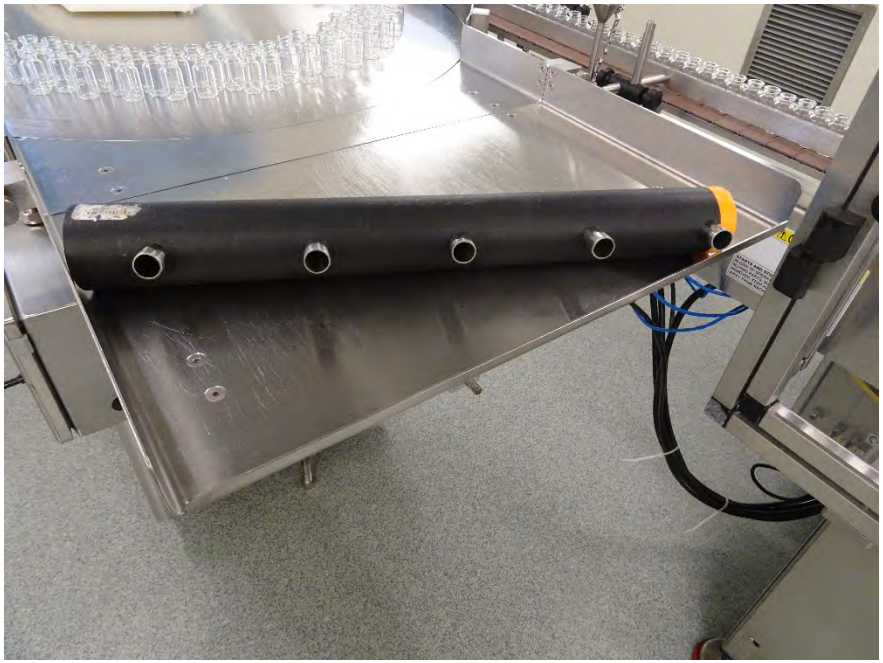
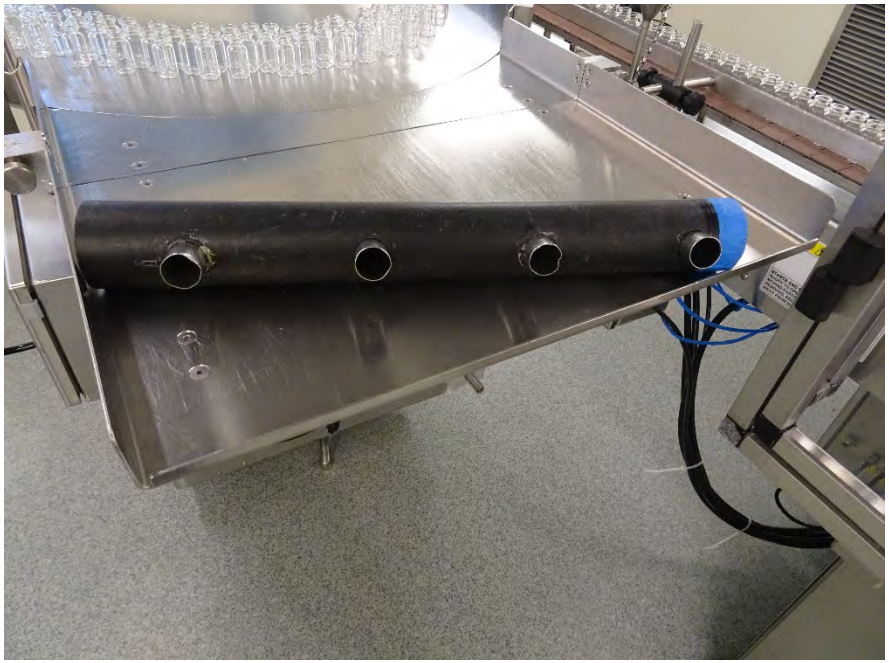




Air Flow Visualization

- **Equipment**
  - Smoke delivered through wand

Air Flow Visualization

- **Frequency of Testing**
  - During validation of new facility
  - After modifications to an existing facility
  - If HEPA velocities are not within 90 ft./min ± 20% (72 – 108 ft./min)
  - Full evaluation not required on a routine basis*

Air Flow Visualization

- **Frequency of Testing**
  - For a new facility, recommend performing airflow testing once a year for the first three years
  - Subsequently, perform as built airflow studies on a periodic basis and compare to the previous as built
    - Confirm there is no difference based on the video and protocol
    - Recommend every 2-3 years

Air Flow Visualization

- **Testing Requirements**
  - HEPA certification signed off
  - Air balancing between rooms must be approved with all documentation completed
  - Balance the airflow within the fill room
    - This is extremely critical to the process
      - ✓Left to right
      - ✓Front to back

Air Flow Visualization

- **Testing Requirements**
  - Confirm there are no blockage of the air returns
    - For air returns with grills in the wall, use a stainless steel rod with a polished stainless steel plate at the end to check for blockage
  - No alarms with BMS system associated with differential pressure system

Air Flow Visualization

- **Testing Requirements**
  - Evaluate the velocities at the returns
  - Differential pressures cascade set and signed off
  - Room exchanges defined
  - Door interlocks must be defined and working properly

Air Flow Visualization

- **Testing Requirements**
  - Doors
    - Justification for duration the door can be open
    - Speed at which the door opens and closes
    - Define if seals around the door are required
  - Facility ready for operational use

Air Flow Visualization

- **Phase I Testing**
  - Video tape the airflow study
  - Assess the condition of the filling line to ensure there are no areas with significant turbulence
  - If turbulent areas are noted, assess if it can/will increased the risk to the process
  - If the answer is yes, the area must be modified to minimize and/or eliminate the turbulence

Air Flow Visualization

- **Phase I Testing**
  - Sterilized are not on the filling line
  - Evaluate the Grade-A ceiling areas at 06 – 12 inches from the HEPA filter
  - Gowning not required but recommended for all personnel that would be in the video

Air Flow Visualization

- **Phase I Testing**
  - Evaluate for turbulent areas based on
    - Blank ceiling tiles
    - Ceiling and wall interface
    - Lights and Sprinkler heads
    - HEPA grid system
    - Top and corners of the filling cabinet if applicable

Air Flow Visualization

- **Phase I Testing**
  - Automated door opening system
  - Opening the lyophilize doors
  - Storage racks near ceiling
  - Pass through doors into the clean room
  - If the filling cabinet has self contained HEPA filters, this area must be evaluated
  - Evaluate for turbulent areas based on
    - Curtain areas at the ceiling

Air Flow Visualization

- **Phase II Testing**
  - Performed 18 - 24 inches above critical Grade-A processing areas
  - Evaluate airflow towards the air returns
  - Assess when the doors to the room are opened and closed
  - Lexan doors to access the critical areas opened and closed
  - Evaluate when the pass through is open and closed

Air Flow Visualization

- **Phase II Testing**
  - Evaluate the results to determine if there are any design issues that can cause significant airflow issues
  - If any of the following are observed, re-evaluate air balancing within the room
    - Turbulent air over critical areas
    - First Air concepts are not in place
    - Air flows from dirty to clean

Air Flow Visualization

- **Phase II Testing**
  - Interior of filling cabinet does not allow proper air flow within the cabinet
    - Increase the open area at the bottom of the filling cabinet deck and the Lexan
    - Cut large slats into the cabinet
    - Do not drill holes because it becomes extremely difficult to clean and sanitize

Air Flow Visualization

- **Phase II Testing**
  - Curtains can interfere with the airflow
    - Air can flow over the curtains into the critical areas
    - When operator open the curtain, air can interfere with the First Air to the process
    - Air is forced down into the process as apposed to towards the operator

Air Flow Visualization

- **Phase II Testing**
  - Modify the curtain length to optimize the process
  - The curtain is
    - 12-inches off the floor
    - 12-inches below the processing height
    - At the work height
    - 12-inches or more above the processing height

Air Flow Visualization

- **Phase II Testing**
  - Ensure environmental monitoring locations do not impact the critical areas of filling operations
  - Lexan covers/shields do not allow easy access to critical locations
  - Doors open to a lower classified area
  - HEPA filter not over entire critical processing areas

Air Flow Visualization

- **Phase III Setup**
  - Confirm all issues from Phase I and II have been addressed
  - Evaluate how each piece of equipment is introduced into the filling cabinet/area
    - What are the orientation of the operators during operations
    - Can air flow off the Support or Aseptic operator onto the wrapped packages

Air Flow Visualization

- **Phase III Setup**
  - Evaluate how bio-shield/covers on sterile items are removed
  - How is the sterile wrap removed from the filling cabinet
    - Is it placed into a trash receptacle
    - Do the operators hands fall below work height when placing into the receptacle

Air Flow Visualization

- **Phase III Setup**
  - Assess how equipment such as bowls or hoppers are installed
  - Assure the airflow goes from clean to dirty
  - Determine the areas that should to be sanitized after set up

Air Flow Visualization

- **Phase III Setup**
  - Evaluate critical operations for First Air
  - Determine where personnel can/can not stand in proximity to the critical areas
  - Include fill volume/weight check
  - Assess the locations where hands are sanitized with alcohol

Air Flow Visualization

- **Phase III Setup**
  - Ensure environmental monitoring personnel are involved at this phase
    - Assess the set up of viable air and particulate counting systems
    - Evaluate changing plates
    - Review how equipment is sanitized in the clean room
    - Confirm EM does not impact the aseptic process

Air Flow Visualization

- **Phase IV Dynamic**
  - Equipment running and operational
    - Filling
    - Loading stoppers
    - Stoppering
    - Loading stoppers and caps
    - Capping
    - Vials exiting the fill room

Air Flow Visualization

- **Phase V Interventions**
  - Perform all interventions
    - Assess for First Air concepts
    - Optimize placement of personnel while performing an operation
    - Enhance the process if the potential for contamination is significant

Air Flow Visualization

- **Phase VI Final Report**
  - Complete Airflow Report
    - Ensure all issues defined in each Phase has been addressed
    - Optimize all operations and procedures based on the air flow

Air Flow Visualization

- **Phase VI Final Report**
  - Airflow must not present a contamination risk to the process.
  - Airflow patterns must confirm that particles from personnel, operations or equipment will not flow into a zone of higher product risk

Air Flow Visualization

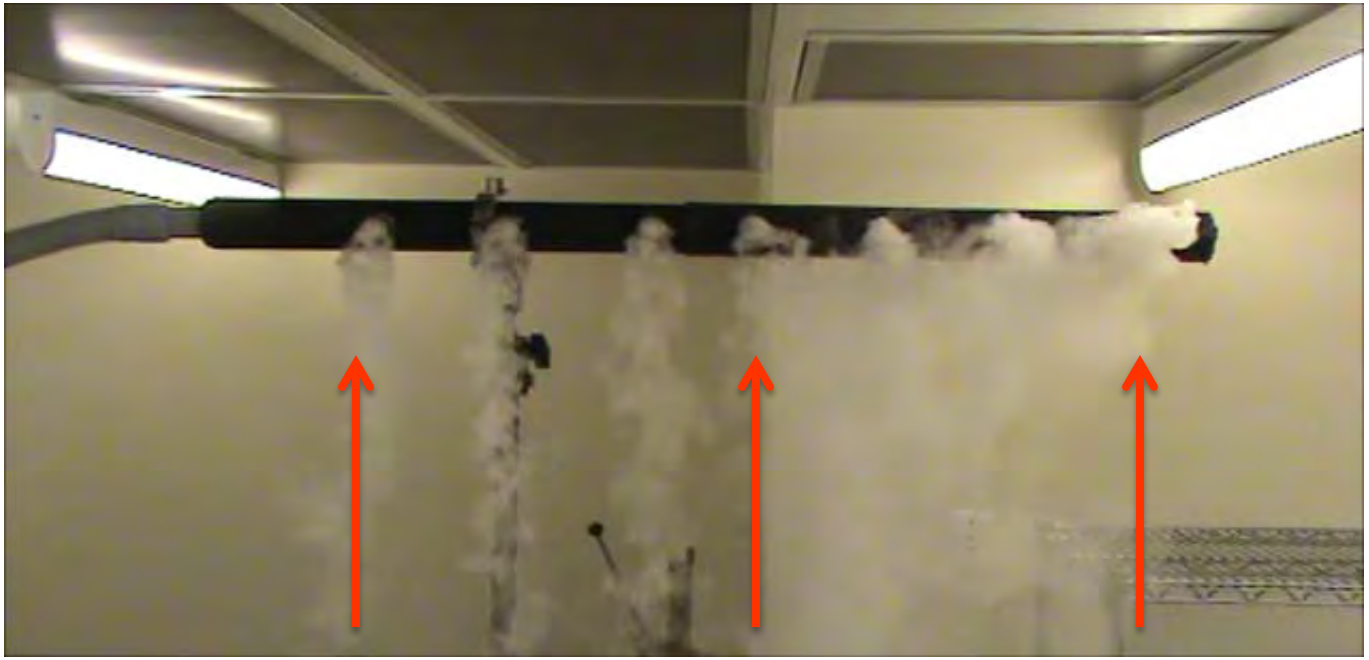
- **Phase V Final**
  - **Evaluation Criteria**
    - **(+++)** Excellent airflow, unidirectional airflow with no turbulence, no breach in First-Air
    - **(++)** Good airflow, slight disruption of unidirectional airflow and/or First-Air, no significant impact on aseptic operations
    - **(+)** Adequate airflow, with disruption of unidirectional airflow and/or breach of First-Air. Acceptable conditions for aseptic processing if procedurally controlled. Sanitization post operation and/or end of fill Environmental Monitoring may be required
    - **(-)** Turbulent airflow with significant swirling and/or tumbling that could compromise the procedure and/or product

Air Flow Visualization

- **Phase VII Training**
  - Use airflow evaluation for aseptic process training
    - Operators should review once per year as part of routine training
    - New employees should review airflow testing as a part of training

Air Flow Visualization

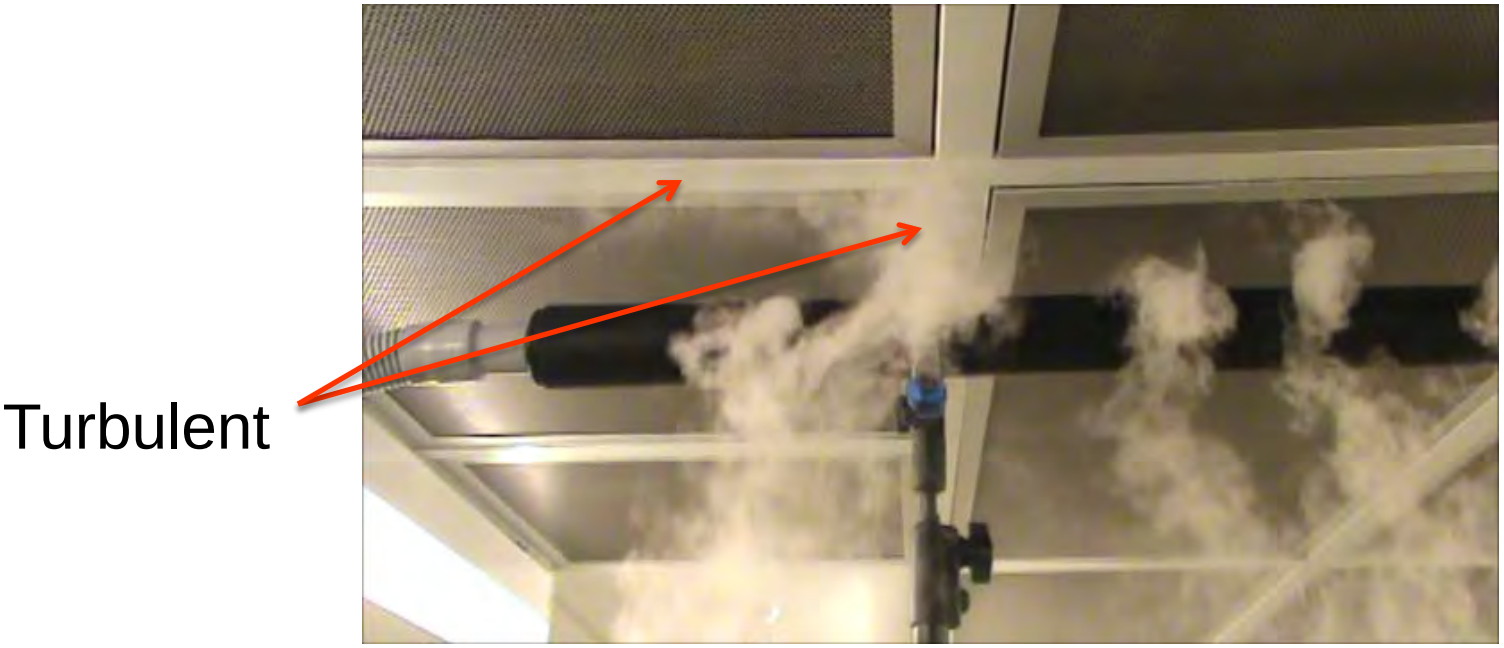
- **Airflow Examples**



Unidirectional Mixed Turbulent

Air Flow Visualization

- **Airflow Examples**
  - Turbulent air at the HEPA grids

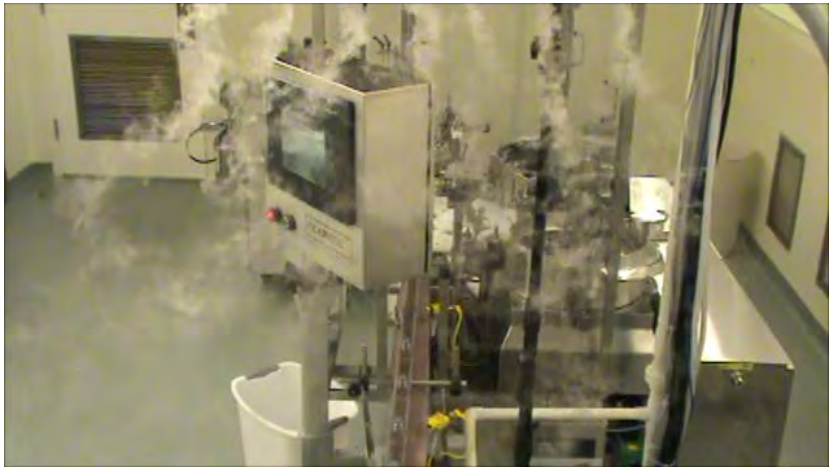


Air Flow Visualization

- **Airflow Examples**
  - Unidirectional air inside/outside cabinet

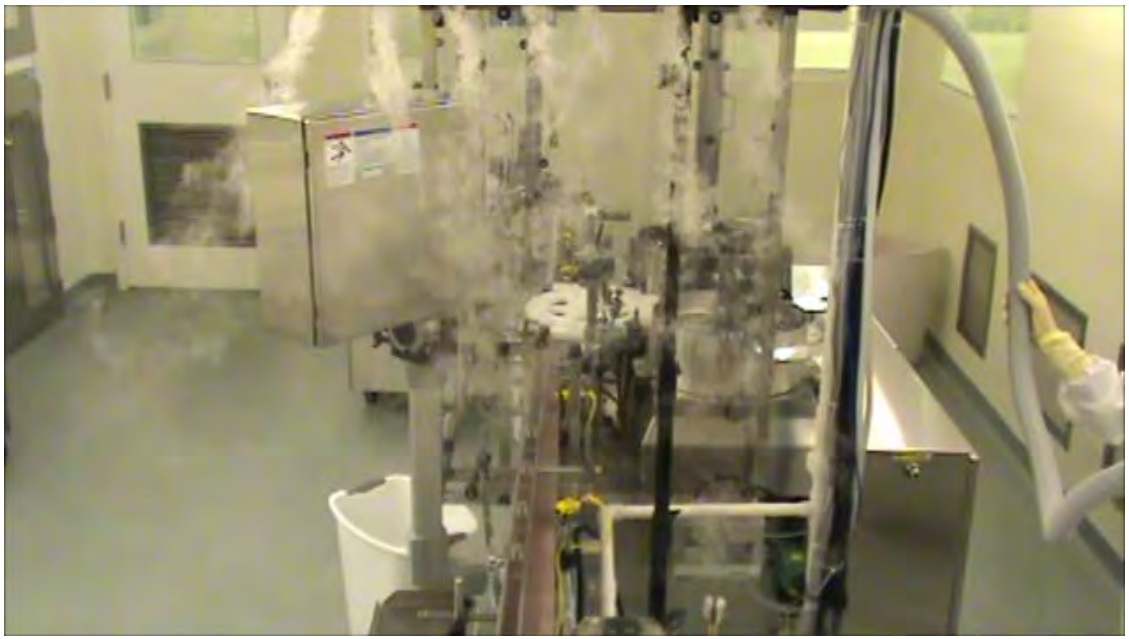
Air Flow Visualization

- **Airflow Examples**
  - Location of HMI screen



Air Flow Visualization

- **Airflow Examples**
  - Optimal position for the HMI screen



Air Flow Visualization

- **Assess the process as well as the EM locations**

Air Flow Visualization

- **Airflow Examples**
  - Loading viable air heads. Sample and exposed vials remains in First-Air

Air Flow Visualization

- **Airflow Examples**
  - Aseptic connection points remain in First-Air

Air Flow Visualization

- **Airflow Examples**
  - Aseptic connection points in First-Air

Air Flow Visualization

- **Airflow Examples**
  - Installing the filling needle using sterile forceps. Note, needle stays in First-Air at all times

Air Flow Visualization

- **Airflow Examples**
  - Removing the sterile wrap and setting filling needle

Air Flow Visualization

- **Airflow Examples**
  - Lowering needle into position

Air Flow Visualization

- **Airflow Examples**
  - Note the different body positions

Air flows over operator onto the sterile open bag

First-Air to the bags

Air Flow Visualization

- **Airflow Examples**
  - Airflow towards the operator keeping the tray of vials in First-Air

Air Flow Visualization

- **Airflow Examples**
  - Forceps tips up or down? Think First-Air

Air Flow Visualization

- **Airflow Examples**
  - Blocking airflow coming out of the stopper bowl creating turbulent air under the bag

Air Flow Visualization

- **Airflow Examples**
  - Loading stoppers from left side is high risk. Note the stoppers are facing up

Product contacting side facing up and exposed

Air Flow Visualization

- **Airflow Examples**
  - Loading stoppers from right side is lower risk. Note the stoppers are facing down

Product contacting side facing down and covered

Air Flow Visualization

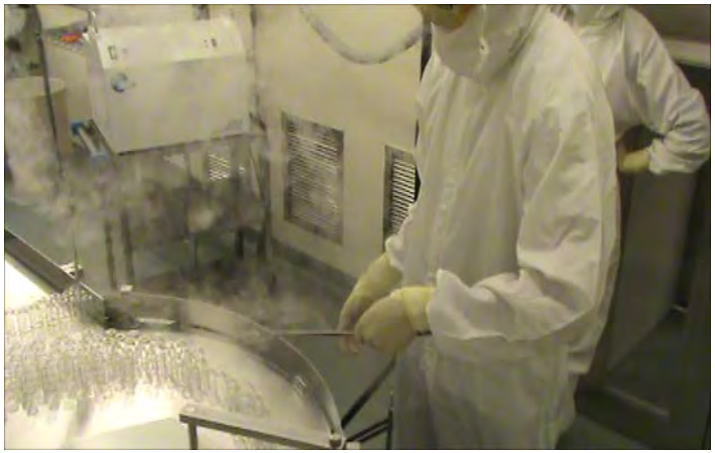
- **Airflow Examples**
  - Removing stopper jam

Hand over bowl

Hand on the side of the bowl

Air Flow Visualization

- **Airflow Examples**
  - Removing fallen vial. Note hand position not over the turn table. Vials in First-Air



Air Flow Visualization

- **Airflow Examples**
  - Removing tray of vials

Sub-optimal
filming position

Air Flow Visualization

- **Airflow Examples**
  - Optimal film position from the left and right sides. Air flows towards operator

Air Flow Visualization

- **Manual Stoppering**
  - Air flows over operator onto the open vials

Air Flow Visualization

- **Manual Stoppering**
  - Air flows towards the operator keeping the vials in First-Air

FDA Smoke Studies Expectations

- To visualize air flow patterns.
- Performed in Aseptic Processing Areas.
- Typically recorded for analysis.
- Performed under static and dynamic conditions.
- Dynamic test should include all operator interventions.

FDA Smoke Studies Expectations

Goals:

- Verify unidirectional air movement from HEPA filters to open product back through returns with a general sweeping action.
- No upward air movement.
- No stagnant areas.
- No refluxing, billowing, channeling or eddy current air patterns.

FDA Smoke Studies Expectations

Goals:

- Unidirectional air flow through process equipment not compromised.
- Large flat areas should not create upward flow.
- Capper/stopper pistons do not disrupt airflow patterns.
- Operator contaminants not swept over open product.

FDA Smoke Studies Expectations

Goals

- Return locations provide proper direction of air exiting critical zone.
- Open area below process equipment for exiting air.
- Sufficient return/exhaust volume to prevent turbulence.

Inspection Observations

- Failure to establish and follow adequate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)].

Inspection Observations

- The following were either 483's and/or Warning Letters:
  - Smoke studies do not fully demonstrate airflow movement away from work surfaces during personnel activities and manual simulations of the aseptic processes as is required by your SOP. Your 483 response does not address this issue and does not offer any corrective action.

Inspection Observations

- Smoke studies do not represent the aseptic process in the fill room.
- Airflow studies are not conducted during Dynamic Conditions.
- Smoke generator does not generate adequate smoke to evaluate the aseptic process.

Inspection Observations

- No training records were available for personnel performing the airflow studies.
- Personnel reviewing and approving airflow studies do not have adequate training to assess the airflow and the impact on the aseptic process.
- Airflow SOP's did not include sufficient detail to perform and assess the acceptance criteria.

Inspection Observations

- Airflow approval matrix did include the same signature matrix as the initial protocol.
- The acceptance criteria was not clearly defined as acceptable or not. Therefore there was no conclusion.
- Airflow acceptance criteria was defined as no turbulence in the Grade-A Areas. However non-unidirectional airflow was noted in numerous locations.

Inspection Observations

- The smoke was only introduced in one direction and therefore did not provide accurate evaluation of the process.
- Filming of the process only showed one angle. Therefore, the process could not be properly evaluated.
- Cleanroom storage racks and return vents were not evaluated during the airflow study.

Inspection Observations

- The airflow showed that the operators hand and equipment was directly over critical areas which increases risk to the product.
- While loading stoppers, air flowed over the operators gloves into the stopper bowl.
- All interventions are not evaluated during airflow studies.

Inspection Observations

- Smoke studies were not performed during freeze dryer loading and unloading.
- Airflow studies for loading the freeze dryer was performed at room temperature and not chilled to 2-8 °C.
- Personnel setting up the fill machine was between the cart and the filling machine. Air flowed over the operator onto all the wrapped parts.

Inspection Observations

- The wand was moved too quickly through the process. Therefore it was difficult to evaluate unidirectional flow.
- Various critical process points were not included in the final video. However, evaluation of the original clips revealed turbulent airflow in these areas.
- There were excessive items in the LAF which caused turbulent airflow in the enclosure.

Inspection Observations

- The light is located between the HEPA filters. The spacing was large which created turbulent air to the process
- Stopper bowl is located against the Lexan barrier which creates a turbulent airflow above the bowl.
- Airflows into the stopper bowl while installing and tightening bolts.

Inspection Observations

- The back lighting in the video used a red light which made it difficult to see the airflow to the process.
- The smoke exited the wand with excessive velocity, which made if difficult to determine unidirectional air flow to the process
- All the original video clips were not retained for the airflow study.

Inspection Observations

- The orientation of the wand caused turbulent air to be delivered to the process. This was deemed acceptable.
- Smoke exited the end of the hose, which made it difficult to determine if unidirectional air was present.
- The operators head was observed in the LAF.

Inspection Observations

- There were two operators in the LAF, which created turbulent airflow to the process.
- The BSC sash was at or below the define protection level during the airflow study. During production, the sash was well above the defined line.

Inspection Observations

- The smoke was surging while exiting the wand. It was unclear if the airflow was turbulent or unidirectional.

- Excessive amount of smoke was delivered to the process. It was unclear if the airflow was turbulent or unidirectional.

Air Flow Visualization

- **Take Away Message**
  - Evaluate airflow video to evaluate their aseptic process
  - Airflow must represent the entire process, setup, interventions environmental monitoring and adding commodities
  - Determine if airflow is a part of aseptic training
  - Assess the risk based on airflow