Airflow Visualization / Aseptic Process Simulation

#sharing challenges and solutions in practice

GMP/FDA Compliance Conference

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Content

Airflow Pattern Visualization

- Regulatory background
- Life Cycle
- Prerequisites / Techniques
- Neutral buoyancy

Link to APS

Aseptic Process Simulation

- Prerequisites
- Preparation
- Execution
- Documentation

Regulatory Background

EU GMP Guideline, Draft Annex 1 (V12, 2020)

Premises

4.4 Grade A: …the maintenance of unidirectional airflow should be demonstrated…
Grade B: …airflow visualization studies should demonstrate that air does not ingress...

4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade… at rest and in operation… video recording...

4.20 RABS & open Isolator: UDAF ... closed Isolator: … demonstrated protection…

4.21 RABS…absence of air ingress during interventions, … door openings.

4.27 iv. As part of the cleanroom qualification… airflow direction and visualization

Personnel

7.19 Airflow visualisation studies … part of the operator's training programme.

see appendix

Regulatory Background

ISO 14644 Cleanrooms and associated controlled environments Part 3 - Test Methods (2019)

ISO International Organization for Standardization

4.2.3 Purpose of airflow direction test and visualization is to demonstrate that the airflow direction and its uniformity of velocity conform to the design and performance specifications

B.3.3.1 Tracer Thread Method	B.3.3.2 Tracer Injection Method		B.3.3.3 Image Processing	B.3.3.4 Measurement of velocity distribution
observing of filaments nylon fibers or thin foil tapes	Imaging of the fog behaviour DI, WfI, N_2, CO_2 alcohol / glycol	+	Video filming of B.3.3.1 / B.3.3.2 and their assessment	Anemometer thermal or ultrasonic

Why do we perform Airflow Visualization Studies ?

To provide visual evidence

- Critical location in A / B
- Unidirectional Airflow
- Overspill (RABS, mousehole open Isolator)
- Differential pressure
- Protection of critical operations
- First Air Principle
- Absence of dead spaces or turbulences
- Operation conditions (as built, at-rest, in-operation)
- Interventions (inherent, corrective, monitoring)

To provide supporting information

- Defining locations for EM programs
- Defining location CI and BI for VHP decontamination cycle development
- Recovery time
- Training purposes
- Investigations

- *may be to assess airflow in C & D*

Life Cycle

Initial Qualification

- Commissioning of new
  - cleanroom / barrier system
  - the equipment within
- Implementation of new
  - processes
  - interventions

Requalification

- event-related, change of qualified / validated condition with possible influence on airflow
  - operation / process / loading scheme
  - cleanroom (incl. inlet / exhaust) / barrier system
  - interventions
- periodically, via risk-based approach of unchanged
  - cleanroom, barrier system, equipment within
  - processes and interventions
  - intervention: check the possibility of grouping

Periodic Review

- periodically documented check if unchanged situation is given

Prerequisites and Techniques

Facility, Barrier System, Equipment

- Completion of OQ (cleanroom, HVAC, filler, etc.)
- Equipment incl. HVAC must work within production air velocity and differential pressure specifications --> Prerequisite, so proof it !
- EM sampling equipment in place and if possible, in operation
- Calibrated systems and sensors
- Studies performed under CNC, but HVAC system running under class A condition

Personnel

- Well trained staff, gowned as during routine production, qualified for interventions
- Detailed procedure for interventions

Prerequisites and Techniques

Video recording

- HD video camera, if necessary, several from different perspectives
- Synchronization
- Black background for proper contrast, if necessary, specific light sources
- Recording from outside and inside
- Sufficent recording time

Fog feed

- Flexible hoses, with or without extension
- Fog curtain or punctual feed
- At 90° to the laminar air flow
- From clean to less-clean
- Parallel to windows

Tracer Injector

- Evaporator, ultrasonic
- Water (de-ionized or WfI)
- Liquid nitrogen
- Carbon dioxide
- Alcohol / Glycol

Documentation

- SOP, Protocol, Script (Testcase), Report
- Predefined acceptance criteria
- Air velocity and differential pressure
- Operating conditions
- Areas and structures to be visualized
- Clear identification of the scenes
- Interventions
- Results and Deviations
- Involved Personnel (during visualization and assessment of videos)

- Videos are raw data (Data Integrity)

Neutral buoyancy...

Tracers should **not** become a source of contamination

--> Therefore, tracers such as water (DI or WfI), nitrogen, a mix of both, or carbon dioxide are widely used as they are residue-free substances

Tracer should **not** diverging in motion from that of the airflow being observed

- Gravity, buoyancy, size and the temperature of the particles have an influence on the behavior of the particles during the visualization study. Dead spaces or turbulences may not be detected

  --> Therefore, the call for particles with neutral buoyancy is getting louder and louder

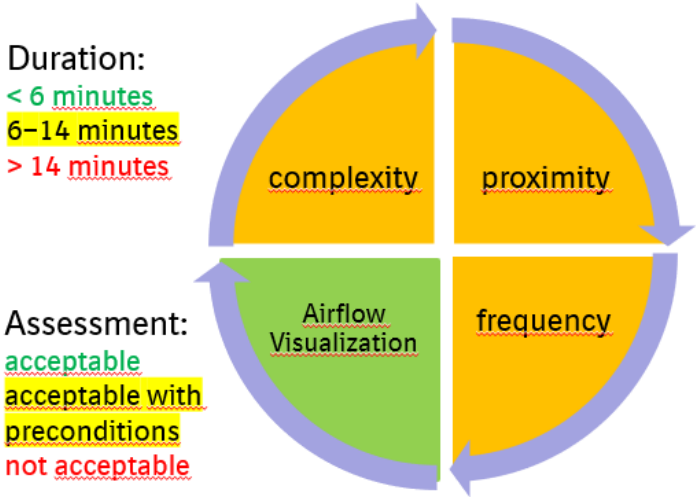
  (DRAFT Guide for Critical Airflow Visualization)

- Alcohol, glycol should have a neutral buoyancy
- Thorough cleaning is necessary after the visualization study

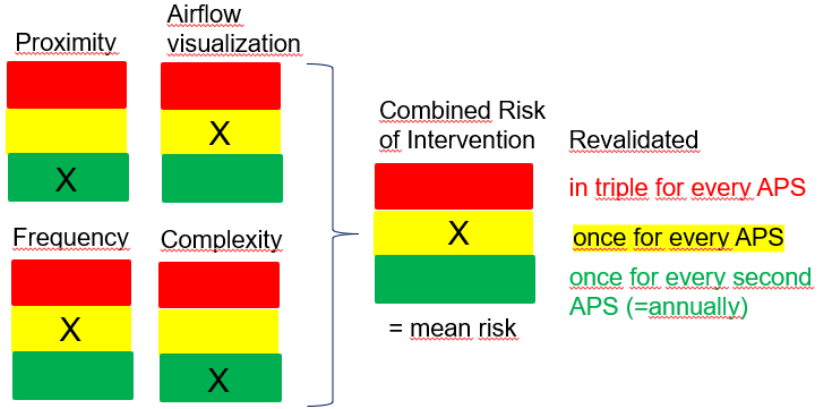
Airflow Visualization Study <--> Aseptic Process Simulation

BI Case Study: Risk based approach for aseptic interventions

objective process with 4 variables and 3 risk levels



Translation into Risk Prioritization Number



Interventions with rating „high risk“ during airflow visualization won‘t be validated, these interventions are not allowed

ASEPTIC PROCESS SIMULATION (MEDIA FILL)

Target

- to evaluate the capability of aseptic processing activities, using microbiological growth promoting media in place of product.

Scope

- APS simulates the aseptic process from the product and component sterilization to final sealing of the container.

Execution

- The media is made to contact all product contact surfaces of the equipment chain, container closure, critical environment and process manipulations which the product itself will undergo.

Simulation of routine production

APS shall include all critical manufacturing steps, specifically:

- All sterilization and decontamination cycles performed up to the sealed container.
- Additional evaluation of aseptic steps for non-filterable formulations.
- For inert atmosphere: replace inert gas with air; exception: anaerobic simulation is intended
- For processes where sterile powders must be added, acceptable substitute material in containers should be used
- The process simulation procedure for lyophilized products should represent the entire aseptic processing chain.
- Simulation of the lyophilization process should duplicate all aspects of the process except those that may affect the viability or recovery of contaminants.

Target -> simulate routine production as closely as possible

APS - allowed differences from the routine

Used containers

To allow any assessment of growth at all, amber glass containers or otherwise opaque containers should be replaced with white glass.

Inert gassing

Typically Nitrogen or other inert gases are used to protect oxygen-sensitive products and also to provide positive pressure for transfer. For APS the Nitrogen should be replaced by air using the same method of delivery and at the same steps.

Which Media Fill is the right?

A microbiological growth medium (e.g., soybean casein digestion medium) should be used; anaerobic growth medium (e.g., liquid thioglycollate medium) **should be used only under special circumstances.**

Special circumstances:

If the process is carried out under inert gas, the following procedure is recommended:
Initial media fill with aerobic and anaerobic media.

Regular anaerobic monitoring is expected for processes in which filling takes place under inert gas. If anaerobes are detected, then it must be checked in the action plan whether a media fill with thioglycolate medium is required.

How often and how many APS?

The number and type of APS should be based on Risk Assessment of the aseptic process.

Initial

-Qualification/validation of a new facility or new production process. APS is one of the last steps in the validation process.

Typically, a minimum of 3 APS are expectation.

Re-Validation

-Semi-annual APS are expectation for qualified lines/ processes.

-after major changes to aseptic process

Risk-based approaches

The risk assessment should be used to define the worst-case manufacturing scenarios for

- operating conditions-including personnel
- interventions
- container closure
- size and configuration
- line speed
- batch size

The Risk Assessment is the basis for the design of the APS.

APS design

APS design should include “worst case” activities and conditions as identified during risk assessment.

- Determination of worst-case conditions for relevant variables.
- Determine representative sizes of container / closure combinations to be used for validation.
- Volume filled per container should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product.
- The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.
- Maximum allowable holding times for sterile products and associated sterile components and devices.
- Method for detection of microbial contamination should be scientifically justified
- Selected culture medium should be capable of growing a specific group of reference microorganisms
- Process simulation should be of sufficient duration to challenge the process, operators, interventions, etc.

Interventions – inherent and corrective

The interventions are grouped into two categories – inherent and corrective

The risk assessment should be used to evaluate the contamination risk due to each intervention.

The type and frequency of each intervention must be identified.

These interventions must be demonstrated as part of the airflow visualization and must be performed under the same conditions as part of the APS.

List and process for Interventions

There should be an approved list of interventions. This list is to be re-evaluated regularly.

There should be established procedures that describe how to perform these interventions.

Only personnel trained/qualified in the interventions should be permitted to perform them.

During an APS these interventions should be incorporated to represent the type and frequency of each type on the approved list.

During routine production operations, any interventions performed should be documented and frequency noted.

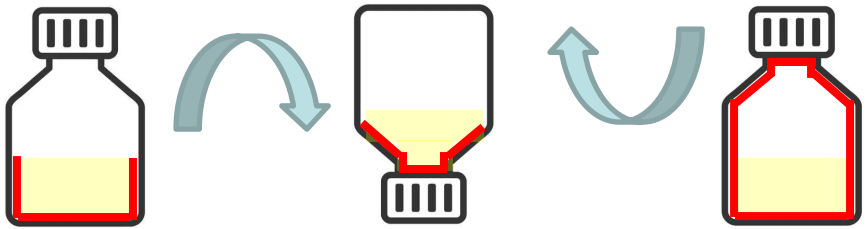
If any unusual interventions are performed, they should be evaluated, and a Risk Assessment performed, as necessary. Based on the risk/evaluation they should be incorporated into the approved list of interventions for APS.

Preparation for incubation

The filling volume should be selected in such a way that the amount of air after closing the container is sufficiently large to ensure germ growth.

Furthermore, make sure that the entire inner surface of the container (including closure) comes into contact with nutrient medium.

This is usually achieved by turning the containers before incubation.



Test units filled with media must be incubated accordingly for at least 14 days.

Incubation conditions according to Ph. Eur:

Soybean-casein-peptone media: 20-25 °C.
Thioglycolate media: 30-35 °C

Incubation

Pre-incubation inspection

The purpose is to remove all non-integral units which would have been removed during normal product inspection. Some examples of units which maybe removed are units with cracks, misaligned or missing stoppers, poor crimps- units with compromised container closures.

Incubation conditions

It should be in the range of 20-35 °C. Incubation time should be not less than 14 days.

A single incubation temperature for 14 days or two temperatures for 7 days each may be used.

Post –incubation inspection

After completion of incubation, all APS units are inspected visually for the presence of microbial growth. Personnel trained to detect low/high levels and different types of microbial growth should perform the inspection.

APS for lyophilized products

Process time:

A shortened residence time in the freeze-drying chamber is generally permissible if all risk factors are adequately simulated.

Freeze-drying process simulation:

The process of loading the partially stoppered units into the lyophilizer, lyophilization process and the final unloading of the chamber must be captured during an APS

For the freeze-drying simulation the vacuum should be interrupted at least twice by chamber ventilation. Sterile air is used to vent the chamber instead of Nitrogen.

Personel Qualification for APS

The requirements and the process for the qualification of personnel should be documented in a procedure and results documented and records maintained per each person.

Pre-requisite

all relevant training such as gowning qualification, clean room and aseptic behavior training, GMP training, procedure training, Initial Qualification- Personnel should participate in a successful APS in which they perform activities which they would normally perform.

Periodic Qualification

Personnel should participate in a successful APS in which they perform activities which they would normally perform once per year at a minimum. Disqualification can occur if the personnel fail to participate in periodic qualification, fail gown certification repeatedly, participate in a failed APS whose failure was directly attributed to their poor aseptic technique.

APS documentation

The APS documentation should include the following informations:

- Derivation for “worst case” scenarios and type of media to be used
- Equipment, room, process flow, filling line and line speed
- Types of container closure to be used and fill volume
- The rationale for the number of units to be filled
- Number and types of interventions
- Environmental monitoring
- Incubation conditions and durations
- Inspection results for pre-incubation inspection and post –incubation inspection
- Conditions of exclusion of vials from incubation
- Conditions for invalidating/cancelling

Thank you for your attention

QUESTIONS ?

Appendix: Regulatory Background

FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (2004)

FDA U.S. FOOD & DRUG ADMINISTRATION

IV. Buildings and Facilities

A. Critical Area – Class 100 (ISO 5)

… it is crucial that airflow patterns 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 … to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions … impact of aseptic interventions, equipment design… Videotape…

Appendix: Regulatory Background

PIC/S PE 009-16, Annex 1 (2022)

3 *Grade A: …the maintenance of laminarity should be demonstrated and validated…*

53 A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively.

54 *It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.*

Appendix: Regulatory Background

USP <797> Pharmaceutical Compounding—Sterile Preparations

Facility Design and Environmental Controls

The airflow … shall be unidirectional (laminar flow), … "first air" free from airborne particulate contamination. … In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.

USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments

Clean Room Classification

… In the evaluation of air movement within a clean room, studying airflow visually by smoke studies or other suitable means is probably more useful than using absolute measures of airflow velocity and change rates…