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Smoke Study-First Air, EU Annex 1, CFD and Regulatory Expectation:

Good Manufacturing Practices (GMP) related to sterile product aseptic manufacturing environments rely on protective airflow mechanisms to ensure the control over airborne contamination. Alongside the protective airflow, pressure differentials that drive airflow cascade ensure GMP compliant contamination control of airborne contamination that may include Microbial carrying particles (MCPs). Airflow visualisation qualification by smoke studies has been clarified as a GMP requirement in EU & PICS Annex 1. The scope of Annex 1 applies to manufacture of sterile medicinal products together with bioburden control processes where bioburden in intermediates, substances, APIs and non-sterile products can also impact patient safety so a wide scope of protective airflow applications is applied.

As a GMP requirement (included in 2008 version of Annex 1): 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.'

Within Annex 1: 2023, the concept of First Air has emerged as a critical element. First Air is defined as "filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone."

The requirement for extensive smoke studies and the integration of First Air protection as a mandated aspect in GMP regulations has brought to the fore an imperative need for a deeper comprehension of airflow dynamics and their implications on sterile product Aseptic manufacturing. This shift beckons us to explore the nuances of protective airflow, particularly in the context of **Computational Fluid Dynamics (CFD) analyses,** to discern the efficacy of airflow patterns in different scenarios.

Computational Fluid Dynamics (CFD) is the branch of mechanics which deals with heat transfer, mass transfer and momentum transfer associated with fluid. It is a powerful analytical tool that enables project teams to **identify, visualize, and interrogate solutions to engineering problems** before putting real-world resources at stake.

Stakeholders involved in Annex 1 implementation have been impacted by introduction of the First Air protection requirement, considering design and in qualification via smoke study airflow visualisation. Such requirements must follow QRM principles where process understanding and knowledge of contamination hazards are essential to mitigate risks in compromise of product quality and potential harm to patients. Risk mitigations must take a Quality by Design (QbD) approach as monitoring alone does not provide assurance of product sterility or in meeting defined bioburden limits.

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Computational Fluid Dynamic (CFD) models help to understand and characterise protective airflows and attributes at different critical process steps. Protection from airborne contamination is required to prevent a compromise in quality of sterile product, product containers and closures and/ or critical surfaces of manufacturing and Cleanroom technologies that may be an in-direct source of product contamination. Fig.1, below shows CFDs that apply to Aseptic process filling of open containers inside barrier technology where Uni-directional airflow (UDAF) is further characterised with localised 'First Air' protection over critical process points. CFD has the advantage of being able to understand and characterise protective airflows prior to the final design and execution of airflow smoke visualisation studies within manufactured technologies and cleanrooms.

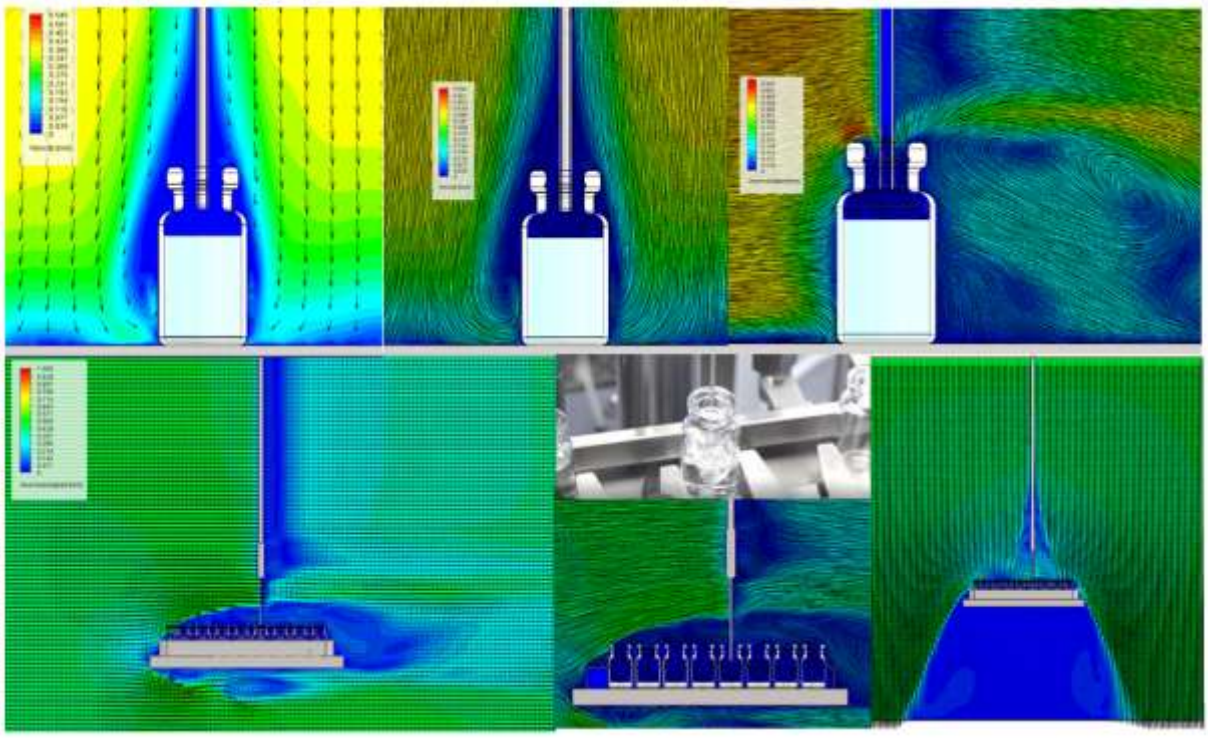

Fig.1. CFD models considering First Air protection of vial containers at Point of Fill considering comparisons of downflow vertical UDAF and Horizontal UDAF for both filling of single vials and filling multiple vials in a Nest. CFD analysis – colours represent air velocity profiles: Blue is zero air velocity.

Analysing what the CFDs inform us about the profile of protective airflow help characterise the attributes of First Air protection and risks of airborne contamination of open containers in Aseptic process filling.

Clearly CFDs indicate there is a significant difference if protective airflows are delivered as downflow Uni-directional airflow (UDAF) and cross flow horizontal UDAF.

Downflow UDAF does provide attributes of protective airflow. However, it becomes clear protective airflow does not sweep into open vials and over sterile product to

keep this critical process point and product clear of airborne contamination as previously thought. Instead, the Vial acts as a 'dead zone' so there is 'dead air' (zero velocity) inside the container. With this characteristic First Air protection is provided as a 'Shield' of protective air around the open container and once this shield is broken or disrupted sterile product in containers are open to contamination .
Cross flow Horizontal UDAF at the point of fill does not exhibit attributes of First air protection as there is excessive turbulence after the airflow passes over an open single container or over a nest of containers. It would be difficult to see how such a horizontal airflow pattern over an open container can be considered as First Air protection hence be in compliance to Annex 1 and QbD - QRM principles.

In further analysis of the CFDs it has also become evident that the 'dead zone' of air inside the container provides an environment where aerosolization of the product occurs. In the filling process localised product aerosolization inside the container and dead air zone can result in product being carried outside the container to both contaminate the outer surfaces of the container and in the locality of filling area.

This risk is particularly important to understand where sterile products are also toxic, biologically hazardous or a GMO: Genetically modified organism e.g. viral vectors. These products require an Aseptic Containment Strategy based on Health Based Exposure levels (HBELs) and OEM Bands of containment with external container contamination must be addressed by appropriate measures that are commensurate with risk.

Protective airflows are defined for different protection requirements relative to criticality. Uni-directional airflow (UDAF) is considered to be inside a barrier system that provides 'People and Process' separation e.g. Isolators and Restricted Access Barrier Systems (RABS). Localised (L)-UDAF is considered for process points where there is at least one open side to the zone of protection e.g. at 'Mouse hole' entry and exits points to Isolators and RABS. Grade A Air supply is protective airflow has been characterised for Capping of vial containers where continuous particle counting, because of inherent particle generation, is not possible.

It is inappropriate to specify Grade A Air supply for any other area than Capping and L-UDAF should be applied and qualified in any other application areas where localised airflow protection is applied. L-UDAF should be qualified to meet the localised protection requirement for airborne particulate levels that apply at the process point subject to protection e.g., L-UDAF; Grade A or L-UDAF Grade B and once qualified environmental monitoring and process monitoring should be applied based on process application and risk assessment.

Definition of First Air protection and clarity

The regulatory expectations of the protective airflow First Air are defined in Annex 1 Glossary; ''*First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone*''

In reality, HEPA filtered airflow supply will be 'interrupted' prior to contacting exposed product and product contact surfaces via contact with Air diffusers and support frames, lighting above the air diffusers, VHP/ vH202 injection nozzles (if applied) and air flow velocity sensors. Any such interruptions should not be impactful to First air protection, meaning air that passes over such surfaces should reform and exhibit uni-directional airflow characteristics when applied at critical points that require airflow protection.

'First Air' commences at the exit of the HEPA filtered air flow supply and en-route to provide First air protection the airflow should not pass over surfaces that provide extraneous particulate and microbial contamination to the protective airflow e.g. they are not particle shedding surfaces and are subjected to a bio-decontaminated/ disinfection process and afterwards are not open to re-contamination.

First air' should not be compromised via disruptive influences that impact First Air protection.

Importantly in any airflow visualisation of protective airflows once the UDAF supply including 'First Air' from a HEPA filtered source has passed the critical point of First air protection any turbulences (non-UDAF) and airflow below that potentially may include additional particulate concentration levels as a result of entrainment from surfaces subject to particulate settlement must not re-introduce into the First Air protection. Considering the CFD example, Fig 1., protective First Air after passing over the Point of Filling (PoF) and open product containers of sterile product should not re-introduce into the UDAF protective First air above the open containers.

Air velocity profiles:
Inside a barrier system there are two UDAF zones that work together to characterise protective airflow. The initial part of protective airflow is above any installed process equipment hence not subjected to significant adverse airflow disruptions. Once the airflow enters into the zone with process equipment with complex surface profiles there are resultant changes of airflow direction and changes in the velocity profile. Some airflows will speed up over surfaces and may slow down afterwards as airflow changes direction. Importantly the airflow velocity qualifications (measurements e.g. 0.45m/s +/- 20%) should apply within the UDAF zone above process equipment so disruptive airflows do not confuse air velocity results. Once the protective airflow flows over process equipment the focus moves to uni-directional airflow patterns with less focus on specific air velocity values.

Airflow visualisation studies and characterisation of profile:
When protective airflow patterns are unknown, typically in new projects it is recommended to characterize airflow via use of CFD models. It is encouraged to include CFDs as part of Design Qualification (DQ) as a risk mitigation to unacceptable outcomes in following formal airflow visualisation qualification via smoke studies. Making design changes after Smoke study qualifications to improve airflow profiles that are considered unacceptable is a significant project risk. Care should be taken in selecting critical points that require CFD studies that are

commensurate with risk as such studies can be extensive, time and resource intensive.
When airflow visualisation study protocols are developed it is important to define expectations of what the protective airflow should look like and where turbulences are expected and considered acceptable e.g. not impacting First Air protection.

Such a definition of expected airflow profiles becomes the acceptance criterion in smoke study protocols to mitigate against subjectivity in assessing smoke study videos as to what is and is not acceptable.

Execution of airflow visualisation needs to be considered in all process stages when protective airflow is required, including set-up (with open barrier doors) in operations and for any inherent and corrective interventions.

The type of smoke generator and integration of smoke supply and distribution and associated camera locations that present the airflow profile as videos for review needs to be part of the airflow visualisation study design.

As a formal qualification requirement airflow visualisation should not be considered as an R&D study with ‘make do’ integration that can compromise at rest and in-operation studies of operational process equipment and operator interactions in processing.

As smoke studies are a ‘contaminating event’ the execution of formal qualification smoke studies should follow environmental control Classification (to ISO14644-1) where (IQOQ) qualified equipment can be run and studies completed without risk of subsequent environmental control setting changes that may impact protective airflow patterns.

Classification is focused around particles only and the ability of the air handling and filtration systems to meet the air cleanliness levels and clean up rates with at rest and in-operation studies completed.

Classification applies before formal Environmental Qualification (to Annex1) where both total particulate and microbial conditions in are established and qualified ahead of APS: Aseptic Process Simulations. Smoke studies are likely to combine different methods of smoke distribution so ‘mass smoke’ (with technical integration for supply and distribution) can be used to assess airflow patterns and airflow cascades together and more targeted studies with hand held smoke generation devices at localised points of identified risk where First air protection is required. CFDs will play an increasing role to help characterise protective airflows at design stages of projects as risk mitigation that an actual airflow pattern will meet protective requirements and First air protection. More CFD studies are required to characterise airflows over the complete filling process e.g. container entries (where L-UDAF may apply), accumulation areas e.g. rotary tables and Point(s) of Fill, stopper feed and insertion (that require First air protection in Grade A UDAF) and Capping with Grade A Air supply protection and interaction of ‘Grade A Air supply’ zone with the adjacent Grade A zone.

The closer to the point of protection where First Air applies where airflow interruptions occur e.g. airflow passing over parts of process equipment the more the risks are of impactful turbulences that may compromise First Air protection, hence aerodynamic design matters in such (and all) critical localities.

Robotics have great benefits but design integration needs to be considered in respect of interaction with First Air protection so benefits are not compromised by adding risks that result in loss of protective airflow. No process is free of contamination risks and although technologies may mitigate risks the integration into a process must follow QRM and QbD principles.

The impact of Annex 1 revision on the aspect of protective airflow is therefore impacting all stakeholders where improvements are considered to be required in aerodynamic design, Airflow visualisation study design and Smoke study execution.

One of the next areas of study in protective airflow will be in environmental monitoring systems and their interaction and detectability at critical process points where First Air protection applies. Continuous Total particle and microbial monitoring is required in Grade A Aseptic processing zones.

It will be necessary to detect when contamination is entering into a critical process point of First air protection and/or there is loss of protection (First air interruption) opening the product and product contact surfaces to risk of airborne contamination.

Annex 1 has now linked Environmental Monitoring (EM) with Process Monitoring (PrM) and in the context of protective airflows the air velocities and pressure differentials are the process parameters of control that need monitoring with associated alarm and response management in deviation from specified levels. (Ref:PHSS)

As a GAMP Group , We provide Comprehensive Smoke Study Services which includes 360 Degree Multi Angle Smoke Study Project Execution, CFD Project Execution & Consultation & Smoke Study Remediation Projects.