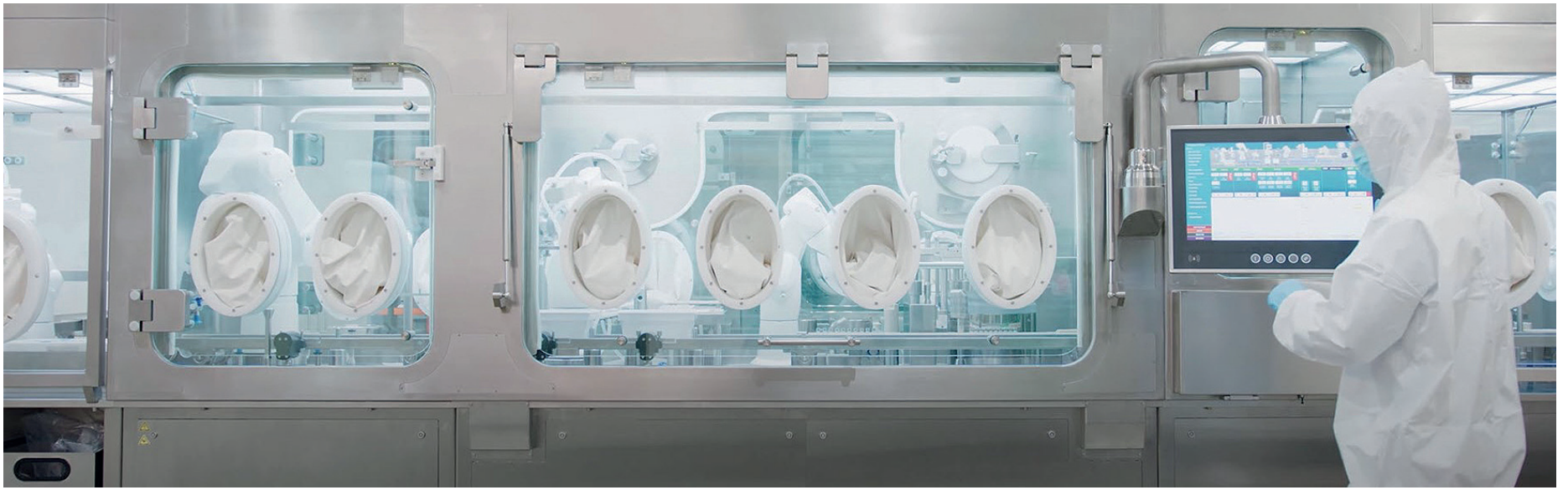
CONTAINMENT



Annex 1 and "first air": What is it and how is it used?

First Air as a concept is a major update in the new Annex 1 to continue global harmonisation of regulatory standards, **Josh Russell** from AST explains what is it and how is it used to improve clarity and compliance

One of the important points of emphasis in the revised Annex 1 is the regulatory codification of air handling guidelines and parameters, including the First Air principle. The stakeholders behind the Annex, last revised in 2008, took the opportunity to delve into greater specificity in prescription, application, scope, and language, in harmony with other prominent guidelines ("unidirectional" in place of "laminar" as an example).

It's clear that the regulation seeks to be cohesive, coherent, and exhaustive. While segmented, enumerated by section, the regulation is better viewed as a whole. And indeed, many of the new and augmented concepts within Annex 1, whether it's the concept of a Contamination Control Strategy, the updates on environmental monitoring, air handling/airflow requirements, or the expanded focus on barrier technology, they all work together to address the central concern of the document: the safe manufacturing of sterile products. That's where the collective efficacy of the concepts and parameters laid out in Annex 1 are evident.

Many are looking at these requirements through the lens of operational realities and day-to-day challenges. Taking the holistic perspective, a helpful guiding question is: What strategies must be implemented to harmonise the actions necessary for the integrity and protection of critical zones with the necessary operations and processes of sterile manufacturing? When critical zones are accounted for and prioritised in the design and execution of sterile production processes, then the safety and quality of the product is a repeatable, expected outcome.

This is where the quality of First Air becomes crucial. An indispensable aspect of proper aseptic technique, First Air, is defined generally as uninterrupted unidirectional filtered airflow, and specifically in Annex 1 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."

First Air as a concept is specified in name or function by multiple regulatory bodies and pharmaceutical organisations, including USP, PDA, ISO, and the FDA, amongst others, and its inclusion in the revised Annex 1 is evidence of the continuing global harmonisation of standards across regulatory bodies. But how does unidirectional airflow interact with a critical zone from an operational point of view?

First Air speaks to the quality necessary to protect a product and maintain the integrity of a critical zone, and unidirectional airflow is the mechanism by which that happens. Annex 1 specifies that the airflow should be homogenous and sweep away from the product continuously at a specified and validated velocity.

Originating as a principle of product protection during manual aseptic manipulations, First Air has long been considered necessary to maintain Grade A air over exposed and unsealed sterile products. With the advancements in technology, specifically isolator technology, First Air has been further strengthened by localised unidirectional airflow, an attribute Annex 1 highlights (4.4). The air handling attributes and low-risk environments offered by isolator technology have led to a marked change in the expectations around aseptic processing operations.

This is reflected in Annex 1, which advocates explicitly for aseptic processing within an isolator or lesser barrier technology unless scientifically justified (4.3). Regulatory bodies like the FDA have also indicated that the justification should be strong, and such situations should be the exception.

And as those higher standards show, no one operational element or tool ever stands alone. The holistic approach outlined in Annex 1 invokes an important point: The entirety of the aseptic processing programme should work towards the single goal of the safe, repeatable aseptic production of a product. The CCS, process design, and technology should all work to support the integrity of critical zones and the efficacy of First-Air defence.

In actual real-world settings, then, how can operators ensure First Air remains at its most effective and uninterrupted over critical zones? Here, Annex 1 also offers insight.

> **Annex 1 offers insight into how operators can ensure First Air remains at its most effective and uninterrupted over critical zones**

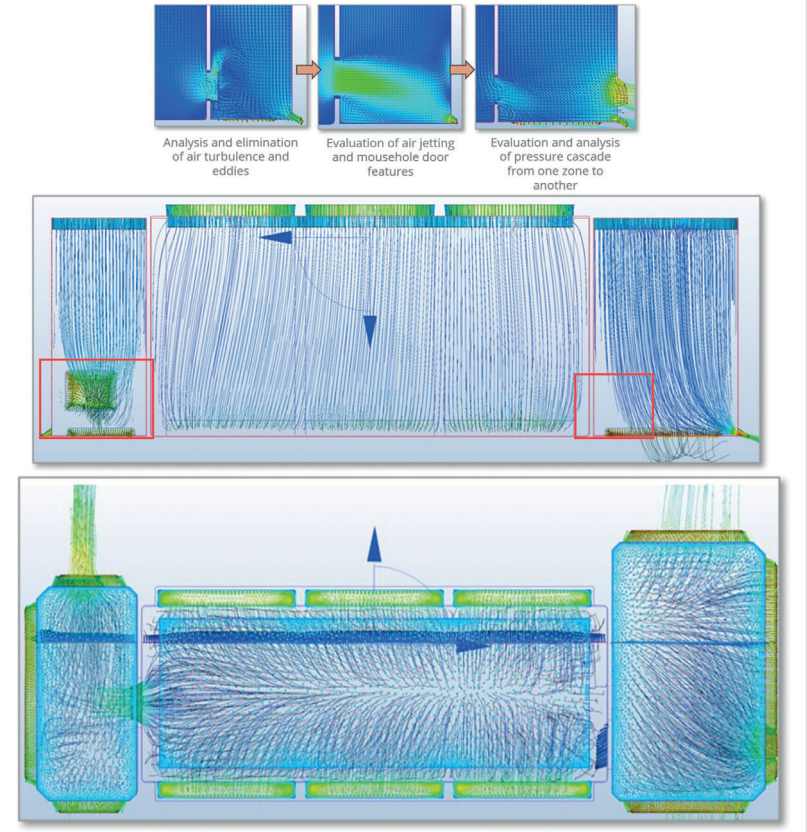
Critical zone operations: Key considerations

Airflow visualisation is a significant point of emphasis in the revised Annex 1 and functions both as a quality-by-design tool and a necessary means of validation for air pressure, air velocity, and airflow quality, amongst other aspects of a system and the larger operation. Smoke studies are used to validate that an aseptic system is functioning as intended and that critical zones remain under the protection of First Air throughout the duration of processing.

As a QbD tool, smoke studies can be augmented with the use of CFD (computational fluid dynamics) analysis. CFD is used to build precise, predictive models that simulate the properties of a design. At-rest and in-situ simulations can demonstrate critical zone processes and parameters, including airflow, air velocity, air ingress, and automated filling and closing procedures. It can also be used to assess the integrity and functional design of an aseptic environment.

AST's approach to Isolator technology

Figure 1: CFD (computational fluid dynamics) can identify and resolve airflow discrepancies to ensure optimal airflow dynamics in the design and build of the isolator.



leveraged comprehensive CFD analysis to ensure that Grade A air was maintained and that the isolator design would enforce First Air. The AST team utilised CFD to anticipate design limitations or airflow anomalies and resolve them in the final design and build of the isolator. Issues like dead zones where unidirectional air may fail to reach, structural obstructions of the filters, air diffuser membrane placement, and pressure differences between modules that can cause air vortices are all obstacles to unidirectional airflow that can be mitigated with a quality-by-design approach (Figure 1).

Regardless of the tools used in the design phase, all aseptic systems must be authenticated by smoke studies that confirm First Air remains in place as well as verify crucial aspects of the system functionality. These studies are also used to evaluate other aspects of contamination control measures like sampling protocol and placement of microbial monitoring. As another example, recent discussions have centred around reconciling the Annex 1 requirement for sterilising indirect and direct product contacting parts with the requirement that all critical parts are kept in First Air during aseptic setup. How can First Air be demonstrably confirmed while setup and installation take place? Beyond the proper protocol and precautions taken by personnel, both CFD analysis and smoke studies offer a solution.

Special attention should be paid to

Figure 2: AST has tested and implemented robotic and automated methods that maintain First Air in the most advanced, sensitive fill-finish operations.

necessary operational processes and tools that are used in the vicinity of First Air and have the potential to affect it. The emphasis in Annex 1 on appropriate technologies starts with the environment of the process itself. This document and other regulatory trends point to a clear solution: barrier technology and, more specifically, isolator technology. If the goal of sterile medical production is to ensure a low-risk, Grade A environment, and guarantee the integrity of critical zone processing, there is no better tool available to life science professionals than a well-designed isolator.

Advanced automation and robotics are additional tools that should be utilised to support First Air. Automation and robotics support First Air both by what they remove as well as what they add. Sources of contamination, the unpredictability and inconsistency of manual operations, and risk levels of select interventions are all areas robotics and automation can reduce or eliminate while improving the overall process by adding smoother movements for operations, a high degree of repeatability, and process efficiencies like increased throughput speed and minimisation of product exposure.

As it pertains to maintaining First Air, just like if humans were conducting aseptic manipulations, robotics must operate using proper aseptic technique. Design considerations for the motion, speed, and process areas should all aim to minimise air turbulence and partial obstructions of unidirectional airflow.

Any elements in or around the area of First Air (including robotic or automated components and process tools like fill needles) should be designed to minimise air disturbance, possess a hygienic construction, and have low-particle shedding thresholds. Proper working position should be implemented in the design to reinforce critical zone protection.

The final piece of the airflow puzzle is a qualified, proven aseptic processing system utilised with comprehensive training and the continuous use of the tools, resources, and protocols outlined in the operation's CCS and Pharmaceutical Quality System (PQS).

The regulatory burden of proof around the manufacture of sterile products is more stringent than ever, and the pharmaceutical industry continues to feel growing pains as it strategises for the future of sterile product manufacturing.

Ultimately, the specificity and rigorous quality of these regulatory trends point to an encouraging truth: the industry has the capabilities and technology at its disposal to consistently achieve new standards of product safety and quality.

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