



Understanding the Impact of Annex 1 on Isolator Design

An optimal engineering design is crucial for aseptic operation and cleaning.



The final version of Annex 1 was published at the end of August 2022. The first draft publication of version 9 of Annex 1 of the EU GMP Guidance on 20 December 2017 aroused a great deal of interest globally – on the one hand, because it was the first

publication on the topic after almost a decade and, on the other, because PIC/S and WHO co-authored the document.

Table of content

Restricted access barrier systems

Isolator design

Cleaning

Surface decontamination

Automation

Containment requirements

Barrier systems in Annex 1: RABS and isolators

The expressions “Contamination Control Strategy (CCS)” and “Quality Risk Management (QRM)” are mentioned frequently in the document, along with barrier systems, such as isolators or restricted access barrier systems (RABS).

This article describes the impact on isolator design for aseptic processing and how contamination control strategies are observed in relation to isolators. Compared to RABS, isolators have a closed barrier between the surroundings and the interior of the isolator in which the sterile product is processed. During production, access to the interior of the isolator is only possible through validated transfer systems, such as decontamination airlocks (e.g., using hydrogen peroxide [vH₂O₂]), or e-beam, dry heat tunnels (i.e., depyrogenation tunnel), rapid transfer ports (RTPs), or through interventions via the gloves attached to the isolator.

The most important points in the EU GMP Annex 1 with regard to isolators are: equipment design, cleaning, surface decontamination and automation. The starting point for every CCS is the risk observation of the design of the isolator

system, including the installation of equipment in an isolator, such as a fill/ finish machine for vials, syringes, etc. Most of the design failures could occur during the risk observation of the isolator system. The design forms the basis for cleaning in order to prevent a possible particulate or microbiological contamination of the sterile products, or to avoid cross-contamination in the case of a multi-product system. The entire design is also important for the subsequent surface decontamination with vH₂O₂. A high degree of automation reduces the manual interventions in the aseptic area through the gloves attached to the isolator. If highly active/toxic substances are to be manufactured in the isolator (or substances with an increased bio-safety factor), the protection of employees is a further important factor.

Consider section 4.3 of GMP Annex 1, which says:

Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

The document expressly indicates that RABS or isolators should be used, which means that RABS or isolators are the favored technologies of the future for handling sterile products.

The following differences between RABS and isolators should be mentioned:

RABS are installed in a grade B room, while isolators are installed in a grade D room. The installation of an isolator in a grade D cleanroom means more comfort for the operator when wearing the required cleanroom clothing. Training employees for a grade D cleanroom is also less intensive than training them for a grade B cleanroom.

RABS systems are classified into the following systems: passive RABS, active RABS, or closed RABS. Apart from the closed RABS, the operator always has access to critical areas within the RABS. With the isolator, access is only possible using gloves at the isolator, just like with the closed RABS.

In most cases, RABS are decontaminated via the room. With isolators, there is an integrated and validated decontamination system, for example, with vH₂O₂.

With the isolator, the aseptic critical zone is self-contained, while with most RABS, the aseptic critical zone is opened to the surrounding room during interventions.

Isolators are suitable for handling highly active, toxic substances or for substances that require a higher biosafety level, and they can also handle substances with an extremely low acceptable daily exposure (ADE) or permitted daily exposure (PDE) when further technical measures are implemented.

The use of isolators in sterile manufacturing has rapidly increased over the past 10 years. The main reasons are the increased safety of the product in the isolator, as well as the large number of highly active substances that have entered the market in recent years or are expected to do so in the coming years.

Isolator design

Manufacturing control starts with the aseptic engineering design. The design of an isolator system, including its installations, is the basis for all further requirements, such as cleaning or surface decontamination. The design plays an important role in a variety of ways.

Consider section 4.19 of GMP Annex 1:

i. Isolators:

a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.

The hygienic design plays an important role in ensuring this first air within the isolator system. No installations should be located, and no handling carried out

above critical operations that could lead to possible contamination of the sterile product. When observing critical operations, consider all transfers, interventions, movement sequences in the isolator, and so on.

“The hygienic design plays an important role in ensuring first air within the system.” Richard

Denk

The investigation of every individual process step on a GMP Annex 1 compliant aseptic hygiene design plays an important role here. Another important point when it comes to aseptic engineering design is cleaning.

Cleaning

The aseptic engineering design also plays an important role in cleaning with regard to avoiding contamination and cross-contamination. Consider section 5.4 of GMP Annex 1, which says:

The cleaning process should be validated to:

- i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.*
- ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.*

In this paragraph special attention should be paid to the wording: “The cleaning process should be validated.” Many of the process systems within an isolator are cleaned manually. To be able to perform this manual cleaning in a validated way, a

process and system design are required that permit validation. In addition, highly qualified employees are required to carry out this validated cleaning process. In the future, the author expects that complex and unwieldy manufacturing/ filling processes will be simplified, and a suitable hygienic design used. A hygienic risk assessment is certainly a beneficial tool for simplifying the system design.

An optimal process and isolator hygienic design also enables the handling of highly active toxic pharmaceutical products or pharmaceutical products that require an increased biosafety level. For several years the quantity of these substances has been increasing steadily. The prognosis for the next few years shows that many new substances currently in the preclinical or clinical phase are being classified as highly active, toxic, or with an increased biosafety level. As well as the process and isolator hygienic design, further important aspects play a role in the cleaning of these pharmaceutical products. It is important to consider the following questions:

Which PDE or ADE limit value is required?

Can the materials that are used in the isolator and their surface qualities be cleaned to the required PDE or ADE, and which surface limit values should be considered?

Surface decontamination

Hygienic design and cleaning to remove particulate and microbiological contamination are important attributes for surface decontamination of the inner surfaces of isolators and of their installations (e.g., a vial or syringe filling line, an incubator, or other utilities for manufacturing cell and gene therapies). Consider section 4.22 of GMP Annex 1, which says:

i. For isolators

The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be

appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.

This section has several messages in terms of isolators: decontamination methods should be validated and controlled within defined cycle parameters and the process should be automated and should use a sporicidal agent.

In most isolators, surface decontamination is carried out with vaporized or sprayed hydrogen peroxide (H₂O₂) as the sporicidal agent. Direct spraying of micro-nebulized H₂O₂ into the isolator system produces a quick distribution with a smaller amount compared to vaporizing H₂O₂.

The decontamination cycle, using the selected agent, must be validated in accordance with GMP to generate a reliably aseptic atmosphere inside the isolator. The phrase “controlled with defined cycle parameters” does not mean solely the amount and time of the H₂O₂ in the isolator system:

Following questions should be considered:

Automation

Automation, including robotics, can make manufacturing of sterile products more efficient, quicker, and safer. Robotic systems are mentioned specifically in section 2.1 of GMP Annex 1:

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.

Robotic work processes are widely used in pharmaceutical packaging, and their use has been expanding; they are now employed for handling sterile products, free of any manual interventions. The International Society for Pharmaceutical Engineering (ISPE) DACH [Germany/Austria/Switzerland] Future Robotics special interest group (SIG) was founded by the author in 2019. The SIG concerns itself with possible new work processes for robotic systems, the facility of the future using robotics, and the regulatory requirements from the EU GMP Annex 1 for using robotics.

For example, a new work process for robotic systems is to place molded parts in transport containers and transport them to the washing machine and, after washing, back to the isolator. This process needs to take into account transfers between individual cleanroom grades.

Another work process is aseptic filling and automated handling of sterile finished products by means of robotic systems in isolators, as well as implementing their technical and regulatory compliance with current good manufacturing practice (CGMP). It is necessary, for example, to adapt viable monitoring to fully automated robotic solutions in aseptic manufacture. In GMP Annex 1, the application of rapid microbial monitoring is mentioned, but the technical and organizational measures needed to replace the current monitoring methods using settle plates with rapid microbial testing methods need to be redefined. This topic will be addressed by the ISPE Future Robotics SIG in 2021.

Containment requirements

The production of highly active and hazardous substances in the biopharmaceutical industry has increased rapidly in recent years, requiring consideration of environment, health, and safety protection. Viral vectors, for example, require high protection for the employee as well as prevention of cross-contamination with other substances.

Consider section 4.14 of GMP Annex 1, which says regarding the topic of containment of highly active and dangerous substances:

... Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials)...

In addition to the pressure concept, the following aspects need to be taken into consideration for fill/finish of parenteral pharmaceuticals in an isolator system:

Is there an Accepted Daily Exposure (ADE) or Permitted Daily Exposure (PDE) that sets a limit value for exposure, such as that found in the European Medicines Agency's guideline on setting health-based exposure limits? This limit value is important for calculating cleaning limit values as well as for determining how to protect employees during manufacturing.

Which biological safety level (BSL) is required, and which technical and organizational measures are necessary to achieve this BSL?

Is this a monoproduction or a multi-purpose system? On a multi-purpose system, the necessary cross-contamination requirements have to be observed. For products with an ADE/PDE, these requirements are determined by toxicologists. For viral vectors, there currently are no defined limit values, so a no-tolerance level from the previous to the subsequent product is assumed.

A quality risk management (QRM) process is needed that covers the requirements of GMP for product protection as well as protection of employees and the environment. A contamination control strategy CCS is derived from the QRM. Furthermore, prevention of cross-contamination and containment strategies must be developed.

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Annex 1

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