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Opinion Paper

Barrier Technologies proposed text from PHSS Annex 1 focus group for revision of clauses/ section in version 12 of Annex 1 through the targeted consultation process.

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Introduction

The PHSS are one of the eleven EC appointed commenting platforms in the targeted consultation process on Annex 1, with version 12 how in the process of review and commenting. Two sections of Annex 1 are considered by the PHSS to need significantly more clarity and differentiation of technologies and approaches to qualification. This article has a focus on Barrier technologies with a follow up article and Webinars also planned for the section on Qualification of Cleanrooms and clean-air devices (that includes classification).

It is considered the current section in Annex 1 version 12 does not fully differentiate Isolators and Restricted Access Barriers (RABS) and their set-up for use in sterile product manufacturing. The following is recommended replacement text (in draft) that a PHSS Annex 1 Focus group have prepared to put forward to the EC/EMA as part of overall commenting on Annex 1 version 12 that has a deadline for submission on 20 July 2020.

Proposed changes to clauses 4.18 to 4.24 on Barrier technologies

The following is proposed text for replacement of text in version 12 of Annex 1. In addition to the proposed text to help the reader there is some background to the justification of why text change is considered as required to support clarity for all stakeholders; Industry, ATMP community, Healthcare support services and regulators.

Proposed PHSS text for clause changes in Annex 1 version 12 and justifications for revision.

Annex 1 clause 4.18. Within a correctly designed and operated aseptic manufacturing facility, people are likely to be the greatest source of contamination. Isolator or Restricted Access Barrier Systems (RABS) technologies provide an enclosed environment with physical separation between the enclosed processing area and the surrounding environment where human microorganisms and other potential contaminants are present. A physical barrier provides control of access to the processing environment and reduces the risk of contamination of the product, containers, closures, and direct and in-direct product contacting surfaces during aseptic processing activities.

The physical separation provided by the barrier can be applied in open and closed system configurations and when combined with protective airflow, effective control of the processing environment, surface and airborne contamination can be achieved. RABS should utilise UDAF, typically within a rigid barrier whilst isolators may employ rigid or flexible film continuous form barriers with UDAF or non-UDAF airflow. The selection of the system utilised should be based upon risk assessment that considers the manufacturing activities, the likelihood of product contamination and the risk that the product formulation presents to the patient. Barrier access control should be provided for isolators and considered for RABS to prevent unqualified intrusion.

Justification for change in Annex 1 version 12 clause 4.18 text:

The PHSS consider it important to emphasis the contamination risks and control provided by barrier technology with a much clearer differentiation of the available technologies of Isolators and RABS. Currently in version 12 of Annex 1 the glossary is used to try and differentiate between the open and closed system configurations of Isolator and RABS technologies and this is such an important differentiation it is considered guidance should be provided in the main body of Annex 1 text.

Annex 1 clause 4.18 continued…

Isolator and RABS technologies, and the associated processes, should be designed to provide protection of the enclosed environment during processing activities and in-process transfer of materials. Entry and exit of materials into the isolator or RABS should utilise validated transfer technologies such as:

i. Direct transfer from a steriliser.
ii. Systems that provide surface microbial reduction to support batch-wise or continuous material transfers
iii. Rapid transfer technologies (RTT) or transfer isolators that provide closed system transfers.
iv. No touch transfer systems (NTT) for entry of pre-sterilised ready to use product containers within a primary sterile barrier via a stepwise de-bagging of inherent protective secondary packaging that is applied to protect the sterile barrier and containers through the supply chain.
v. Transfer openings in the physical RABS barrier with localised protective airflow.

Justification for change in Annex 1 version 12 clause 4.18 text:

Transfer of materials into and out of barrier technologies is one of the significant contamination risk factors and typically require application of available technologies that are integrated into the barrier system.

Some technologies have been around for some time, but some are new developments that offer alternative approaches that in principle are encouraged in Annex 1 version 12. One technology that has had significant development and implementation as qualified systems is NTT: No-Touch-transfer of pre-sterilised container entry of pre-sterilised containers for filling. Such technology initially supported the increase in small batch filling, primarily of biological products but recent development has also included high speed filling lines.

Currently there is no mention of NTT technology in Annex 1 despite the significant development by machine manufacturers, container suppliers to support semi and automated NTT De-bagging systems that protect the sterile barrier (outside surfaces of primary barrier enclosing a nest of pre-sterilised containers) in transfer into the Grade A filling zone. NTT as available and qualified technology needs recognition and guidance in Annex 1, so such alternative technology is considered to follow the QRM principles and is defined in a contamination control strategy (CCS).

Annex 1 clause 4.19. The design of the isolators or RABS should take into account all critical factors associated with these technologies including; the quality of the air and surfaces inside the enclosures and the surrounding environment, the materials and components to be transferred, the integration of the processing equipment, the cleaning and subsequent bio-decontamination of the inner surfaces of the barrier and any installed process equipment, and if applicable, any associated sterilisation processes.

The risk of contamination associated with the manufacturing operations and the activities conducted within the critical zone should be assessed, mitigated and control measures defined in a CCS. All interventions into the critical zone should be reduced to a minimum and all qualified in aseptic process simulations.

Grade A continuity should be maintained from RABS to remote freeze dryers when partially stoppered vials are in transfer.

Isolators used in aseptic manufacturing including open container filling should utilise automated sporicidal bio-decontamination. Isolators used for aseptic preparation of closed containers or closed systems may, if justified, utilise a manual disinfection program that includes periodic application of a sporicidal agent. RABS may similarly utilise manual disinfection using a validated disinfection process or alternatively apply an automated bio-decontamination process. Automated bio-decontamination with a sporicidal agent may be applied to Closed RABS or as combined Cleanroom and Open RABS bio-decontamination.

Closed system Isolator operator access doors should remain closed after set-up and throughout all processing activities. Open system Isolators designed to support continuous entry of product containers and closures and the continuous egress of filled containers should utilise UDAF and an overpressure in the critical zone to maintain the required environmental conditions. Open RABS utilise barrier screens that permits an overspill of supply UDAF below critical processing points into the surrounding environment. Any RABS open barrier door intrusions should be minimised with an intent of being rare and if justified detailed in the CCS and qualified during APS.

Closed RABS maintain the supply of UDAF within the Grade A critical zone using physical barrier screens that minimise any outflow into the surrounding environment to provide enhanced physical separation and a contribution towards aseptic containment.

Justification for proposed change in Annex 1 version 12 clause 4.19 text.

Barrier technology design has a series of factors to consider, risk assess and apply as control measures in a process design for contamination control. One of the important differentiators in design configuration and use is the 'Open and Closed system' application of how UDAF airflow is managed and how access control is applied. Such is the importance the differentiation the proposed text provides a clearer understanding of open and closed system Isolators and open and closed system RABS principle configurations within the body of Annex 1 text.

Annex 1 clause 4.20. Set-up of Isolators for aseptic manufacturing that includes the transfer and assembly of sterilised in-direct product contact parts into the barrier via specified open door intrusions should apply bioburden control measures before closure of the barrier and an automated sporicidal bio-decontamination process to establish the required conditions. Alternative approaches that apply in-place bio-decontamination as the sole method to assure in-direct product contact surfaces are free of microorganisms should be assessed, justified, appropriately controlled, and defined in the CCS.

Prior to the automated sporicidal bio-decontamination process, sterilised parts should be wrapped during transfer and protected during assembly. On removal of protective wrapping before closing the barrier for the bio-decontamination process protection measures to control bioburden should be in-place including but not limited to operational UDAF and additional operator gowning such as eye covering and face mask.
Product contacting parts including pre-sterilised single use systems or installed systems that utilise CIP/SIP should only be exposed to Grade A conditions.

Set-up of RABS for aseptic manufacturing may include the transfer and assembly of sterilised product contacting and in-direct product contacting parts into a Grade A environment using appropriate control measures and protection procedures with considerations of:

I. Open barrier door installation of sterilised parts should not compromise the critical zone or sterility of parts being installed.
II. Protection of the critical zone from airborne contamination during open barrier transfers and set-up should include surrounding overhead localised-UDAF that as a minimum cover the span of the open barrier access door and RABS UDAF airflow that confirms (by air visualisation studies) outflow from the critical zone through to the surrounding environment.
III. The same level of critical zone protection during open barrier door intrusions during aseptic manufacturing.

In closed isolator systems where airflow may not be unidirectional, the Grade A conditions should be demonstrated to provide adequate protection for exposed products and critical surfaces.
The design of the open isolator systems and RABS should ensure a positive airflow from the critical zones to the surrounding environment. Where containment is required, localized air extraction and/or zone pressure bubbles may be utilised to prevent direct airborne contamination transfer to the surrounding environment.

Negative pressure isolators should only be used when containment of the product is considered essential and risk control measures are applied to ensure the critical zone conditions and product sterility are not compromised.

Justification for proposed change in Annex 1 v12 clause 4.21 text.

One of the fundamental differences in Isolators and RABS use in aseptic manufacturing for filling of sterile products is the set-up and how assurance of sterility is managed for In-direct product contacting parts e.g. container closures feeder contact surfaces. In variance sterilised parts are installed into RABS after Grade A conditions are established and in Isolators sterilised parts are installed into Isolators with bioburden control measures before Grade A conditions are established, typically via an automated vH202/VHP bio-decontamination process. The replacement text recognises the variance in set-up and difference in contamination control measures to assure surface sterility of in-direct product contacting parts. The PHSS have provided supportive guidance in the form of Clarity on GMP Guidance notes (reviewed by MHRA before publication) on set-up of Isolators and assurance of sterility for in-direct product contacting parts.

Clause 4.21 of Annex 1. For open and closed RABS used for aseptic manufacturing of sterile products, the surrounding environment should meet Grade B requirements. The background environment for open isolator systems used for aseptic manufacturing should, as a minimum, meet Grade C microbiological control requirements to mitigate risks of microbial contamination transfer from the surround together with Grade D non-viable particle levels. The background environment for closed isolator systems should correspond to a minimum of Grade D. For an isolator, where additional process risks are identified, a higher grade of background should be implemented. The background environment should be justified, risk assessed and defined in the CCS.

Airflow studies performed to demonstrate effective protection may include smoke pattern visualisation and where appropriate computational fluid dynamic (CFD) studies (in design) and an LR Method to challenge and verify appropriate control of airborne particles. At mouse hole material transfer points that interface with barrier zones of different grades, localised UDAF (L-UDAF) should

be qualified to confirm an absence of adverse airborne contamination ingress to a higher-grade zone.

Justification for proposed change in Annex 1 v12 clause 4.21 text.

The background environment of barrier technology and the characterisation of protective airflow patterns within are connected in the control of contamination risks and together are key to application of the barrier system. Airflow characterisation as protective is a key requirement where consideration of methods applied may need extending past smoke studies particularly to reduce risks of adverse airflow conditions by design and where protection from airborne contamination transfer may not be physically visible by smoke studies alone.

4.22. Risk assessments for isolators and RABS operations should consider the disinfection/bio-decontamination, the extent of automation, the impact of barrier glove manipulations considering the potential to compromise 'First air' protection of critical process points and the impact from potential loss of barrier/ glove integrity.

Justification for proposed change in Annex 1 v12 clause 4.22 text.

Added to consideration of barrier technology disinfection / bio-decontamination in risk assessments there needs to be other key factors taken account of including the extent of automation that be default reduces operator interventions and associated contamination risks plus the possible compromise of 'First air' protection when operators do complete inherent and corrective barrier interventions. The principles of First air protection have long been established in barrier technology use but without recognition in Annex 1.

Clause 4.23 of Annex 1. The materials used for barrier glove systems, should be demonstrated to have appropriate mechanical and chemical resistance appropriate for the life cycle of operation before replacement. A barrier glove management strategy should be stated in the CCS with consideration of the selection for purpose, integrity testing (visual and physical), replacement frequency and assessment of actions for any in event of post use or end of batch integrity test failure together.

For isolators, integrity testing of the barrier system, and separate leak testing of the glove systems should be performed using appropriate methodology. The testing should be performed at defined periods, as a minimum at the beginning and end of each batch or campaign. Glove integrity monitoring should include a visual inspection following any manipulation of the gloves that may affect the integrity of the system. For single unit batch sizes, integrity may be verified based on other criteria, such as the beginning and end of each manufacturing session.

RABS barrier gloves should be sterilized and secured in protective wrappings before installation. If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed.
Both visual and physical integrity testing, should be completed before sterilisation together with, as a minimum, visual inspection for defects during operation. Based on risk assessment RABS gloves may also be physically integrity tested in-place with a suitable methodology.

Isolator gloves should be cleaned, and bioburden reduced before installation onto barrier glove ports. Gloves should be bio-decontaminated in place by a suitable method to assure critical surfaces are free of microorganisms. Where automated bio-decontamination processes are applied gloves should be presented on exposure holders, so all critical surfaces are exposed to the sporicidal bio-decontamination process.

Justification for proposed change in Annex 1 v12 clause 4.23 text.

There is a clear need to differentiate management of barrier glove sterilisation and bio-decontamination of gloves between Isolators and RABS. Also, variances need to be made clear on the application of integrity test methods and their timing of implementation for the different barrier technologies. The introduction of the Barrier glove management strategy will be further supported by industry guidance, including from the PHSS, to provide a more holistic approach to managing glove integrity and impact of integrity loss.

Clause 4.24 of Annex 1. For isolators and RABS the bio-decontamination methods should be validated and controlled.

For isolator systems applied to aseptic manufacturing, an automated, validated and controlled bio-decontamination process should apply a sporicidal agent in a suitable form e.g. gaseous, aerosolized or vaporized to ensure full microbial bio-decontamination of the interior surfaces that form the aseptic boundary including UDAF barrier HEPA filters and any air diffuser screens. The bio-decontamination process should combine a cleaning and sporicidal disinfection step to render the interior surfaces of the isolator Grade A zone free of viable microorganisms. The cleaning process, prior to the disinfection step is essential to reduce bioburden and remove any residues; e.g. fatty deposits or cleaning agent residues that remain may inhibit the effectiveness of the bio-decontamination process or transfer to product as a contaminant.

Evidence should also be available to demonstrate that the agent used and associated residues does not adversely impact the product produced within the isolator or RABS and the material surfaces of the barrier system and any installed equipment.

For RABS systems, the disinfection should include the periodic application of a sporicidal agent at defined intervals using a method that has been validated and demonstrated to robustly disinfect the interior and ensure a suitable environment.

The holding time after achieving Grade A conditions and before use should be validated. The manufacturing hold time of Grade A conditions from start of use until end of operations (batch of campaign) and before repeating bio-decontamination should be qualified.

Justification for proposed change in Annex 1 v12 clause 4.23 text.

The bio-decontamination method and its application must clearly follow scientific principles as a critical measure in bio-contamination control in barrier technology. A recent regulatory Blog: 'Fragility of VHP' indicated the fragility of scientific knowledge and understanding in limitations of penetration capability of bio-decontamination agents that resulted in regulatory observations with poor application and over claiming assurance of surface sterility. This regulatory expectation presented by a Blog indicates this clause needs to be expanded and reinforced to provide guidance of expectations and application. In addition, more needs to be stated on residue impact both on efficacy of the bio-decontamination/ disinfection process and in contaminating a product via residues from a disinfection process.

Summary

The proposed text changes on the clauses of Annex 1 version 12 related to Barrier technology are in draft but provide an insight of the proposed text prepared by a PHSS industry working group for consideration of the Annex 1 Inspectors working group with the purpose to add clarity to assist all sides (Industry and regulators alike). Without clarity there will be challenges of interpretation leading to possible observations in non-compliance or failure to meet expectations and possible

limitations in taking up alternative new technologies where there is no clear connection with Annex 1 text.

With the extended deadline of Annex 1 comments submission to the EC/EMA until 20 July 2020 there has been more time for review of incoming comments, prepared alternative text and cross group co-ordination (facilitated by the PDA) to discuss points of comment concern.

This 'open' article on the proposed Annex 1 text on Barrier technologies is published before the deadline for comment submission to provide an insight to the wider EJPPS readership and an opportunity to remark on the proposed text.