MICROBIAL MONITORING RABS GLOVES: UNRAVELLING THE IMPLICATIONS OF DIRECTIONAL USE

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The industry has placed significant emphasis on testing the integrity and frequency of Isolator and RABS gloves (3-6) since the recent revision of the EU GMP Annex 1 and associated PIC/s guideline (1,2). However, glove management involves more than just Integrity testing. This article addresses the Environmental Monitoring of Isolator and RABS gloves surfaces as an essential aspect of glove management.

Barrier systems such as RABS or isolators typically feature glove ports. These ports are used for installing gloves after being washed and sterilized, if they are not purchased ready to use. Before installation, a visual inspection ensures packaging and glove integrity before unwrapping and installing the gloves in their respective RABS ports. After the installation, physical testing using a pressure decay machine is generally performed to ensure the glove's integrity before use. These gloves are then utilized for aseptic interventions like set-up, inherent or corrective intervention to maintain manufacturing continuity. At batch completion, gloves are sampled directly using contact plates or swabs. Glove integrity checks are conducted after each batch or periodically (weekly to monthly, depending on site protocols). While some barrier systems require gloves to be used in one direction (either right or left), specific gloves, like nitrile, PVC, neoprene, or Polyurethane ones, may allow for use in both directions, enabling operators to insert either hand for required activities.

We have all experienced the scrutinizing gaze of an inspector or external auditor at least once. Often, their inquiries leave us pondering, "How did I miss that?" Despite being the process owner or Subject Matter Expert (SME), unexpected questions can catch us off guard.

Picture this scenario: an auditor observes an aseptic activity through a window during an onsite tour, focusing on an aseptic operator engaged in a set-up or intervention within the Restricted Access Barrier System (RABS) or an isolator. The auditor poses a seemingly straightforward question: "Is the Isolator glove used in both directions?" Your confident response— "Yes, in both directions"— initiates a realization that this seemingly innocuous question marks the beginning of a challenging journey in isolator gloves microbial monitoring.

Before delving into the complexities, let's rewind to the moment of realization. Most Barrier Systems, whether RABS or Isolators, are equipped with gloves for operators to perform aseptic operations such as set-ups, inherent (also called routine) or corrective (also called non-routine) interventions during the manufacturing of medicinal products. The catch lies in the glove ports of some Barrier Systems, allowing gloves to be used interchangeably (left or right). This flexibility enables operators to insert either hand into the same glove port based on the type of intervention. However, not comprehending the implications of this flexibility can be a pitfall.

Returning to the auditor's query about using Isolator gloves in both directions, the implications become evident. Answering in the affirmative triggers a realization that interventions performed with the opposite side are often not sampled, as the logical side of the glove is typically selected for sampling based on the direction of the thumb of the barrier System drawing (P&ID).

Now that we realize the implication of the affirmative answer, it is time to draw an assessment of the impact of monitoring only one side of RABS gloves; this involves a holistic review of the gloves monitoring by:

1. Mapping the aseptic set-up and interventions to confirm which gloves are used interchangeably.
2. Reviewing procedures to identify instructions allowing the use of gloves in both directions and not specifying the operator's hand to be used.
3. Interviewing operators to confirm their use of both sides of the gloves or if they perform interventions with a single hand, specifying which hand.
4. Scrutinizing batch records to confirm using one or two gloves for each intervention and analyze trends in the data. In most cases, batch records will only document corrective interventions.
5. re-watching the smoke studies to endorse that gloves are not used in both directions.
6. Reviewing RABS gloves' microbial monitoring, ideally defining a probability of failure using historical data.
7. Evaluating Grade A Environmental Monitoring data against sample locations and surrounding areas where the gloves are used.

Compile this data and determine whether the lack of microbial monitoring on the other side of gloves could affect product sterility assurance. Your analysis should include Aseptic Process Simulation (APS) results in addition to product bioburden, sterility, and endotoxin results by providing a science-based justification to ensure product quality. Based on your findings, two decisions can be considered and the Contamination Control Strategy (CCS) document will be revised depending on the chosen approach to reflect and justify the selected decision:

- If the decision is to designate the direction of each RABS glove, clear instructions and visuals should be provided at the glove ports indicating the appropriate hand or direction for glove use. The microbial monitoring sampling plan will remain unchanged.
- If the decision is to allow gloves to be used interchangeably (left or right), instructions and sampling plans should be updated accordingly. The Environmental Monitoring Risk Assessment should be revised to incorporate this flexibility, with identified controls such as sampling both sides of gloves or only the gloves used on both sides. Finally, other processes may be updated such as APS.

Conclusion:

The scrutiny of RABS or Isolator gloves' microbial monitoring compared to their usage reveals a nuanced challenge with implications for aseptic operations. The seemingly straightforward question posed by the auditor—whether the Isolator gloves are used in both directions—unveils a complex web of considerations that demand meticulous attention.

Our exploration emphasizes the importance of a meticulous assessment. A holistic view emerges through mapping processes, reviewing procedures, interviewing operators, and analyzing monitoring data. The correlation between glove usage and environmental monitoring data highlights potential risks. Updating risk assessments, and protocols, refining monitoring practices, and aligning with historical data enhance these strategies. This article offers a blueprint for organizations to navigate directional Isolator or RABS glove challenges, fostering a culture of continual improvement in pharmaceutical manufacturing.

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SHORT Biography:

Walid, Co-founder and Managing Director at QP Pro Services, is an experienced professional specializing in GMP and GDP activities. As a senior consultant, he focuses on contamination control, sterility assurance, and inspection readiness. Walid, an Acting Qualified Person (QP) and Responsible Person (RP), boasts extensive expertise in non-sterile and sterile processes, including drug substance, drug product manufacturing, and Advanced Therapy Medicinal Products (ATMP). His auditing proficiency spans Contract Manufacturing Organizations (CMOs), API manufacturers, and suppliers. Walid has successfully prepared sites for inspections by regulatory bodies like the US FDA, EMEA, ANVISA, and WHO. Engaged in professional organizations, he contributes to conferences and working groups, serving as a Board member. Additionally, Walid demonstrates a commitment to education as a professor/lecturer at Brussels and Liège University. He is the Co-founder of the QP Academy, dedicated to training Qualified Persons. As the Founder of QPM Consulting and Co-founder of QP Pro Services (www.qpproservices.com), Walid provides consultancy support to the pharmaceutical industry, serving as a strategic partner for business continuity.

LONG Biography:

Walid El Azab, Co-founder and Managing Director at QP Pro Services, is a seasoned professional with expertise in GMP and GDP activities. He serves as a senior consultant specializing in contamination control, sterility assurance, and inspection readiness. Walid is an accomplished author, contributing articles and book chapters on contamination control.

As an Acting Qualified Person (QP) and Responsible Person (RP), Walid brings comprehensive experience in non-sterile and sterile processes, covering drug substance, drug product manufacturing, and Advanced Therapy Medicinal Products (ATMP). His auditing proficiency extends to diverse entities such as Contract Manufacturing Organizations (CMOs), Active Pharmaceutical Ingredient (API) manufacturers, and suppliers. Walid has successfully prepared multiple sites for inspection readiness with regulatory bodies, including the US FDA, EMEA, ANVISA, WHO, and PIC/s authorities.

Actively engaged in professional organizations like ECA, PDA, EIPG, and A3P, Walid contributes to writing industrial guidelines, as a committee member for conferences and working groups. He currently serves as a Board member of UPIP-VAPI and participates in

PDA Letter, A3P Working Group, and ECA Working Group. Additionally, Walid demonstrates a commitment to education as a professor/lecturer at Brussels and Liège University. He is the Co-founder of the QP Academy, dedicated to training Qualified Persons.

As the Co-founder of QPM Consulting and QP Pro Services (www.qpproservices.com), Walid provides consultancy support to the pharmaceutical industry, serving as a strategic partner for business continuity.