When Sterility Meets Sensitivity: Engineering Isolators for Cell-Based Therapies

Practical strategies for integrating isolator technology into cell and tissue therapy manufacturing environments

The industry has long recognized **challenges posed** by vaporized hydrogen peroxide (VPHP) decontamination in cell therapy manufacturing- particularly in relation to material compatibility and process sensitivity.

While isolators offer enhanced sterility assurance and operator protection, their integration into cell therapy processes has historically required careful consideration of product stability, timing, and cost. Experience across multiple facilities has highlighted several recurring areas of complexity that continue to inform isolator design and operational strategy.

Historical Challenges

- Material & Product Sensitivity to H2O2
- Process Time Constraints
- Complex Material Flow and Transfer
- Cost and Resource Considerations

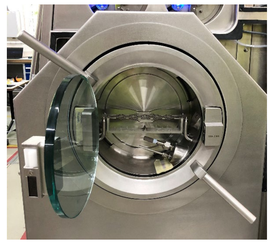
Why still consider an isolator versus a BSC?

- Enhanced Contamination Control
- Controlled & Validated Environment
- Alignment w/ Evolving Regulatory Expectations
- Reduced Human-Factor Variability
- Operator & Product Protection
- Support for Extended Operations
- Lower Environmental Burden
- Lifecycle Cost Efficiency

Engineered Solutions

Aseptic Liquid Transfer Systems

- Aseptic transfer of liquid materials or products from outside the isolator into the working environment.
- Based on the Alpha-Beta concept and is made via a port and connector single-use system (SUS)
- Liquid product or material avoids VPHP while supporting Grade A / ISO 5 continuity



Ultra Fast Decon Port

- Smaller space = quicker VPHP decon cycle (can be <5 min)
- Developed for time-sensitive vial or bag transfers
- Allows for direct entry into working space post-decontamination

Air Exchange Only Cycle

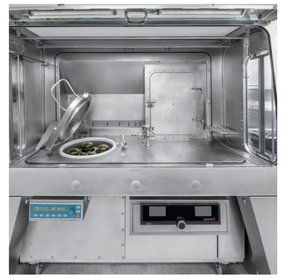
- Alternate cycle mode that excludes VPHP, replacing airlock air with filtered air at a rate achieving the defined number of air exchanges per minute.
- Manual disinfection or overwrap removal required before loading (≤3-log reduction vs. 6-log with VPHP).
- Post-exchange air in working chamber and airlock validated to Grade A / ISO 5 particle criteria.
- Business case, risk assessment, and CCS determine applicability. Consider supporting EM requirements.

Abbreviated Airlock Cycle

- Customized airlock cycle where transfer gasket between airlock and chamber deflates ~1-2 min into aeration cycle (~4-6 min cycle)
- Airlock H2O2 ppm is above 1 ppm prior to opening to previously decontaminated working chamber. However, because of the VPHP diffusion from the airlock to chamber, plus active recirculation of air, the working environment has the ability to be validated to <1 ppm H2O2

Integrate Equipment

- Specific vendors are able to support integration of numerous pieces of equipment
- Integration of equipment allows for the process to stay within the isolator environment, resulting in less “in & out” transfer
- Integrated equipment has historically included incubators, centrifuges, microscopes, filling systems, robotics, and additional. This will continue to evolve as customers work with their vendors



Design & Workflow Adaptations enable practical solutions that maintain control and efficiency during sensitive processing.

- Work with experienced operators to understand material in, material out, waste accumulation, and all required equipment & support materials. **More than 1 airlock dramatically** aids workspace efficiency, especially with simultaneous material in & out activities.
- **Optimize glove port layout & location** for bimanual operations and team flow.
- If intended to have various working chambers, **qualify each chamber’s decontamination cycle separately** versus all at once (all transfer doors open) to support various processing and preparation activities & times.

- Design isolator with **additional tri-clamps and cable glands** to support processing equipment use in the isolator, allowing your space to support future innovation if no such equipment is currently utilized.
- Do not forget ‘simple’. If you have limited VPHP-sensitive material, **utilize a secondary container** (prepped in a BSC) to transfer in material and note this in your CCS.
- Do not assume the correct glove size and material. **Invite an isolator glove vendor on-site** & have your workforce try on various sizes & materials – operator dexterity & glove size optimization increases control.
- Consider working with consumable vendors to **update Material of Construction where possible** (i.e., changing from PE to PA/PE/PA). Minimizes H2O2 uptake & aeration cycle time.

Operational Learnings & Future Considerations

Cell-based therapies are high-value, short-shelf-life products that can directly impact patient survival. These realities justify rethinking traditional approaches to sterile manufacturing. Use your contamination control strategy and internal risk assessments as instruments of confidence to defend aseptic process decisions. Working in an isolator does not replace aseptic behavior; it amplifies its importance and defines the integrity of sterility assurance.

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