Gloveless Robotic Isolator Technology: Mitigating Biopharma Industry's Implicit Biases on Contamination Control from an Early Adopter of Advanced Aseptic Technology

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Disclosure

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- Overcoming Barriers to Implementation
- Decontamination Cycle Validation
- Environmental Monitoring

Electric Vehicles (EVs) & Advanced Aseptic Technologies

Conventional Aseptic Processing

- Inherently risky
- Fundamentally unchanged since 1960s
- Susceptible to external microbial & particulate contamination
- Cleanroom personnel pose the greatest risk for contamination of the Critical zone
- Extensive training of personnel in aseptic practices, principles, and behaviors
- Reliant on airflow velocity and behavior to protect Critical Zone
- Manual decontamination, "*spray and pray*"
- Requires cultivation-based microbial environmental monitoring of the environment (EM)

Image: ©2020 Nash Community College, Press Releases, Student Life 03/30/2017

"It is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible."
2004 US FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing - CGMP

Advanced Aseptic Technology: Closed Robotic Isolator

- Validated vapor-phase hydrogen peroxide (VPHP) auto decontamination cycles
- Sterile Single Use product flow path / fill needle
- No glove ports
- No operator interventions
- Non-aseptic set up
- Pressurized w/auto leak detection
- Prohibits opening of isolator post-decontamination
- External contamination potential eliminated
- Simplified operator training
- Operator-to-operator variability eliminated by automation

Image credit Cytiva

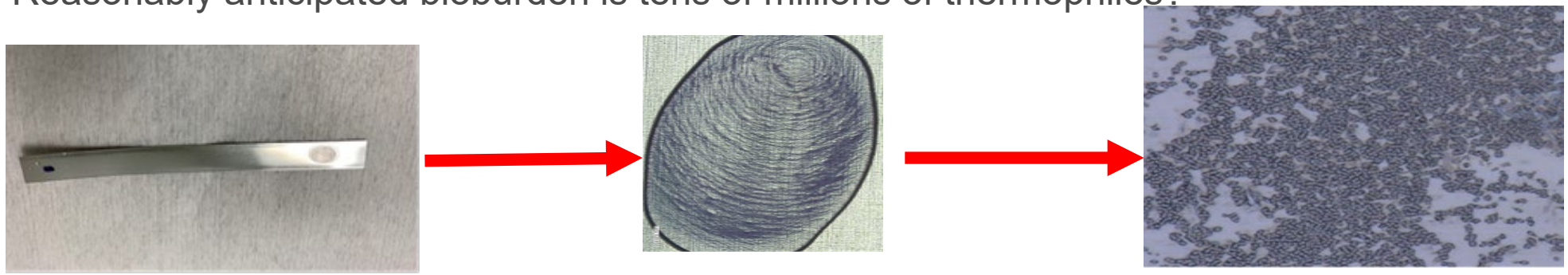
"Advanced aseptic technologies can be defined as those that do not rely on the direct intervention of human operators during processing"

United States Pharmacopeia, <1116> Microbiological Control and Monitoring of Aseptic Processing Environments

Barriers to Implementation

Validation of Vapor-Phase Hydrogen Peroxide Decontamination Cycles

- Standard validation 6-log Biological Indicators (BIs)
  - >1M CFU (colony forming unit) per carrier
- Resistant species: *Geobacillus stearothermophilus (thermophile)*
- Same method as sterilization chamber (e.g., autoclave, depyrogenation oven)
- Reasonably anticipated bioburden is tens of millions of thermophiles?



"Overkill sterilization can be defined as a method in which the destruction of a high concentration of a resistant microorganism supports the destruction of reasonably anticipated bioburden present in routine processing."

USP <1229> Sterilization of Compendial Articles

Optimized VPHP Cycle Using 4-Log BIs

Total Kill analysis method

- Same species: ~50K CFU per BI
- Same BI locations
- Lower dose
- Shorter dwell time
- Higher ppm H2O2

US FDA

- ADMA Biologics submitted as trans-BLA PAS Sept. 2022
- Supplement approval received Jan. 2023

Parameter	Initial	Optimized
Biological Indicator	>10^6 endospore population	>10^4 endospore population
VPHP Dose	8.9 mL	3.3 mL
VPHP Dwell Time	561 sec.	264 sec.

Percent Change: Initial vs. Optimized VPHP				
	Dose Volume	**Dwell Time**	**Cycle Time**	**Avg. ppm (max)**
	-63%	**-53%**	**-62%**	**+12%**

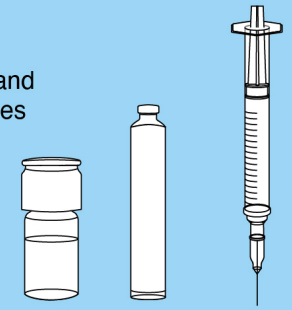
Barriers to Implementation

- External contamination risk eliminated
- Closed isolators don't easily accommodate conventional EM testing
- Inherent risk of contaminating the test during handling
- Availability of rapid microbiology methods
- Exceptionally low counts - ultimately a non-value-added effort

Cultivation Based Environmental Monitoring

1 standardized closed robotic workcell

>250
media fills and GMP batches



0% failure rate

zero positive units from 52 media fills which cover more than 184,000 units

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Environmental Monitoring for Closed Robotic Workcells Used in Aseptic Processing

Data to support advanced environmental monitoring strategies

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RESEARCH ARTICLE

Environmental Monitoring for Closed Robotic Workcells Used in Aseptic Processing: Data to Support Advanced Environmental Monitoring Strategies

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Abstract
The human operator is acknowledged as the greatest potential source of contamination in aseptic processing. To avoid contamination, barrier systems have progressively reduced the amount of human intervention in the critical zone. This study extends the trajectory of enhanced patient safety through the elimination of human intervention in aseptic filling. Eight companies that are users of closed robotic workcells have aggregated their usage data from 2018 to 2021. The study analyzes the critical design elements and performance of the Cytiva SA25 Aseptic Filling Workcell. The SA25 is a standardized, fully closed robotic system for aseptic filling of vials, syringes, and cartridges that eliminates operator intervention in the critical zone. The standardized design means that the system is not modified to suit a particular application and the same environmental monitoring strategy can be used across different installations. The SA25 provides significantly increased sterility assurance when producing sterile injectables. Users have observed non-viable particle levels well within ISO 5/Grade A air requirements, with extremely low probabilities of entering a dosage container. There have been zero cases of microbial growth in more than 250 media fills and good manufacturing practice (GMP) batches. Across all dosage formats and sizes, the aseptic process is repeatable, with more than 99.3% of units meeting acceptance criteria. These data demonstrate that eliminating risk through design is successful in the SA25, with an improved aseptic process in comparison to filling systems using Restricted Access Barrier Systems (RABS) or isolators with glove ports. One of the contributing companies to this article achieved an industry first. The U.S. FDA-approved commercial production of their biologic drugs without the requirement for routine viable environmental monitoring (EM), requiring viable EM only during process simulations. Based on the data presented and planned future research, new regulatory consideration should be made for closed robotic workcells to ensure that regulations meant for previous technologies with different risk profiles are not inappropriately applied.

Keywords Aseptic filling · Aseptic processing · Robotics · Environmental monitoring · Advanced manufacturing

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> *"This should be required reading for anyone not using isolation or closed system technologies. If you are using anything less capable than what is described in this publication you made a mistake."*
>
> James P. Agalloco,
> President, Agalloco and Associates

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Thank you!