Using Quality Risk Management to De-Risk Aseptic Processing Operations

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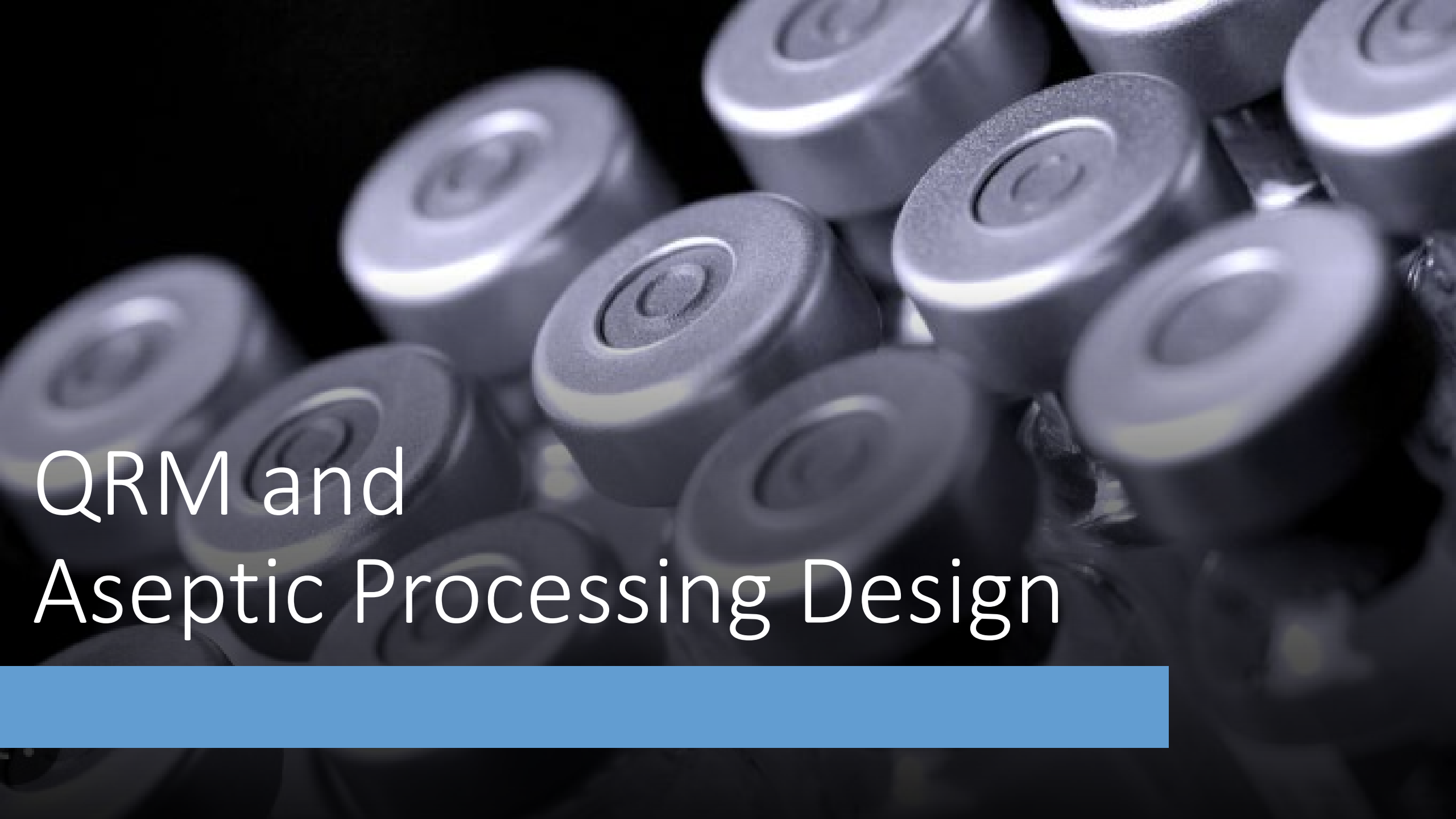
QRM and Aseptic Processing Design

Case Studies

De-Risking Opportunities

Summary



QRM and Aseptic Processing Design

Aseptic Processing: Complexity and Significance of Contamination Risks

- "Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment. Aseptic processing involves more **variables** than terminal sterilization. Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. **Any** manual or mechanical **manipulation** of the sterilized drug, components, containers, or closures prior to or during aseptic assembly **poses the risk of contamination** and thus necessitates careful control."

- Environmental conditions in the ISO 5 area "must be **designed** to maintain product sterility."

- "Sterile drug manufacturers should have a keen awareness of the public health implications of distributing a nonsterile product. Poor CGMP conditions at a manufacturing facility **can ultimately pose a life-threatening health risk** to a patient."

- FDA Guidance on Sterile Drug Products Produced by Aseptic Processing (2004)

Using QRM to De-Risk Your Operation: *Lifecycle Knowledge May Trigger Risk Review*

- A robust facility infrastructure: "includes **suitable equipment and well-designed facilities** for manufacturing... Robustness can be affected by multiple factors, such as an aging facility, insufficient maintenance or an operational design that is **vulnerable to human error.**"

- "Risks to supply can be reduced by addressing these factors, as well as through the use of modern technology, such as digitalization, automation, isolation technology, amongst others."

- QRM includes "taking into account **new knowledge** and **experience**." Lifecycle events can "impact the original quality risk management decision."

- ICH Q9(R1), Quality Risk Management
Published by ICH in January 2023

Contamination Control Strategy: *Using QRM to De-Risk Your Aseptic Process*

- "Processes, equipment, facilities and manufacturing activities should be managed **in accordance with QRM principles** to provide a **proactive** means of **identifying**, scientifically evaluating and controlling potential risks to quality… In the first instance, **QRM priorities** should include **appropriate design** of the **facility, equipment and processes,** followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations."

- A **Contamination Control Strategy (CCS)** should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination **prevention**.

- The CCS **should be actively reviewed** and, where appropriate, **updated** and should **drive continual improvement** of the manufacturing and control methods. Its effectiveness should form part of the periodic management review.

- EU Annex I: Manufacture of Medicinal Sterile Products (August 2022)

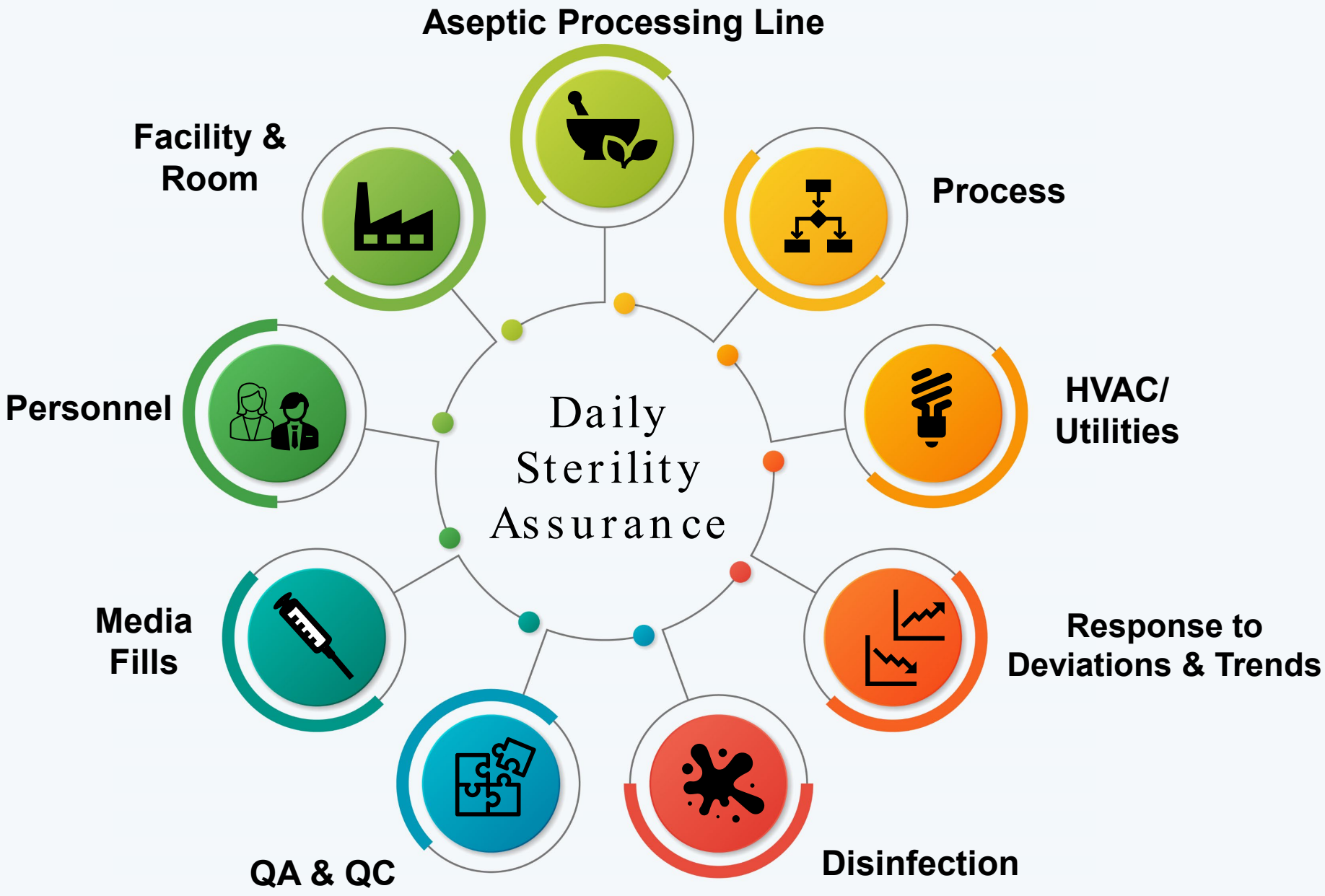
How do you prevent contamination?

DESIGN

EXECUTION

MONITORING

OVERSIGHT



The Macro Model of "Daily Sterility Assurance" (Aseptic Processing)

Current Approach *(21st Century)*	Old Approach *(20th Century)*
Automation	Manually intensive
Integrated	Unit operations
Separation (enclosures; isolation)	Partial barriers

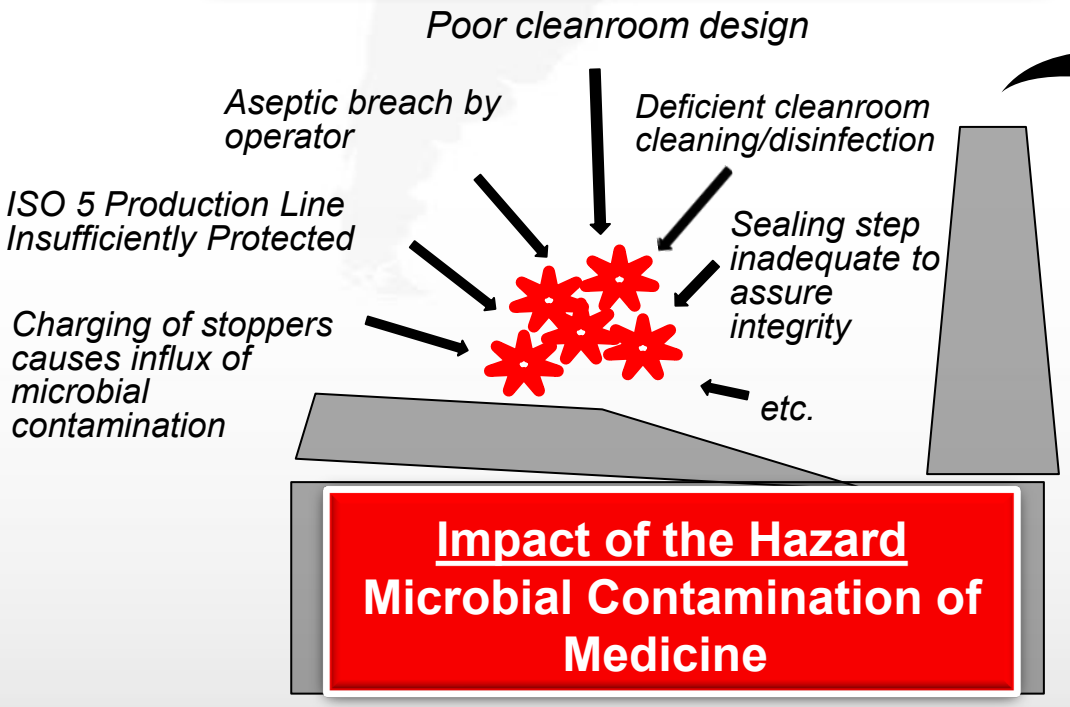
Design Principles

- Optimize cleanroom layout, operational space, air volume, process flow and material flow
- Protect aseptic line with robust isolator-barrier technology that prevents ingress of lower quality air into the ISO 5 (Class 100) area
- Minimize exposure of all sterile product elements and equipment to potential contamination hazards
- Enable vigilant oversight of environmental control via robust building management systems, environmental monitoring, and detectability of deviations in process execution

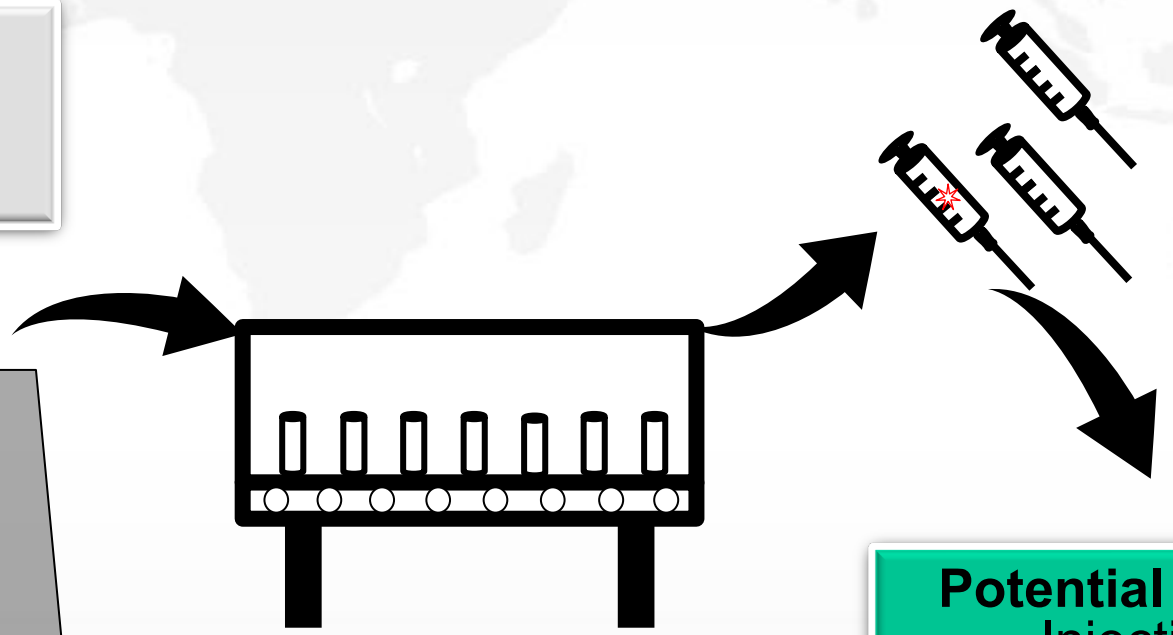
Hazard Identification (e.g.)

Identifying hazardous situations that may lead to contamination is a critical first step in QRM

A single variable, or a combination of variables, can lead to contamination…



Impact of the Hazard
Microbial Contamination of Medicine



Potential for Harm
Injection of contaminated medicine leads to risk of severe patient harm

Critical Role of SMEs in Risk Management: Importance of Microbiologist

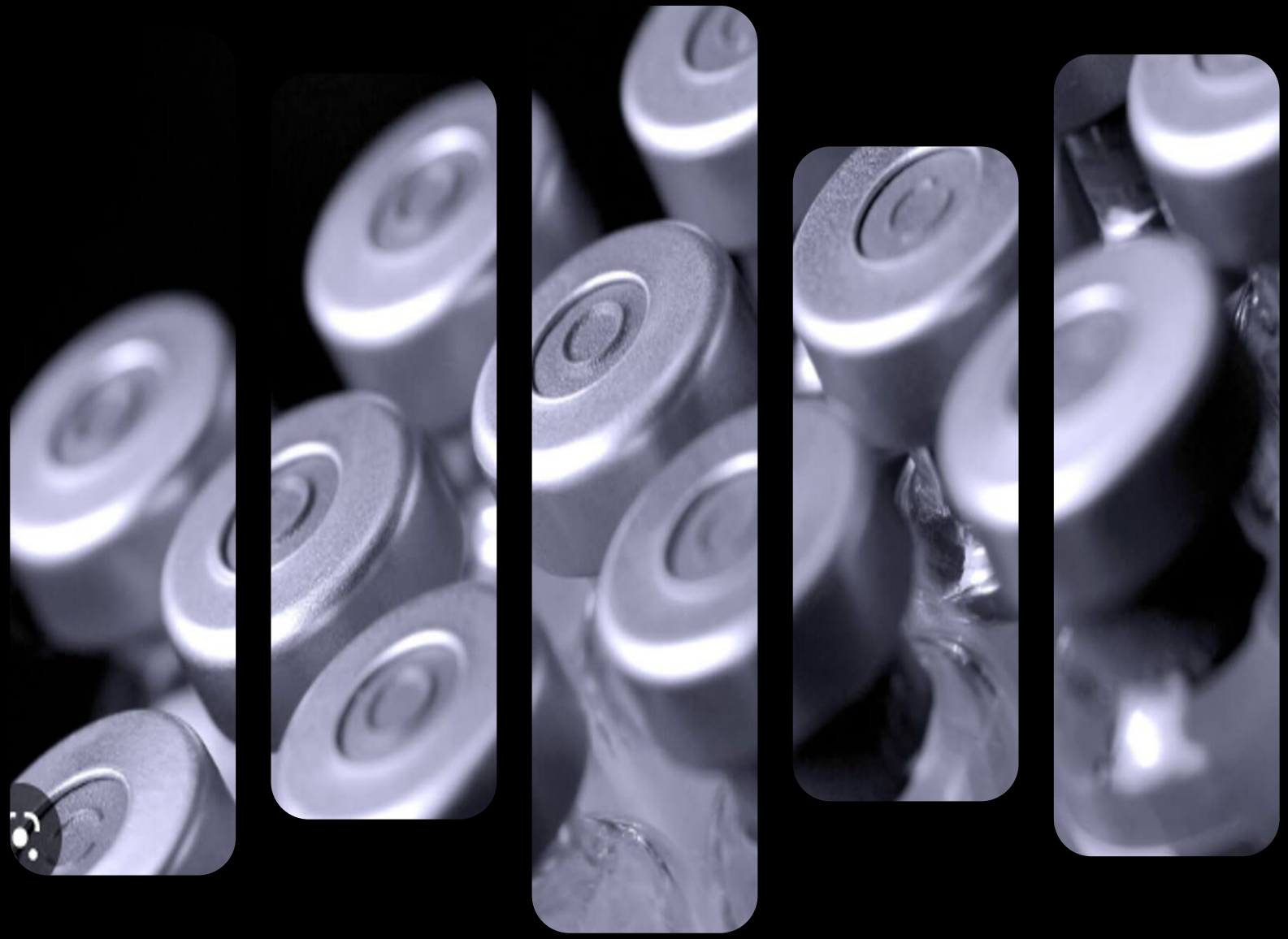
OAI sites with sterility problems frequently had insufficient staff qualified in the science of microbiology.

Are qualified microbiologists doing the following?

1. Conducting and supervising microbiology tests in the QC laboratory
2. Participating routinely on multi-disciplinary teams that make manufacturing design, control, and validation decisions

Microbiology SMEs contribute essential knowledge to enable sound judgments and effective risks management (e.g.):

- **Design**: identifying hazards in aseptic operations; risk reduction options
- **Investigations**: scope and cause of the problem (deviations, rejects, complaints, etc.)
- Defining standards for **Media fills, Environmental Monitoring, Bioburden,** etc.
- **Sanitary system** design & control (e.g., piping, sanitization, biofilm prevention)
- **Disinfection** selection, procedures, and validation
- **Conducting Internal and External Audits** (lead or team member), e.g., evaluating operator aseptic technique and cleanroom behavior; contract laboratory audits
- **Training of employees** on basic microbiology and asepsis
- Selecting appropriate **lab technology** and **test methods**

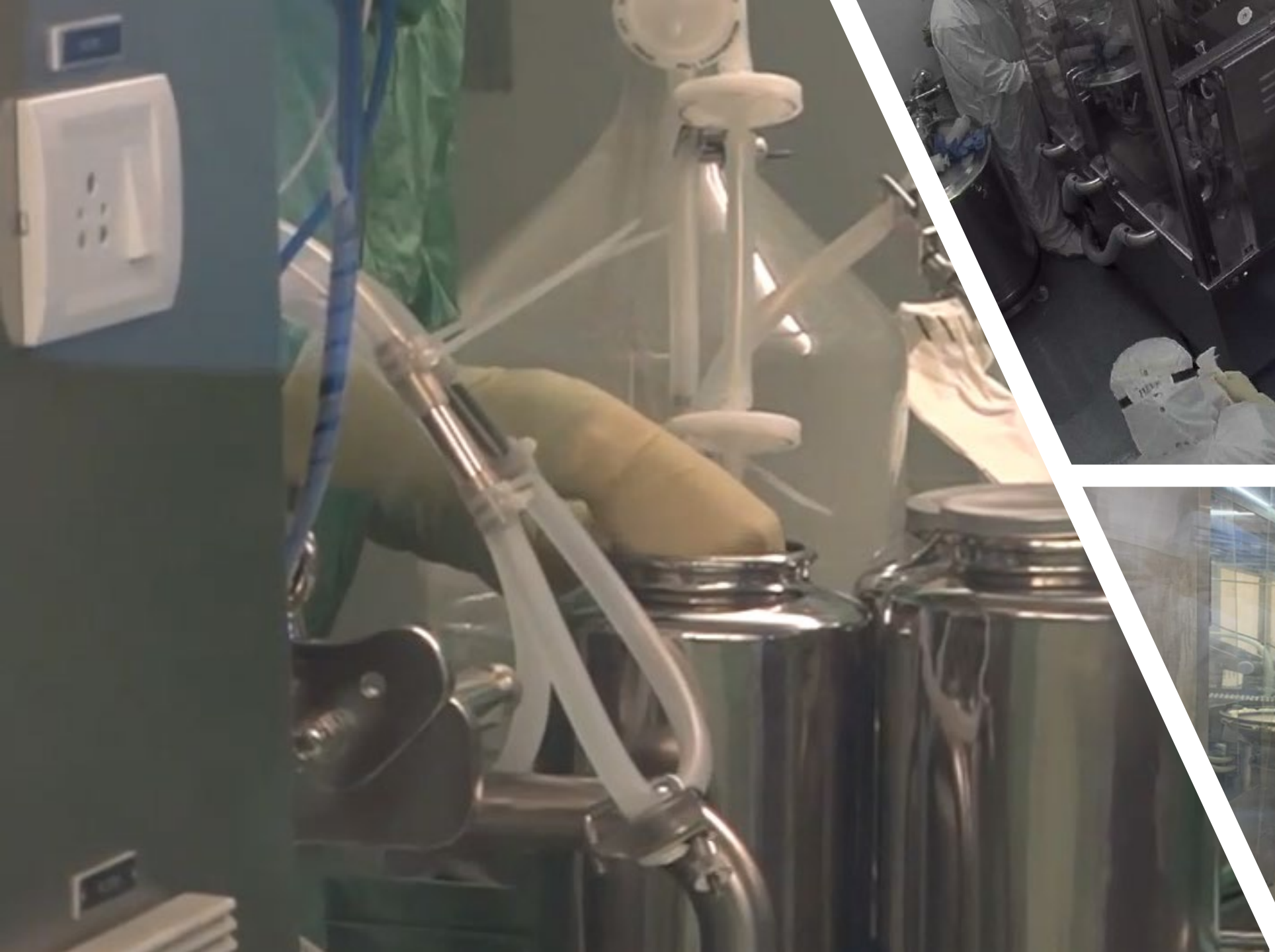


Case Studies

Inadequate Aseptic Processing Operation Design

Partial barrier concept: rigid wall enclosure surrounding the line, along with cleanroom curtains. Not a RABS or isolator concept. Inspection found:

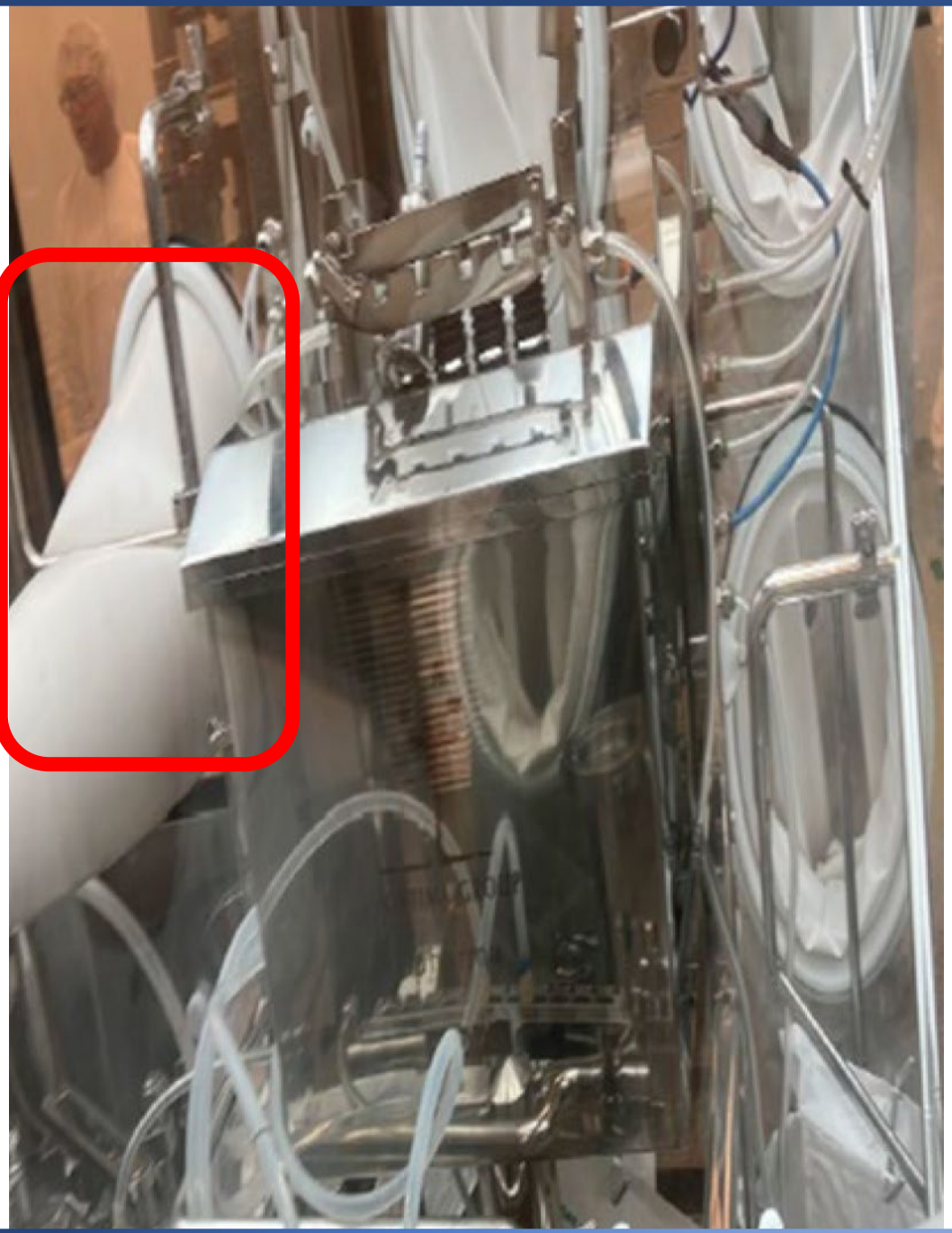
- Setup was manually intensive and not performed aseptically.
  - Poor setup of product contact equipment in enclosure.
  - Multiple aseptic connections after the sterilizing filters (rather than an SIP design).
- Excessive high-risk, highly manually intensive human interventions in ISO 5 area during production (several hundred during a batch).
- Limited barrier enclosure design vulnerable to influx of lower quality air from the surrounding ISO 7 cleanroom.
  - Product contact equipment were poorly protected and compromised assurance of ISO 5 air.
  - Lengthy interventions with enclosure doors open, including door near exposed filling needles. Connections performed under unacceptable air classifications.
- FDA informed company that facility, equipment, and process had fundamental design flaws.



Deficient RABS Operation Example 1

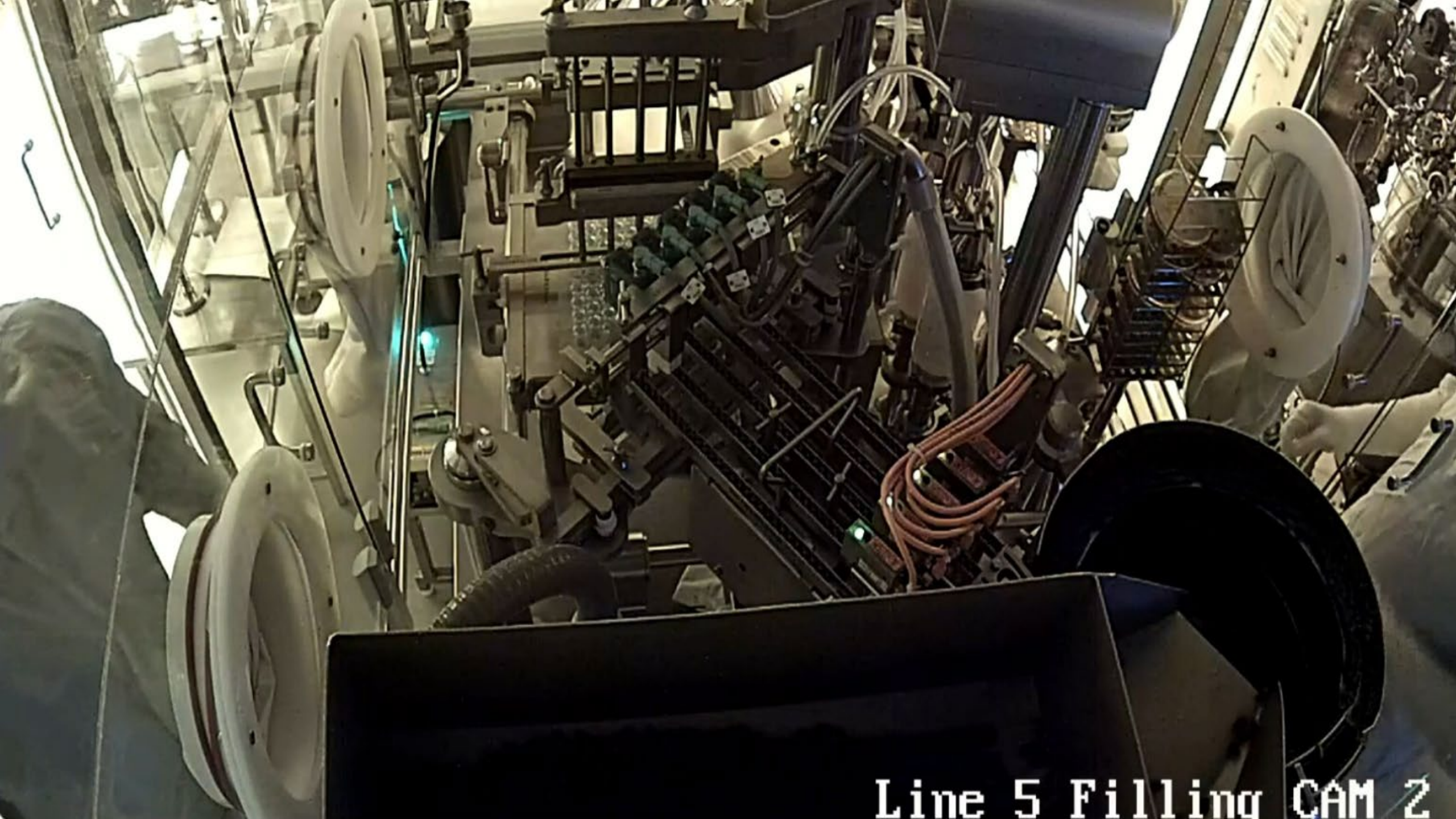
RABS glove suitability was not assured. Significant deficiencies included:

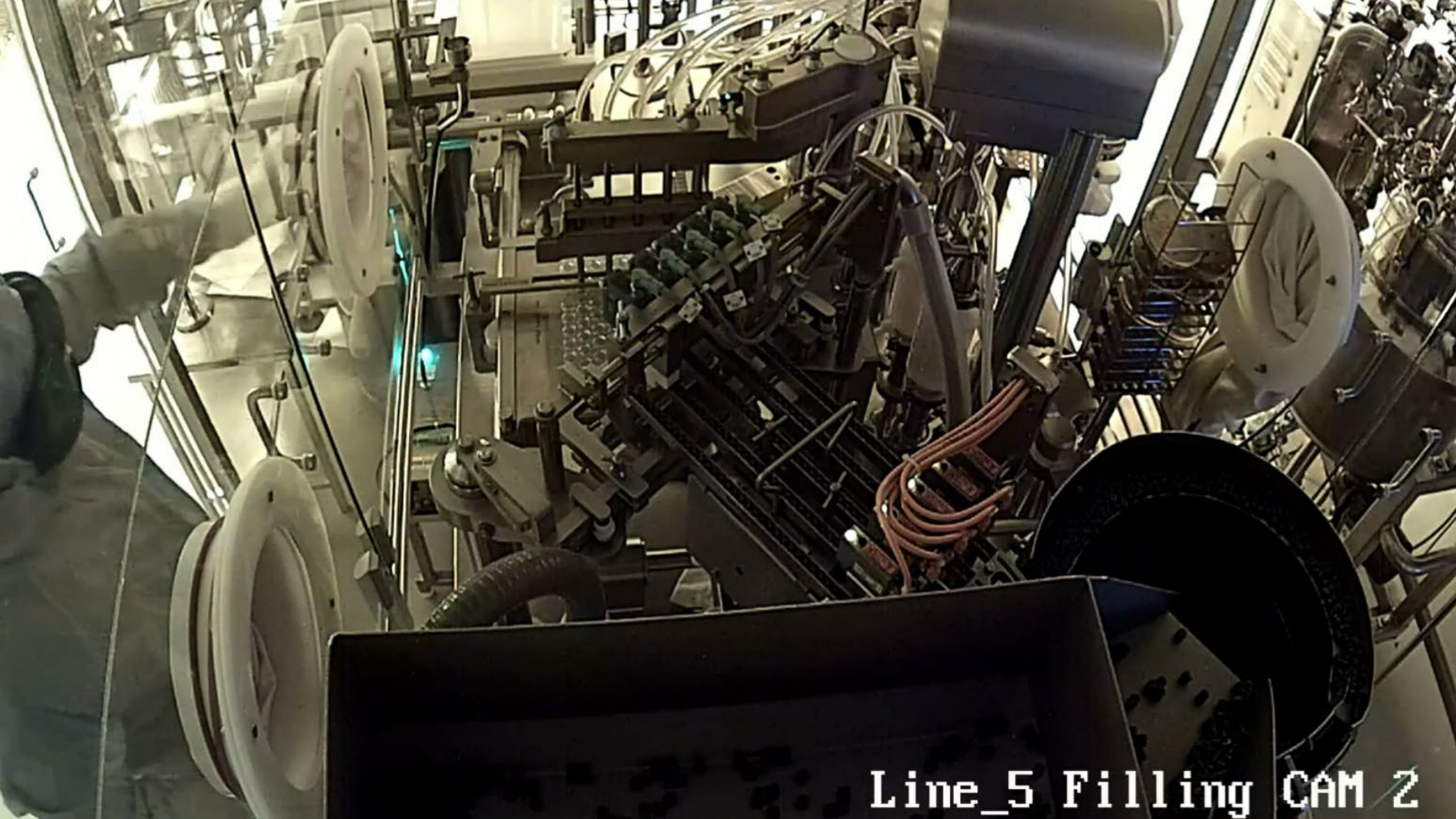
- **Glove sterilization frequency**
  - Gloves sterilized, installed, and used for 2 years without re-sterilization
    - Insufficiently executed manual wipe-down between batches
      Interventions disrupted first air in several instances
- **Glove maintenance**
  - Ineffective maintenance program (e.g., preventive maintenance schedules; inadequate execution of repairs)
  - Leak test frequency only once/month
- RABS glove tears due to **poor equipment design**
  - Recurring root cause: tears and punctures **while performing interventions in the closed RABS (cRABS)**
    - Gloves stretched, contacted sharp machine surfaces
  - Subsequent investigations failed to review age of torn gloves and long-term exposure to disinfectants
- Firm intended to operate a cRABS but opened the door **during** batch operations.

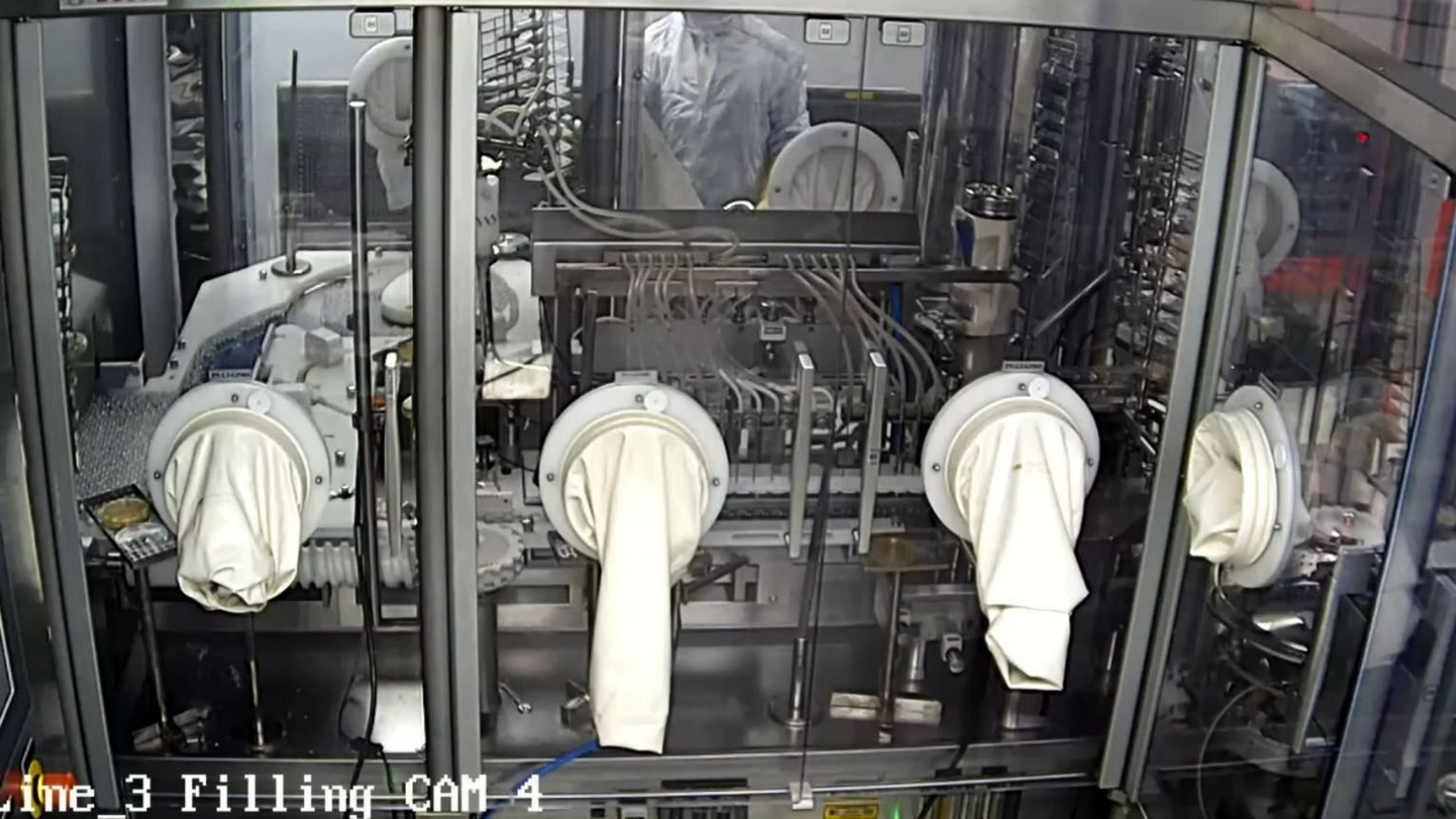


Deficient RABS Operation Example 2

- Open RABS
- Firm lacked sufficient risk-based rationale to support:
  - multi-day campaigning of stopper bowls, stopper tracks, and other sterile contact equipment.
  - the maximum use time of RABS gloves between sterilizations
  - a maximum and appropriate duration for open-door interventions (also, no duration was established in SOPs).


Line 5 Filling CAM 2


Line_5 Filling CAM 2


ime_3 Filling CAM 4

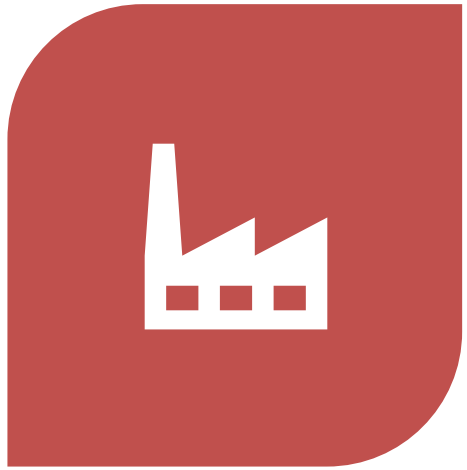
De-Risking Opportunities

Aseptic Processing:

De-risking Opportunities *(e.g.)*

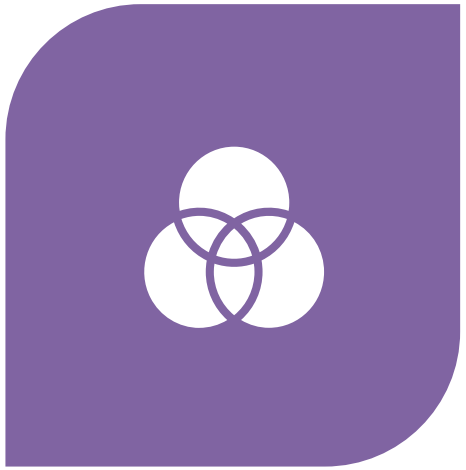
- **Facility:** modern infrastructure
- **Utilities:** SIP instead of aseptic connections should be norm in 2024
- **Equipment:** Isolator or Restricted Access Barrier
- **Cleanroom Design:** ensure appropriate layout and space for appropriate flow and to perform interventions aseptically
- **Integrated Transfers:** including automated loading of lyophilizers; RTPs; etc.
- **Automation**: change from manual interventions to automated steps (e.g., *robotics*)
- **Better Smoke Study Interpretation for Hazard Identification** – expert reviews of risks, and implementation of needed risk reductions
- **Digitalization**: Building Management Systems (improved software leverages continuous monitoring for earlier detection and more proactive facility control in line with Pharma 4.0), etc.
- **Rapid Testing/Monitoring Technologies:** to augment monitoring and control for better detection, quantification, and identification

Summary: De-Risking Aseptic Processing



MANUFACTURING CAPABILITY DETERMINES QUALITY OF OUTPUTS (MEDICINES)

ROBUST DESIGN OF FACILITIES, EQUIPMENT, PROCESSES, SYSTEMS, AND PROCEDURES IS CRITICAL TO ASSURING STERILITY



DE-RISKING DECISIONS ARE DRIVEN BY A COMPLIANT QUALITY SYSTEM, WHICH IS THE FOUNDATION FOR SUSTAINABLE COMPLIANCE AND QUALITY ASSURANCE

Acknowledgements

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