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MEDICAL MANUFACTURING COMPANY, *MONZA, ITALY*

ASEPTIC EXPERTISE AND DELIVERY OF SERVICES

CASE STUDY: COMPLIANCE AND REGULATORY ISSUES

Aseptic Expertise and Delivery of Services

PROJECT OVERVIEW

In February 2024, CAI was approached by a leading pharma industry services company that provides solutions including end-to-end drug development, clinical trial services, and commercial manufacturing solutions to customers of all sizes. Commercial Production had ceased for two months after routine semi-annual requalification of the aseptic simulation process (APS or media fill) performed on a contract manufacturing site's sterile line detected one contaminated unit (Batch Size over eighteen thousand units incubated).

Site leadership hired CAI for their aseptic expertise and services, to perform independent observations and provide feedback on the practices and behaviors on the line after the recent aseptic process simulation (media fill) failure as a deviation corrective action. Client Relationship management was imperative from the start of the project and the team engaged with the site to build a collaborative relationship. An operational excellence strategy was implemented with several improvement techniques to ensure the startup of manufacturing activities in a timely manner and prevent a drug shortage due to a reoccurrence.

CLIENT:
Confidential

LOCATION:
Monza, Italy

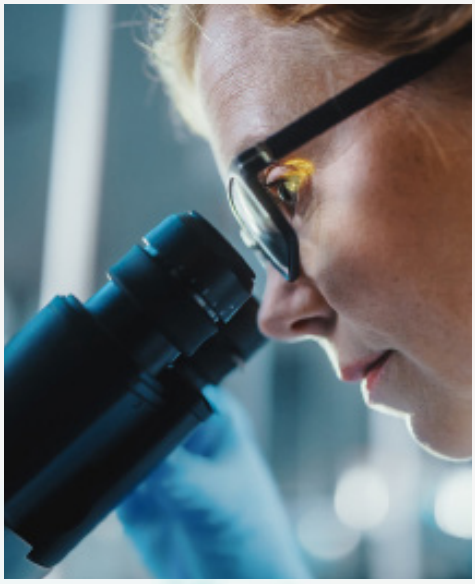
TIME FRAME:
2 months

CONTRACT SIZE:
Unknown

CLIENT CHALLENGES

Following the detection of one contaminated unit during the routine requalification of the aseptic simulation process, the client requested CAI's support.

The contamination detected within the vial was identified as Staphyococcus cohnii, a Gram-positive coagulase-negative, commonly colonizes human skin. There were more than 60 batches manufactured on that line since the last successful APS. The most recent successful APS was 6 months earlier.



The site used multiple techniques to identify potential root causes during the Deviation investigation including the 5 Whys, Fishbone, and Risk Registration Scoring Matrix. These analyses highlighted the most likely root causes as well as contributory root causes.

Two specific types of abnormal activities were observed:

- During set-up, an irregular, non-routine opening of the RABS door was observed based on difficult-to-open needle sheaths.
- Three (3) stopper interventions were completed in a suboptimal manner.

CAI documented the following process and equipment observations:

- The sterile line was an open RABs type and was older than other lines. Setup occurred via operator knowledge with guidance from Team leads and quality on the floor instead of step by step procedures.
- Some equipment was heavy and difficult to install. There was no stainless-steel step was available for operators to provide easier access.
- No IPA wipes were available; therefore, all aseptic wipe downs were performed via IPA spray and cloths. This caused excessive waste management and handling issue for the production team.
- Sanitisation techniques were observed and compared across shifts to verify consistency.

CAI worked with site personnel, providing feedback on all observations documented in specific Cleanroom Observation Checklists for the Dry Run, Effectiveness (water) Runs, and requalification APS (Media Fill) Runs. The Dry Run provided the opportunity to retrain the operators on the new procedures and provide coaching and oversight for the new and updated behaviors.

After the Dry Run was observed, CA recommended several Effectiveness (water) Runs which would verify that all operators were fully retrained, recommendations were in place, and behaviors modified prior to the APS (media fill) to increase probability of success.

CAI SOLUTIONS

CAI outlined a project overview to the client using number of Operational Excellence (OE) techniques including value stream mapping, statistical tools, and 3Ps.

It was important for CAI to map the process as well as provide a Value Stream Map, ref. Figure 1 and 2. Process Flow, Value Stream Mapping, including Time Value Mapping using both the written procedure and how the process really worked highlighted non value added processes (e.g. repeated processes such as the needle sheath Statistical techniques)

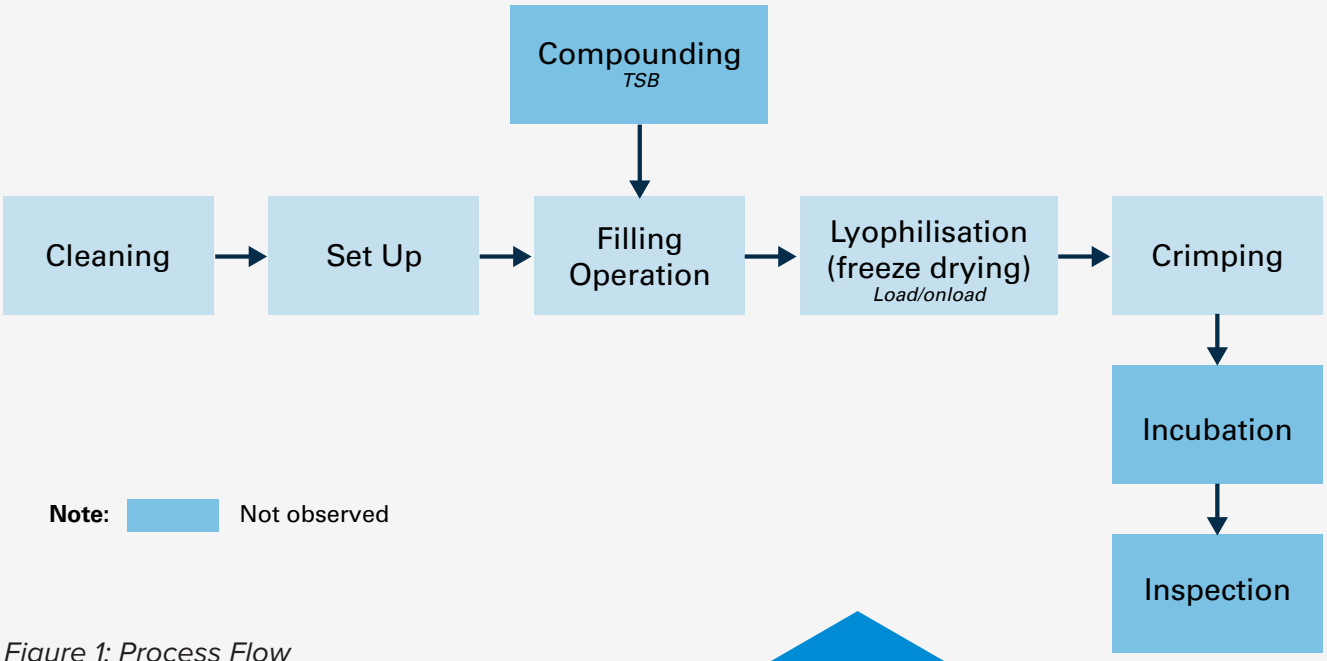


Figure 1: Process Flow

CAI observed the aseptic rooms Cleaning, Equipment Set-Up, Filling Operations, Lyophilization and the Capping/Crimping operations. During each operation, CAI observed the practices and behaviors.

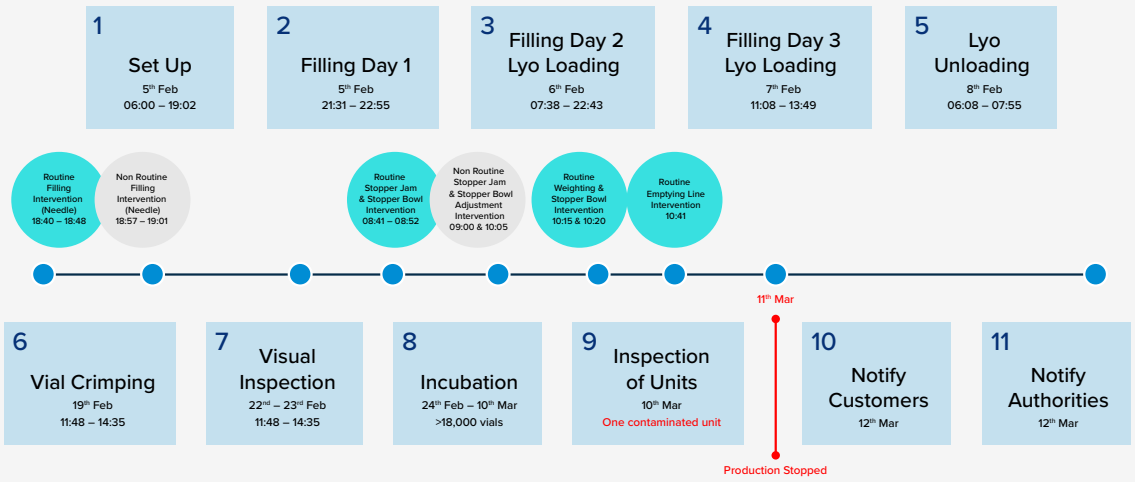


Figure 2: Value Stream Map - Timeline

Use of the 3Ps, Process (Procedure), People, and Plant, was instrumental in the success of this project. This framing verifies important production milestones were adhered to in providing the necessary aseptic protocols, observation checklists, strategy documents, and continuous improvements to ensure a successful requalification aseptic simulation process (APS or media fill).

- **People:** Discussing Aseptic Techniques with Production, Team Leads, Quality, and Sterility and Operations. Reviewing the aseptic techniques, practices, and behaviours then documenting improvements and sharing lessons learned.
- **Plant:** While this project was focused on operational issues, some inefficiencies and opportunities were observed, and recommendations were provided. Identified specific issues with autoclave cycle times, WFI usage and process, and equipment design and age.
- **Procedures:** Reviewed, updated, and developed procedures and On the Job (OJT) training to aid production startup.

Statistical Techniques were used by CAI to assess the relevance of the results and data gathered; the team was committed to a data driven approach throughout the project. The use of graphical techniques to analysis improvements throughout the aseptic process was integral to the success of the analysis and to documenting and implemented the risk assessment recommendations

IMPROVEMENT RECOMMENDATIONS

A continuous improvement project was set up to track and record the improvement recommendations to the sterile line. All training activities were also tracked via the document management system.

Improvement in aseptic behaviour and practices were observed during sterile line operations and changes in practices were made which were implemented across all sterile lines on site. Industry best practices and expectations from the following sources were incorporated into checklists and protocols used on site:

- The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use ANNEX I, Manufacture of Sterile Medicinal Products
- Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, U.S. Department of Health and Human Services, Food and Drug Administration
- World Health Organization WHO Technical Report Series, No. 961, 2011 Annex 6, WHO good manufacturing practices for sterile pharmaceutical products

Aseptic Expertise and Delivery of Services

PROJECT SUCCESS

CAI's presence on site provided guidance and assurance on Annex 1 requirements implementation through the delivery of an Operational Excellence Project that finished on time and within budget. The operators were re-trained on aseptic practices and behaviours. New improvements were made to the affected sterile filling line in relation to instrumentation, bin management, equipment and set up, as per CAI's recommendations. The requalification of the sterile filling line through the aseptic simulation process (APS or media fill) passed and CAI is providing ongoing routine oversight for a number of months to aid in commercial production.

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