Contamination Control Strategy, Check! Now What? Lifecycle Management of CCS

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Introduction

Establishing a Contamination Control Strategy (CCS) is a requirement per EU Annex 1 (Aug 2022). Once a CCS is established, the challenge becomes; "how do I ensure appropriate lifecycle management and effectiveness monitoring for my CCS?" This poster presents regulatory requirements and industry guidance for CCS lifecycle as well as examples of integrating CCS review into existing quality management system processes to ensure CCS remains updated and accurate. Additionally, the use of tools to automate and digitize monitoring of the effectiveness of CCS are presented. The goal is to ensure sustainable CCS lifecycle management, which enables appropriate prevention, detection, and remediation, complying with regulatory requirements and ensuring safe products for patients.

Regulatory Requirements

Regulations require periodic review, effectiveness assessment, and continuous improvement of CCS.

EU Annex 1 (2022):

2.3 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. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.

2.6 The CCS should consider all aspects of contamination control with ongoing and periodic review resulting in updates within the pharmaceutical quality system as appropriate. Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.

Industry Guidance

Available industry guidance provides good practices for performance/trend/data review for CCS.

PDA Technical Report No. 90, Contamination Control Strategy Development in Pharmaceutical Manufacturing (2023):

11.1 Trending and Metrics

Metrics, including key performance indicators (KPIs), permit firms to respond to signals from the CCS. Metrics should effectively assess the holistic performance of the CCS and include both predictive and reactive measurements. Each metric should be assessed during the periodic review; **Table 11.1-1** presents some examples.

Table 11.1-1 Examples of Metrics to Be Assessed during Periodic Review

Predictive Metrics	Reactive Metrics
KPIs related to quality culture	Facility nonconformances related to controls within the CCS (e.g., EM deviations)
Capital improvement focused on contamination control including new control and measurement technologies	Process nonconformances related to controls within the CCS (e.g., EM or raw material pyrogen/endotoxin trend)
Mitigation of contamination control risks as assessed through CRM activities	Product nonconformances related to controls within the CCS (e.g., sterility test failure)
CAPA effectiveness and on-time implementation	Process capability and voucher performance
Conformance to schedule for planned contamination control qualifications and validations	EM trending across the site and deviations, root cause analysis, risks assessments, and mitigations in response to adverse trends
Conformance to schedule for planned contamination control risk assessments	Other deviations associated with contamination control including, but not limited to, control failures, training gaps, facility knowledge transfer
Conformance to schedule for maintenance activities related to the CCS	Unplanned/corrective maintenance

The goal of trending is to permit a holistic analysis of control information over a period of time or across different circumstances. Such analysis facilitates identification of patterns, potential influences, and genuine root causes of nonconformances.

Metrics, KPIs, and data relevant to routine monitoring should be categorized and trended to monitor the holistic performance of CCS, for example:

- Root causes of nonconformances (e.g., control designs, training, knowledge, communication)
- Control charting of both variable data (e.g., numerical quantities and composition of microbial flora recovered in lower classification cleanrooms) and attribute data (e.g., presence or absence of colonies recovered in Grade A location monitoring)

12.0 CCS Governance and Effectiveness Review

The CCS should also be reviewed periodically (preferably reviewed annually) for effectiveness to ensure it remains current with the process and aligned with industry standards, specifically the potential need to adopt new, more effective technologies. The periodic review should be done by a multi-departmental team to monitor the effectiveness of contamination controls related to the process, product, personnel, and facility/utilities, including, but not limited to, evaluating quality trends, contamination events, change control, and validation activities. A practical way to achieve this and reduce the administrative burden is to formally monitor these elements throughout the year in regular meetings of the multi-departmental team that will be involved in the periodic review.

PDA Technical Report No. 69, Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations (2015)

The design approach presented in this chapter emphasizes the importance of implementing a contamination-control program that covers the process from beginning to end and includes built-in mechanisms for frequent reevaluations and feedback throughout the product lifecycle. The strategy should take into consideration components of the production and control system (**Figure 4.0-1**). In addition, the design and routine manufacturing process must be supported by robust quality systems to document, review, correct, and improve the processes.

PHSS Contamination Control Strategy Guidance Explanation Document (2023):

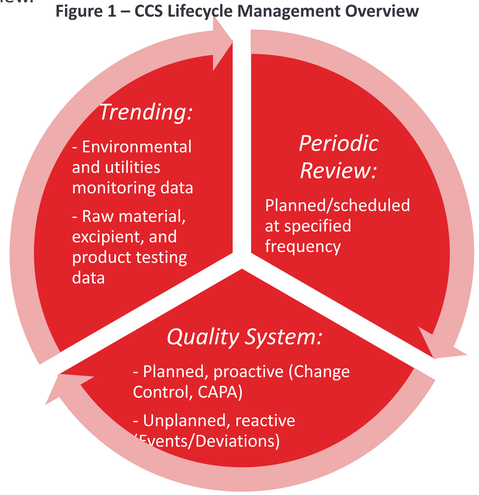
The CCS is supported by governance and lifecycle strategies (including response management) to ensure that effective processes and systems are in place, remain in control, address, and mitigate risk when it occurs, to ensure the minimization of contamination and proliferation.

The collective effectiveness of the controls that combine to assure sterility of products and/or bioburden control requires assessment. Such an assessment will include performance/ trend and deviation incidence rate reviews related to Key performance Indicators (KPIs).

CCS Lifecycle Management

Once a CCS and corresponding risk assessments (RAs) have been developed, it is critical to ensure the CCS/RAs remain current and accurate. The CCS should be reviewed both proactively (scheduled frequency) and reactively (in response to data or as required by Quality System (QS) records). A trend or contamination-related event/deviation should trigger review of the CCS/RAs and the CCS/RAs should be updated as an outcome of QS such as CAPAs, to accurately reflect the current status of the controls. In the current case study, this feedback loop for CCS review/update was built directly into the QS deviation workflow as part of the investigation plan template and into the Documentation Management System for periodic review.

Figure 1 – CCS Lifecycle Management Overview



CCS Effectiveness Monitoring and Continuous Improvement

CCS Effectiveness Monitoring

It is important to monitor the overall effectiveness of the CCS. The measurement and visualization tool/metric must be appropriate and accurate. Below is a case study summary showing the evolution of global CCS effectiveness monitoring using product testing and financial data.

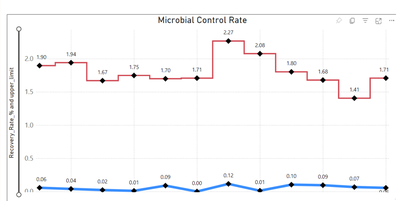


Figure 3 – CCS Microbial Control Rate Example

Figure 2 – Case Study: Journey of Global CCS Effectiveness Monitoring

Financial Loss due to microbial contamination (amount in USD)

- Automated data pull - events from QS
- Manual categorization by finance personnel
- Automated Qlik Sense® data visualization

Future Efficiencies Using Artificial Intelligence (AI)

- Fully automated, predictive
- Holistic evaluation of multiple data types (detection controls such as EM/utility trends, product testing)

CCS Events (# of deviations due to microbial contamination)

- Automated data pull from QS - predefined list of values for deviation categories related to microbial events
- Automated data visualization in Microsoft Power BI

Microbial Control Rate (# action level results/total # of tests)

- Manual data entry by SME into spreadsheet
- Minitab® data analysis initially, then transitioned to automated Microsoft Power BI data visualization

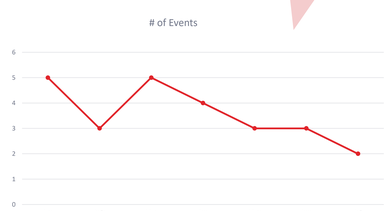


Figure 4 – CCS Events Example

Continuous Improvement

Use of Quality System (QS) or Laboratory Management System (LMS) as source data enables direct association with actual deviations and contamination events or raw data.

In this case study, there have been several iterations over the years as technology became available and global systems integrated. Ideally, for a global organization:

- Single validated electronic database (source)
- Automated, real time data visualization and analysis
- Dashboard accessibility for reporting to site and global leadership
- Data entry is accurate

Lessons Learned / Summary

Lessons Learned:

- An appropriate and validated link to existing data systems is important
- Determining appropriate and meaningful metrics/KPI can be difficult and may take time to ensure sufficient data is available
- Program/tool considerations – visualization/dashboarding/data analysis
- It can be challenging to ascertain categories are being applied correctly by many users to ensure accuracy

Benefits/Summary:

- Incorporating CCS lifecycle management requirements as part of standard processes/workflows brings CCS "to life"
- CCS effectiveness monitoring data accessibility and visualization
- Use of automated analysis: timeliness = "real time"
- Integrated quality systems/common data source (e.g., Quality Management System, electronic database) and ideally, globally-accessible tools/dashboard support a successful global CCS lifecycle management and effectiveness monitoring program