Establishing a Contamination Control Strategy/Program: From Global Development to Site Implementation

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Introduction

The necessity – from a patient and business perspective – along with increased pressure from regulators to establish contamination control programs at pharmaceutical manufacturing facilities, have led to a need to define what elements would comprise such a program and how the program would be sustained to ensure continued success. Contamination control encompasses all aspects of contamination such as particulate, microbial, product carryover, chemical (e.g., cleaning material residue), as well as viral, where applicable. This article aims to outline the strategy from global development through site implementation, within the lens of lifecycle management to ensure continuous improvement. Local strategies can easily be derived from this approach.

Regulatory Expectations

Contamination Control, Microbial Control or Particulate Contamination are terms, which can be found in several guidance documents or standards (e.g. FDA Guidance for Industry - Drug Products Produced by Aseptic Processing or ISO 14698-1: 2003, Cleanrooms and associated controlled environments - Biocontamination control) for years. However, the new draft of Eudralex - Good Manufacturing Practice (GMP) guidelines, Annex 1 "Manufacture of Sterile Products", released for review in December 2017 and in February 2020 for targeted review (but still not effective), emphasizes the role of Quality Risk Management in pharmaceutical manufacturing. In particular, the document clearly states that "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 organizational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods."

Furthermore, the document lists 15 specific requirements which should be included in such a contamination control strategy/program (CCS/CCP) and highlights, that additional requirements can be added.

Most organizations likely already have many of these elements of a CCS/CCP available, but they may not be collated through a holistic single source document and may not include a life-cycle approach

(including periodic review and update), as it appears to be the intent of the future EU-GMP Annex 1 requirements.

Therefore, the overall current challenge for the industry is bringing all the information and programs together, adding one or the other currently missing aspect to a holistic, multi-element, and formally documented strategy/program with systematic interacting mechanisms and a defined life-cycle approach to assure a high degree of elimination of all potential contamination sources/ways and which should be implemented globally (across all sites, where applicable).

Elements of a CCS/CCP

As described above, the new EU-GMP Annex 1 Guide will require a holistic documented strategy/program related to Contamination Control. Annex 1 will provide 15 key elements for such a strategy/program; they are summarized in the light blue boxes in Figure 1.

However, companies should keep in mind that this is a minimum requirements list and that it is beneficial to include additional elements and a strong support structure for such holistic programs.

Figure 1 below shows one possible approach for such a program. But companies should focus additionally on comprehensive Proactive and Reactive elements in their CCS/CCPs, as well as include a defined lifecycle strategy with a knowledge management and sharing tool/mechanism.

Refer to the bullet points below for examples:

- Proactive Aspects:
  - » Embed CCS/CCP in the company culture and mindset, everyone needs to be aware of CCS/CCP and the associated programs.
  - » Thorough Risk Management Strategy.
  - » Continuous Self-Assessments/Gap Assessments regarding the defined CCS/CCP elements.

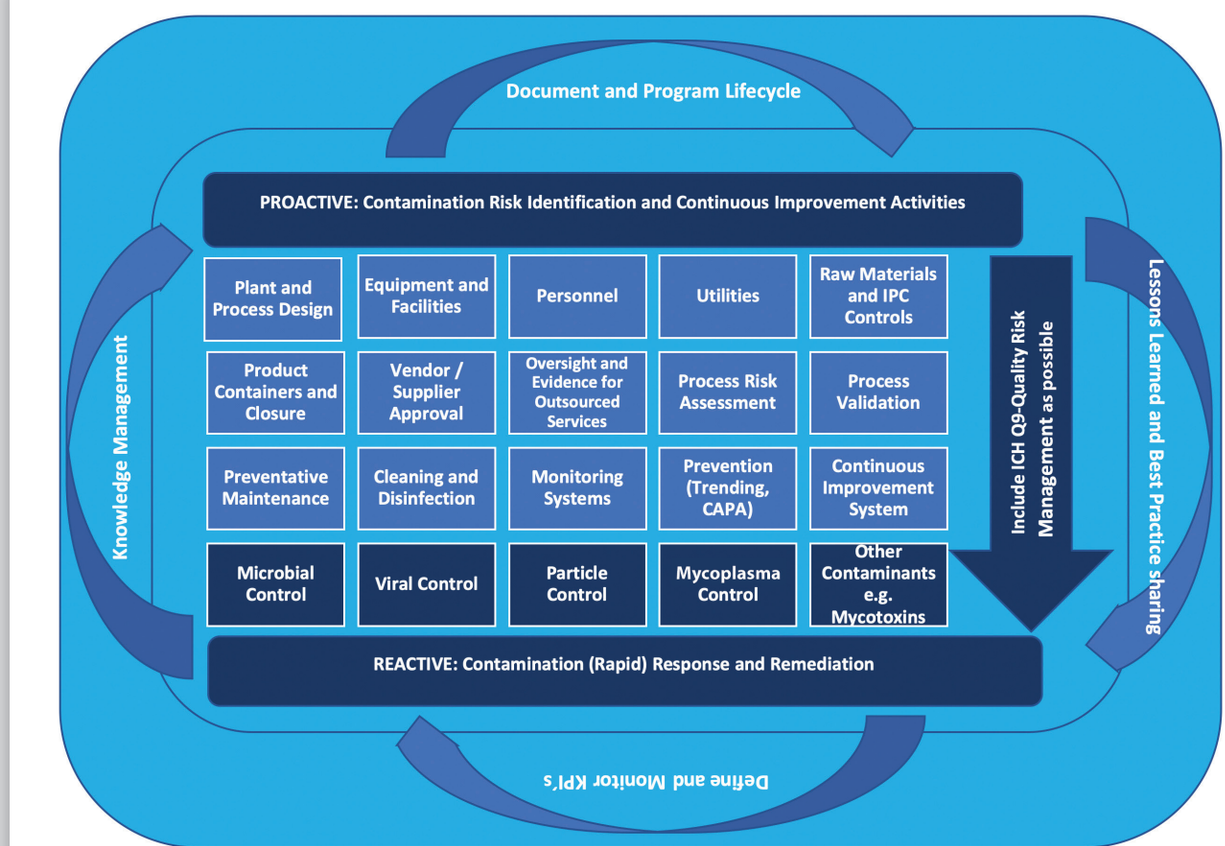

Figure 1. Elements of a holistic CCS/CCP and supporting aspects

  - » Continuous Improvements.
  - » Inclusion of CCS/CCP topics in daily huddle meetings.
  - » Establishing a program where focus areas (e.g. preventative maintenance for gaskets, difficult to clean equipment, bioreactor processes) are identified for improvement opportunities on a routine basis.
- Reactive Aspects:
  - » Define a Rapid Contamination Response Approach (and a team).
  - » Good CAPA Management, including a thorough investigation and contamination impact assessment.
- Supporting Aspects:
  - » Define a Lifecycle for the CCS/CCP program and CCS/CCP document (including revision/update and a compendial/regulatory requirement review).
  - » Define meaningful KPIs (Key Performance Indicators) and how success looks like for the individual program.
  - » Share best practices and lessons learned and establish a knowledge database, as applicable.

The next section describes how Takeda implemented a global contamination control program over a portion of its manufacturing network using the holistic approach described above. This program was implemented at Shire, before Shire's acquisition by Takeda.

Case Study

As a global company, establishment of a contamination control strategy/program at Takeda involved a partnership between both global and site entities. Global functions provided the structured elements based on regulatory expectations and industry best practices whereby sites then based their own site CCS/CCP. Sites provided the aspects unique to their manufacturing facility as to how they comply to the global requirements, as well as feeding into the global program their own site best practices to be shared with the overall community.

Building the foundation – developing a global program

Contamination control was identified by the company's leadership team as one of the top "Right First Time" strategic initiatives. The high visibility and sponsorship of the program by the leadership team was a key factor in driving the implementation of the program across the network.

A cross-functional team led by Global Microbiology consisted of experts in microbiology, quality control/quality assurance, engineering, facilities, manufacturing, operational excellence, and leads for the operational business units (i.e. Biologics, Plasma) who defined the key CCS/CCP elements and sub-topics for each element. A comprehensive list drawing from established global procedures and regulatory guidance formed the basis of the global CCS/CCP program. To bolster the program further, defining elements exclusive to CCS/CCP were included. These elements were the proactive contamination prevention and reactive contamination response parts, which has previously been described.

Also distinctive to the global CCS/CCP was defining best practices from SMEs (Subject Matter Experts), within the industry, but most importantly, as identified and established at sites within the company itself. To achieve this, a small team consisting of Global Microbiology, Engineering, and the Operational Business Unit lead performed several site visits using a standardized questionnaire based on the identified key CCS/CCP elements. Best practices and opportunities for improvement were identified and incorporated into the global program with the added benefit of a closer look with outside eyes at the site, leading to recommended improvement opportunities.

Site implementation – bridging the gap between global requirements and individual site practices

With over 10 manufacturing sites that each had their own diversities (e.g. new vs. ageing facilities, different product manufacturing processes, different equipment, different organizational structure and support), it was critical to identify site representatives that would be the site CCS/CCP owner and liaison to the global program. A standardized site specific CCS/CCP template format was used to ensure consistency across the sites and a Contamination Control Community of Practice (CoP) was established to allow sites to raise questions and share experiences (with the eventual goal for this community to be a forum for the network to share best practices, lessons learned, etc. to strengthen each site's program and success in contamination prevention).

In addition to the site CCS/CCP representative, each facility established their own site CCS/CCP team that would meet and discuss contamination control relevant topics at regularly defined intervals. Some sites even created a dedicated CCS/CCP lead role to manage this topic on a full-time basis at the site. These site teams are also actively involved in rapid responses, which is a global requirement that draws upon operational excellence concepts and DMAIC (Define, Measure, Analyze, Improve, and Control) tools.

As expected, improvement opportunities were discovered in the process of adapting to the global CCS/CCP. Project plans were put in place to acknowledge these areas of improvement and outline the course of action to boost current site-specific contamination control efforts. Examples include enhanced preventative maintenance programs for e.g. gaskets, consideration of wear/stress for defining frequency of replacement of elastomers and increased aseptic awareness trainings. The latter example became, and continues to be, a critical piece of the CCS/CCP that is constantly being improved upon, including collaborations with external vendors and introduction of virtual reality trainings.

Lifecycle management – how to keep the program moving and improving

Embedding lifecycle management ensures that the global program and each site program is reviewed and given the opportunity to

improve regularly. The first step to do this is to have a requirement that the program must be revisited at a regularly defined time (e.g. 2 years). Minimally, this ensures that the program is reviewed routinely. The second step is to establish KPIs and metrics to measure against, to show whether circumstances have improved/worsened/stabilized, and to be able to see what the next step would be for improvement and/or sustaining a stable process/environment. Lastly, and more challenging, is to maintain engagement across the network through CoPs, awareness fairs, trainings, etc. to keep contamination control in the forefront.

As the program evolves, there needs to be an effort to incrementally add more requirements or contamination control aspects to be addressed and guidance that would push the limits of proactive contamination control rather than reactive.

Sustainability as an Integral Part of CCS/CCP

A robust sustainability strategy for such global holistic programs is key for long-term success. Very often, such highly visible large-scale programs are rolled-out under time pressure in order to complete all defined milestones within the timelines. One to two years after the roll-out, the focus shifts, unfortunately, often heavily on other projects, with the former projects getting less and less visibility and consequently, less attention and less priority. Therefore, a pre-defined (before complete rollout) robust sustainability strategy is an integral and important part for a holistic CCS/CCP. Below are some recommendations on how such a strategy can look like.

- A defined team (best possibly and as applicable, a global team) should own and oversee a CCS/CCP.
- Mindset and awareness are key! Awareness campaigns/ activities shall be planned and repeated on a regular basis (e.g. included in annual reoccurring trainings).
- A good global, as well as intra-facility, communication strategy for all topics around CCS/CCP should be established.
- KPIs and tracking metrics should be defined for the CCS/CCP and collected and monitored regularly (e.g. quarterly).
- Lessons Learned and best practices around CCS/CCP topics should be collected and shared regularly.
- Perform internal (sites) and external (industry) benchmarking.
- Perform site visits and site assessments on a regular basis by cross-functional teams (e.g. from personnel at the site, from other sites, or global). Consider accounting for these site visits during annual budget planning discussions if travel is involved.

Benefits and Challenges

The benefits are clear for implementing a CCS/CCP through a global approach, but that does not mean that it is without any challenges. Table 1 outlines some examples of benefits and challenges to implementation and sustaining of a CCS/CCP, some of which were referred to in the previous section.

Table 1. Examples of Benefits and Challenges

Benefits		Challenges	
✓	Harmonized global approach across sites on key CCS/CCP elements	×	Competing priorities
✓	Consistent requirements to measure oneself against	×	Budget and resource restrictions (e.g. for higher cost projects involving facility and equipment design)
✓	Community engagement and feedback loop through, e.g. global and site community of practices	×	Changing the culture to encourage a proactive mindset

The question remains – how to overcome these challenges? Recommendations are listed below, based on lessons learned from the initial program roll-out at Takeda:

- Communication!
  - » There needs to be frequent and regular communication and feedback from all stakeholders. The strategy and timelines should be transparent and achievable – each site in a network is distinct and have their own set of experience and challenges that must be considered when rolling out such a strategy.
- Clearly distinguish between mandatory requirements and optional best practices.
  - » The best practices collected from site assessment visits, community of practice discussions, and industry are key for being proactive in contamination control. Originally, Takeda combined requirements and best practices into a holistic single CCS/CCP document. After initial site implementation, it is now realized that requirements need to be clearly separated to reduce confusion in what needs to be enforced vs. "nice to have". Then, the best practices would be used as a supplement to enhance the requirements, to be regularly updated and later become requirements, if applicable, on a global level.
- Appoint a dedicated CCS/CCP role at each site.
  - » While a site CCS/CCP representative may be identified at each site, this may not be the person's primary responsibility. However, contamination control is a full-time job that requires constant cross-functional interactions and championing to drive improvements.

Conclusion

By identifying and capturing the necessary elements of a CCS/CCP in a formally documented, global strategy/program with systematic interacting mechanisms and a defined life-cycle approach, a pharmaceutical company will gain benefits in a wide variety of aspects. These aspects include a better overview of how all processes interact, removal of redundancies, increasing the possibility to proactively influence changes and strategies in elements related to contamination control, to identify potential gaps, and to avoid product loss and thus, support patient supply.

At the same time, companies will be prepared to fulfill increasing and upcoming regulatory expectations related to CCS/CCP, especially once the new EU-GMP Annex 1 guideline will be effective.

Budget/Workload restrictions or mindset barriers might create setbacks for implementing a CCS/CCP through a global as well as site-specific approach, but the benefits certainly outweigh these potential restrictions/challenges. Collaboration and strong communication with stakeholders at global and site levels are essential for overcoming such challenges and maintaining program sustainability.

References

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Author Biographies

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