How to create CCS?

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Q1 Creating a contamination control strategy (CCS) is now a requirement defined in Annex 1 of the European good manufacturing practice regulations (1). The document does not describe how to create such a strategy. Can you provide us with some best practice information?

A1 Any company that must comply with that regulation have until Aug. 25, 2023 to be compliant. Several industry associations are working on or have already issued some best practice documentation to their members. Therefore, it may be beneficial to become a member of such an organization.

In the meantime, the following are some best practices:
Define the CCS scope, which should encompass sterile products, and any products or ingredients requiring bioburden control. Identify all contaminants, including those that impact quality, sterility, or efficacy.

Position the CCS, which means developing the CCS relative to process and facility design. The CCS will be related to the site master file and the site's pharmaceutical quality system (PQS), as well as the life cycles for the products manufactured on site.

Establish the CCS structure, which is typically a Site Master CCS that is an overarching approach to contamination control document. The Site Master CCS links the detailed area CCS documents together, which address the area specifics and product specific information.

A CCS is a holistic approach to contamination control that will take into account all existing measures in place. These are likely to include (in no particular order) housekeeping, materials storage and management, personnel and material flows, facility and equipment design, process design and controls, heating, ventilation, and air conditioning (HVAC) and utilities, preventive maintenance, corrective and preventive actions, training, cleaning and disinfection, outsourced activities, continuous improvement, and quality by design.

The control measures in these will comprise:

- Technical control measures based on science and knowledge of process, product, and risks.
- Organizational/procedural control measures defined in the PQS based on quality risk management principles.

The goal of the CCS is to document detailed process knowledge and all associated potential contamination sources, and how the company assures appropriate controls to manage the risks at an acceptable level. Furthermore, the CCS documents the interrelation of the various control measures. As mentioned, many control measures are in place, but it may not be clear if there are any gaps (i.e., lack of a comprehensive overview).

This may still sound abstract, so here is an example. For a cleanroom suite, a company has gowning and operating procedures in place, HVAC installed, and is monitoring differential pressure, room temperature and relative humidity, amongst other measures. That is considered good practice and addresses regulatory requirements. However, it does not describe what the gowning procedure is achieving, (i.e., whether the gowning is reducing the shedding of particles, or whether the gowns are of the appropriate material and size). It also does not address whether this gowning regime is appropriate

in relation to the contamination in the rooms, as controlled by the HVAC system and as measured by the room monitoring system. Only if this is reviewed, assessed, and documented as part of a CCS, will it be known if the technical and procedural controls are balanced and represent compliant controls.

Hopefully, this shows that a CCS is not merely a regulatory requirement, but provides significant benefits to the industry, not least to help understand the controls holistically.

Q2 My colleagues and I have been discussing the new requirement for a contamination control strategy (CCS) contained in the European Union's 2022 Annex 1 revision. Can you provide some guidance on what should be included in the CCS?
A2 The concept of contamination/containment control has been around for quite some time. The 2004 FDA Guidance for Industry states, "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". The revised Annex 1 guideline takes things a step further by stating, "A [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 guideline also states, "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".

The Parenteral Drug Association's (PDA's) Technical Report states, "The ongoing evolution of contamination control principles that this document addresses is a shift to a holistic approach, where practices are designed to work together to achieve proactive contamination control and are evaluated for their collective effectiveness".

What does this all mean to pharmaceutical manufacturers? Let's start with what we have already in place. All companies should have contamination control elements addressing various aspects of the manufacturing process including but not limited to process design, microbial control, facilities, utilities, raw materials, environmental, personnel training and qualification, equipment qualification, and a robust quality management system. Some of the specific contamination control elements included in these categories would be the existence of bioburden and endotoxin attributes, particulate monitoring, process validations, material and personnel flow, product quarantine practices, smoke studies, media fills, gowning qualification, cleanroom practices, microbial monitoring during production, cleaning validation, extractables/leachables, container closure integrity, etc. The strategy in CCS is how the company ties all these elements together in a holistic approach that is interdependent, multi-disciplinary, and tailored to the operation. This requires the company to be deliberate in risk assessing how changes to any of the elements affects the other elements under the umbrella of the CCS.

The overall objective of the CCS is to describe what control elements are in place, why they are effective, and that potential contamination is controlled from the beginning to the end of the manufacturing process.

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