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Contamination Control Strategy – What is the Inspector's Point of View?

Excerpt from the GMP Compliance Adviser, Chapter 12.A.4

by Xenia Dimont

The concept of contamination control is not entirely new in the context of the EU GMP Guideline – the basic principles are already contained in Chapter 5 of the Guideline regarding cross-contamination and in Annex 2 regarding specific risks for biological products. However, the development of this concept has been furthered significantly in the revised Annex 1 with the *Contamination Control Strategy* (CCS) and it represents one of the few actually new requirements in the revised Annex 1.

With the CCS, an additional quality assurance instrument has been introduced in the updated Annex 1, which is intended to enable the control of potential sources of contamination by microorganisms, endotoxins/pyrogens and particles through a site-wide holistic approach and multimodal control.

To this end, by using QRM principles and a sound understanding of the processes and technologies, site-wide contamination risks including potential interactions are identified. Critical control points are defined, suitable prevention, monitoring and control measures are taken and all relevant results are considered in their entirety.

Through a holistic evaluation of the collective effectiveness of all measures and the continuous improvement of the CCS is conducted in pursuit of the ultimate goal: maximum sterility assurance.

Creation of a CCS

The initial implementation of an appropriate contamination control strategy (CCS) poses a challenge for many companies. As the new version of Annex 1 does not provide any specific requirements in this regard, the decision regarding the conception and form of the CCS is at the discretion of the respective manufacturer, provided that all necessary elements are included, and the purpose of the CCS formulated in the updated Annex 1 is thus fulfilled.

Based on the current findings, implementation as described below (which is structurally similar to the design of a site master file or validation master plan in the broadest sense) appears both appropriate and practicable:

Conception of the CCS as an overarching document:

- Definition of the purpose of the CCS and its basic principles
- Methodology for identifying relevant elements and critical control points
- List of the relevant elements identified
- Identification of critical control points and associated monitoring measures
- Assessment of existing elements and systems (such as existing risk analyses, change and deviation management, etc.) with regard to their suitability for integration into

the CCS, for example through a gap analysis

- Description of the approach to assess the collective effectiveness of all CCS measures
- Procedures for keeping the CCS up-to-date and for continuous improvement of the CCS through ongoing and regular reviews (including definition of the review frequency)
- Listing to the applicable referenced or subordinate documents such as existing elements, systems, documents, for example:
    - Risk analyses
    - SOPs (e.g. for personnel qualification, supplier management)
    - Systems for environmental, personnel and utility media monitoring

Integration of the above-mentioned CCS document into the Pharmaceutical Quality System (PQS) as a quality assurance tool with a focus on sterility assurance:

- A well-structured, concise and comprehensibly written document
- Mutual link to other relevant PQS elements (such as QRM, PQR, CAPA etc.), systems and subordinate documents (risk analyses, SOPs etc.)
- Content and format according to chapter 4 of the EU GMP Guidelines and analogous to the other specification documents established in the company.

Who is responsible for the preparation, review and approval of the CCS?

As the CCS is a new requirement, there is as yet no experience of *best practice* regarding the definition of responsibilities for preparation, review and approval. It is quite possible that the views on this allocation of roles could vary, particularly in the initial phase of monitoring. From a current perspective, the following allocation of roles appears to be obvious:

- The creation and development of the CCS is carried out under the leadership of the quality assurance department by a multidisciplinary team comprising representatives with specific expertise from all relevant departments.
- The key functions, including the Head of Manufacturing, the Head of Quality Control and the Qualified Person, are involved in the process either as authors or reviewers of the document.
- Final approval is granted by the Management Board, which thus fulfills its task of overall supervision on the one hand and fulfills its responsibility to provide the necessary resources for the CCS on the other.

Expectations for the first inspections

The concept of the contamination control strategy was already presented in the first draft of the new Annex 1 in 2017. The revised draft of 2020 clearly showed that this is a significant new element that is likely to be included in the final version of the document. Accordingly, affected companies and facilities have had ample opportunity to familiarize themselves with the concept and make the necessary preparations. Thus, it is expected during the first inspections that a CCS has already been implemented or is about to be implemented. In view of the fact that CCS is a comprehensive, far-reaching and demanding new requirement in sterile manufacturing, it will take some time until sufficient practical experience has been gained before a generally recognized procedure or a so-called gold standard for the implementation of CCS emerges.

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