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How to Develop and Document a Contamination Control Strategy

– ECA Task Force on Contamination Control Strategy –

An ECA Foundation Guidance Document

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Content

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How to Develop and Document a Contamination Control Strategy	
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Disclaimer

This document has been issued to support and guide the reader when preparing a Contamination Control Strategy (CCS) and the required documentation. The authors have compiled the content to the best of their knowledge and belief based on their own experience. This document does not constitute a binding guideline and does not release the user from the responsibility to adapt the contents to his processes and circumstances. It also does not guarantee the fulfilment of regulatory expectations and acceptance of the respective CCS by the competent authorities.

The attached documents may serve to facilitate the preparation (Attachment 3), as non-binding examples (Attachment 1 and 2), or as supplementary information (Attachment 4). They do not claim to be complete or generally applicable.

PLEASE NOTE: Text quoted from the Annex 1 is written in italics!
For the ease of reading, "sterile manufacturing" in this document and its attachments also cover "low-bioburden manufacturing" and "bioburden-controlled manufacturing." In cases where "sterility" shall be achieved, this is indicated in the context.
The term "risk assessment" or "risk analysis" is used interchangeably — specific definitions differentiating the words to be defined by the pharmaceutical manufacturers.
The term "Key Performance Indicator (KPI)" and "Quality Performance Parameters (QPP)" can be used interchangeably.

1. Background

For pharmaceutical manufacturers and their suppliers, contamination of any kind that leads to product or production losses represents a significant risk. As recent events in the past, such as foreign particulate contamination (https://www.fiercepharma.com/pharma/contaminant-moderna-covid-19-vaccine-vials-found-japan-was-metallic-particles-report), have shown, this can lead to supply bottlenecks for individual medicinal products or groups of medicinal products.

Manufacturers should design their production facilities, equipment, and processes and implement Quality Risk Management (QRM) to ensure appropriate contamination control to minimize or detect contamination. Since measures affect different stages of a manufacturing process and often fall under the responsibility of other departments (e.g., quality control, quality assurance, or manufacturing), it may not always ensure that the data obtained in the process, e.g., from the original qualifications and validations, process controls and ongoing environmental monitoring, are linked with each other. This also applies to corrective and preventive actions that are often taken as a result of deviations and trend analyses but are neither integrated into a strategy for a holistic view nor is there a linkage of all critical control points and the evaluation of the effectiveness of all controls (design, procedures, technology, and organization). However, a holistic view is proposed in the draft revision of Annex 1 version 12 (2020) for particulates, microbial, and pyrogen contamination.

2. Introduction

Annex 1 draft version 12 (2020) "Manufacture of Sterile Products" deals with the demanding challenge of controlling contamination in a wide range of sterile product types:

- Finished dosage forms, Finished products, or Drug Products
- Active Substance, Active Ingredients, or Drug Substances
- Excipients
- Primary packaging materials

Any time Annex 1 is referenced in this document, it refers to Annex 1 draft version 12 (2020).

Slightly different from the impression conveyed by the title, Annex 1 not only targets the status of "sterile" products. It also gives guidance to products that are not intended to be sterile:

"However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments, and low bioburden biological intermediates but where the control and reduction of microbial, particulate and pyrogen contamination is considered important."

In general, Annex 1 strongly relies on the principles of Quality Risk Management but contains specific and explicit requirements on the other hand (refer to Section 4.2).

The intent of Annex 1 can be understood to ensure "Contamination Control", the approach and the level of details should be commensurate with the type of process and product. Depending on the process and product type, the intent of Annex 1 can be understood as the adequate approach to ensure

- Sterility Assurance
- Bioburden control / low bioburden
- Pyrogen / endotoxin control
- Control of foreign particulate matter

In summary, the entirety of measures to achieve the intent of Annex 1 can be summarized as the

Contamination Control Strategy

as defined in Annex 1:

"Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."

Additional elements of potential contamination source (e.g., virus, cross-contamination) being identified should be included in the CCS as applicable (refer to attachment 2 or 3).

3. Contamination Control Strategy (CCS) – the Elements listed in Annex 1

Like a Site Master File (SMF), which provides an overview of the facility, the CCS document provides an overview of the totality of contamination control measures and their linkage to an overall strategy, the CCS.

The proposed elements to be considered for the CCS are listed in Annex 1:

"2.5 The development of the CCS requires thorough technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g., pyrogen, endotoxins) as well as particulate matter (e.g., glass and other visible and sub-visible particulates). Elements to be considered within a documented CCS should include (but are not limited to):

i. Design of both the plant and processes.
ii. Premises and equipment.
iii. Number does not appear in the listing
iv. Personnel.
v. Utilities.
vi. Raw material controls – including in-process controls.
vii. Product containers and closures.
viii. Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS), and services.
ix. For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.
x. Process risk assessment.
xi. Process validation.
xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.
xiii. Cleaning and disinfection.
xiv. Monitoring systems – including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.

xv. Prevention – trending, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more comprehensive investigational tools.
xvi. Continuous improvement based on information derived from the above. "

Acknowledging that this listing provides headers and keywords, it is not exhaustive. Therefore, deeper consideration has to be given to the elements, sub-structures should be implemented, and even new elements may need to be introduced, depending on the specific contamination control requirements for individual products and processes. Following are four examples of additional elements that could play a role depending on the manufacturing or product conditions:

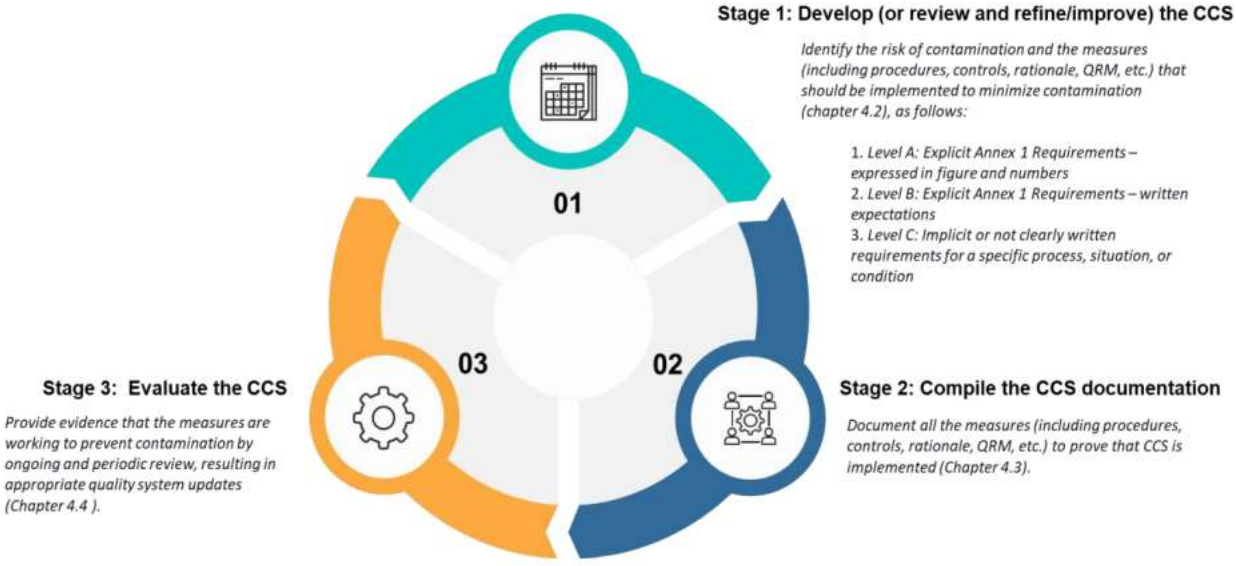
xvii. Pest Control
xviii. Virus Safety
xix. Deviation Management/CAPA
xx. Aseptic Process Simulation

The document's structure is not predetermined and can be based, for example, on the table of contents of Annex 1, on the order of enumeration according to Chapter 2.5 (V12, 2020), or even be designed individually.

4. Development and Documentation of a Company's CCS

Consultation with industry partners has shown that there are different statuses of "CCS-readiness." However, the consultation also revealed that the interpretation of the term "strategy" is not the same among all involved partners. On the one hand, "strategy" is understood as "The way to implement CCS," and on the other hand, it is understood as "the approach to demonstrate that the CCS is in place." Also, some companies use the term Contamination Control Program as a synonym to the CCS.

Figure 1: Contamination Control Strategy Implementation Process



4.1. The "3-Stage-Approach"

Thus, the ECA came to the 3-stage-approach to achieve "CCS-readiness."

- Stage 1: Development (or review and refinement/improvement) of the CCS
- State 2: Compilation of the CCS documents
- Stage 3: Evaluation of the CCS

This document is intended to provide guidance for two possible cases:

1. For a new plant, new equipment, e.g., for:
    - Mapping of the manufacturing processes to identify possible sources of contamination.
    - Carry out a risk assessment to evaluate the risk of contamination.
    - Establish preventive measures and their controls in a holistic system (including the definition of responsibilities).
    - Assess and manage the residual risk of contamination.

2. For an existing facility that has already carried out a risk assessment, e.g., for:
    - Evaluation of existing contamination control measures
    - Analysis and overview of possible gaps
    - Risk assessment and, if necessary, the addition of further measures and integration into the overall system (including determination of responsibilities)
    - Manage the residual risk of contamination.

The table below supports the user to assess the status of "CCS-readiness implementation" and indicates the required activities:

Company	**Stage 1** Develop the CCS	**Stage 2** Compile the CCS-Document	**Stage 3** Evaluate the CCS
is new in sterile manufacturing has little experience	- Identify what needs to be done to ensure contamination control - Apply the principles of QRM* - Prepare the documentation	Compile the documentation in an easily accessible/readable structured way; in Attachment 2 or 3. Refer to Section 4.3.	Refer to section 4.4
is in a matured state	Review the existing contamination control measures based on the principles of QRM*: - Critically review existing concepts - Gap assessment and missing elements. (Refer to attachment 1) - Prepare the documentation, rationale, etc.		
has broad and proven experience	CCS is fully implemented: - - re-assess the existing gap assessment to confirm compliance: - Confirmed ・go to Stage 2! - Not confirmed ・・cover the missing elements (apply QRM principles).		

* Refer to Section 4.2

4.2. Stage 1: Develop the CCS

4.2.1. The principles

Developing a CCS must be based on an in-depth understanding of the specific processes and products, fundamental and scientific know-how in sterile manufacturing, QRM, and contamination control. Fundamental requirements are laid down in numerous guidelines, regulations, codes and standards, and technical reports, which outline state-of-the-art approaches. A list of these reference documents is provided as Attachment 4, "Guiding documents,"; which does not claim to be exhaustive.

The term "the element" refers to the elements No. i. – xvi. (Refer to Section 3) and additional elements of relevance in connection with contamination control. The steps mentioned in the enumeration above (bullet points) provide the underlying principle for the CCS.

The following sections provide some suggestions for the CCS development based on the three different stages (further elaborated under items 4.2.2. – 4.2.4), keeping in mind that the fundamental principle is QRM, the steps of which may be summarized as follows:

1. Understand the impact of a change in elements of the CCS
2. Identify what could present a risk for product and/or patient safety
3. Develop measures to eliminate the risks or reduce them to an acceptable level (residual risks) or to provide evidence that the risks are under control
4. Perform and/or implement the measures and ensure the resulting tasks and procedures are reliably implemented
5. Document the evidence of the actions taken
6. Evaluate the effectiveness of the measures (e.g., controls, procedural, structural, etc.) in place and identify improvements to be implemented where needed

Please note: These steps 1-6 are not an explicit part of any guideline. However, they are derived from the general idea of QRM and can be deduced from, e.g., ICH Q9 Quality Risk Management.

Steps 1 to 3 are about preparing and documenting the risk assessments.

The measures may be one-time, periodic, or permanent activities. Typical measures performed in step 4 are:

- Qualification of related systems
- Validation of manufacturing processes, cleaning, decontamination, sterilization processes, etc.
- Monitoring
- Preparation and implementation of Standard Operating Procedures (SOPs)
- Definition, implementation of the controls (e.g., In-Process-Control "IPC", QC release testing)
- Training of personnel

Step 5 documents the historical results of the measures identified in step 4. Finally, step 6 is about trending and analysing the historical results of the measures to identify the remedial action/improvement needed in the process.

Note: To make this CCS **holistic document** clear and the ideas applicable for a broad spectrum of readers, the ECA has renounced identifying and describing situations where the general approaches may not be applicable; furthermore, the document is not focused on processes with idiosyncrasies. It is – as in any case – the pharmaceutical manufacturer's responsibility to select and apply the correct approach for its products and processes. The included case studies are to illustrate the general approaches.

4.2.1.1 Degree of detail

The requirements in Annex 1 are divided into different levels of details, and three different levels may be identified:

Level A: Explicit requirements: expressed in figures and numbers; refer to section 4.2.2.

Level B: Explicit requirements: described in words; refer to section 4.2.3.

Level C: Implicit or unclearly defined requirements for a specific process, situation, or condition; refer to section 4.2.4.

4.2.2. Level A: Explicit Annex 1 Requirements – expressed in figures and numbers

The level A objective is to list the different Annex 1 requirements, compared to the processes, procedures, and the surrounding manufacturing environment. Explicit Annex 1 requirements may not always be fully applicable depending on the topic, yet QRM can be applied to ascertain compliance. Identified requirements need to be documented and justified in a company's Pharmaceutical Quality Systems (PQS). At the end of level A, the manufacturer should have gap-assessed processes against the Annex 1 requirements and should have identified remediation measures to put in place.

Example: Table 1: Maximum permitted airborne particulate concentration during classification.

Table 1: Maximum permitted airborne particulate concentration during classification

Grade	Maximum limits for particulates $\geq 0.5\ \mu m/m^3$		Maximum limits for particulates $\geq 5\ \mu m/m^3$	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not applicable	Not applicable
B	3 520	352 000	Not applicable	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[(a)]	29 000	Not defined[(a)]

[(a)] For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and historical data where applicable.

4.2.3. Level B: Explicit Annex 1 Requirements – described in words

The majority of requirements in Annex 1 are described in the text; some are clear or unambiguous, whereas others require interpretation and adaptation to specific situations.

Thus, in many cases, QRM has to be applied for the implementation of these requirements. The QRM approach has to be used for each element No. i. – xvi. and other elements of relevance in connection with Contamination Control.

Examples:

Example 1

"A suitable sampling schedule should be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value (dryness fraction) and superheat."

Example 2

"4.11 The transfer of materials, equipment, and components into an aseptic processing area should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into the area through double-ended sterilizers (e.g., through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilization on transfer of the items is not possible, a procedure which achieves the same objective of not introducing contaminant should be validated and implemented, (e.g., using an effective transfer disinfection, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter)."

For the requirements outlined in 4.11, the intention of the requirements has to be understood and interpreted for the specific processes, and for this QRM has to be applied. Annex 1 can only describe a general set of measures (minimum requirement), which needs to be supplemented and specified by the manufacturer based on QRM on the real processes, installations, and conditions.

Some examples for questions, which may result from 4.11:

- Is the installed (planned) unidirectional flow an appropriate risk mitigation measure?
- Can the material be sterilized at that stage as needed for mitigation?
- Is the installed (planned) double-ended sterilizer appropriately mitigating the risk?
- Can depyrogenation or sterility be proven where needed?

Questions as provided above as examples need to be considered, and risks and risk mitigation, respectively reduction needs to be addressed and documented following the QRM procedure.

For the explicit requirements, Annex 1 allows to use of alternative approaches and support them with rationales:

"Where alternative approaches are used, these should be supported by appropriate rationales and risk assessment and should meet the intent of this Annex."

The rationales may be developed and documented in risk assessments.

4.2.4. Level C: Implicit or vaguely defined requirements for a specific process, situation, or condition

Where requirements are implicit, it is mandatory to apply the QRM principles stringently; Steps 1-6 have been presented in Section 4.2.1.

QRM process and the respective results are required to be documented.

For example:

"9.31 Microorganisms detected in Grade A zone and Grade B area should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in Grade C and D areas (for example where action limits or alert levels are exceeded or where atypical or potentially objectionable microorganisms are recovered). The approach to organism identification and investigation should be documented."

4.3. Stage 2: Compile the CCS Documentation

When having the CCS with all its elements in place, the next challenge is to compile the CCS document, i.e., compile the individual documents to have them readily accessible during routine operations and inspections.

As there may be many documents, the questions are: How to compile them in one document to have good documentation, verification, and easy access to them?

The CCS document has to compile or mostly reference documents providing evidence that the CCS with its elements and correlation are reliably implemented. Such documents are mainly:

- Risk Assessments / Risk Analyses
- Qualification and Validation reports
- Maintenance programs (including calibration programs)
- Monitoring and controls plans (e.g., IPC, QC release instructions)
- SOPs / policies / working instructions, etc.
- Master batch records, product specifications (e.g., QTPP document), and release specifications
- Raw or starting material specifications
- General QA documents
- Approved documents, rationales, strategies, etc.
- Monitoring results
- Trending results and reports (e.g., historical EM, Continuous Process Verification "CPV," etc.)
- Complaint management and complaints related to potential contamination during manufacturing, e.g., foreign particulates

For this purpose, the ECA has prepared templates to compile CCS documents; **attachment 2 and attachment 3**. The attachments show what this document can look like. However, no experience is available regarding regulatory inspections, as the corresponding revision of Annex 1 has not yet been finalized and set effective.

The CCS Document template (Attachment 3) follows the structure of the elements No. i. – xvi. It has the main chapter for each element and numerous sub-chapters for more details. Furthermore, it allows adding more chapters as considered necessary, depending on the individual products, processes, and conditions.

In its chapters and sub-chapters, the document mentions relevant elements to be considered for the CCS. Thus, it is the "backbone," providing the platform to briefly summarize the main ideas for the respective section and add references to the respective documents.

4.4. Stage 3: Evaluate the CCS

The intent of the CCS is not only to document all the measures and controls in a holistic document. It also allows manufacturers to have a holistic view of their contamination control measures and how well it prevents contamination.

As explicitly suggested by Annex 1: *"2.6 The CCS should consider all aspects of contamination control and its life cycle with ongoing and periodic review resulting in updates within the quality system as appropriate."*

Manufacturers have to review/analyse data gathered by controls to define if:

1. The measures are working in preventing contamination.
2. The residual risk of contamination is still acceptable based on defined regulatory and process limits and parameters.
3. The CCS should be reviewed and improvements implemented as applicable.

The frequency of a periodic CCS review depends on several variables that the manufacturers have to identify, for example:

- Change in the process; the change control should trigger the review of the existing risk assessments where necessary.
- Deviations that may conclude that the contamination program in place is lacking and trigger the review of existing risk assessments where necessary.
- Introduction of new equipment, a new product that would lead to the creation or review of existing risk assessments
- Results from routine data trending and analysis that indicate a potential gap in the CCS

Any defined frequency could be modified on a risk-based approach (e.g., absence of trends, deviations)

5. Responsibilities/Ownership

Related responsibilities and required resources within an organization need to be clarified to bring a strategy to life and translate it into daily operations. As defined in Chapters 1 and 2 of the EU GMP part 1 and also in EU GMP part 2, the general responsibility for quality lies with the senior management. However, responsibility for individual sub-areas may be delegated to qualified staff, depending on their expertise, qualifications, training, and responsibilities as listed in their respective job descriptions. Accordingly, the responsibilities for the ongoing review and updating of a CCS should also be defined and documented, i.e., an "oversight" position that receives any change notifications or changes control information from the sub-areas (of the different elements) and initiates discussion on potential adjustments CCS. For this, an option could be to integrate into any change control an assessment of whether or not the intended change could impact Contamination Control.

6. Future challenges in the holistic evaluation of the CCS performance

Our industry tends to use a one-level or two-level model to analyze the data and trend them (e.g., EM data, bioburden data, release, or stability data vs. time). This type of model analysis only allows to view in a silo and rely on an expert to confirm a correlation between the data. Still, this may lead to subconscious bias in the conclusion made by the expert. Consequently, using a multi-level model data analysis is suggested to have a holistic view. Using a multi-model data analysis would allow confirming the interlink between KPIs if any.

One of the challenges that manufacturers may encounter is a holistic view of big quantities of data gathered by the control systems in place.

Annex 1 stipulates that manufacturers have approaches to use such data and do not purely rely on product testing.

"2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be

placed on any terminal process or finished product test." Consequently, manufacturer can not only rely on the sterility or other quality aspects (release testing) to ensure product is safe of contaminant".

Some manufacturers may turn to big data analytics that allows analysing KPIs at multi-model rather than a one model analysis. Big data analytics tends to offer its user the possibility to capture, store, analyze, share, transfer, visualize and query.

The goal is to identify and collect the data/information needed to present a holistic view and help make decisions. The question to ask is what data can help the manufacturers to evaluate the CCS?

When evaluating the performance, the CCS cross-functional team may want to involve a statistician or a data scientist to help analyze the data.

In the future, the goal may be to confirm that the data analysed helps to look ahead (proactive) rather than behind (reactive).