Preparing a Contamination Control Strategy

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Background

Annex 1 requirement

Previously not explicitly stated

Little guidance has been available on content detail or preparation

Different approaches have resulted

Help is here for harmonising the approach – we're going to look at a recently available free tool

Guidance and Example Docs

- PHSS (*Pharmaceutical and Healthcare Sciences Society*)
  - In 2018, published a "white paper" on control strategy for contamination in sterile facilities. This paper has only ever been available to PHSS members (AU$195 per year) at a cost of approximately $18.
- A3P (***A****ssociation pour les* ***P****roduits* ***P****ropres et* ***P****arentéraux – Association for Clean and Parenteral Products*)
  - In mid 2021, published a concept case study approach to CCS preparation
  - https://www.a3p.org/en/contamination-control-strategy-practices-a-case-study-of-a-ccs-implementation/
- ECA Foundation
  - In January 2022 published two comprehensive documents
    - ECA Task Force Contamination Control Strategy Guideline (PDF)
    - ECA Task Force Contamination Control Strategy Template (Word document)
  - Both documents can be downloaded for free (with registration) from the ECA Foundation website. The template is also provided as part of the guideline PDF.

ECA Task Force (CCS)

ECA is European (German-centred) organisation, which influences the make up of the task force. It is comprised of:

- Industry experts (Lily, Boehringer Ingleheim, GE Healthcare, CSL Behring, Steris)
- Eminent consulting experts
- WHO representation

What is a Contamination Control Strategy?

- "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."

Elements of a CCS

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 … 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 … modern methods that optimize the detection of environmental contamination.

Not intended to be comprehensive. Additional suggestions include viral safety and pest control, among others

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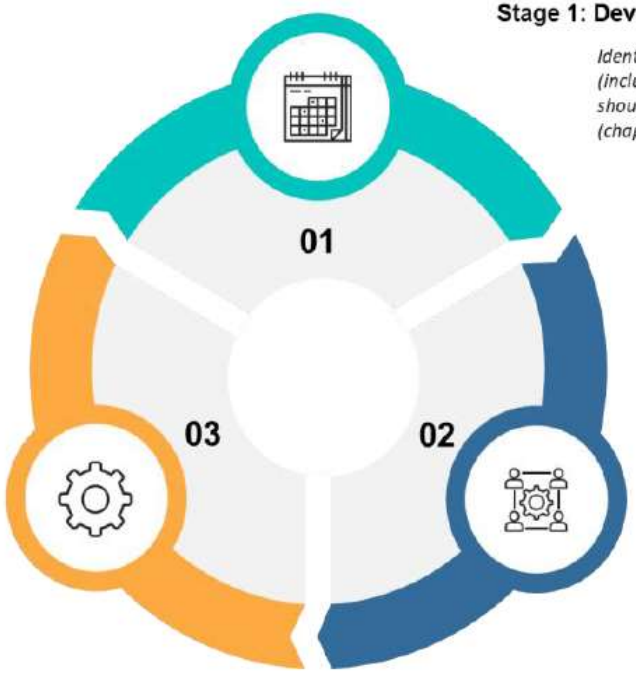
The ECA Foundation Approach



Stage 1: Develop (or review and refine/improve) the CCS

Identify the risk of contamination and the measures (including procedures, controls, rationale, QRM, etc.) that should be implemented to minimize contamination (chapter 4.2), as follows:

1. *Level A: Explicit Annex 1 Requirements – expressed in figure and numbers*
2. *Level B: Explicit Annex 1 Requirements – written expectations*
3. *Level C: Implicit or not clearly written requirements for a specific process, situation, or condition*

Stage 2: Compile the CCS documentation

Document all the measures (including procedures, controls, rationale, QRM, etc.) to prove that CCS is implemented (Chapter 4.3).

Stage 3: Evaluate the CCS

Provide evidence that the measures are working to prevent contamination by ongoing and periodic review, resulting in appropriate quality system updates (Chapter 4.4).

Aligns with FDA 3 stages of validation

Existing vs New Facilities

ECA recommend a decision tree to assist with understanding the level of effort required for your stage of facility/process maturity.

The less mature a site is the more work is required at Stage 1	Stages 2 and 3 look similar regardless of maturity

Stage 1 – Develop the CCS

- The guide outlines a 6-step process aligned with the principles of Quality Risk Management, to assist with the systematic application of the development phase
  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 – *allows stage 2*
  6. Evaluate the effectiveness of the measures (e.g., controls, procedural, structural, etc.) in place and identify improvements to be implemented where needed – *establishes the principles for stage 3.*

Stage 1 – Develop the CCS

Steps 1-3 are risk / gap assessment related activities

Step 4 is the implementation of risk mitigation or regulatory obligation, and may include:

- 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 is the compilation of evidence

Step 6 is the evaluation for effectiveness checking and continuous improvement

Stage 1 – Develop the CCS

- ECA "Degree of Detail" (of QRM effort) levels for Annex 1 requirements

Level	Description	Example	Relative Degree of Detail
A	Explicit requirements: expressed in figures and numbers	Limit values	Typically minimal QRM, except where strict compliance cannot be maintained
B	Explicit requirements: described in words	Unequivocal statements with minimal ambiguity	Increased levels of QRM, especially where statements may have different interpretations for different circumstances
C	Implicit or unclearly defined requirements for a specific process, situation, or condition	Requirements featuring equivocal statements, such as "… should be considered" or "may …"	High levels of QRM, used to determine and justify the approaches taken where optional activity is stated

Stage 1 – Develop the CCS

So, basically

- Prepare assessment(s) that assess each element of the CCS for your facility against the (relevant) requirements of Annex 1
- Use the "Degree of Detail" levels to determine the level of evidence, risk management or other justification that may be required to support the implemented strategy
- Collate the evidence, etc. available for a single source document
- Initiate a periodic review that will incrementally re-assess

Stage 2 – Compile the CCS

When compiling and preparing the CCS the central document should be developed as a narrative to describe the strategies in place.

Instead of being the repository for all of the information (which would become unwieldy), the central document should reference evidentiary documents including:

- 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

Stage 3 – Evaluate the CCS

Annex 1 explicitly requires ongoing lifecycle evaluation of the CCS. There is no guidance in the Annex on frequency or format

The manufacturer may decide on the format, however, it should be proceduralised

The manufacturer may decide the frequency, but use QRM principles to determine this, considering that evaluation may be prompted also by:

- 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

ECA Tools

- ECA have provided a gap assessment template in the guideline to assist with the steps 1-3 of Stage 1.

Key areas	Key elements	Detailed CCS Elements	Annex 1 draft reference	Identified potential gaps (or documentation improvement need) versus Annex 1 draft expectations	Key supporting site strategies, rationales, risk assessments Include reference and title	Key site procedures Include reference and title

- This information then forms the basis of preparation for the central document narrative

ECA Tools

ECA have provided a CCS template, based on the Feb 2020 draft of Annex 1

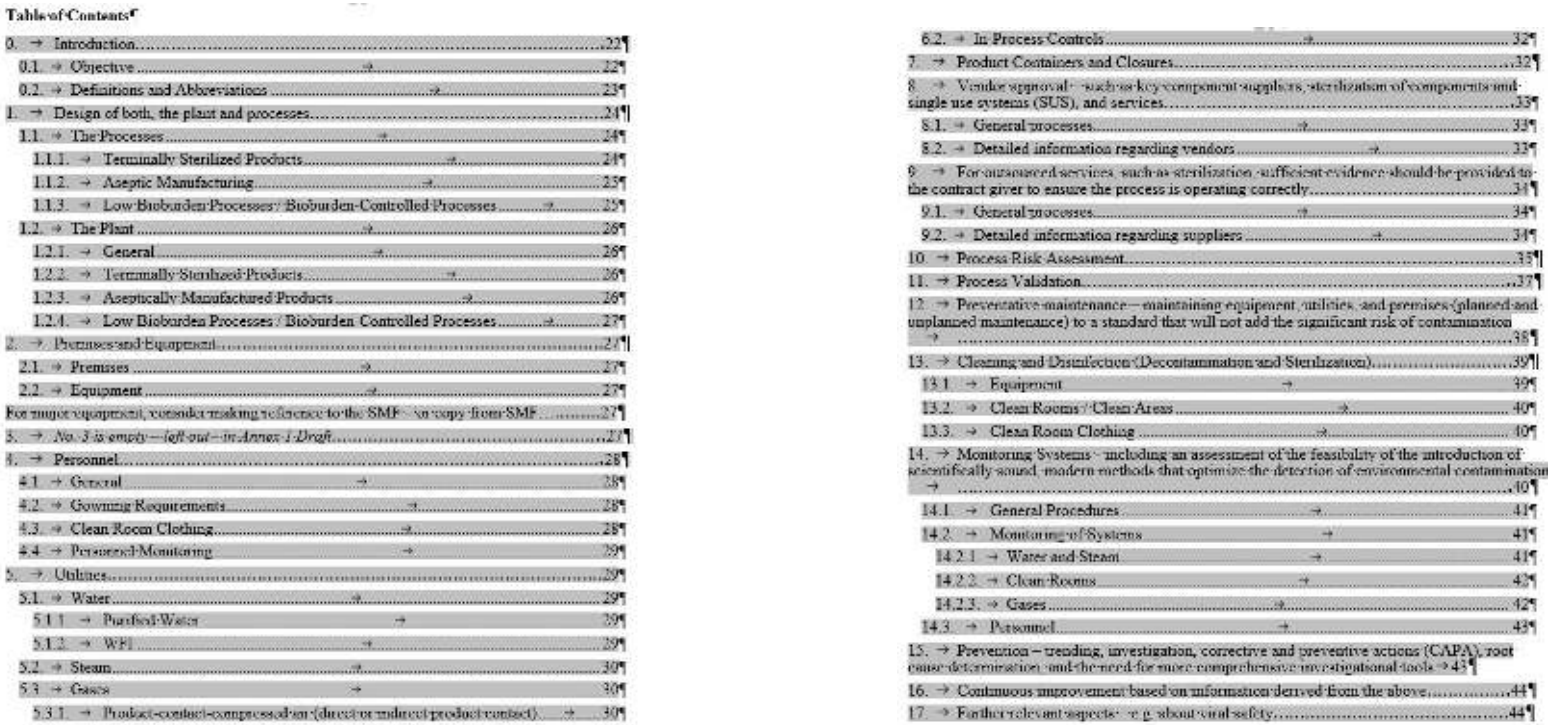


Table of Contents

ECA Tools

- The template provides a series of (empty) tables to help prompt for the types of information that might be included in each section. Some examples below

4.2. → Clean Room Clothing

Description	Reference Document	
	Title	No.
Material, quality, and design of clean room clothing is adequate for the respective clean room Grade		
Changing and replacement of clean room clothing		
Cleaning of clean room clothing		
Sterilization of clean room clothing		
Validation of the sterilization process		

13.2. → Clean Rooms / Clean Areas

Room No. / Area	Grade	Activity	Reference Document	
			Title	No.
	A	Cleaning		
		Disinfection		
	B	Cleaning		
		Disinfection		
	C	Cleaning		
		Disinfection		
	D	Cleaning		
		Disinfection		

7. Product Containers and Closures

Relevant aspects

- → different products, their container and closures
- → CCI tests
- → Routine process for testing container closure integrity

Description	Reference Document	
	Title	No.
Container Type – Specification		
Closure Type – Specification		
Container System Qualification		
Container Closure Integrity Testing		
Routine tests for container closure integrity		

Summary

Contamination Control Strategy is the collation of information you should already have

The intent is to collate into a single source, what has previously been decentralised

A central document should make it easier to evaluate and consider holistically for gaps and improvement opportunities

Regulators will be *very* interested in this document come inspection time

ECA have brought a simple set of tools to the public, which should be very helpful for those who are just starting their CCS journey.

Thank you