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iRACI From Risk to Control: Mastering Contamination in Pharma

DESIGNED FOR CONTROL: HOW TO STRUCTURE A CONTAMINATION CONTROL STRATEGY

Fábio Teles | 5th june 2025

DESIGNED FOR CONTROL: HOW TO STRUCTURE A CONTAMINATION CONTROL STRATEGY

(Overview of Annex 1)

Overview of Annex 1

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

Legal context for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation 2019/6 on the Community code relating to veterinary medicinal products. This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Commission Directive (EU) 2017/1572 for medicinal products for human use, Directive 91/412/EEC for veterinary use, and Commission Delegated Regulation (EU) 2017/1569 for investigational medicinal products for human use and arrangements for inspections supplementing Regulation (EU) No 536/2014 on clinical trials.
This Annex is intended to assist national authorities in the application of the EU legislation. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

Deadline for coming into operation:
- *25 August 2023 : one year from the date of publication in Eudralex Volume 4*
- *25 August 2024 : two years from the date of publication in Eudralex Volume 4 for point 8.123*

Overview of Annex 1

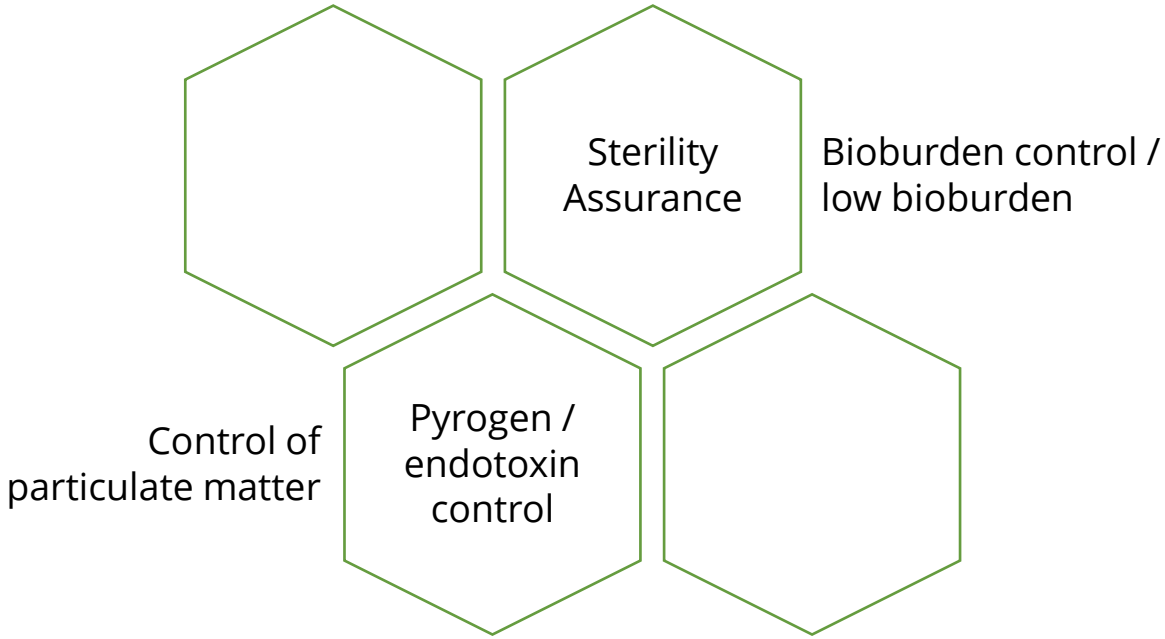
Scope

"This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product."

*" However, some of the principles and guidance, such as **contamination control strategy**, design of premises, cleanroom classification, qualification, validation, 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 endotoxin/pyrogen contamination is considered important."*

Overview of Annex 1

Scope



⇨ Annex 1 is NOT about “avoiding cross-contamination”

Overview of Annex 1

"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 organisational) and monitoring measures employed to manage risks to medicinal product quality and safety."

"The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review."

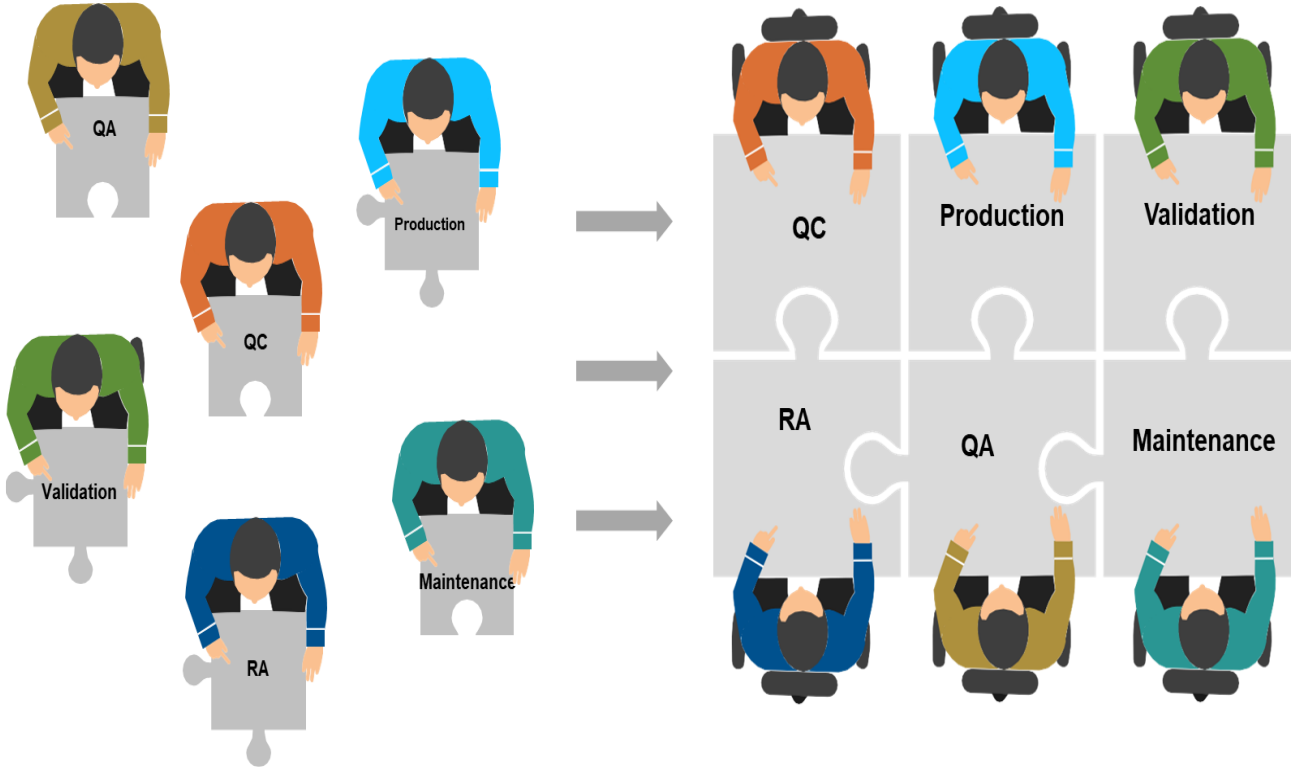
"Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood."

DESIGNED FOR CONTROL: HOW TO STRUCTURE A CONTAMINATION CONTROL STRATEGY

(Implementation and Management)

Implementation and Management

"Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, 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."



Implementation and Management

Like a Site Master File (SMF), which provides an overview of the facility, the CCS document is a living document, which provides an overview of the totality of contamination control measures, linked to an overarching strategy, the CCS.

"The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review."

Implementation and Management

CCS shall contemplate

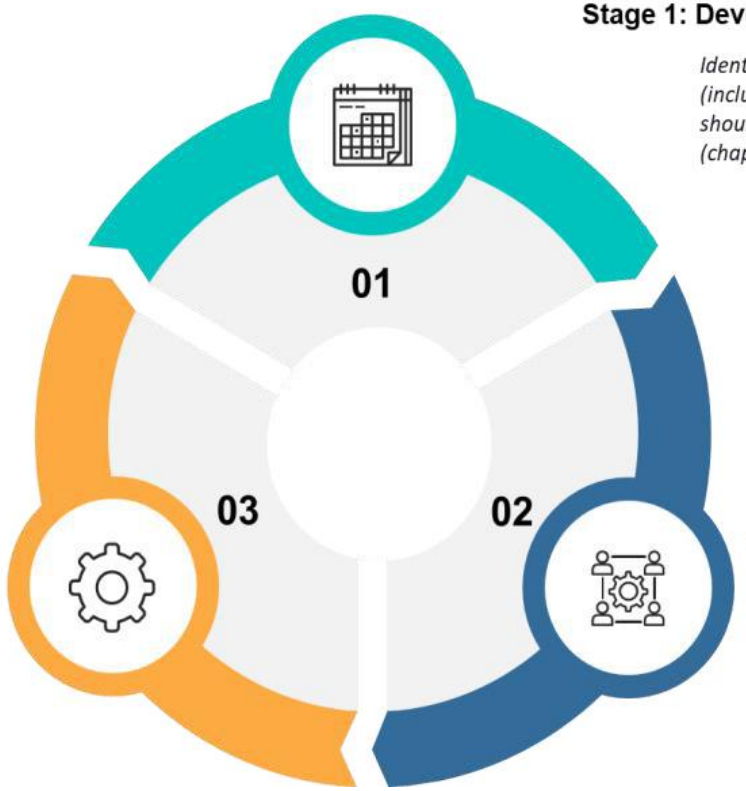
- Design of both the plant and processes including the associated documentation.
- Premises and equipment.
- Personnel.
- Utilities.
- Cleaning and disinfection.
- Raw material controls – including in-process controls.
- Product containers and closures.
- Vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers.
- Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.

Implementation and Management

CCS shall contemplate

- Validation of sterilisation processes.
- Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination.
- Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination.
- Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools.
- Continuous improvement based on information derived from the above.

Implementation and Management



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).

Contamination Control Strategy Implementation Process - ECA Task Force on Contamination Control Strategy

Implementation and Management

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

1. For a new plant, new equipment, e.g., for:

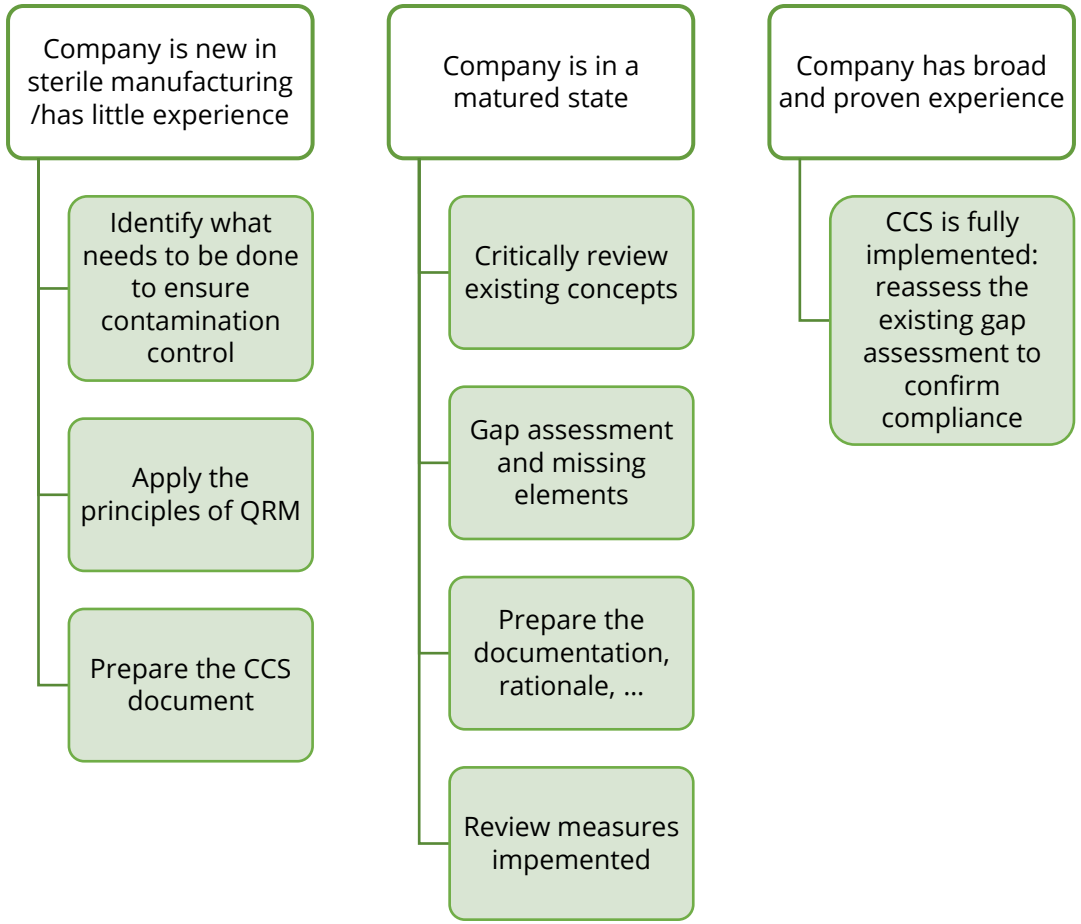
- Mapping of the manufacturing processes to identify possible sources of contamination.
- Carry out a risk assessment to evaluate the risk of contamination.
- Establish preventive measures and their controls in a holistic system (including the definition of responsibilities and communication).
- Assess 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 and communication)
- Manage the residual risk of contamination.

Implementation and Management

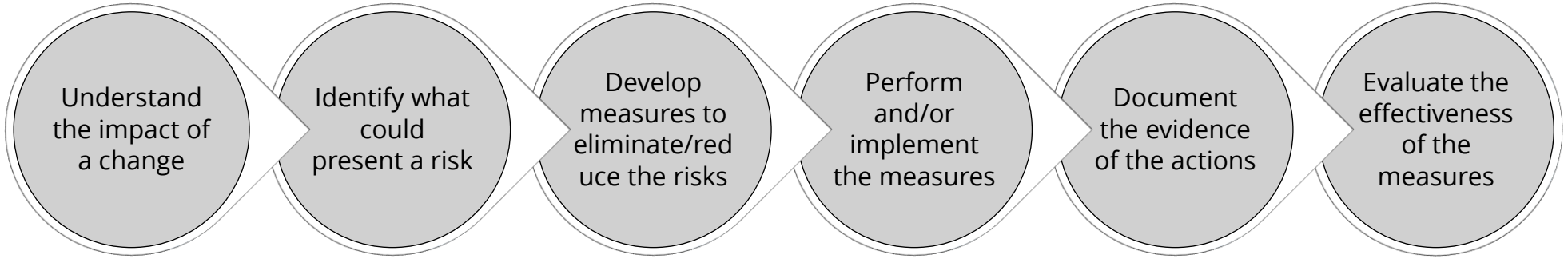
Stage 1: Develop the CCS



Implementation and Management

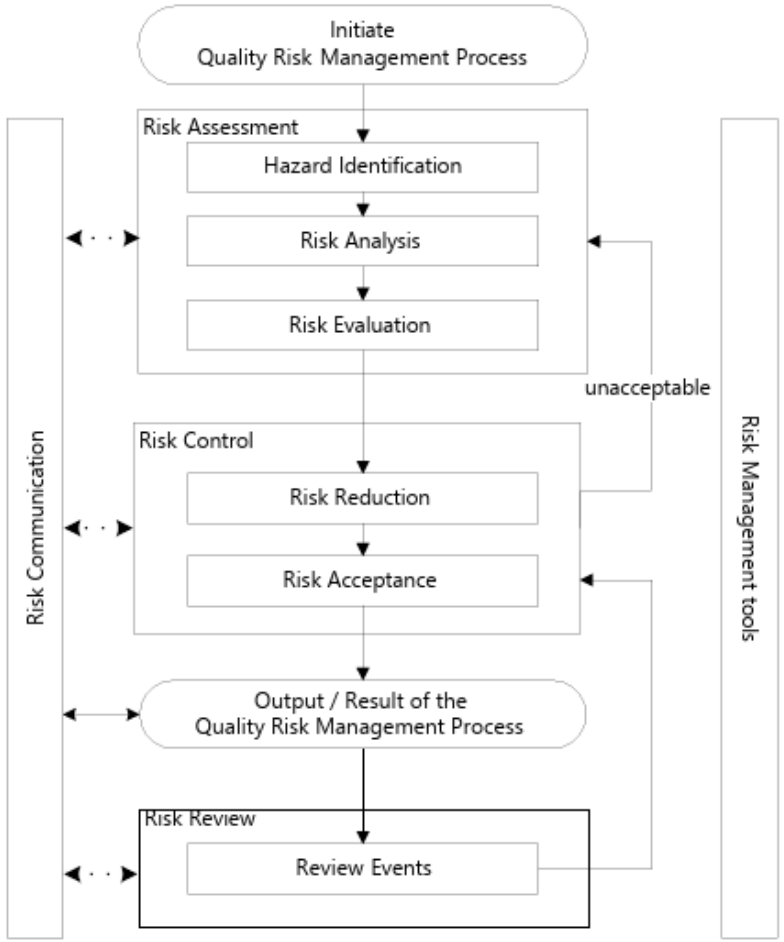
Stage 1: Develop the CCS

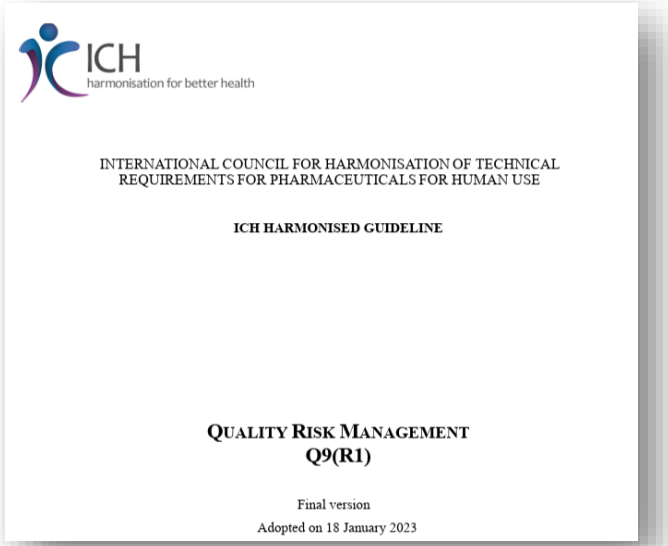
In stage 1, the manufacturer should define the CCS scope that also details the type of contaminant to control in the company's processes.



Implementation and Management

Figure 1: Overview of a typical quality risk management process




ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

QUALITY RISK MANAGEMENT
Q9(R1)

Final version
Adopted on 18 January 2023

Implementation and Management

Risk evaluation tools listed in ICH Q9

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering;
- Supporting statistical tools.

Implementation and Management

FMEA (*Failure Mode Effects Analysis*)

FMEA provides an assessment of potential failures for processes and their likely effects on results and/or product performance.

Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control potential failures.

FMEA methodically breaks down process analysis

Potential Areas of Use(s): - prioritize risks and monitor the effectiveness of risk control activities.

Implementation and Management

FMEA (*Failure Mode Effects Analysis*)

Severity: Considers the potential impact elemental impurities could have in the finished drug product.

Probability: Considers the potential of elemental impurities to be present.

Detectability: Ability to detect potential elemental impurities present.

Severity and probability are classified in 1 (low), 5 (medium) and 10 (high). Detectability is evaluated considering the following risk levels 0,1 (high), 0,2 (medium) and 1 (low).

Implementation and Management

HACCP *(Hazard Analysis and Critical Control Points)*

É uma abordagem estruturada que aplica princípios técnicos e científicos para analisar, avaliar, prevenir e controlar o risco ou consequência(s) adversa(s) de perigo(s) devido ao design, desenvolvimento, produção e uso de produtos.

1. Conduct a hazard analysis and identify preventive measures for each step of the process
2. Determine the critical control points
3. Establish critical limits
4. Establish a system to monitor the critical control points
5. Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
6. Establish system to verify that the HACCP system is working effectively
7. Establish a record-keeping system

Implementation and Management

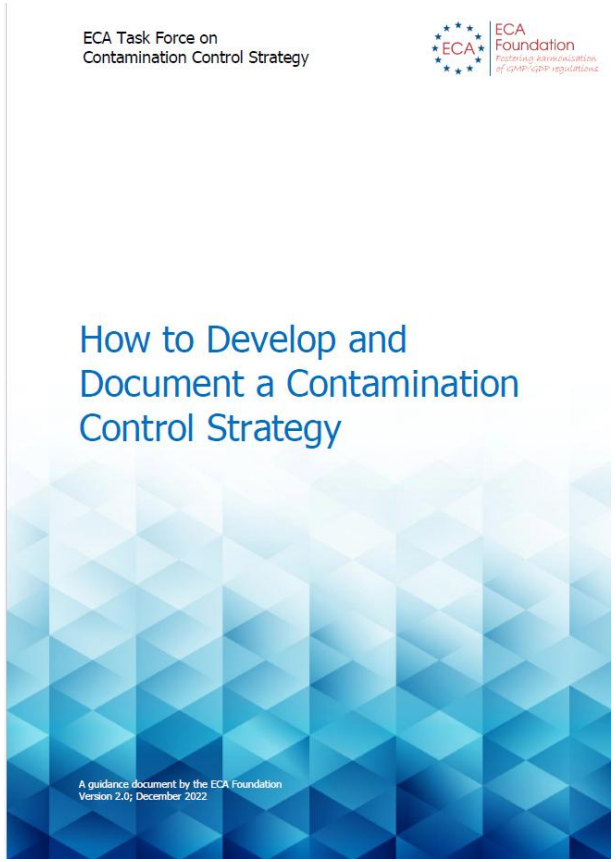
Stage 2: Compile the CCS Documentation

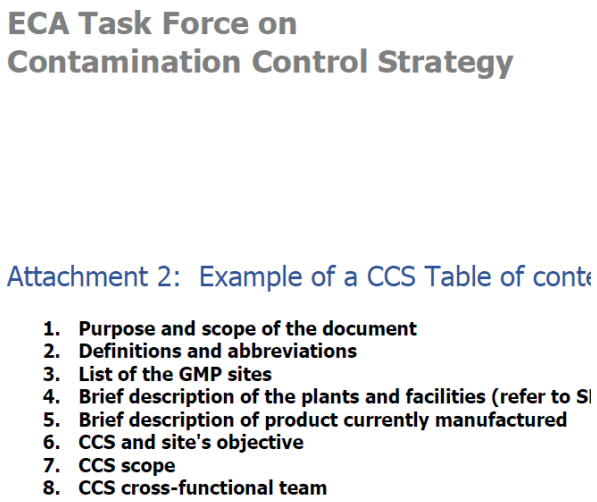
Compile the documents (e.g., VMP, RAs, rationales, GAPassessment,...) in an easily accessible/readable structured way

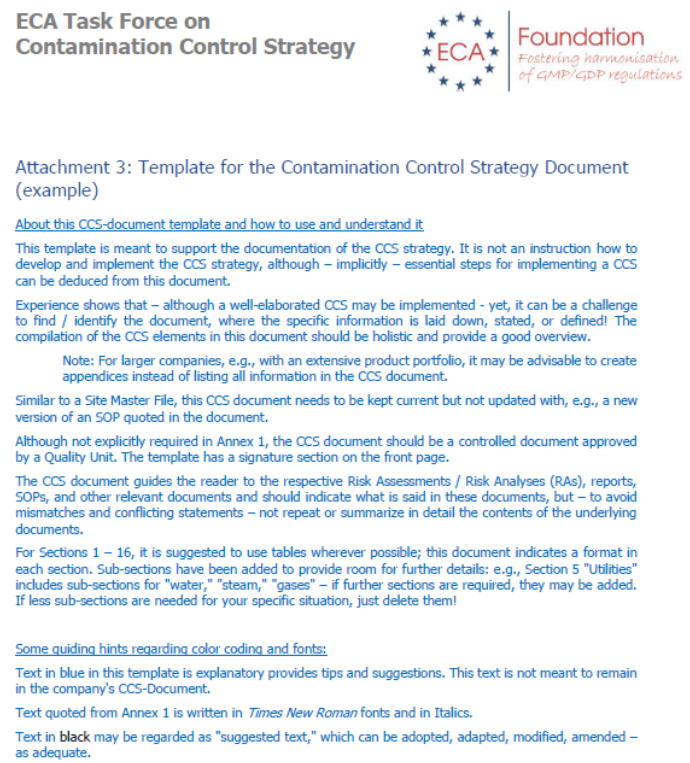
How to compile them in one document?

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

Implementation and Management







Implementation and Management

Risk ID (define unique no.)	Operation / Process Step	Risk Mitigation Actions	Procedures	Risk Level (after risk mitigation) S	P	D	RPN	RPN accepted? (Yes / No)
7	Air Locks	All cleanrooms are separated from non-classified areas through airlocks (SAS), that are classified with the same cleanliness grade as the cleanroom into which they lead (or a higher grade, for most SAS that lead to production areas). In Level 0, the area for sachets production and packaging is segregated from tablets and capsules area. Both areas are connected to the main corridor through personnel specific airlocks and material specific airlocks. SAS 2.11 is only for materials exit. Airlocks have pressure indicators and have a mechanism that allows only one door to be open at a time.	SOPX5432	5	1	1	5	Yes
8	Personnel Flow	Personnel entrance in Lev... area and multiple airlocks ... corridor. Only in the main ... sachets operations, they ... through a second airlock (... manual packaging. For tal ... personnel specific airlock. ... In production areas, there ... people involved in the pro ... External personnel flow is ... are separated from produ ... corridor, through windows ... All areas are identified.						
9	Material Flow	All materials destined for l ... controlled area (SAS that ... leading to the lift. Upon ar ... multiple SAS flows prever						

Raw Material (Starting Material) Controls Description	Reference Document	
	Title	No.
Test specifications for each starting material are prepared and approved; specifications follow the Marketing Authorization		
Incoming goods' testing		
Sampling		
QC-Testing		
Starting Material release procedure		

Implementation and Management

Stage 3: Evaluate the CCS

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

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

- The measures are working in preventing contamination.
- The residual risk of contamination is still acceptable.
- The CCS should be reviewed and improvements implemented as applicable.

Implementation and Management

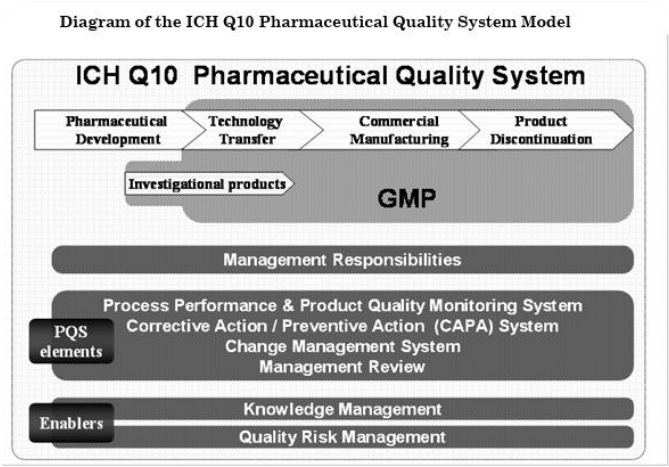
Stage 3: Evaluate the CCS

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 / excursions that may conclude that the contamination program in place is deficient, which should trigger the review of existing risk assessments where necessary.
- Introduction of new equipment or a new product that would require the creation of new or review of existing risk assessments
- Results from routine data trending and analysis that indicate a potential gap in the CCS.

Implementation and Management

Stage 3: Evaluate the CCS



Implementation and Management

Stage 3: Evaluate the CCS

Summary and Conclusions	Gaps identified
	Processes that are not under control
	Measures to be implemented
	How to monitor / evaluate the effetivness of the measures

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CONTROL STRATEGY

Thank you for your attention!

Fábio Teles| 05th June 2025