ECA Foundation
Fostering harmonisation of GMP/GDP regulations

How to Develop and Document a Contamination Control Strategy

– ECA Task Force on Contamination Control Strategy –

An ECA Foundation Guidance Document

Content

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:

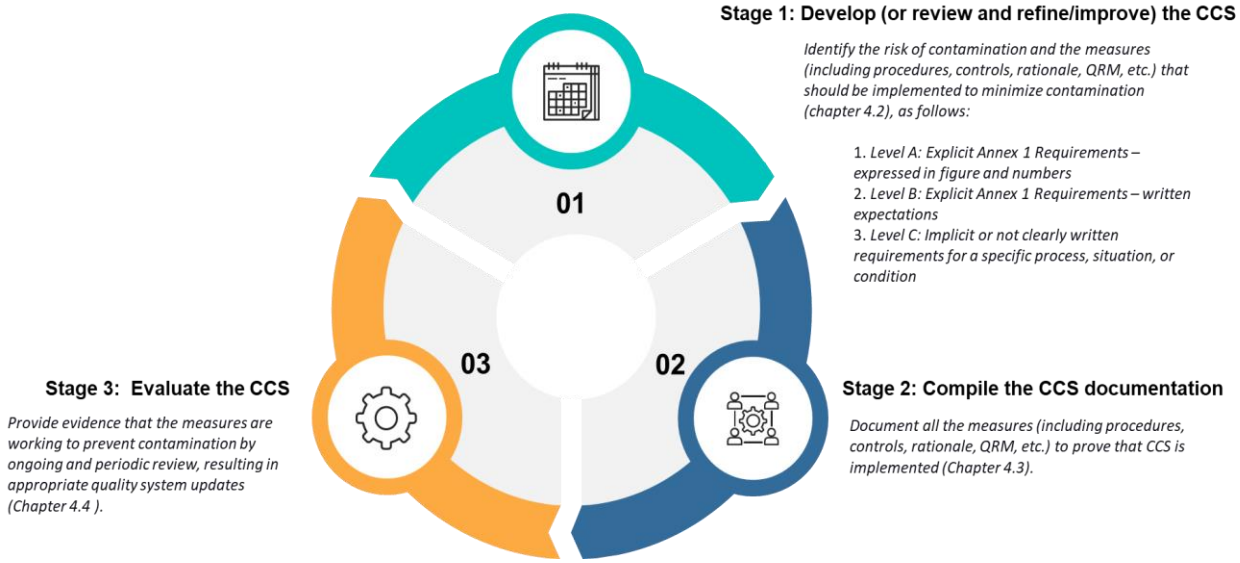
xvii. Pest Control
xviii. Virus Safety
xix. Deviation Management/CAPA
xx. Aseptic Process Simulation

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 ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	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).

Attachment 1: Example of a gap assessment (non-exhaustive)

Key Areas	Key Elements	Detailed CCS Elements		Annex 1 rev12 draft reference	Identified potential gaps (or documentation improvement need) versus Annex 1 draft expectations	Key supporting Site Strategies, Rationales, Risk assessments *Include Reference, title and if possible hyperlink to the*	Key Site Procedures *Include Reference, title and hyperlink to the document*
Facilities, equipment, Utilities and Infrastructure Design, Qualification, Maintenance and Control	**Facilities**	**Facilities Design**	Facility design requirements (plant layout, air filtration, material of construction, cleanability, airlock design, logical and chronological activities flows)	4.1, 4.2, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9 4.10, 4.11, 4.12, 4.13, 4.17 6.6 6.21	4.1 explain how controls and monitoring are "***scientifically justified and capable*** *of evaluating the state of environmental conditions for cleanrooms, airlocks and pass-throughs used for material and equipment transfer* " 4.3 Barriers should be considered in the CCS." ***Any alternative approaches to the use of RABS and Isolators should be justified*** " Develop the current material transfer and airlocks sections using wording of 4.10, 4.11, 4.12, 4.13	*To be filled out accordingly*	*To be filled out accordingly*
			HVAC system design requirements (Air Filtration/HEPA Filters, Pressure cascades, Temperature, RH, locations of air inlets & outlets, ducts cleanability, air exchanges rates, alarms settings and controls ..)	4.13, 4.14, 4.15, 4.16 4.35	Develop an adequate section to cover 4.16 "**Setpoints and the criticality of pressure differentials** *should be documented within the CCS* " / "*where* ***alarm delays are set, these should be assessed and justified*** *within the CCS* "	*To be filled out accordingly*	*To be filled out accordingly*
			Area Classification / Grade cascading	4.1, 4.4, 4.12, 4.13, 4.20 8.14	No gap identified		
			Physical segregation of activities (dedicated facility/area, use of closed systems, other containment systems, ...) / Barriers	4.2, 4.3, 4.4 4.18, 4.19, 4.20, 4.21, 4.22, 4.23 8.10, 8.14, 8.15, 8.16	4.3 Use of barriers should be considered in the CCS : any alternative approaches to the ***use of RABS or isolators should be justified***	*To be filled out accordingly*	*To be filled out accordingly*
			Localized Unidirectional Air Flow application/protection, dust control systems	4.2, 4.25 4.6	No gap identified		
		Classification & Qualification of Facilities / Barriers	Qualification Program and control (AFPT, Air velocity...)	4.15, 4.21, 4.26, 4.27, 4.28, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34	4.30 & 4.33 develop the current section to explain how current strategy fulfills the requirement for the sampling locations and their positioning during classification " *critical processing locations should be* ***based on a documented risks assessment and knowledge of the process*** *and operations* " and during qualification "*the number of sampling locations s* ***hould be based on a documented risk assessment, including the results of the classification, air visualization and knowledge of the process*** *and operations* "	*To be filled out accordingly*	*To be filled out accordingly*
		Facility Cleaning and Disinfection	Cleaning Programs (agents selection, frequency, materials...) / Practices	4.22, 4.36, 4.37	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Sanitization agents validation (including verification against local flora)	4.24, 4.37, 4.38	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Pest Control	Pest control Program / Traps location maps	*Identified as additional risk beyond Annex 1 requirements*	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Maintenance	Program for facilities (including Fit and Finish program)	5.3, 5.6	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Periodic HEPA filters integrity testing	4.34	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Maintenance practices for product protection	5.6	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Return to service after maintenance	5.6, 5.7	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Waste Management	Waste flow and segregation		No gap identified	*To be filled out accordingly*	*To be filled out accordingly+B2:H17*

Key Areas	Key Elements	Detailed CCS Elements		Annex 1 rev12 draft reference	Identified potential gaps (or documentation improvement need) versus Annex 1 draft expectations	Key supporting Site Strategies, Rationales, Risk assessments *Include Reference, title and if possible hyperlink to the*	Key Site Procedures *Include Reference, title and hyperlink to the document*
Facilities, equipment, Utilities and Infrastructure Design, Qualification, Maintenance and Control	Equipment	**Equipment Design**	Equipment design requirements /capability / cleanability	5.1, 5.2, 5.3, 5.8 5.9 8.34	5.9 Include in the CCS the **more precise requirement for particles counters maximum tubing length and minimum bend radius**	*To be filled out accordingly*	*To be filled out accordingly*
			Operational practices (out of place or in place cleaning of pieces of equipment, draining, drying, steaming, sterilization,...)	5.6	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Equipment integrity and storage conditions after cleaning and sterilization (system integrity , storage under positive pressure prior to use...)	4.11 8.45, 8.46, 8.47, 8.48	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Preventive and Corrective Maintenance	Maintenance Program for equipment	5.6	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Maintenance practices for product protection	5.6	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Return to service after maintenance	5.6, 5.7	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Qualification and Validation of Equipment	Cleaning / Sterilization of all Equipment (e.g. tanks, filtration systems, filler parts, isolator decontamination etc) - Validation Program	5.4, 5.5	5.5 "***Indirect Contact parts should be sterilized***"	*To be filled out accordingly*	*To be filled out accordingly*
	Utilities	**Utilities Design (Water systems, Clean steam, Compressed gases)**	Utilities generation and distribution systems design (materials of construction, loops, recirculation conditions, heat exchangers design, process control limits, on-line control systems, sanitization capabilities, ...), Quality levels and applications	6.1, 6.2, 6.3, 6.4, 6.5, 6.6 6.7, 6.8, 6.9, 6.10, 6.11 6.16, 6.17 6.18, 6.19	6.19 add to existing chapter for gases that "***any transfer pipework or tubing that is located after the final sterilizing filter***" **is sterilized**	*To be filled out accordingly*	*To be filled out accordingly*
		Sanitization	Sanitization Program (method, frequency...)	6.10, 6.12	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Preventive and Corrective Maintenance	Maintenance Program for utilities	6.11	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
			Maintenance practices for product protection	6.12, 6.20 6.22, 6.23	6.22, 6.23 Create adequate section to document the contamination control of heating, cooling and hydraulic systems	*To be filled out accordingly*	*To be filled out accordingly*
			Return to service after maintenance	6.12	No gap identified	*To be filled out accordingly*	*To be filled out accordingly*
		Qualification and Validation of Utilities	Utilities Qualification Strategy and control	6.13 6.15	6.13 iii explain how current risk based strategy (including the frequency) fulfills the requirement "*a sample from the point at the end of the distribution loop* ***each day that the water is used***"	*To be filled out accordingly*	*To be filled out accordingly*
Process Design, Validation and Control	Process	**Process Design**	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Aseptic Intervention Management	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Glove Control Strategy (RABS, Isolator)	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Sterilization Validation	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Sterilization Validation	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Sterilizing Filtration Validation and integrity testing strategy	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Sterile hold times validation	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Process Validation incl. Product hold times	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
Product, Container Closures Design, validation and Control	Materials and Components	**Product properties, CQAs**	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Selection of Material and Components (native, RTU, RTS)	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Material / Component Flow and Storage	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Supplier Management	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
			To be filled out accordingly	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Qualification of Material and Components	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Lab Equipment and Methods	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
	Container / Closure systems	**Selection of Container / Closure System**	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*
		Qualification of Container / Closure System	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*	*To be filled out accordingly*

Attachment 2: Example of a CCS Table of content

1. **Purpose and scope of the document**
2. **Definitions and abbreviations**
3. **List of the GMP sites**
4. **Brief description of the plants and facilities (refer to SMF)**
5. **Brief description of product currently manufactured**
6. **CCS and site's objective**
7. **CCS cross-functional team**
8. **Roles and responsibilities**
9. **CCS communication and decision-making process**
10. **QRM scope in regard to the CCS requirements**
    a. Reference to gap assessment vs. the CCS requirements
11. **Elements to consider for the CCS**
    a. **Facility layout**
        i. Cleanroom classification
        ii. Cleanroom Pressure, temperature, humidity, etc.
        iii. HVAC layout
        iv. Maintenance program
        v. Control access to the defined area
    b. **Intermediate, product, material & Personnel Flow**
    c. **Utilities**
        i. Water
            1. QRM and controls
            2. Preventive maintenance program
            3. Qualification (reference) and routine monitoring
        ii. Compressed gas
            1. QRM and controls
            2. Preventive maintenance program
            3. Qualification (reference) and routine monitoring
        iii. Steam
            1. QRM and controls
            2. Preventive maintenance program
            3. Qualification (reference) and routine monitoring
        iv. Equipment
            1. Process equipment cleaning validation
            2. Qualification (reference)
            3. QRM and controls
        v. Premises

1. Cleanroom qualification
2. Cleaning and disinfection
3. Maintenance program
4. Material transfer and disinfection

d. Process contamination risk assessment

i. Product A
   1. List of the QRM
   2. List of the routine sampling and controls

ii. Product B

e. Aseptic manipulation and intervention risk assessment

f. Visual inspection

g. Single Use Systems

i. Particulate monitoring

ii. Integrity monitoring

h. Third party management

I. Personnel Training and qualification

12. CCS Evaluation

a. Overview of the critical controls

b. Contamination residual risk threshold

c. List of the QRM part of the CCS (See Annex C)

d. Routine KPI and target (see Annex B)

e. Periodic review of the CCS

f. Elements that trigger the CCS review

13. Continuous improvement and governance decision (see annex A)

14. Conclusion

15. References

16. Document history

17. Annexes

a. List/link of QRM related to CCS

b. List/link of the procedures/policies related to CCS

c. List/Link to the rationale, strategy/position paper, etc.

d. Link to gap analysis

e. Summary of the improvement to implement

f. Summary of the KPI to follow in routine. Including e.g., EM data, etc.

Attachment 3: Template for the Contamination Control Strategy Document (example)

About this CCS-document template and how to use and understand it

This template is meant to support the documentation of the CCS strategy. It is not an instruction on developing and implementing the CCS strategy, although – implicitly – essential steps for implementing a CCS can be deduced from this document.

Experience shows that although a well-elaborated CCS may be implemented, it can be challenging to find/identify the document where the specific information is laid down, stated, or defined! The compilation of the CCS elements in this document should be holistic and overview.

> Note: For larger companies, e.g., with an extensive product portfolio, it may be advisable to create appendices instead of listing all information in the CCS document.

Like a Site Master File, this CCS document needs to be kept current but not updated with, e.g., a new version of an SOP quoted in the document.

Although not explicitly required in Annex 1, the CCS document should be controlled. Thus, approval is required. The template has a signature section on the front page.

The CCS document guides the reader to the respective Risk Assessments / Risk Analyses (RAs), reports, SOPs, and other relevant documents and should cover the main purpose of these documents, but – to avoid mismatches and conflicting statements – not repeat or summarize in detail the contents of the underlying documents.

For Sections 1 – 16, it is suggested to use tables wherever possible; this document indicates a format in each section. Sub-sections have been added to provide room for further details: e.g., Section 5 "Utilities" has been sub-sections for "water," "steam," "gases" – if other sections are required, they may be added. If less sub-sections are needed for your specific situation, delete them!

Some guiding hints regarding color coding and fonts:

Text in blue in this template is explanatory provides tips and suggestions. This text is not meant to remain in the company's CCS-Document.

Text quoted from Annex 1 is written in Times New Roman fonts.

Text in black may be regarded as "suggested text," which can be adopted, adapted, modified, amended – as adequate.

Contamination Control Strategy

Document Approval

Name	Function	Responsible for Section(s)	Date / Signature
	QA	Approval of the CCS-document	

Different functions may be responsible for different sections of the document

Table of Contents

0. Introduction

0.1. Objective

This document is based on Annex 1, which requires to develop of a Contamination Control Strategy based on the following principles (quoted from Annex 1):

"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)."

The elements to be considered are listed in Annex 1:

i. Design of both the plant and processes.
ii. Premises and equipment.
iii. Nothing mentioned under this number
iv. Personnel.
v. Utilities.
vi. Raw material controls – including in-process controls.
vii. Product containers and closures.
viii. Vendor approval includes 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 the significant risk of contamination.
xiii. Cleaning and disinfection.
xiv. Monitoring systems – including an assessment of the feasibility of introducing 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.
xvii. Add more elements that are applicable!

This CCS-Document summarizes how our company approached each of the elements and how we maintain the standard to ensure an adequate level of contamination control. This document considers quality risk assessment and the overall approach to managing microbiological, particulate, and cross-contamination of products manufactured in the sites. It makes to relevant

documents, where details are defined and documented to avoid mismatches; this CCS document does not repeat details provided in other documents.

To facilitate reading and understanding of the document, the document follows some rules:

- To maintain apparent reference to the Elements mentioned in Annex 1, the numbers of Sections 1 – 16 refer precisely to the numbers of the elements. As relevant, sub-sections may need to be added.
- If text is quoted from Annex 1, it is written in Times New Roman fonts.
- Whenever clear guidance is provided in regulatory documents, design, processes, and procedures are based on this guidance (e.g., clean room grades and related particle and microbiological requirements). Thus, such details are not repeated.
- The principles of Quality Risk Management have been applied.
- Reference to documents (reports, instructing documents, SOPs, etc.) is provided in each section.

Approval of the CCS document with ongoing review and update is recommended, and it is therefore appropriate to include this document as part of the Site Master File. The document should be included in the project documentation for a facility under construction or major facility revamping or development.

0.2. Definitions and Abbreviations

Term / Abbreviation	Definition / Long Version
CCS	Contamination Control Strategy: 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 the 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.
CCS-document	This document compiles references to all documents related to the CCS as well as conclusions on how to ascertain and maintain contamination control.
The Elements	The elements mentioned in Annex 1 under i. – xvi., which refer to Sections 1 – 16 of this document.
PV	Process Validation
QRM	Quality Risk Management
RA	Risk Assessment / Risk Analysis

Term / Abbreviation	Definition / Long Version
SMF	Site Master File

Add further Definitions and Abbreviations as required

1. Design of both the plant and processes

Provide the name of the products and associated manufacturing facilities. Provide some information of the:

- product presentation (e.g., syringes, vials, cartridge)
- formulation or product-specific variants (e.g., volumes, strength)

1.1. The Processes

Describe the different processes, list the sequential stages, and detail the associated controls – terminally sterilized products, aseptic manufacturing, low bioburden, bioburden controlled – a brief description to evaluate if the CCS is adequate.

Add information about the type of microbial contamination that the product would support growth. Describe any stage of the manufacturing process that could decrease or deactivate contamination. Explain if the product could support the proliferation of microbial during the shelf-life. Add some information on the closure system integrity and controls in place. Refer to any document that determines the risk of contamination.

State some information around the measures in place to ensure the security of the aseptic process and the sterility assurance level of terminally sterilized products:

= initial and ongoing validation (media fill)

= equipment and process qualification and requalification

= process validation and ongoing verification

= personnel qualification and requalification and disqualification

= describe the samples taken from each batch for microbial and particle control or sterility assurance.

= refer product microbial and particulate contamination assessment

1.1.1. Terminally Sterilized Products

Describe specific information about sterilization methods / processes.

Mention / list the products / types of products manufactured as terminally sterilized products

Product Name	Product Type	Container	
		Volume	Material

1.1.2. Aseptic Manufacturing

Mention / list the products / types of product manufactured under aseptic conditions

Product Name	Product Type	Container	
		Volume	Material

1.1.3. Low Bioburden Processes / Bioburden-Controlled Processes

Mention / list the products / types of product manufactured as low bioburden / bioburden controlled products

Product Name	Product Type	Container	
		Volume	Material

1.2. The Plant

1.2.1. General

The plant is designed to ensure the process steps are performed in the clean room Grades are required according to Annex 1.

Access to the clean room grades is via separate air-locks for personnel and material.

Layouts of the different areas may be inserted to show hygienic zones, personnel, and material flow. Reference to SMF may be helpful.

Provide details of the type of contamination control systems are in place, such as RABS, Isolator, etc., describe or provide the drawing of the facility HVAC systems.

Describe the utilities being used for the process (e.g., Oxygen, nitrogen) and refer to the specific section for the contamination control

Provide some general cleanroom information such as cleanroom finishes, air supplied quality, the material of construction, access to cleanroom, presence of interlock, etc.

Provide information on the cleanroom contamination control such as viable and non-viable contamination control measures, type of systems to prevent airborne contamination during the process (e.g., unidirectional flow), pressure differential, maintenance of the cleanroom and HVAC systems/filters, temperature, relative humidity, etc.

1.2.2. Terminally Sterilized Products

Process Step	Clean room grade

1.2.3. Aseptically Manufactured Products

Process Step	Clean room grade

Process Step	Clean room grade

1.2.4. Low Bioburden Processes / Bioburden-Controlled Processes

Process Step	Clean Room Grade

2. Premises and Equipment

Although not part of the elements listed in Annex 1, reference to Qualification (SOPs, Master Plan etc.) may be made here.

2.1. Premises

Concerning Premises, refer to Section 1.2

2.2. Equipment

For major equipment, consider making reference to the SMF – or copy from SMF.

3. No. 3 is empty – left out - in Annex 1 Draft

4. Personnel

4.1. General

Personnel is trained in all areas of their responsibilities. More details about the areas and the applicable procedures are provided:

Type of Training	Reference Document	
	Title	No.
Induction training		
General GMP-training		
Hygienic behavior		
Personnel Qualification		

4.2. Gowning Requirements

Description	Reference Document	
	Title	No.
Gowning requirements for the different clean room grades are defined.		

4.3. 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		

4.4. Personnel Monitoring

Note: Section 14 in Annex 1 is about monitoring, thus, in this template, Personnel Monitoring is mentioned in Section 14.3. Personnel Monitoring may either be mentioned under Section 4 "Personnel" or in Section 14 – a matter of taste. But: cross-reference should be made.

Summarize the personnel contamination control methods in place and the gowning. States if any of these activities are qualified and describe the qualification process and periodic qualification

Description	Reference Document	
	Title	No.
RAs, SOPs, evaluation	Refer to section 14	

5. Utilities

Consider making reference to SMF!

Briefly describe the method of preparation / distribution – refer to the monitoring Section.

5.1. Water

5.1.1. Purified Water

Description	Reference Document	
	Title	No.
Specification		
Preparation		
Distribution		
Monitoring	refer to Section 14.2.1	

5.1.2. WFI

Description	Reference Document	
	Title	No.
Specification		

Description	Reference Document	
	Title	No.
Preparation		
Distribution		
Monitoring	refer to Section 14.2.1	

5.2. Steam

Description	Reference Document	
	Title	No.
Specification		
Preparation		
Distribution		
Monitoring	refer to Section 14.2.1	

5.3. Gases

5.3.1. Product-contact-compressed air (direct or indirect product contact)

Description	Reference Document	
	Title	No.
Specification		
Preparation		
Distribution		
Monitoring	refer to Section 14.2.4	

5.3.2. N_2

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section 14.2.4	

5.3.3. CO_2

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section 14.2.4	

5.3.4. O_2

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section 14.2.4	

5.3.5. Further Gases

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section 14.2.4	

6. Raw Material Controls – including in-process controls

Relevant aspects

- how starting materials are sampled and tested
- microbiological requirements and endotoxin limits are part of the specification.

6.1. 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		

6.2. In-Process Controls

Relevant aspects

- the stages for contamination-control-related IPC-testing
- the limits

Description	Reference Document	
	Title	No.
Stages at which IPC-tests are performed		
Bioburden limits for the respective stages		

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		

8. Vendor approval – such as key component suppliers, sterilization of components and single-use systems (SUS), and services

8.1. General processes

Relevant aspects:

- SOP for vendor qualification (presumably the same SOP as for supplier qualification, which is relevant in Section 9) – consider combining Sections 8 and 9 or make cross-references!
- Routine vendor evaluation / auditing
- List critical vendors such as primary packaging component or raw material, critical consumable, or SUS,

Description	Reference Document	
	Title	No.
Vendor / supplier qualification process		
Vendor / supplier evaluation		
Vendor / supplier auditing		

8.2. Detailed information regarding vendors

Component	Vendor	Reference Document

		Title	No.
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	

9. For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly

Note: This Section is quite similar to section 8

Provide a detail or refer to SMF of the outsourced activity such as microbial or release testing performed by an external laboratory

9.1. General processes

Refer to Section 8.1

9.2. Detailed information regarding suppliers

Service	Contract acceptor	Reference Document	
		Title	No.

Service	Contract acceptor	Reference Document	
		Title	No.
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Process Validation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Process Validation	
		Contract	
		Qualification document	
		Audit Report	
		Annual evaluation	
		Process Validation	

10. Process Risk Assessment

The title "process risk assessment" is somehow narrowing the scope of the general requirement to base decisions on Quality Risk Management – suggestion to broaden the scope (but still keep the title for clear reference to Annex 1)

Relevant aspects:

- SOP(s)
- Registers
- Overview of existing RAs for manufacturing / cleaning / decontamination / sterilization

Description	Reference Document	
	Title	No.

Description	Reference Document	
	Title	No.
The concept of QRM is implemented throughout the organization (SOP)		
A register of RAs is maintained by QA		
RAs for manufacturing processes:		
RAs for aseptic manufacturing processes:		
RAs for cleaning processes:		
RAs for decontamination processes:		
RAs for sterilization processes:		

11. Process Validation

Following the GMP-requirements, all manufacturing processes have been validated and re-validation takes place on a regular basis / processes are under continuous verification Processes are re-validated after Changes that require re-validation.

Process Validation is based on a QRM approach and the underlying RAs mentioned in Section 10.

Note: The CCS does not refer to general cleaning validation but should focus on microbiological aspects.

Relevant aspects:

- Process Validation SOP
- PV-reports reports

Description	Reference Document	
	Title	No.
The concept of PV is described in SOP		
The concept of continuous process verification is described in SOP		
Aseptic process simulation is performed according to SOP		
PV-reports for manufacturing processes:		
Aseptic process simulation reports (media fill reports)		
PV-reports for cleaning processes:		

Description	Reference Document	
	Title	No.
PV-reports for decontamination processes:		
PV-reports for sterilization processes:		

12. Preventative maintenance – maintaining equipment, utilities, and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination

Relevant aspects – presumably covered in SOP(s):

- The way to define maintenance requirements (e.g., vendor involvement, in-house-experience, involvement of external companies)
- QA involvement
- How are maintenance plans developed (servicing / inspection / replacement actions and for the system) - Are log-book-entries considered
- The basis for the development of the maintenance program (frequency for performing maintenance actions)
- Calibration
- Responsibility for system approval after maintenance
- Refer to the document that lists the planned maintenance activities to ensure systems, plan, and equipment is operational to prevent contamination.
- Refer to the existing maintenance program document, refer to all formal assessments and confirm that the contamination control is optimal.
- Describe the procedure when recurring or critical maintenance schedule is exceeded and how the implication on product quality is investigated.

13. Cleaning and Disinfection (Decontamination and Sterilization)

Procedures are in place for cleaning and disinfection, decontamination, and sterilization.

Note: "decontamination and sterilization" are not mentioned in the enumeration in Annex 1; however, it appears feasible to cover these important aspects in this section.

List the procedures and make reference to the SOP numbers and – as applicable – validation reports (cross-references to Section 0 should be considered)

Also, summarize the contamination control treatments to minimize surface and personnel contaminations.

Consider listing and detailing the contamination control product or system used and their purpose.

13.1. Equipment

Equipment Type	Activity	Reference Document	
		Title	No.
	Cleaning		
	Disinfection		
	Cleaning		
	Disinfection		
	Cleaning		
	Disinfection		
	Cleaning		
	Disinfection		
	Cleaning		
	Disinfection		
	Cleaning		
	Disinfection		

Equipment Type	Activity	Reference Document	
		Title	No.

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		

13.3. Clean Room Clothing

Refer to Section 4.3

14. Monitoring Systems - including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination

Relevant aspects:

- Reference to Risk Assessments, which lead to the sampling points
- SOPs

- Reference the summary reports and how the description of how trending is done (SOP!) and conclusions are drawn.

14.1. General Procedures

Description	Reference Document	
	Title	No.
Instruction on how to develop sampling points / frequency / warning and action limits		
Instruction for the preparation of reports		
SOP on how to perform trending		

14.2. Monitoring of Systems

14.2.1. Environment

Summarize and cross-reference with the relevant section of this document to describe the viable and non-viable monitoring and testing methods associated. Describe if the sampling is performed by internal or external personnel and the overall oversight by the quality department.

Describe the frequency, location, and type of sampling, including the definition of the alert and action limits. State the frequency of the historical EM data review and analysis.

Refer to the section discussing the filter integrity, the velocity of air supplied, smoke studies, pressure differential, temperature, relative humidity, etc.

Refer to the microbial media and incubation program used, air exposure of the media (e.g., settle plate) validated, etc.

14.2.2. Water and Steam

Type	Activity	Reference Document	
		Title	No.
City Water optional!	RA		
	Monitoring SOP		
	Summary Report		
Purified Water	RA		
	Monitoring SOP		
	Summary Report		
Clean Steam	RA		

Type	Activity	Reference Document	
		Title	No.
	Monitoring SOP		
	Summary Report		

14.2.3. Clean Rooms

Consider further differentiation into different areas and / or clean room grades

Type	Activity	Reference Document	
		Title	No.
viable monitoring	RA		
	Monitoring SOP		
	Summary Report		
Non-viable monitoring	RA		
	Monitoring SOP		
	Summary Report		

14.2.4. Gases

Type	Activity	Reference Document	
		Title	No.
Product-contact-compressed air	RA		
	Monitoring SOP		
	Summary Report		
N_2	RA		
	Monitoring SOP		
	Summary Report		
CO_2	RA		
	Monitoring SOP		
	Summary Report		
O_2	RA		
	Monitoring SOP		

Type	Activity	Reference Document	
		Title	No.
	Summary Report		
Further	RA		
	Monitoring SOP		
	Summary Report		

14.3. Personnel

Note: see remark in Section 4.4

Area Grade	Activity	Reference Document	
		Title	No.
Grade B	RA		
	Monitoring SOP		
	Summary Report		
Grade C	RA		
	Monitoring SOP		
	Summary Report		
Grade D	RA		
	Monitoring SOP		
	Summary Report		

15. Prevention – trending, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more comprehensive investigational tools

Refer to the document that describe the requirement for an effective investigation, quality management systems, and the document that describes the deviations process and CAPA including document that track and trend reoccurrence and CAPA effectiveness.

State the procedure in place to address reoccurring deviation to ensure proper contamination control states.

Description	Reference Document

	Title	No.
Incidents and deviations are managed via:		
Investigation of incidents and deviations (Root causes analyses) is described in SOP:		
Corrective and preventive actions (CAPAs) are managed according to:		

16. Continuous improvement based on information derived from the above

Summarize processes and procedures for continuous improvement and include the document subject to periodic updates

- preparation of reports (frequency!), e.g., management reports or PQRs
- evaluation of incidents and deviations and related CAPAs
- trending analysis of EM, product quality review, etc.
- internal communication/escalation via regular or extraordinary meetings with defined participants.
- KPIs and their evaluation

In this section also provide some information about the trigger that would lead to improvement derived from data reviewing (e.g., visual inspection defect characterization).

17. Further relevant aspects – e.g., with regard to viral safety

18. References:

List the regulatory, literature, or industrial references used if needed.

19. Attachments

Attachment 4: Relevant/Helpful Guidelines and Documents:

Regulatory:

i) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Chapter 3: Premises and Equipment, (2014)*
ii) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Chapter 5: Production, (2014)*
iii) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Part II: Basic Requirements for Active Substances used as Starting Materials, (2014)*
iv) *European Union, Guidelines of 19 March 2015 on the formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use, Official Journal of the European Union, (2015/C 95/02), (2015)*
v) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, (2018)*
vi) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Annex 3 Manufacture of Radiopharmaceuticals, (2008)*
vii) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Annex 14 Manufacture of Medicinal Products Derived from Human Blood or Plasma, (2011)*
viii) *European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, (2017)*
ix) *European Union, Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use, Official Journal of the European Union, (2013/C 343/01), (2013),*
x) *European Union, Guidelines of 19 March 2015 on principles of Good Distribution Practice of active substances for medicinal products for human use, Official Journal of the European Union, (2015/C 95/01), (2015)*
xi) *EMA Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (20 November 2014)*
xii) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, subpart C = Building and Facilities, sec. 211.42 Design and construction features (b), (c)*
xiii) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, Subpart F - Production and Process Controls,* ***sec.*** *211.113 Control of microbial contamination (a), (b)*
xiv) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, Subpart B - Organization and Personnel, sec.211.28 Personnel responsibilities (a)*
xv) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, Subpart E - Control of*

Components and Drug Product Containers and Closures, sec. 211.80 General requirements. (b)

xvi) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, Subpart E - Control of Components and Drug Product Containers and Closures, sec. 211.84 Testing and approval or rejection of components, drug product containers, and closures (d)*

xvii) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, Subpart D - Equipment, sec. 211.67 Equipment cleaning and maintenance (a)*

xviii) *U.S. Food & Drug Administration, Code of Federal Regulation Title 21, part 211 current good manufacturing practice for finished pharmaceuticals, Subpart C - Buildings and Facilities, sec. 211.56 Sanitation (c)*

xix) *U.S. Department of Health and Human Services Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, (2004)*

xx) *U.S. Department of Health and Human Services Food and Drug Administration, Guidance for Industry - Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing, (2020)*

xxi) *U.S. Department of Health and Human Services Food and Drug Administration, Guidance for Industry - Guidance for Industry Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross Contamination, (2013)*

xxii) *U.S. Department of Health and Human Services Food and Drug Administration, Guidance for Industry Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, Draft Guidance. https://www.fda.gov/media/88905/download (accessed Jan 6, 2021)*

xxiii) *pharmaceutical inspection co-operation scheme gmp guide, 2nd targeted consultation document on revision of annex 1*

xxiv) *pharmaceutical inspection co-operation scheme gmp guide, ps inf 25 2019 (rev. 1) draft, manufacture of advanced therapy medicinal products for human use*

xxv) *pharmaceutical inspection co-operation scheme gmp guide, ps inf 26 2019 (rev. 1) draft, manufacture of biological medicinal substances and products for human use*

xxvi) *pharmaceutical inspection co-operation scheme gmp guide, pe 009-15 (part i), guide to good manufacturing practice for medicinal products part i*

xxvii) *pharmaceutical inspection co-operation scheme gmp guide, pe 009-15 (part ii), guide to good manufacturing practice for medicinal products part ii*

xxviii) *pharmaceutical inspection co-operation scheme gmp guide, pe 009-15 (annexes), guide to good manufacturing practice for medicinal products annexes*

xxix) *world health organisation, good manufacturing practices for pharmaceutical products: main principles, annex 2, who technical report series 986, 2014,*

xxx) *world health organisation, who good manufacturing practices for active pharmaceutical ingredients (bulk drug substances), annex 2, who technical report series 957, 2010*

xxxi) *world health organisation, points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance annex 6, who technical report series 1025, 2020*

xxxii) *world health organisation, who good manufacturing practices for sterile pharmaceutical products, annex 6, who technical report series 961, 2011*

xxxiii) *world health organisation, who good manufacturing practices for biological products, annex 3, who technical report series 996, 2016*

xxxiv) *who good manufacturing practices for the manufacture of investigational pharmaceutical products for clinical trials in humans, annex 7, who technical report series 863, 1996*

xxxv) *who good manufacturing practices for radiopharmaceutical products annex 2, who technical report series 1025, 2020*

xxxvi) *WHO GMP for Pharmaceutical Products containing Hazardous Substances, TRS 957, Annex-3 (2010)*

xxxvii) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use, Quality Risk Management, Q8 (R2), Pharmaceutical Development, August 2009. https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf (Accessed Nov 29, 2021)

xxxviii) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use, Quality Risk Management Q9, November. https://database.ich.org/sites/default/files/Q9%20Guideline.pdf (accessed Nov 29, 2021).

xxxix) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use, pharmaceutical quality system Q10. https://database.ich.org/sites/default/files/Q10%20Guideline.pdf (accessed Nov 29, 2021).

Industry:

I. ECA Guidelines for the Evaluation and Investigation of Microbiological Deviations
- Chapter 1 - Deviation Handling of Microbiological Environmental Monitoring Excursions in Non-Sterile Pharmaceutical Manufacturing
- Chapter 2 - Lab Investigations – Endotoxin Out of Specification (OOS)/ Out of Trend (OOT)/ Atypical Results Investigations
- Chapter 3 - Guidance for Sterility Test Failures

II. ECA Standard Operating Procedure (SOP): Laboratory Data Management - Out of Specification (OOS) Results

III. ECA Laboratory Data Management Guidance: Out of Expectation (OOE) and Out of Trend (OOT) Results

IV. ECA Good Practice Guide on Validation

V. ECA Good Practice Guide "Visual Inspection of Medicinal Products for Parenteral Use - Version 3.2"

VI. Container Closure Integrity Testing of Medicinal Products for Parenteral Use - Position Paper - Version 2.0

VII. USP general chapter discussing contamination control: <1116>; <1072>; <1231>; <1229>; etc.