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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.

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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

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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

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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.

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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

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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

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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		

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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

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		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.

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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.

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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:		

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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.

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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		

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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

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- 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		

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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

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	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