Attachment 3: Template for the Contamination Control Strategy Document

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 how to develop and implement 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 - yet it can be a challenge 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 provide a good 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.

Similar to 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 a controlled document approved by a Quality Unit. 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 indicate what is said in 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" includes sub-sections for "water," "steam," "gases" – if further sections are required, they may be added. If less sub-sections are needed for your specific situation, just delete them!

Some guiding hints regarding color coding and fonts:

Text in blue in this template is explanatory and 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 and in Italics.

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 – There is no single
CCS-SME

Table of Contents

A. Introduction:

A.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, including the associated documentation.*
ii. *Premises and equipment.*
iii. *Personnel.*
iv. *Utilities.*
v. *Raw material controls – including in-process controls.*
vi. *Product containers and closures.*
vii. *Vendor approval includes key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers.*
viii. *Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilization services.*
ix. *Process risk assessment.*
x. *Process validation.*
xi. *Validation of sterilization processes.*
xii. *Preventative maintenance – maintaining equipment, utilities, and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination.*
xiii. *Cleaning and disinfection.*
xiv. *Monitoring systems – including an assessment of the feasibility of introducing scientifically sound, alternative methods that optimize the detection of environmental contamination.*
xv. *Prevention mechanisms – trend analysis, detailed, investigation, root cause determination, corrective and preventive actions (CAPA), and the need for comprehensive investigational tools.*
xvi. *Continuous improvement based on information derived from the above.*

Add more elements if applicable! – e.g., further conditions that need contamination control, summary and conclusion, attachments, document history

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:

- In order to maintain clear reference to the Elements mentioned in Annex 1, the numbers of Sections B.1 – B.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 *italics*.
- Whenever there is 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.

A.2 Definitions and Abbreviations

Term / Abbreviation	Definition / Long Version
CCS	Contamination Control Strategy: *A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to 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 B.1 – B.16 of this document.
PV	Process Validation
QRM	Quality Risk Management
RA	Risk Assessment / Risk Analysis
SMF	Site Master File

Term / Abbreviation	Definition / Long Version
SV	Sterilization Validation

Add further Definitions and Abbreviations as required

B. Documentation of the Contamination Control Strategy

B.1. Design of both the plant and processes including the associated documentation

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)

B.1.1. The plant

B.1.1.1. 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 could be extremely useful at this point.

B.1.1.2. Aseptically Manufactured Products

Process Step	Clean room grade	High level Contamination control measures

B.1.1.3. **Low Bioburden Processes / Bioburden-Controlled Processes**

Process Step	Clean room grade	High level Contamination control measures

Process Step	Clean room grade	High level Contamination control measures

B.1.2. **The Processes:**

Describe the different processes– Aseptically Manufactured products and low bioburden / bioburden controlled – a brief description to evaluate if the CCS is adequate.

B.1.2.1. Aseptic Manufacturing

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

Product Name	Product Type	Container	
		Volume	Material
Adalimumab	Monoclonal Antibodies		

B.1.2.2. 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

Product Name	Product Type	Container	
		Volume	Material

B.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.

B.2.1. Premises

Concerning Premises, refer to Section B.1.2.

B.2.2. Equipment

For major equipment in regard to contamination control, consider making reference to the SMF – or copy from SMF.

List major equipment related to contamination prevention such as autoclave and refer to the measure in place in the section of the CCS e.g. B11

B.3. Personnel:

B.3.1. 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	Training program	
General GMP-training	cGMP training module	
Hygienic behavior	clean room behavior, Training Module on Overview of Maintenance of clean room,	

Type of Training	Reference Document	
	Title	No.
	clean room behavior and Environment Monitoring	
Personnel Qualification	Personnel gowning qualification	

B.3.2. **Gowning Requirements**

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

B.3.3. **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		

B.3.4. **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 B.4 "Personnel" or in Section B.14. – a matter of taste. But: cross-reference should be made.

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

In this section, add the information around aseptic media fill, aseptic intervention risk assessment, monitoring after intervention. Finally, give an explanation on the residual risk accepted.

B.4. **Utilities**

Consider making reference to SMF!

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

Brief description of the contamination prevention program in place such as sanitization, decontamination, etc.

B.4.1. Water

B.4.1.1. Purified Water

Description	Reference Document	
	Title	No.
Risk Assessment		
Specification	Purified Water Specification	
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.1.2. **WFI**

Description	Reference Document	
	Title	No.
Specification	WFI Specification	
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.2. **Steam**

Description	Reference Document	
	Title	No.
Specification	Pure steam Specification	
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3. **Gases**

B.4.3.1. **Product-contact-compressed air (direct or indirect product contact)**

Description	Reference Document	
	Title	No.
Specification	OPERATIONAL PROCEDURE FOR COMPRESSED AIR / GAS GENERATION AND DISTRIBUTION SYSTEMS	
	MONITORING AND SAMPLING PROCEDURE FOR IN HOUSE GENERATED NITRIGEN GAS, COMPRESSED AIR & PROCESS AIR DISTRIBUTION SYSTEM	

Description	Reference Document	
	Title	No.
	MICROBIOLOGICAL MONITORING OF COMPRESSED GASSES	
	OPERATION AND CLEANING OF COMPRESSED AIR/NITROGEN AIR SAMPLER	
Preparation		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.2. **N_2**

Description	Reference Document	
	Title	No.
Specification	Nitrogen Specification	
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.3. **CO_2**

Description	Reference Document	
	Title	No.
Specification	Carbon dioxide specification	
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.4. **O_2**

Description	Reference Document	
	Title	No.
Specification	Oxygen Specification	
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.4.3.5. **Further Gases**

Description	Reference Document	
	Title	No.
Specification		
Storage		
Distribution		
Monitoring	refer to Section B.14.	

B.5. 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 raw material specification.

Raw Material (Starting Material) Controls Description	Reference Document	
	Title	No.
Test specifications for each starting material are prepared	SAMPLE, TESTING, RELEASING AND	

Raw Material (Starting Material) Controls Description	Reference Document	
	Title	No.
and approved; specifications follow the Marketing Authorization	RETESTING OF RAW MATERIALS, PACKING MATERIALS AND CONSUMABLES	
Incoming goods' testing	PROCEDURE FOR HANDLING OF RAW MATERIALS AND CONSUMABLES IN MANUFACTURING AREA (PB1 PB2 & PB3)	
Sampling	DISPENSING OF RAW MATERIALS, SOLVENTS AND LIQUID	
QC-Testing	ALPHANUMERIC CODIFICATION FOR PROCESS RAW MATERIALS	
Starting Material release procedure		

B.5.1. **In-Process Controls**

Relevant aspects

- the stages for contamination-control-related IPC-testing
- the limits
- link this section to the section B.1.1

Description	Reference Document	
	Title	No.
Stages at which IPC-tests are performed	In process Control and Management of reserve samples, in process and finished product Sampling	
Bioburden limits for the respective stages		

B.6. **Product Containers and Closures:**

Relevant aspects

- different products, their container and closures
- CCI tests
- Routine process for testing container closure integrity
- When containers are a SUS or other material refer to the extractible and leachable reports and include the monitoring on these containers to prevent contamination (e.g. particulate, integrity test).

Description	Reference Document	
	Title	No.
Container Type - Specification	HANDLING AND TESTING OF MEDIA FILL STUDY SAMPLES	
	OPERATION AND CLEANING OF CCIT VESSEL	
	OPERATION AND CLEANING OF LEAK TEST APPARATUS (MAKE: VEEGO)	
	OPERATION AND CLEANING OF LEAK TEST APPARATUS (MAKE: VEEGO)	
Closure Type - Specification		
Container System Qualification		
Container Closure Integrity Testing		

Description	Reference Document	
	Title	No.
Routine tests for container closure integrity		
Extractables & Leachables (where applicable)		

B.7. **Vendor approval – such as key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers**

B.7.1. General processes

Relevant aspects:

- SOP for vendor qualification (presumably the same SOP as for supplier qualification, which is relevant in Section B.8.) – consider combining Sections B.7. and B.8. or make cross-references!
- Routine vendor evaluation / auditing

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

B.7.2. **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	

B.8. **Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilization services.**

Note: This Section is quite similar to section B.7.

B.8.1. General processes

Refer to Section B.7.1.

B.8.2. Detailed information regarding suppliers

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	

B.9. **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 / depyrogenation

Description	Reference Document	
	Title	No.
The concept of QRM is implemented throughout the organization (SOP)	Quality Risk Management	
A register of RAs is maintained by QA		
RAs for manufacturing processes:		
RAs for aseptic manufacturing processes:	Risk assessment for manufacturing process in cleanroom facility	
RAs for cleaning processes:	Risk assessment for manufqacturing process in cleanroom facility	

Description	Reference Document	
	Title	No.
RAs for decontamination (incl. depyrogenation) processes:	Risk Assessment for Introduction of integral vial filling line (Vial washing, dehydrogenated tunnel sterilize, vial filling stoppering machine, and vial sealing machine) Introduction block 1 facility for processing of vial dosage form.	

RAs for sterilization processes are part of B.11.

B.10. **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 B.9.

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

Relevant aspects:

- Process Validation SOP
- PV-reports

Description	Reference Document	
	Title	No.
The concept of PV is described in SOP	PROCESS VALIDATION	
The concept of continuous process verification is described in SOP		
Aseptic process simulation is performed according to SOP	PROCEDURE FOR ASEPTIC PROCESS SIMULATION	
PV-reports for manufacturing processes:	Process Validation Report	
Aseptic process simulation reports (media fill reports)		
	Aseptic media fill batch record (1.0 ml long PFS)	
	Aseptic process simulation protocol	
	aseptic process simulation report (semi-automatic filling and manual stoppering / cap sealing for vials)	
	Aseptic process validation report	
	aseptic process stimulation report 4r vials (vial filling line PB1)	
PV-reports for cleaning processes:	Cleaning validation	
	Study protocol of cleaning validation for drug product	

Description	Reference Document	
	Title	No.
	manufacturing accessories and equipment's	
PV-reports for decontamination processes:		
PV-reports for depyrogenation processes:	protocol for sterility evaluation of depyrogenated vials using sterile SCDM.	

B.11. Validation of sterilization processes:

Following the GMP-requirements, all sterilization 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.

Validation of sterilization processes is based on a QRM approach and the underlying RAs mentioned in Section B.9.

Note: The CCS does also refer to depyrogenation processes and their validation but this topic is covered in the previous chapter B.10.

Relevant aspects for the validation of sterilization processes:

- Sterilization Validation SOP or VMP
- SV-reports

Description	Reference Document	
	Title	No.
The concept of SV is described in SOP or VMP		
The concept of continuous process verification or re-validation of sterilization processes is described in SOP or VMP	Study protocol for continuous process verification	
SV-reports for sterilization processes		

It is also an option to cover the validation of sterilization processes in Section 10 and make a cross-reference to Section 10 here, in Section 11. – Importance of sterilization processes may trigger the decision whether to handle Validation of sterilization processes in a separate Section or not.

B.12. **Preventative maintenancel**

Tenance – maintaining equipment, utilities, and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional 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
- Risk assessments

If CC aspects are addressed in the documents for preventive maintenance programs, an additionally reference to these documents may be useful.

B.13. **Cleaning and Disinfection**

Procedures are in place for cleaning and disinfection.

Note: "decontamination" is 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 B.10. should be considered)

B.13.1. Equipment

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

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

B.13.2. **Clean Rooms / Clean Areas**

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

B.13.3 **Clean Room Clothing:**

Refer to Section B.3.3.

B.14. **Monitoring Systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative 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.

B.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		

B.14.2. **Monitoring of Systems:**

B.14.2.1. **Water and Steam:**

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

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

B.14.2.2. **Clean Rooms:**

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.

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

Type	Activity	Reference Document	
		Title	No.
Viable environmental monitoring	RA	Risk Assessment for selection of Viable monitoring for second floor manufacturing facility	
		Rationale for selection of non-Viable monitoring locations for second floor Manufacturing facility.	
		Risk assessment for selection of Viable particle monitoring at AST Filling area	

Type	Activity	Reference Document	
		Title	No.
		Risk assessment for Selection for viable monitoring for ground floor warehouse Area.	
		Risk assessment for selection of viable monitoring for pass box ground floor Microbiology area.	
		Risk assessment for selection of viable monitoring for ground floor manufacturing facility (Microbiology area)	
		Rationale for selection of viable monitoring location of sealing suspended verticle LAF in DSP area (PB3)	
		Rationale for selection of viable monitoring locations ground floor main building (S1) for dispensing booth, sampling booth, solvent dispensing booth and dynamic pass box.	
		Rationale for selection of viable monitoring locations ground floor warehouse solvent dispensing area	
		Rationale for selection of viable monitoring locations ground floor	

Type	Activity	Reference Document	
		Title	No.
		warehouse dispensing area	
		Rationale for selection of viable monitoring locations ground floor main building (S1) quality control analytical area	
		Rationale for selection of viable monitoring locations ground floor main building (S1) microbiology area (passbox)	
		Rationale for selection of viable monitoring locations of vial filling and sealing machine PB1 area	
		Rationale for selection of non viable monitoring locations sealing suspended laminar air flow/verticle LAF PB1 area	
		Rationale for selection of viable monitoring locations of dynamic passbox in vial filling area (NKP line) PB1 area	
		Rationale for selection of viable monitoring locations of sealing suspended laminar air flow/verticle LAF PB1 area	
		Risk Assessment for Installation of online NVPC and Active air	

Type	Activity	Reference Document	
		Title	No.
		Microbial Environment monitoring system	
	Monitoring SOP	MICROBIOLOGICAL ENVIRONMENATL MONITORING PROGRAM IN CLEAN ROOM AND MICROBIAL ENVIRONMENTAL MONITORING PROGRAM IN ASEPTIC AREA	
	Summary Report		
Non-viable (physical) environmental monitoring	RA	Risk Assessment for non viable particle count monitoring for ground floor microbiology	
		Rationale for selection of non viable monitoring locations ground floor main building (S1) quality control analytical area	
		Risk Assessment for selection of Non-viable particle count monitoring for AST Filling Area	
		Rationale for selection of non viable monitoring locations ground floor main building (S1) microbiology area	

Type	Activity	Reference Document	
		Title	No.
		Rationale for selection of non viable monitoring locations sealing suspended laminar air flow/vertical LAF PB1 area	
		Rationale for selection of non viable monitoring locations of PB1 DP area	
		Rationale for selection of non viable monitoring locations of dynamic pass box in vial filling area (NKP line)PB1 area	
	Monitoring SOP	ONLINE MONITORING OF VIABLE AND NON-VIABLE PARTICLES . PROCEDURE FOR NVPC MONITORING IN CLEAN ROOM	
	Summary Report		

B.14.2.3. **Gases**

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

Type	Activity	Reference Document	
		Title	No.
N_2	RA		
	Monitoring SOP		
	Summary Report		
CO_2	RA		
	Monitoring SOP		
	Summary Report		
O_2	RA		
	Monitoring SOP		
	Summary Report		
Further	RA		
	Monitoring SOP		
	Summary Report		

B.14.2.4. **Personnel**

Note: see remark in Section B.3.4.

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		

B.15. **Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA), and the need for 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:		

B.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 (define 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.

B.17. Further relevant aspects – e.g., with regard to viral safety (where applicable)

C. **Summary and Conclusion (including identified gaps and how to assess them)**

Summarize the results and conclusions.

During the preparation of the document, you may have come across areas that need further improvement, assessment or for which no or insufficient regulations are available. Then, this may be recorded in this section (or by adding sub-sections). Include the path forward (schedule, responsibilities) to rectify the deficits.

"Summary and Conclusions …. " may also be at the beginning!

D. References

List the regulatory, literature, or industrial references used as feasible.

E. Attachments

As applicable

F. Document History

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/defauslt/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.