The Challenges and Successful Annex 1 Implementation

A Bio Farma Case Study

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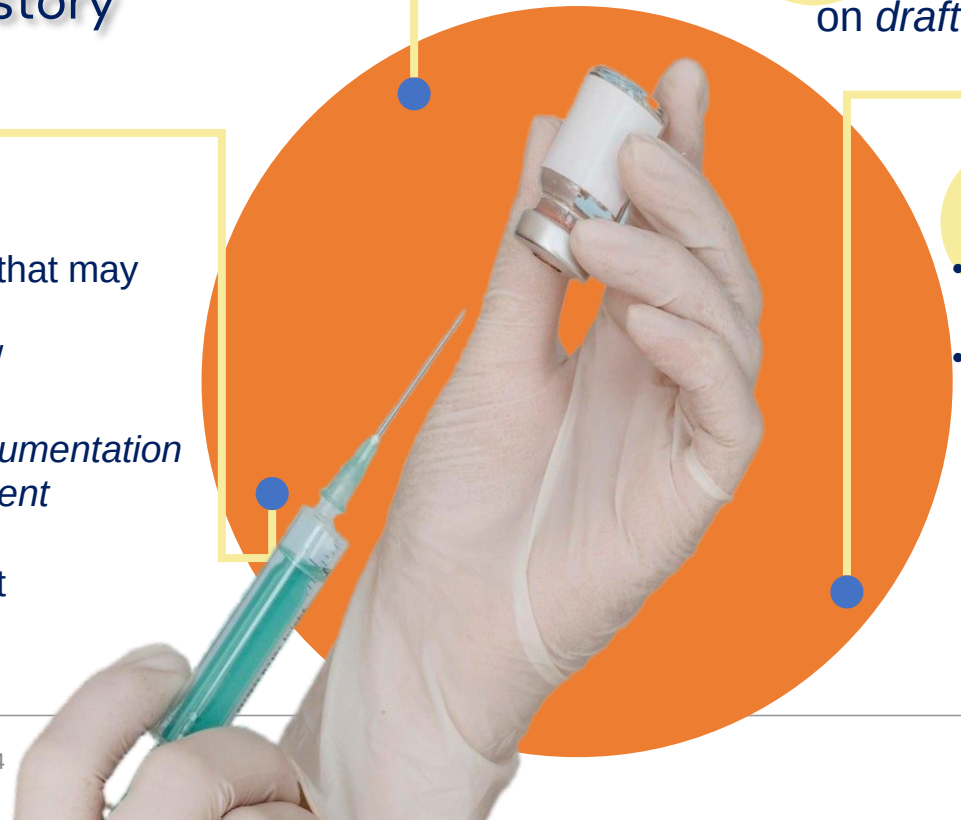
PDA Implementation of CCS & PUPSIT Workshop 2024

Developing CCS
—a brief history

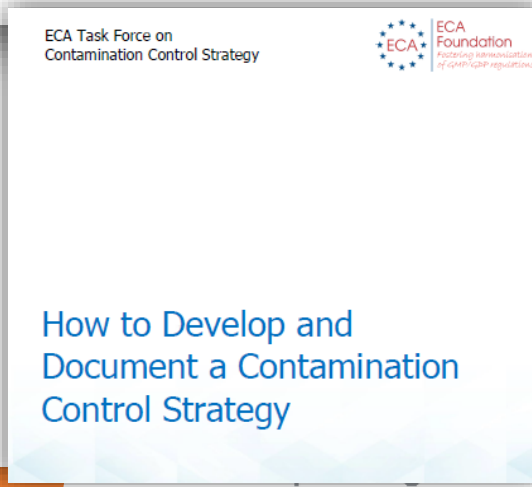
2000s
- QRM to control the contamination risk that may occur
- Internal regulation / documentation:
  - *High Level Documentation (Top Management Commitment)*
  - QRM document
  - SOPs

2019
- Started to develop CCS based on *draft* Annex 1 EU GMP



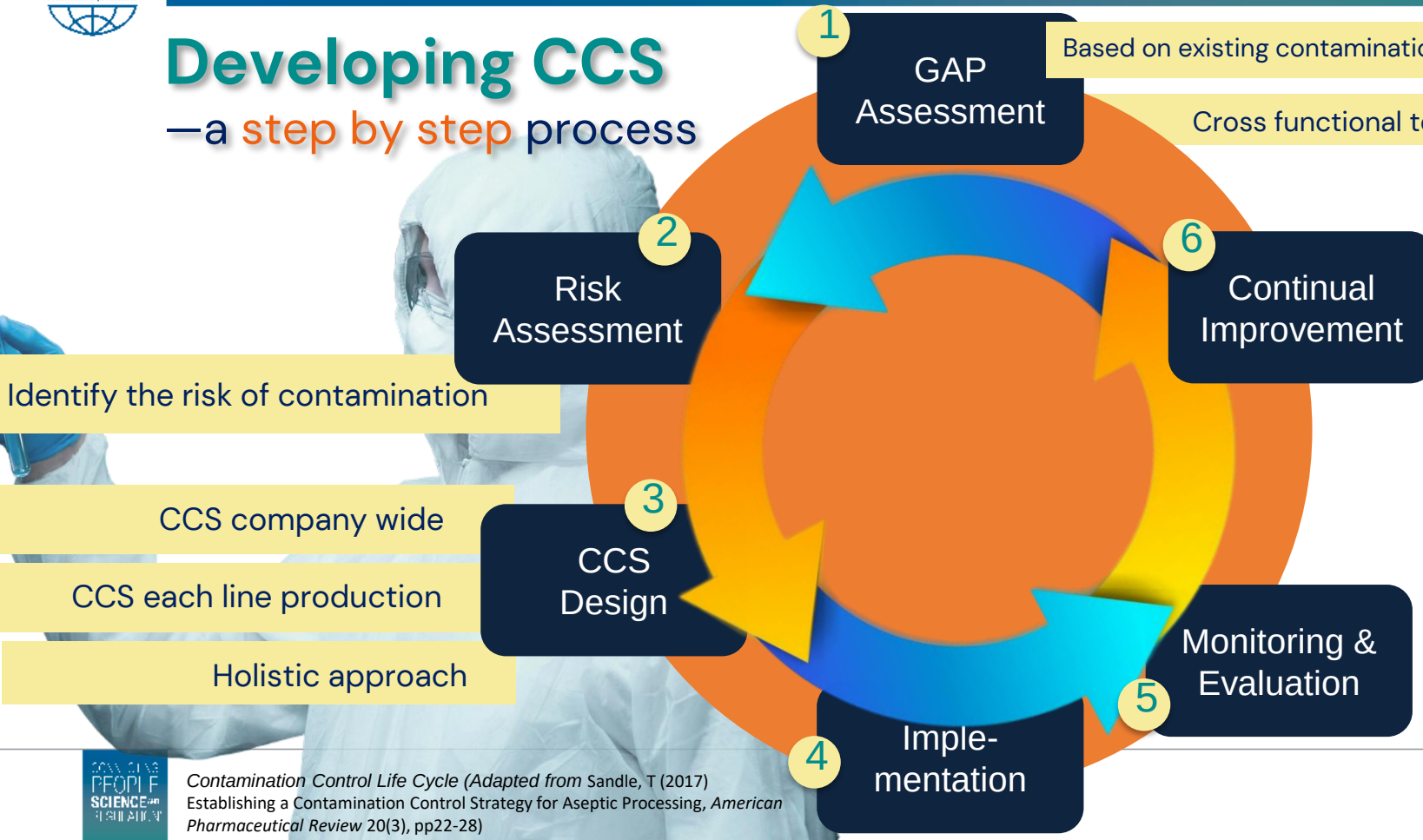
2023
- Development based on Annex 1 (August, 2022)
- Improvement of CCS documentation:
  - *High Level Documentation (Top Management Commitment)*
  - *Policy*
  - GAP Assessment
  - SOP
  - *CCS – QRM document*

Adapted Guidelines



Developing CCS

—a step by step process



Contamination Control Life Cycle (Adapted from Sandle, T (2017) Establishing a Contamination Control Strategy for Aseptic Processing, *American Pharmaceutical Review* 20(3), pp22-28)

1. Gap Assessment

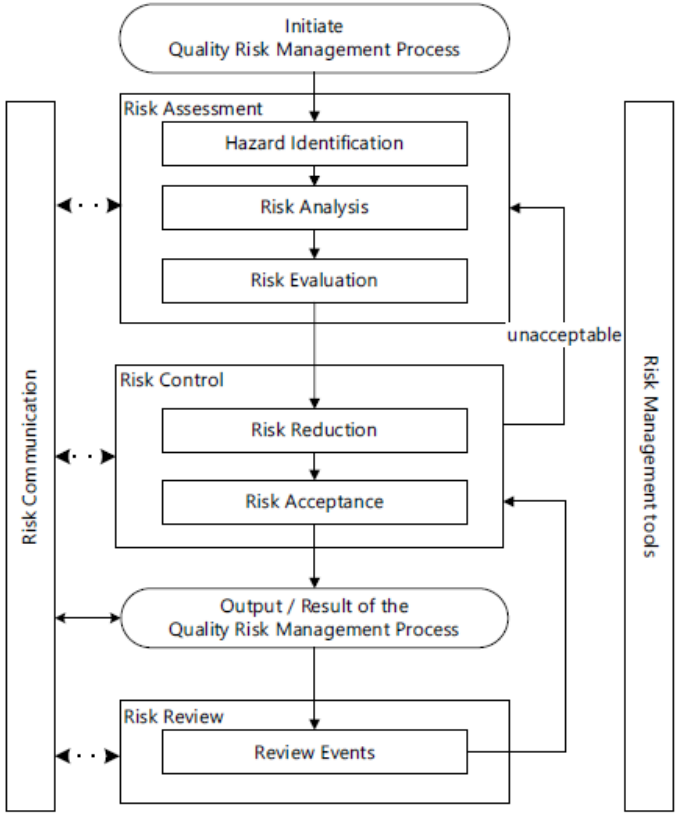
—asses the compliance with Annex 1

EudraLex EU ANNEX 1 (AUG-2022)				WHO TRS 1044, ANNEX 2 (DEC-2022)		BIOFARMA GAP ASSESSMENT				ACTION PLAN		
Bab	Judul Bab	Poin	Content		Content	(1) Internal Reference Relevant to Specified Department/ Facility *(Insert relevant document such as QRM, Validation/Qualification Report/SOP/Masterplan/Training, etc.)*	(2) Content of Relevant Reference *(Mention the chapter/section of each relevant reference if comply to the regulation)*	(3) Identified potential Gap *(or improvement needed)* and Rationale *(Existing control/Process/Desain in Place)*	(4) (Conclusion) No Gap / Partially Comply / Gap	(5) Action Plan	(6) Timeline	(7) PIC
2	Principle											
		6.87	The integrity of the sterilised filter assembly **should be verified** by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of **integrity caused by the filter preparation prior to use**. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:		The integrity of the sterilized filter assembly should be verified by integrity testing before use (pre-use post-sterilization integrity test or PUPSIT) to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilization due to process constraints (such as the filtration of very small volumes of solution). In these cases, an alternative approach may be taken provided that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include:	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 •Integritas filter sterilisasi diuji sebelum (PUPSIT) dan setelah digunakan, sesuai yang dipersyaratkan" SM-I.16 Terdapat pertimbangan yang perlu diperhatikan pada saat menggunakan single use system di SM-I-16 Hal. 21: 5.Penggunaan komponen SUS (Single Use System) untuk proses aseptis perlu menjadi pertimbangan pada saat desain proses. Akan tetapi perlu dikaji kembali juga mengenai hal – hal seperti berikut dalam penggunaannya : a.Handling material agar tidak ada kebocoran / lubang yang dapat mempengaruhi integritas kemasannya b.Dampak pada kualitas SUS yang tidak sesuai terhadap produk c.Performa filter sterilisasi saat pre-use integrity d.Tata cara pembukaan kemasan terluar e.Risiko kontaminasi partikel f.Kompleksitas operasi manual, perakitan dan koneksi yang akan digunakan pada proses	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	ALL RELATED PRODUCTION DEPARTEMENT QA SYSTEM (CCS) JUSTIFICATION HAS TO BE MENTIONED IN CCS-QRM
			i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized;	i.	in-depth knowledge and control of the filter sterilization process to ensure that the potential for damage to the filter is minimized;	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16 Hal 21	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	
			ii. In depth knowledge and control of the supply chain to include:	ii.	in-depth knowledge and control of the supply chain to include:	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	
			• Contract sterilisation facilities;		- contract sterilization facilities;	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16 Hal 21	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	
			• Defined transport mechanisms;		- defined transport mechanisms;	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16 Hal 21	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	
			• Packaging of the sterilised filter, to prevent damage to the filter during transportation and storage;		- packaging of the sterilized filter to prevent damage to the filter during transportation and storage;	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16 Hal 21	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	
			iii. In depth process knowledge such as:	iii.	in-depth process knowledge, such as:	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16 Hal 21	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	
			• The specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test;		- the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test;	100K-SIS-CCS SM-I-16	100K-SIS-CCS Hal.11 SM-I1.16 Hal 21	Ketentuan terkait PUPSIT sudah tercantum di SM dan SOP CCS tetapi belum terimplementasi di Bio farma	Partially Comply	Wajib di produk akhir, kecuali bisa dibuktikan bahwa produk tidak memiliki karakteristik filter flaw masking dan justifikasi sesuai point i, ii dan iii.	2024	

2. Risk Assessment

- Risk management is applied in the development and maintenance of the CCS
- Risk Management is perform :
  - Identify,
  - Assess,
  - Reduce/eliminate (where applicable)
  - Control

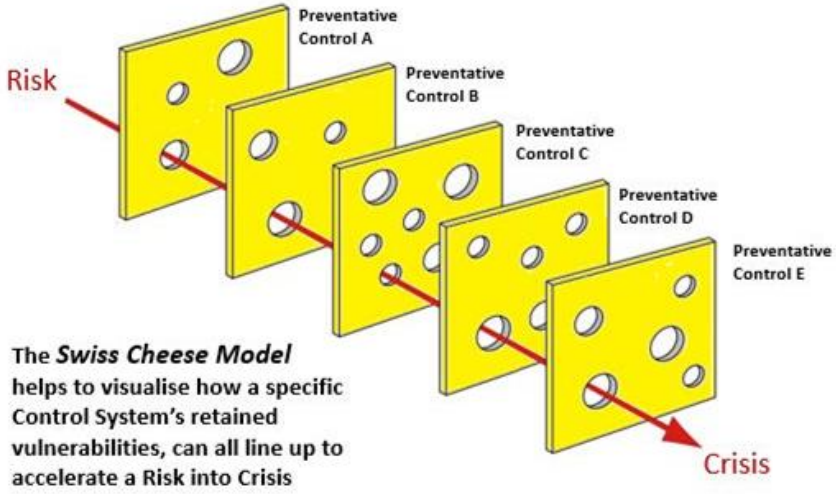
  Related to Contamination Risks.
- Justification of residual risk related to contamination risk



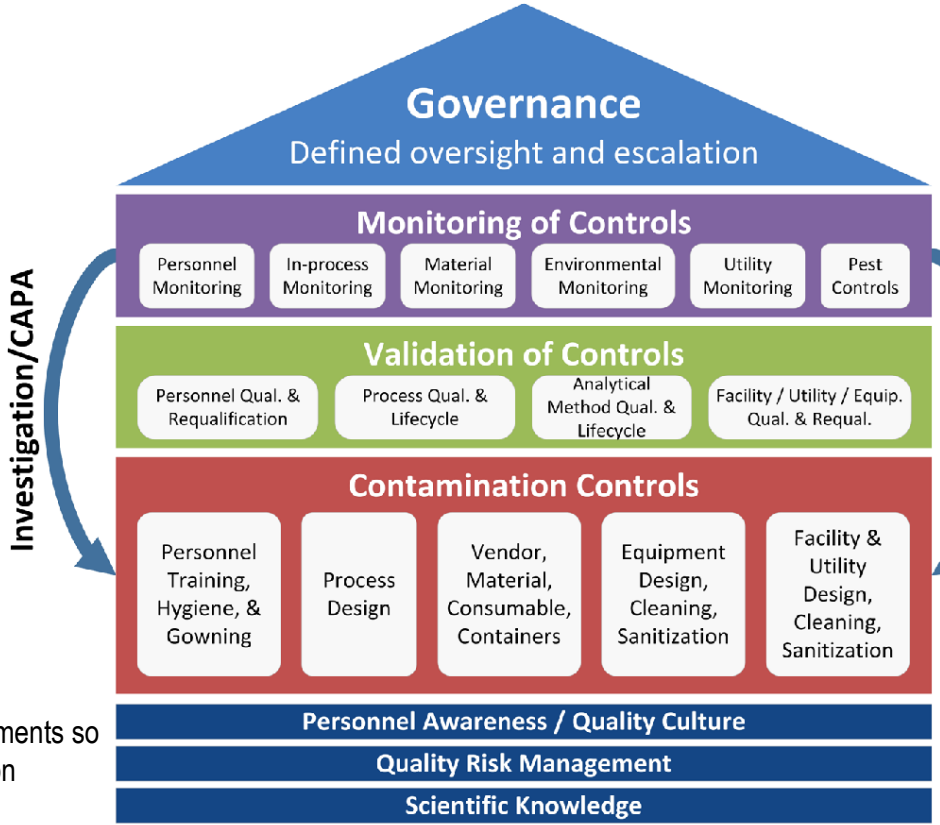
ICH Q9, 2023

3. CCS Design

– Holistic Approach



The ***Swiss Cheese Model*** helps to visualise how a specific Control System's retained vulnerabilities, can all line up to accelerate a Risk into Crisis



The CCS must be designed with layered/redundant control elements so that no single failure in each elements can lead to contamination

(PDA TR 90, 2023)

Developing CCS

— Documentation

CCS company wide

CCS each line production

This CCS-Document summarizes how a company approached each of the elements and how company maintain the standard to ensure an adequate level of contamination control.

(How to Develop and Document a Contamination Control Strategy. A guidance document by the ECA Foundation Version 2.0; December 2022)

Developing CCS

— Documentation

- High level documentation
- The CCS document has to **compile** or **mostly reference documents** providing evidence that the CCS with its elements are reliably implemented
- CCS → a "living document" that needs to be continuously updated and improved.

B.11. Validation of sterilisation processes

Following the GMP-requirements, all sterilisation 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 sterilisation 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 sterilisation processes:

- Sterilisation 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		
SV-reports for sterilization processes		

(How to Develop and Document a Contamination Control Strategy. A guidance document by the ECA Foundation Version 2.0; December 2022)

Developing CCS (PDA TR 90, 2023)

— Documentation

1. PURPOSE

Step	Purpose
1.1	This document outlines a contamination control strategy to safeguard product quality from microbial, particulate, pyrogen/endotoxin, and viral contamination.

2. BACKGROUND

Step	Background
2.1	A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods. Contamination control and steps taken to minimize the risk of contamination from microbial and particulate sources are a series of successively linked events or measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered altogether. The development of the CCS requires thorough technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g., pyrogens, endotoxins) as well as foreign particulate matter (e.g., glass and other visible and sub-visible particles).

3. SCOPE

Step	Scope
3.1	This document describes, at a high level, the manufacturing process and associated contamination controls for <product/processes> at the <facility/area>. <Product> is a <type of product, e.g., chemically derived drug substance for an injectable drug product>. If this CCS is specific to one portion of the product, refer to CCS for the other portions of the supply chain if internal (or refer to QTA if externally sourced), for example: The API for <product name> is obtained from <external company, facility name>. This is governed by a formal Quality Agreement [Reference(s): [XXX]. Detailed guidance on contamination controls for the <API name> production processes is captured in a separate document owned by the <external company>.
3.2	The strategy is multifaceted and includes controls associated with the following: Manufacturing process design, risk assessment, validation, monitoring Facility design and environmental controls

4. RESPONSIBILITY

Step	Role	Responsibility
4.1	Quality	Ensure this policy remains current
4.2	Site Employees involved in GMP activities	Ensure adherence to the principles and policies outlined in this document

5. CONTAMINTION CONTROL STRATEGY ELEMENTS: Sections may be rearranged as deemed appropriate by the site. Add other important site-specific controls where appropriate.

Step	Contamination Control Elements
All elements of the CCS are summarized or referenced in the following sections to illustrate how these individual controls work together to effect holistic control.	
5.1	Manufacturing Process Design, Risk Assessment, Validation, and Monitoring (TR90 **Sections 7.0, 8.0,** and **9.0**) In this section, include a short description of the process. Add a process map that identifies important process contamination controls including antimicrobial agents, impurity removal steps, process hold times, and microbiological/particulate testing points. Add overview of how process design controls the potential for microbial ingress, survival and growth/proliferation, microbial removal steps, aseptic process simulation (APS), and risk assessments and validations related to these process contamination controls. Add rationale for process testing scheme and limits for microbial (bio and endotoxin), viral, and particulates.
5.2	Facilities Design and Environmental Controls (TR90 **Section 5.0**) Refer to current version of GMP drawings of facility maps with area classification outlined. Add overview of facility layout showing area classifications, areas of segregation, direction of flows (e.g., upstream, downstream, warehouse, raw material sampling). Include overview of areas of enhanced biosafety levels. Add overview for major environmental controls: design, temperature and humidity, air pressure cascade, cleaning and disinfection, access control and facility flows, and pest control. Add overview of barrier technologies, if applicable (e.g., isolators, RABS). NOTE: Environmental monitoring is in **Section 5.3**.
5.3	Environmental Monitoring (**TR90 Section 7.0**) Add overview of environmental monitoring, limits, and status of environmental qualification and periodicity of requalification.
5.4	Equipment Handling, Cleaning, and Sanitization/Sterilization (TR90 Section 9.2)

CCS Documentation Example

— Documentation

MAL waste out 43.GF.22 untuk selanjutnya ditangani sesuai p
pengolahan limbah.

- Transportasi material antar ruangan dilakukan menggunakar
(roda dorong), dimana terdapat kereta dorong khusus untuk
berkelas dan general area. Roda dorong untuk general area tid
masuk ke dalam ruang berkelas, begitu pula sebaliknya.
- Untuk transfer material bersih dari kelas D menuju kelas C d
mitigasi dengan menggunakan trolley tertutup atau w
tambahan plastik, untuk mencegah adanya kontaminasi silan
perpindahan material dari ruang berkelas-CNC(general)-ruang

Dokumen rujukan strategi pengendalian kontaminasi terkait alur material di fasili
Gd 43 Lt GF dapat dilihat pada Tabel berikut:

Tabel 6.8 Dokumen CCS terkait Alur Material di Fasilitas FPV1 Gd 43 Lt G

Parameter	Dokumen Referensi	
	Judul	ID
Penanganan Material dari Luar ke dalam Ruang Produksi	Penanganan Material dari dan ke Ruang Berkelas	100K-SIS-32
Alur Material	Deskripsi Sarana Formulasi dan Pengisian Vaksin & Pelarut	267K-Desk-01
Alur Material Bersih	Denah Fasilitas Formulasi dan Pengisian Vaksin 1 – Gedung#43 Lantai GF (Alur Material Bersih)	267-XLIII-GF-FL-04B
Alur Material Kotor	Denah Fasilitas Formulasi dan Pengisian Vaksin 1 – Gedung#43 Lantai GF (Alur Material Kotor)	267-XLIII-GF-FL-05B
Pencucian Vial	Pengoperasian dan Pemeliharaan Depyrogenation Tunnel MARCHESINI DEPYR-901	267K-VWash-01
Pembungkusan Material yang Akan Disterilisasi	Proku Pembungkusan Material untuk Disterilisasi	267K-Pster-01

6.5 Material

- Tata cara penanganan material mulai dari penerimaan, permohonan uji, peng
sesuai prosedur dan spesifikasi yang berlaku, penetapan status
penyimpanan di Gudang Persediaan hingga distribusi ke masing-masing fa
telah diatur pada SOP 100K-SIS-RMM.
- Dokumen rujukan strategi pengendalian kontaminasi terkait pengend
material di Fasilitas FPV1 Gd 43 Lt GF dapat dilihat pada table berikut

Tabel 6.29 Dokumen CCS terkait Penanganan Material

Parameter	Dokumen Referensi	
	Judul	ID
Penanganan Material	Pengendalian Material dan Media	SM-53.1
	Raw Material Management	100K-SIS-RMM
Sampling Bahan Baku	Sampling Bahan Baku	204K-SAM-RM
Pengelolaan Kedatangan Material	Karantina Barang Persediaan	103K-KRT-BRG
Rilis Bahan Baku	Raw Material Management	100K-SIS-RMM

6.15.3 Pemantauan Kualitas Utilitas

- Terdapat prosedur monitoring rutin terhadap kualitas WFI dan PW yang digunakan sesuai 100K-MON-AIR. Parameter untuk WFI yakni TOC, konduktivitas, endotoksin, bioburden, pathogen spesifik, dan pH. Untuk PW parameter yang dipantau yakni TOC, konduktivitas, bioburden, patogen spesifik, dan pH. Sedangkan untuk *pre-treatment water* yakni parameter pemerian, klorida, sulfat, kesadahan, mangan, besi, zat organik, zat padat terlarut, bioburden dan keberadaan patogen spesifik. Masing-masing parameter merujuk ke spesifikasi air masing-masing (sesuai spesifikasi 100S-BL-AIR). Untuk justifikasi penetapan periode dan titik pementauan dilakukan sesuai dengan kajian Analisa risiko.

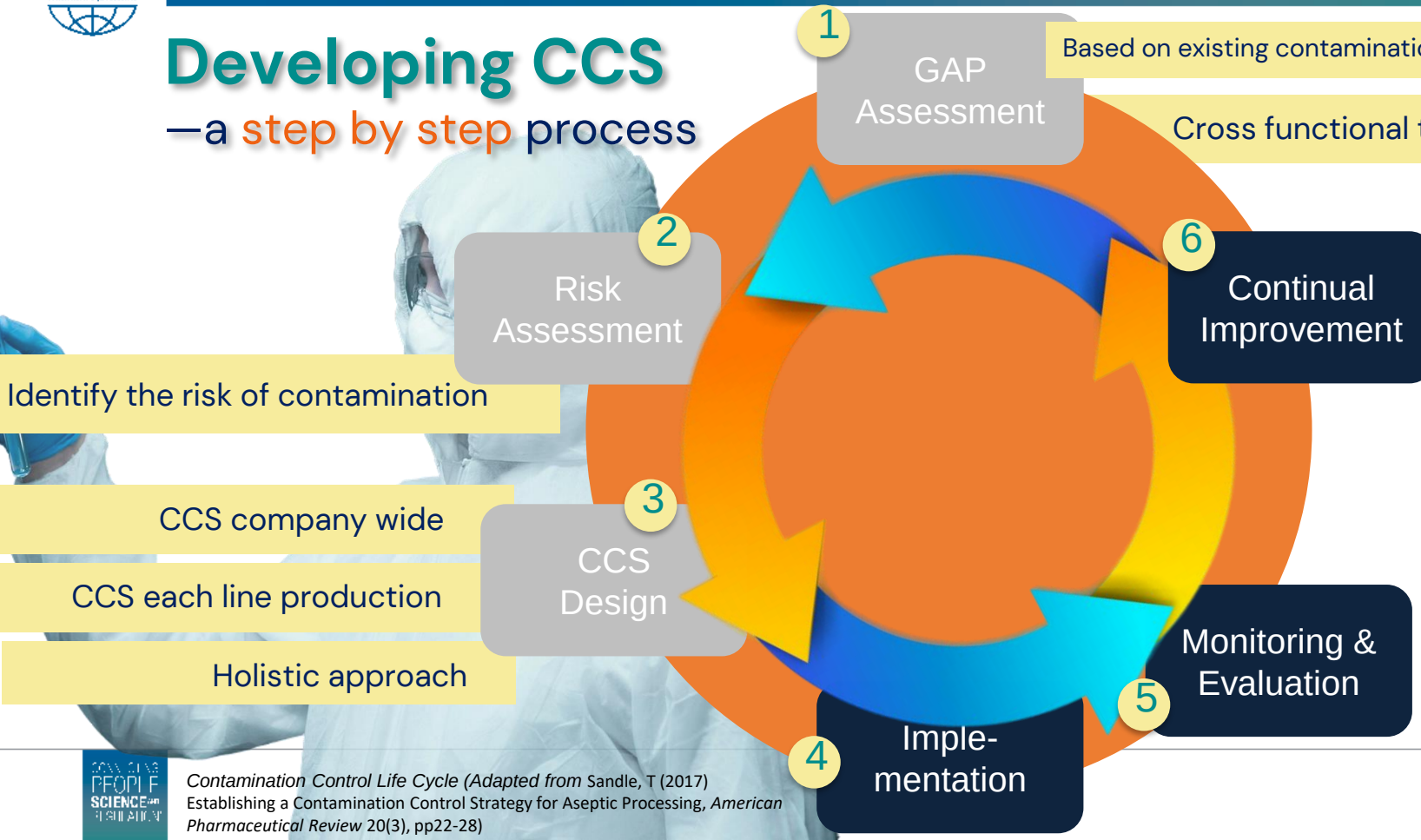
Deskripsi	Dokumen Referensi	
	Judul Dokumen	No.
Spesifikasi	Spesifikasi *Pretreatment Water* (PTW), *Purified Water* (PW), *Water For Injection* (WFI), *Pure Steam* (PS)	100S-BL-AIR
Pemantauan	Pemantauan Kualitas Air	100K-MON-AIR
Risk Analisis terkait	Pemantauan Titik Sampling *Pure Steam*	100-RA-PS
	Frekuensi sampling *Water For Injection* (WFI)	100-RA-WFI

- Pemantauan kualitas udara tekan yang dihasilkan dilakukan merujuk pada 100K-MON-CA dengan persyaratan sesuai 100S-BL-CA.

Deskripsi	Dokumen Referensi	
	Judul Dokumen	No.
Spesifikasi	Spesifikasi Udara Tekan – Compressed Air	100S-BL-CA
Pemantauan	Pengoperasian dan Pemeliharaan Kompresor Udara Atlas Copco	100K-MON-CA
Risk Analisis	Klasifikasi Titik Uji*Compressed Air*	100-RA-CA02

Developing CCS

—a step by step process



Contamination Control Life Cycle (Adapted from Sandle, T (2017) Establishing a Contamination Control Strategy for Aseptic Processing, *American Pharmaceutical Review* 20(3), pp22-28)

Challenges

—discovering the difficulties

Numerous facilities and a variety of products.

Various understanding

Multiproduct Facility design

Cross Contamination Avoidance Strategy

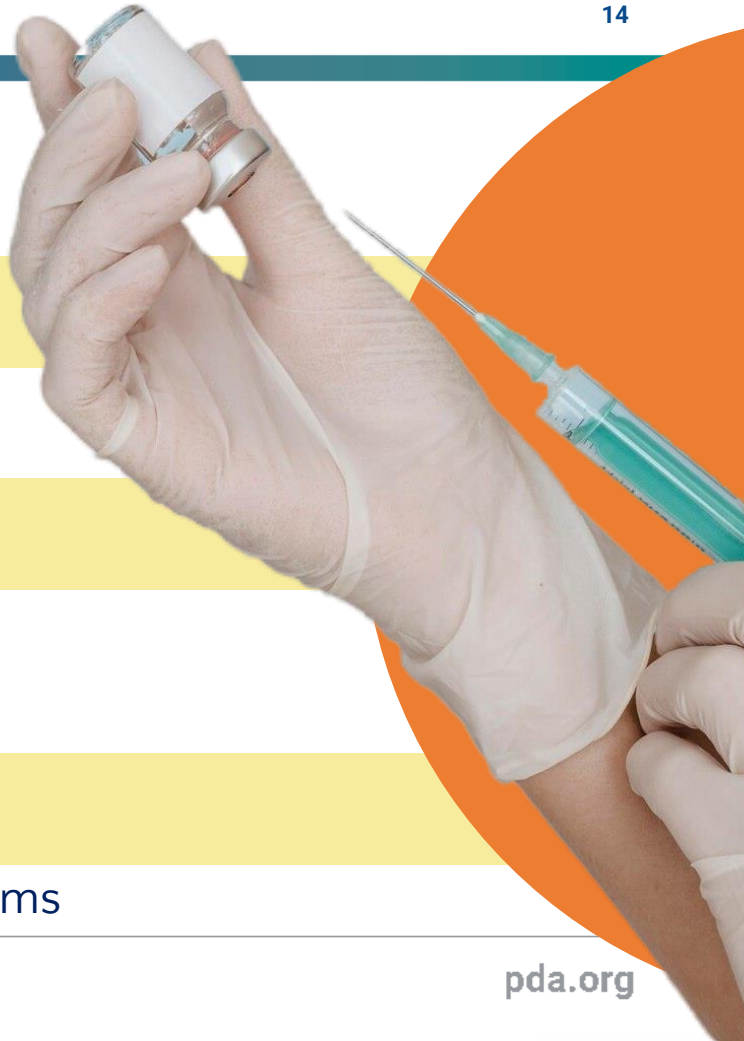
Legacy facility

Integrating Technologies

Bussiness and Resource Challenge

Key Takeaways

—the essentials to remember



Bio Farma as DS & DP Manufacturer

- Critical point should be for DP
- Gradually implement and comply for DS process

Robust Strategy in Improving The CCS

- Short Term Plan
- Long Term Plan
- Increase Monitoring and Detectability of Contamination

Collaborative Approach

- Form a Task Force involving all cross-functional teams

Thank you!

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