# How to implement a CCS according to Annex 1

## (“A Guide to the Guide”)

within ***GMP/FDA Compliance Conference***
as part of **GMP-Pharma Congress 2022**

1st June 2022, Duesseldorf

*Robert G. Schwarz*


CONCEPT HEIDELBERG
Pharmaceutical Quality Training. Conferences. Services.
GMP-PHARMA CONGRESS
GXP Train CON

# Agenda

- ECA's Guide on
  "How to Develop and Document a Contamination Control Strategy"
- Implementation from the scratch (for newbies in GMP)
- Putting together the pieces (for the ambitious advanced in GMP)

# Where you can find our CCS Guide

https://www.eca-foundation.org/download-ccs-guide.html

# The ECA‘s CCS Task Force

- Arjan Langen (GE Healthcare) - Global Sterility Assurance Director
- Axel Schroeder (Concept Heidelberg) – Operation Director
- Dr. Christine Arbesser-Rastburg (Consultant) – Senior Consultant
- Dr. Ingrid Walther (Pharma Consulting Walther) - GMP-compliance consultant
- Isabelle Hoenen (Lilly) – Associate Senior Consultant for Sterility Assurance
- Luigi Scaffidi (Boehringer-Ingelheim) - Manager Qualification / Validation (Aseptic Quality Assurance)
- Rainer Gnibl (GMP-Inspector | Munich, Bavaria Germany)
- Robert G. Schwarz (GXP-TrainCon) – University Lecturer, Trainer and Consultant
- Stephan Loew ( CSL Behring) – Senior Manager Technical support Laboratories
- Dr. Ulrich Kissel (KisselPharmaConsulting GmbH) - Founder and CEO of KisselPharmaConsulting GmbH
- Vimal Sachdeva (WHO) - Senior GxP Inspector
- Walid El Azab (STERIS) – Senior Manager Technical Services


CONCEPT HEIDELBERG
Pharmaceutical Quality Training. Conferences. Services.
GMP-PHARMA CONGRESS
GXP Train CON

# Reason for the CCS Guide

Based on the latest Draft of EU GMP-Guideline Annex 1 a Contamination Control Strategy needs to be implemented when producing sterile products:

*"**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."*

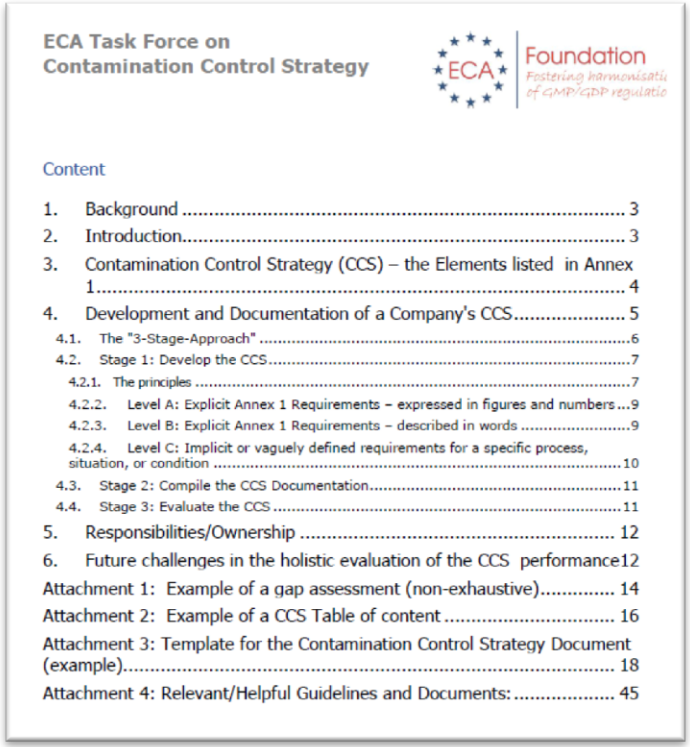
# Basis for the CCS Guide

## Section 2.0 Principle – Introduction of Contamination Control Strategy:

*Elements to be considered within such a **documented contamination control strategy** should include (but not be limited to):*

i. *Design of both the plant and process.*
ii. *Premises and equipment.*
iii.
iv. *Personnel.*
v. *Utilities.*
vi. *Raw material control – 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.*

# The guide‘s content



ECA Task Force on
Contamination Control Strategy

ECA Foundation
Fostering harmonisation of GMP/GDP regulation

Content



1. Identifying the CCS level
2. Explaining the CCS implementation steps
3. Providing information for the CCS documentation
4. Discussing future challenges
5. Providing examples



CONCEPT HEIDELBERG
Pharmaceutical Quality Training. Conferences. Services.

GMP-PHARMA CONGRESS

GXP Train CON

# Levels – Degree of detail

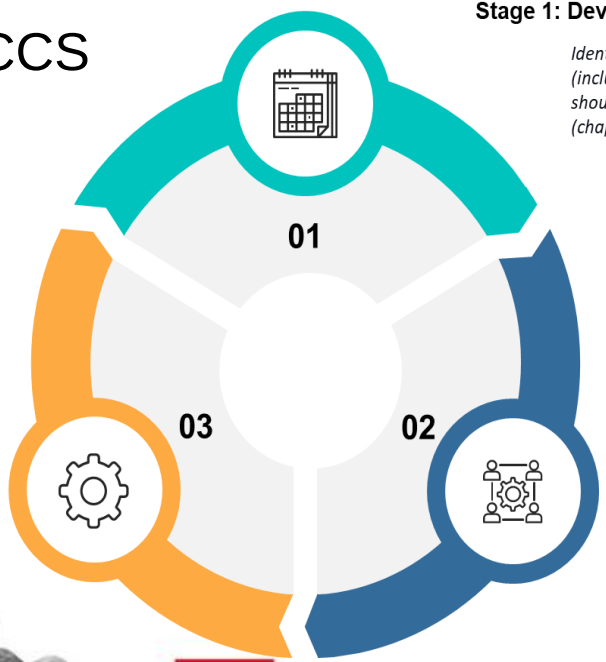
- Level A: Explicit requirements expressed in figures and numbers (refer to section 4.2.2.)

- 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.)

# The 3 Stage Approach

- Stage 1: Development (or review and refinement/improvement) of the CCS
- Stage 2: Compilation of the CCS documents
- Stage 3: Evaluation of the CCS




**Stage 1: Develop (or review and refine/improve) the CCS**

*Identify the risk of contamination and the measures (including procedures, controls, rationale, QRM, etc.) that should be implemented to minimize contamination (chapter 4.2), as follows:*

1. *Level A: Explicit Annex 1 Requirements – expressed in figure and numbers*
2. *Level B: Explicit Annex 1 Requirements – written expectations*
3. *Level C: Implicit or not clearly written requirements for a specific process, situation, or condition*

**Stage 2: Compile the CCS documentation**

*Document all the measures (including procedures, controls, rationale, QRM, etc.) to prove that CCS is implemented (Chapter 4.3).*

**Stage 3: Evaluate the CCS**

*Provide evidence that the measures are working to prevent contamination by ongoing and periodic review, resulting in appropriate quality system updates (Chapter 4.4 ).*



CONCEPT HEIDELBERG
Pharmaceutical Quality Training. Conferences. Services.

GMP-PHARMA CONGRESS

GXP Train CON

# Creation of a CCS document is depending on product & site

*“Similar to 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.”*

If this is followed and visualized throughout the process of document creation it supports to find the required degree of details.

# Attachments

- Attachment 1 is an example of a classical gap-analysis
  - Degree of detail should be aligned over the whole document
  - Justification of an action threshold if it is the decision point for mitigation actions (FMEA and FMECA)

- Attachment 2 is an example of an “all in one solution”
  - Designed for descriptive and risk-assessment part

- Attachment 3 is an example of a straight CCS document for the most advanced companies with little to none gaps (referral document)

# What is contamination anyway?

- Contamination:
  The presence or introduction of a hazard

- Contaminant:
  A substance that is "foreign" to this place, process - *exogen*

- Impurity:
  Unwanted substance generated throughout a process - *endogen*
  (Annex 1 is not that accurate)

# Definitions

*Contamination is a matter of quantity!*

*Non-critical contamination: below a threshold (acceptance limit)*

**Critical contamination: Quantity of contamination exceeds a risk-based threshold (acceptance limit) ⇨ this is what we typically mean when we talk about "contamination"**

# General Types of Contamination

- Physical
- Chemical
- Microbial

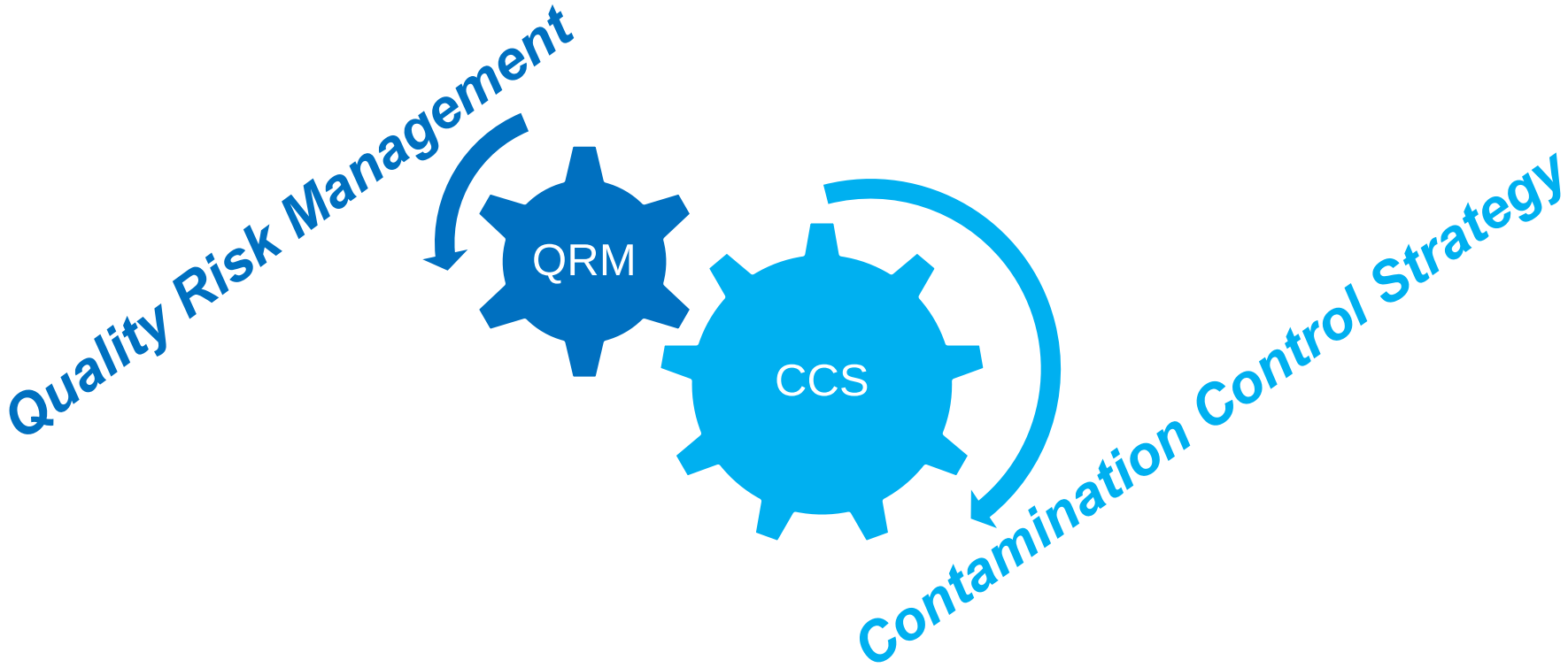
# Types of Contamination in Scope of GMP regulations

- Microbial
- Cross-Contamination
- Particles

# Types of Contamination in (formal) Scope of Annex 1

- Microbial
- Pyrogens
- Particles

# Crucially linked





CONCEPT HEIDELBERG
Pharmaceutical Quality Training. Conferences. Services.
GMP-PHARMA CONGRESS
GXP Train CON

# QRM

- Use of QRM principles is key in identifying, analyzing and mitigating contamination risks

- A well designed QRM process helps implementing the new Annex 1 requirements

- The HACCP methodology seems suitable in setting up a Contamination Control Strategy

# The paradigm change

- CCS relies more on robust processes and validated systems than spotchecks

- Quality can‘t be tested into the process it‘s it‘s inherent attribute (QbD principles)

- Testing may be errornous

# Isn‘t Contamination Control totally covered by Environmental Monitoring?

*If not, why not?*

# Road Map to Contamination Control

**Map Out the Processes**

**Identify the Contamination Sources**

**Evaluate the Contamination Risk**

**Identify the set of controls**

# Risk evaluation tools listed in ICH Q9

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

# CCS implementation depends on the facility status

For a new plant, new equipment:

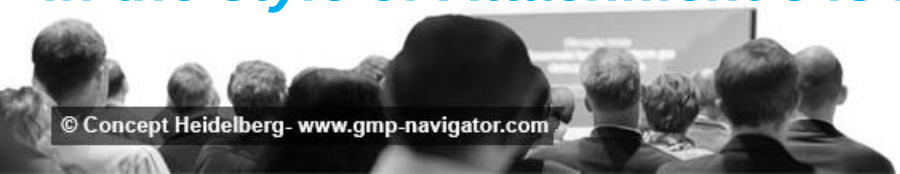
1. Mapping of the manufacturing process to identify possible sources of contamination.
2. Carry out a risk assessment to evaluate the risk of contamination.
3. Establish preventive measures and their controls in a holistic system (including the definition of responsibilities).
4. Assess and manage the residual risk of contamination

# Templates for CCS documents

- Attachment 2 could be preferably used to have one document for different CCS measures incl. their risk assessment
  - All in one solution for small(er) companies

- Attachment 3 could be preferably used to have one reference document with different risk assessments for different CCS measures

***The larger the company is/gets the more a CCS documentation in the style of Attachment 3 is recommended***



# Stage approach - Summary for newbies

| Company experience | Stage 1<br>Develop the CCS | Stage 2<br>Compile the CCS-Document | Stage 3<br>Evaluate the CCS |
|---|---|---|---|
| **New in sterile manufacturing and has little experience** | • Identify what needs to be done to ensure contamination control<br>• Apply the principles of QRM according section 4.2<br>• Prepare the documentation | Compile the documentation in an easily accessible/readable structured way, usage of Attachment 2 and 3 possible<br>Refer to Section 4.3. | Refer to section 4.4 |

# CCS - What‘s old?

Contamination Control of

- Design of both the plant & process
- Premises and equipment
- Personnel
- Utilities
- Raw material control (incl. IPCs)
- Product containers & closures
- Vendor approval
- Outsourced services

- Process risk assessment
- Process validation.
- Preventative maintenance
- Cleaning and disinfection.
- Monitoring systems
- CAPAs
- Continuous improvement

# CCS - What‘s new?

Contamination Control of

- Design of both the plant & process
- Premises and equipment
- Personnel
- Utilities
- Raw material control (incl. IPCs)
- Product containers & closures
- Vendor approval
- Outsourced services

- Process risk assessment
- Process validation.
- Preventative maintenance
- Cleaning and disinfection.
- Monitoring systems
- CAPAs
- Continuous improvement

# Putting the pieces together…

… in one comprehensive document

Evaluating the interaction with the different, maybe until now, isolated actions and measurements

# Major Task for existing QMS

## Gap-Analysis

1. Step:  check level of alignment for the CCS scope and documentation structure expectations
2. Step: Identify the gaps between current CCS & CCS Document and the latest public EU GMP-Guideline Annex 1 draft
3. Step: Identify current best practices for critical new or revised expectations and for CCS documentation
4. Step: Create a table to facilitate the formalization of the CCS gap assessment and the further CCS document update following the existing content structure

# Major Task for existing QMS (2)

Gap-Analysis (2)

5. Step: Reference all key supporting site strategies, rationales, risk assessments, ...

6. Step: Update the CCS document and develop an improvement plan

7. Step: Final compilation and approval by Senior Management

# Measurement evaluation

- **Always prefer technical over organizational measurements**

and

- *Preventive over corrective measurements*

There is no 100% safe measurement - it is the sum of the measurements that make the holes in the fish net smaller

# Content of the CCS documentation for advanced

- Try to avoid redundancies!
- In best case the CCS document only consists of references to existing documents
- Sometimes PQS and or QMS may require an additional document where the CCS document just refers to
- Use Doc-Links in electronical document management systems (also during inspections)

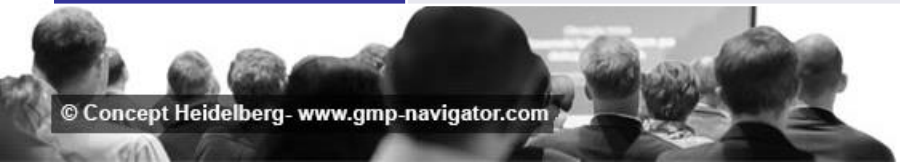
# CCS implementation depends on the facility status

For an existing facility that has already carried out a risk assessment:

1. Evaluation of existing contamination control measures.
2. Analysis and overview of possible gaps.
3. Risk assessment and, if necessary, addition of further measures and integration into the overall system (including determination of responsibilities).
4. Assess and manage the residual risk of contamination.

# Stage approach - Summary for advanced

| Company experience | Stage 1<br>Develop the CCS | Stage 2<br>Compile the CCS-Document | Stage 3<br>Evaluate the CCS |
|---|---|---|---|
| **is in a matured state** | Review the existing contamination control measures based on the principles of QRM according section 4.2:<br>• Critically review existing concepts<br>• Gap assessment and missing elements. (Refer to Attachment 1)<br>• Prepare the documentation, rationale, etc. | Compile the documentation in an easily accessible/readable structured way, usage of internal templates or Attachment 2 or 3.possible<br>Refer to Section 4.3. | Refer to section 4.4 |
| **has broad and proven experience** | CCS is fully implemented:<br>• re-assess the existing Gap-assessment to confirm compliance:<br>➢ *Confirmed → go to Stage 2!*<br>➢ **Not confirmed → cover the missing elements (apply QRM principles).** | Compile the documentation in an easily accessible/readable structured way, usage of internal templates or Attachment 2 or 3.possible<br>Refer to Section 4.3. | Refer to section 4.4 |



# Document finished – check?!

- Annex 1 also follows the life cycle concept ("***ongoing and periodic review and update***")

- Periodic evaluation either via
  - Revision of Quality Risk Management documents or
  - Evaluation Plan & Evaluation Report

- Besides periodic evaluation the Change Control System should include a change-based evaluation if there is an impact of changes on the CCS
  - If an impact is given this should result in a revision of the Quality Risk Management documents

# My recommendations

- Avoid redundancies wherever possible
  - Be even careful with summaries
- References need no revision number
  - Don‘t update the CCS documentation if a SOP is revised
- Handle it like your SMF
- Define responsibilities for different topics
  - The larger a company is there‘s not only one “CCS SME” – be realistic!
- Keep it clear and readable
  - Prefer tables over sole text passages

# and please! …don‘t forget cross-contamination!!!

4 Premises (Section – 4.12):

“Where the CCS indicates that the risk of cross-contamination is high, separate changing rooms for entering and leaving production areas should be considered.“

In the glossary itself cross-contamination isn’t part of the definition of contamination:

*“**Contamination** – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particulate matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.”*

# Acknowledgements


- This presentation contains ideas and strategies od the whole ECA‘s CCS Taskforce
- Additionally a big thank you to
  - Dr. Ingrid Walther

    and
  - Walid El Azab

  Some parts of this presentation are based on their presentation as part of the European GMP Conference from 2022/04/26: “The New ECA Contamination Control Strategy Guide”


# Contact data for follow-up questions

Source: https://www.xn--3d-mnnchen-t5a.de/


DI (FH) Robert G. Schwarz


robert.schwarz@gxp-traincon.eu



CONCEPT HEIDELBERG
Pharmaceutical Quality Training. Conferences. Services.

GMP-PHARMA CONGRESS

GXP Train CON

# Disclaimer

This Presentation is for the exclusive use of the recipients to whom it is addressed.

The views and opinions presented herein represent independent work of the author and do not necessarily represent those of the clients he works for, other experts in the field, authorities or authority representatives. It does not provide legal advice and does not have legally binding effect.

The information contained in this presentation is given for general information only (i.e. for the purpose of education and discussion). It is not intended to be, and it should not supplant, replace or amend any regulations or regulatory guidance. Decisions and actions should be based on the relevant regulations, guidance documents and pharmacopeial chapters, not on this presentation. The author does not endorse or approve, and assumes no responsibility for, the content, accuracy or completeness of the information presented.

No regulatory authority in Austria or in any other country has in any way opined upon the accuracy or adequacy of this Presentation or the materials contained herein.

Except to the extent otherwise indicated, this Presentation presents information as of the date hereof. The delivery of this Presentation shall not, under any circumstances, create any implication that there will be no change after the date hereof. In furnishing this Presentation, the Preparers reserve the right to amend or replace this Presentation at any time and undertake no obligation to update any of the information contained in the Presentation or to correct any inaccuracies that may become apparent.

Conversely, any omission or truncation of regulatory requirements found within this training does not relieve any entity or person of their legal obligations to fully comply with all requirements of the regulation.

Go to the Source Documents!

This Presentation and the information contained herein is confidential, by its acceptance of the Presentation, each recipient agrees that it will not, and it will permit any third party to, copy, reproduce or distribute to others this Presentation, in whole or in part, at any time without the prior written consent of the author, and that it will keep confidential all information contained herein not already in the public domain.