INTRODUCTION TO CCS DEVELOPMENT & A CASE STUDY

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Topics to Cover

- Introduction to CCS and PDA Tech. Report 90
- How to build CCS
- CCS Case Study

Introduction to CCS and PDA TR. 90

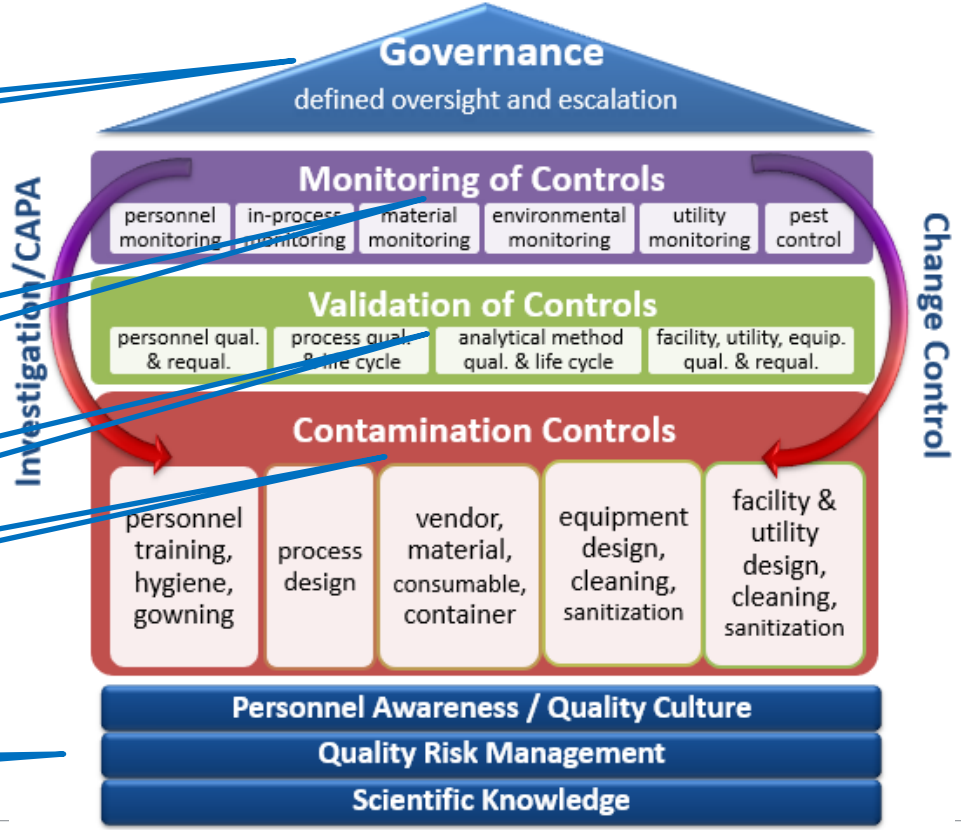
Definition: Contamination Control Strategy

"A planned set of processes and measures for the identification, assessment, control, and monitoring of contamination risks that include microorganisms, pyrogens/endotoxins, and foreign particles, derived from current product and process understanding, that assures process performance and product quality."

– TR90 Glossary

The House of CCS

- the **Oversight**
- the **Continuous Improvement** loops
- the **On-going Monitoring** of Control
- the **Confidence** in Controls
- the **Pillars** of Control
- the **Foundations**



"Drug manufacturers have employed contamination control measures for decades as a core element of good manufacturing practices.

Commonly, these are a collection of practices that were **developed separately** and applied **without clear consideration for their interdependence**."

– TR90 Introduction

"Holistic"

Contamination Control means

Doing the Right Thing

for Your Process

considering **your surrounding risks**

and **your surrounding controls**

Why does new Annex 1 focus on CCS?

Here's what EMA said in 2015 about the planned revision:

- *"The revised guideline will **clarify to what extent Q9 and Q10 should be followed** in the design and implementation of facilities, equipment and processes for the manufacture of sterile medicinal products. Other changes that may require new GMP guidance include those for the revision to the Ph.Eur. monograph on **methods other than distillation for the production of water for injection**.*
- *Since the current guideline is used to provide **guidance on the conditions of the manufacture of some non-sterile finished products and the early stages in the manufacture of a range of products**, the revised guideline will also clarify these areas of applicability utilising quality risk management principles. The scope and title of the guideline should therefore be broadened to encompass these references. It is stressed that this is a clarification of current practices and that **no new expectations will be created**."*

  – 2015 Concept paper on Annex 1 revision

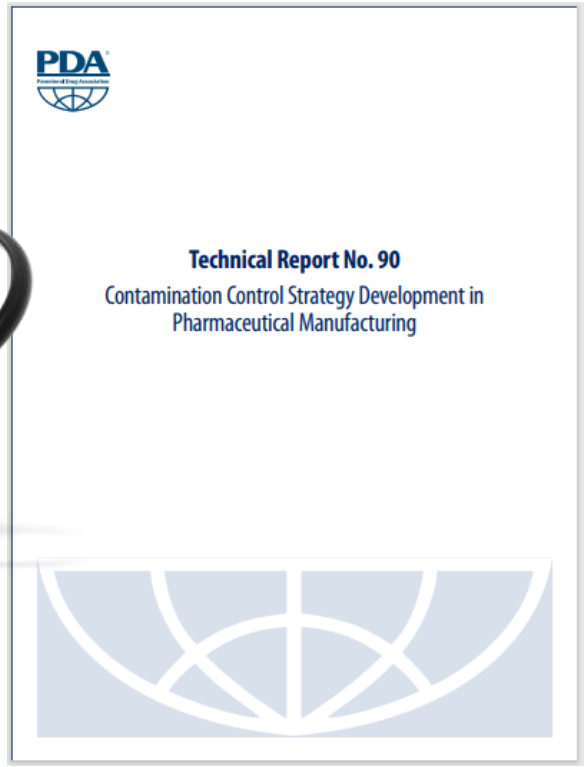
Why focus on CCS?

Possibly to reduce **Drug Shortages**

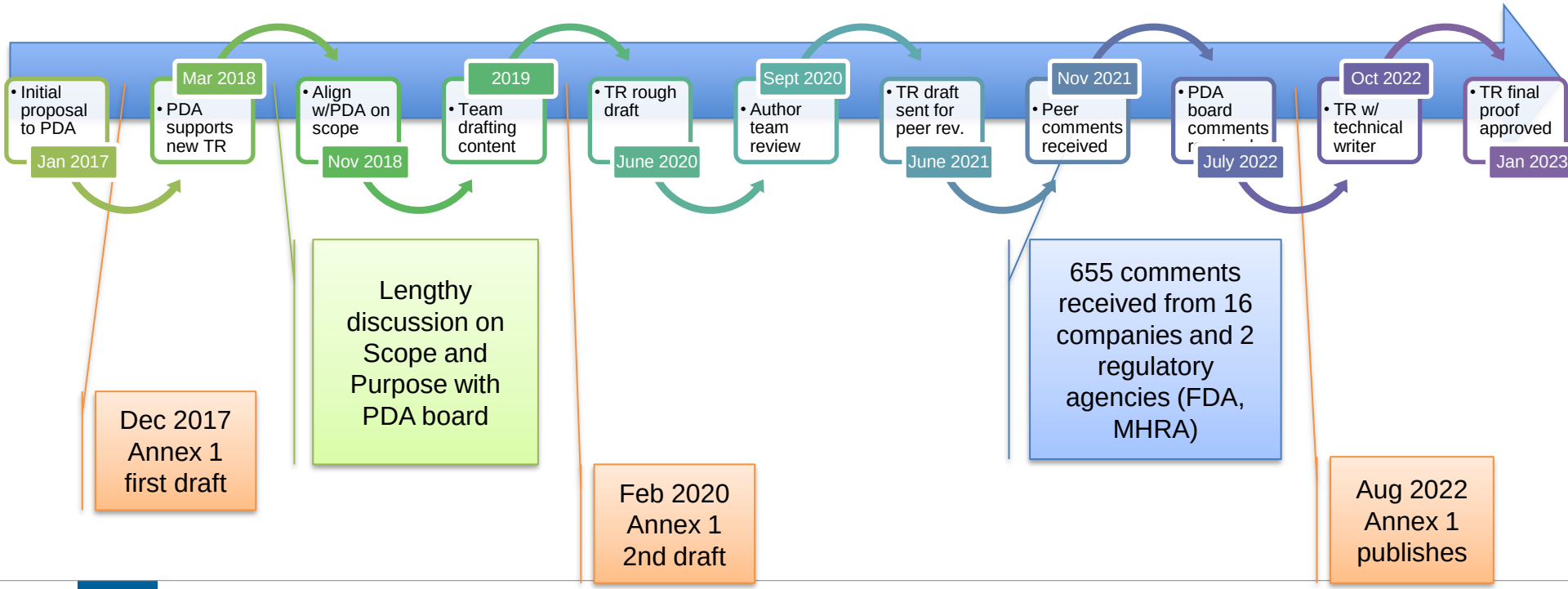
“Between 2000 and 2018, (drug) shortages in the EU increased 20-fold”

- Medicine shortages in the EU: causes and solutions, 30-09-2022
Medicine shortages in the EU: causes and solutions | News | European Parliament (europa.eu)

TR 90 Introduction



TR 90 Timeline



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TR 90 Highlights

– List of process & technical information needed to inform the CCS (section 3.0)

Process Knowledge

- Potential ingress points for contaminants to enter the process stream including particulates, microorganisms, viruses/bacteriophages, spores, endotoxins, and other microbial by-products (e.g., exotoxins, proteases, and other metabolites)
- Potential proliferation points for microorganisms and viruses, including bacteriophages, to grow in the raw materials, solutions, process equipment, and process stream, thereby, allowing formation of undesirable microbial by-products
- Microbial growth potential identified for each process step by assessing attributes such as pH, temperature, nutrients, water activity, and duration of exposure and/or by performing a profiling study of process matrices such as the antimicrobial effectiveness test
- Viral proliferation potential identified for each process step considering the presence of viral/bacteriophage cell hosts
- Process removal or reduction capability for potential contaminants (e.g., filtration, heating, and chromatography)
- History of contamination events and trends (from microbial, viral, or foreign particulate matter), microbiological and endotoxin concentration, and microbial flora profile for existing processes

Note: The viral aspects noted above are only applicable for processes that use living cell systems.

Technical Knowledge

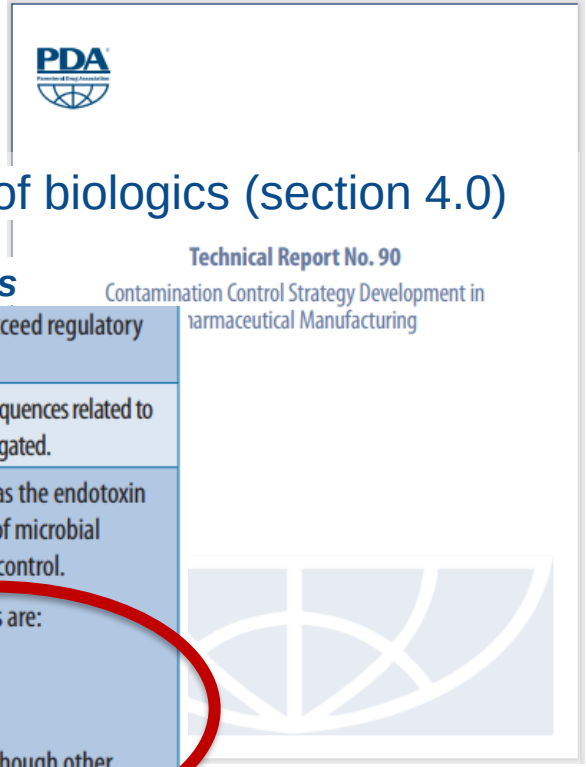
- Microbial attributes, behavior, and biofilm development (PDA Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations)
- Aseptic processing (PDA Points to Consider for Aseptic Processing, Parts 1 and 2)
- Viral attributes, behavior, and host infection (PDA Technical Report No. 83: Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response)
- Process design principles (PDA Technical Report No. 41 (rev. 2008): Virus Filtration; Technical Report No. 42: Process Validation of Protein Manufacturing; Technical Report No. 44: Quality Risk Management for Aseptic Processes; Technical Report No. 45: Filtration of Liquids Using Cellulose-Based Depth Filters; Technical Report No. 60: Process Validation: A Lifecycle Approach; Technical Report No. 81: Cell-Based Therapy Control Strategy; PDA Points to Consider for Aseptic Processing, Parts 1 and 2)
- Facility and utility design principles (ISPE Baseline Guide: Volume 3 – Sterile Product Manufacturing Facilities; PDA *Points to Consider for Aging Facilities*)
- Equipment design principles (PDA Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products; PDA Points to Consider for the Aseptic Processing of Pharmaceutical Products in Isolators)
- Cleaning, disinfection, decontamination, sanitization, sterilization principles (PDA Technical Report No. 1 (Rev. 2007): Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control; Technical Report No. 3 (Rev. 2013): Validation of Dry Heat Processes Used for Depyrogenation and Sterilization; Technical Report No. 26 (Rev.

TR 90 Highlights

- Current expectations for in-process monitoring limits of biologics (section 4.0)

excerpt from **Table 4.4.1.1 *In-Process Monitoring Considerations***

Alert Levels and Action Limits	Microbial action levels should be based on process capability and current industry standards and not exceed regulatory requirements, where applicable. Action level excursions should be investigated.
	Alert levels should be based on the historical data, and an adverse trend should be investigated to prevent consequences related to process, product, and facility contamination. Any organisms recovered from critical zones (A/B) should be investigated.
	In-process endotoxin excursion levels should take into consideration the product specifications as well as the endotoxin levels of the inputs (e.g., raw materials, WFI). In addition, as endotoxins are indicative of certain types of microbial contamination, action and alert levels should be within the expectations for a process under microbial control.
	Bioburden action levels should be established case by case. Current expectations for biological products are: • Bioreactor ≤10 CFU/10 mL (mammalian processes) • Culture purity (microbial fermentations) • Downstream process ≤100 CFU/10 mL • For DP processes, the DP bulk should contain ≤10 CFU/100 mL prior to the sterile filtration step, though other volumes may be used if scientifically justified.



TR 90 Highlights

– Holistic vs. Non-holistic examples (throughout, 2 examples below)

Table 9.0-1 Holistic Approach to Equipment Considerations

Non-Holistic Approach	Holistic Approach
Nonsterile equipment is always appropriate for nonsterile processes	Design the equipment controls to prevent and reduce contamination risk under worst-case circumstances
Cleaning is validated and therefore cannot be a root cause or contributing factor for contamination	Design the equipment handling procedures with the understanding that validated cleaning practices can be overchallenged by poor equipment hold practices; nonsterile equipment with any residual moisture will foul with biofilm over time
Perform only testing after a clean hold time is exceeded but do not reclean	Perform full cleaning after a clean hold time is exceeded to reduce any build-up of biofilm, which can be more difficult to remove later

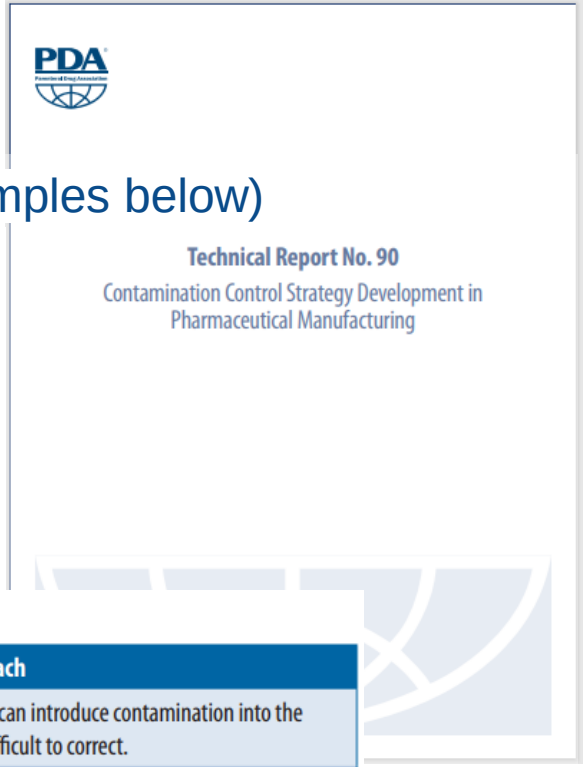


Table 5.1.4-1 Holistic Approach to Utility Considerations

Non-Holistic Approach	Holistic Approach
A critical utility is a standalone piece of equipment	Critical utilities are a major part of the overall CCS; they can introduce contamination into the facility, equipment, and process stream that are very difficult to correct.
Microbial contamination cannot occur if the utility monitoring test results are passing	Microbiological testing has known limitations; the physical parameter data for HVAC, water, and gas offer early warning signs of performance issues that can lead to serious contamination. Physical parameters are monitored, and atypical trends are responded to in a timely manner.
Only action-level results require investigation and CAPA	Any atypical result or trend, including sub-alert level results, can be an early warning sign and may warrant investigation.

TR 90 Highlights

- Table of practical considerations based on experience of authors (Appendix 1)

15.0 Appendix 1: Practical Considerations of Contamination Control Strategy Elements

Tables 15.0-1–15.0-10 provide practical considerations for many elements of contamination control system (CCS) with an explanation of the relevant benefit of preventing contamination.

Table 15.0-1 Structure of the Manufacturing Areas

Closed Processes	Closed systems are a physical barrier between the environment and materials in a manufacturing process
	Closed process provides protection from the introduction of contamination from the environment because introduction of materials into the equipment is restricted to closed connectors
	A closed system prevents release of inherent contaminants into the manufacturing environment
	Inherent bioburden of the process is contained
	Prevent interaction of humans with the product or direct product contact surfaces
	Isolator surfaces can be decontaminated with a validated process
	Understand sequence operation to prevent downstream contamination
	Open processes rely significantly on appropriate gowning and operator training/aseptic practices/hygienic behavior to protect process from human originating contaminates
	Multiple barriers are required to protect against contamination in open manufacturing systems
	Design of facilities should consider flows of people, product, materials, equipment, and waste to prevent contamination and cross-contamination

Table 15.0-7 Composition of DS and DP

Growth Source	Determine whether the composition of intermediates and buffers allow microbial growth or inhibit microbial growth, based on nutrient content, pH, water activity
	Understand that extended hold times create vulnerability to contamination if the composition allows growth
	Store material in an integral container to prevent contamination ingress
Downstream Processes	Check downstream bioburden or endotoxin reduction steps after introduction of growth-enhancing materials
Bioburden Removal	Filtering solutions and intermediates
	Removing bioburden from materials and buffers/media before adding to process stream via filtration, autoclaving, or other sterilization
Viral Removal or Inactivation	Low pH or detergent step, which inactivates enveloped viruses
	Nanofiltration
Benefit to Preventing Contamination	
• Understanding the points in the process that are vulnerable to microbial contamination allows for effective CCS to be built. The vulnerable points warrant strict control of the potential sources of microbial ingress (materials, equipment, environment, personnel), may warrant a bioburden removal, possibly viral removal, and in-process monitoring	

Examples of assessing microbial excursions in intermediates (Appendix 2)

Vulnerability Scoring: Microorganism Characteristics

Characteristics of Microorganism	Common Source:	Gram stain:
Microorganism Identified: *Stenotrophomonas maltophilia* [a]	☐ Human microbiota ☐ Environmental, soil ☒ Water-borne microorganism	☐ coccus Gram + ☐ coccus Gram – ☐ rod Gram + ☒ rod Gram –
CFU per sample volume: 120 CFU/10 mL Estimated CFU/total working volume (50 L): 6.0×10^5 CFU/50 L	Is the microorganism able to produce by-products: endotoxin, exotoxin, mycotoxin, protease, or penicillin?	☐ Mold ☐ Yeast ☐ Other ☒ Yes, list here: Endotoxin, Flagellar proteins, Exotoxins, Proteases [a,b] ☐ No ☐ Unknown
	Spore-forming?	☐ Yes ☒ No
	Cell size: 1.5 x 0.5 µm [a] Spore size: N/A May pass 0.2-µm filter (cell or spore)?	☐ Yes ☒ No ☐ Unknown

Vulnerability Scoring: Process Growth Potential

To determine the Likelihood of Proliferation, evaluate if the specific microorganism's growth requirements are met by the process conditions, e.g., temperature, pH, time, antimicrobial properties. Production of extracellular microbial by-products is growth-phase dependent, occurring in late exponential or stationary phases. Scientific references should be included in the impact assessment files as appropriate to support the information entered below.

Parameter	Process Conditions*		Microorganism Growth Requirements	Late Exponential Growth Permitted? (Yes / No)
	Previous Step(s) ☒ N/A if steps are separated by bioburden removal operation	Step that Yielded Excursion: Eluate end of hold		

Likelihood of Late Exponential Growth Score

☒ Low	By-product-generating growth of the microorganism(s) Not permitted by process conditions (a conclusion of "No" above)
☐ High	By-product-generating growth of the microorganism(s) Is permitted by process conditions (a conclusion of "Yes" above)

Severity Scoring of Downstream Removal Capability

Severity Score	
☒ Low	Downstream process **Will** remove or kill the microorganism(s) and clear any possible by-products from the specific microorganism(s), OR Downstream process **May not** remove or kill the microorganism(s) and/or clear possible by-products from the specific microorganism(s), but there is direct evidence that potential by-products are not affecting product quality, e.g., endotoxin results, accelerated stability results.
☐ High	Downstream process **May not** remove or kill the microorganism(s) and/or clear any possible by-products from the specific microorganism(s)

Document Rationale for Severity Score

Cell removal: *S. maltophilia* are removed by downstream 0.2-µm filtration, and downstream bioburden results demonstrate reduction to 0 CFU/10 mL

By-product removal: Downstream purification steps may not remove all microbial by-products but there is direct evidence that potential by-products are not affecting product quality. Endotoxin results demonstrate endotoxin was below the detectable level at the step being assessed.

Accelerated stability results demonstrated acceptable results, indicating there was no detectable damage from potential microbial protease activity.

Overall Score

Overall Risk Matrix	Severity Score	
Likelihood of Proliferation Score	Low	High
V1	Acceptable	Acceptable with Action
V2	Acceptable	Unacceptable
V3	Acceptable	Unacceptable

Overall Risk Score	Impact(s)	Remediation Action
☒ Acceptable	• No patient impact • No product quality impact	Action required to prevent recurrence unless justification approved by the Quality unit
☐ Acceptable with Action	• No patient impact • No product quality impact	Action required to prevent recurrence
☐ Unacceptable	• Potential impact on the patient • Unacceptable potential for impact on product quality	Action required to reject product lot and prevent recurrence Refer to Deviation for product disposition

TR 90 Highlights

- Four Case Studies (Appendix 3)

17.1 Case Study 1: Contamination Related to Equipment Maintenance

Reference: Case Studies of Microbial Contamination in Biologic Product Manufacturing by Kalavati Suvarna, PhD, Patricia Hughes, PhD, Richard L. Friedman; American Pharmaceutical Review, January 1, 2011

17.2 Case Study 2: Contamination Related to Blow-Fill-Seal Equipment Design and Maintenance

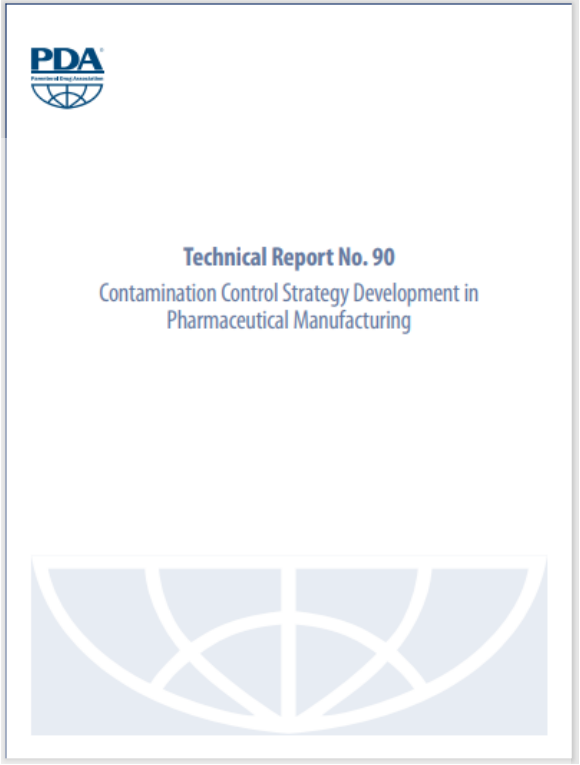
Reference: Commentary Aseptic Processing Contamination Case Studies and the Pharmaceutical Quality System by Richard L. Friedman; PDA Journal of Pharmaceutical Science and Technology, Vol. 59, No. 2, March–April 2005

17.3 Case Study 3: Contamination Related to Facility Construction

Reference: Commentary Aseptic Processing Contamination Case Studies and the Pharmaceutical Quality System by Richard L. Friedman, PDA Journal of Pharmaceutical Science and Technology, Vol. 59, No. 2, March–April 2005

17.4 Case Study 4: Disruption Recovery Program

Reference: The PDA TR-90 authoring team developed the following recovery program example based on their professional experiences.



TR 90 Highlights

– Template CCS document and practical tips (Appendix 5)

Tips for Contamination Control Strategy Document

- **Use factual, active voice**. Describe the controls that do occur at the site, not what "shall" occur. State the rationale for these controls, especially when that rationale is critical to the overall strategy or not obvious/common.

- **Target 30-50 pages.** Include visuals and avoid too many details. Instead, refer to other detailed GMP documents (e.g., SOPs, Batch Records, site master file, reports, risk assessments).

- **Align the format** to your company/site procedure requirements.

- **The Audience** of the Contamination Control Strategy document is:
  - Inspectors: This document will be given to inspectors to orient them to a site's overall strategy, procedures, and data related to contamination control.
  - All GMP site employees: This document is a holistic overview to help readers understand the interconnectedness of all elements of the CCS and to ensure future changes do not adversely impact the state of contamination control.

- **The Scope** of your Contamination Control Strategy document: It may be facility-specific and/or process-specific, depending on the organization.
  - The CCS should be prepared and owned by the responsible site for their portion of the supply chain. When multiple CCSs are needed to cover the full, end-to-end supply chain, they should reference one another.
  - For multiproduct facilities, where the manufacturing processes are similar and the same CCS is employed (e.g., fill-finish operations), one strategy document may cover all processes/products at the site.
  - For multiproduct facilities, where manufacturing processes and/or associated CCSs vary

How to Build CCS

How to Begin Building the CCS

True whether crafting a new CCS or re-evaluating an existing CCS

Step 1. Assemble interdisciplinary Team

Step 2. Assess Strengths and Vulnerabilities

Step 3. Author the CCS; Track the gaps

How to Begin Building the CCS

Step 1. Assemble interdisciplinary Team

- Facilitator (doesn't have to be CCS expert)
- SME Team Members : (some member can be ad-hoc)
  - Quality Risk Management
  - Manufacturing Operations / Process Experts
  - Contamination Control / Sterility Assurance
  - Engineering / Facilities / Utilities
  - Equipment
  - Validation
  - Raw Materials / Vendor Oversight
  - Quality Control
  - Quality Assurance

How to Begin Building the CCS

Step 2. Assess Strengths and Vulnerabilities

Prioritize

Determine which risk assessments are needed and prioritize them

What is the risk of process contamination?

from Personnel?

from Equipment?

from the Environment?

from **Raw Materials and Consumables**?

*from **Product-contact Utilities**?*

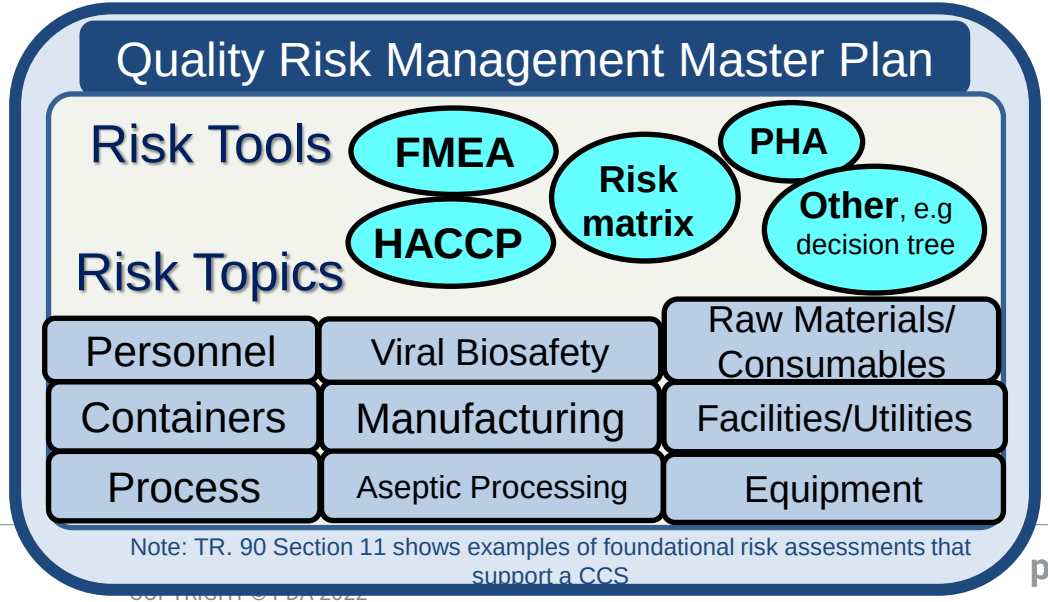
*from **Product Containers?***

How to Begin Building the CCS

Step 2. Assess Strengths and Vulnerabilities

Prioritize

CCS requires a Risk Library which is managed via a QRM Master Plan



Note: TR. 90 Section 11 shows examples of foundational risk assessments that support a CCS

How to Begin Building the CCS

Step 2. Assess Strengths and Vulnerabilities

Prioritize your efforts

For new CCS

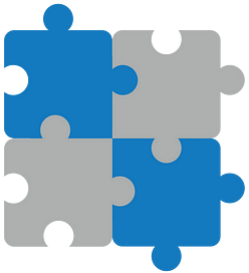
- Highlight importance to Senior Leaders early – use Annex 1
- Get Contamination Control SME involved at the design stage
- Rapidly identify risks that are unique to your process
- Prioritize the risk assessments – focus on elements that are hard to change later, e.g. facility design, process design, raw material selection
- Existing technologies with proven history may be adequate BUT don't miss the opportunity to innovate CCS elements in new facilities

For existing CCS

- Gather performance history on every CCS element
- Re-evaluate with fresh eyes – take this opportunity to improve
- AND many existing CCS elements are probably still useful

How to Begin Building the CCS

Step 3. Author the CCS; Track the gaps



1. Expect to find gaps or mis-alignments in CCS practices when authoring a CCS document for the first time

2. Correct the ‘easy-fixes’ before finalizing CCS document

3. Track longer-term gaps in Quality system, e.g. CAPA

Case Study:

Comparing CCS of 3 Low Bioburden Drug Substance Processes

	Process 1	Process 2	Process 3
Key Features	Open steps, at start and end Reusable equipment, complex pathways Synthetic raw materials	Few open steps, only at start Single-use systems, connections made manually, thermal welding Biologic raw materials	No open steps Single-use systems, pre-assembled kits, few manual connections Biologic raw materials
			

Expanded from TR. 90 Appendix 4

	Process 1 	Process 2 	Process 3 
Key Features	Open steps, at start and end of process - Ingress from Environment & Personnel	Few open steps, only at start - Ingress from Environment & Personnel	No open steps
Key Risks for CCS	Reusable equipment, complex pathways - Challenges to clean/sterilize - Deadlegs/misalignments Synthetic raw materials - Fouling during storage	Single-use systems, connections made manually, thermal welding - Leaks, Personnel technique - Vendor quality defects Biologic raw materials - Adventitious agents, prions	Single-use systems, pre-assembled kits, few manual connections - Vendor quality defects Biologic raw materials - Adventitious agents, prions

	Process 1	Process 2	Process 3
			
Key Features	Open steps, at start and end - Environment & Personnel - Strict cleanroom controls - CCS Awareness Campaign & Coaching (alongside training)	Few open steps, only at start - Environment & Personnel - Strict cleanroom controls - CCS Awareness Campaign & Coaching (alongside training)	No open steps - Downgraded cleanroom controls
Key Risks for CCS	Reusable equipment, complex - Challenges to clean/sterilize - Deadlegs/misalignments - Conservative practices, audits - Regular slope audits Synthetic raw materials - Fouling during storage - Temp, humidity control	Single-use systems, connections made manually, thermal welding - Leaks, Personnel technique - Vendor quality defects - Targeted, hands-on training - Inspection of consumables, pre-use inflate bags - Partner with vendors Biologic raw materials - Adventitious agents, prions - Pre-use testing - Treatment where possible	Single-use systems, pre-assembled kits, few manual connections - Vendor quality defects - Inspection of consumables, pre-use inflation of bags - Partner with vendors Biologic raw materials - Adventitious agents, prions - Pre-use testing - Treatment where possible
Key Controls to Enhance for CCS			

Process 1

Process 2

Process 3

All the CCS elements apply to every process…. the Highlighted elements are **enhanced** controls to address the process-specific risks

Process 1

Governance
defined oversight and escalation

Monitoring of Controls
personnel monitoring | in-process monitoring | material monitoring | environmental monitoring | utility monitoring | pest control

Validation of Controls
personnel qual. & requal. | process qual. & life cycle | analytical method qual. & life cycle | facility, utility, equip. qual. & requal.

Contamination Controls
personnel training, hygiene, gowning | process design | vendor, material, consumable, container | equipment design, cleaning, sanitization | facility & utility design, cleaning, sanitization

Process 2

Governance
defined oversight and escalation

Monitoring of Controls
personnel monitoring | in-process monitoring | material monitoring | environmental monitoring | utility monitoring | pest control

Validation of Controls
personnel qual. & requal. | process qual. & life cycle | analytical method qual. & life cycle | facility, utility, equip. qual. & requal.

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personnel training, hygiene, gowning | process design | vendor, material, consumable, container | equipment design, cleaning, sanitization | facility & utility design, cleaning, sanitization

Process 3

Governance
defined oversight and escalation

Monitoring of Controls
personnel monitoring | in-process monitoring | material monitoring | environmental monitoring | utility monitoring | pest control

Validation of Controls
personnel qual. & requal. | process qual. & life cycle | analytical method qual. & life cycle | facility, utility, equip. qual. & requal.

Contamination Controls
personnel training, hygiene, gowning | process design | vendor, material, consumable, container | equipment design, cleaning, sanitization | facility & utility design, cleaning, sanitization

Thank You