Process and Challenges of Drafting a Science-Based CCS

Rebecca Michel

Director, Microbiology

Tolmar

PDA Parenteral Drug Association

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What is a CCS?

- A CCS is a document that identifies and assesses risks, explores ways to mitigate them, and defines preventative actions for sterile products. It also consolidates all measures in the pharma quality system that contribute to sterility assurance.
- It should be science based and have a holistic approach.
- Relevant knowledge base is each area is required.
- A CCS is not a one and done document just to meet a regulatory requirement, this document is a living document that should be reviewed and updated at a defined routine frequency and should be reviewed and updated as part of the change control process whenever major or significant changes are being made to a process or manufacturing site.
- Cannot be developed by one SME only.

Annex 1

- Number of time “CCS” is mentioned in Annex 1?

52

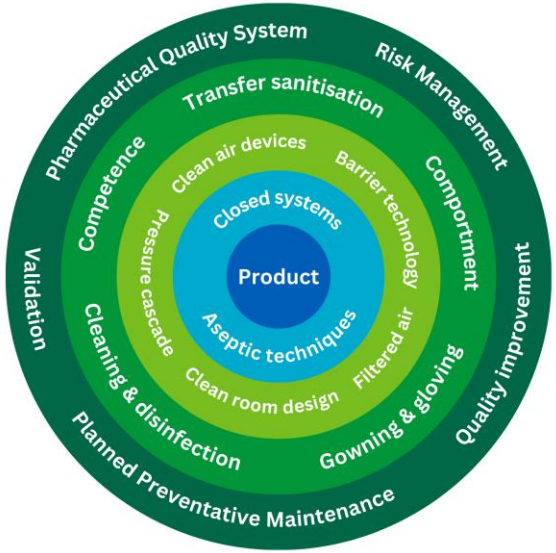
- Number of times “knowledge” is mentioned in Annex 1?

16

What holistic approach means?

- Aspects of contamination control strategy include an overview of how all processes interact and how each process affects another.

- It helps align and remove redundancies, increases the possibility to proactively influence changes and strategies in elements related to contamination control, identify potential gaps, and avoid product loss by having robust controls.
- Risk in one area may create unseen risk in other areas.



Key Aspects of a CCS-Important aspects of a documented contamination control strategy are developed per current regulatory thinking as outlined in the current EU Annex 1:

- Pharmaceutical Quality Systems
- Design of both the plant and process
- Equipment and facilities
- Personnel
- Utilities
- Raw materials control
- In-process controls
- Product containers and closures
- Vendor approval
- Process risk assessment
- Process validation
- Preventative maintenance
- Cleaning and disinfection
- Monitoring systems
- Continuous improvement

Obtaining buy in and defining the CCS Team

- Management- You will need to bring in your senior leadership and educate them on the importance of such a process and document. Designate a member of the leadership team as a Sponsor of the project and commit to providing updates and risks to project progress.

- Key points:
  - This is a requirement of the regulations
  - This will improve processes and procedures to be more compliant
  - This will help guide inspections and shows regulators continuous improvement is important to the company.

Obtaining buy in and defining the CCS Team

- Other departments- Remember how many times Annex 1 mentions knowledge base? Is there a single person in your company that has all the knowledge? It's important to build a knowledge-based team.

- Select at least 1 Subject Matter Expert (SME) from each of the following departments to be on the team:
  - Facilities and Engineering
  - Quality Assurance
  - Validations
  - Microbiology and Sterility Assurance
  - Manufacturing
  - MS&T
  - Process Development

Open Mindedness- Internal Gap Assessments may be Missing Blind spots

Grade A Barrier requires over 90% coverage. With no unidirectional flow outside air as well as human borne contaminants can enter the barrier and product

If air from the Grade B room is sucked into the Grade A RABS inlet, it leaves Grade B room devoid of clean air and contaminants cannot be removed.

Internal Risk Assessments may not reflect real life risk

- Paper based risk assessment do not identify risk
- In depth knowledge of the system assessed is key
- Residual risk should also be evaluated

Open RABS at low height. Gloves on two sides of RABS door. Human borne contamination due to air bouncing off the operator's head and operator breathing into the RABS through the opening between the two doors.

Why risk assessments fail

- No formalized process
- No defined acceptable risk levels
- Poor timing of the risk assessments
  - Not starting risk assessments in the design phase
- Wrong team members identified or one person performs the entire risk assessment
- Never 100% accurate, avoid expectations of this
- Neglecting to keep risk assessments current (reflecting current regulatory expectations)
- Not assessing each product, bracketing or ignoring product types or manufacturing lines: cell therapies, cell banks, and multi-product facilities have myriad of risks
- Considering perceived risk instead of understanding real-world risk
- Performing paper-based risk assessments without understanding systems

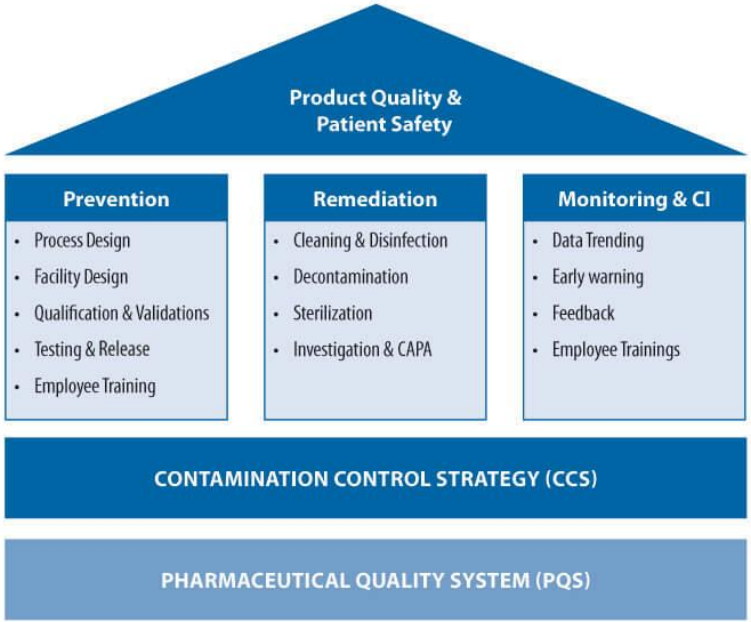
Use of risk assessment templates; every product or process is not the same

Information needed to be successful

- Regulations (CFR, EU Annex 1)
- Standards (ISO cleanroom standards)
- Regulatory guidance's (FDA Aseptic Guidance)
- USP <1116> etc
- PDA or other technical reports
- External consultants with specific expertise
- Knowledgeable SME's within the company

Pharmaceutical Quality Systems(PQS)- Expertise to assess gaps and evaluate risk

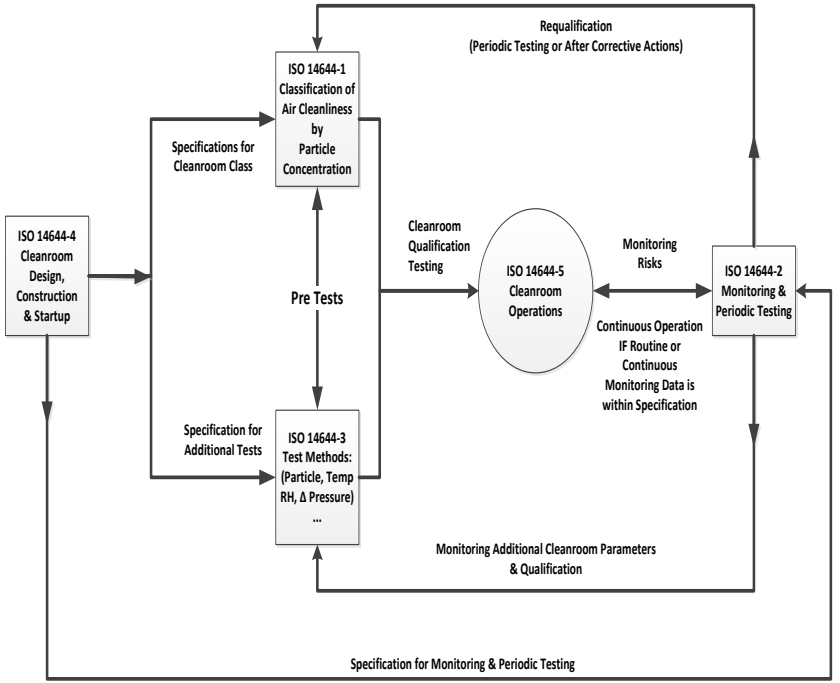
- Good understanding risk management and how the company applies it to processes
- Knowledge with the quality systems and management responsibilities and how the company uses science- and risk-based approaches at each lifecycle stage
- Quality by Design concepts



PDA Important Pillars for Success of CCS

Premises- Expertise to assess gaps and evaluate risk

- Good understanding of facility requirements for the type of product
- Well versed with the entire family of ISO cleanroom standards
- The understanding affect of airflows in the cleanrooms as well as within the barriers
- Knowing the challenges of modern technologies such as RABS and isolators and the integration within the cleanroom environment



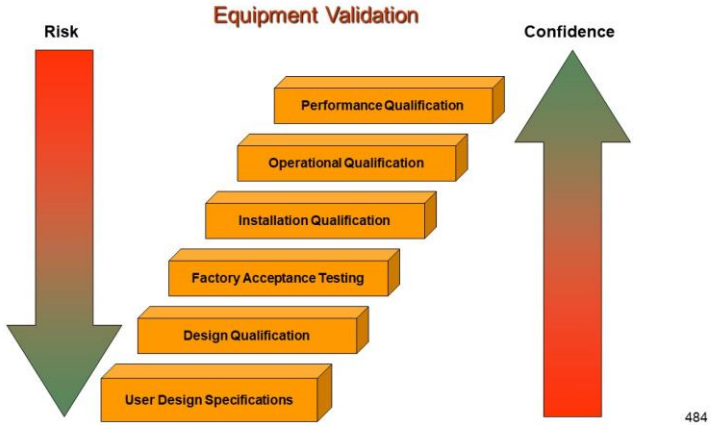
Premises- Expertise to assess gaps and evaluate risk

Barrier and Cleanroom Integration Issue

Airflow in the Grade B room, placement of HEPA filters and returns as well as pressure differentials inadequate Instead of air flowing out of the barrier during door opening, room air enters the unidirectional Grade A barrier.

Equipment- Expertise to assess gaps and evaluate risk

- A strong understanding of the validation approach to equipment used.
- Knowledge of standards and guidance documents and industry expectations for equipment used in manufacturing and for monitoring



Utilities- Expertise to assess gaps and evaluate risk

- An understanding of pharmaceutical water systems and design and quality monitoring requirements
- Knowledge of compressed gases and requirements for viable and non-viable particulates
- Understanding of utility system designs and how they are used and potential contamination risks for different types of products and processes

Personnel- Expertise to assess gaps and evaluate risk

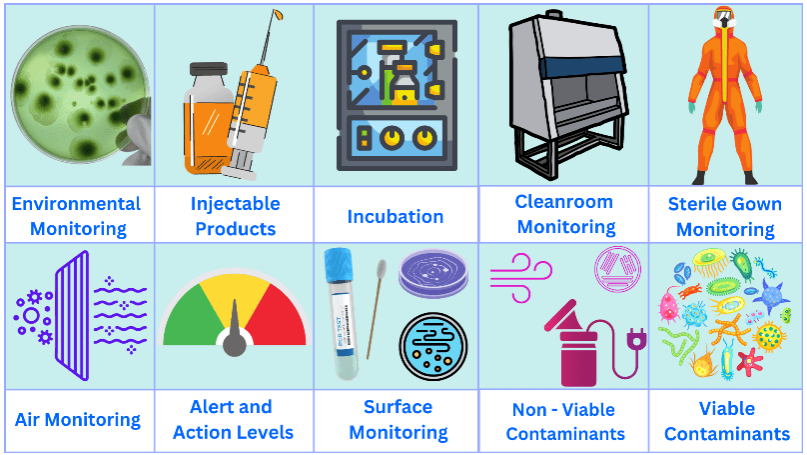
- Knowledge of hygiene and gowning requirements
- Understanding of the training programs and qualifications of personnel
- Gowning supplier expectations, requirements and qualifications and knowledge of the gowning management processes and procedures

Production- Expertise to assess gaps and evaluate risk

- Understanding of material and process flow
- Knowledge of production processes and area classifications required based on activities being performed
- Process validation experience and contamination risks identified
- Packaging requirements and container closure integrity knowledge
- A good understanding of sterilization processes used (aseptic vs terminally sterilized)

Environmental and Process Monitoring- Expertise to assess gaps and evaluate risk

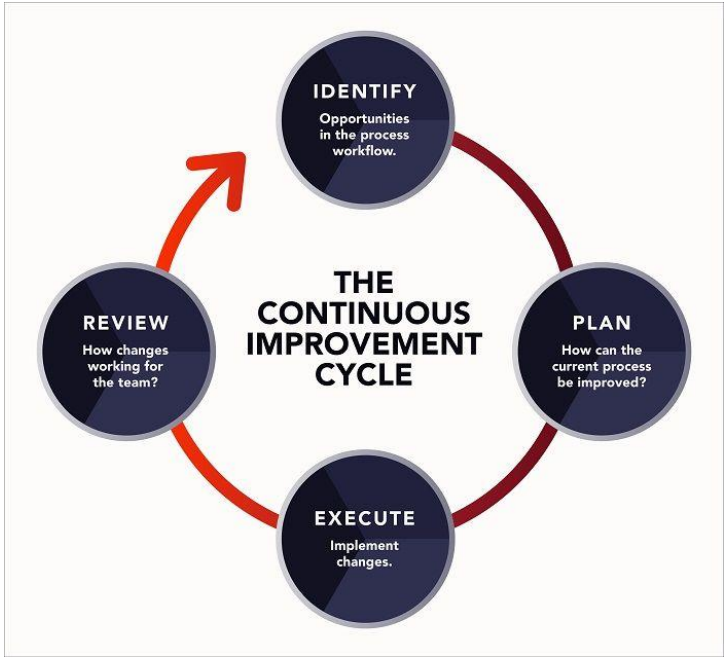
- Understanding of current process monitoring equipment and alarms.
  - Including HEPA air flow monitoring and equipment sensors
- Knowledge of the viable and non-viable monitoring program and how the alert and action limits were established
- Knowledge of the building management system and the equipment that is continuously monitored.



Quality Control- Expertise to assess gaps and evaluate risk

- Knowledge of product testing requirements and specifications
- Understanding of how to prevent and control contamination within the lab practices
- Knowledge of lab design and controls in place to prevent contamination

Continuous Improvement is not what we should be afraid of

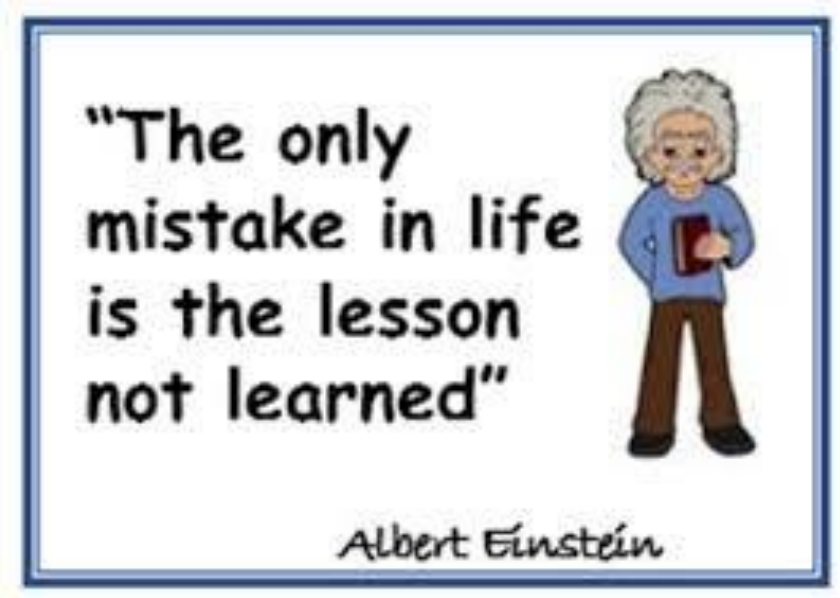


CCS Challenges- Real Life

- Educating leadership on the importance of this process
- Identifying the team
- Keeping momentum
- Alignment on the gaps and actions to take to mitigate risk

CCS Lessons Learned- Real Life

- Have a timeline and hold each other accountable
- Create milestones and celebrate them
- Communicate regularly on updates and status
- Treat the process like a project and manage it



Conclusion

- The most important thing is that the elements described in the CCS are risk based and scientifically justified.
- The strategy needs to consider all aspects of contamination control and its life cycle with ongoing and periodic review and update of the strategy as appropriate.
- The process needs to be a collaborative one and you need subject matter experts from all the areas to be involved and engaged in the process.

Thank You!