GIG CYMRU NHS WALES
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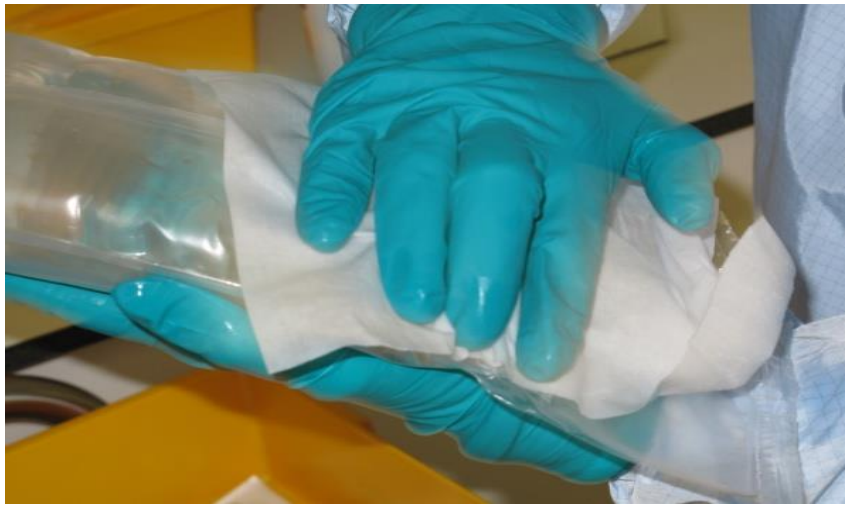
Contamination Control Strategy
An Example



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Betsi Cadwaladr University Health Board North Wales

Introduction/Outline

- North Wales
- Annex 1 – brief refresher
- Available Guidance
- An example from North Wales
- Further work/ Improvements
- Take Home messages

Welcome To North Wales?

- 3 Aseptic Units
  - SACT
  - CIVAS
  - PN
  - Radiopharmacy
- One with an MS licence for aseptic production.

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CCS – Annex 1 Reminder

A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and to assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety.

The Purpose of a CCS?

- The CCS should consider all integral elements of sterile product manufacturing/ aseptic preparation, including QRM principles and supporting risk assessments of Contamination Control and monitoring (detectability of contamination event).
- It should describe all control measures required to prevent / reduce risk of microbiological, non-viable particulate and endotoxin /pyrogenic contamination.

The Purpose of a CCS

- The combined strategy of the CCS should establish robust assurance of contamination prevention.
- The CCS should be based on Quality Risk Management (QRM) principles, utilising Risk assessment processes and periodic review that results in improvements within the PQS.

The CCS

- The need for a CCS plays a significant role within annex 1 and requirements are clear.
- Annex 1 – in place August 2023.
- Doesn’t just start and end within the production unit.

- Holistic from beginning to end.
- The CCS "living" or dynamic document that is updated in response to quality improvement, CAPA and audit.

What Do We Need To Do?

- Daunting!
- What does it all mean?
- Another thing we have to do!!
- Why do we need one?
- We have PQS, investigations, deviations, complaints……etc
- Take a step back and assess

We are already Controlling Contamination Aren't we?

- Facility and equipment design and qualification.
- Validation processes.
- Staff Training/Competencies
- Quality systems
- Media Fills/sterility tests
- Cleanroom clothing.
- Cleaning schedules
- Process design
- Microbiological control
- Environmental control
- Raw Material control
- QC testing
- Clean room behaviour

What we don't have

- Comprehensive plan that brings it all together and is documented.

- That is Holistic and end to end i.e not just limited to production processes and facilities.

North Wales Example

- Started during covid pandemic.
- Reflected on what we had already
- Assessed the controls that were in place.
- Assessed what additionality needed
  - A CCS to bring all the tools we use for contamination control together.
  - Wanted to create a live/living document, that was dynamic and embedded culture of the team.

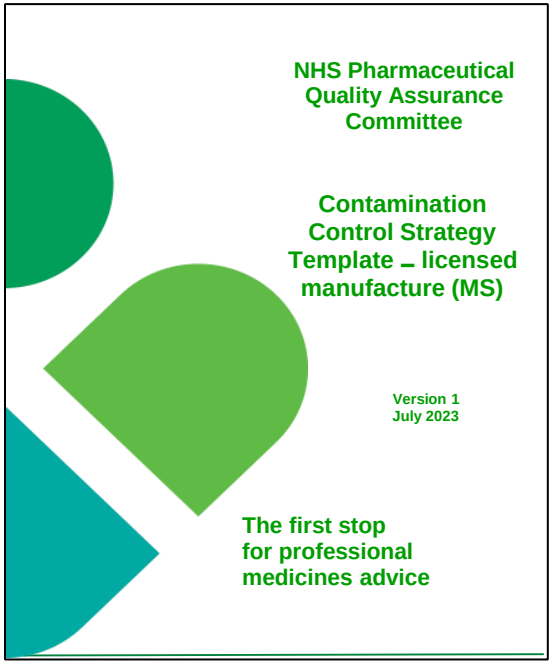
North Wales Example

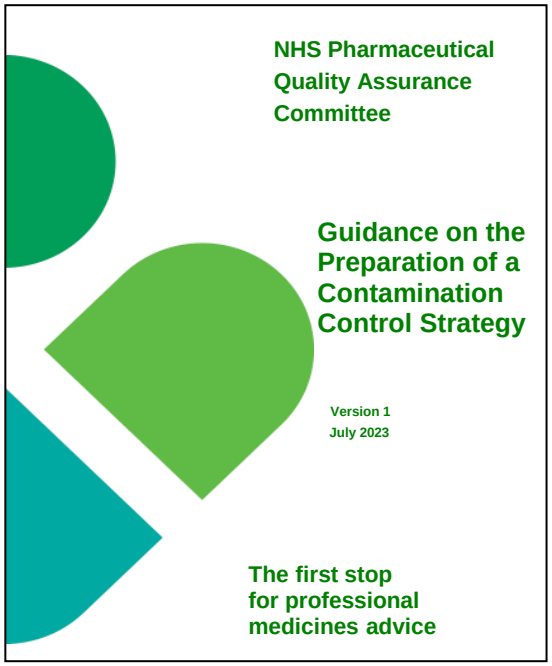
- Google……what is everyone else doing?
- Realised that you couldn't use an off the shelf CCS and plug and play
- For it to be useful it needed to be bespoke for our service
- But where do you start!!!

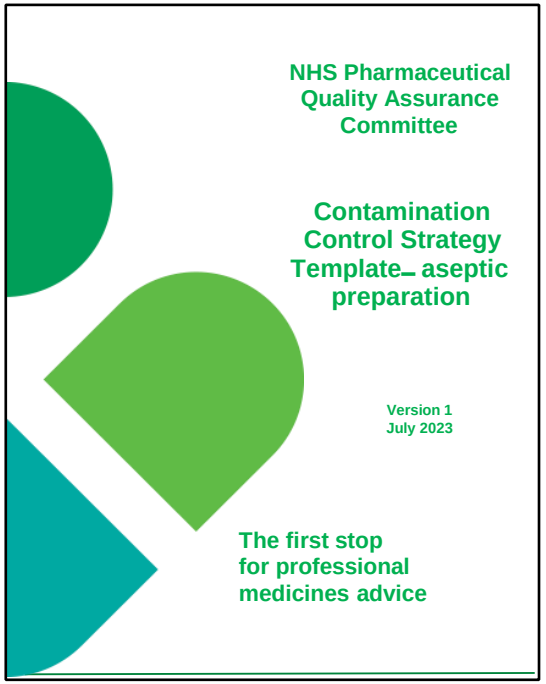
Annex 1

- Design of both the plant and processes.
- Premises and equipment.
- Personnel.
- Utilities.
- Raw material controls.
- Product containers and closures.
- Vendor approval.
- Management of outsourced activities.
- Process risk management.
- Process validation.
- Validation of sterilisation processes.
- Preventative maintenance
- Cleaning and disinfection.
- Monitoring systems
- Prevention mechanisms
- Continuous improvement

Supporting documents





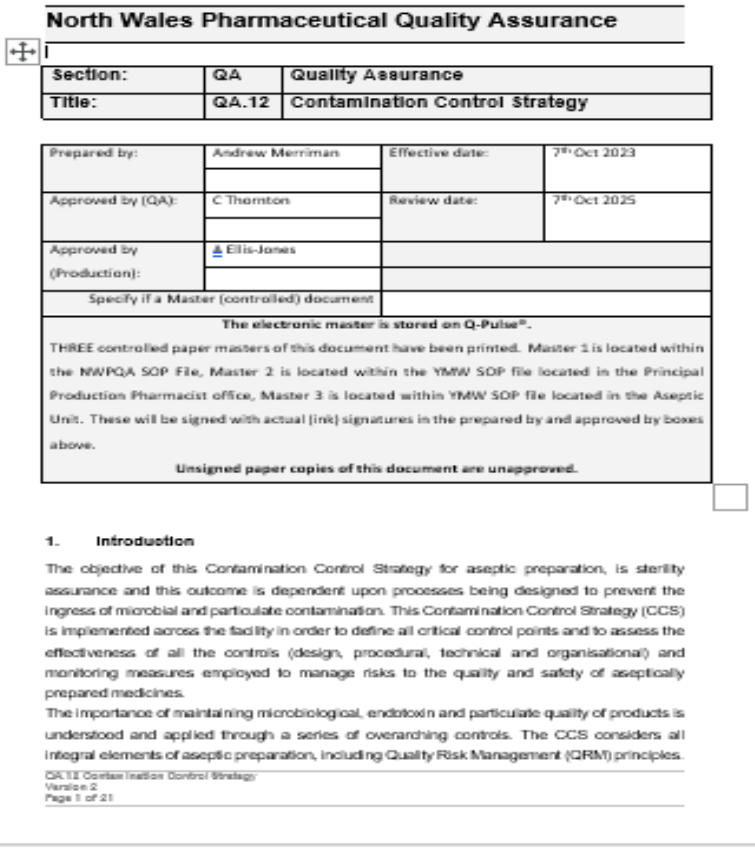


What Do We Mean By Holistic?

- Interdependent
- Multi disciplinary
  - work together to get best strategy
- Overarching
- Tailored - bespoke
- Deliberate – Concentrate on the why
- Not a generic list of rules

CCS document

- Developed a CCS Document
- Used Annex 1 list
- Utilised SPS guidance
- Outlines current controls in place.
- FMEA of each section



North Wales Pharmaceutical Quality Assurance

Section:	QA	Quality Assurance
Title:	QA.12	Contamination Control Strategy

Prepared by:	Andrew Merriman	Effective date:	7th Oct 2023
Approved by (QA):	C Thornton	Review date:	7th Oct 2025
Approved by (Production):	Ellis-Jones		
Specify if a Master (controlled) document			

The electronic master is stored on Q-Pulse®.

THREE controlled paper masters of this document have been printed. Master 1 is located within the NWPQA SOP File, Master 2 is located within the YMW SOP file located in the Principal Production Pharmacist office, Master 3 is located within YMW SOP file located in the Aseptic Unit. These will be signed with actual (ink) signatures in the prepared by and approved by boxes above.

Unsigned paper copies of this document are unapproved.

1. Introduction

The objective of this Contamination Control Strategy for aseptic preparation, is sterility assurance and this outcome is dependent upon processes being designed to prevent the ingress of microbial and particulate contamination. This Contamination Control Strategy (CCS) is implemented across the facility in order to define all critical control points and to assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to the quality and safety of aseptically prepared medicines.

The importance of maintaining microbiological, endotoxin and particulate quality of products is understood and applied through a series of overarching controls. The CCS considers all integral elements of aseptic preparation, including Quality Risk Management (QRM) principles.

QA.12 Contamination Control Strategy
Version 2
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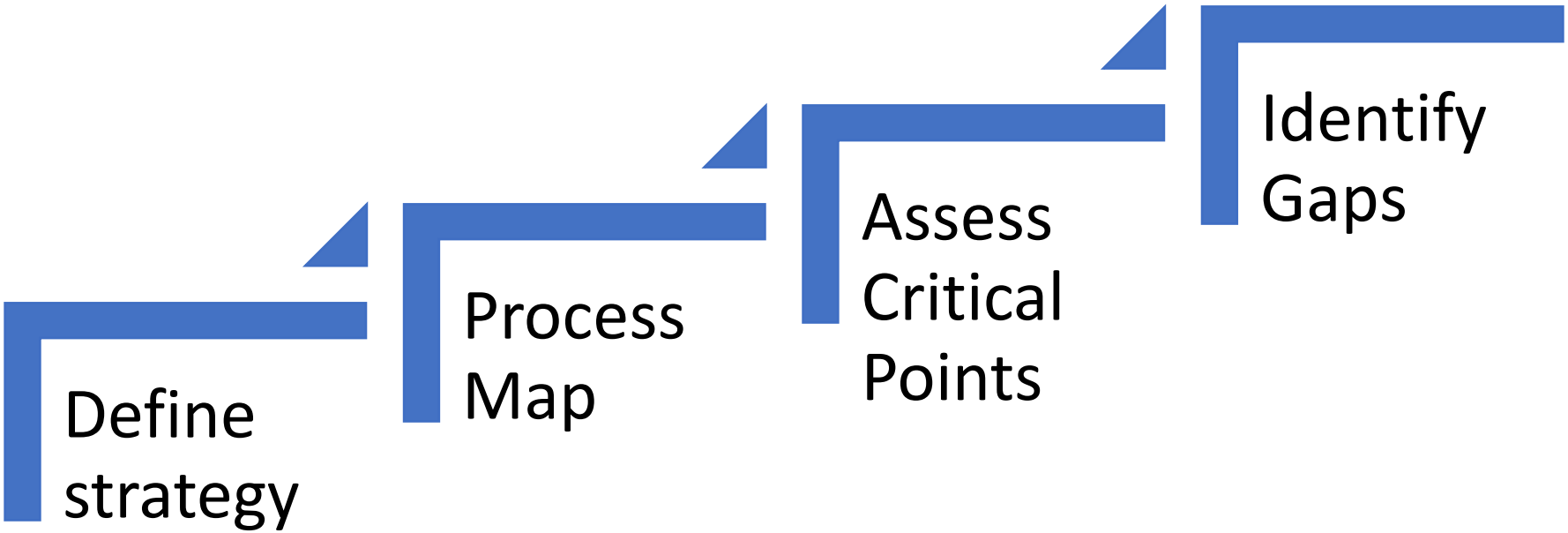
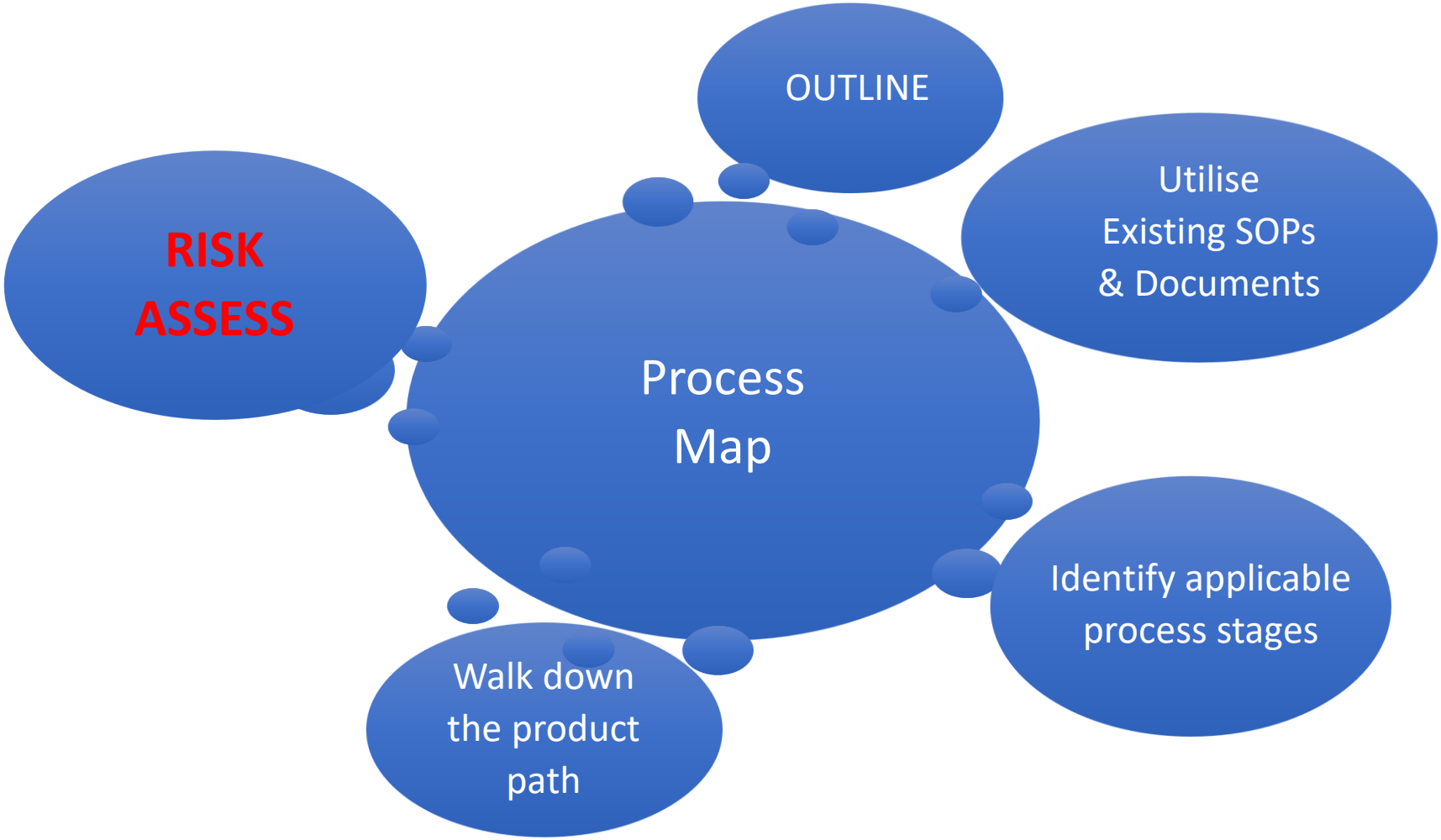
Strategy – Start with the end in sight



Process Map


OUTLINE
Utilise
Existing SOPs
& Documents
RISK
ASSESS
Process
Map
Identify applicable
process stages
Walk down
the product
path

Process Map

- Identified key end to end processes/stages for our service.
- Performed an FMEA on each of them.
- Through our scoring system identified higher risk areas.
- Informed priority areas to target with a more in depth RA.

Multidisciplinary

- Team - different areas of the service
- Technical Services Lead
- Production Lead
- QA/PQS reps
- QC reps
- Joined up approach, not just one person.

FMEA

Appendix 3: FMEA Scoring System

FMEA scoring system		
Severity	**Example**	**Score**
Critical	Severe impact on product quality/GMP adherence/Patient Safety.	4
Major	High risk to product quality/GMP.	3
Minor	Low risk to product quality / GMP impact	2
Other	Negligible impact on any aspect of patient safety/GMP	1
Occurrence	**Example**	**Score**
Highly likely	A frequently identified risk/process failure (weekly)	4
Likely	A commonly identified risk/process failure (weekly-monthly)	3
Unlikely	An uncommon risk that is identified infrequently (monthly –yearly)	2
Highly unlikely / never	A onetime event caused by an almost complete system failure.	1
Detectability	**Example**	**Score**
Highly detectable	Automated methods of removing or controlling risk	1
Detectable	A combination of automated controls with manual checks to provide assurance	2
Can be detected	Manual procedure driven methods of detection relying of human identification	3
Undetectable		4

Minor	Moderate	Major	Critical
1 – 10	11 – 30	31 – 50	51 – 64

Example FMEA Scores

Part 4: Procedures

Area of Risk	Part/Process *What is the function?*	Failure Mode *What could go wrong?*	Failure Effect *How does this affect process function?*	SEVERITY	Causes *Root cause or reason for potential system failure?*	OCCURENCE	Control *What controls are in place to prevent failure?*	DETECTION	RPN Score (S x O x D)
PROCEDURE CROSS CONTAMINATION RISK ASSESSMENT									
Cleaning of rooms and isolators	To provide a suitable regime for cleaning including agents for use depending on room/area EU GMP Grade	Cleaning schedule not followed. Incorrect cleaning agents not used	Potential loss of environmental control and insufficient removal of chemical residues.	3	Inadequate operator technique. Lack of staff or time resource. Unavailability of cleaning agents. Operator not complying with cleaning schedule.	1	Cleaning agents and schedule validated. Operator training provided. Cleaning procedure and schedule published in SOP. Environmental monitoring procedure in place.	2	6
Transfer Disinfection	To provide a process for the chemical and physical removal of contamination from items transferred from unclassified to Grade A environments	Insufficient decontamination of ingredients and consumables.	Introduction of contamination into clean room environments and critical zones.	3	Poor operator technique. Insufficient time allowed.	2	SOP containing detailed procedure. Validated process. Timers available. Operators trained in the process.	2	12
Monitoring	To provide continual assessment of the physical and microbiological environment using a number of sample types and test intervals	Missed or delayed monitoring could delay identification of a loss of control in the aseptic unit environment	Can prevent or delay identification of increased risk to products	3	Poor planning. Operator error. Unavailability of appropriate media. Plate desiccation.	1	SOPs in place for sessional monitoring of critical zones and the cleanrooms. QC involvement and additional checks. Monitoring schedule published in SOP. Colour coded media plates.	1	3
Process Validation	To ensure that processes are challenged with media to assess suitability	Missed process validations. Non-validated methods introduced to manufacturing unit.	Products manufactured by non-validated methods may be of a substandard quality. If routine validations changes	4	Lack of resource leading to either delayed or missed validation activities. Lack of material resource.	2	Validation master plan in place. Validation part of all operator training.	2	16

Risk Assessment

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QA.12 Appendix 6 CCS Risk Assessment
CCS RA 01: Cleanroom Clothing and Change Room Facilities

BCU IHC: East	**Site: YMH**	**Dept: Pharmacy**
Specific Area: Pharmacy Aseptic Services Department		
Assessor(s): Andrew Merriman	**Job Title: Pharmacy Technical Services lead**	**Date: 01/03/2023**

RISK RATING

Low Risk - Action only if low cost remedy, easy to implement, re-assess if process/procedure, guidance or legislation changes, keep under review.
Moderate Risk - Action that is cost effective in reducing the risk and planned and implemented within a reasonable time scale.
High Risk - Urgent action to remove or reduce the risk. To be escalated to senior management. Consideration given to stopping process.

	Insignificant Injury (1)	Minor Injury (2)	Significant Injury (3)	Serious Injury (4)	Major Injury / Fatality (5)
Highly Unlikely (1)	1	2	3	4	5
Unlikely (2)	2	4	6	8	10
Possible (3)	3	6	9	12	15
Likely (4)	4	8	12	16	20
Highly Likely (5)	5	10	15	20	25

Risk Assessment

Issue/Non-conformance	Risk Associated	Existing Control Measures	Current Risk Rating H M L	Action Required	Residual Risk Rating H M L
7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure gown cleanliness is maintained. Outdoor clothing including socks (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Single or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks	Staff not wearing appropriate cleanroom clothing increases the risk of operators contaminating the environment and increases the bioburden challenge to the grade B and grade A critical zones and increases the risk of contamination of aseptically prepared products.	• AHU provides sufficient air supply for a robust pressure cascade throughout the facility • Pressure differentials are appropriate for the facility and constantly monitored through the FMS system. • Routine sessional environmental monitoring programme is in place and results reviewed and trended with any OOS results and trends being investigated. • Quarterly monitoring of the facility occurs every 3 months with results noted and reported and any OOS investigated. • Cleanroom devices (Pharmaceutical Isolators) are working to specification to protect the grade A environments, they are continually monitored and there is cycle of servicing and preventative maintenance. • Cleanroom clothing is worn throughout the facility and there s a two stage	Medium L -3 C- 3 Score- 9	1. Staff to wear gloves and masks in preparation room 2. Staff to change trousers when they arrive at work so external trouser not exposed in the aseptic unit. 3. In 2nd change room staff to wear cleanroom boots to limit exposure of trousers below cleanroom coats. 4. Consider introduction of cleanroom socks 5. Cubicles to built within the 1st change room to facilitate changing into a single or two piece suit for the preparation area.	Low L – 1 C- 3 Score 3

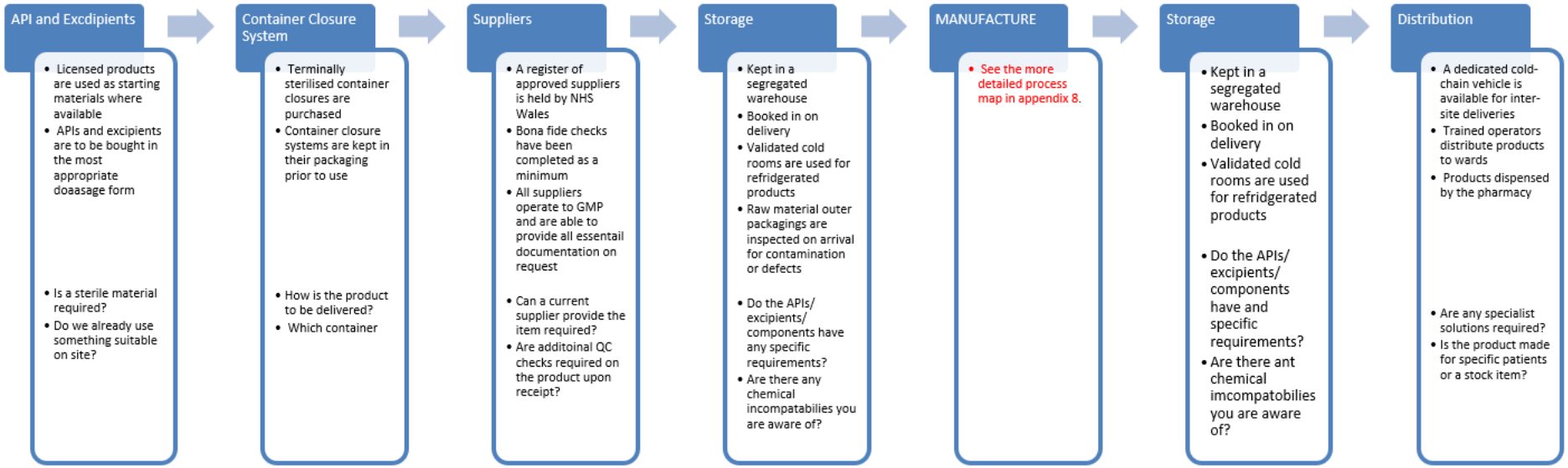
Some RA's Performed

- Cleanroom clothing
- Facilities
- Process Validation
- Negative pressure isolators
- Transfer Decontamination
- Cleaning of Rooms
- Sterility Assurance
- Environmental Monitoring
- Product Assembly
- Aseptic processing
- Training
- Storage areas

The RA's Identified Areas for Improvement

- Improvements made to our cleanroom clothing.
- There were gaps in our process validations and transfer decontamination verification.
- Transfer decontamination process needed improving – De-Grime stage.
- Ageing equipment e.g Isolators -

New Product Process Map



What else have we changed?

- Change control process improved - now includes contamination control considerations and impacts.
- Contamination control is now an integral part of monthly PQS meetings.
- It is also integral to our annual PQR's
  - Risk assessments are reviewed as part of this.

More Work To Be Done

- Work still needed to embed into culture.
- Current RA is a generic document – needs to be more specific to the CCS.
- Increasing number of RA's.
- Work so far has predominantly looked at microbial contamination.
- Continue to review FMEA and build on/expand RA's

More work to be done

- Work to be done on the end to end element within our CCS
- Continuous improvement – have processes in place for this but haven't assessed if they can be improved.
- Developing a culture whereby the CCS will continue to evolve and adapt but its early days.

Take away messages

- Annex 1 requirement but the annex states what's needed but not how to get there.
- The CCS brings all the process controls you have together.
- Focus on the why rather than the what.
- Make it bespoke for your service.
- Holistic - CCS series of interdependent practices, all aspects of GMP, multidisciplinary and end to end.

Take away messages

- Utilise QRM principles and Risk assess key elements of the CCS to identify gaps or areas for improvement.
- Use the guidance and example templates on the SPS website – will help you get started.
- The CCS needs to be a living and dynamic document that evolves, adapts and improves continuously.

Any Questions?