

Regulatory updates and trends



PDA 11 November 2022

Andrew Hopkins

- **Regulatory updates and trends**

1. Reg updates
2. Annex 1 (and links to other medicinal products)
3. Trends/Expectations
4. Challenges

- Annex 21 (implementation date 21 Aug 2022)
 - CTR (Annex 11) effective 2022
 - Part IV (Implementation date 22 May 2017)
 - Annex 2 A (PIC/S)
 - Annex 1 (Effective 25 Aug 2023 except Lyo)
-
- 8.123 Lyophilizers and associated product transfer and loading/unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilisation should be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation should be justified and documented as part of the CCS.



Annex 1 (history and main focusses)

- Started in 2014 (really 2012)
- International group including (TGA/USFDA/PMDA/Taiwan FDA)
- Update to give more explanation of current expectations !?
- Introduction of new structure (Classification versus routine monitoring, utilities section, monitoring all together with APS (toolbox concept))
- Introduction of QRM – key element of this is Contamination control strategy (but concept is throughout the document)
- Larger document
- And no, PUPSIT is not new!!!!!!
- Why? - To make sure what we do is safe

Annex 1 (links to other products)

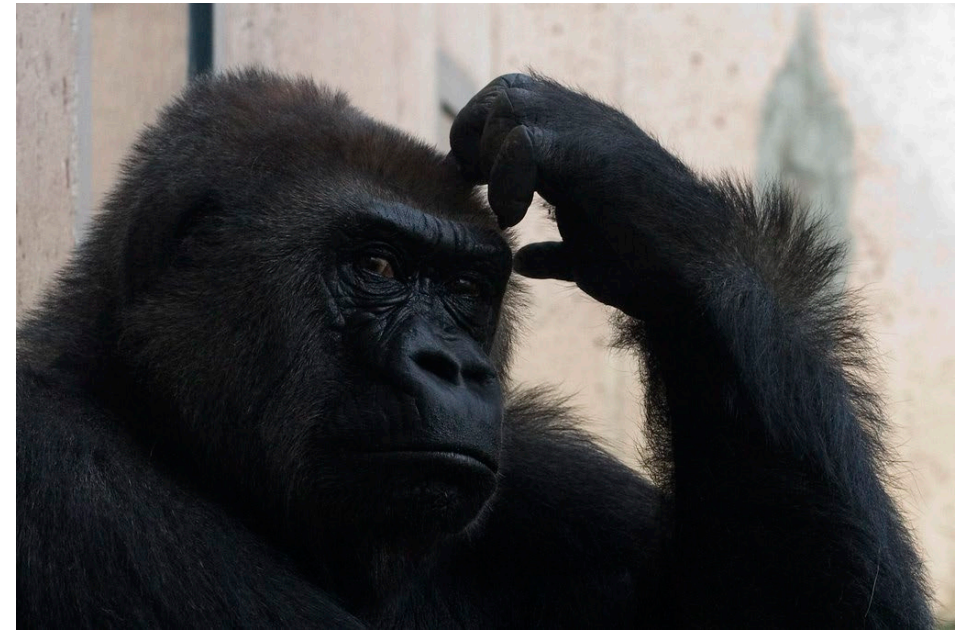
- Scope is open for use for other products (Low Bioburden, Creams and ointments even OSD etc.)
- Non mandatory – but still need to explain what we mean when we use terminology

E.g. Use a grade A, with grade C background for a low bioburden BDS. Need to explain our rationale, what we include and what we do not include

Annex 1 (links to other products)

Annex1 and ATMPs

- Does Annex 1 apply?
- Part IV of EU GMP specifically states that none of the other GMPs apply (Unless otherwise stated)
- However, some inspectors have stated they will use Part 1 and Annexes as “interpretative” documents
- For PIC/S, Annex 2A is written for ATMPs and states that other parts of GMPS apply



Annex 1 (Trends)

Annex1, EMA guidance on sterilization of medicinal products, CFR 211.113, USFDA Aseptic guidance 2004

- All have one main overall aim, minimizing contamination risk
- Emphasizing the need to look at Facility, equipment and process design to do this (not, “it is all ok because we did a risk assessment, and the monitoring is great!!!!!!!!”):

“The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data”

“9.35 APS should not be used to justify practices that pose unnecessary contamination risks”

Annex 1 (Trends)

- Recent conference experience

“4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.”

- Smoke studies:
 - Must show the process clearly
 - Must review both the airflow but also the process

Annex 1 (potential bumps in the road)

- Contamination control strategy fit for purpose
- Still not clear on CCI
- Large infusions bags
- Filter requalification every 6 months
- Risk assessment to inform everything we are doing (we have been empowered, need to make sure we do not abuse this)
- Smoke studies (expectation is grade A and B but not clear in the text)



Annex 1 (Other challenges)

- Appropriate application of QRM need to show an understanding and justification of all we do – Background of Isolator through to design of the EM system
- Knowledge Management (Industry and Regulators)
- Critical and unbiased thinking
- Keeping up with new technologies
- Less reliance on monitoring

“In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. **Monitoring or testing alone does not give assurance of sterility.**”



Source: BMGF, via WHO

Pre-use/Post Sterilization Integrity Testing Results of the SFQRM Work

Maik Jornitz, CEO G-CON Manufacturing Inc.

- Annex 1 and PUPSIT
- Reasons stated to use PUPSIT
- SFQRM Task Force – Working Blocks
 - Masking Studies
 - Data Mining
 - PtC PUIST Implementation
 - Risk Assessment
- Conclusion & Activities
- Question & Answer Session

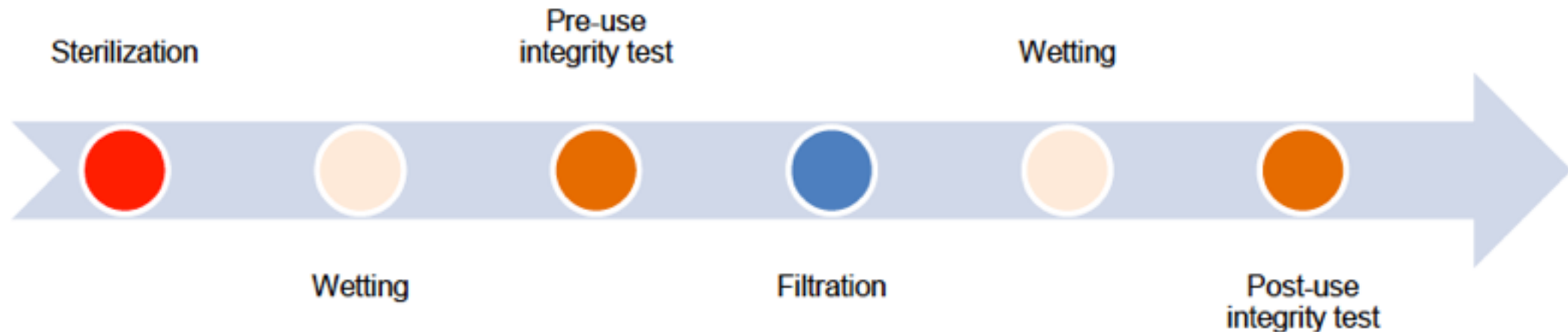
First Things First – What is PUPSIT ?

Paragraph 113:

The integrity of the sterilised filter should be verified before use...

PUPSIT = Pre-use/Post Sterilization Integrity Test

Used to determine whether the terminal sterilizing grade filter in front of filling is integral after the sterilization of the filter.



8.87 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:*

- i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized.
- ii. In depth knowledge and control of the supply chain to include:
 - Contract sterilisation facilities.
 - Defined transport mechanisms.
 - Packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.
- iii. In depth process knowledge such as:
 - 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.
 - Pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.

EU GMP guide annexes: Supplementary requirements: Annex 1: Manufacture of sterile medicinal products

[Back to top ▲](#)

▶ Collapse all items in this list

■ 1. How should the integrity of sterilising filters be verified? H+V June 2007

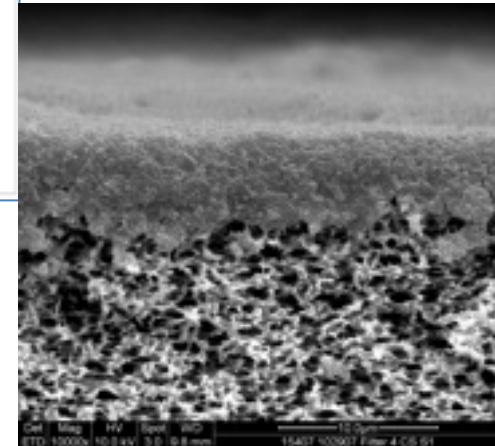
Annex 1, paragraph 85 states, 'the integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test.'

The filter-sterilisation process may be physically stressful for the filter. For example, high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2 µm in size.

The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons, filters should be tested both before use but after sterilisation and again after use.

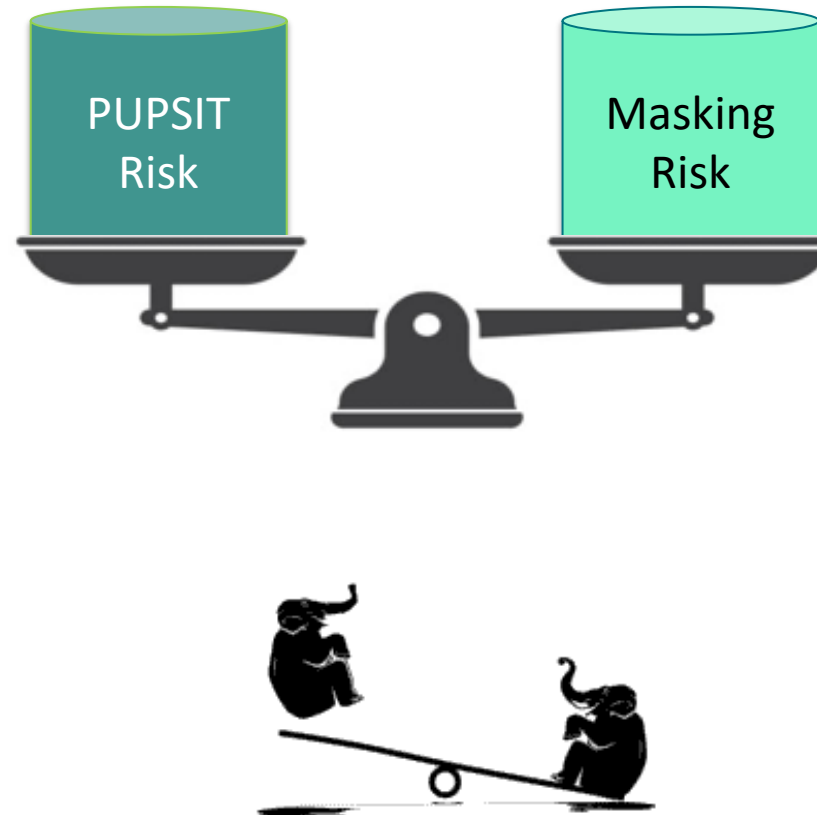
Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing.

Concern: Bridging covers a smaller flaw



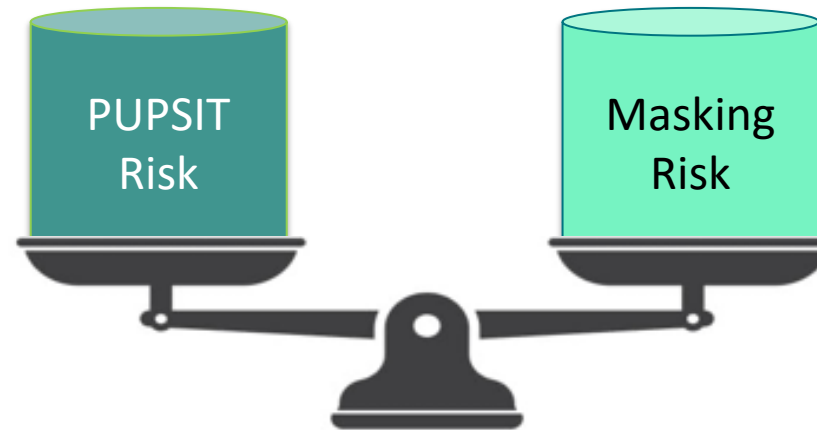
The Risk Balance

- Increased complexity of the filtration set-up
- Manipulation of the sterilized filtrate side
- Microbial ingress of the filtrate side
- Product dilution with wetting fluid
- With product wetting, unknown effects on the product by the test gas and time
- ...



- Flawed filter will not be detected by the post-use test
- Microbial penetration potential not being detected
- Sterilization process detriments are not detected
- ...

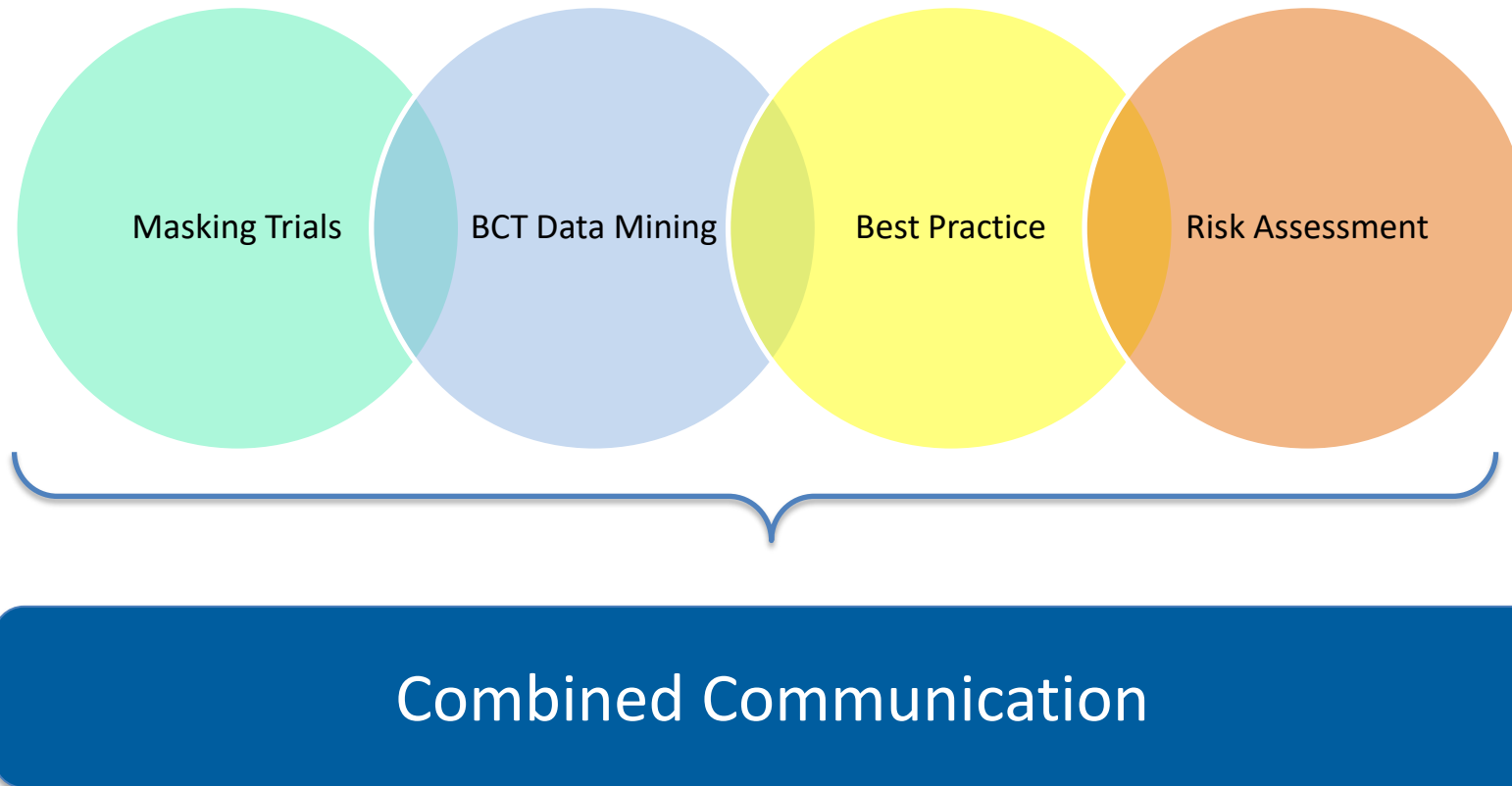
- Increased complexity of the filtration set-up
- Manipulation of the sterilized filtrate side
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- ...



**We needed
scientific data for
a resolution !**



- Flawed filter will not be detected by the post-use test
- Microbial penetration potential not being detected
- Sterilization process detriments are not detected
- ...



Masking Trial, Phase 1 Test

- Filter manufacturers collected marginal flawed 10" filter cartridges
- Filters were water wetted and integrity tested (Bubble Point)
- The filters were subjected to the blocking solution (Ovaltine 24g/L concentration) at constant pressure (10 psig) till >90% blocking rate
- Post-use the filters were flushed with water (50L/m²) and integrity tested (Bubble Point)
- Both integrity tests were performed with automated integrity test systems

Masking
Trials

Foulant
Concentration

24 g/L

Worst Case
Scenario

>90%

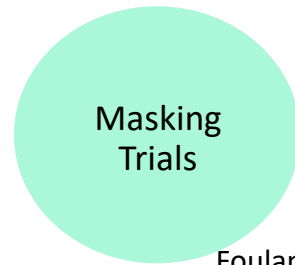
Blocking Rate

 24 filters tested → 2 passed post-use (>90% blocked)

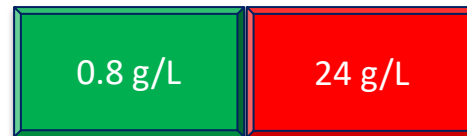
Masking Trial, Phase 2 Test

- Filter manufacturers collected 47 mm disc filters and a defined 10 micron hole was laser drilled into it
- Filters were water wetted and integrity tested (Bubble Point)
- The filters were subjected to the blocking solution (at 24 g/L and 0.8 g/L concentration) at constant pressure (10 psig) at 25%, 50%, 75% and 90% blocking rate
- Post-use the filters were flushed with water (50L/m²) and integrity tested (Bubble Point)
- The integrity tests were performed with automated integrity test systems and manual

8 filters tested at 24 g/L → all failed
44 filters tested at 0.8 g/L → 2 passed (81%, 97% blockage)



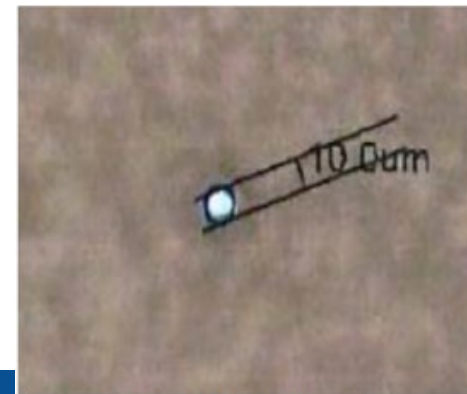
Foulant Concentration



Multi Parameter Scenario



Blocking Rate



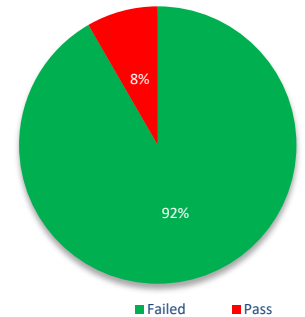
47 mm laser drilled membrane disc

Masking Trial – Summary

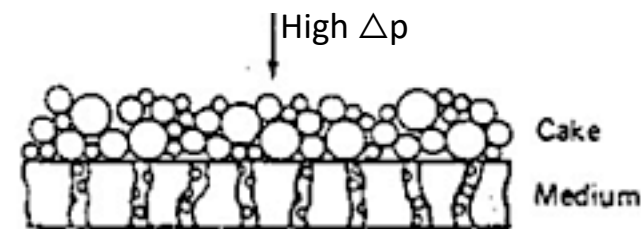
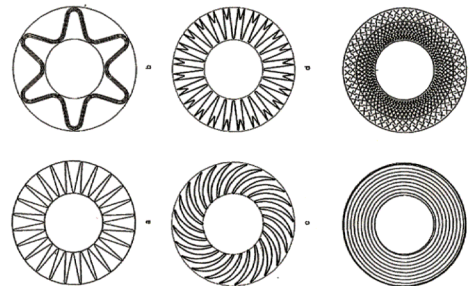
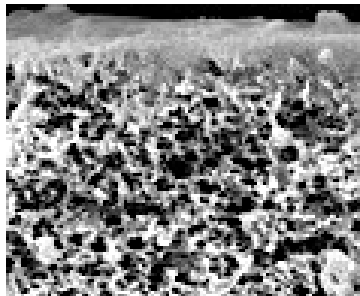
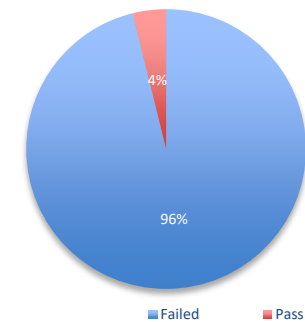
- ✓ Masking of filter flaws can happen under extreme circumstances of fouling and blocking of a sterilizing grade filter
- ✓ The masking possibility depends very much on the process, product and filter capacity conditions
 - Foulant concentration
 - Filter combination and membrane composition
 - Pressure conditions (cake compaction)

Masking Trials

Masking Phase 1

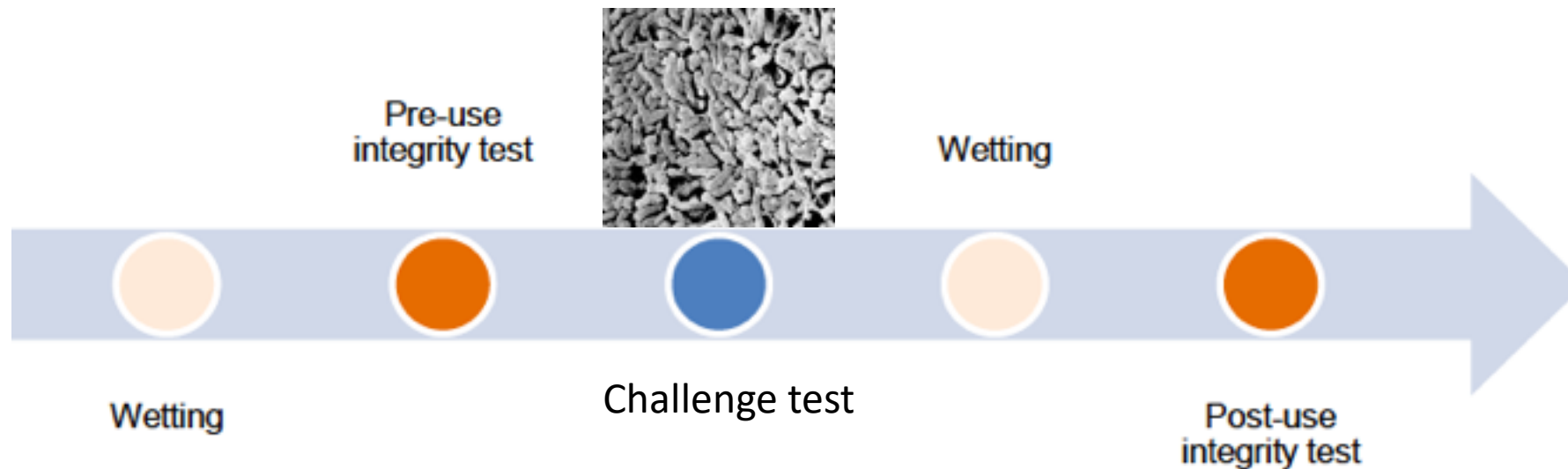


Masking Phase 2

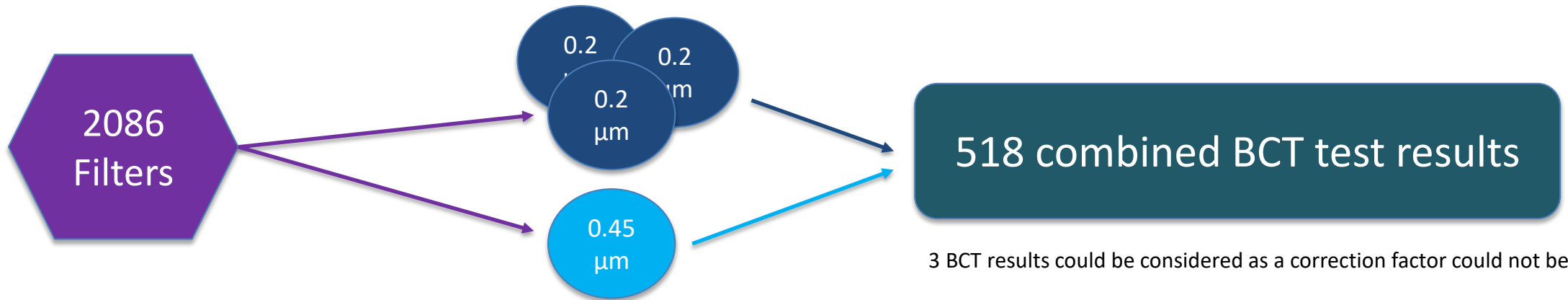


- The data mining integrity test data source were the pre- and post product bacteria challenge test integrity tests performed in filter process validation
- The bacteria challenge tested level is $> 10^7$ cfu B. dim. per cm^2 filtration area with various products

BCT
Data
Mining



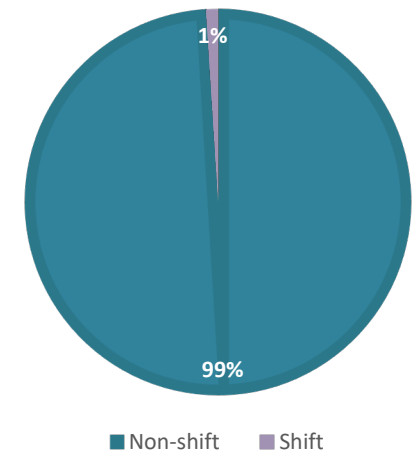
- ✓ Data have been submitted by two users and all four participating filter manufacturers' filter validation laboratories, with each BCT consisting of three 0.2-micron filters and one 0.45 micron filter (control filter)
- ✓ This data set includes pre-test and post- test BPs on 2086 filters (1,571 x 0.2 micron filters and 515 x 0.45 micron filters), representing 531 BCTs on 518 different fluids. The data set actually comprises 518 average corrected ratios from the combined test and control filters for each test (3 x 0.2, 1 x 0.45 micron)



- Out of 518 average Bubble Point ratio data points (2086 filters), there are 5 outliers (<1%) where the Bubble Point shifted
- Reviewing the outliers, it seems the fluids used were high foulant fluids and cause pore plugging
- In addition, the conditions of a bacteria challenge test are extreme, and not representative typical production conditions
- As with the Masking trials the Bubble Point shift experienced is rare

BCT
Data
Mining

SHIFT OF BUBBLE POINT



Best practice PtC

- Was required to address a multitude of questions
 - PUPSIT risks
 - PUPSIT installation
 - Flushing
 - Drying
 - Testing redundant filters
 - Pressure conditions
 - Etc...
- To raise the awareness about the actions which require to be taken
- To be able to add some guidance and alignment

Points to Consider for Pre-use Post-Sterilization Integrity Testing (PUPSIT) Implementation

Contents

Introduction/Purpose of this Document

Table of Contents

Background Information

- Definition of a Sterilizing Grade Filter
- Overview of Filter Integrity Testing
- Operation of Integrity Testers
- Selection of Integrity Test Method

Understanding Risk Drivers for PUPSIT Implementation

- Patient Sterility Risk
- Discard (Product Availability) Risk

Integration of PUPSIT into the Manufacturing Operation

Execution of PUPSIT Inside of Isolator / RABS systems

- Selection of Wetting Fluid Used to Perform PUPSIT
- Considerations when Using Water as the Wetting Fluid
- Considerations when Using the Process Solution as the Wetting Fluid
- Need for Redundant Filtration of the Process Stream
- Venting/Back Pressure Considerations
- Temperature Considerations
- Considerations related to maintaining sterility
- Typical steps in PUPSIT Operation
- Change Control Considerations in Maintaining a Robust PUPSIT Process

Two Examples of PUPSIT Implementation

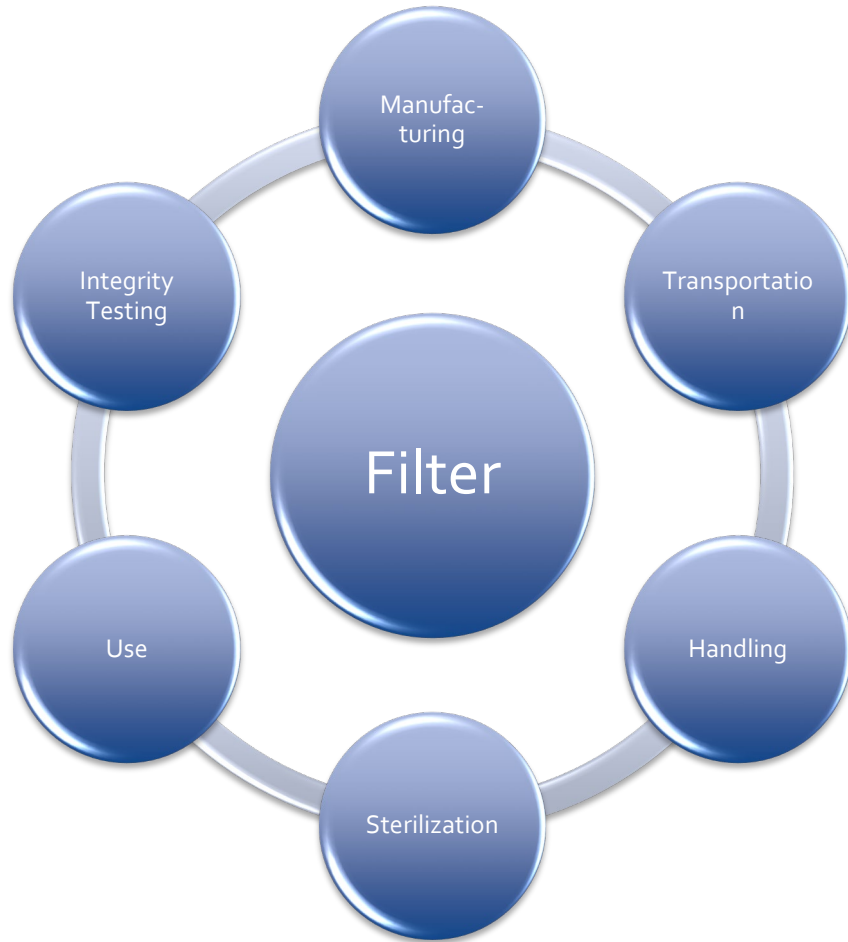
- Example 1: Hard piped highly automated system.
- Example 2: Single use manual system.

Definitions

Reference Documents

Best
Practice

- PUPSIT use and implementation requires a multitude of considerations to function safe and sound
- The implementation is not easy, but rather complex and will increase the complexity on the filtrate side of the sterilizing grade filter
- Wetting solution choice requires detailed analysis in regard to the activities after PUPSIT, which should not influence the quality of the filter and filter's retentivity
- Redundant filter system become even more complex and in instances end-users moved to a single filtration step
- There is no easy "one-fits-all" solution, every application needs to be evaluated



Includes:

- Filter Manufacturers “Quality” Survey Response
- Detailed quality control steps during the manufacturing process
- Filter use control sheets (preventative & detection) have been established, incl.:
 - ✓ Receiving
 - ✓ Storage
 - ✓ Transfer to Manufacturing
 - ✓ Filter installation
 - ✓ Wetting
 - ✓ Drying
 - ✓ Vent & Flush
 - ✓ Product filtration
 - ✓ Post-use test

The primary findings from the FTA and risk control mapping exercises were:

- There are many opportunities for failure of the sterilizing grade filters throughout the value stream, and
- These opportunities can be effectively controlled

A typical unit operation/process step contained an average of nineteen (19) individual faults that could ultimately lead to the failure of a filter to sterilize product.

Each fault had an average of four (4) redundant risk controls (not including of sterility testing of sterilized drug product) that served either to prevent the fault from occurring, or to enable the detection of the fault with sufficient time to correct before patient safety would be in jeopardy.

- PUPSIT has been in Annex 1 since the beginning but sporadically enforced when the Q&A 2007 was published with the suggestion of masking possibilities
- Scientific evidence of masking and perceived risks were needed
- SFQRM group established the scientific evidence, plus looked at the risks and installation implications involved
- The SFQRM data and information can be used as a basis to evaluate every terminal filtration application and run a risk assessment to determine whether PUPSIT would be of need or not
- All work stream results have been published via PDA

Masking
Trials

BCT Data
Mining

Best
Practice

Risk
Assess-
ment

Project Marvin – Robotic Automation in the Biotechnology Sector

Shada Warreth
11 Nov 2022





Consortium Partners



- Project commenced in Feb 2018
- EI funded project and is part of the Innovation Partnership Programme
- Lead Company: PM Group
- Lead Institution: UCD
- Other Consortium Partners:
 - NIBRT
 - Lonza
 - Novartis
 - KUKA Ireland





Project Aim

Develop a novel solution to **automate** the **EM collection process**, comprising a state-of-the-art mobile robotic platform and an open web-based software system.

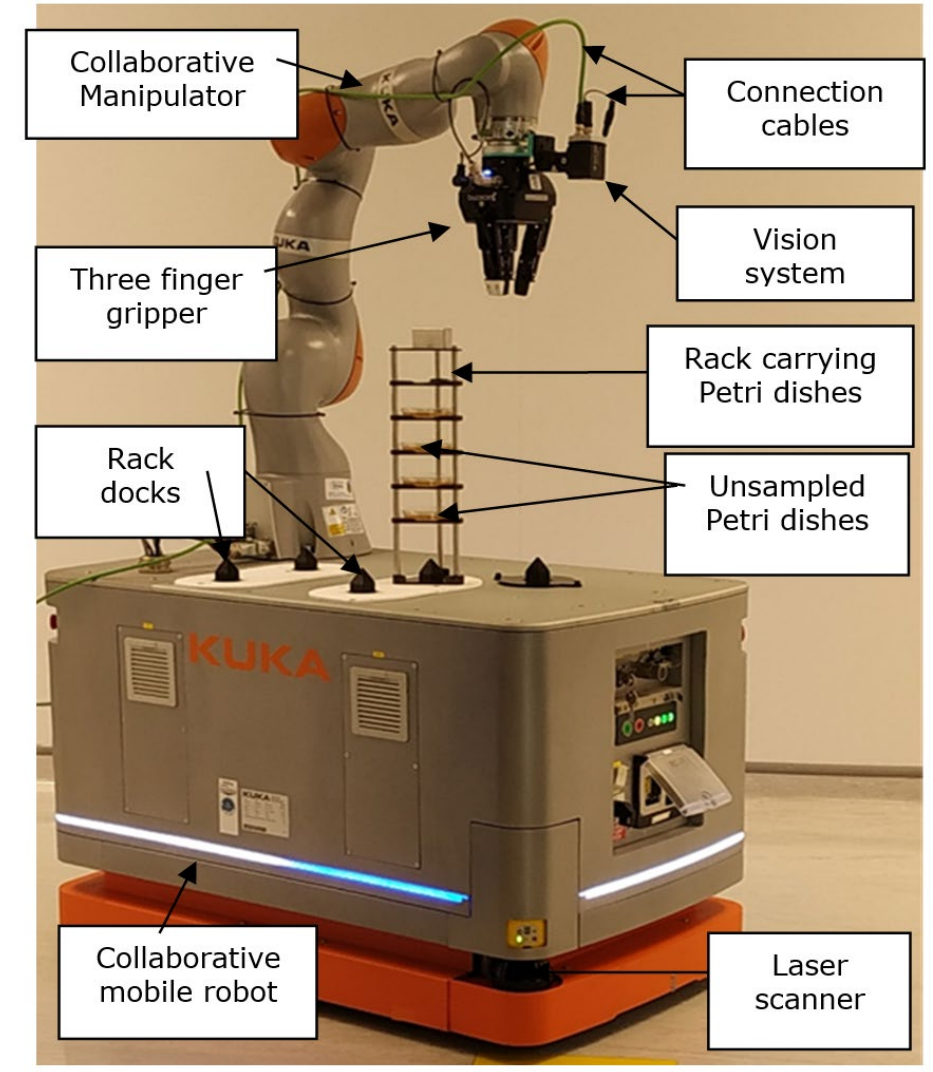




Process

- ✓ Sampling route identified and mapped
- ✓ Sampling method identified – settle plates
- ✓ Robotic arm and sampling rack designed
- ✓ Platform interfaced with Lonza's EM software solution - MODA™ platform
- ✓ Barcode scanner setup
- ✓ Series of robotic applications developed
- ✓ Settle plate samples were taken by robot and by operator (for comparison).

Full application was designed, developed and tested by UCD – LAMS (Laboratory for Advanced Manufacturing Simulation and Robotics)

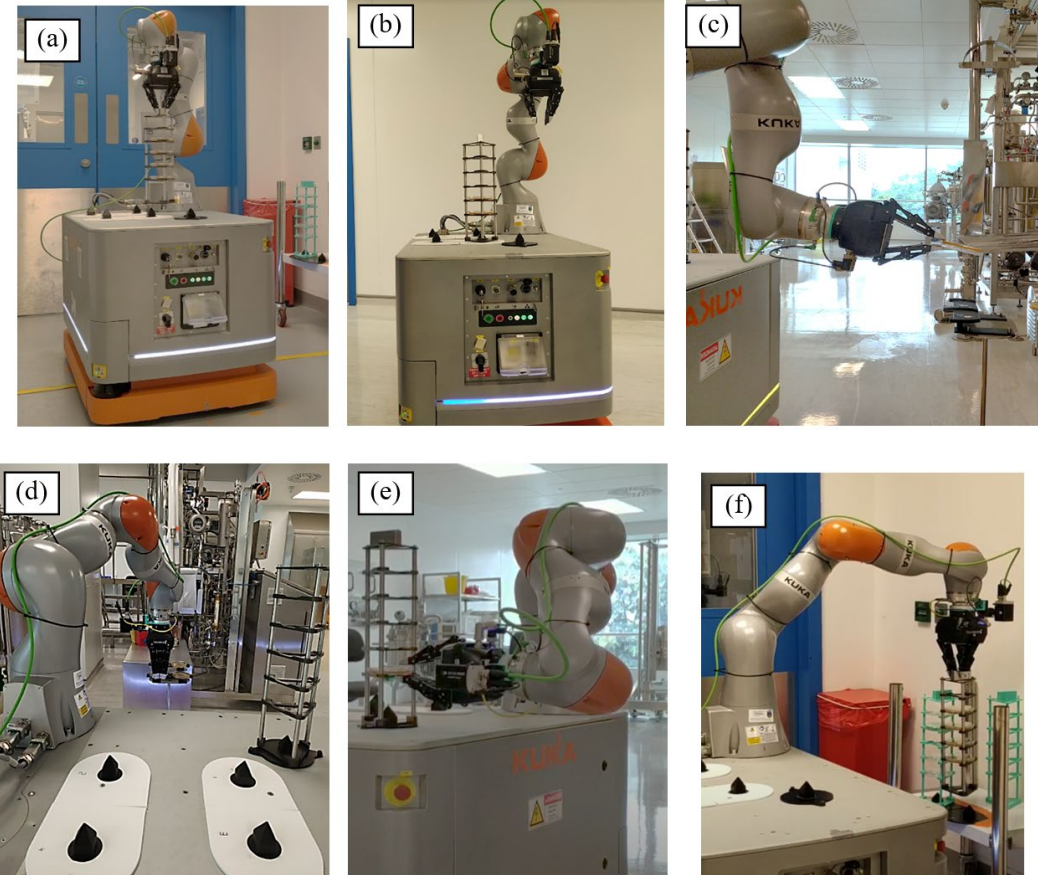




Sampling Route



Map showing the sampling locations and the planned path



(a) Collecting rack carrying unsampled petri dishes (b) Transport of unsampled dishes to sampling location (c) Placing the dish in Location (d) Collecting petri dish after sampling (e) Placing sampled petri dish onto rack (f) Returning rack containing the sampled petri dish to MAL.



Project Outcomes



<https://www.youtube.com/watch?v=6biPKTZJR1Y>



Where Does This Fit in with Annex I?



1 Scope

The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing systems and closed systems). This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

Table 2: Maximum permitted microbial contamination level during qualification

Grade	Air sample CFU/m ³	Settle plates (diameter 90 mm) CFU/4 hours ^(a)	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

3 Pharmaceutical Quality System (POS)

- iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.

9 Environmental & process monitoring

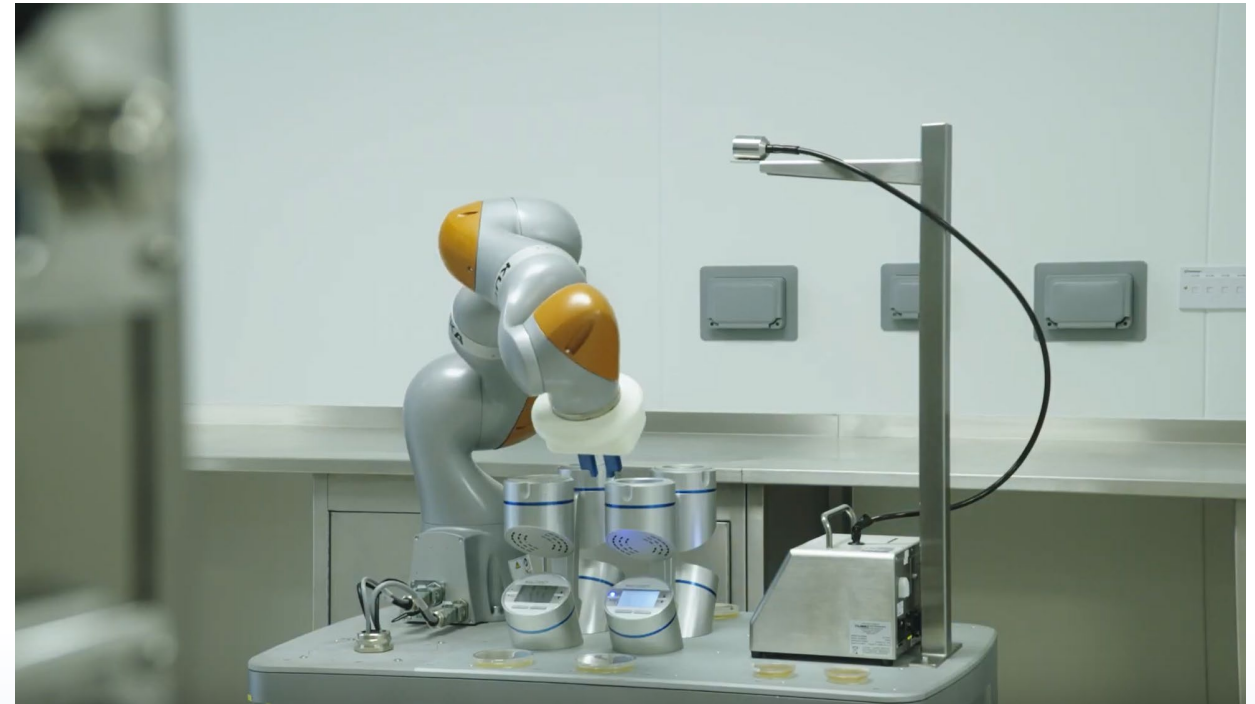
9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.

9.8 Sampling methods should not pose a risk of contamination to the manufacturing operations.



Summary

- ✓ Successful project.
- ✓ Confirmed that repetitive tasks such as EM have the potential to be automated.
- ✓ Use of robots can be utilised as part of company CCS.





Further Reading

Introducing Mobile Collaborative Robots into Bioprocessing Environments: Personalised Drug Manufacturing and Environmental Monitoring

by  Robins Mathew ¹,  Robert McGee ¹,  Kevin Roche ¹ ,  Shada Warreth ² and  Nikolaos Papakostas ^{1,*}  

¹ Laboratory for Advanced Manufacturing Simulation and Robotics (LAMS), School of Mechanical and Materials Engineering, University College Dublin, D04 V1W8 Dublin, Ireland

² National Institute for Bioprocessing Research and Training, A94 X099 Dublin, Ireland

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Thank you



Contact: shada.warreth@nibr.ie

Excursions in non-aseptic areas
and the importance of a CCS



Annex 1

Overcoming challenges in Implementation

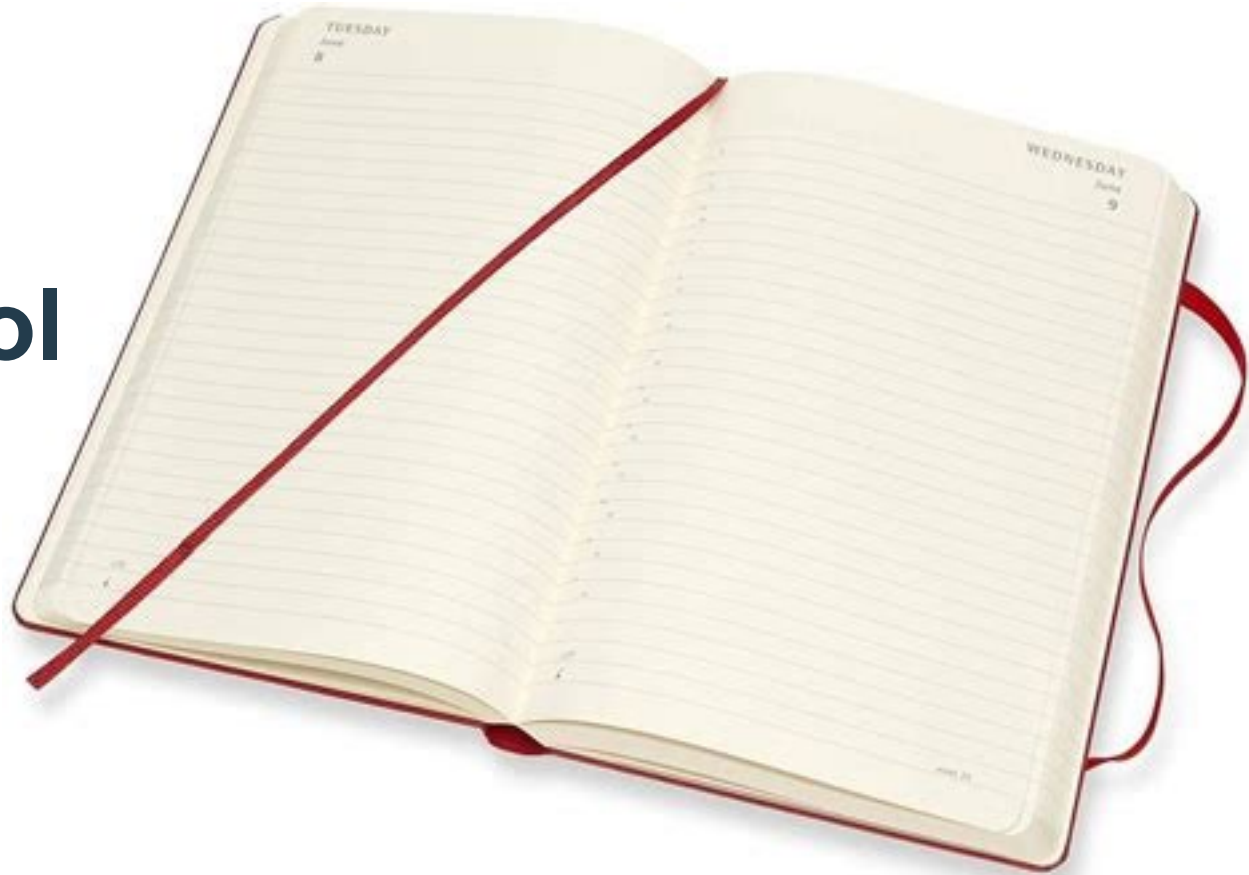
Dublin- 11 November 2022

Patrick Nieuwenhuizen
Director / Senior Consultant



● Agenda

- ▶ **Annex 1**
- ▶ **Contamination Control**
- ▶ **A business case**
- ▶ **Recap**



Annex 1 Scope



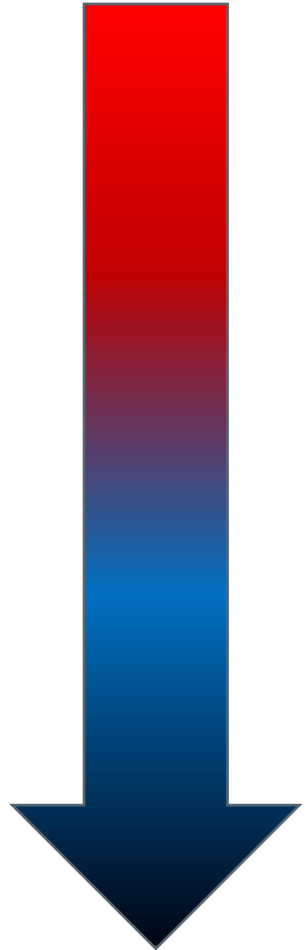
The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a

to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product

● CCS elements to include (but not limited to.....)

➤ Section 2.4 summarizes 15 elements to consider at a minimum

1. Design of both plant and processes
2. Premises and equipment
3. Personnel
4. Utilities
5. Raw material control – including in-process controls
6. Product containers and closures
7. Vendor approval, such as key component suppliers
8. Outsourced activities, such as sterilization
9. Process risk assessment
10. Process validation
11. Preventive maintenance
12. Cleaning and disinfection
13. Monitoring systems
14. Prevention – trending, investigation, CAPA
15. Continuous improvement based on the information derived from above



End-to-End Evaluation

Understand the importance of contamination control

It is the sum of all aspects

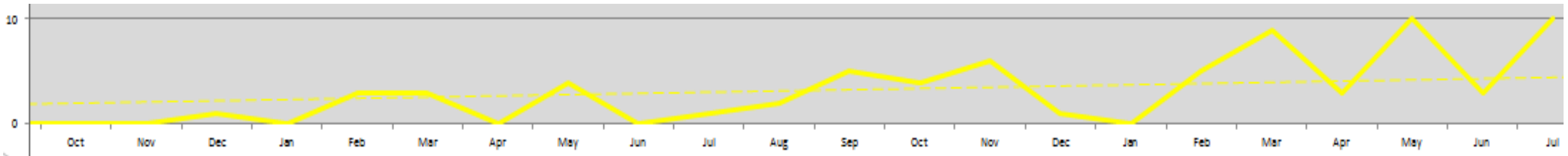




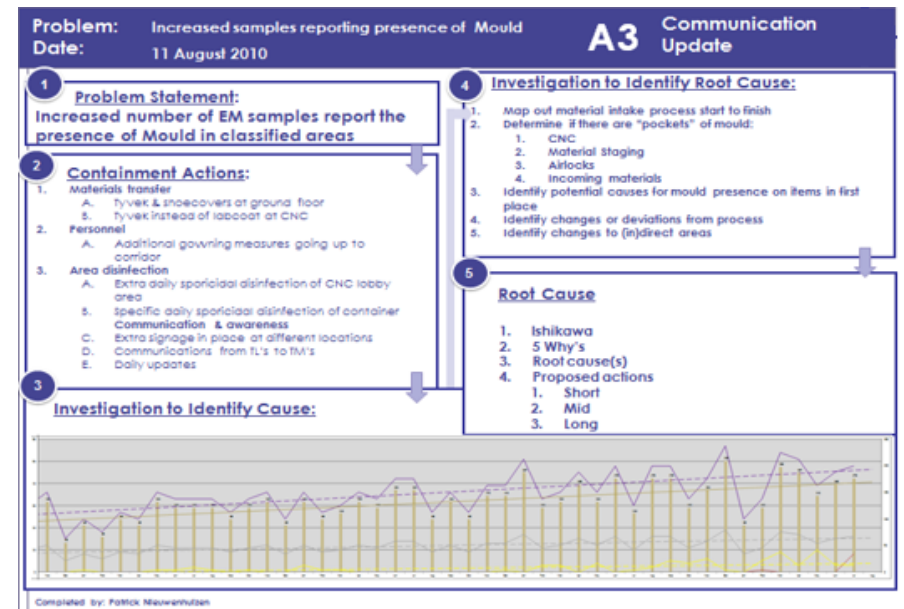
A case study

A case study

Increased levels of mould detected in non-aseptic areas of a pharmaceutical facility

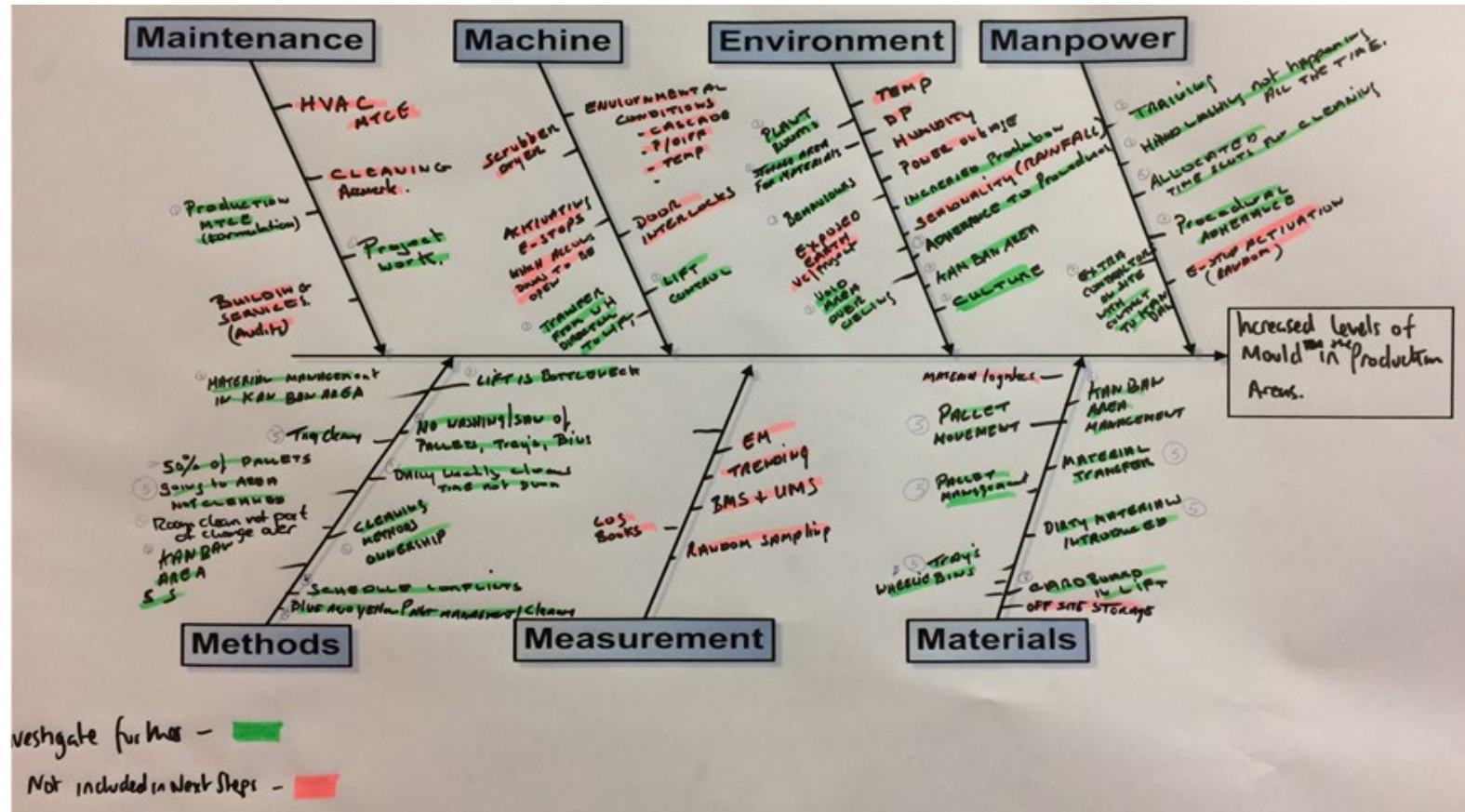


- Investigation team – members only
- Define what the issue is
 - Equally important, what is it not!
- Communication is key
 - Structure

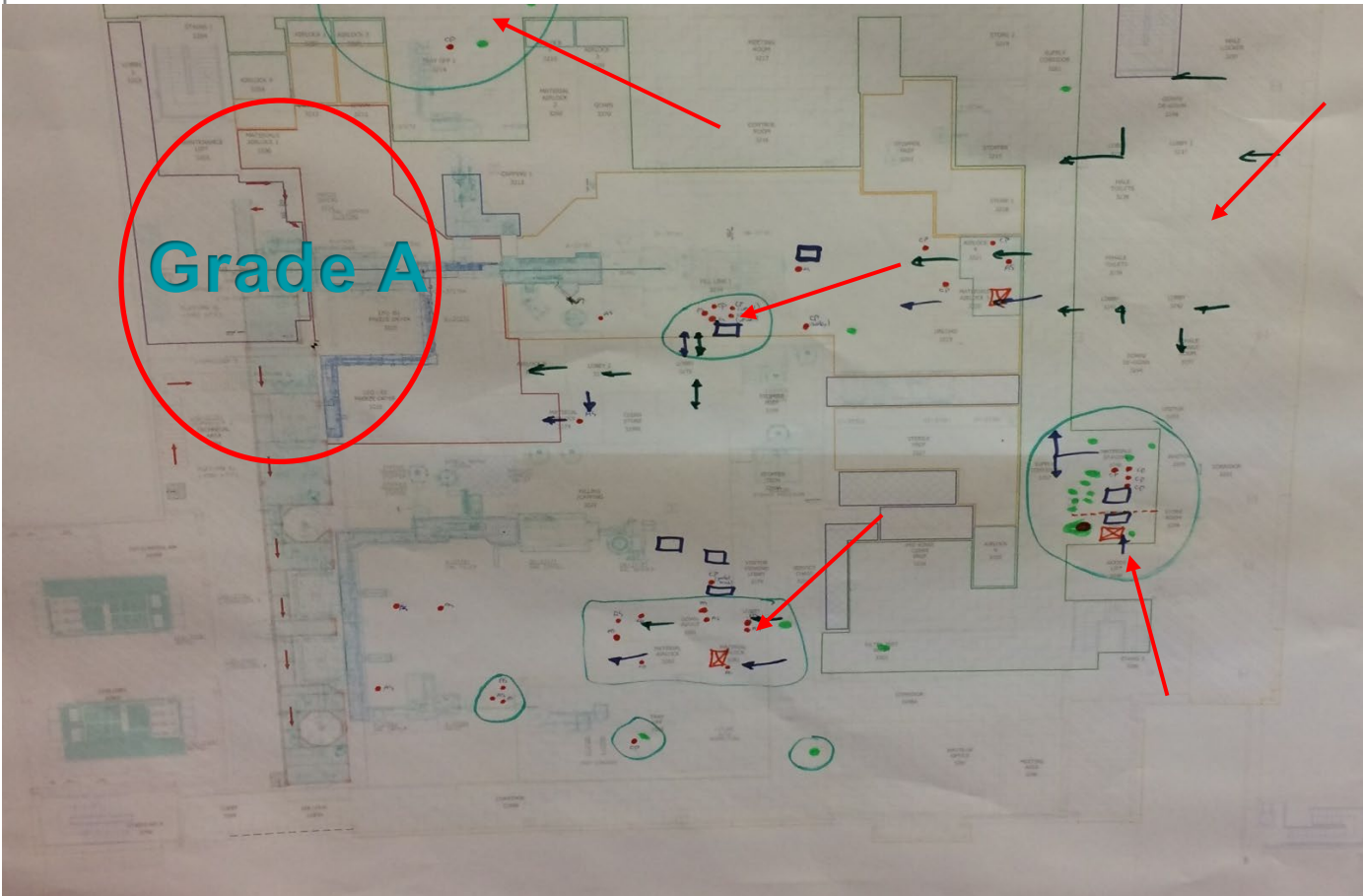
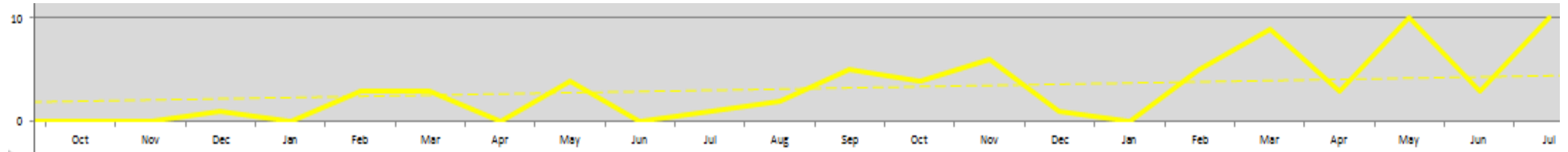


Investigate

- Brain dump
 - ❑ Everybody has their say
- Use CCS categories
- Rule in / out
 - ❑ Support with data



Where do we see the issue

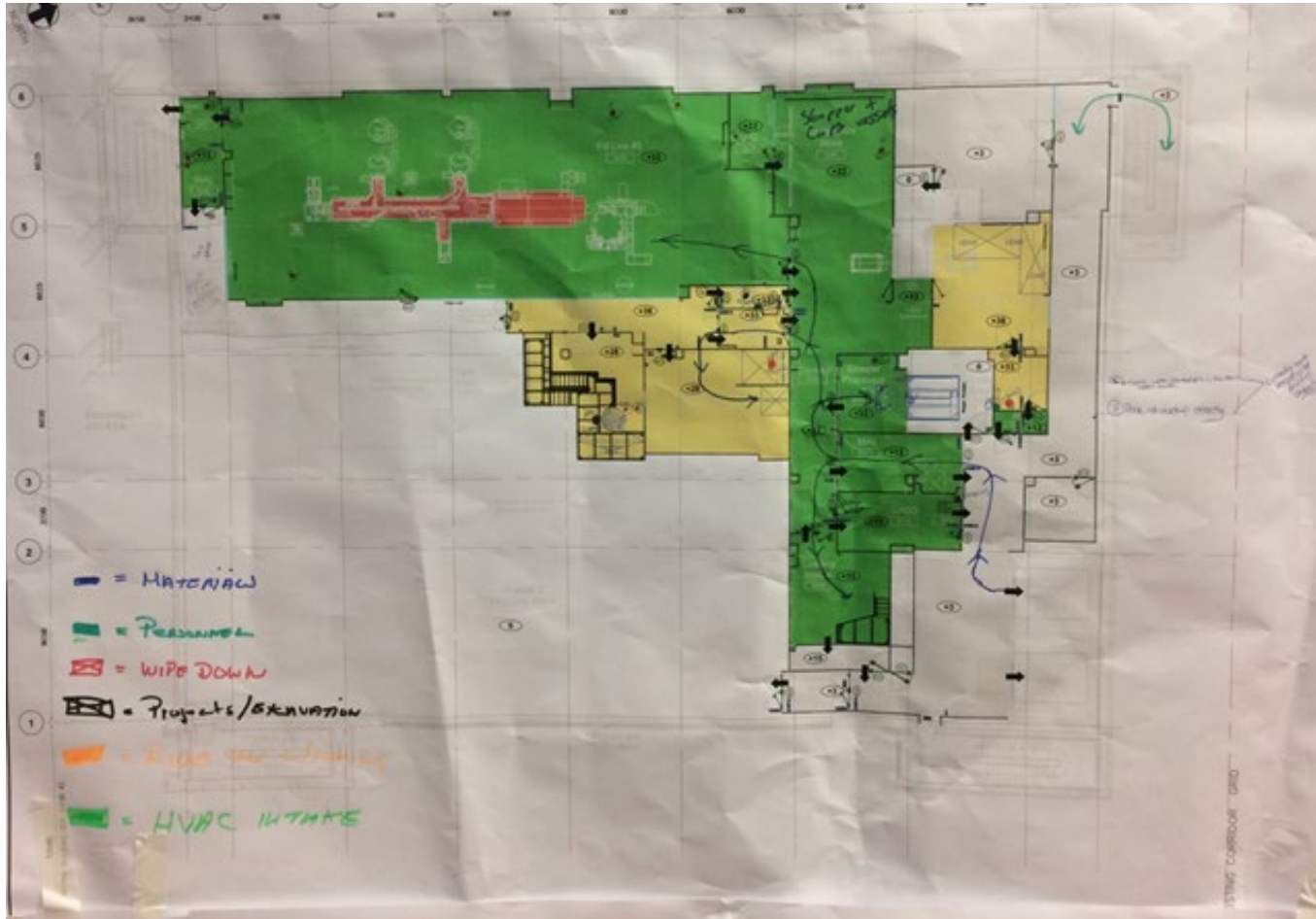


- Grade C general prep air & surface
- Grade C/D airlock air & surface

Additional Monitoring

- Non-classified staging (CNC)
- Non-classified material intake (CNC)
- Non-classified Gowning Areas

What is the current process?



Contamination Control Strategy

- HVAC
 - ΔP / Filters / RH% / °C
- Personnel flows
- Material flows
 - Material intake
- Cleaning & Disinfection Program

● Activities?

What has changed?

- Documents, including previous revisions
 - ❑ Something changed without Change Control?
- Production activities
 - ❑ Standard activities, increase in production, campaigning etc.
- Interview people

What is actually happening?

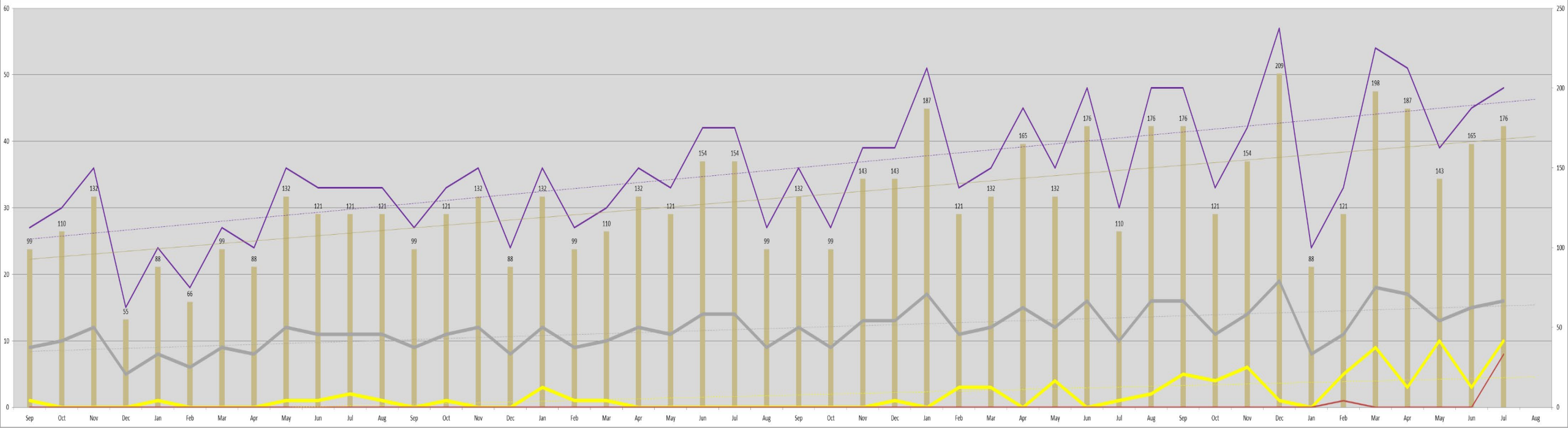


A picture says more than a thousand words

Factual data

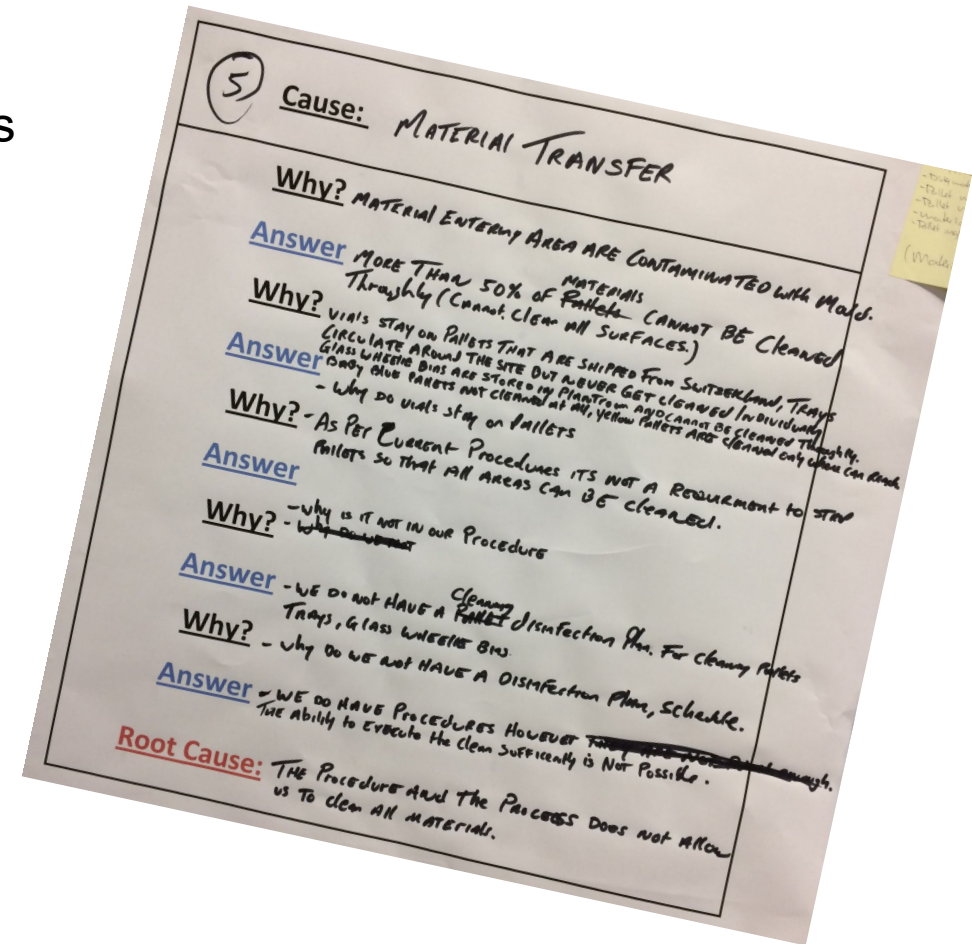
➤ Try to quantify and make visual

- Number occurrences
- Number of personnel
- Number of batches
-



Categorise

- Make buckets of most probable causes
 - ❑ Why could these happen – Data!
 - ❑ Where do these fit in the CCS
 - Use Ishikawa diagram & CCS categories
- Gaps in CCS?
 - ❑ Remediation actions!



Outcome

➤ All materials disinfected in with sporicide & IPA

- Except for “bulk” materials from warehouse

➤ Pallet management

- Procedures ambiguous
- Different practices



➤ Increase in production activities

- Number of batches manufactured doubled
- “standard items” to be moved in the area increased as a result
- Increased presence of personnel



➤ Cross contamination during gowning stages



● Often not a single root cause

- Direct contributing factors
 - Material intake
 - Gowning procedure & process
 - Disinfection regime

- Indirect contributing factors
 - Procedures unclear and ambiguous

DIRECT

INDIRECT

Sum of all

Action plan communication & buy in

- Short – Medium – Long Term Actions
- Where will it lead to
- Timelines / costs / support
- What if we don't do XYZ
 - Scientific evidence from investigation

ACTION PLAN



**If an action plan is not accepted,
people indirectly accept the issue being there**

● A year later.....



- Not all actions proposed implemented

- Budget
- Personnel
- Time
- Ownership



- Similar issue re-appeared with one difference

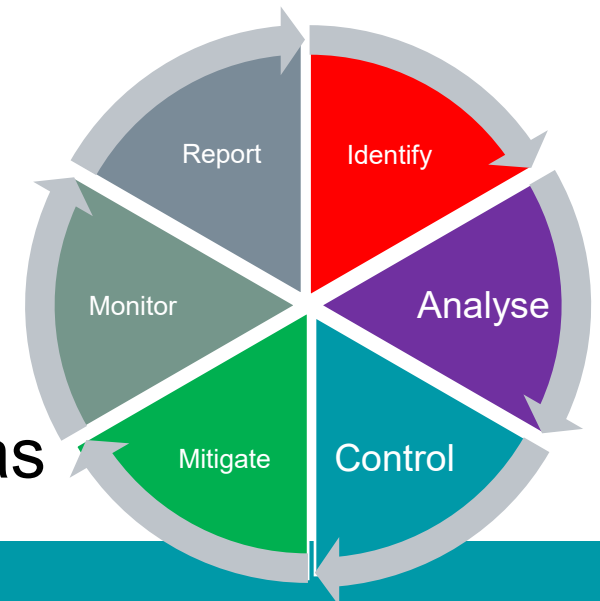
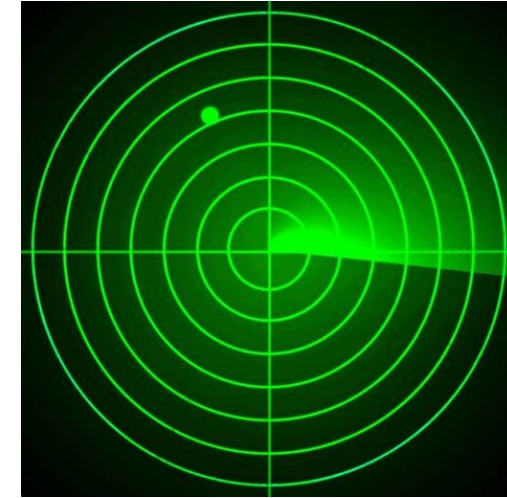
! Ingress to Grade A – batch impact !

- CCS information & data from investigation extrapolated
 - All actions agreed and implemented
- Overall mold levels decreased
- No presence of mould in Grade A/B



Recap - Contamination Control Strategy

- Major Deviations
- Change Controls
 - Changes to the Manufacturing Process
- Periodically
 - Some “small changes” can accumulate to a bigger risk
 - Same applies to minor deviations
- Update controls
 - Action
 - Ownership
- Monitor effectiveness – also in non-aseptic areas





Thank You...!!!

© PharmaLex

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Visual Inspection and Container Closure Integrity

Corey Bishop, Amgen Ireland



Visual inspection: WORDING IN 2008 version

124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

- Inspect every container
- Controlled illumination
- Regular eye checks
- AVI/SAVI should be validated
- Performance of AVI checked regularly
- Record VI results

EUDRALEX UPDATED WORDING IN ANNEX 1 2022

8.30 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on routine and trend data), should be investigated. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently should trigger an investigation as it indicates a possible failure of the original inspection process.

Understand Criticality of known defects prior to commercialisation

Require batch defect limits

Require a defect library

Perform an AQL

8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, should be taken from inspection.

MVI engineering controls

Inspectors must be qualified

Eye breaks/distractions

EUDRALEX UPDATED WORDING IN ANNEX 1 2022

8.32 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.

- AVI should detect known critical defects.
- Be better or equal to MVI
- Pre use required

8.33 Results of the inspection should be recorded and defect types and numbers trended. Reject levels for the various defect types should also be trended based on statistical principles. Impact to product on the market should be assessed as part of the investigation when adverse trends are observed.

Trending

Defect criticality

PDA TR#43

- *Critical*: A Nonconformity that is likely to result in personal injury or potential hazard to the patient. This classification includes any nonconformity that compromises the integrity of the container, and risks microbiological contamination of a sterile product.
- *Major A*: A Nonconformity leading to serious impairments, for example, a malfunction that makes the packaging unusable.
- *Major B*: A Nonconformity leading to impairments of a lesser degree, for example, reduced efficiency in production.
- *Minor*: A Nonconformity that does not impact product quality or process capability.
- *N/A*: An imperfection classification that is less than the size, magnitude and impact of a nonconformity is considered not applicable. Therefore an imperfection that is considered to be non-applicable is acceptable.
- *Limit Sample*: An actual physical unit that is agreed to between the drug manufacturer and the glass manufacturer that defines the approximate maximum degree of acceptability for a specified non-conformance. Creation of limit samples between the user and the manufacturer is optional.

- PDA TR#43 gives a good starting point for what critical/major/minor means. TR#43 can be a starting point for typical glass related defects and all other known defects can be assigned with criticality based on a risk assessment. TR#76 can also be used for classification of defects in elastomers and the seal area.
- The defined criticalities for each defect can be included in the defect library.

Defect Library

PDA TR#43

Chip

Location: General

Class: Critical if seal integrity is compromised; Major A if seal integrity is intact; Major B otherwise



Container with a small section or fragment of glass broken out or missing.

PDA Glass Task Force
Tubular Glass Vial Lexicon

18

- PDA TR#43 gives a good template for a defect library as a starting point.
- Engineering runs and WFI batches can be used to understand typical inherent defects for inclusion.
- Library can contain examples of each defect with clear written descriptions and criticality.
- Initial training of personnel should be carried out with a defect library, in some cases examples of non-defective images considered to reduce levels of false rejects.
- Regular updates to the library when applicable to contain new information on current defects or new defects.

Batch Defect limits

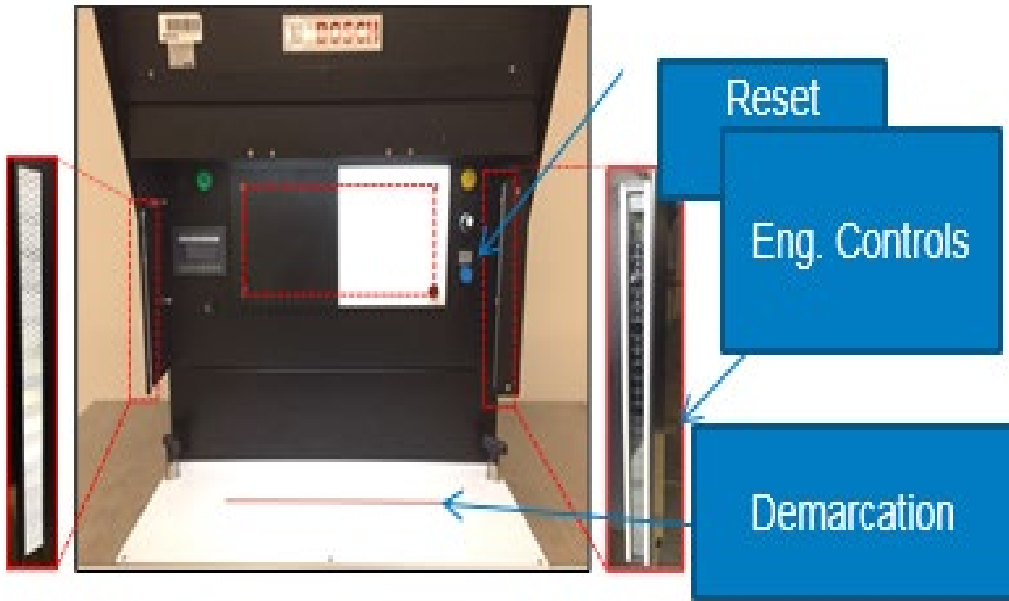
- Limits are applied to defect categories to highlight atypical lots to investigate, these limits are usually based on historical data to understand the normal defect rates.
- USP 1790 gives an option to apply limits to criticality groupings: critical, major, minor and particles or by component groupings vial body, stopper, seal, solution and particles.
- Defects can be classified at the point of inspection or offline post batch inspection by trained personnel using defect manuals / aids for consistency in results.
- Limits can be reviewed periodically to ensure defects rates are evaluated against a true representation of the process.

AQL Sampling

Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers.

- The above wording can be interpreted as performing an AQL sampling on each batch.
- AQL can be performed using a statistical sample size and sampling from the beginning, middle and end of each batch
- Were a two stage inspection process is used for inspecting lots, sampling is taken from the accepted AVI and MVI portions.
- Ideally Quality personnel perform the AQL on each batch.

Inspector Qualification & Process Controls



- Before training it is recommended as per USP1790 operators be tested for visual acuity and colour perception.
- Training may include phased approach i.e training on defect library and videos first followed by hands on training for the method with subject matter experts.
- Sufficient time must be allowed to inspect each container with larger more complex containers given more time.
- The time spent on each container can be controlled using a pacing device / timer to aid operators.
- Qualification of the inspector may be done under normal operating conditions, three successful inspections of the test set is recommended.

AVI Methods & Qualification



- Panels containing defects used to qualify inspectors are used to qualify automated equipment.
- Non Defective units can also be included to validate the process.
- The equipment can be challenged using a reduced defect set prior to start up to confirm camera position, focus and lighting.
- When moving onto a new batch previous batch challenge can be used in place of another if the product or container size is the same.
- Discussions across industry on the intent of challenging the equipment at regular intervals during a batch and the GMP concerns around this.

inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.

Batch Trending

- Creation of a mastering monitoring plan for each product type.
- Includes the performance parameters to monitor in addition to their control chart type and signalling rules.
- Electronic systems which collect and summarise the batch data can be used for analysing the data.
- If signal or limit excursions occur a deviation or other similar investigational record is opened to investigate the excursion.

CCI IN ANNEX 1 2008

Finishing of sterile products

116. Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.

117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

118. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion.

123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

- Validated closure
- 100% integrity testing for ampoules.
- Test Lyo vials.

New CCI requirements

Finishing of sterile products

8.20 Open primary packaging containers should be maintained under grade A conditions with the appropriate background for the technology as described in paragraph 4.20. For partially stoppered vials or pre-filled syringes (see paragraph 8.126).

8.21 Final containers should be closed by appropriately validated methods.

8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤ 100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.

8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.

8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.

24

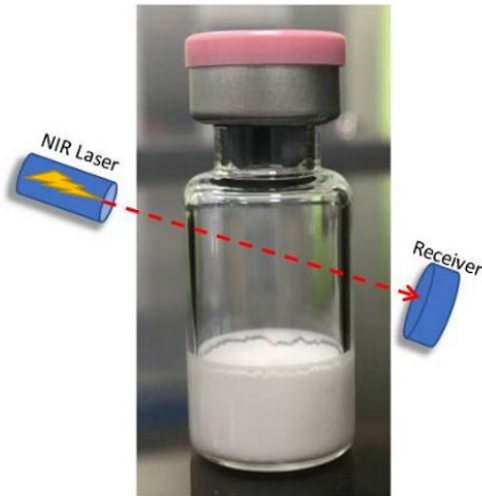
8.25 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).

- New container types included BFS/FFS and large bags, the critical parameters should be monitored.
- 100% testing for Ampoules, BFS and small bags sealed by fusion.
- All other containers require samples taken based on process knowledge of the container closure system.
- VI is not an integrity method.
- Containers sealed under vacuum tested prior to release.
- Transportation testing.

Options For 100% CCI Testing

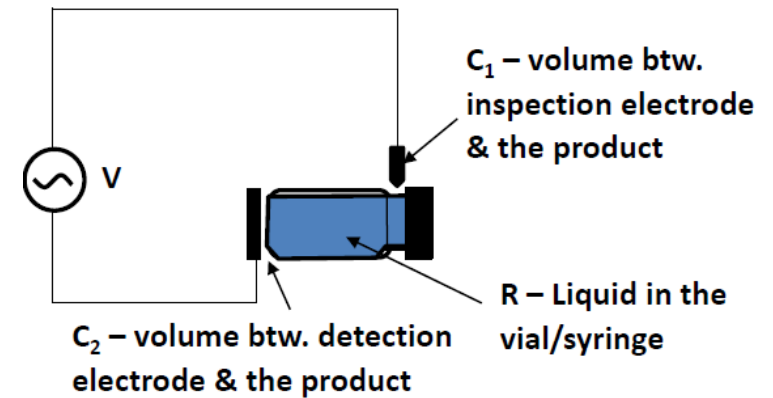
Headspace Gas Analyser (HGA)

- Provides 100% non destructive testing.
- Can be used on both lyo and liquid products.
- Can measure CO₂, O₂ and Vacuum.



High Voltage Leak Detection (HVLD)

- Provides 100% testing.
- Can be used only on liquid products.
- May cause product degradation depending on the product.



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Sterilisation of Indirect Contact Parts

Maria Ginnelly





Brussels, 22.8.2022
C(2022) 5938 final

GUIDELINES

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for
Human and Veterinary Use

What the regulation states:

5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. **Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).**

Where do we start?



A good starting point is to clearly define the what is in/out of scope by applying QRM principals to ensure we meet the requirements.



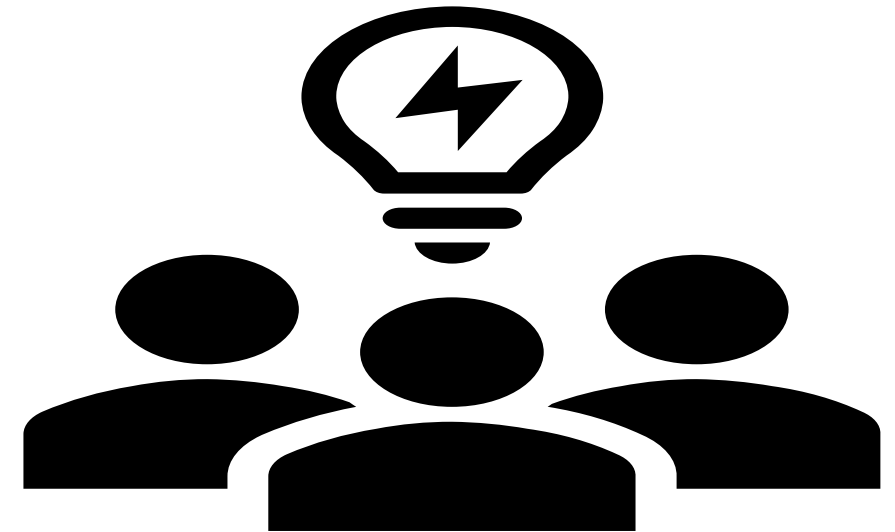
We must consider surfaces that may present a indirect route or transfer of contamination such as:

- Indirect equipment i.e. Stoppering bowl, hopper and track etc.
- Tooling that maybe used post installation of indirect parts:
 - Jigs used to provide repeatability/accuracy of alignment of parts.
 - Forceps/bespoke tooling used for interventions within the Grade A i.e. jammed stopper in tracks.

Identifying risks in the process?



QRA – Cross Functional team with SME’s from across the facility



Things for Consideration:

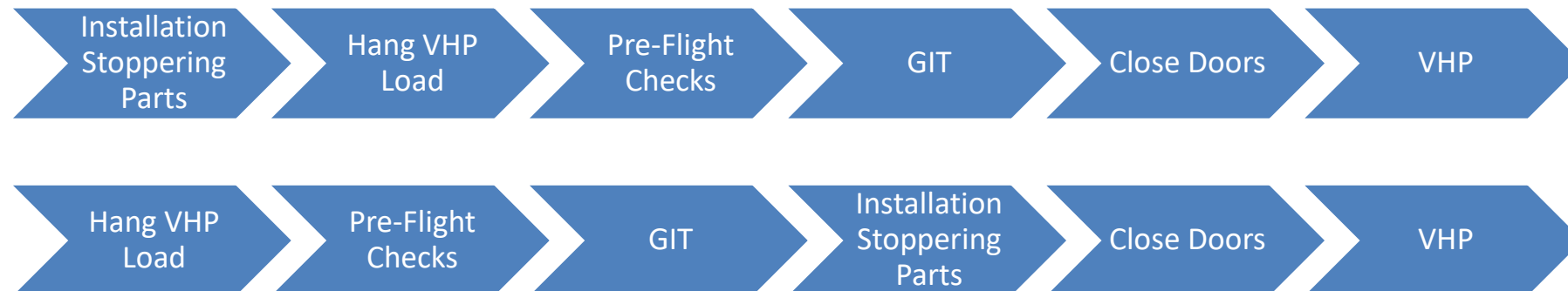
Wrapping and Equipment storage

- **Many types of wrapping available across the industry:**
 - Ready to use/self seal are popular easy to use option, but maybe limited to sizing which may impact larger items.
 - Heat sealing bags are more common for the larger items such as stopper bowls/hoppers. Limiting factors is the use of the equipment when wrapping under LAF if space maybe limited (use of mobile work stations alleviate this issue)
 - Testing will be required to ensure tensile strength (IOQ)
 - How many layers to aid transfer of equipment to final location and provide sterility assurance / integrity
- **How are bagged items stored**
 - Stored single/double wrapped
 - Open/closed trolleys



Process Steps

- Consideration to be given to limit the time indirect parts are exposed pre VHP®/vH2O2.
- Ideally any handling/interaction of parts post installation should be engineered out where possible, and if not, assessment should provide mitigation to ensure indirect parts are not handled in a way to increase bio load pre VHP®/vH2O2.
 - This may result in any tooling/jigs used for alignment of parts also requiring sterilisation if interacting/touch of indirect surfaces post installation.
 - Additional gowning and aseptic technique when handling parts may be preventative aid to prevent increase of bio load.
 - If parts installed by engineering group, upskill maybe required on sterile gowning/aseptic technique
- Hanging of VHP®/vH2O2 load i.e. environmental monitoring plates, tape, wates bags etc. May impede the installation of parts?



Hold times Requirement

Step 8.46 states:

If sterilised items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established.

Is it necessary to qualify a hold time of parts if such parts are opened/exposed during open barrier door installation and parts will be open to contamination exposure (both particle and microbial)?

- **Hold times will be required if some indirect load remains wrapped (smaller items such as forceps/bespoke tooling) for the duration of the VHP[®]/vH2O2. Such hold would be achieved via Aseptic Process simulation trial.**
 - **Benefit to risk on the additional manipulation to remove final wrap in Grade A post VHP[®]/vH2O2 cycle Vs Tooling in contact with stoppers sterilised/exposed to grade A only.**
- **Some papers discuss mitigation steps to avoid excessive handling which may lead to extraneous bioburden. Recommendation is to understand the levels of bioburden resulting from such behaviour or long term exposure.**
 - **Such data/studies maybe useful in the event of a breach of integrity is found on the final layer.**

Installation of parts

Gowning- Process mapping will identify potential risks of bioburden contamination during open door assembly of the isolator. Hoods, masks sterile gloves/gauntlets to reduce any risk.

Environmental monitoring- Monitoring of the surrounding environment maybe required as data to support low bioburden environment during installation.

Handling- Handling of parts should be performed using good aseptic technique ensuring not to touch of indirect product contact surfaces to minimise the risk of bioburden contamination transfer.

If possible, wrapping should be designed for parts to be installed in place without full remove/exposed critical surfaces.

protective wrapping to remain on parts where possible until final closing of the doors.

The isolator HVAC to be active and providing unidirectional airflow during installation of the parts.

Particle Generation- If tooling is required to open final protective layer, ensure tooling does not generate particulates that may pose a risk to the process.

- **Using QRM will identify in scope/out of scope on parts and potential contamination risk in the process.**
- **Consider where parts are held/stored post sterilization as it may have an impact on quantity of required layers (impact to autoclave cycle and integrity of final layer). Storage should be robust and not allow non integral bags to form**
- **Manipulation/Handling will have a potential impact on level of gowning required to prevent bio-contamination prior to VHP[®]/vH2O2 cycle**
- **Removal of final layer from indirect parts should be the final step immediately before closing barrier doors**

Annex 1: Overcoming Challenges in Implementation



Bernadette is Director at Quartz Quality, providing Consultancy support to the Pharmaceutical and Biopharmaceutical industries.

Bernadette is an experienced Quality Executive with over 25 years' experience in the Pharma and Biopharma industry across biologics manufacturing, aseptic filling, oral dose and inhalation platforms, working with both clinical and commercial products. She has extensive experience in hosting and remediating regulatory inspections with HPRA, US FDA and other worldwide agencies. With expertise in Quality Systems and Operational Quality, she has proven capability in Product Life Cycle Management and Quality Risk Management.



**Bernadette
O'Brien**



Contamination Control Strategy Preparation and Pitfalls

PDA Annex 1
Overcoming Challenges and Implementation

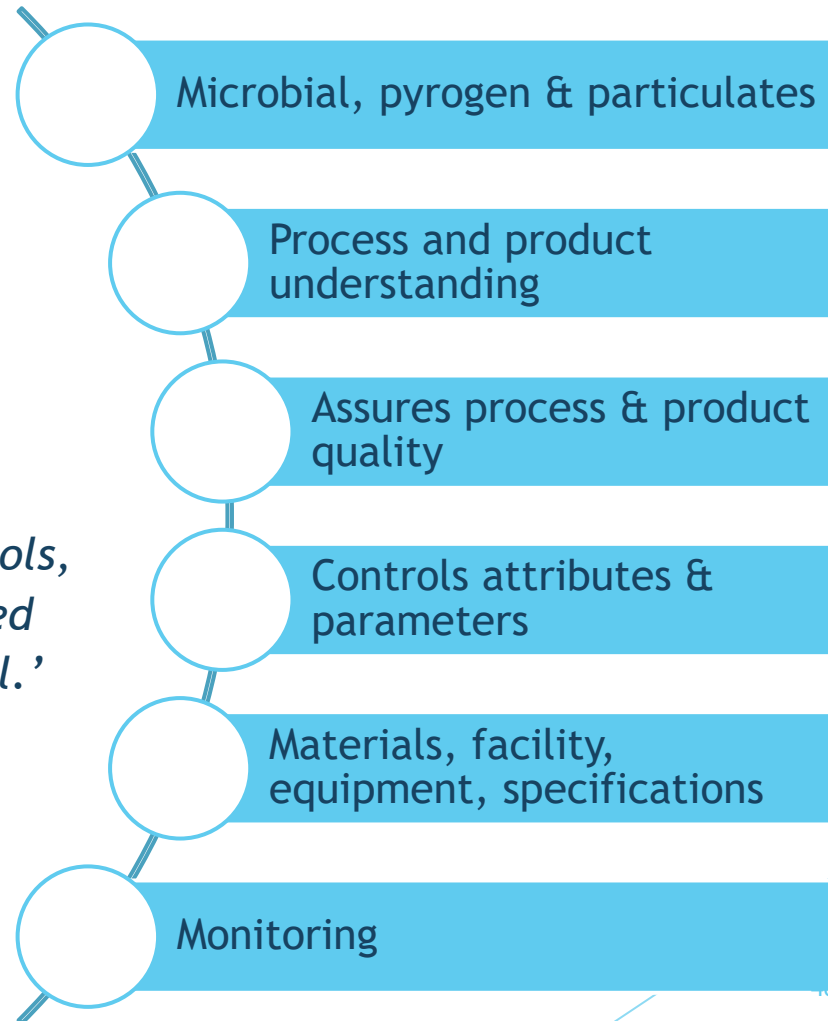
11th November 2022



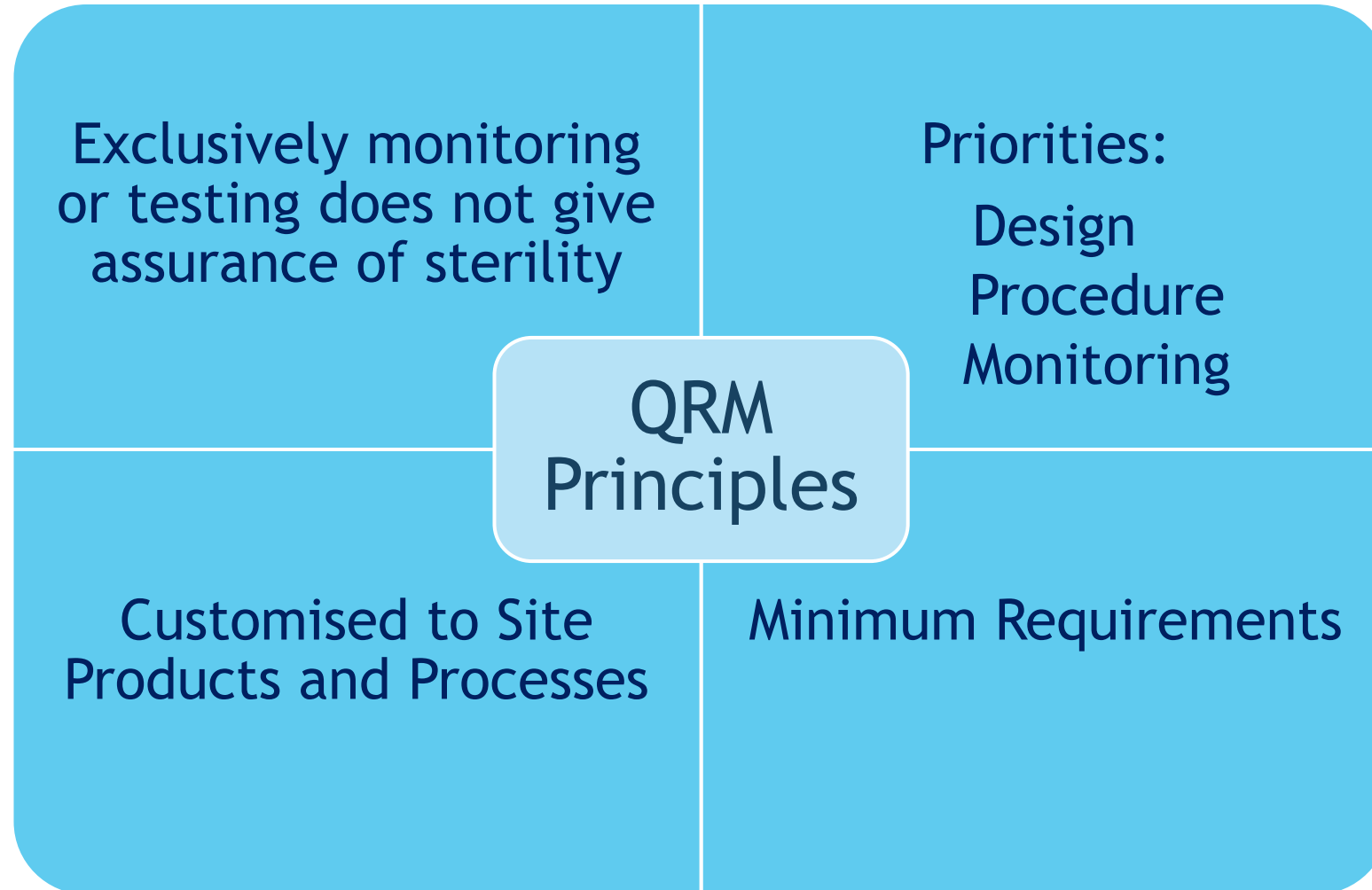
Contamination Control Strategy

‘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.’

Annex 1



Principles



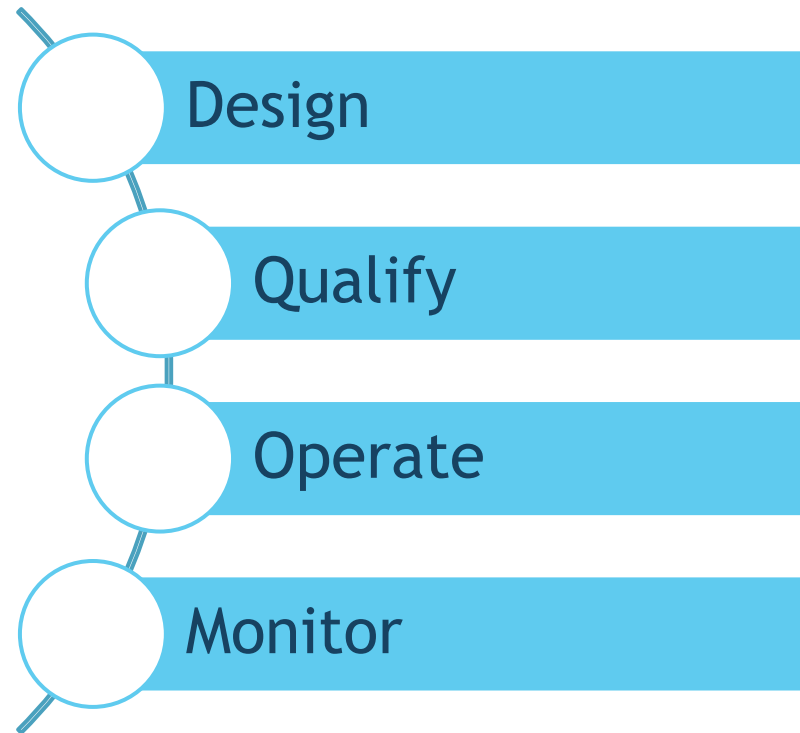
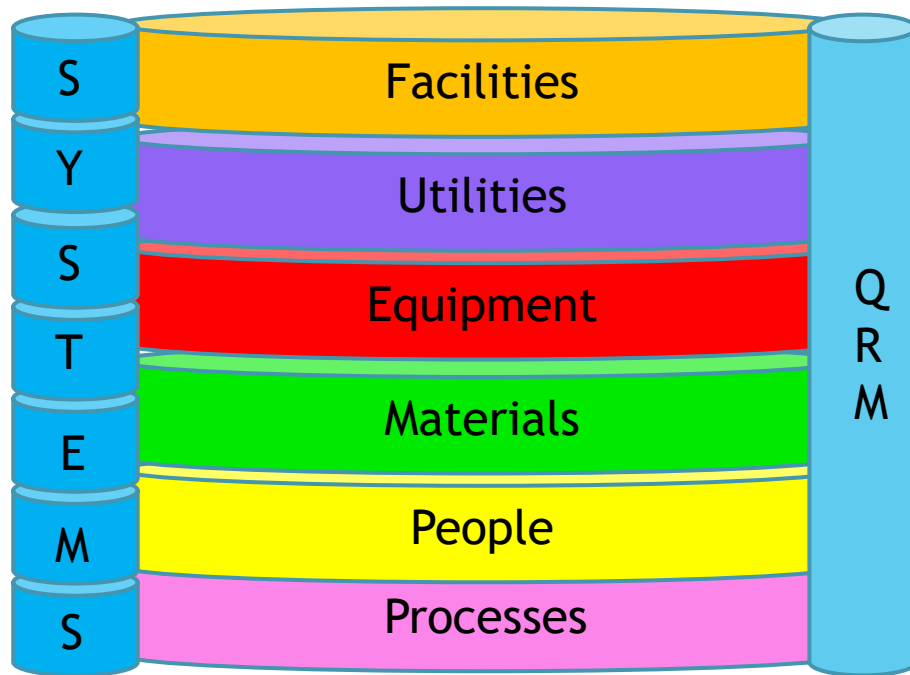
Provide the Strategy

Annex 1 Compliance
Robust
Contamination
Controls

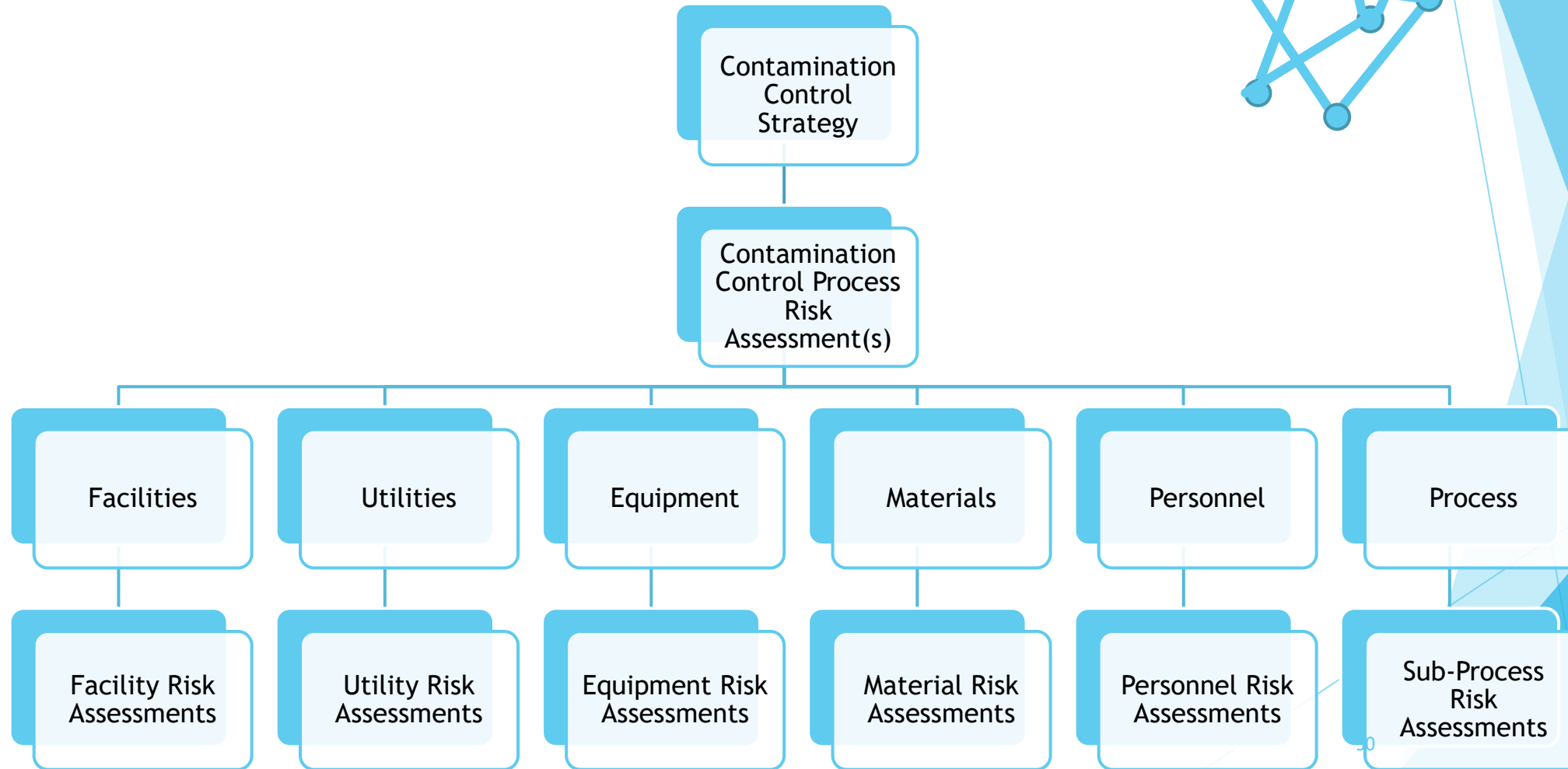
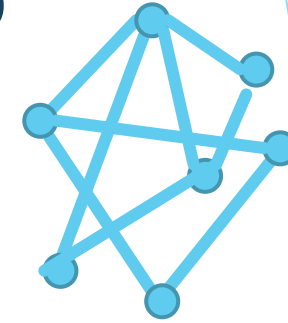
We are
here



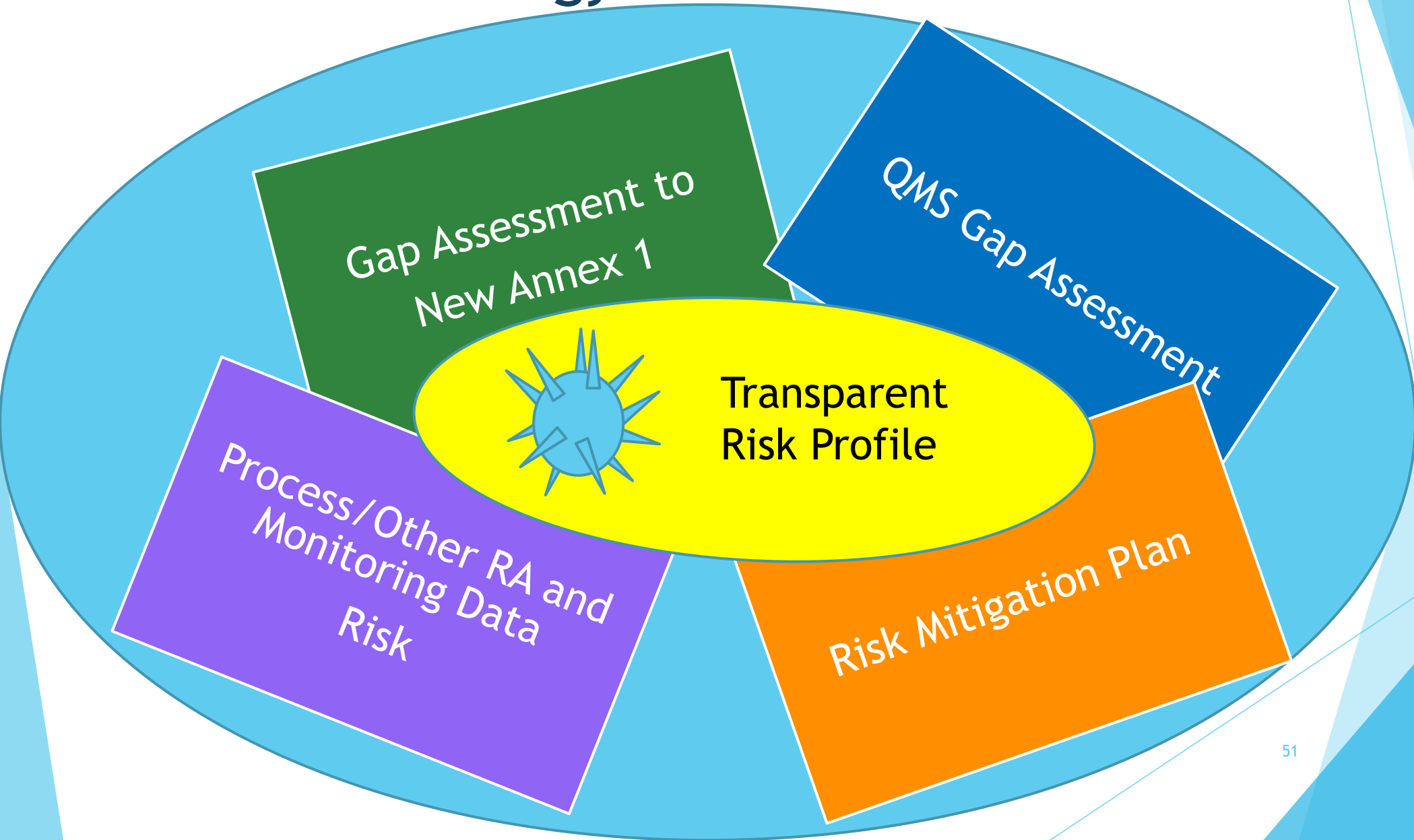
Scope



Contamination Control Strategy Map



Risk Based Strategy



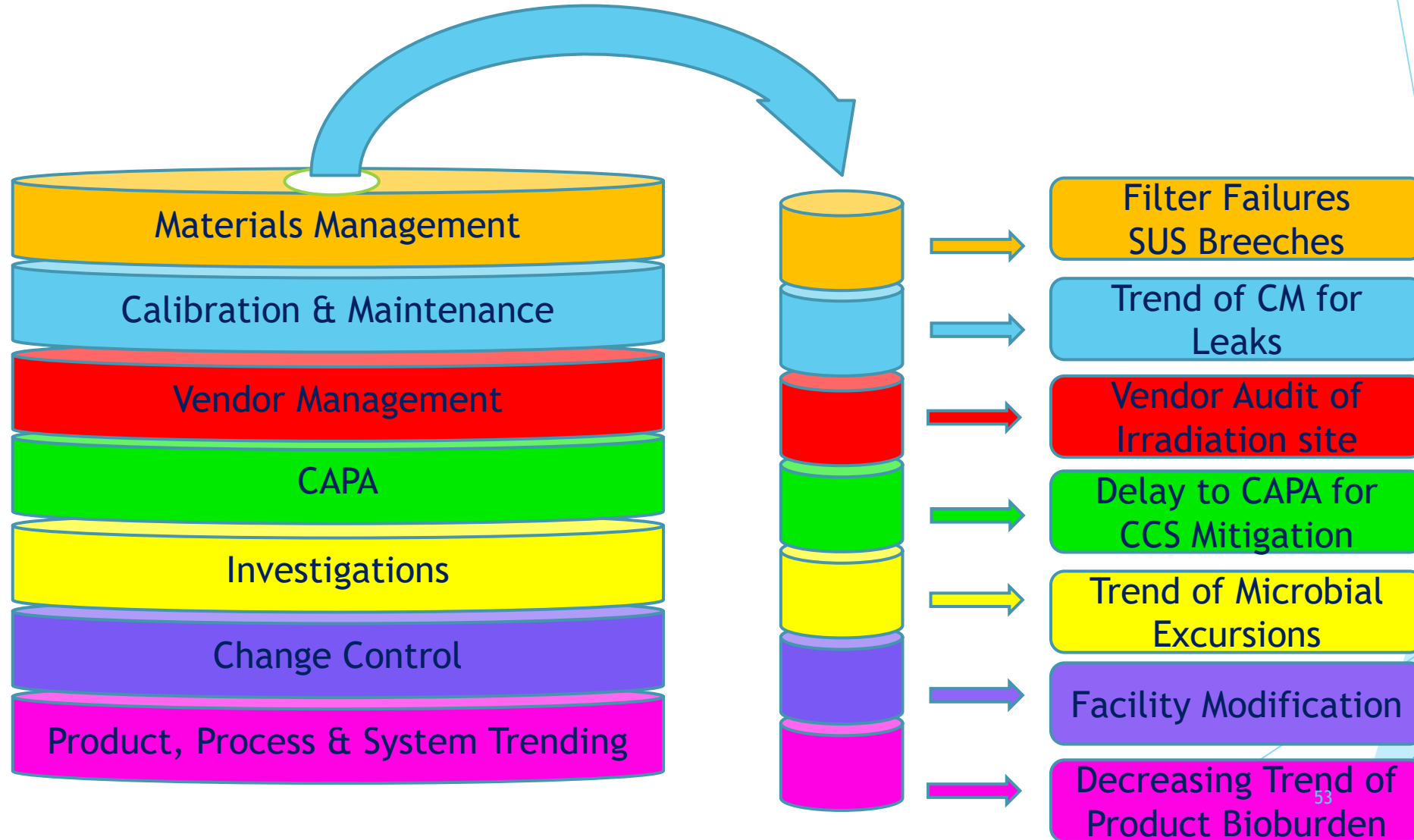
Its an Evolution



-  Emerging Trend
-  Process Change
-  CAPA Closure
-  Investigation Learnings



Contamination Control Quality Governance



CCS Document Pitfalls

Striving for
Perfection

Lack of
Transparent
Risk Profile

No Mitigation/
Improvement
Actions

Off the Shelf
Approach

Generic
System
References

Not revised to
reflect
changes



CCS Pitfalls

Excessive Use of
FMEA

Inappropriate
Risk Ratings

Duplicate of
Contradictory
RAs

Mitigations not
Tracked in QMS

Ageing Sites not
keeping pace
with Technology

Absence of
Contamination
Focussed
Governance



In Summary

