MINISTRY OF INDUSTRY AND TRADE OF RUSSIA

GMP

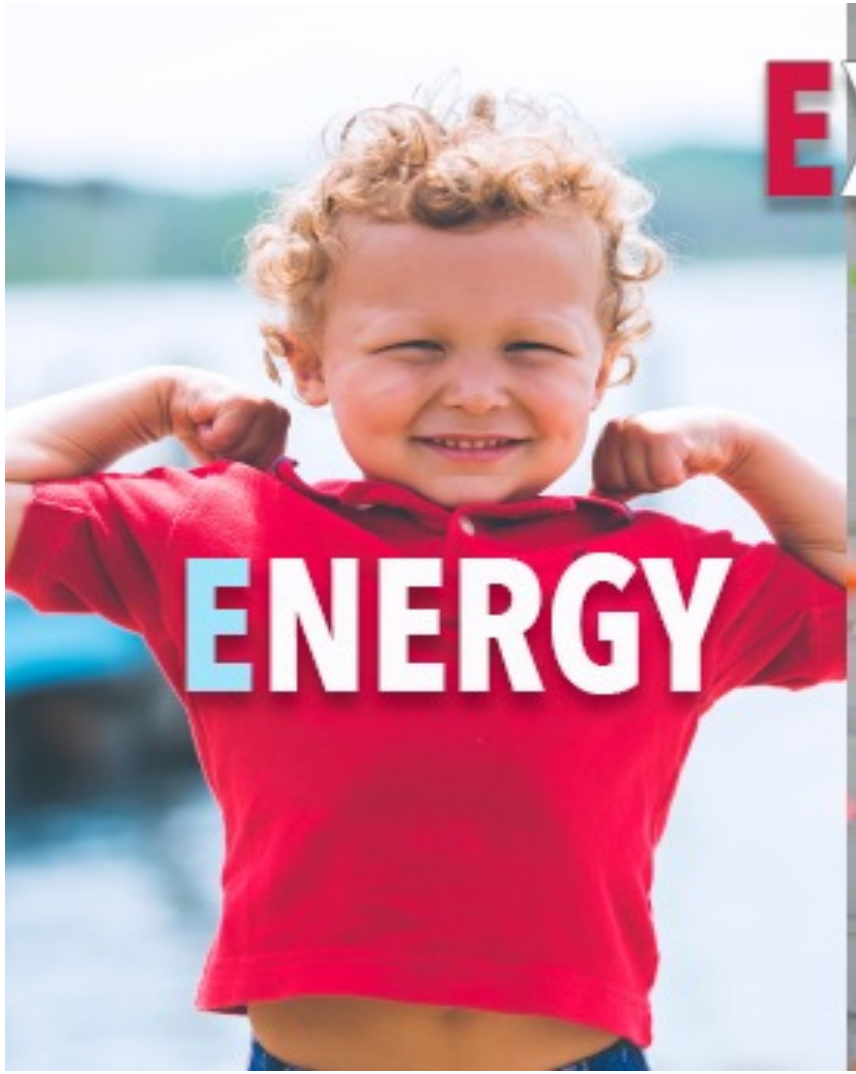
10th PAN-RUSSIAN GMP CONFERENCE

CCS- KEY POINTS FOR THE INSPECTOR TO CONSIDER

WAYNE MÜLLER
CHAIR OF GMP TC AMA
CHIEF INSPECTOR SAHPRA

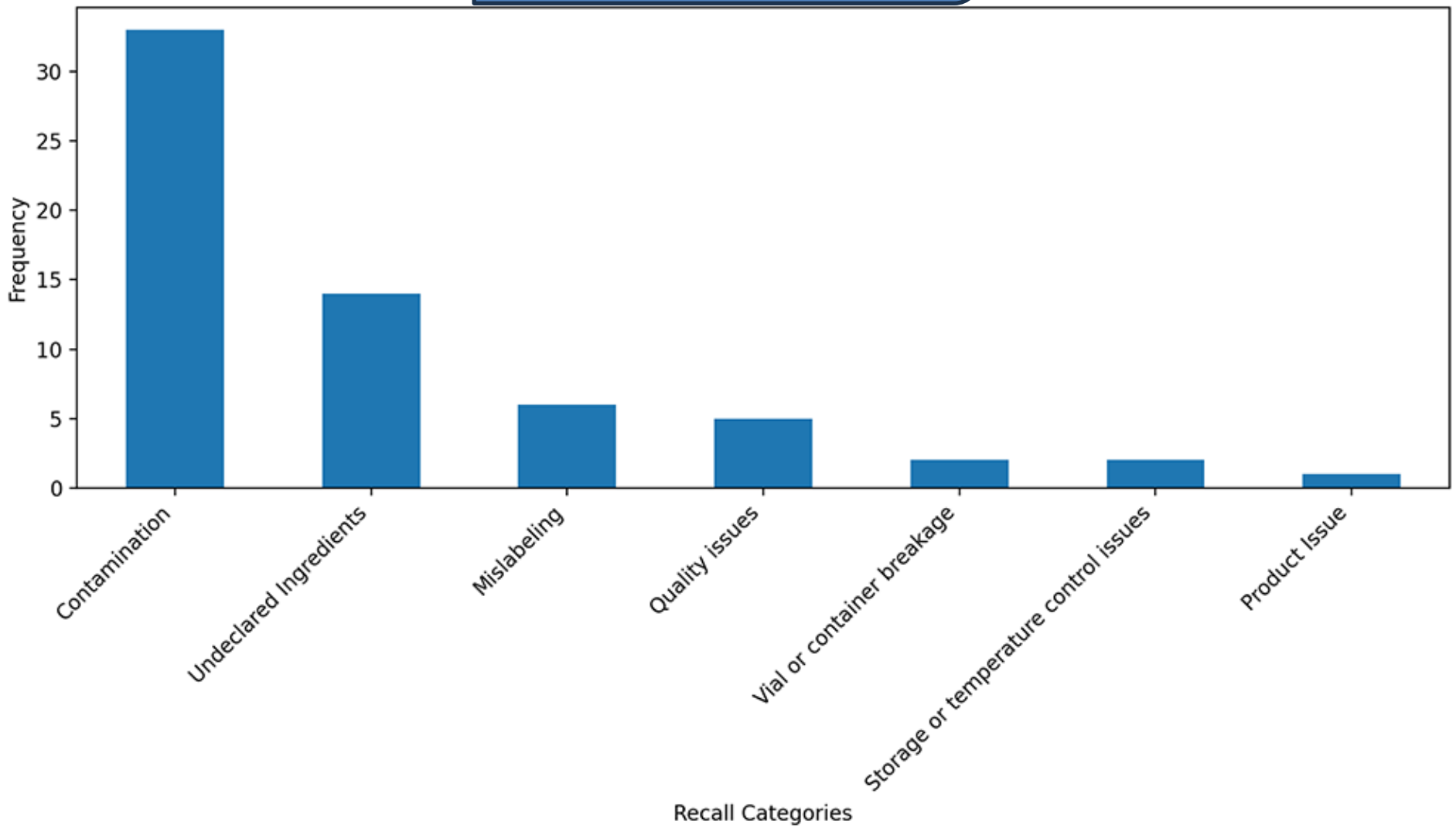
- ✓ PLEASE ASK - WE ARE HERE TO INTERACT AND HOPEFULLY FIND SOME ASPECTS TO APPLY BACK IN OUR INSPECTORATES
- SO DON'T BE HESITANT AND AFTERWARDS SAY
- ….. WHY DIDN'T I ASK
- ***IT'S YOUR WORKSHOP and we all here to learn and improve our skills***
- ***Interact and Engage (even at breaks)***

3 x E (Energized, Enthused, EXCITED)



WILL THIS BABY GET BETTER IT IS UP TO YOU

Failure of CCS

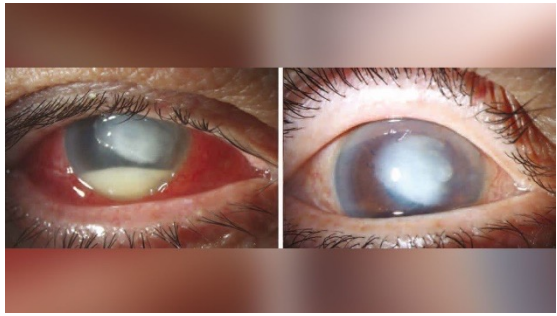


FAILURES OF CCS

A string of deadly incidents connected to contaminated and substandard medicines have emerged in recent months.

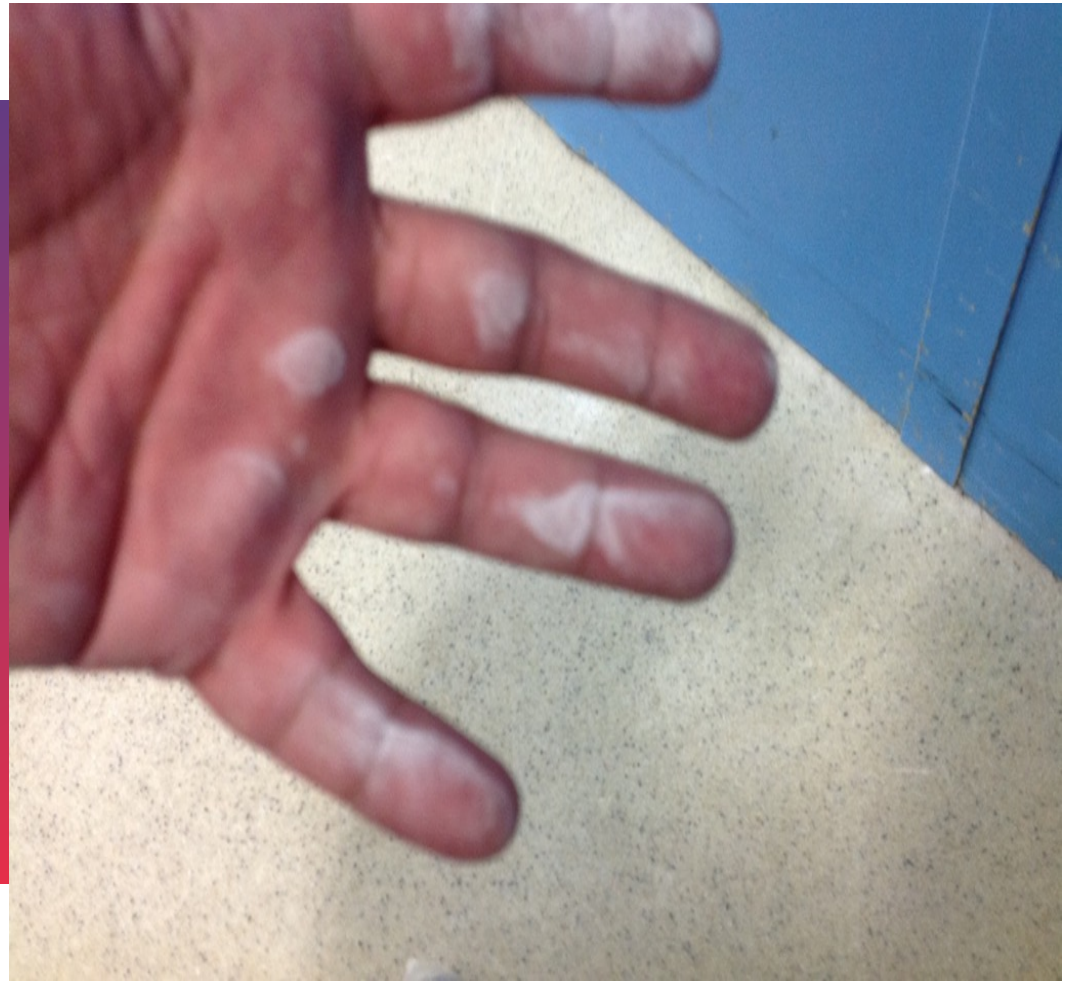
Cough syrups contaminated with ethylene glycol (EG) and diethylene glycol (DEG) have led to deaths of 70 children in The Gambia, more than 200 in Indonesia, and – most recently – 19 in Uzbekistan.

Eye drops were recalled in the U.S. in 2023 and early 2025 due to bacterial and fungal contamination from unsanitary manufacturing conditions, leading to severe infections, vision loss, and even death.



WHAT IS CONTAMINATION

Contamination is defined as the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API (Active Pharmaceutical Ingredient) during production, sampling, packaging or repackaging, storage or transport



GUIDELINES

Annex 1, in sections 2.3 and 2.4, sets out expectations in relation to assessing and assuring the effectiveness of the contamination controls and the monitoring methods that are in place.

- **WHO TRS 1044 annex 2 (Sec 2.3);**

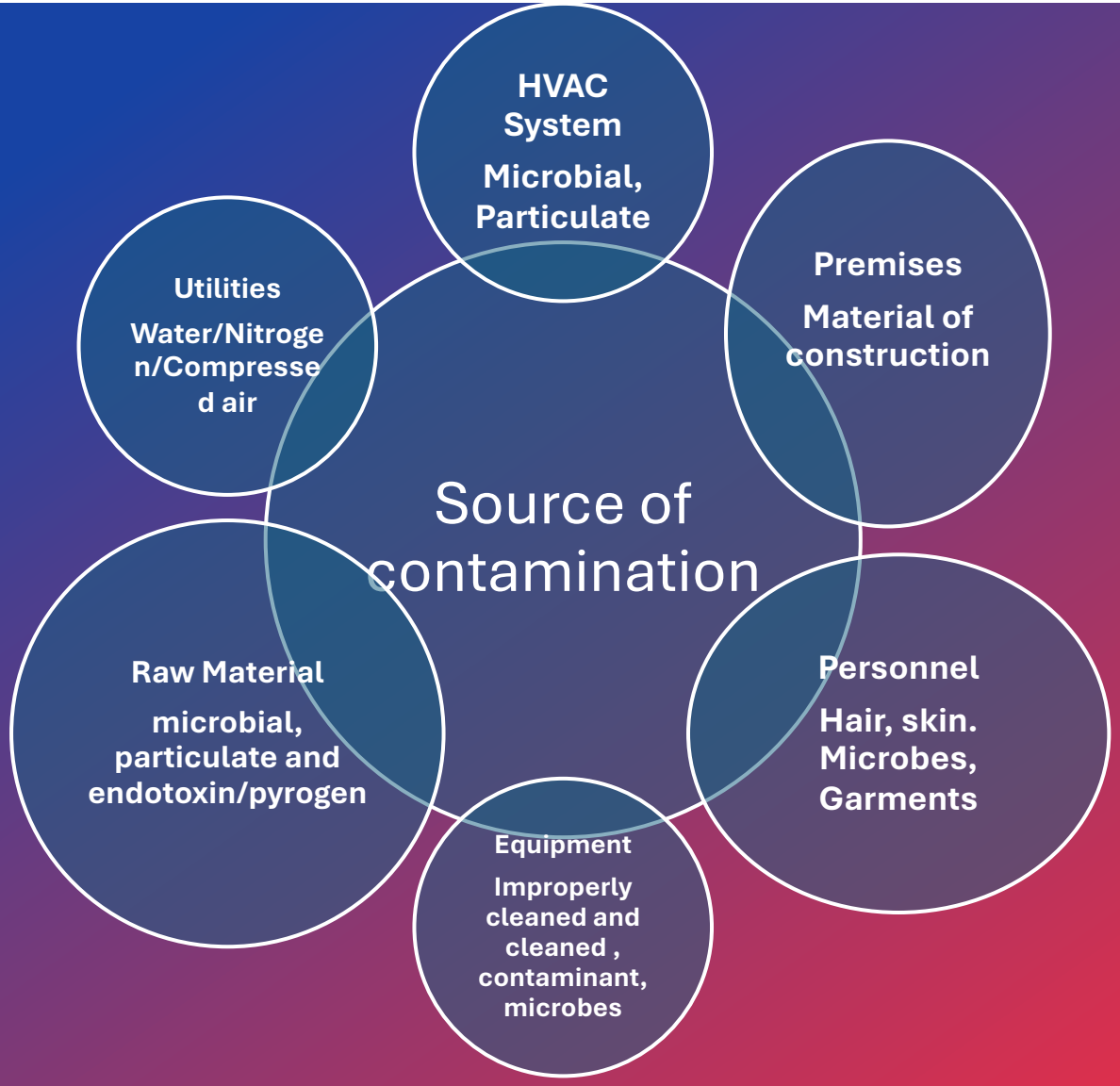
‘A CCS should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks to medicinal product quality’

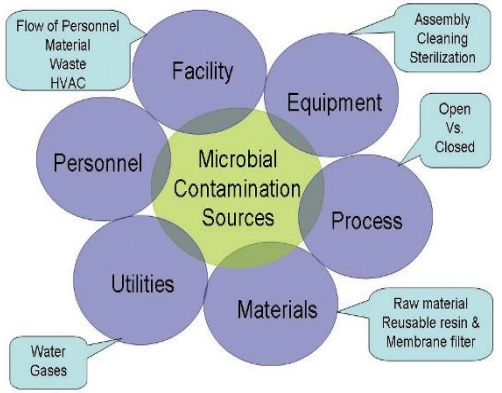
- **WHO TRS 1044 annex 2 (Sec 2.2)**

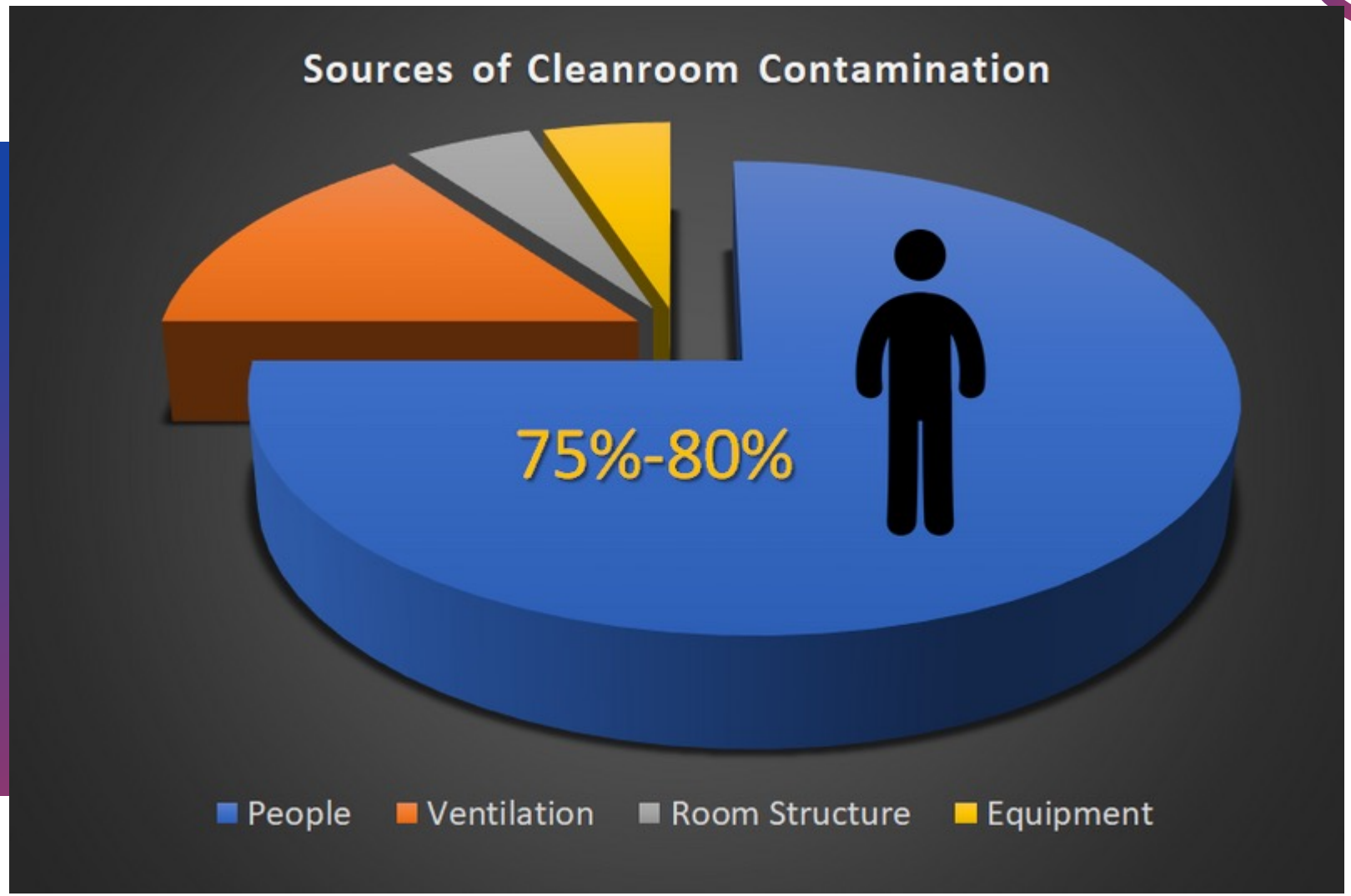
Processes, equipment, facilities and manufacturing activities should be managed in accordance with the principles of quality risk management to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.

VERY IMPORTANT CONSIDERATIONS

- Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures.
- These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.
- The combined strategy of the CCS should establish robust assurance of contamination prevention.
- The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods.'
- CCS effectiveness should form part of periodic management review.

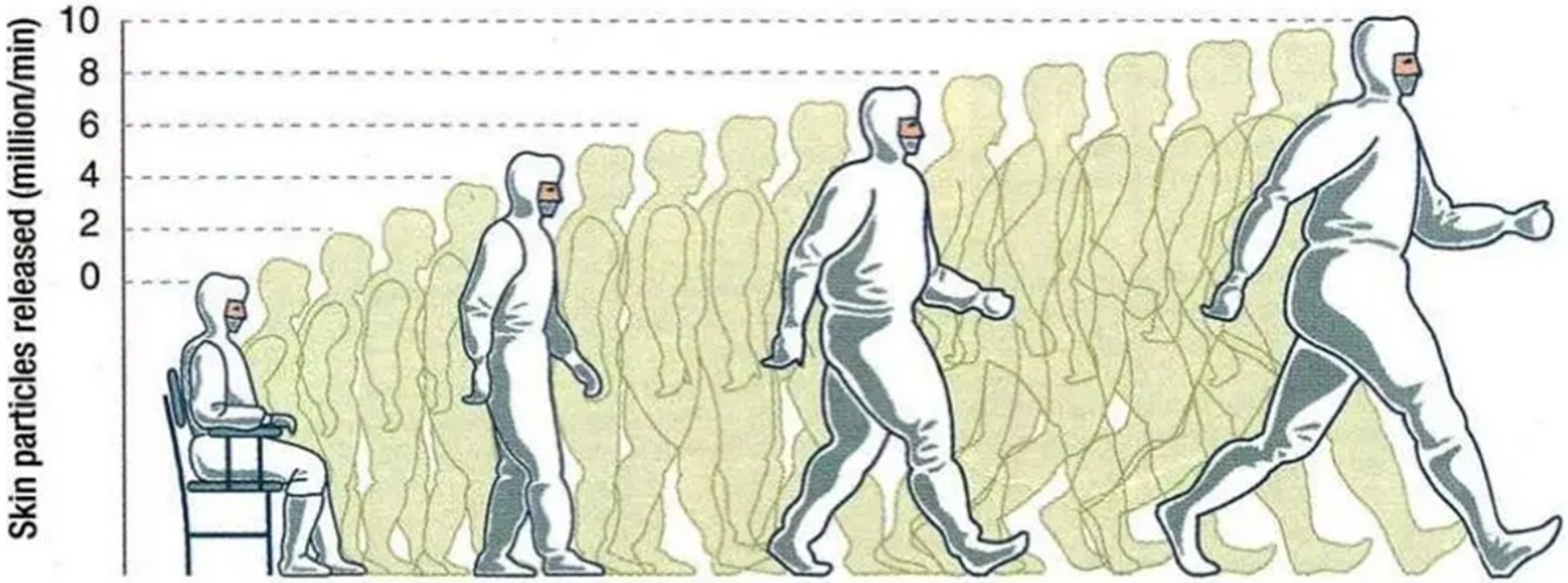

HVAC System
Microbial, Particulate
Utilities
Water/Nitrogen/Compressed air
Premises
Material of construction
Source of contamination
Raw Material
microbial, particulate and endotoxin/pyrogen
Personnel
Hair, skin. Microbes, Garments
Equipment
Improperly cleaned and cleaned , contaminant, microbes


Flow of Personnel Material Waste HVAC
Facility
Assembly Cleaning Sterilization
Equipment
Open Vs. Closed
Personnel
Microbial Contamination Sources
Process
Utilities
Materials
Raw material Reusable resin & Membrane filter
Water Gases



Operators who smoke would exhale millions of residual tobacco smoke particles, ranging from thousands to over 100,000 particles/l, which would significantly contaminate a cleanroom and violate its strict particle count standards.

The skin we shed



Source: Dr. Ken Goldstein Cleanroom Consultants, and Mike Fitzpatrick, Lockwood Greene, Cleanrooms East 99

WHAT IS A CCS

This is a technical document that evaluates the potential sources of contamination, the potential failure modes, the risk mitigation processes put in place and how its periodically updated.

A contamination control strategy (CCS) is a system that considers all the integral elements of pharmaceutical product manufacturing.

Quality Risk Management (QRM) principles that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality of the product

Key Focus Areas for Minimizing Contamination Risks:

- Facility design
- Equipment selection & design
- Processes
- Monitoring systems
- Personnel training & behaviour
- Raw & packaging materials control

Core Emphasis:

- Quality Risk Management – Applied throughout all aspects
- Contamination Control Strategy – A documented, integrated approach

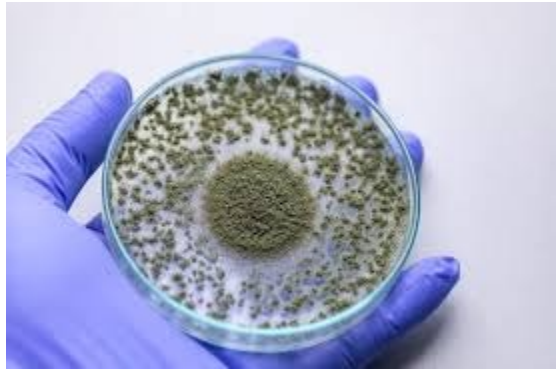
Contamination Control Strategy (CCS)-A documented strategy integrating all contamination prevention & control measures

Key Components:

- Holistic Approach aligned with QRM principles
- Covers facility, systems, and processes
- Elements to be considered – section 2.5 of Annex 1
- Identify contamination sources (microbial, particulate, etc.)
- Critical Control Points – Identified areas for monitoring
- Effectiveness Assessment – Evaluating controls & monitoring measures

Must be risk-based and continuously improved

Application to non- sterile products



ELEMENTS

permitted total particle concentration for monitoring

Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total pa ≥ 5 µm/m³	
At rest	In operation	At rest	In operat
3 520	3 520	29	29
3 520	352 000	29	2 930
352 000	3 520 000	2 930	29 300
3 520 000	Not predetermined[a]	29 300	Not predete

Premises design

HVAC

Filtration levels

Materials of construct

Airlocks

Equipment

Type of Equipment

Isolators/ Open RABS/

Utilities

Nitrogen

Compressed

WFI

PWS

Environmental Control

NVPC

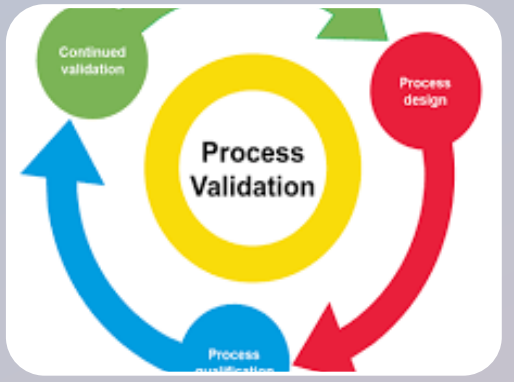
VPC

Temperature

Humidity

Pressure differentials

ELEMENTS



Personnel

Qualification

Aseptic Techniques

Training

MFS

Gowning Techniques

Cleaning and Disinfection

Cleaning Validation

Types of disinfectants

Preparation

Rotation

Monitoring

CIP/SIP

Process validation and risk assessment

Critical Process Parameters

Critical Quality Attributes

Process controls

Process Analytical Technologies

Raw Material Management

Transportation condition

Defined CMAs

Certificate of analysis

DMF type

Bioburden testing on receipt

Sterile material

ELEMENTS

Preventative Maintenance

Defined SOPs

Defined schedules

Quality risk principles

Checklists

Handling of breakdowns

Product Containers and closures

Type 1 Glass for ampoules and vials

Approach to leak testing

Sealing mechanisms

Product container development studies

Outsourced Activities

Sterilisation of Rubber stoppers

Gamma radiation

Testing activities (QC and Micro)

Washing of gowns

HVAC Qualifications

SLA/ Monitoring

QMS Components

Root cause

OOS

Deviation management

Excursions

Out of trends

CAPA

CAPA effectiveness

ELEMENTS

Media Fill Studies/ Validation of the sterilization Processes

SAL 10-6

Vendor Qualification

INSPECTION OF A CCS DOCUMENT

- ✓ Ascertain the presence of a contamination control strategy document or policy
- ✓ Review the incorporation of risk management principles in identifying of process failure modes and process monitoring and process controls
- ✓ Review the proposed risk for each component and how its mitigated.
- ✓ Verify the proposed risk controls that are said to be in place and their suitability and verify the practice and application.
- ✓ Verify the process knowledge from the contamination control strategy.
- ✓ Verify the qualification of the contamination controlling team and their knowledge on the subject matters.
- ✓ Verify the approach to continuous improvement and how changes are continuously incorporated.

Documents to inspect as part of the CCS

- AHU designs, area classification and pressure zoning diagrams
- AHU qualifications to show that the ACPH, Recoveries, PDs, NVPC, VPC. Airflow studies for the areas in question are being met.
- People and material flow diagrams showing appropriate change rooms and airlocks that show contamination control e.g. presence of bubble, cascades and sink airlocks and what they will be trying to achieve.
- Appropriateness of the Area in use e.g. Grade D for vial decartoning, vial washing, clarity checks, depyrogenation, Grade A/C for bulk compounding, A/C for filtration, B buffer and A laminar flows for filling.
- SOP for movement of components in all grades of the facility
- SOP for personnel qualification
- SOP for environmental monitoring (NVPC/VPC)
- SOP for disinfectant preparation, monitoring and rotations
- Disinfectant Studies, hold times and efficacy studies

Documents to inspect as part of the CCS

- ✓ Depyrogenation tunnel qualification documents
- ✓ Certificates of conformance of clean room papers, MOC equipment
- ✓ Certificates of conformance of aseptic gowns
- ✓ Autoclave qualification, depyrogenation tunnel qualification, washing machine qualification, filling LAF qualification and dynamic pass boxes qualification.
- ✓ SOP for CIP/SIP with end points determination.
- ✓ Approach to personnel monitoring
- ✓ Approach to Environment monitoring
- ✓ SOP for line set up and aseptic techniques implored for the same.
- ✓ Interventions handling and controlling
- ✓ Personnel training on aseptic techniques.

Documents to inspect as part of the CCS

- Technical assessment on the type of probes used, allowable length, allowable bends amongst others.
- Sterile filters compatibility studies
- Sterile filters integrity check
- SOP for aseptic assembly of components
- SOP for aseptic filtration and its validation
- SOP for handling of nitrogen and compressed gases on the filling line.
- SOP for lyophilization
- Qualification of the lyophilization recipes
- Handling of the vent filters, lyophilisation , manufacturing tanks, nitrogen, compressed air etc

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Documents to inspect as part of the CCS

- Continuous particle counts machine SOPs/ URS/ Privileges/Reports
- Filling line design i.e separation of the filling line, from sealing and crimping lines and continuity of the LAF without provisions of any breaks.
- SOPs for line clearance of mobile LAFs and their monitoring.
- SOPs for vendor qualification and ongoing monitoring.
- COAs and testing of incoming raw materials
- SOP for sampling, testing and handling of PWS/WFI
- Aseptic Process Simulation reports

GAP ANALYSIS

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Examples:

Requirement	How is the requirement fulfilled?	To do
Table 1: Maximum permitted total particle concentration for classification Grade | Maximum limits for total particle ≥ 0.5 µm/m³ (at rest | in operation) | Maximum limits for total particle ≥ 5 µm/m³ (at rest | in operation)	The requirements set forth in this table are defined in SOP-MD-3485	n/a

Final Version Annex 1 (Aug 2022)	Changes: compared 2017 - 2022	Relevanz?	How is the requirement impmented	Gaps	suggested measures	Cost estimate
Steam used as a direct sterilising agent						
6.17 Steam used as a direct sterilising agent should be of suitable quality and should not contain additives at a level that could cause contamination of product or equipment. For a generator supplying pure steam used for the direct sterilisation of materials or product-	Parameters such as non-condensble gases, dryness, overheat	relevant change, adaptation required	Clean steam is routinely monitored according to SOP-M29866 and SOP-MA-1043; specifications are describes TI-7025.	procedure has to be adapted	Prepare a documented risk assessment	

Annex 1			GAP assessment						Cross reference table			
Section (# + Name)	Sub-section # (or paragraph/ bullet #)	Guideline text	Currently applicable (yes/no/?)	Impact (yes/no/?)	Rationale	Action(s)	Responsible	Due date	Corresponding Document(s)	Responsible department /SME	Company's Annex 1 Compliant (yes/no)	Corresponding guidelines (GMP/ISO/?)
1 Scope	Paragraph 1	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	yes	no	QMS covers QRM	See respective sub-sections on changed topics.	QA	n.a.	POL-01 POL-03	QA QA	yes	-

KEY TAKE AWAYS

- ✓ Annex I emphasizes a risk-based approach (QRM) for contamination control.
- ✓ Must be applied throughout the manufacturing lifecycle, not just specific aspects.
- ✓ Guides facility design, equipment controls, procedures, and monitoring.
- ✓ Proactive risk identification, evaluation and control
- ✓ Risk-based decisions
- ✓ Integration in QMS with management oversight and regular reviews

KEY TAKE AWAYS

- Companies often use non-standard risk assessment tools, or heavily customized versions of standard tools such as FMEA or HACCP. As GMP Inspectors, we need to be able to assess the adequacy of the designs of those tools and approaches.
- Critical Control Points (CCPs) must be monitored and reviewed.
- Regular effectiveness reviews and Continuous improvement

KEY TAKE AWAYS

I. Process understanding
II. Process risks identification
III. Process controls evaluation
IV. Process residual risk mitigation
V. Sterility Assurance Level.

RISK ANALYSIS

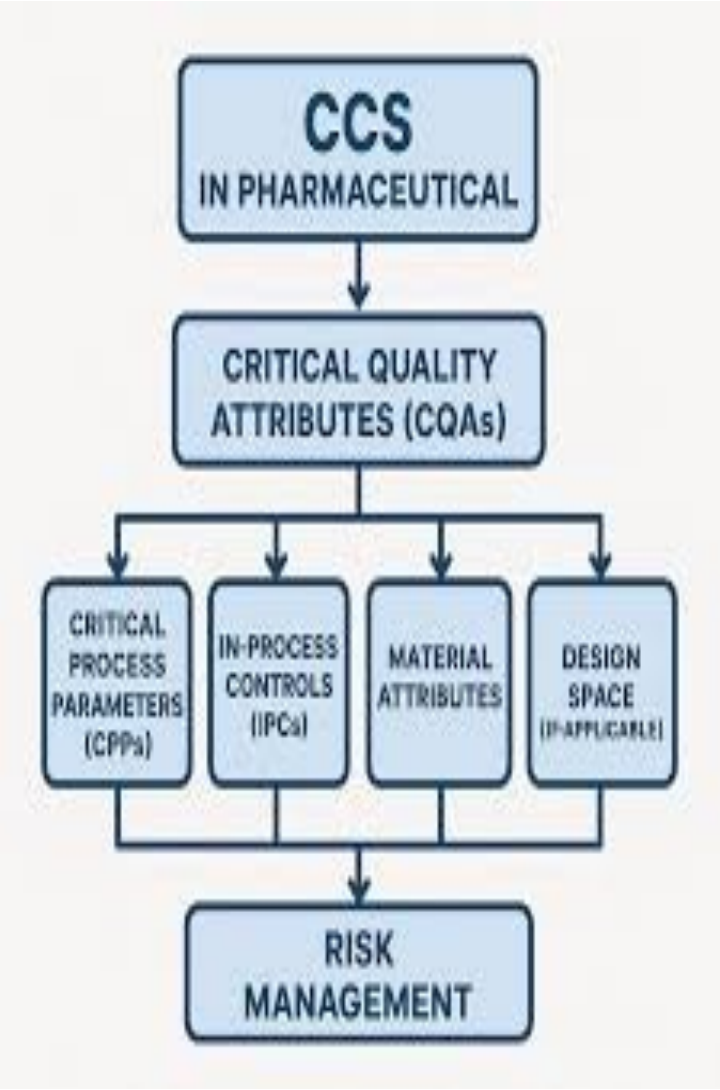
QUALITY RISK EVALUATION RECORD
Location:
Name of Facility/ Utility /Equipment /Process /Unit Operation: ***CONTAMINATION CONTROL STRATEGY RISK ASSESSMENT – EYE DROPS MANUFACTURING PROCESS*** **QRM Ref. No.: QA/QRM/2024/156**

P: Probability, S: Severity, D: Detectability, RPN: Risk Priority Number.

System	Sub-systems	Risk Identification				Risk Assessment & Classification					Existing Controls	Existing Testing	Risk Control				Revised Risk Assessment & Classification				
		Function	Failure Mode	Probable causes	Effect	S	P	D	RPN SXP XD	Risk Accepted (Y/N)			Mitigation Strategy Recommended	Stage	Respons -ibility	Target Date	S	P	D	RPN SXP XD	Risk Accepted (Y/N)
Starting Materials	Starting Material Delivery and Receipt	Delivery and Receipt of materials (raw materials and packaging materials) from suppliers	1. Delivery vehicle contaminated with Microbial and particulate material	1. Material containers damaged on transport 2. Delivery vehicle not cleaned.	Starting material contaminated with microbial and particulate material that results in contaminated product to consumer.	4	2	2	16	Y	1. Vehicle inspection prior to acceptance of delivery as per SOP CL-WH-020 Attachment 1 2. Material Inspection checklist as per SOP CL-WH-020 Attachment 1 3. Containers checked for evidence of spillage, damage, defaced labels, tampering, other irregularities as per SOP CL-WH-001 Checking Incoming Materials for Contamination and Other Irregularities 4. Materials de-dusted in respective dedusting areas before receipt into quarantine, as per SOP CL-QA-031 5. Incoming Materials Receiving, Holding, Quarantine and Storage procedure SOP CL-WH-020	N/A	N/A	N/A	N/A	N/A	N/A	4	2	2	16	Y
			2. Material received from unapproved vendor or unapproved vendor site	1. No vendor management or purchasing system to control buying of materials. 2. Vendors not qualified/audited	Quality and purity of material unknown and potential contamination of starting material resulting in contaminated product to consumer.	4	3	3	36	N	1. Group QA procedure in place for auditing Raw and packaging material suppliers as per Quality Audits Management SOP GQA-036 2. Delivery note/invoice suppliers verified against Approved Suppliers List SOP CL-QA-080 for raw materials and SOP-QA-083 for packaging materials 3. All vendors (manufacturers and brokers) set up in the Oracle Purchasing Data, purchase orders can only be placed on these vendors 4. Purchasing of materials (raw and packaging) as per SOP CL-PRO-001 5. Materials specifications in place and testing to specifications as per SOP CL-QC-CHE-015 (raw materials) and CL-QC-CHE-088 (packaging materials).	1. Each lot of raw material and packaging material tested as per specifications by QC lab.	1. Raw material vendor audits to be progressed as planned by GQA 2. Vendor assessment of the Irradiation facility (Synegy) used by primary component supplier to be verified by GQA at next audit of the Component Supplier	Ongoing	GQA	Dec 2024	4	2	2	16	Y

CCS is mandatory – A documented, integrated strategy for contamination prevention.

- Planning the Inspection - Has the CCS document transferred to you as this is vital
- Assess the team that compiled the document
- How old is the document and how often is it revised
- Is CCS part of Agenda of Quality Review
- Always compare the document to what you see in the plant and other documents – LIVING DOCUMENT
- Are the elements listed in the New Annex covered
- Review the RA and interrogate the scoring S?P?D



What are the Key Elements of Contamination Control Strategy CCS?

Agon