Sterility Assurance & Quality Risk Management Conference

PDA®
Parenteral Drug Association
Midwest Chapter

PDA /ANSI Standard 03-2025: An innovative new QRM tool for Microbial Contamination Control

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Let's Talk about your Organization

- Does your organization have infinite Time?
- Does your organization have infinite Personnel?
- Does your organization have infinite Budget?
- None of the Above.

What is your manufacturing space?

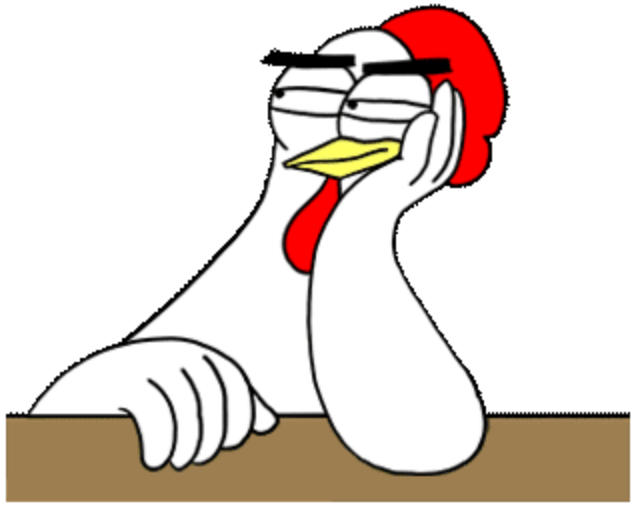
- How many of you work on small molecules?
- How many of you work on large molecules?
- How many of you work in the CGT space?

What is your QRM experience?

- What is QRM? Am I in the wrong room?
- I think I read the SOP.
- I completed the OJT.
- I have participated in 1 to a few risk assessments.
- I have participated in many risk assessments.
- I am an experienced expert.

For people who have participated, how did it go?

Awesome!



It’s done.

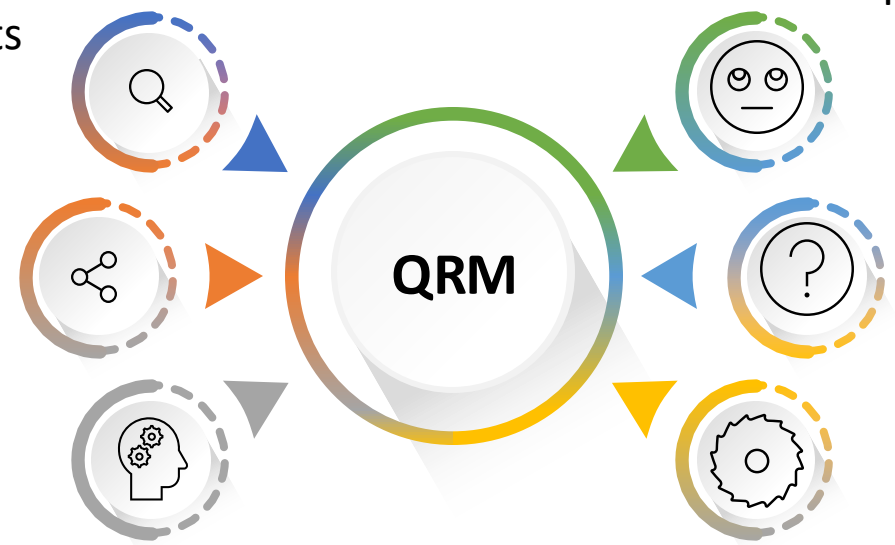
Ugh, Never again!

Applying QRM Principles

Science and Evidence based risk assessments

Multi-dimensional approach to decision making

Risk-based decision making (RBDM)



Recognizing uncertainty

Well-defined scope/objective and risk question

Selecting the correct tool for the job

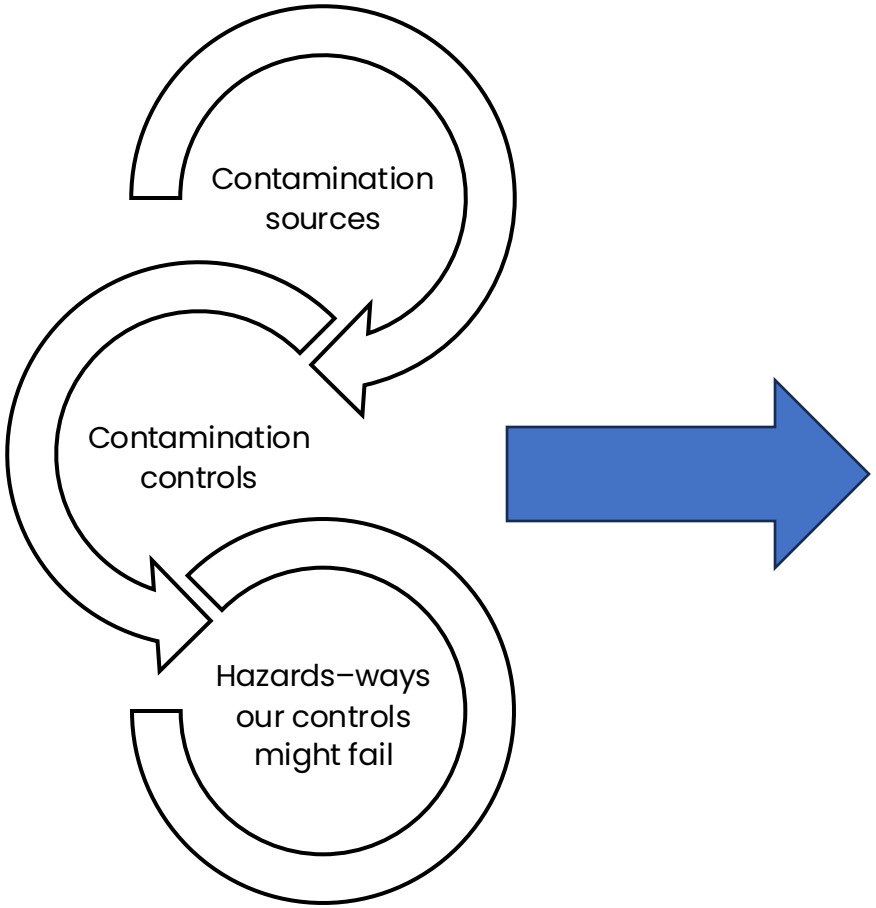
Figure from: Amanda McFarland, ValSource

A New Approach

PDA ANSI Standard 03-2025 Standard Practice for Quality Risk Management of Aseptic Processes

- Primary driver: measuring the strength of the controls that are currently in place.
- Less concerned with individual controls, focuses on the strength and effectiveness of the **totality** of controls!
- Industry standardized method which enables a consistent mechanism to assess contamination risks.
- Focuses on means of **preventing** contamination.
- The design of the tool is intended to drive organizations toward developing a control strategy which **anticipates** and **mitigates** risks before they are realized.
- Provides a standard framework of risk ranking criteria which emphasize the use of historical data and scientific knowledge aimed at minimizing the under/over estimating risk levels.
- May be used to assess a singular manufacturing process/unit operation process or to holistically evaluate a platform of controls.
- Used in conjunction with a lifecycle approach to Quality Risk Management (ICH Q9 R1).

A New Approach - Visualized



- Examine the controls
- Focus on how the controls might fail
- Determine the effectiveness of the suite of controls
- Evaluate the strength of the control by through examining if they are leading or lagging indicators of failure

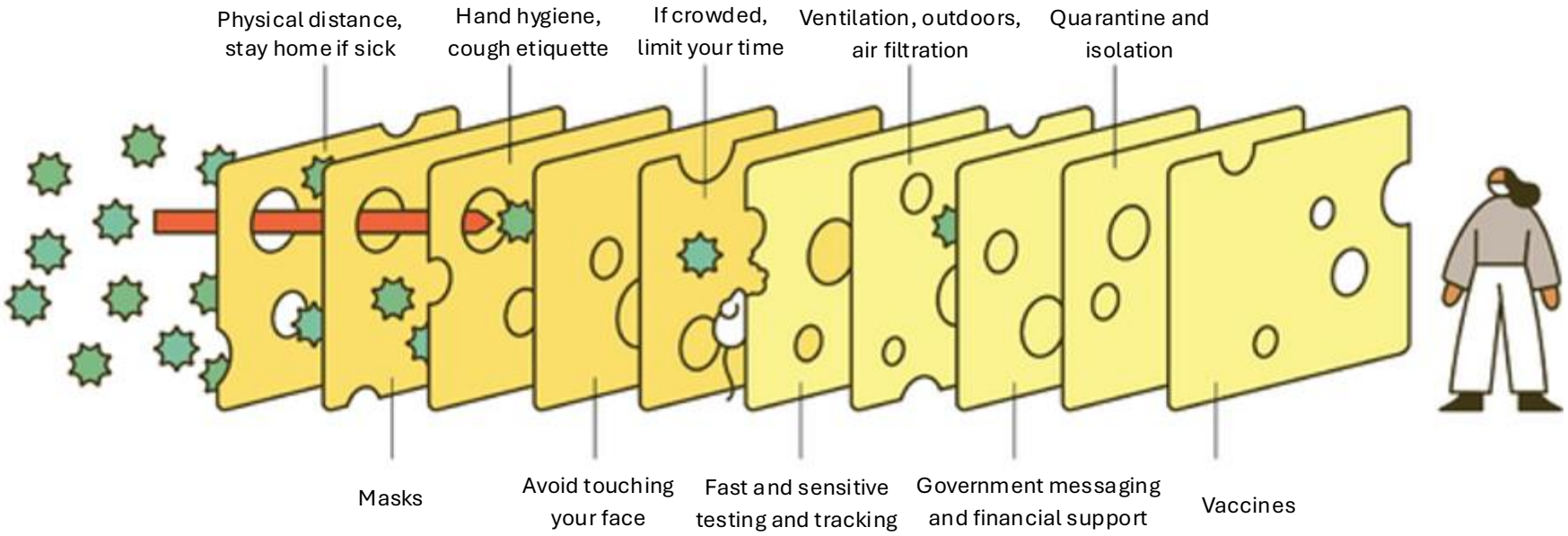
Layers of Protection

Multiple Layers Improve Success

The Swiss Cheese Respiratory Pandemic Defense recognizes that no single intervention is perfect at preventing the spread of the coronavirus. Each intervention (layer) has holes.

Personal responsibilities

Shared responsibilities



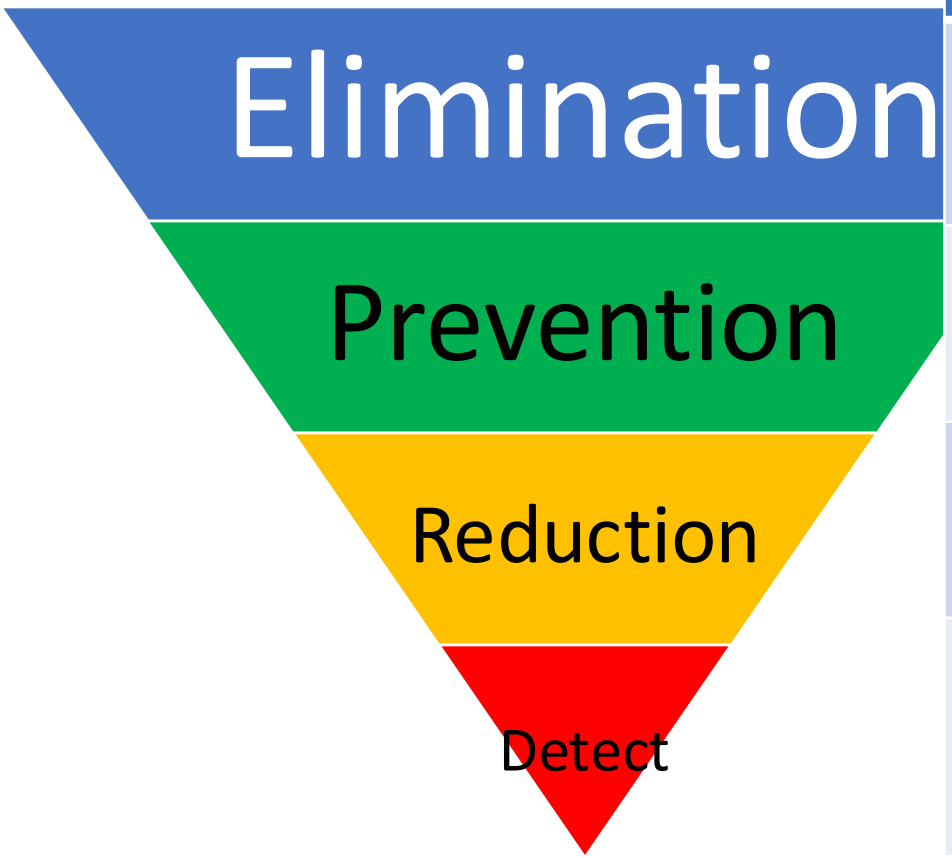
Source: Adapted from Ian M. Mackay (virologydownunder.com) and James T. Reason. Illustration by Rose Wong

PDA / ANSI Standard 03-2025
Standard Practice for Quality Risk Management of Aseptic Processes

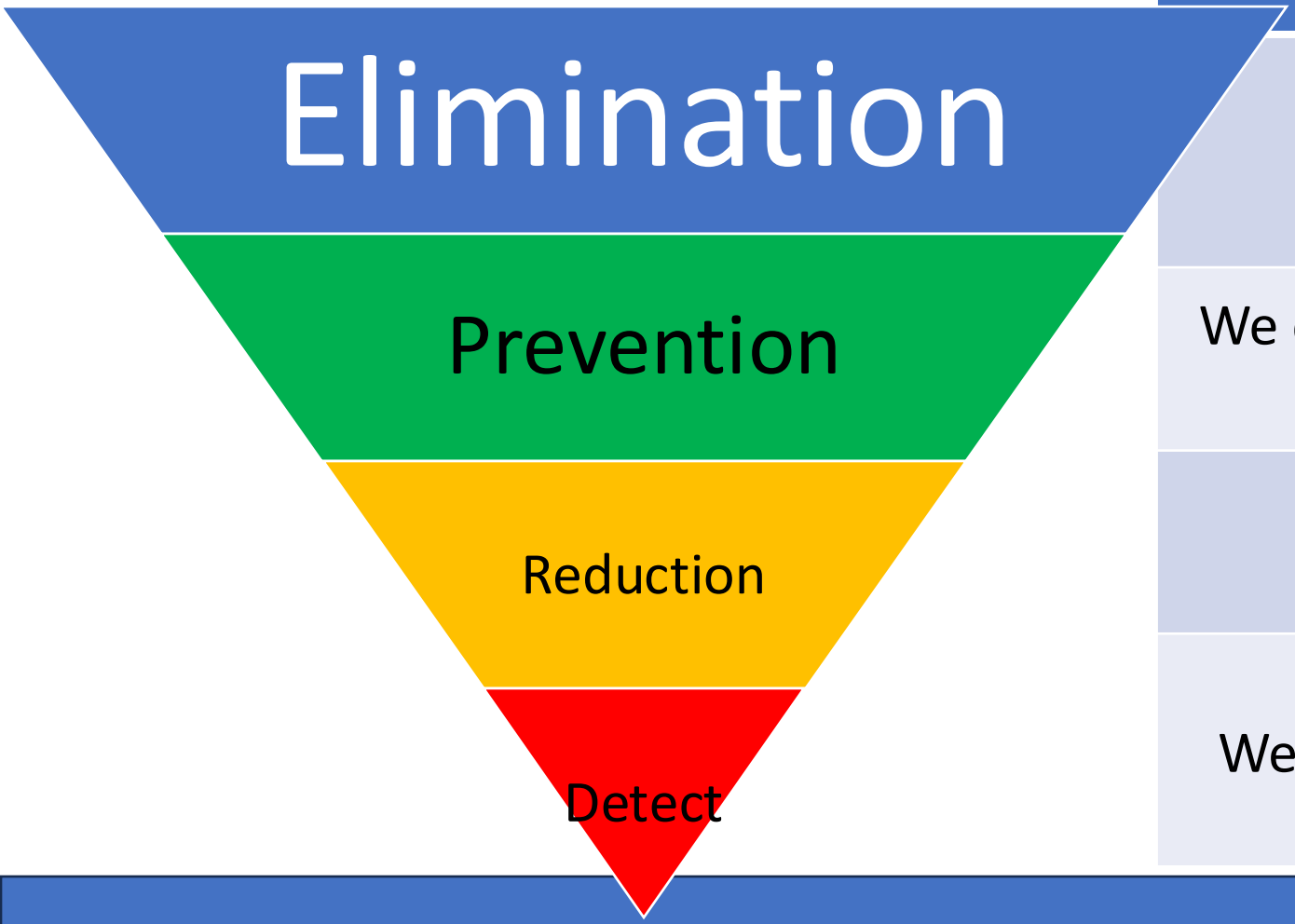
- Evaluate entire suite of Aseptic Processing Controls
- Criteria based on **reliable** evidence
- Detection linked to **prediction**
- Controls ranked according to ability to:

Eliminate | Prevent | Reduce | Detect

Controls for Potential Contamination Sources



Effectiveness	Description	Examples
Highest	Total Removal of the source	Isolator Technology Automation / Robots Pre-sterilization of items
Medium	Reduce the likelihood from the source	Decontamination First Air Principles
Low	Minimize contamination from the source	HEPA Filtration Aseptic Techniques
Lowest	Detection of Contamination	Quality Oversight Environmental Monitoring Post Batch Testing



People
Robots, No more interventions.
We could use an isolator to create a barrier between people and product!
We can train and gown operators!
We could sample the operator’s gowning.

Detection Controls – Leading and Lagging

Leading Indicator

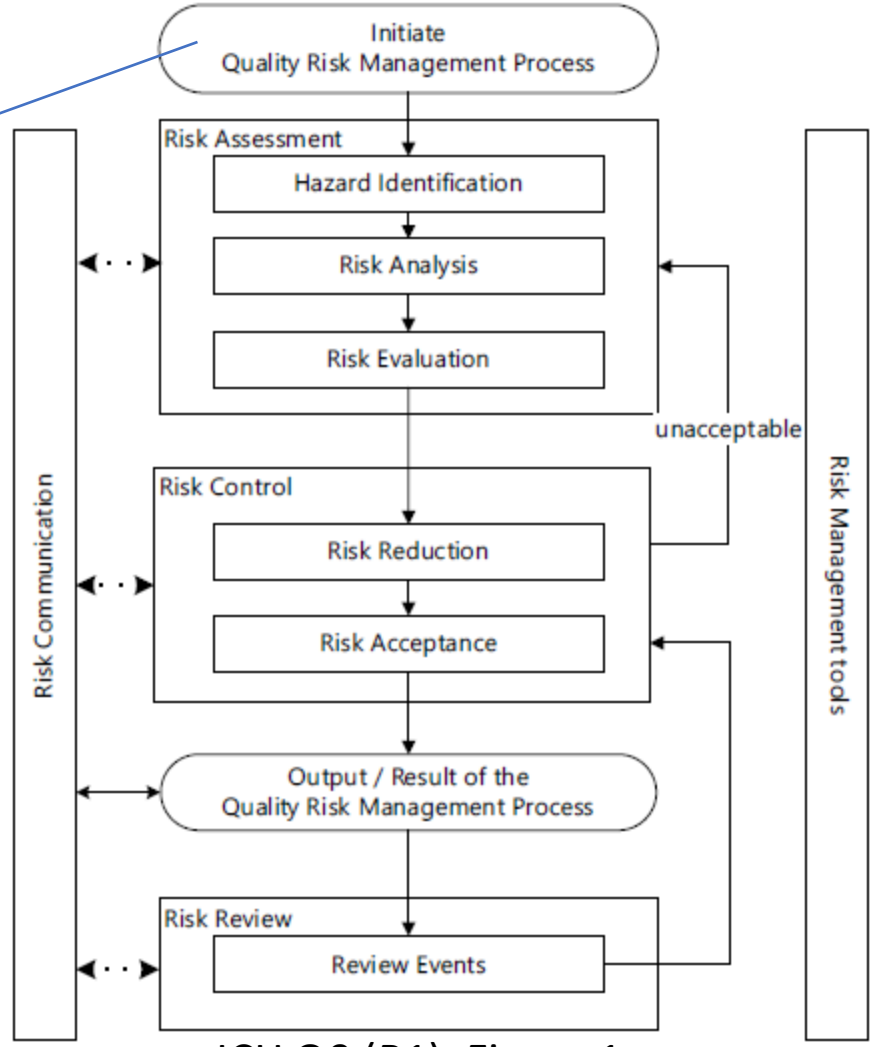
- **Leading indicators** are the most **effective** types of detection.
- **Predictive of a failure or hazard BEFORE it happens.** Therefore, the product is not lost or adulterated.
  - Sub-excursion (e.g., alert) level environmental monitoring trend analysis
  - Monitoring of clean room area adjacent to the critical space
  - Differential pressure trends
  - Near miss analysis

Lagging Indicators

- **Lagging indicators** are the most **common** process related detection measures.
  - Environmental monitoring
  - In-process product testing
  - Post-use filter integrity testing
  - Visual inspection of filled vials
  - Trending of deviations, adverse events, batch rejection, and recall events
- While informative, these are too **late** to corrective and will result in unavailability of the impacted material.

PDA ANSI Process

Define the scope, select tool and team

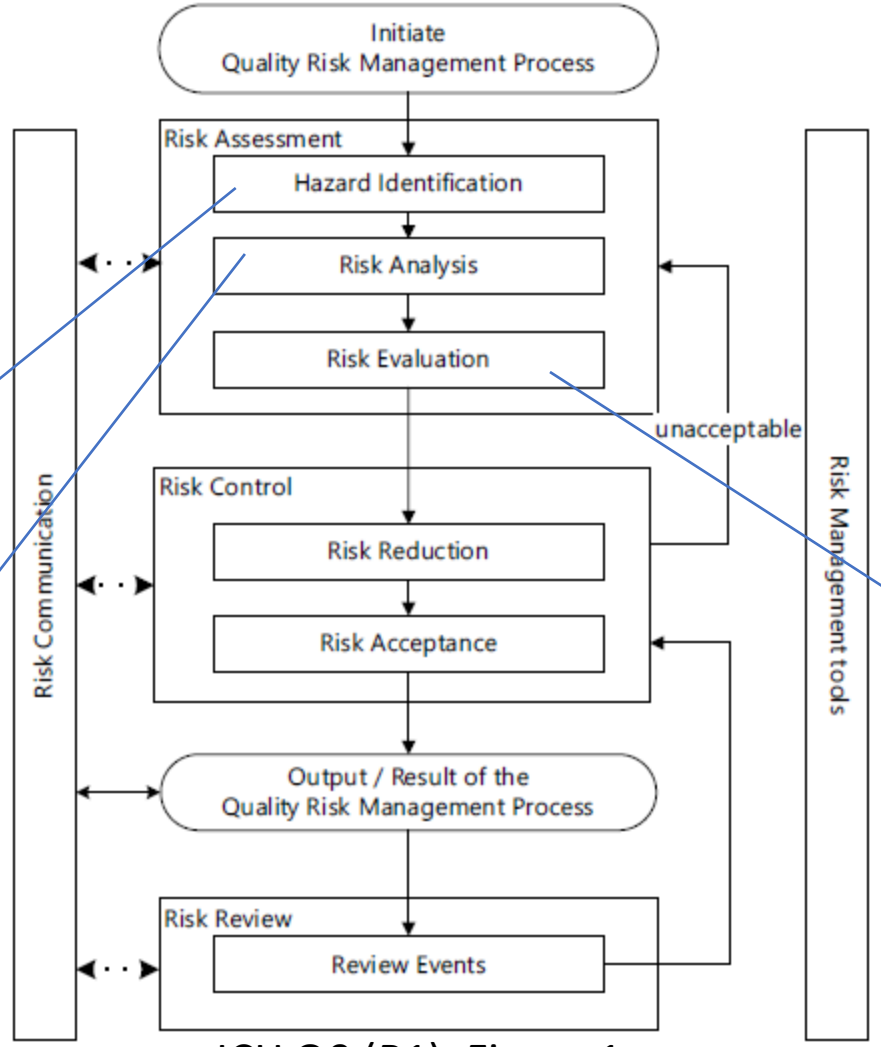


ICH Q9 (R1): Figure 1

PDA ANSI Process

Identify **sources** of contamination
Identify contamination **controls**
Identify **hazards** for each control
Identify **causes** for each contamination control
Identify possible prevention controls and detection controls for each hazard

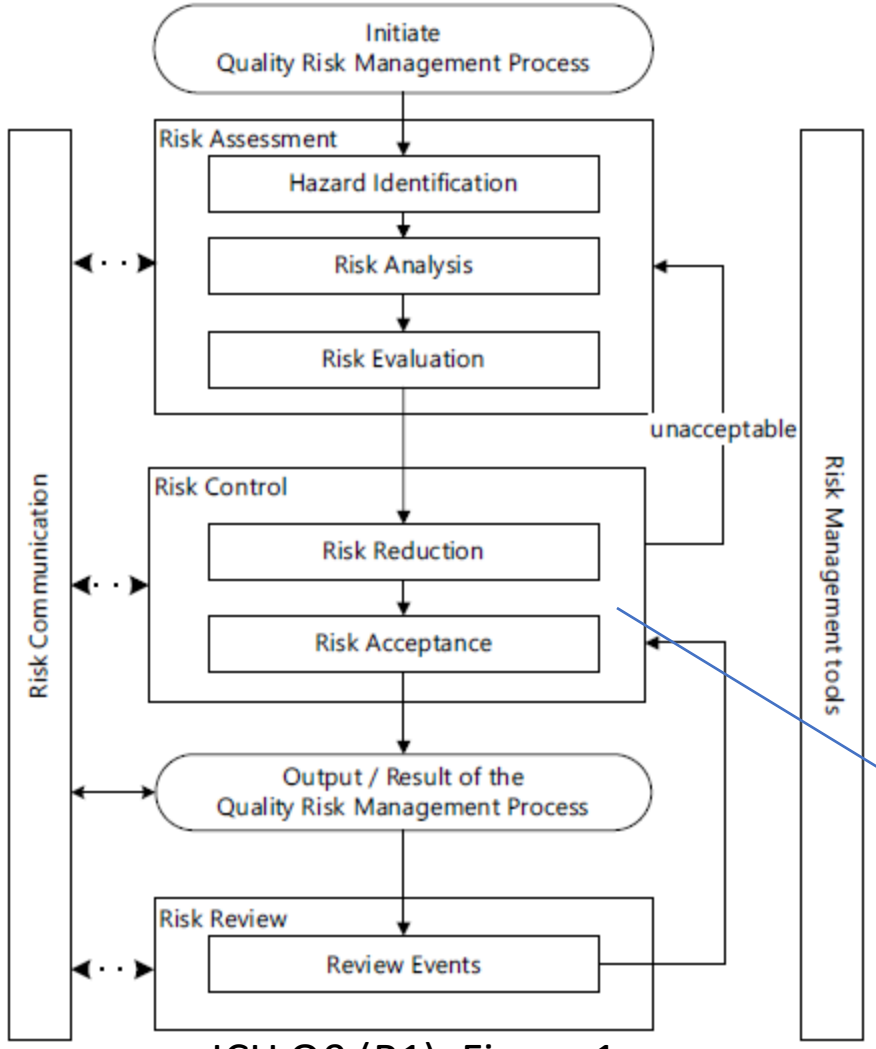
Score Prevention and Detection Ratings



ICH Q9 (R1): Figure 1

Assess against the Improvement Priority Matrix (IPM)

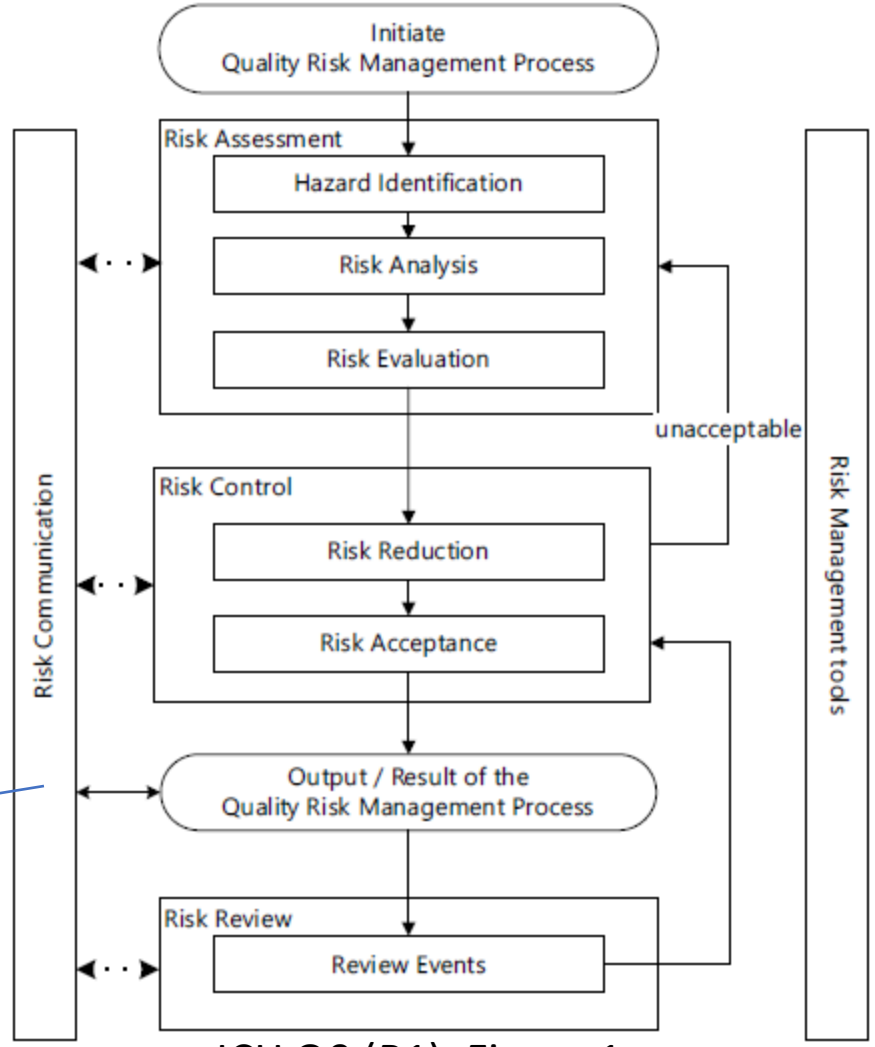
PDA ANSI Process



ICH Q9 (R1): Figure 1

Improve or **accept** controls based on IPM

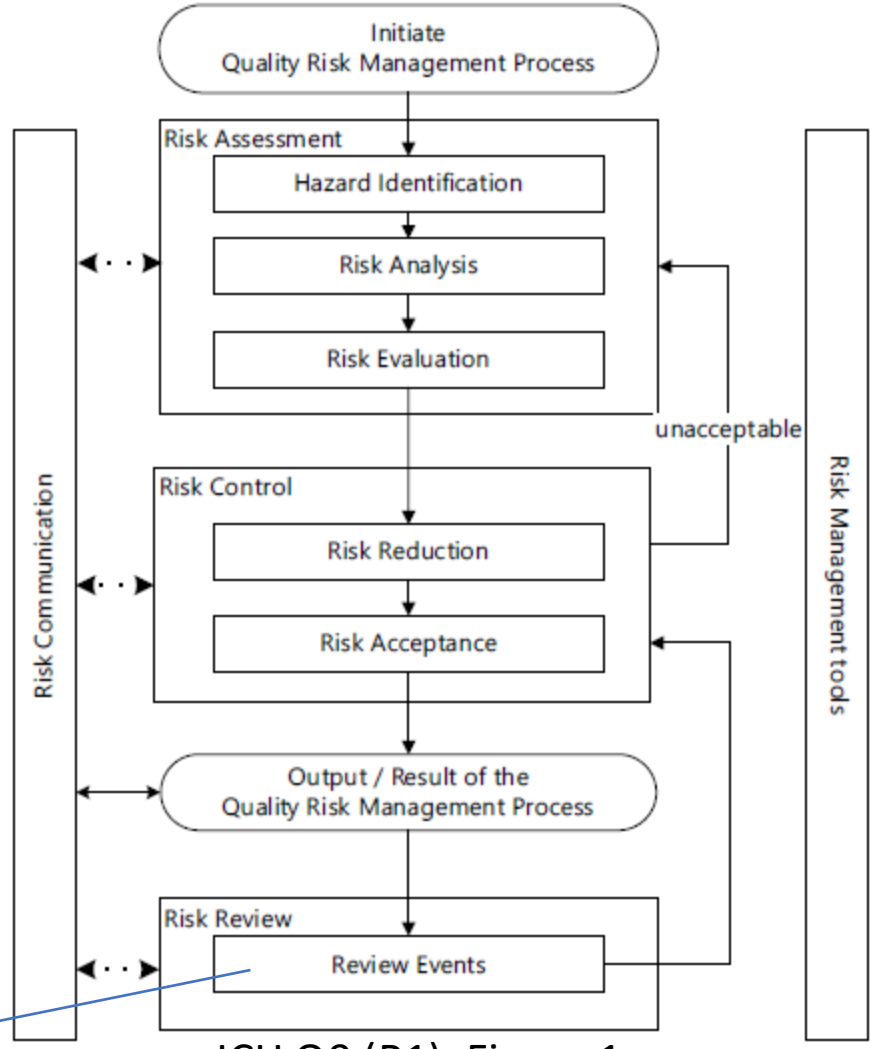
PDA ANSI Process



ICH Q9 (R1): Figure 1

Create Risk Dashboard

PDA ANSI Process



ICH Q9 (R1): Figure 1

Execute Risk Review

PDA ANSI Process

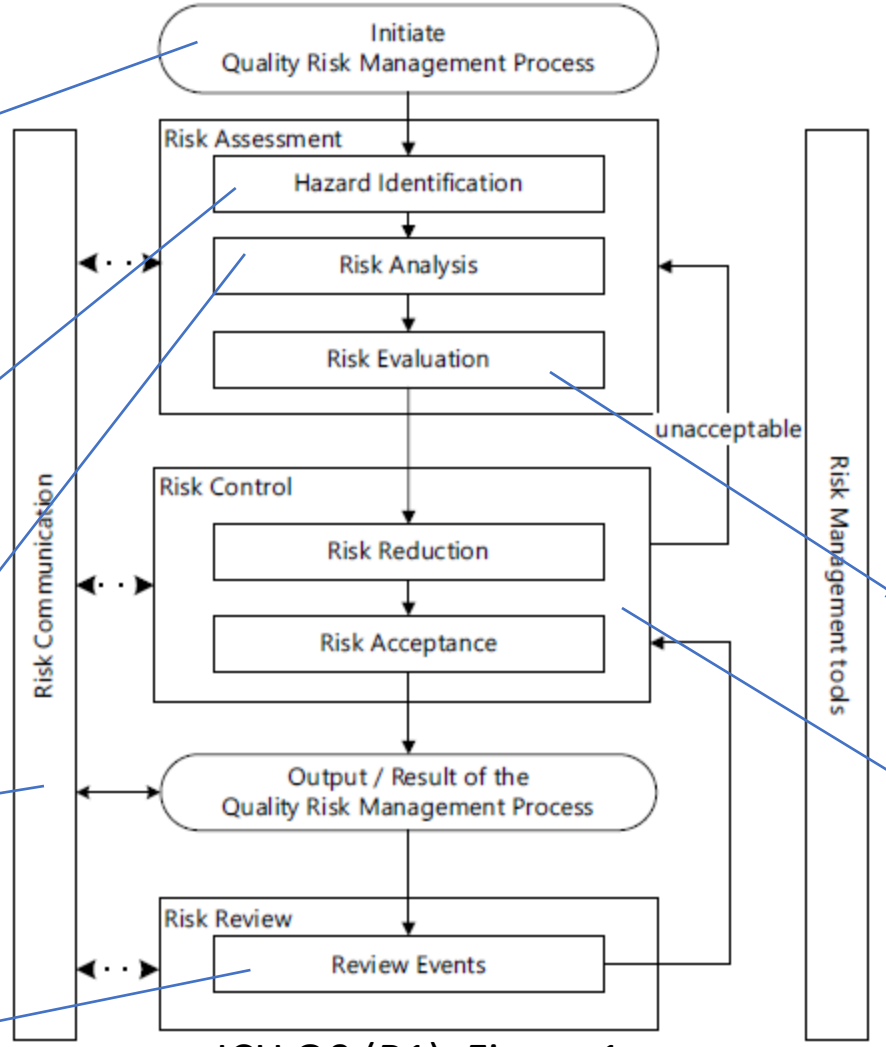
Define the scope, select tool and team

Identify **sources** of contamination
Identify contamination **controls**
Identify **hazards** for each control
Identify **causes** for each contamination control
Identify possible prevention controls and detection controls for each hazard

Score Prevention and Detection Ratings

Create Risk Dashboard

Execute Risk Review



ICH Q9 (R1): Figure 1

Assess against the Improvement Priority Matrix (IPM)

Improve or **accept** controls based on IPM

Risk Evaluation Phase

Type	Preventive	Detection
Rating	Strong	Predictive
	Moderate	Informative
	Limited	Delayed / Inconsistent

- A **few strong** prevention controls provide more assurance than a long list of limited controls.
- Note: Occurrence is NOT a factor.

Ratings and Definitions

Prevention Controls	
Rating	Meaning
Strong	There is sound scientific evidence that the (suite of) preventive control(s) reliably prevent the hazard.
Moderate	There is some evidence that the (suite of) preventive control(s) prevent the hazard, however, the evidence is limited and/or the hazard may intermittently occur.
Limited	There is minimal or no evidence that the (suite of) preventive control(s) reliably prevent the hazard, or the evidence suggests the controls are variable in performance, incomplete, and/or unreliable. If predictive detection (e.g., leading detection indicators) controls are in place, this rating does not apply.

Detection Controls	
Rating	Meaning
Predictive	Suite of detection mechanisms detect precursor(s)/leading indicator(s) to enable preventive or defensive action to avoid the hazard.
Informative	Suite of detection mechanisms provide information to detect the hazard with enough time to avoid the impact.
Delayed / Inconsistent	Suite of detection controls provides information with insufficient time to avoid the impact, AND/OR are not confirmed to be effective.

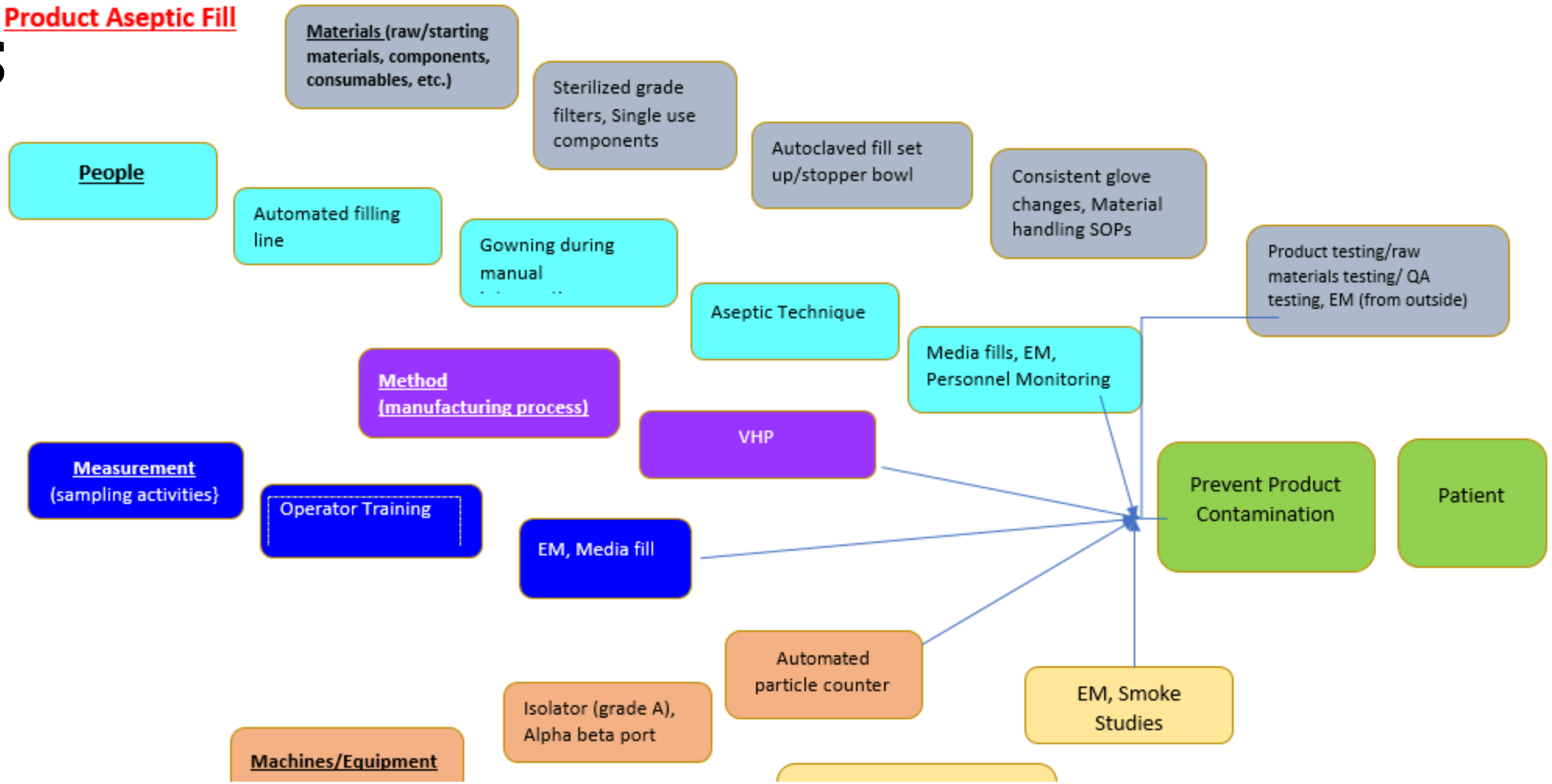
Risk Evaluation Phase

Detection Controls	Preventive Controls: Limited	Preventive Controls: Moderate	Preventive Controls: Strong
Predictive	**N/A** – suite of detection controls that meet predictive criteria also prevent the hazard from happening.	**Improvement Priority 6** Consider implementing additional or different preventive controls and/or gathering more evidence, or revisiting options to eliminate hazard.	**Improvement possible but not a priority.** Consider revisiting options to eliminate hazard. Opportunity exists to eliminate controls that do not contribute to prevention or prediction.
Informative	**Improvement Priority 2** • Implement additional controls or different preventive controls and/or gather more evidence, or • Revisit options to eliminate hazard. Would losing product put your patients at risk (e.g., drug shortage). If yes, this box is RED. Otherwise, this box is YELLOW.	**Improvement Priority 4** • Implement additional controls or different preventive controls and/or gather more evidence, and • Improve detection controls, or • Revisit options to eliminate hazard.	**Improvement Priority 7** Consider improving detection controls, or revisiting options to eliminate hazard.
Delayed/ Unreliable	**Improvement Priority 1** • Implement additional controls or different preventive controls and/or gather more evidence, and • Improve detection controls, or • Revisit options to eliminate hazard.	**Improvement Priority 3** • Implement additional or different preventive controls and/or gather more evidence, and • Improve detection controls, or • revisit options to eliminate hazard.	**Improvement Priority 5** • Improve detection controls, or • revisit options to eliminate hazard.

Outcomes

	Stoppers Prepared	Product Aseptic Fill
People	**Yes**	**Yes**
Contamination controls that could eliminate the source of contamination	• Automation/robotics (no people needed). • Alpha Beta port (enclosed in a bag/enclosed system).	• Automated filling line
contamination controls that could prevent contamination	• Gowning (extra barrier)	• Gowning during manual interventions
contamination controls that could reduce or minimize contamination	• aseptic technique training/SOP training (proper technique).	• Aseptic technique
contamination controls that could detect contamination	• Environmental Monitoring (EM) • Personnel monitoring • Media fills	• Media fills • EM • Personnel Monitoring
Method (manufacturing process)	**Yes**	**Yes**

Outcomes


Product Aseptic Fill
Materials (raw/starting materials, components, consumables, etc.)
Sterilized grade filters, Single use components
Autoclaved fill set up/stopper bowl
Consistent glove changes, Material handling SOPs
People
Automated filling line
Gowning during manual
Aseptic Technique
Product testing/raw materials testing/ QA testing, EM (from outside)
Media fills, EM, Personnel Monitoring
Method (manufacturing process)
VHP
Measurement (sampling activities)
Operator Training
EM, Media fill
Prevent Product Contamination
Patient
Automated particle counter
Isolator (grade A), Alpha beta port
EM, Smoke Studies
Machines/Equipment

Outcomes

Contamination Control	Hazard/Failure Mode (Stoppers)	Possible Cause
Automation	• Cyber-attack (IP4) • power failure (SP) • code error (IP4)	• Internet link, • no UPS system, • Insufficient testing
• Have a back up generator for power failures--Strong. • Proper validation qualification to prevent code errors. -- Moderate • Update/ keep security up to date/ Air gap--Moderate. • Continuous Monitoring-- Strong		
Daily Monitoring- Predictive Alarms –Informative Periodic review -- Delayed		

Contamination Control	Hazard/Failure Mode (Stoppers)	Possible Cause
Alpha/ Beta Port	• Faulty gasket (IP3) • mixed vendor parts	• No vendor control (IP3) • maintenance issue (IP4) • poorly documented specs
Vendor inspections -- Moderate QC--Moderate Properly established PM schedule--Moderate Good SOP/Good documentation--Moderate		

Be Proactive

- Focus on **Leading** Indicators – Predictive, allowing for adjustment **before** the product becomes adulterated.
- **Lagging** Indicators are delayed and are informative that a process failure has **already** occurred.
- Patient safety may be protected by discarding or quarantining product.
- Reminder: Lack of **availability** is included in the definition of harm and therefore should be minimized. Discarding product will protect a patient from loss of product quality, but it may introduce another type of damage to health.

New Modalities

- For new modalities with limited sample sizes and short shelf lives, patients cannot wait for **legacy** testing and release policies and procedure.

- Robust contamination control enables **faster** delivery of life changing products to patients.

Not Just for Audits

- Instead of starting from scratch, Contamination Control risk assessments are a great quick start for contamination Root Cause Analysis activities.
- Assessment of totality of controls enables your organization to eliminate redundant or ineffective controls.
- **Recommendation**: Ensure training on and access to QRM documentation to your investigators and change controllers.

Final Thought

- QRM is a compulsory activity in our industry. You have to do it. However:
  - it can either be a dusty document on a real or virtual bookshelf that only gets used when a Health Authority visits;

-OR-

  - a strategic and tactical tool for your organization to achieve higher success rates, fewer discrepancies, minimize contamination events, and lead to better patient outcomes.

Conclusion

- This innovative tool can assist organizations to:
  - **Proactively** identify and assess contamination risks.
  - Focus on the strength and totality of controls to enact **strategies** that are effective and valuable.
  - **Prioritize** improvements in a standardized manner.
  - Support the Contamination Control Strategy with an **Industry Standardized** method.
- Leading to:
  - **Fewer** contamination events and investigations.
  - Higher **success** rates.
  - AND **Better** Patient Outcomes

Thank You

VALSOURCE

Innovative Solutions. Sustainable Results.

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Bio

Patrick Mains is currently a Senior Consultant at ValSource. He supports organizations in the pharmaceutical industry using his expertise in Quality Risk Management for pharmaceutical and biopharmaceutical products as well as cell and gene therapies. With over 30 years of experience in the biopharma industry, Patrick has had various roles in Quality Control, Project Management, Site Compliance/Inspection Management, Quality Systems, and Global Quality across multiple organizations.