Quality Risk Management (QRM)

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AGENDA

- Introduction to QRM and overview of ASTM E2500 – Steve
- Risk Management – Mike
- Risk Tool Selection – Steve
- Risk Assessment – Mike
- Workshop

Risk Perception

Required to be done by …

- Regulatory agency
- Upcoming inspection
- Corporate policy

OR

Useful tool that …

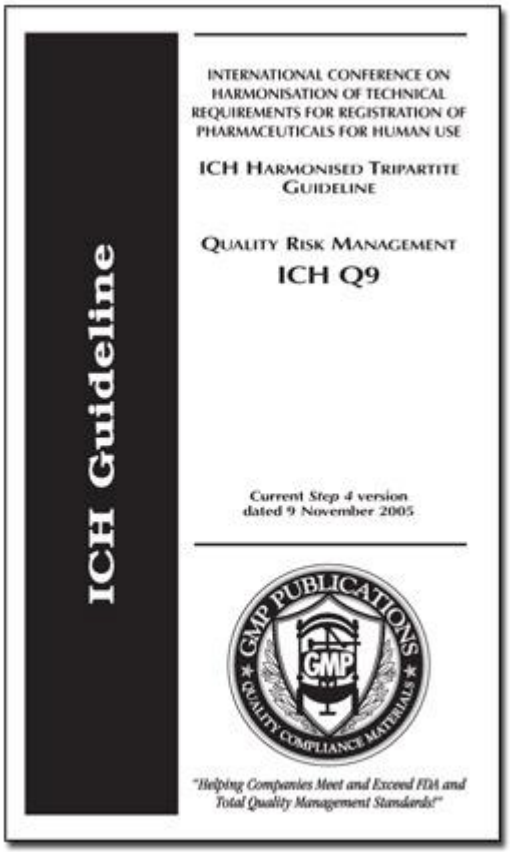
- Provides common understanding of process
- Helps qualify equipment or validate process
- Identifies gaps in process understanding

What is Risk?

- ICH Q9 and ISO/IEC Guide 51
  Definition:

  The combination of the probability of occurrence of harm and the severity of that harm

- Note: Detection is not specifically discussed in the definition



Risk Management is Universal

- All industries use risk assessment in an attempt to answer the following questions:
  - What can go wrong?
  - How often does it happen?
  - How bad are the consequences?
  - Is the risk acceptable?

Military

Aerospace

Commercial Aviation

Petrochemical

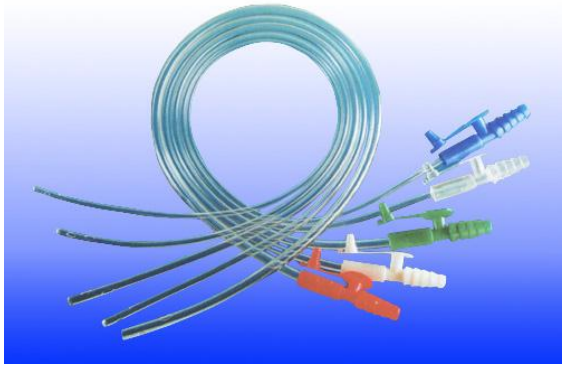
Rail

Nuclear

Risk Management in Human Health

Medical Device Industry

- Utilized Risk Assessments for a long time
- Driven from the automotive industry
- Utilize primarily a Failure Mode Effect Analysis (FMEA) approach
- Product focused



Pharma/Biotech Industries

- Relatively new to Risk Assessment/Management
- Driven with a focus on optimizing design and validation
- Focused on equipment and process

Key Terminology

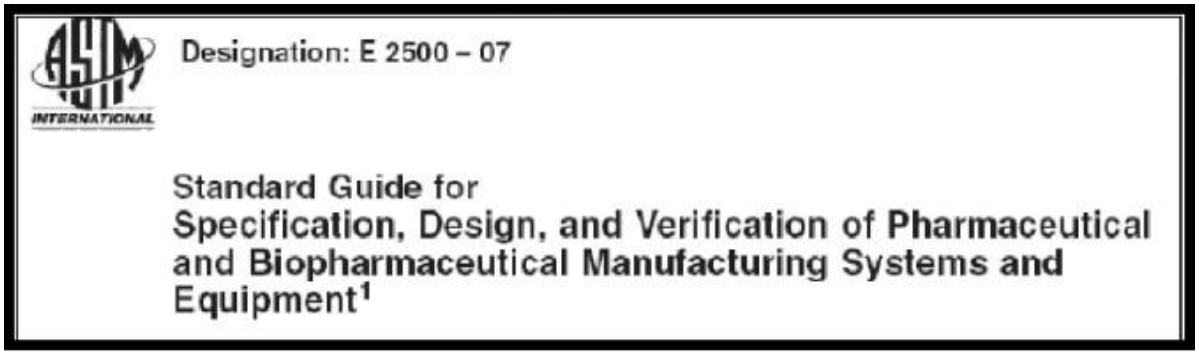
- **Harm:** Damage to health, including the damage that can occur from loss of product quality or availability
- **Hazard:** The potential source of harm (ISO/IEC Guide 51)
- **Risk:** The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51)
- **Control:** The approach defined to maintain the output of a specific process within a desired range
- **Severity:** A measure of the possible consequences of a hazard
- **Occurrence:** The frequency with which an event happens
- **Detectability:** The ability to discover or determine the existence, presence, or fact of a hazard

Risk Assessments

- Risk assessment is an attempt to answer the following questions:
  - What can go wrong?
    - Risk
  - How bad are the consequences?
    - Severity
  - How often does/will it happen?
    - Probability of Occurrence
  - If it happened, how would we know?
    - Likelihood of Detection
  - Is the risk acceptable?
    - Risk Evaluation, Remediation

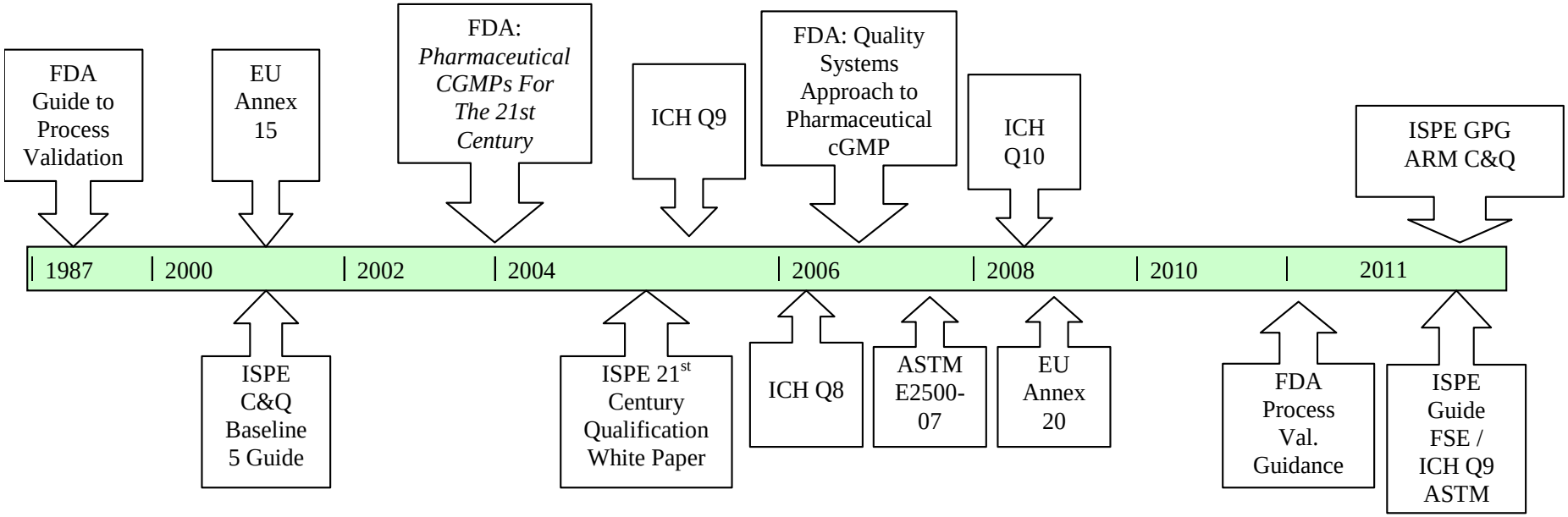
Risk Management in Pharma/Biotech

- ASTM E2500-07
  - A consensus standard based on sound scientific, engineering and quality principles that separates business risk from patient safety risk
  - Focus on product and process design through detailed requirements and mitigating risks in the design phase


Designation: E 2500 – 07

Standard Guide for
Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment[1]

Evolution Of Commissioning & Qualification

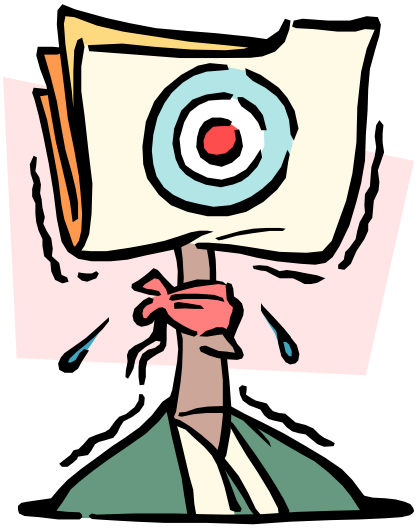


Question…

- Why change our work cultures & regulatory framework to move from the traditional qualification approach to a value added model?

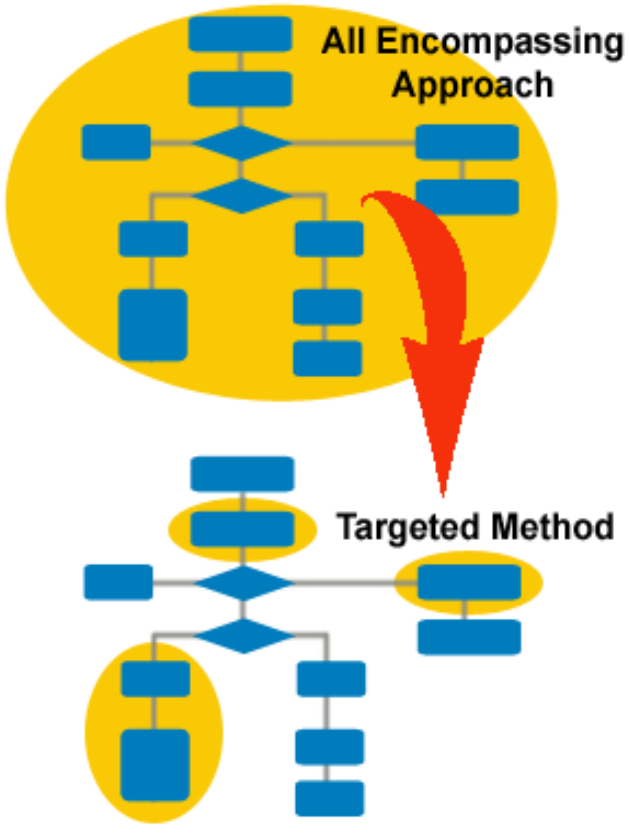
Qualification – A Broken Process

- IQ/OQ had become more intensive than PQ
- Organizations refused to leverage commissioning
- Automated systems and the controlled equipment were qualified separately and inefficiently
- Deviations for trivial items diluted Q-unit attention
- “Change-is-bad” attitudes driven by cost/time



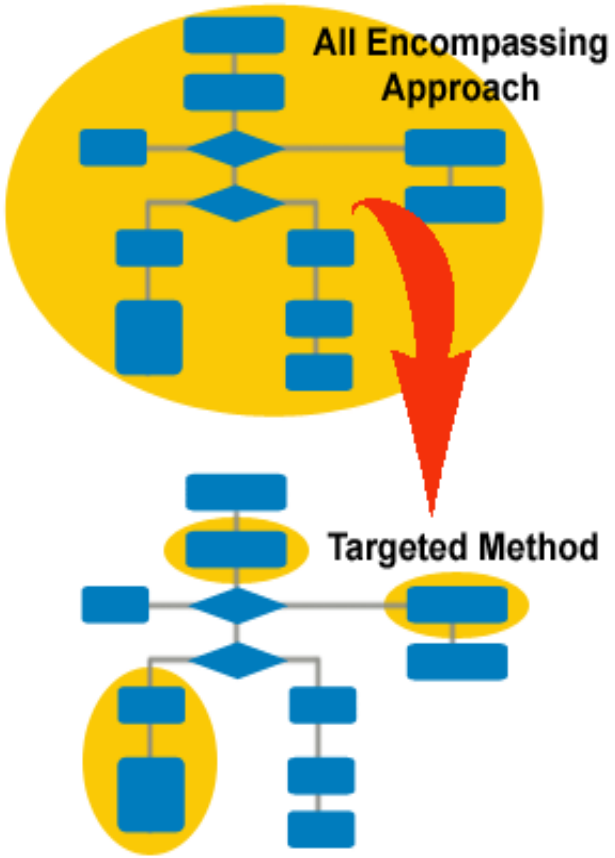
What is a Science and Risk Based Approach (RBA)?

- A paradigm shift in the global pharmaceutical industry
- Pharma and Regulatory Agencies applying an all-encompassing approach to qualification
- Using focused methodologies to assess the scope of qualification



What is a Science and Risk Based Approach (RBA)?

- The identification and control of risks to product quality
- Formality and documentation commensurate with risk
- The use of (GEP) to verify installation and operation
- Verification that system performance meets product and process user requirements



Think about it:
If everything is critical, then nothing is.

10 Principles for Risk-Based Qualification

1. Focus on that which affects product quality
2. Process User Requirements key to acceptability (IQ/OQ subordinate to PQ)
3. Risk assessments and process knowledge used to identify critical elements
4. Only critical features/functions to be qualified
5. All activities must contribute value

ISPE White Paper "Risk Based Qualification for the 21st Century" March 2005

10 Principles for Risk-Based Qualification

6. Risk-based asset delivery – not “cookbook” requirements
7. Value-added documents based on technical merit
8. Use of supplier documentation
9. Test planning (and one-time testing)
10. Foster innovation – all change is not bad

ISPE White Paper “Risk Based Qualification for the 21st Century” March 2005

Qualification -“Traditional” vs. RBA

Traditional Approach

- (Product) User Requirements not Formally Documented
- Protocols Developed from “Templates”
- IQ/OQ Protocols “Preapproved”
- Commissioning not Leveraged
- Engineering and “Validation” Personnel Often Distinct
- Emphasis on Documents – Not System Performance

Risk-Based Approach

- Process Requirements Documented, Approved
- Risk Assessments Determine Critical Aspects of Design
- Engineering Testing (“Commissioning”) Verification
- All Documents with Technical Merit Used as Evidence of Fitness for Use
- Emphasis on Meeting Process Requirements

ASTM Standard E 2500-07

"ASTM Standard for Specification, Design & Verification of Pharmaceutical & Biopharmaceutical Manufacturing Systems & Equipment"

- The ASTM Standard provides a science and "risk based" approach to assure that GMP equipment & systems are:
  - Fit for use
  - Perform satisfactorily
  - May be used in the manufacturing, processing, packaging and holding of a drug

ASTM Standard – Summary

- Describes a risk and science-based approach to:
  - Specification, design, and verification of manufacturing systems/equipment that have the potential to affect product quality and patient safety
  - A systematic, efficient, and effective way of ensuring that manufacturing systems and equipment are fit for intended use

- Provides manufacturing capability to support defined and controlled processes meeting defined quality requirements

ASTM Standard – Scope

- Applicable to all elements of pharmaceutical and biopharmaceutical *manufacturing systems*:
  - Facility equipment, process equipment, supporting utilities
  - **Associated process control and automation systems**, that have the potential to affect product quality and public safety
- Applicable to new and existing manufacturing elements
- May be used for the implementation of changes to existing elements, and their continuous improvement during operation

Bridge From Baseline Guide 5 to Risk-Based ASTM Verification

cGMP Risk-Based Sea-Change

Verification – The 'New' (*old)* Approach

- A systematic approach should be defined to verify that Manufacturing Elements, acting singly or in combination, ***are fit for intended use***, have been properly installed, and operating correctly
- This verification approach should be defined and documented
- The extent of verification and the level of detail of documentation should be based on risk to product quality and patient safety, complexity, and novelty of the manufacturing system

Critical Aspects of Manufacturing Systems

- ***Critical aspects*** are typically:
  - Functions, features, abilities, and performance or quality characteristics necessary to ensure consistent product quality and patient safety
  - Should be identified and documented based on scientific product and process understanding
- Verification activities should focus on these aspects of manufacturing systems and should be documented

Know Your Critical P's & Q's (& A's)

- Critical Quality Attributes (CQA)
- Critical Process Parameters (CPP)
- Critical Aspects (CA)

Critical Quality Attributes

- From ICH Q8: A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- Essential to producing the desired outcome
  - In life sciences risk approach, relating specifically to product quality and/or patient safety requirements
  - Product identity, potency, size/dissolution (easy to swallow/digest), clean/sterile, and so on

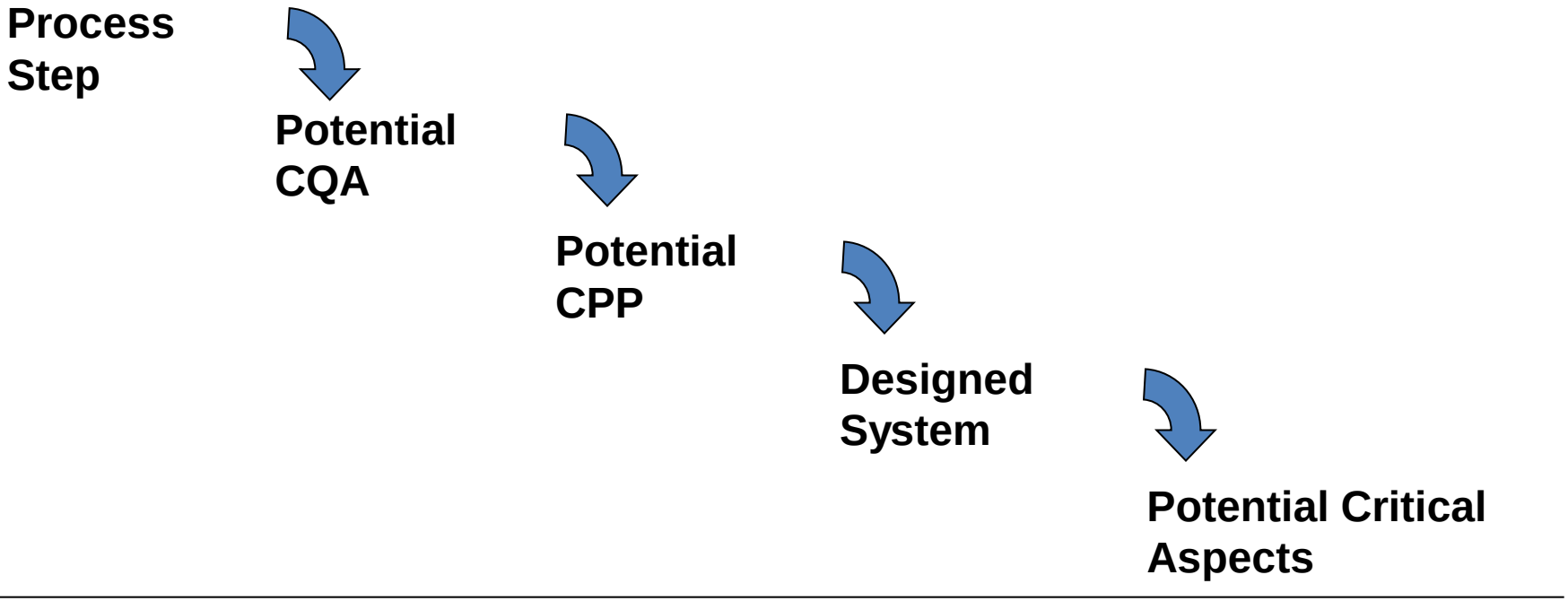
Critical Process Parameters (CPP)

- From ICH Q8: A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality
  - The control targets and ranges for critical attributes
  - Control setpoints, alarm points, time, etc.

Critical Aspects

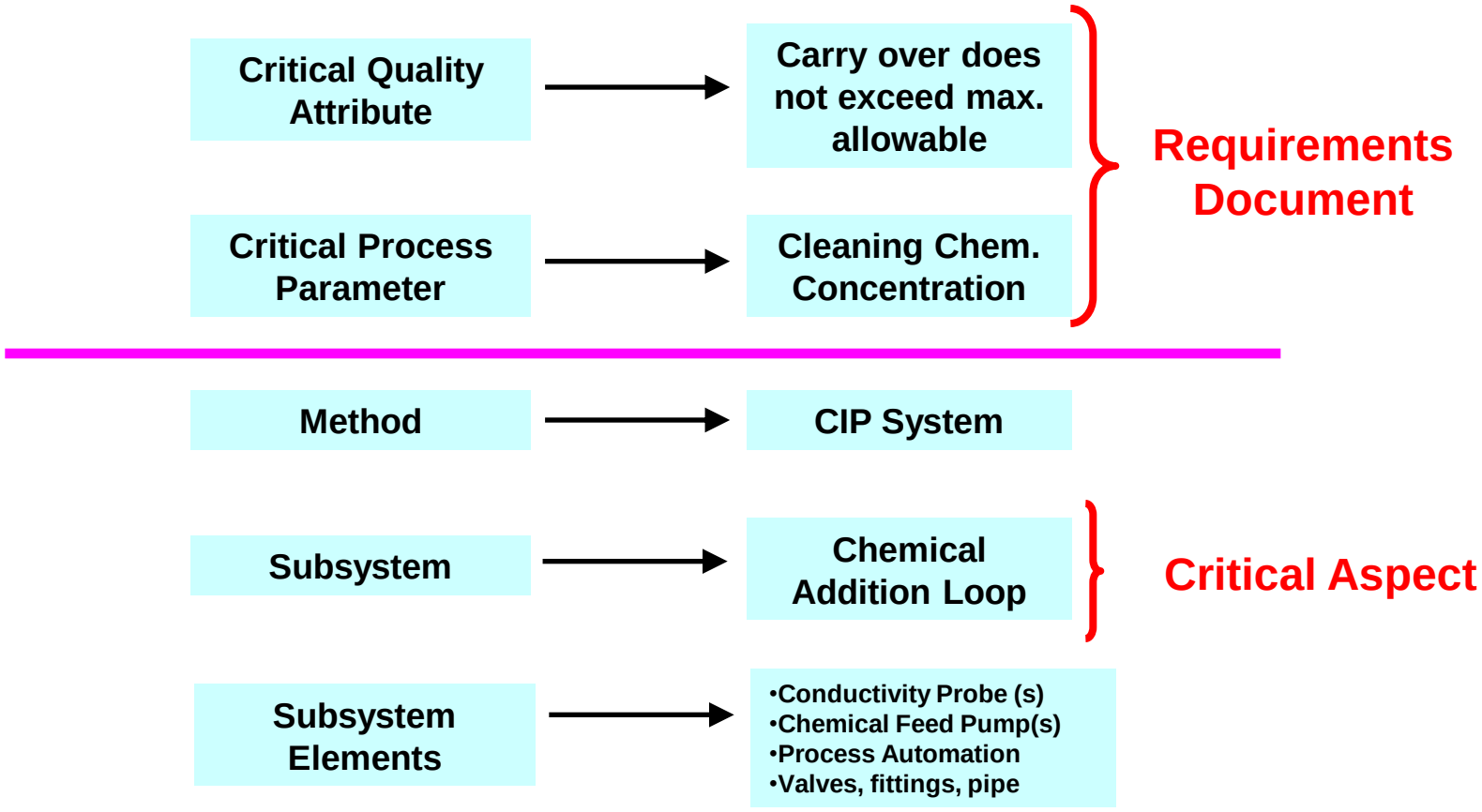
- Operational Definition (manufacturing systems): Functions and/or features of a manufacturing system that control manufacturing processes
  - product quality or patient safety requirements
  - ensuring a CQA is met

System Design Example



Process Step	Potential CQA	Potential CPP	Designed System	Potential Critical Aspects
Distillation	Impurity Profile	Solvent ratio, Temperature, Final volume, Solvent add rate, Proc Time, Agitation rate	Reactor	Temperature control, Flow load cell control, IPC test (sample device) Agitation rate control

CIP System Hierarchy Example



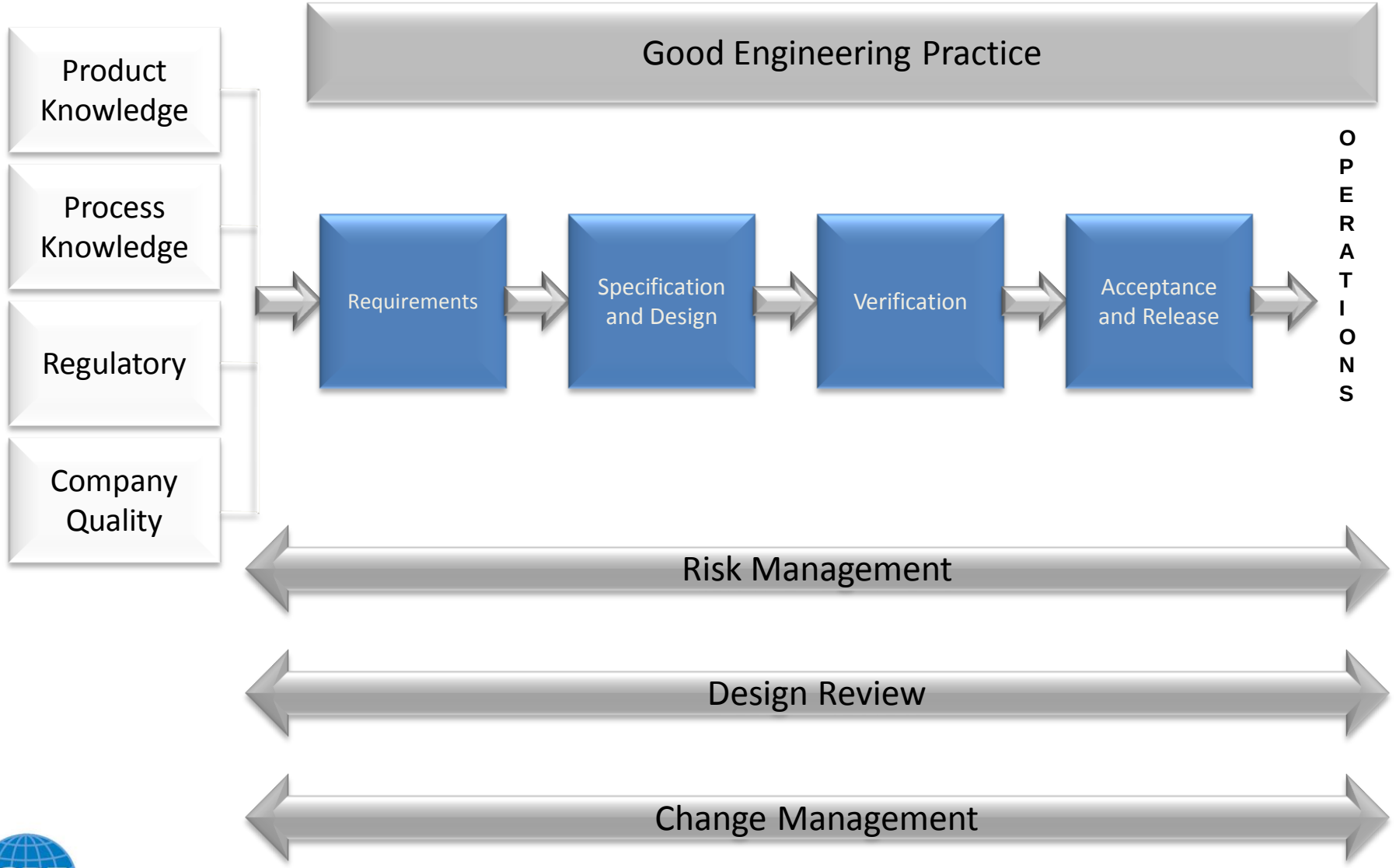
Relationship of CQA, CPP, and Critical Aspects

Process Step	• Mixing
CQA	• Potency
CPP	• Mixing Time, Mixing Speed
Critical Aspect(s)	• Ability to control, monitor, alarm mixing time and speed

Relationship of CQA, CPP, and Critical Aspects

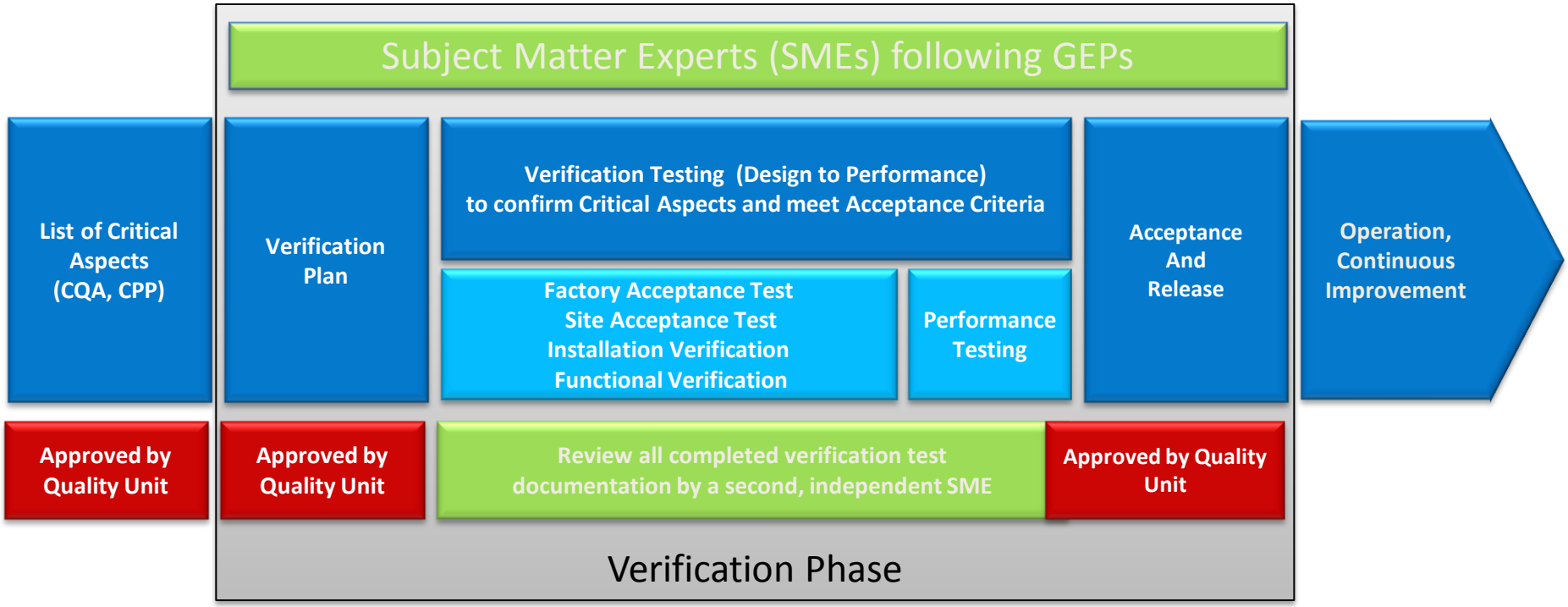
Process Step	• Depyrogenation
CQA	• Pyrogen Free
CPP	• Belt Speed, Temperature
Critical Aspect(s)	• Ability to control, monitor, alarm belt speed and tunnel temperature

ASTM E2500-07 Lifecycle Phases



Reference: Figure 1: ASTM E2500-07, pg 3

Verification Process Flow Chart



CHECK: Your Program Alignment

- Where is your program today?
- Is your risk management program aligned with ICH Q9 and ASTM E2500?
- Is your site discussing these guidance documents?
- Have you defined CQA's, CPP's and CA's?
- Is this process living or static?

Risk Management

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Risk Management vs. Risk Assessment

Risk Assessment (ICH Q9)
A systematic process of organizing information to support a Risk decision to be made within a Risk Management process. The process consists of the identification of Hazards and the analysis and evaluation of Risks associated with exposure to those Hazards.

Risk Assessment

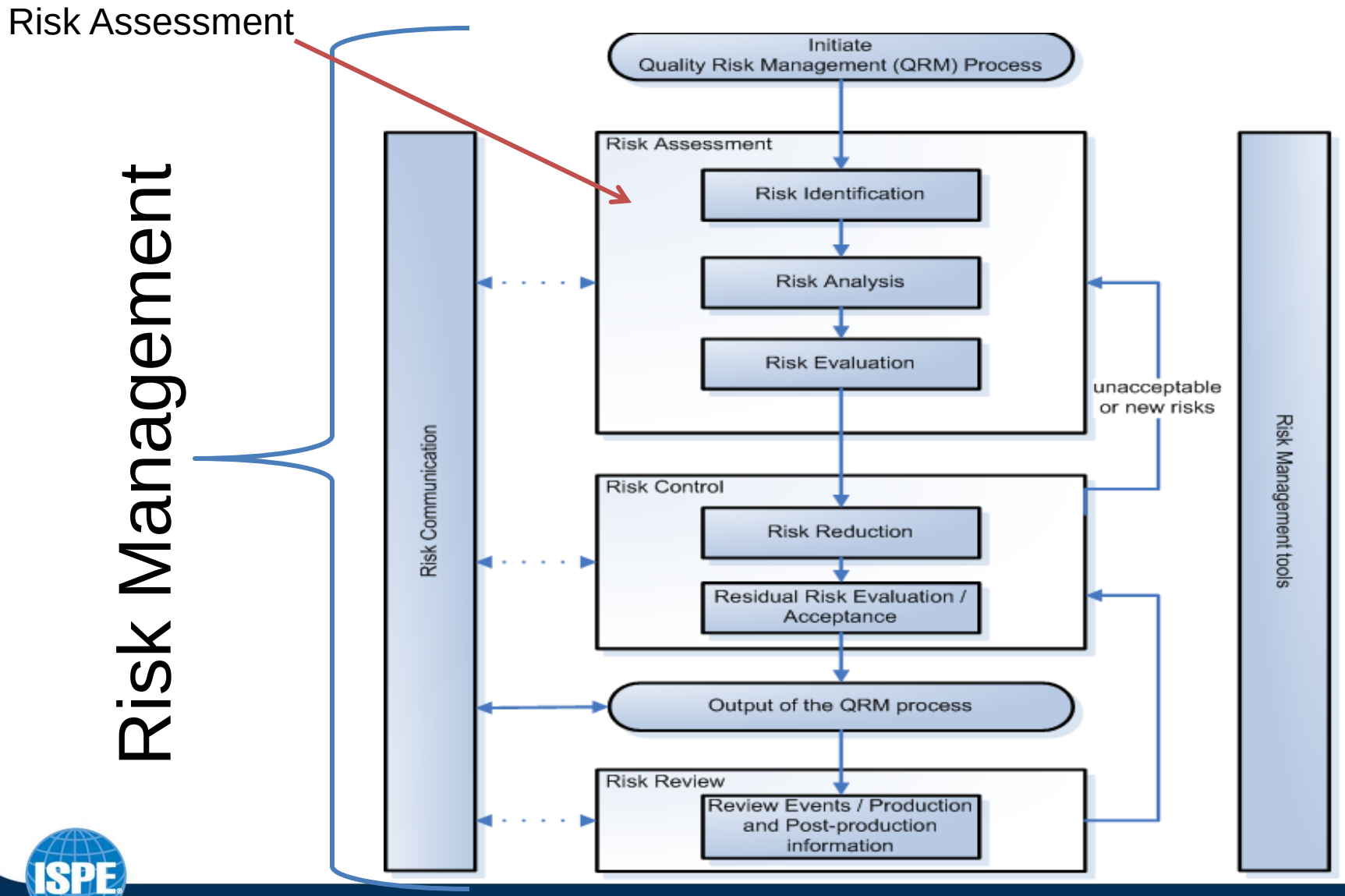
- Specific event
- Point in time
- Subject Matter Expert
- Deep technical knowledge
- Produces individual documents consisting of hazards and risk evaluations

Risk Management

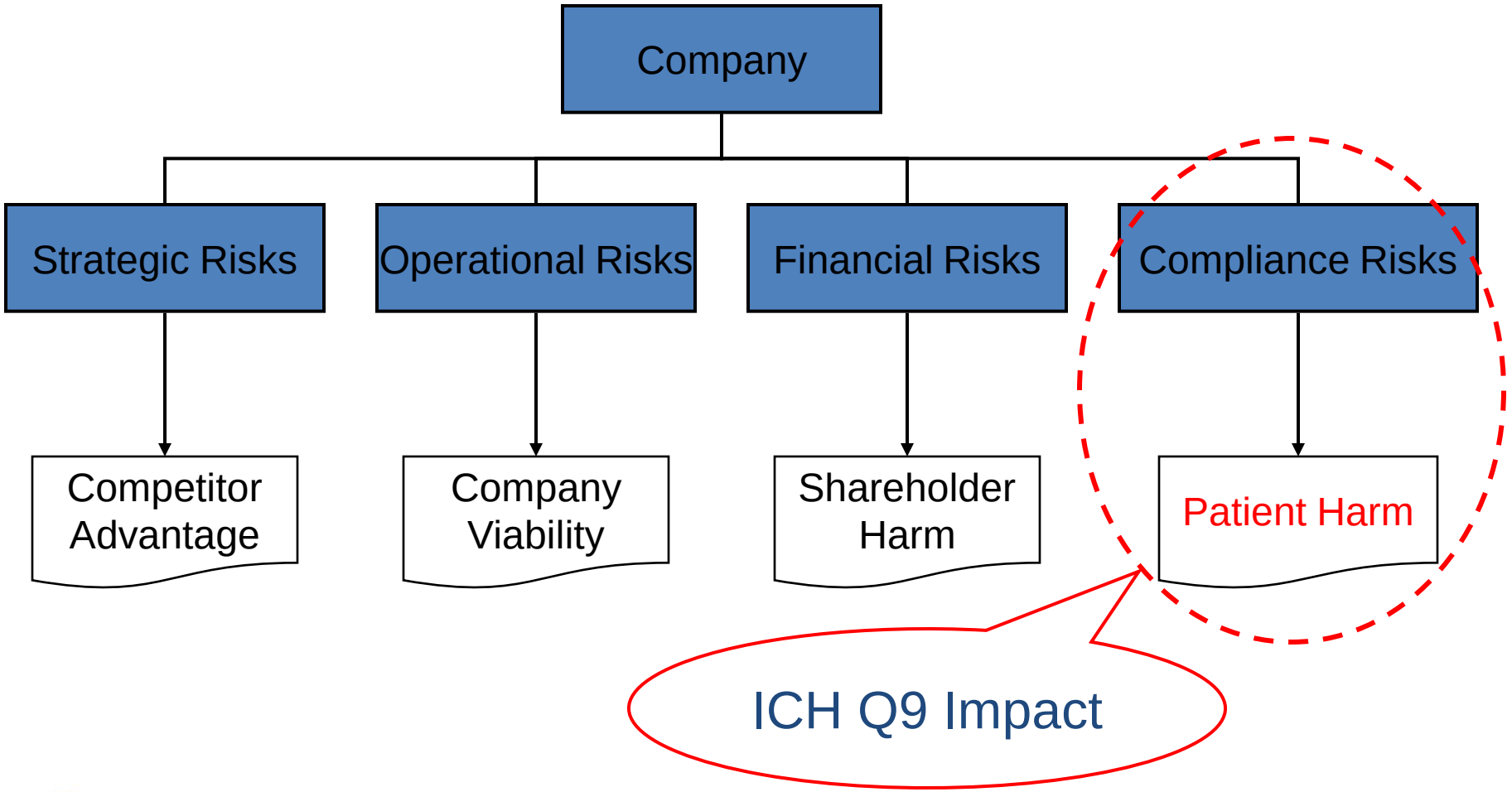
- Overall risk program
- Living
- Management accountability
- Processes to coordinate, facilitate and improve science-based decision making with respect to risk

Risk Management (ICH Q9)
A systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating and controlling Risk.

Risk Assessment vs. Risk Management



Risk Management is Broad



Risk Management Program

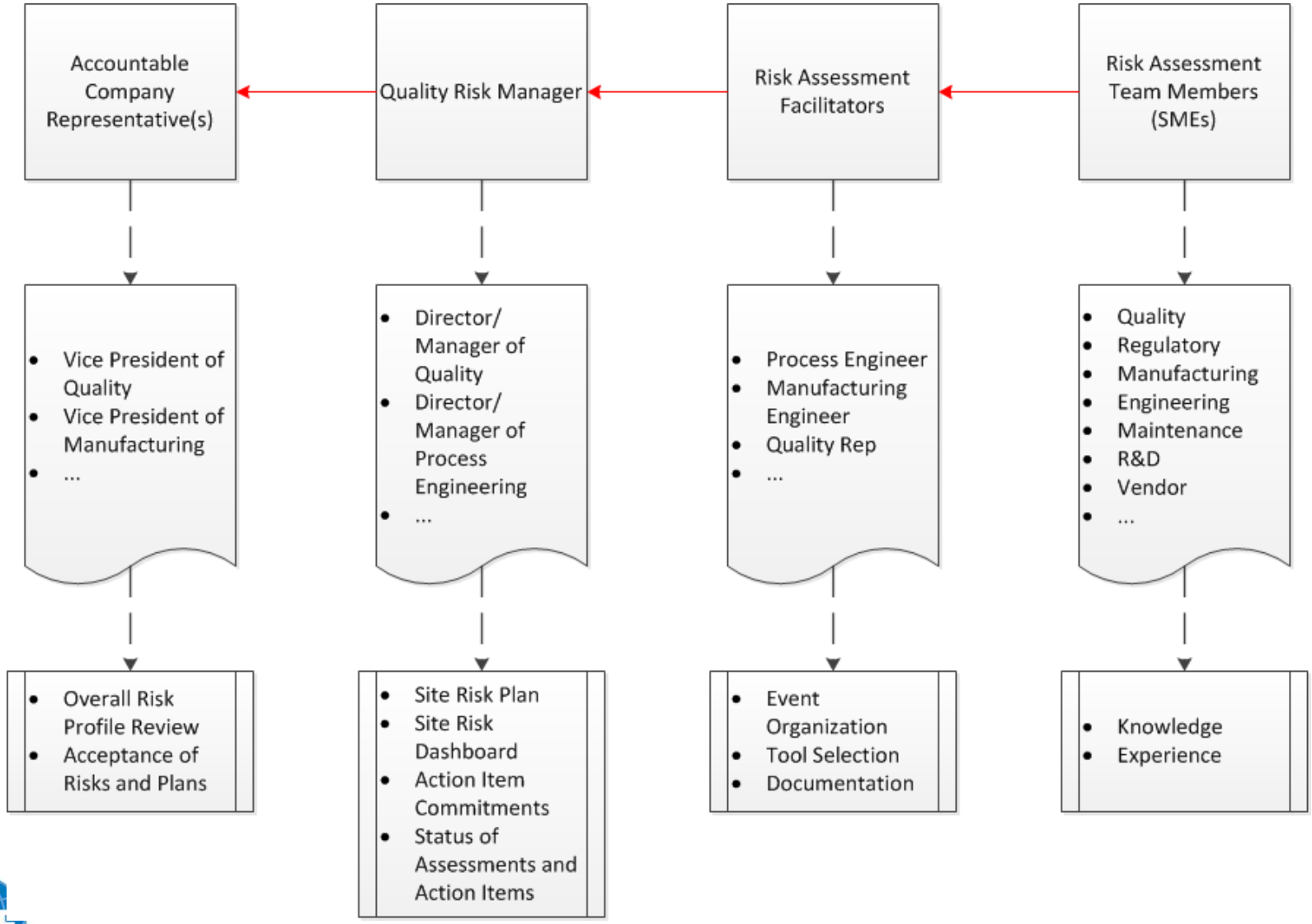
The QRM lifecycle is intended to be a continuous holistic process, and each phase of the product lifecycle is to include:

- identification of known and foreseeable Hazards associated with a product, process, or system
- estimation and evaluation of associated Risks
- control of Risks
- monitoring the effectiveness of the control
- communication of Risks to the appropriate stakeholders

QRM Responsibilities

- Identify the personnel or functional groups with responsibility for the execution of specific risk management activities
- Ensure these responsibilities are upheld
- The key to successful risk management is the commitment of management and a focused, interdisciplinary team

Organizational Structure



QRM Responsibilities

- Senior Management
  - Ensure adequate resources are available
  - Ensure QRM is planned and coordinated across various functions and departments
  - Ensure the QRM process is defined, deployed, and reviewed
  - Ensure the process is living – actions prioritized, improvements implemented, documents updated
  - Communicate risks to stakeholders as appropriate
- Subject Matter Experts (SMEs)
  - Individuals who have the appropriate level of knowledge and experience to support QRM activities
  - Experts from several areas should be included: quality, engineering, regulatory, production operations, clinical, and others support QRM activities
- Other
  - Team Leader – Unbiased, independent expert in Risk Management
  - QRM Owner – Responsible person for ensuring QRM activities are completed

Risk Management Team

- Accountable management group that meets to:
  - Implement risk program (procedures, training, enhancements)
  - Prioritizes Risk Assessment (RA) activities
  - Identify RA team leader
  - Assign RA team members
  - Review risk results
  - Integrate risk results and assign priorities for risk reduction activities
  - Review risk revisions after implementation of activities
  - Verify close-out of risk assessment events
- Communicate risks to company officers as appropriate

Risk Planning

- Identify the planned risk assessment events that will occur during the year
- Prioritize the events
- Identify the team leader for the events
- Integrate results of unplanned risk evaluations into the priorities
- Provide input on priority of risk mitigation projects

Risk Approval

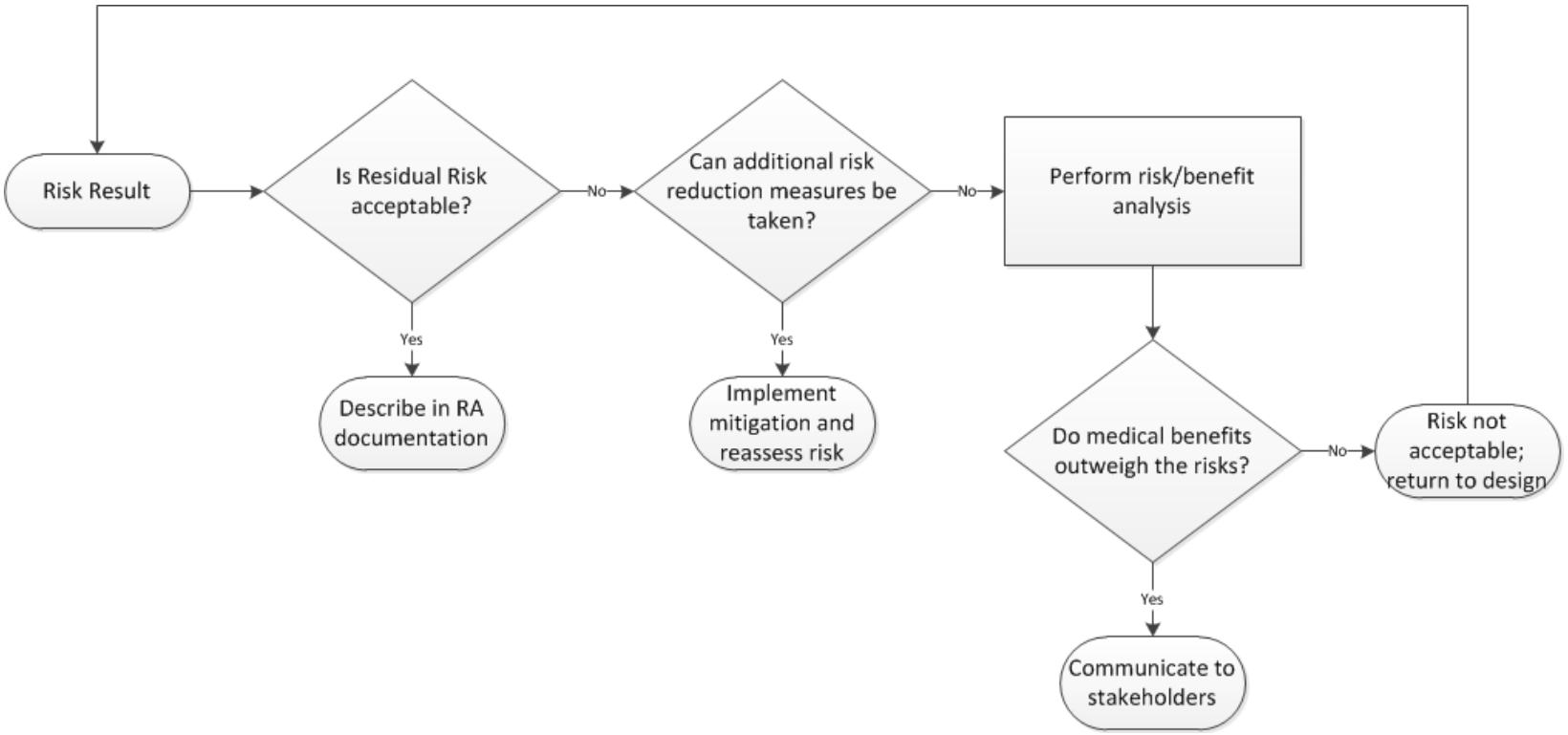
- Review results of risk assessments for awareness
- Approve risk results and recommendations (accept identified risk or drive improvements)
- Review status of identified actions for implementation and effectiveness
- Approve updated report after risk reduction
- Agree to risk event close-out

Define Criteria

- Criteria required for risk control and residual risk acceptance

Risk Level	Required Action/Acceptability
High	Mitigation required; residual risk is unacceptable – further mitigation or a risk/benefit analysis is required in order to accept the residual risk
Medium	Mitigation required unless appropriate justification is provided
Low	No further action required; residual risk is acceptable

Evaluation of Residual Risk



Risk Profile

- The overall Risk associated with a system, product, or process, including the nature, gravity, and pervasiveness of these Risks
- The process flow helps to decide and document the risk profile
- The risk profile must be reviewed and approved by responsible management
- The risk profile must continued to be reviewed when updated or changed

CHECK: Risk Management

- Who is accountable for the risk management program?
- Who are the members of the risk management team?
- How are risk assessment activities and results prioritized?
- Are potential risk team leaders identified and trained?
- Are SMEs identified and trained?
- Who maintains the risk management files?
  - Reports
  - Minutes including decisions
  - Plans
- Are approvers defined?
- Are stakeholders aware of risk processes and risk profiles?

Risk Tools

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Risk Assessment Tools

Numerous Tools Exist:

- Failure Modes and Effects Analysis (FMEA)
- Fault Tree Analysis (FTA)
- Fishbone Diagrams (Ishikawa Diagrams)
- Hazards Analysis and Critical Control Points (HACCP)
- Hazard and Operability Studies (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and Filtering (RR&F)

Tool Selection

- "*When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable*" – ICH Q9 Section 4.3
- i.e. QRM tool selection is a function of the risk assessment problem statement
- and practitioners must have knowledge and expertise across an array of QRM tools
- "*It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used*" – ICH Q9 EWG Briefing Pack

Consequences of Tool Selection

- The capability to manage quality risks may suffer if a “one size fits all” approach is applied to selecting a QRM tool
- Meaningful, effective, and efficient QRM results when the selected tool fits the problem statement and intent of the risk assessment
- Tool selection will impact usefulness, ease of execution, quality, a validity of the risk assessment
- Simple tools used with limited process knowledge of risk topic is straightforward
- Complex tools provide greater insight and value with advanced process knowledge or problem statement is complex

Recommended Reading

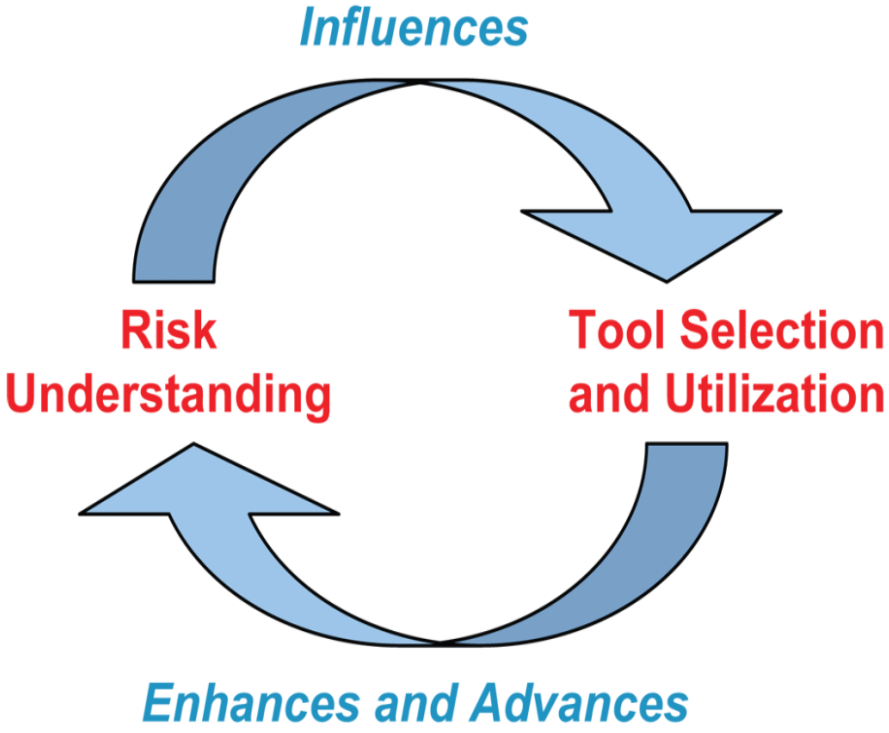
Quality Risk Management (QRM) Tool Selection: Getting to Right First Time

- Written by Kristen Murray and Stephen Reich from Pfizer, Inc.
- Pharmaceutical Engineering, The Official Magazine of ISPE
- July/August 2011, Vol. 31 No. 4
- ISPE Article of the Year

Selecting QRM Tools

Knowledge pertaining to potential risks both influences, and is influenced by, the selection of QRM tools.

The paradox: QRM tools are typically used to facilitate and organize risk identification, yet it is premature to select a QRM tool before knowing the nature of the risks to be assessed.



Selecting QRM Tools

The paradox is overcome by risk management facilitators who focus the team on the following aspects of risk management prior to tool selection:

- defining a preliminary risk problem statement
- defining the scope and boundaries of the risk assessment
- identifying available data to support the assessment
- undergoing a preliminary risk identification exercise

Selecting QRM Tools

- Preliminary risk identification may be quickly performed
- Depending on the complexity and criticality of the risks, this preliminary understanding may be achieved through:
  - informal means, such as unstructured team discussions or
  - more structured brainstorming exercises, such as fishbone or affinity diagramming

Tool Selection Questions

1. What is the problem statement or intent of the risk assessment?

2. What is the scope of the assessment? Is it large, complex, and/or critical?

3. What is the nature of the potential negative events (risks) to be assessed? Physical and tangible hazards, system or process failure modes, deviations or nonconformance with quality systems procedures, others?

4. Are the risks and their causes well-known or are there substantial unknowns?

5. Are the causes of the risks likely independent or interdependent?

Tool Selection Questions

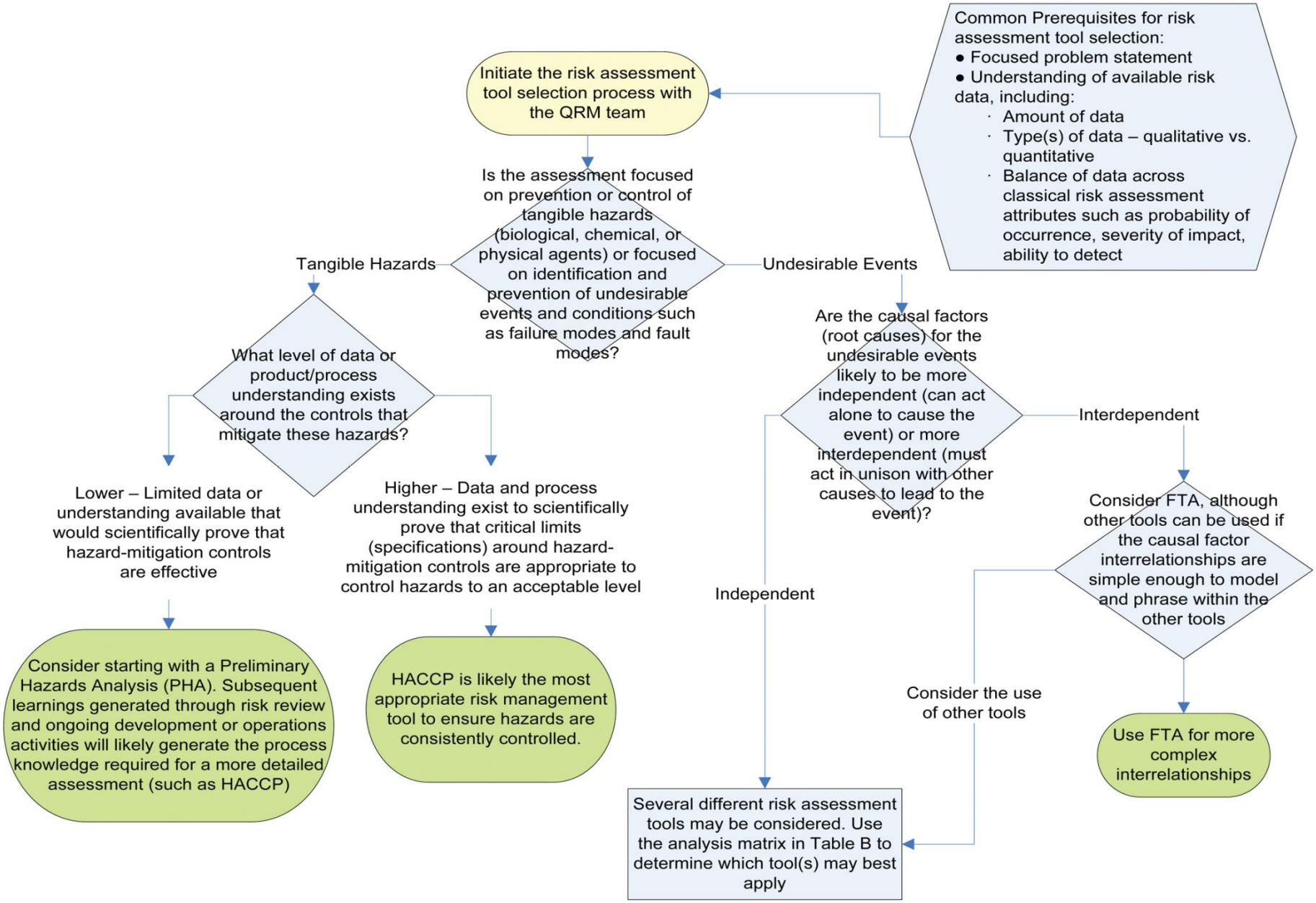
6. What levels of data or understanding exist for these risks? Alternatively, where is the current product/process/system in its lifecycle?

7. Are available data sets predominantly qualitative or quantitative?

8. Do methods or data exist that may rate the risks from the standpoint of classical factors such as probability of occurrence, severity of impact, and/or capability to detect?

9. What is the expected output type for the risk assessment (rank-ordered risk register, hazard control plan, design of experiments plan, etc.)?

10. Who will the risk assessment be submitted to (or likely reviewed by)?



QRM Tool Selection Decision Tree

Considerations	FMEA	FTA	Fishbone/ Ishikawa	HACCP	HAZOP	PHA	RR&F
If process/products/system knowledge is limited (ex. early lifecycle phases)	X	✓1	✓	X	✓1,2	✓	✓2
If process/products/system knowledge is advanced (ex. later lifecycle phases)	✓	✓	✓	✓	✓	X	✓
If problem statement is simple or elegant assessment is appropriate	✓2	✓	✓	✓2	✓2	✓	✓
If problem statement is highly complex or detailed assessment is required	✓	✓1	X	✓	✓1	X	X
If risk ranking is required	✓	X	X	X	X	✓	✓
If risk detection capability is limited	X	✓	✓	✓	!	!	!
If risk data is more qualitative in nature	X	✓	✓	X	✓2	✓	✓
If risk data is more quantitative in nature	✓	✓	X	✓	✓	✓	✓
If demonstration of the effectiveness of risk controls is required	✓	X	X	✓	X	X	X
If risk identification is a challenge, if hidden risks need to be revealed, or if structured brainstorming is required	X	✓	✓	X	✓	X	X

✓ Tool is likely a suitable fit under this consideration and is designed or capable to perform this way.

X Tool may have less (or no) capability to deliver under this consideration or may be either overly complicated or too simplistic for the task.

! Tool may be suitable, however effectiveness may be limited due to challenges in rating some probabilities of occurrence. It may be challenging to rate risk probabilities if there is limited means to detect those risks in the first place.

1 Brainstorming capability of this tool may be particularly beneficial for this type of assessment.

2 Capabilities of this tool can be scaled back to accommodate qualitative or more simple assessments.

Tool Analysis Matrix

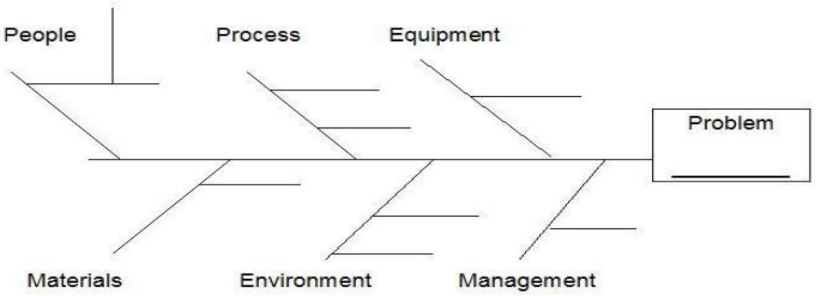
- The QRM tool analysis matrix lists seven of the most frequently utilized QRM tools
- The rows list considerations that are largely derived from the key prerequisite questions
- The seven common QRM tools are rated across the columns for their general compatibility with the listed considerations

The full benefits of QRM are consistently realized only when the best tools are selected for the job. In this regard, organizations should endeavor to standardize around the process of intelligently considering, debating, and then selecting the best QRM tool each time they commence a risk-based initiative

Desired Output

Failure Investigation

- Consider FTA, Fishbone or HAZOP
  - Brainstorming identifies a broader list of potential risks
- Don't use FMEA, HACCP
  - Don't have data for risk ranking



Failure Mode and Effects Analysis (FMEA) Worksheet

System, Product, or Process:				Owner:				
Background				Rating				
Description	Potential Failure Mode	Potential Effect of Failure	Root Causes	SEV	OCC	DET	RPN	Owner

Risk Prioritization

- Consider FMEA, PHA
  - Provides relative ranking of risks
- Don't use FTA, Fishbone
  - Doesn't provide mechanism for risk ranking

CHECK: Risk Tools

- Does your procedure allow for use of different tools?
- Is there expertise to help define which tool will be most effective?
- How are the results from the different tools compiled?

Risk Assessment

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Risk Assessment (RA)

- Documentation
- Alignment

Identify what is critical to patient safety and product quality

- Want all operational groups to give the same answer
- Want to document the critical items in the batch record during manufacturing
- Want to utilize the results in equipment verification and process validation
- Want to prioritize risk areas for improvement
- Want to aid assessment of product impact during failure investigations

- Investigations
- Continuous Improvement
- Support Validation

RA Goal

Confirm risks to patient safety and product quality are sufficiently mitigated

- Conduct exercise from a perspective of “what is the risk to patient”
- Equipment is fit for its intended purpose:
  - Equipment is capable of meeting the process requirements
  - Equipment is capable of controlling risks to the patient
- Process controls reduce risk
  - Controls in place and effective

RA Goal Is NOT…

- Long
- Tedious
- Brain-numbing

- Contentious
- Argumentative
- 2 versus 3

When is RA Performed?

- Planned events of defined systems
- Quality Systems
  - CAPA
  - Deviations
  - Change Controls
  - SOP and Training development
- Laboratory
  - OOS
  - Periodic retesting
- Quality
  - EM
  - Auditing
  - Quality defects
- Continuous improvement prioritization
- Facility/Equipment
  - Design
  - Qualification
  - Process Validation
  - Calibration/Maintenance
- Product Development
  - Process Design
  - Process Scale-up
  - Cleaning validation
  - Container Closure System
- Material Management
  - Package design
  - Label control
  - Instructions for use
- In-process testing and sampling

Planned Risk Assessment

- Focus for this conversation is planned events on defined systems
- Develop formalized RA process for mfg. process, equipment, facility and utilities
- Focus on high and medium severity risks that impact patient safety

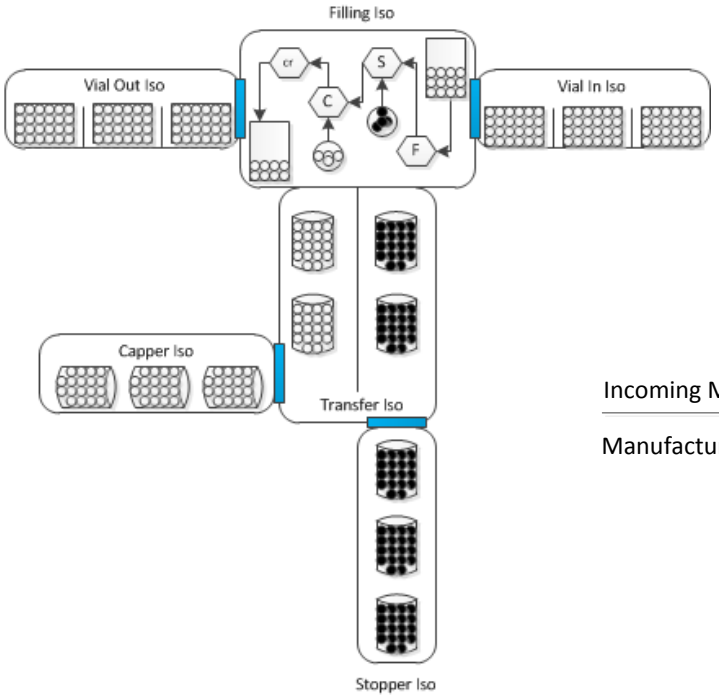
RA Team

- Define team leader
- Define team members
- Conduct training on risk process, if needed
- Verify resources have the time to participate fully
- Verify resources have the knowledge to participate fully

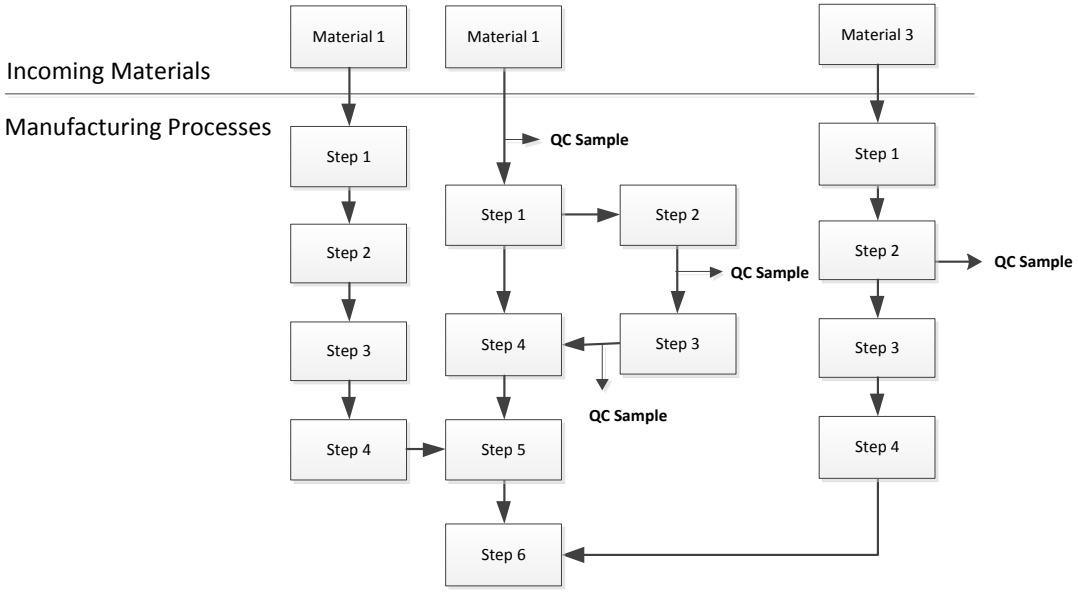
RA Process

- Define the system boundary
- Define the process steps
- Identify the hazards, harms and causes
- Identify the controls
- Evaluate the severity, occurrence, and detection (?)
- Identify the risk mitigation actions

Define the System Boundary



From incoming material to secondary packaging for process xxx



Identify Process Areas

- Docking
- Manual Cleaning
- VHP Cycle
- Environmental Monitoring
- Vial In Tray Handling
- Vial Loading
- Filling
- Stopper Handling
- Stoppering
- Cap Handling
- Capping
- Crimping
- Vial Unloading
- Vial Out Tray Handling
- Undocking

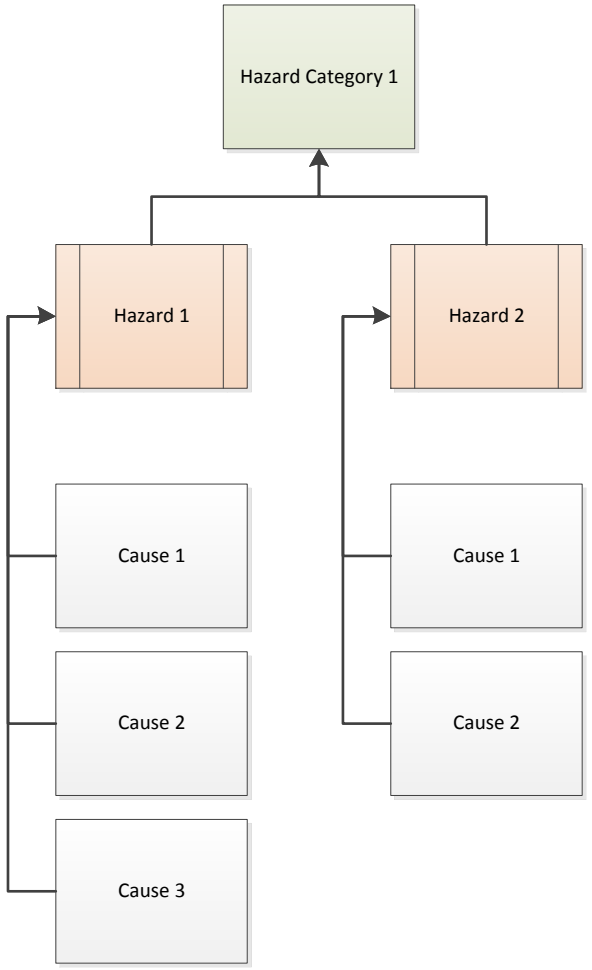
Maintain a focus on the process steps within the defined boundary:

- Assume everything coming in across the boundary is good
- Address materials, lab, other supporting processes in separate risk assessments
- Address pulling samples as it can impact process being run

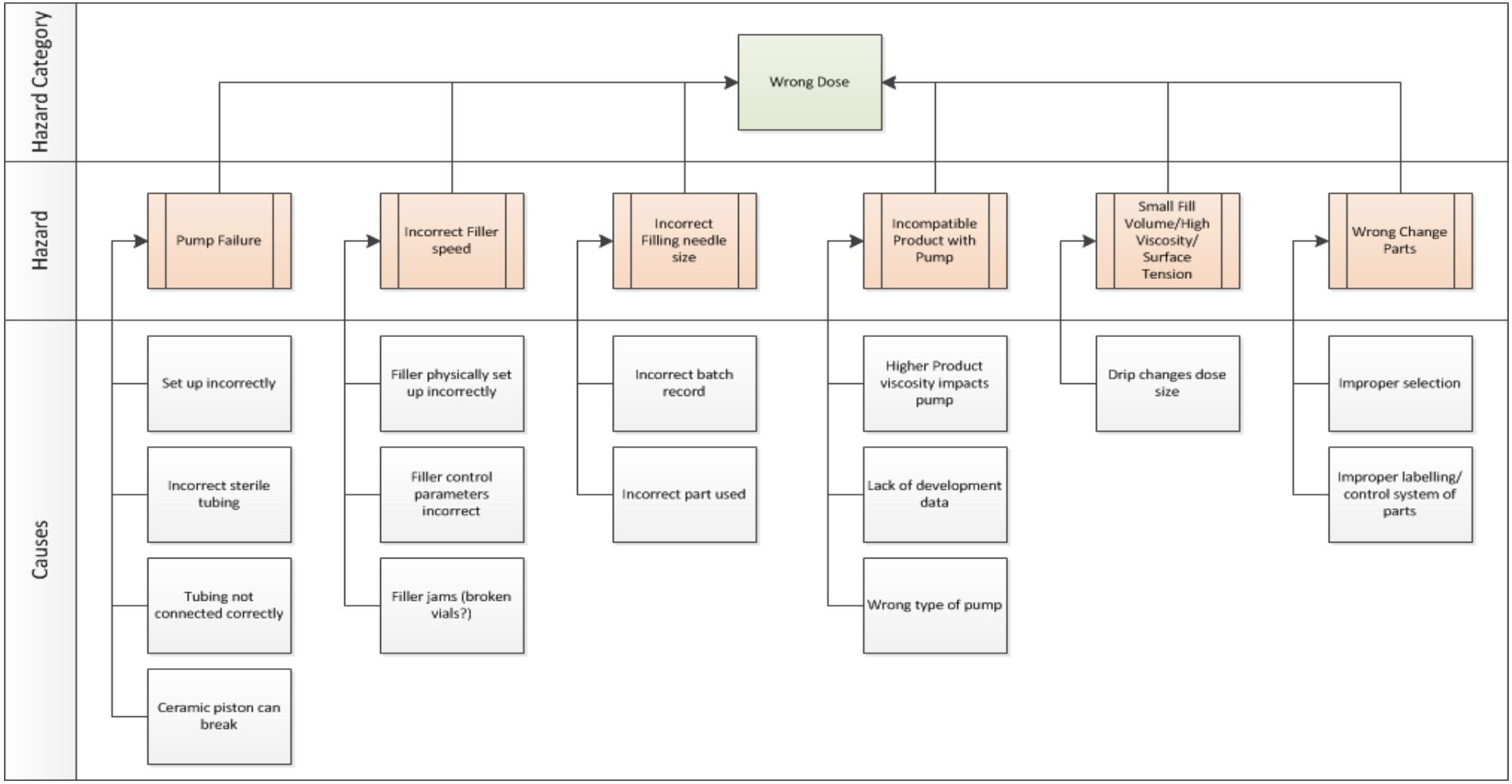
Conduct Hazard Analysis

1. Identify high level hazard categories
2. Document the hazards that relate to each category
3. Identify the causes for each hazard

- Brainstorm to catch hidden hazards or causes
- Representation from multiple groups with different knowledge of the process
- Capture risk, but avoid controls or severity until later



Hazard Analysis Example

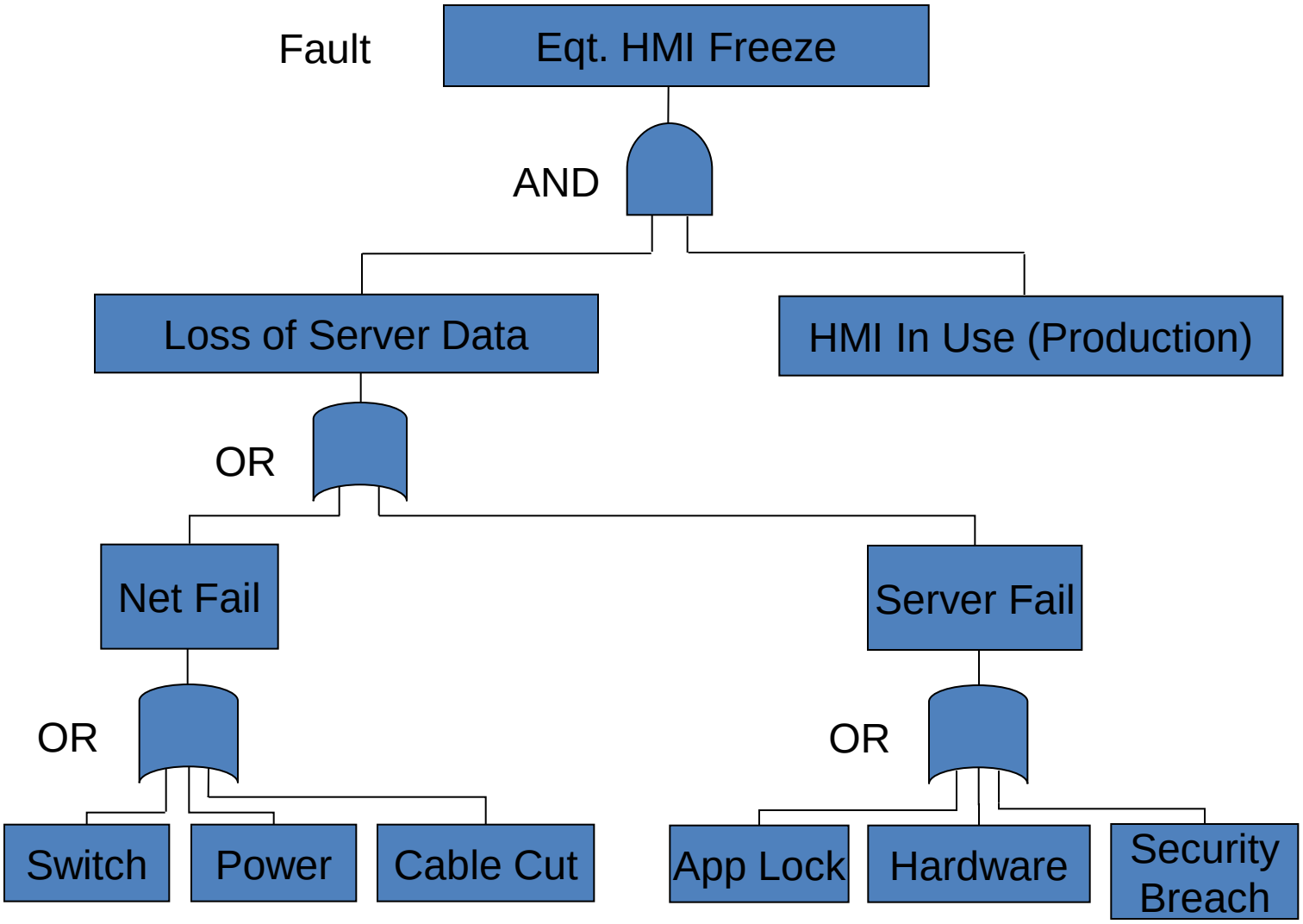


Conduct Risk Assessment

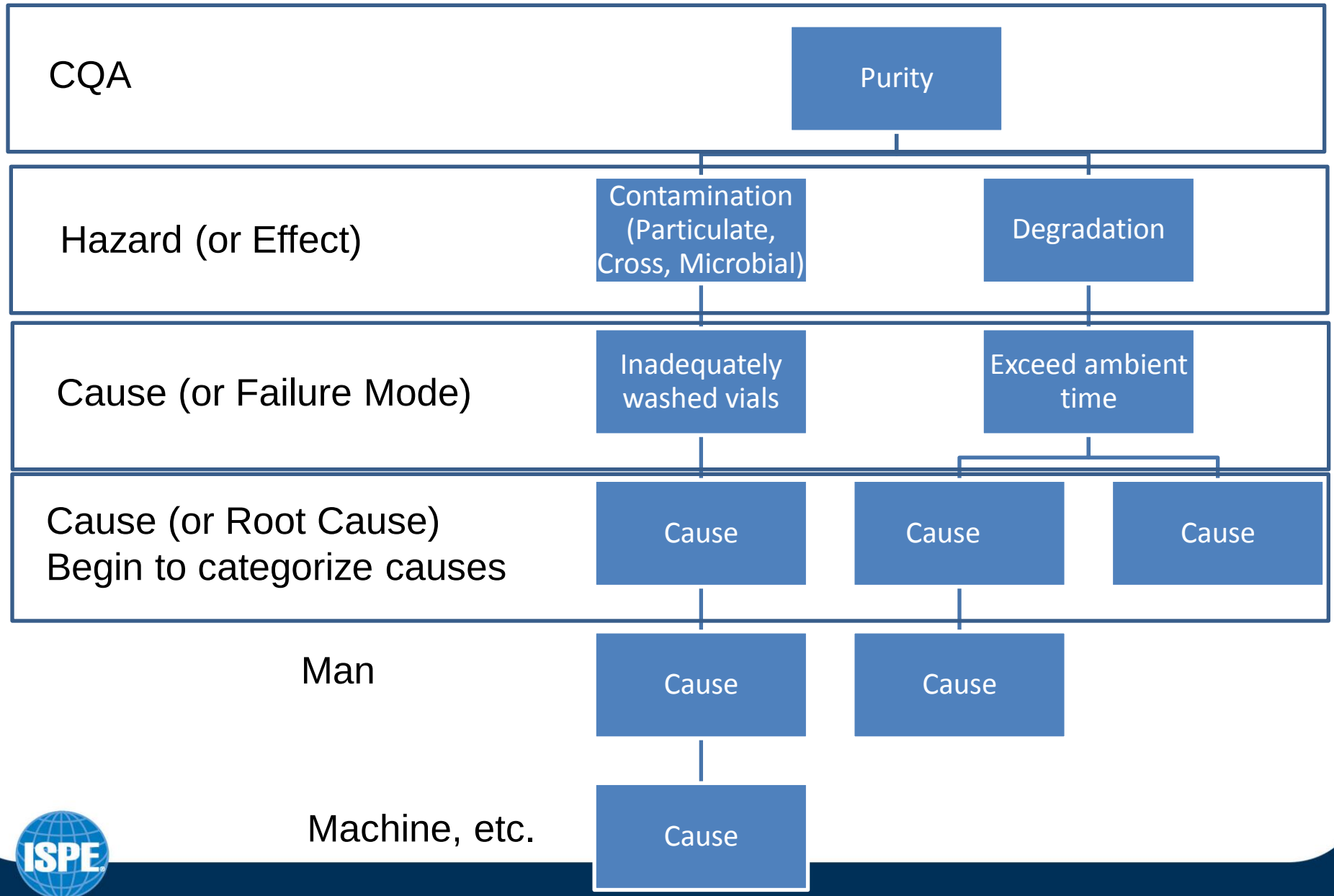
- Use pFMEA approach
- Before starting the pFMEA, facilitator can fill in multiple columns with the results of the Hazard Analysis
- Goal is to still break the process into steps to make it more manageable
- Add a few columns with each step, feels more manageable and team can measure progress

Line Number	Hazard Category	Hazard	Severity to Patient	Severity to Quality	Process Area(s) Affected	Cause
1	Wrong Dose	Pump Failure			Filling	Pump Setup Incorrectly
2	Wrong Dose	Pump Failure			Filling	Incorrect tubing
3	Wrong Dose	Incorrect Filler Speed			Filling	Filler Setup Incorrectly

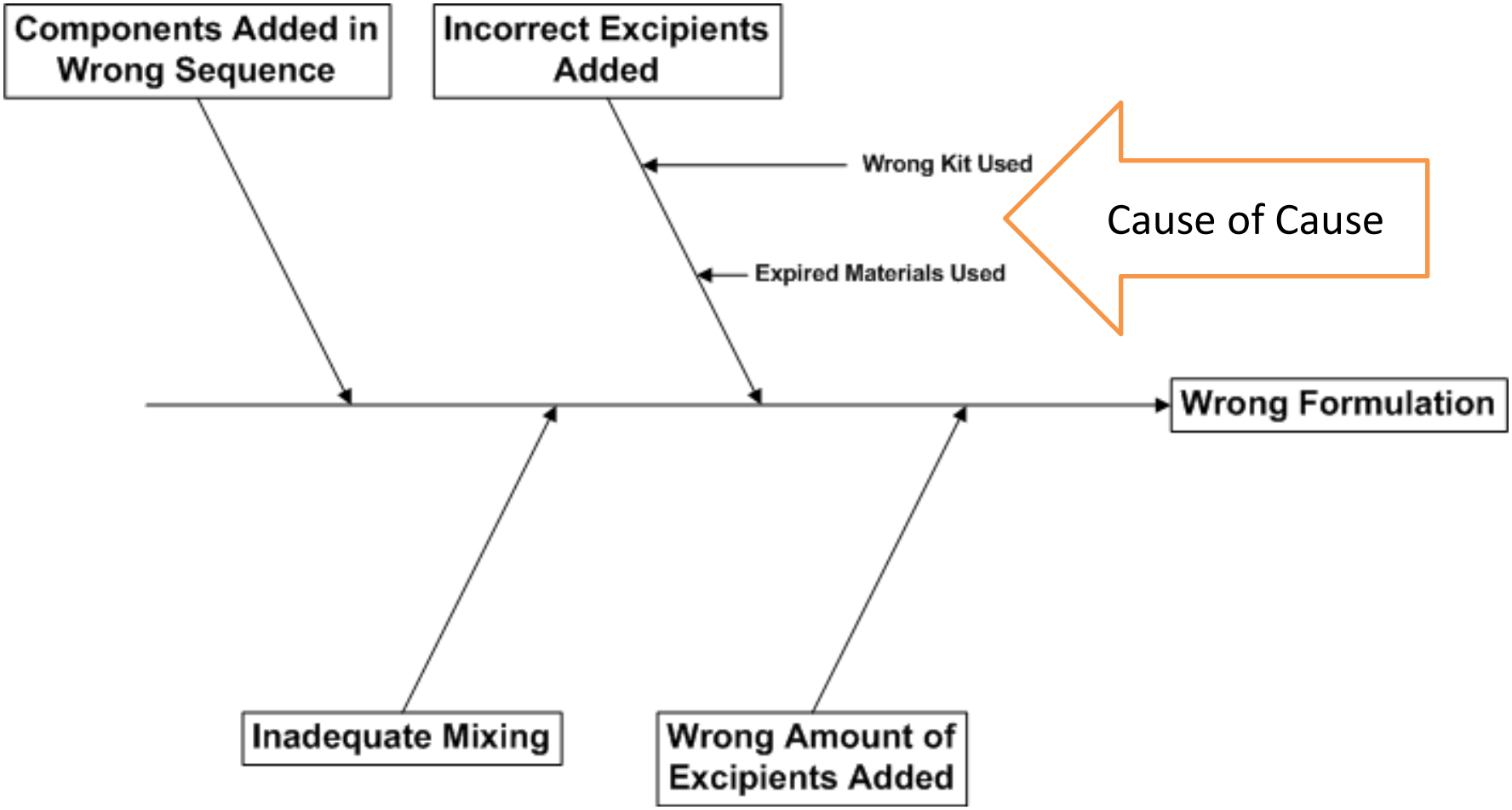
Simple System FTA (One Branch)



FTA Supporting FMEA



Cause and Effect Diagram



Controls

- Identify design control(s)
  - What was built into the design of the equipment or system?
- Identify other/process control(s)
  - What is defined in the SOP, training, monitoring, or other systems?
- Identify the detection mechanism(s)
  - List all alarms, indicators, gauges, visual inspection, or lab results used to detect and out of limit condition.
- List specifications/acceptance criteria and supporting rationale
  - Provide the agreed upon reference now so it can be found later.

Line Number	Hazard Category	Hazard	Severity to Patient	Severity to Quality	Process Area(s) Affected	Cause	Controls from Process / Equipment Design	Specification / Acceptance Criteria	Rationale for Specification	Other Control Mechanisms	Specification / Acceptance Criteria	Rationale for Specification	Detection Mechanism for Hazard	Notes
1														
2														

Risk & Operational Control Strategy

- Categorize the risk
  - Follow procedure requirements if specified
  - High, medium low: Goal is to differentiate for prioritization
- Identify the operational process control strategies
  - Process Variable to Monitor
  - SOP
  - Training
  - Equipment Setup
  - Batch Records
  - Preventive Maintenance
  - Calibration
  - Critical Parts Management
  - Validated Computer System
  - Critical Aspect

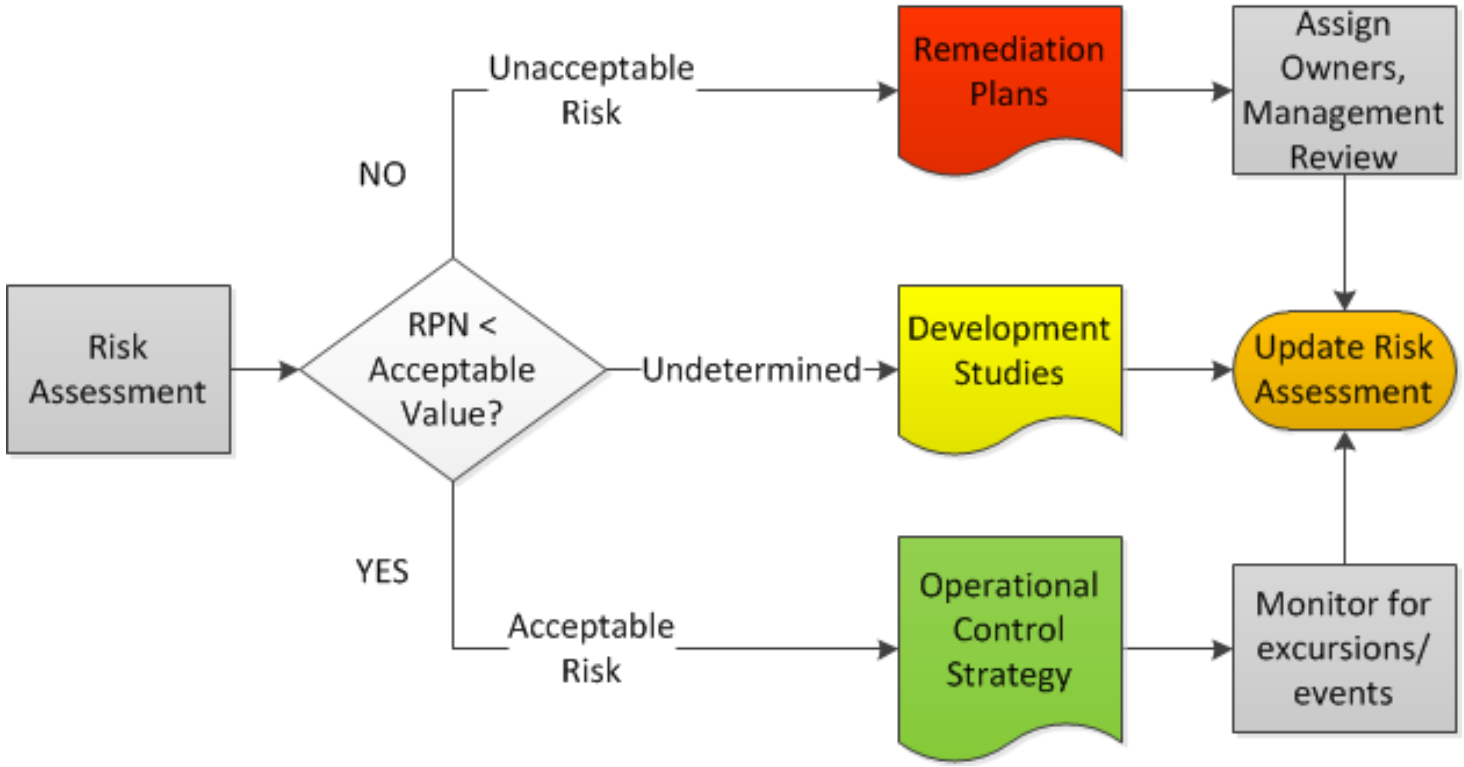
Line Number	Hazard Category	Hazard	Severity to Patient	Severity to Quality	Process Area(s) Affected	Cause	Controls from Process / Equipment Design	Specification / Acceptance Criteria	Rationale for Specification	Other Control Mechanisms	Specification / Acceptance Criteria	Rationale for Specification	Detection Mechanism for Hazard	Occurrence / Detectability	Risk	Process Variable to Monitor	SOP	Training	Equipment setup	Batch Records	Preventative Maintenance	Calibration	Critical Parts Management	Part 11 Systems/ SAP-MES / Recipe Driven Setup	Critical Aspects	Notes
1																										
2																										
3																										

Risk Planning

Hazard	Hazard Area	Causes	Likeliness	Severity	Risk	Controls	Likeliness	Severity	Risk	Owner	Status
Process Failure	Equipment Failure	Improper calibration	1	1	1	Will take as-found readings, add new calibration point(s) in airlock					
		Improper sensor location	1	10	10	Confirm reference static pressure location.					
		Improper/lack of restart	1	10	10						
		Incorrect demolition of infrastructure	1	5	5						
		Lose room access to equipment	1	5	5	List of equipment that must be moved prior to construction					
Cross Contamination	Carryover	Impact to facility from different flow of dirty equipment	1	1	1	Schedule timing of movement					
		Impact to other operations (capping, packaging) from different flow	5	10	50	Schedule timing of movement, procedure changes for timing and appropriate cleaning after moving, training, signage, move equipment at start of second shift?	1	10	10		
		AHU-8, 10 and 15 feeding office areas and other spaces, pulling contaminates from dirty equipment	1	1	1	Not a concern for existing products, need to re-evaluate if new products brought into facility					
		Negative impact on equipment from different flow	1	1	1						
Facility	Environment	Recovery of Temp and Humidity conditions	1	5	5	Metasys, follow alarm procedures					
		Improper use of rooms during construction	1	5	5	Communication with contractors before starting, temporary routes for contractors need to be set up (break room, rest room)					
		Improper construction	1	5	5						
Compliance	Quality System Impacted	Out of date docs	5	10	50	Team to review procedures impacted	1	10	10		
		Can't follow existing procedures – EM, Sanitization, Mfg, Maint, Metrology	1	10	10	Meeting to review what was done after construction complete					
Safety	Improper Safety	Poor safety communication	5	10	50	Safety communication prior to work starting	1	10	10		
		Egress not identified	5	10	50	Add to list of what needs to be updated and communicated, update drawings	1	10	10		
		Incorrect PPE	5	10	50	Needs to be defined	1	10	10		

Risk Priority Number (RPN)

- Severity x Occurrence (x Detection)



Risk Tables

Severity	Explanation
Low	• No impact to patient safety or product quality • Negligible to slight customer annoyance
Med	• Moderate health issue with no irreversible effects • Product malfunction or product is ineffective without potential injury • Customer annoyance or complaint
High	• Serious customer harm, injury, illness, or death

Occurrence/ Detectability	Explanation
Low	• Very remote chance of occurrence and go undetected
Med	• Unlikely to occur but no detection mechanisms or • Moderate Chance of occurrence (with some detectability) or • Likely to occur, but highly detectable
High	• Moderate Chance of occurrence with no detection mechanisms or • Likely to occur, but some detection capability

	Occurrence / Detectability		
Severity	Low	Med	High
Low	Low	Low	Med
Med	Low	Med	High
High	Med	High	High

Risk Tables

Severity	Explanation
Catastrophic	A failure which may cause death
Critical	A failure which may cause severe injury
Marginal	A failure which may cause minor injury
Minor	A failure not serious enough to cause injury

Likelihood	Explanation (Production)	Explanation (New Process)
Frequent	Daily/weekly occurrence	No/very poor controls in place
Probable	Happens once per month	Controls are deemed insufficient to stop a hazard from being reported
Occasional	Happens once per quarter	Controls are in place but are deemed insufficient from some scenarios
Remote	Happens once per year	At least one control is in place for all known scenarios and the controls are deemed sufficient to stop a hazard from being reported
Improbable	Has not been detected or less than once per year	Control coverage is deemed sufficient to stop all known hazards from occurring

	Severity			
Occurrence	Minor	Marginal	Critical	Catastrophic
Frequent	II	I	I	I
Probable	III	II	I	I
Occasional	III	III	II	I
Remote	IV	III	III	I
Improbable	IV	IV	III	III

Severity	Explanation of Risk Level
I	Intolerable risk
II	Undesirable risk, tolerable only if reduction is impractical or technology doesn't exist
III	Tolerable risk, if the cost is too great for the improvement gained
IV	Negligible risk

Risk Tables

Severity	Patient/Safety Impact	Compliance Impact	Process Impact	Severity Rating
Critical	A failure which may cause death or severe injury	Warning Letter, Consent Decree, Audit Finding, 483	Product loss or failure, product shortage	10
Major	A failure which may cause minor injury	Audit comment	Delayed release, Product re-work	5
Minor	A failure not serious enough to cause injury	No compliance impact	No process impact	1

Occurrence/ Likelihood	Explanation (Production)	Explanation (New Process)	Rating
Frequent	Daily/weekly occurrence, or with every batch	No/very poor controls in place	10
Occasional	Happens once per quarter, or with occasional batches	Controls are in place but are deemed insufficient from some scenarios	5
Improbable/ Remote	Has not been detected or detected, less than once per year, or only seen on one batch	Control coverage is deemed sufficient to stop all known hazards from occurring	1

	Occurrence / Likelihood		
Severity	Frequent	Occasional	Improbable/ Remote
Critical	100	50	10
Major	50	25	5
Minor	10	5	1

Risk Report

- Required Content
  - Team
  - Scope/boundary
  - Risk evaluation results
  - Risk items requiring mitigation
  - Proposed action items
- Management Team Minutes
  - Acceptance of risk evaluation
  - Action item prioritization results
  - Follow-up plan

Considerations

- Separate patient risk/product quality impact from controls
  - Brainstorm impacts and then discuss and rank controls
  - Ask “What is the risk you need to control?”
- Differentiate risks, don’t over-analyze them
  - Be careful how many risk rankings are utilized
- Keep the team to a manageable size
  - Include cross-functional viewpoints/experience/process knowledge
- Break up the discussions
  - Brainstorm impacts and then populate table to do risk ranking in a separate meeting
- Clearly identify the control strategy
  - Start-up, in-process, final testing, line clearance, or visual by the operators

Reminders

- Select the *right* risk tool for the desired result
  - Procedures should allow some flexibility in tool selection and use
- Keep it *simple*
  - Low, Med, High may provide sufficient differentiation
- Take a *field trip*
  - Conduct a process area walk through before starting
- Involve *Quality* in the discussions and approvals
- Focus on *Patient Safety* and *Product Quality*
- Predetermine who owns the *output/follow-up*

Reminders

- Start *early* and update as appropriate
  - Impact the design, assist in validation, and establish a plan for the operational control strategy
  - After additional processing experience, failure investigations, and after equipment verification/process validation
- Use the risk assessment process to help *drive improvements and process knowledge*, not just a document for inspections
  - Great training aid as to what is critical and WHY
  - Provides common understanding between groups during failure investigations or regulatory inspections
  - As good as the knowledge in the room at the time of the discussion

CHECK: Risk Assessment

- Which processes integrate risk assessment?
- How is the risk profile updated based on the different assessments?
- How is management notified of the risk results and recommendations?
- What documents are needed?
- What risk tables are utilized?

QUESTIONS

Thank You!

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