Risk Assessment in Aseptic Processing

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Objectives

- Understand basics of Risk Assessment and Management
- Is the risk Real or Perceived
- Apply risk management methods defined in the Quality Systems program
- Identify risks and reduce based on continuous process improvement

Risk Management References

- EU Guidelines to Good Manufacturing Practices Medicinal Products for Human and Veterinary Use (Feb 2008)
  - Mandates use of risk management principles within quality management system

Risk Management References

- Guidelines on Risk Management Systems for Medicinal Products for Human Use (EMEA-Nov 2005)
  - Must meet requirements for description of a risk management systems for an individual medicinal product
  - Develop a risk management plans

Risk Management

- General Information
  - Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach
  - Science-based enforcement
  - Accurate understanding of realistic level of risk
  - New technology to mitigate risk

Quality-Related Risks

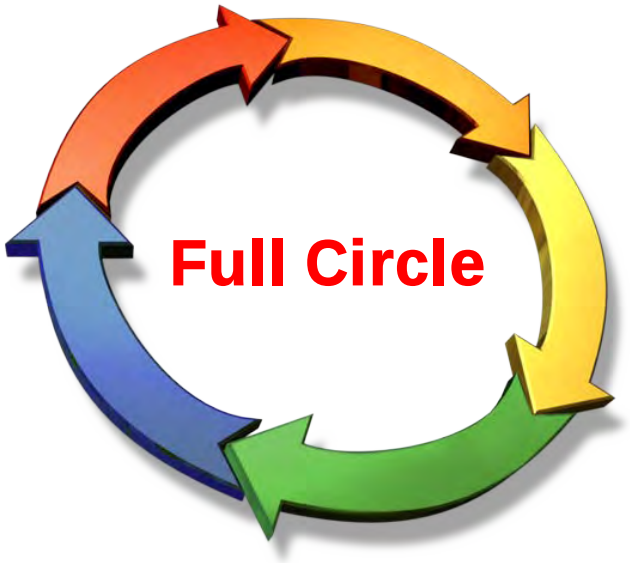
- Operational Risk
  - Facility, equipment and design elements
  - Personnel
  - Environmental conditions
- System Risk
  - Current with cGMP
  - Quality systems checks and controls
  - Documentation
  - Regulatory compliance

Quality-Related Risks

- Process Risk
  - Tech-Transfer
  - Validation
  - Understanding of the process
  - Operations and quality parameters
- Product Risk
  - Quality attributes based on Global Limits and Specifications
  - Safety & Efficacy

Defending Compliance Risks

- Analysis / Risk Assessment
- CAPA Mitigations
- Monitoring
- Good science to support decisions



Benefits of Risk Based Decisions

- Defendable to regulatory agencies
  - Investigations and change control system
  - Justifications for global specifications and quality Action Levels
  - Knowledge based on understanding the process
- Understanding and controlling risk equates to safer products

Risk Assessment

How Risky is Aseptic Processing?

It all depends on what your definition of risk is

Risk Assessment

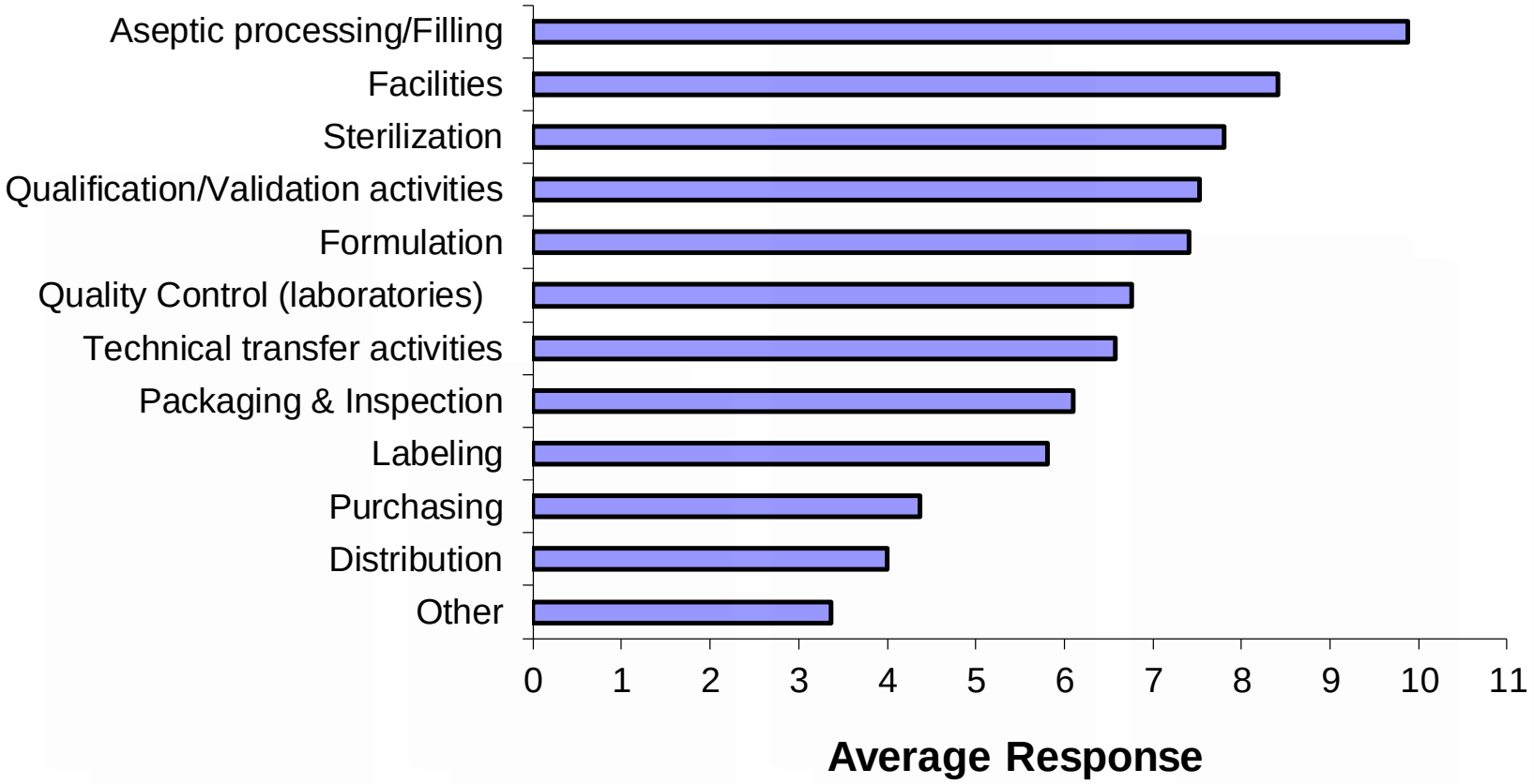
Aseptic processing may
not be as risky as the
regulatory agencies believe.

It may be hazardous,
but if it is well controlled,
it can be less risky
than driving a car

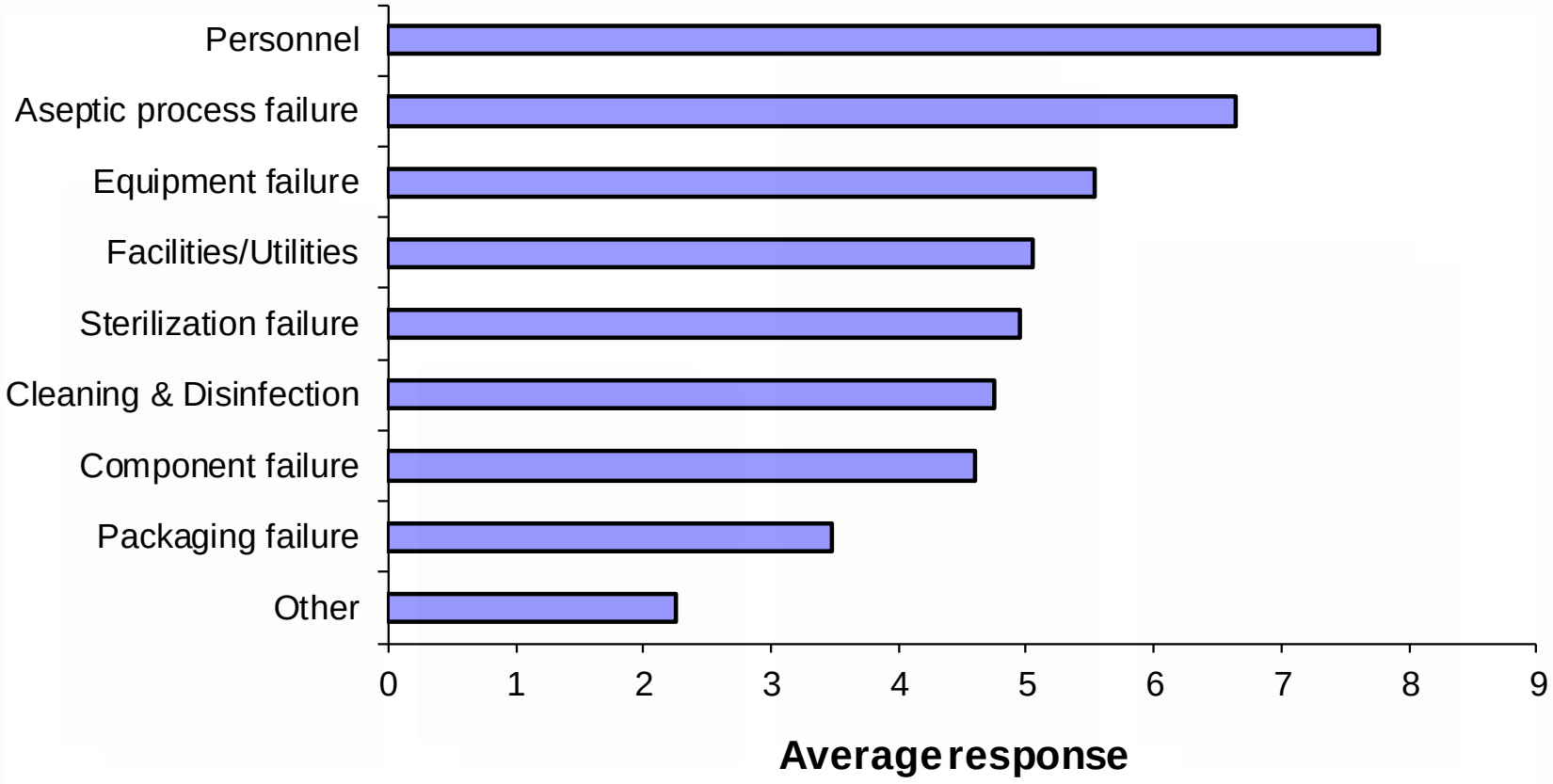
PDA Survey of QMR Practices in the Pharmaceutical Industry

- "The results from the PDA survey provide insights about industry-wide practices of Quality Risk Management,…"
  - Conducted in July 2006
  - Sent to PDA membership with 129 respondents
  - Used as basis for Technical Report No. 44
  - Complete findings published in PDA Journal

What Functional Area has the Most Need for Risk Assessment?



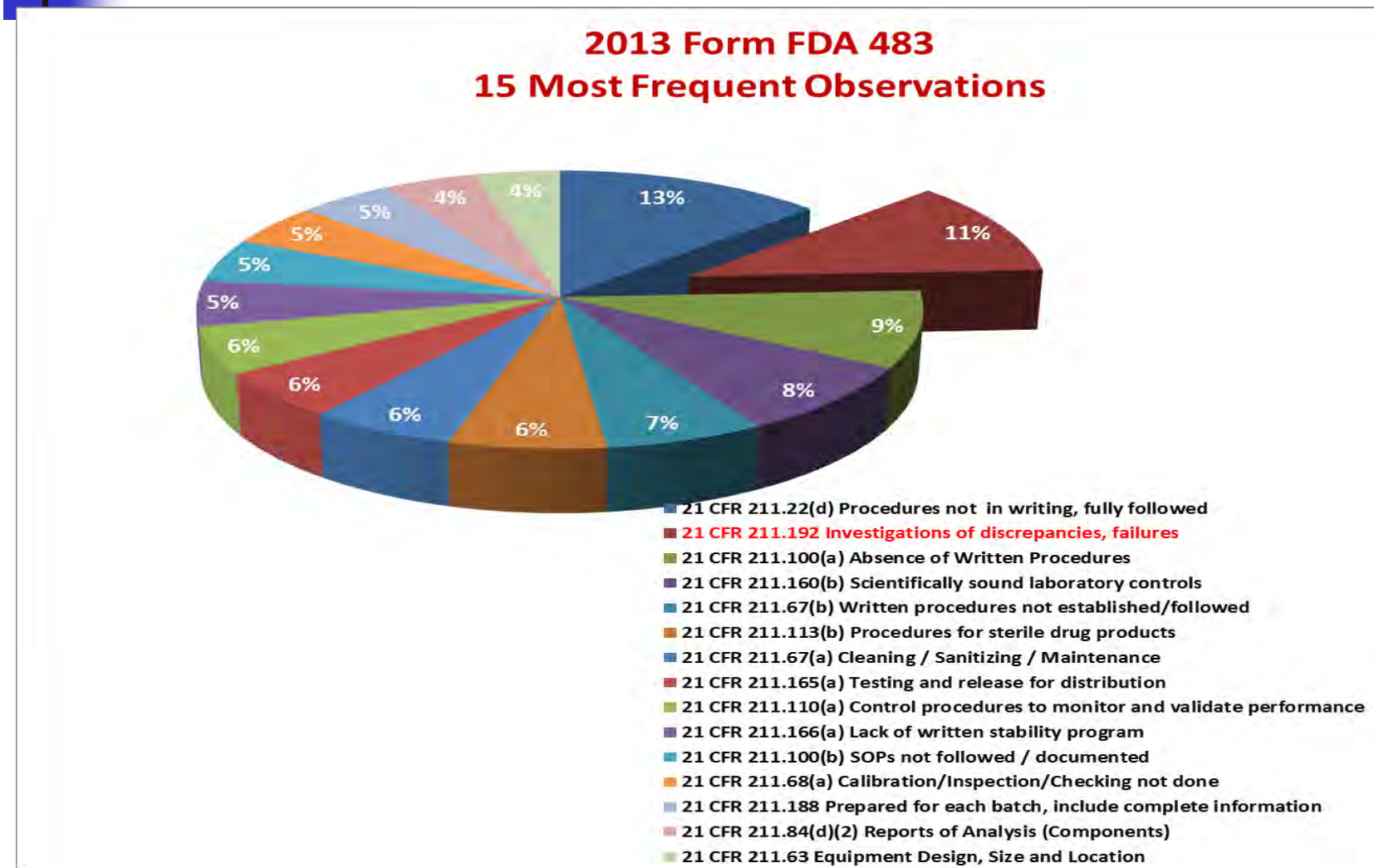
Potential to Contribute to a Sterility Failure in Your Operations?



Survey Results

- “Aseptic Processing/Filling” was identified as having the greatest need for risk assessment and quality risk management.
- Personnel and aseptic technique failures identified as most probable cause of sterility issues. Largest contributors to sterility failure in operations are still “Personnel
- However, personnel training was identified as the strategy most used for controlling and minimizing risk.”

FDA Observations



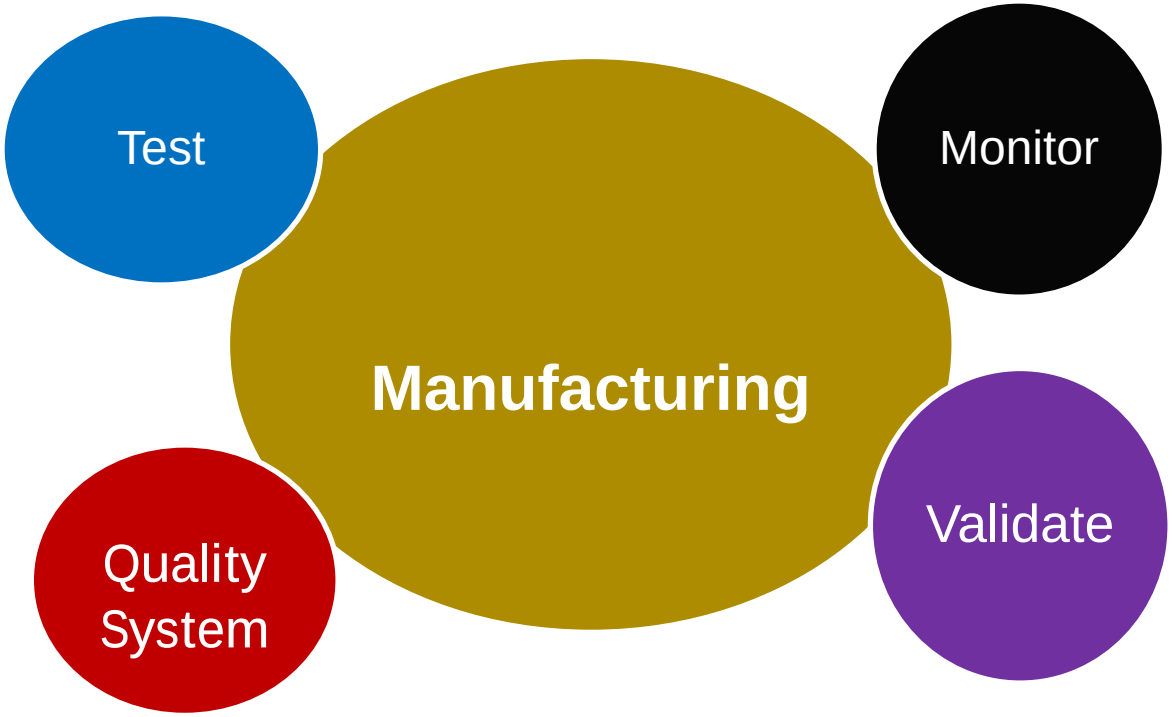
Why is this the Case?

- Reluctance to use new technologies
- Reliance on traditional approaches
- Emphasis on meeting regulatory expectations
- Poor understanding of process risk based on
  - Facility design
  - Equipment choices
  - Manufacturing processes
  - Personnel interactions
- Reluctant to change due to regulatory submissions

Common Misconceptions In the Industry

- If something has not happened yet, it will likely not happen.
- If something has not been cited during an audit or inspection, it must be OK.
- Complying with Health Authority Regulations is enough to assure quality.
- Are manufacturing related problems the result of people making mistakes?
  - Training
  - SOP ‘s
  - Industry perception

Focus on Manufacturing Excellence



Gemba (現場) Means *actual/real place*. Where the value is created; In manufacturing, the Gemba is the production floor.

Kaizen: Concept of continuous improvement

Attaining a Quality Culture

Risk Maturity Level	Risk Processes	Attitude	Behaviour	Skills & Knowledge
Scepticism	No Formal Processes	Accidents will happen	Fear of Blame Culture	Unconscious Incompetence
Awareness	Ad hoc use of Stand Alone Processes	Suspended Belief	Reactive, Fire fighting	Conscious Incompetence
Understanding & Application	Tick Box Approach	Passive Acceptance	Compliance, reliance on registers	Conscious Competence
Embedding & Integration	Risk Management embedded in Business	Active Engagement	Risk-based decision making	Unconscious Competence
Robust Risk Management	Regular review & Improvement	Champion	Innovation, Confident & appropriate Risk Management	Expert

Source: The Chartered Quality Institute, *A guide to Supply Chain Risk Management for the Pharmaceutical and Medical Device Industries and their Suppliers. 2010.*

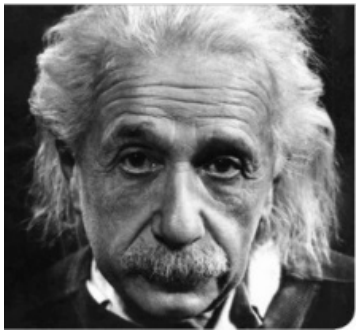
Risk Management and the Scientific Method

Uncover the process Weaknesses and Sources of

VARIATION

"No amount of experimentation can ever prove me right, however a single experiment can prove me wrong”.

Albert Einstein



Reasons for Unforeseen Variation

- Inadequate process understanding
- Insufficient knowledge of critical process parameters when control strategies are designed
- Failure to understand and address changes to process
- Focus on compliance and speed to market
- Poor and/or lack of communication

Hazard

- A danger or peril.
- An unwanted condition which can result in harm
  - Adversely effect the quality of the product
- What are the hazards associated with aseptic processing?
  - Endotoxin
  - Microbial contamination
  - Particulates
  - Sterility assurance and container closure

Risk Assessment

- Primary Steps in Risk Assessment
  - Identification - Determination of the hazards
  - Analysis – Estimation and assessment of risk
  - Evaluation – Evaluate the identified risks against defined risk acceptability criteria

Risk

- Risk is the combination of the severity of hazard, the likelihood of occurrence and the probability of detection
- If a hazard is detected and mitigated before it can cause harm, then there is no risk to the patient.

Risk Points

- What are methods of detection associated with aseptic processing?
  - Sterility test not statistically significant
  - Environmental monitoring that has poor recovery rates
  - Analytical testing, only chemical data
  - Process observation, based in operators knowledge and understanding
  - Final vial inspection, however can’t see microbial contamination

Risk Determination

- Severity – Degree of problem
- Occurrence - The likelihood that it will happen
- Detection - The probability of identifying issue before it harms the patient

RISK =

Severity x Occurrence x Detection

Severity

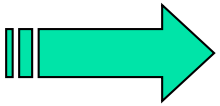
- The result or impact of a hazard
- Harms associated with aseptic processing?
  - Injury to patient
  - Death
  - Company liability
    - Warning letter
    - Consent Decree
    - Recall
    - Shutdown

Probability of Detection

- Is there a detection system in place?
- How robust is the system?
- Is the detection reproducible?
- Is it manual or automated?
- Qualitative or Quantitative Scale?
  - If quantifiable, need to justify ranges/value and the significance of the limits based on risk analysis

Occurrence

- No predictable chance
- Chance 0%
- 1 in a billion



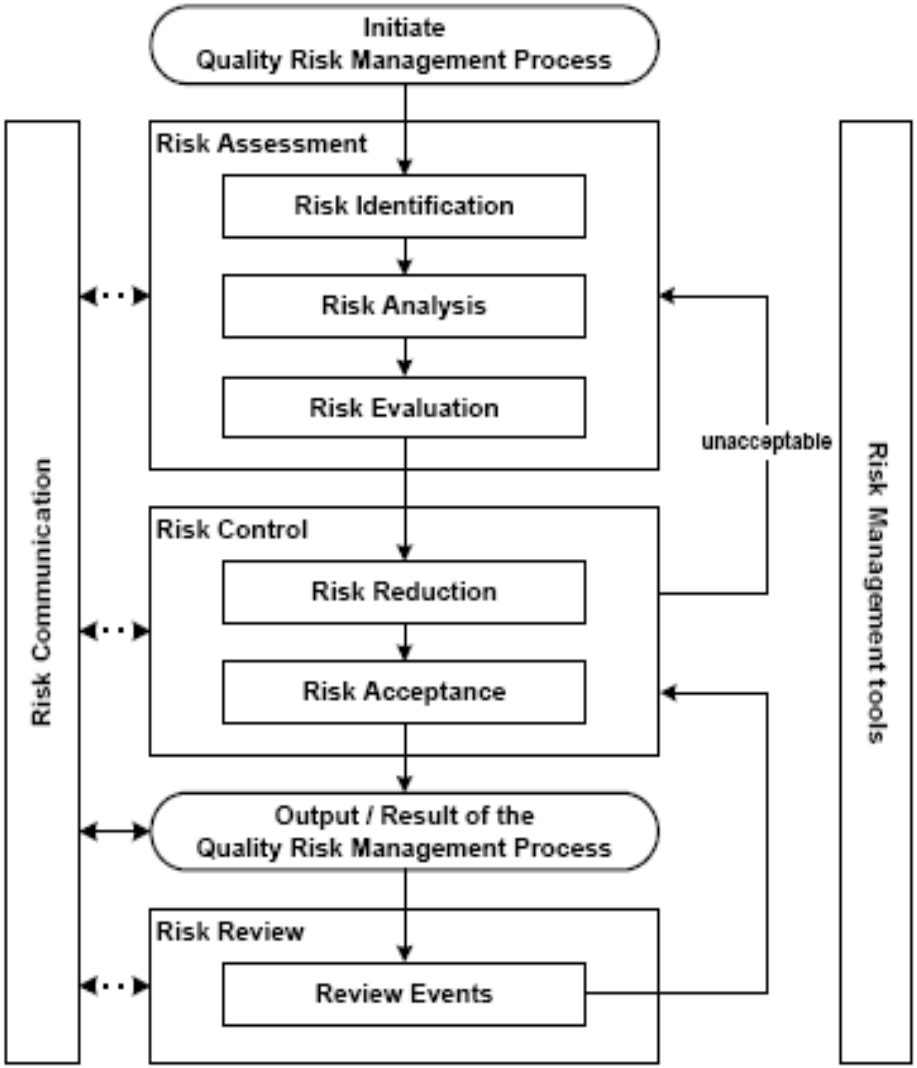
- Predicted to occur
- Chance unknown
- 1 in a million 0.0001%
- 1 in hundred thousand 0.001%
- 1 in ten thousand 0.01%
- 1 in a thousand 0.1%
- 1 in a hundred 1%

Risk Management

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk

Risk Management

Figure 1: Overview of a typical quality risk management process



Risk Management Principles

- Link risk to product quality and patient safety
- Assess uncertainty level and minimize
- Identification & evaluation of hazards
- Determine the risk assessment method
- Goal is improvement, not just identify the risk
- Address short and long term residual risk
- Impact of the assessment outcome
- Follow up on periodic basis
- Avoid using Quality Risk Management (QRM) to justify a predetermined decision

Choose the Right Method

- Avoid creating QRM system without value
- Complexity of method depends on objective
- Pick a method that gets the most value added information to the process
- Understand the evaluation process
- Confirm the decisions are knowledge and/or technical based
- Do not make rush or quick decisions based on time constraints

Risk Culture Factors

- Corporate policies and directives
- Senior management approach to risk
- Leadership commitment to reduced risks
- Top down risk management philosophy willing to take higher risk at the top
- Use diverse assessment team to
  - Assure objectivity
  - Confirm an unbiased approaches
- Inter/Multi-departmental organization

Risk Culture Factors

- Consistent with the validation philosophy
- Decisions based on understanding of the process and change controls in place
- Do not use risk assessment to justify questionable process
- Avoid
  - Checklist approach to eliminate pre-conceived decision
  - Quality Program of the month

Investigation & Decision Making

- Is objective to
  - Justify a decision, such as product release?
  - Decide on course of action for a CAPA?
  - Reduce risk of future event from re-occurring?

QRM & Aseptic Processing

- QRM is essential for making educated decisions related to planning, design, validation, and operation of aseptic processes.
- Implementation of specific methods and techniques are left to individual companies.
- Regulatory agencies have articulated their expectations that firms consider relative risk to product quality and patient safety in thee decisions.

Aseptic Processing & Risk

- Identification and reaction to hazards are key to risk reduction and process success
- What is the relationship between uncertainty, hazard and risk?
- What affect does process design, control, and execution have on the risk of these hazards occurring?
- Are assessment procedures reflective of the level of risk?

Aseptic Processing & Risk

- What is a riskier process system?
  - Technical transfer insufficient detail
  - Insufficient validation
  - Setting up fill machine
  - Process interventions during filling
- What is the most complex process risk?
  - Manual operation
  - Semi-automated process
  - Automated methods

Aseptic Processing & Risk

- Do risk factors change with the following:
  - Type of product
  - Use of the product
  - Type of technology
  - Levels of control
  - Experience of the staff
  - Regulatory history
  - Company culture

Aseptic Processing & Risk

- What makes aseptic processing risky?
  - Source of contamination
  - Process is people dependent
  - SOP's the do not create reproducible results
  - Inability to detect contamination
  - Difficult to measure & correlate contamination
  - Clean rooms and environmental exposure
  - Complexity of process and interventions
  - Impact of failure is always severe to company and patients

Advanced Aseptic Processing

- Does risk change with use of automation and isolators?
  - Elimination or reduction of interventions to minimize contamination
  - Is the impact or severity of failure more, less, or the same?
  - Sterility failure more, less or just as probable?
  - The majority of people, including regulatory agencies think yes

Principles of QRM

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient

Quantify and Evaluate Risk

- The level of validation, effort, formality, and documentation of the QRM process must be commensurate with the level of risk.
- Process steps with unacceptable risk must
  - Be eliminated
  - Change the process
  - Reduced to an acceptable level
- This is continuous process improvement

Risk Assessment of Interventions

- **Intervention Risk Evaluation Model (IREM)**
  - A method designed to identify, evaluate, and rank aseptic processes
  - To improve and optimize process
  - Must be objective, simple, reproducible, and logical.
  - Uses a Key Word Approach to establish assessment criteria.
  - Relies on multi disciplinary departments

Criteria for Success

- Objectivity
  - Using the system, management and operations come up with the same evaluation
- Simplicity
  - All personnel can explain model
- Reproducible
  - Applicable to evaluate most interventions
- Logical
  - Needs to make sense

Step 1: Determine Factors that Contribute Risk per Intervention

- Brain storming session with informed stakeholder group:
  - Closeness to the exposed product or product contact surfaces
  - Difficulty in performing the intervention
  - Frequency of the intervention
  - Time it takes to perform the intervention
  - Condition or exposure of the product or product contact surface during the intervention
  - Reproducible for all operators

Step 1: Determine Factors that Contribute Risk per Intervention

- Brain storming session with informed stakeholder group:
  - Control measures in place to prevent contamination
  - Redundant control measures or subsequent processing which could reduce the effect of contamination
  - Operator training required to perform the intervention
  - Process failures and excursions or non-conformities linked to process failures

Step 2: Consolidate List into Measureable Risk Elements

- The three elements to the program are
  - Complexity
  - Proximity
  - Duration

Step 2: Consolidate List into Measureable Risk Elements

- **Complexity**
  - Defined by the number of steps needed to perform the intervention.
  - Data can be acquired through batch records, SOPs, interviews, observation.
- **Proximity**
  - Since all interventions were found to be performed at about the same distance, distance in inches, as a measurement criterion is of limited value.
  - Defined as the degree to which interventions were performed in the vicinity of exposed product or product contact surfaces, as evidenced by activity relation to first air.
  - Data can be acquired through interviews and observation.
- **Duration**
  - Defined in relation to the time in which product or product contact surface is exposed during the performance of those parts of the intervention that could adversely affect product sterility.
  - Data can be acquired through batch records, interviews, observation.

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Support Information

- There may be other elements to consider. However, these must be objectively measured
- No one element alone fully defines riskiness of the intervention. It is the combination of the elements which present risk
- The elements, key words, and criteria in this case study were selected by the team. They may not be the right elements for all companies, situations, aseptic process

Support Information

- Criteria selected in part by considering the “standard” levels of complexity/steps, duration, and proximity and then identifying those above as potentially contributing more risk and those below less.
- Assumes all interventions are acceptable and performed using proper aseptic technique

Step 3: Set Measurable Ranking Criteria

Duration

Risk Rating	Duration of intervention
High	Greater than 10 minutes
Medium	Less than 10 minutes, but more than 1 minute
Low	Less than 1 minute

Step 3: Set Measurable Ranking Criteria

Complexity

Complexity	Number of Steps to perform the Intervention
High	More than 5 Steps
Medium	2 to 5 Steps
Low	1-Step

Step 3: Set Measurable Ranking Criteria

Proximity

Risk	Proximity to exposed product contact surfaces in the Grade-A areas
High	Operator interferes with the First-Air to the process with their head, body and/or sanitized glove
Medium	Operator interferes with First Air after putting on sterile sleeves/gloves and does not change anything prior to executing the intervention. The sleeves and gloves are not sterile since they were exposed to the Grade-B environment
Low	First air is maintained for the entire process using sterile equipment or tools like forceps

Step 4: Summarize, sort, and evaluate relative risks

- Process improvement
  - Determine which interventions should be included in aseptic process simulations and with what frequency.
  - Make clean room personnel aware of the reason for the criticality of interventions.
  - Make decisions on allocation of resources to reduce or eliminate interventions.

Case Study: Filler Setup

Manual set up of
8-filling needles

Takes over
10 minutes

Step-1 Determination of Overall Risk		Duration		
		Long	Medium	Short
Proximity	High	Risk Class-1	Risk Class-1	Risk Class-1
	Medium	Risk Class-1	Risk Class-1	Risk Class-1
	Low	Risk Class-1	Risk Class-1	Risk Class-1

Case Study: Filler Setup

Manual set up of
8-filling needles

Takes over
10 minutes

Very close
To critical
locations

Step-1 Determination of Overall Risk		Duration: Long	Duration: Medium	Duration: Short
Proximity	Close	Risk Class-1	Risk Class-1	Risk Class-1
	Medium	Risk Class-1	Risk Class-1	Risk Class-1
	Far	Risk Class-1	Risk Class-1	Risk Class-1

Case Study: Filler Setup

Manual set up of
8-filling needles

More than
10 Steps

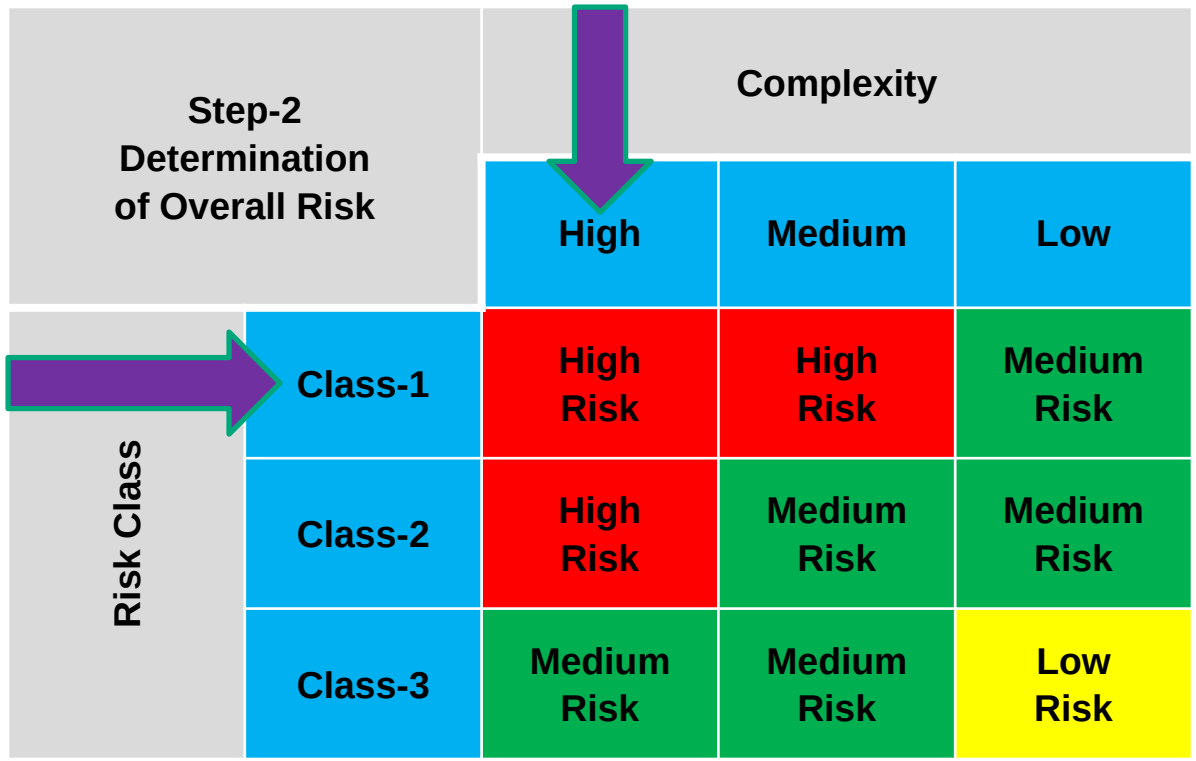
Step-2 Determination of Overall Risk		Complexity		
		High	Medium	Low
Risk Class	Class-1	High Risk	High Risk	Medium Risk
	Class-2	High Risk	Medium Risk	Medium Risk
	Class-3	Medium Risk	Medium Risk	Low Risk

Case Study: Filler Setup

Manual set up of
8-filling needles

More than
10 Steps

Risk
Class-1



Case Study: Filler Setup

Steam In Place of 8-filling needles. Manual manipulation required

Less than 1-minute

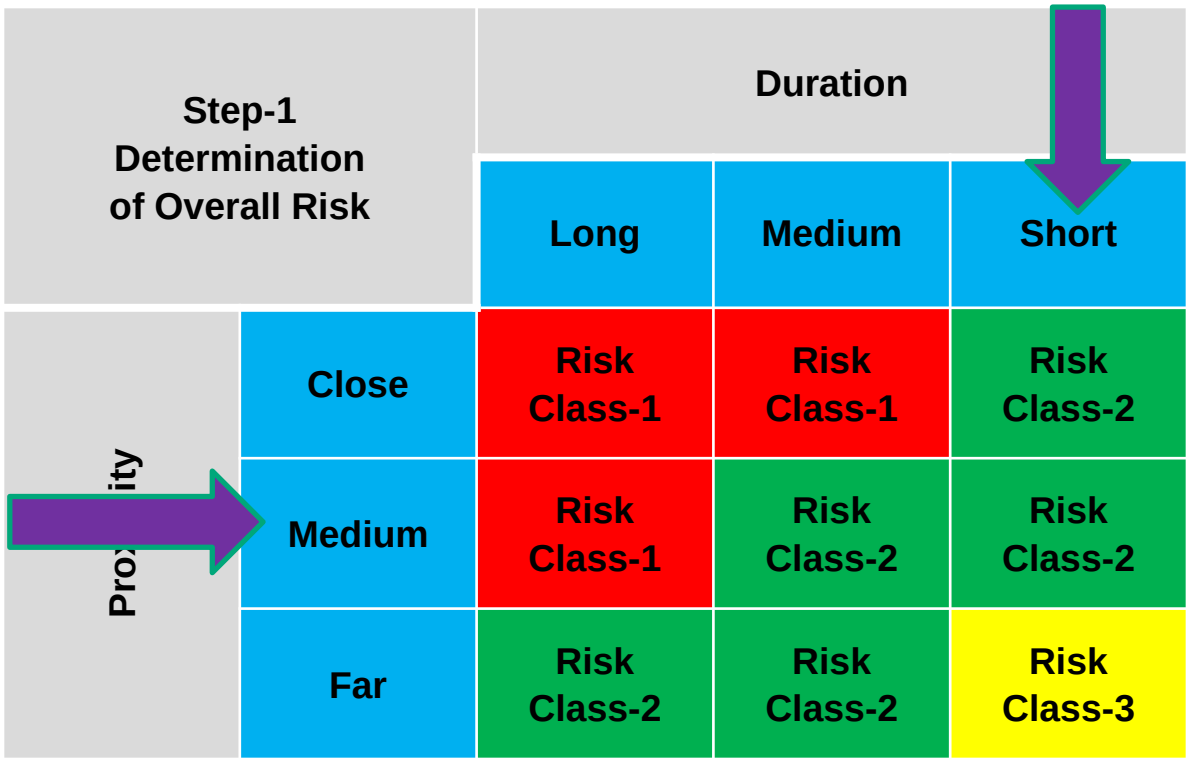
Step-1 Determination of Overall Risk		Duration		
		Long	Medium	Short
Proximity	Close	Risk Class-1	Risk Class-1	Risk Class-1
	Medium	Risk Class-1	Risk Class-1	Risk Class-1
	Far	Risk Class-1	Risk Class-1	Risk Class-1

Case Study: Filler Setup

Steam In Place of 8-filling needles. Manual manipulation required

Less than 1-minute

Semi-automatic system to expose filling needles



Case Study: Filler Setup

Steam In Place of 8-filling needles. Manual manipulation required

Partial Automated system

Risk Class-1

Step-2 Determination of Overall Risk		Complexity		
		High	Medium	Low
Risk Class	Class-1	High Risk	High Risk	Medium Risk
	Class-2	High Risk	Medium Risk	Medium Risk
	Class-3	Medium Risk	Medium Risk	Low Risk

Case Study: Filler Setup

Fully automated Steam In Place of 8-filling needles

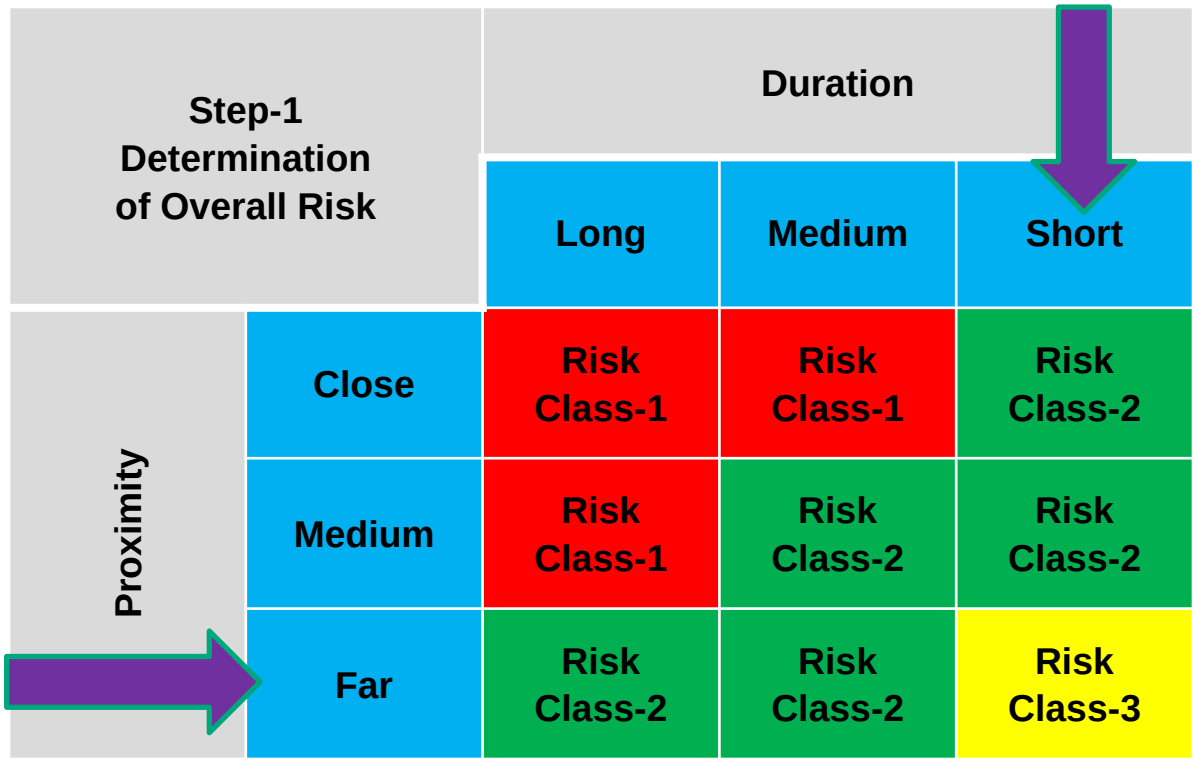
Less than 1-minute

Step-1 Determination of Overall Risk		Duration		
		Long	Medium	Short
Proximity	Close	Risk Class-1	Risk Class-1	Risk Class-1
	Medium	Risk Class-1	Risk Class-1	Risk Class-1
	Far	Risk Class-1	Risk Class-1	Risk Class-1

Case Study: Filler Setup

Fully automated Steam In Place of 8-filling needles

Less than 1-minute

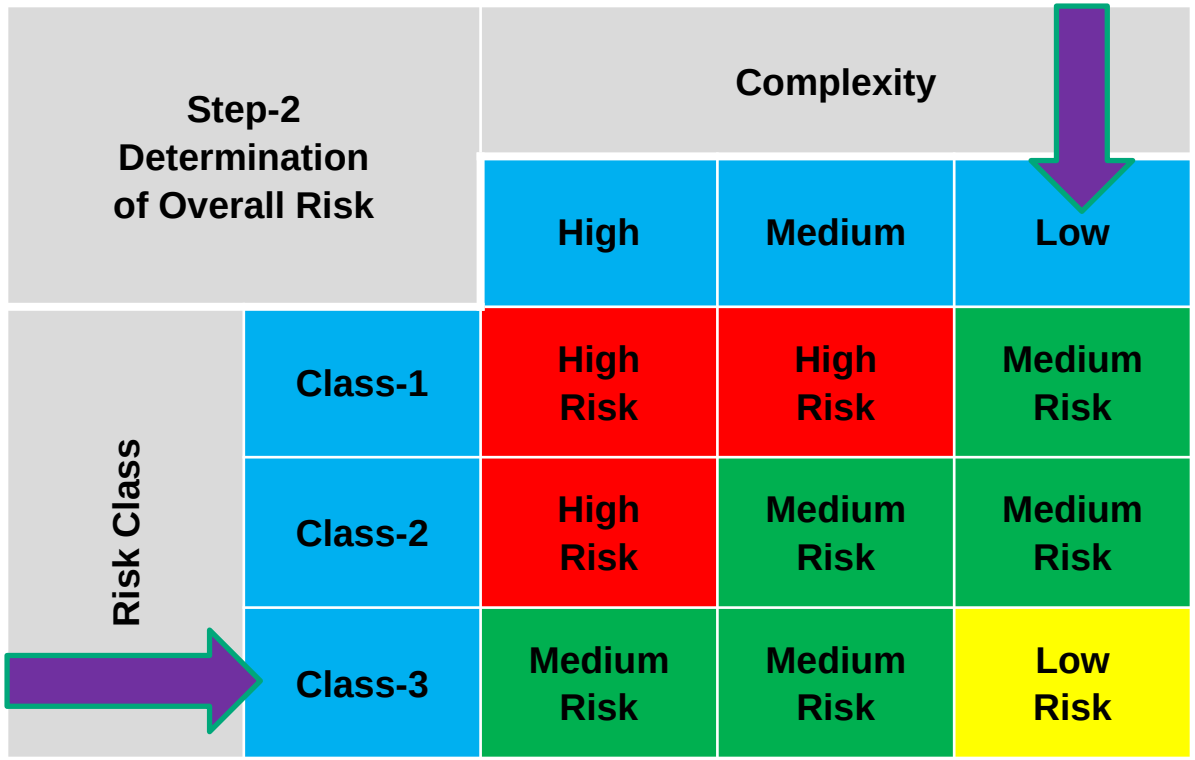


Automatic system to expose filling needles

Case Study: Filler Setup

Fully automated Steam In Place of 8-filling needles

Automatic system



Risk Class-1

Case Study: Filler Setup

Filler Set Up Intervention Risk Determination

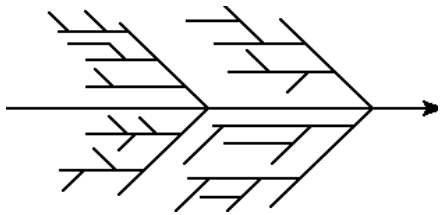
Intervention	Description	Duration	Complexity	Risk	Proximity	Risk
Manual set up	In Grade A fill needles placed in rack and then hoses are attached to pumps	**High**	**High**	**Class-1**	**High**	**High**
Partial Automation SIP set up	Manual removal of the fill needle covers after sterilization	**Low**	**Low**	**Class-2**	**Medium**	**Medium**
Full Automation SIP set up	In Grade A, SIP, intervention is the removal of the fill needle covers after sterilization	**Low**	**Low**	**Class-3**	**Low**	**Low**

Methods to Identify Hazards to Determine Risks

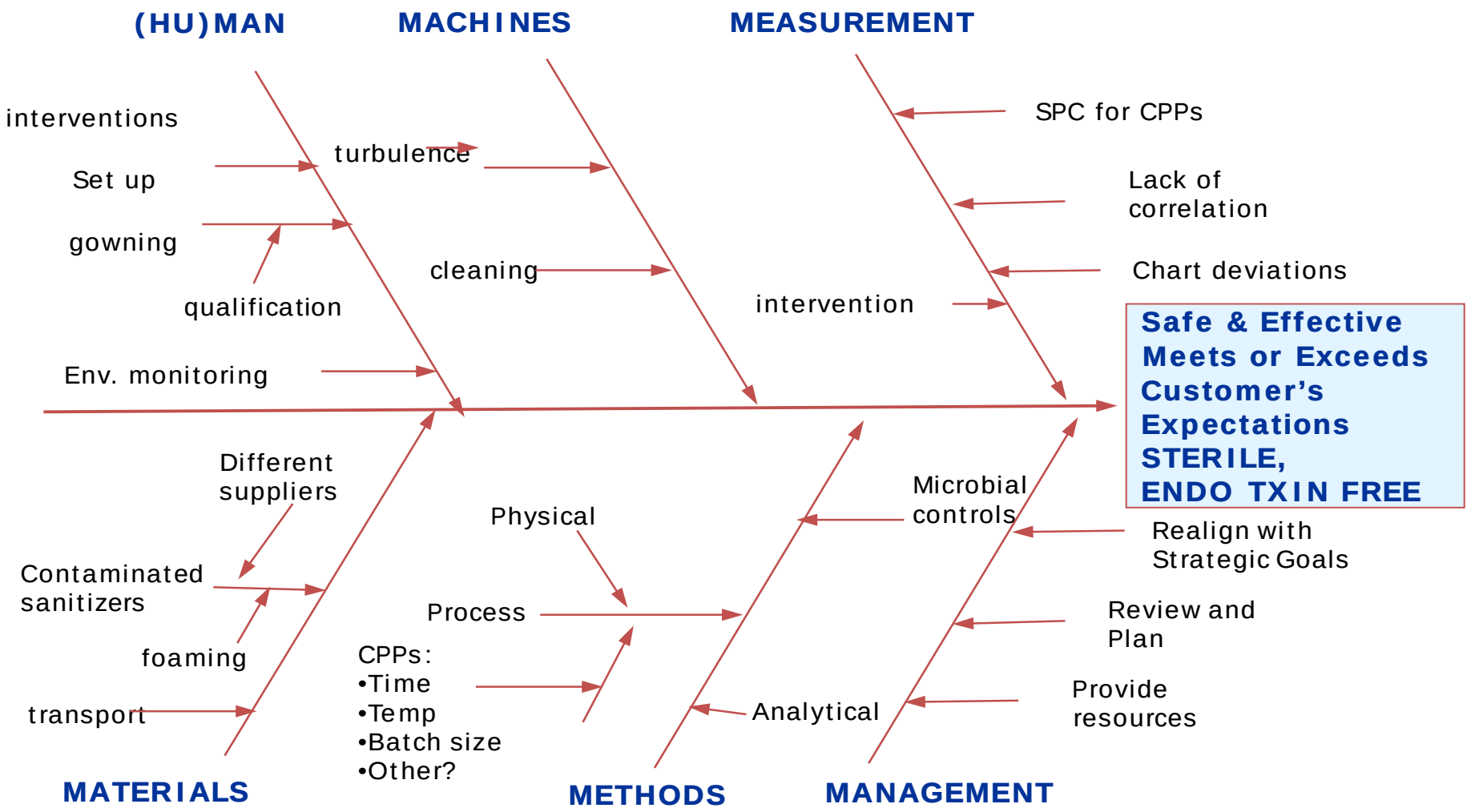
- Cause & Effect / Ishikawa Fish Bone
- Fault Tree Analysis (FTA)
- Failure Modes & Effects Analysis (FMEA)
- Hazards Analysis & Critical Control Points (HACCP)

Cause & Effect Diagrams (Ishikawa / Fish Bone)

- To associate multiple possible causes with a single effect
- Constructed to identify and organize possible causes for it
- Primary Branch: Represents the effect
- Major Branch: Corresponds to a major cause
- Minor Branch: Defines more detailed causal factors



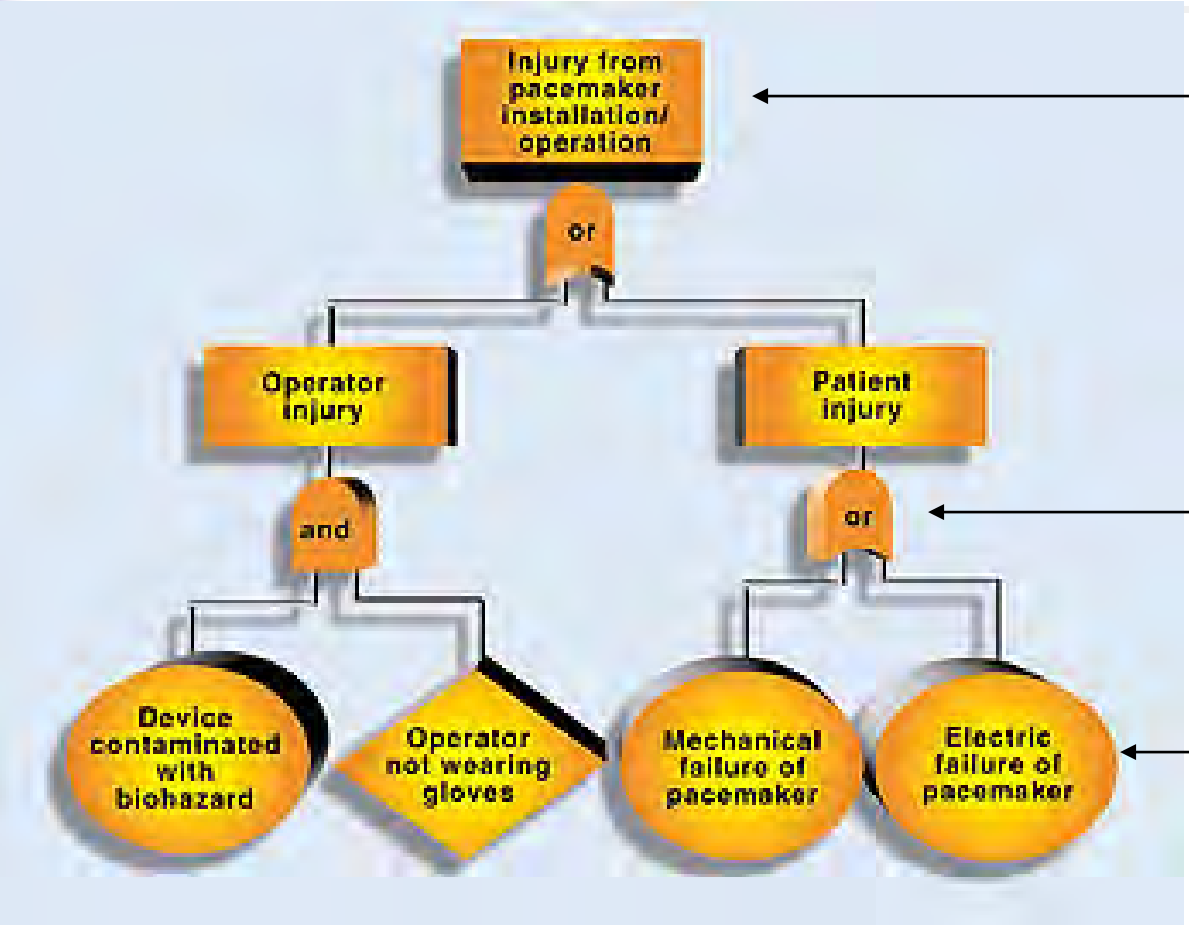
Cause and Effect Diagram



Fault Tree Analysis (FTA)

- Top-down approach (Deductive)
- Identify undesired consequence/failure or top issue and determine contributing events that must occur to produce the event
- Can identify multi-point or interactive failures

FTA Example



Undesired Top Event

Logic Gate

Hazardous situation to further evaluate and mitigate

Failure Modes & Effects Analysis (FMEA)

- Bottom-up approach (Deductive)
- Assume potential component failure or initiating event and try to determine corresponding effect on overall system
- Assumes single point failure

Failure Modes Effect Analysis

Type	Description
FMEA	Bottom-ups Approach and Focus on the product ➢Determine Possible Component Defects ➢Determine undesired outcome ➢Corrective Action

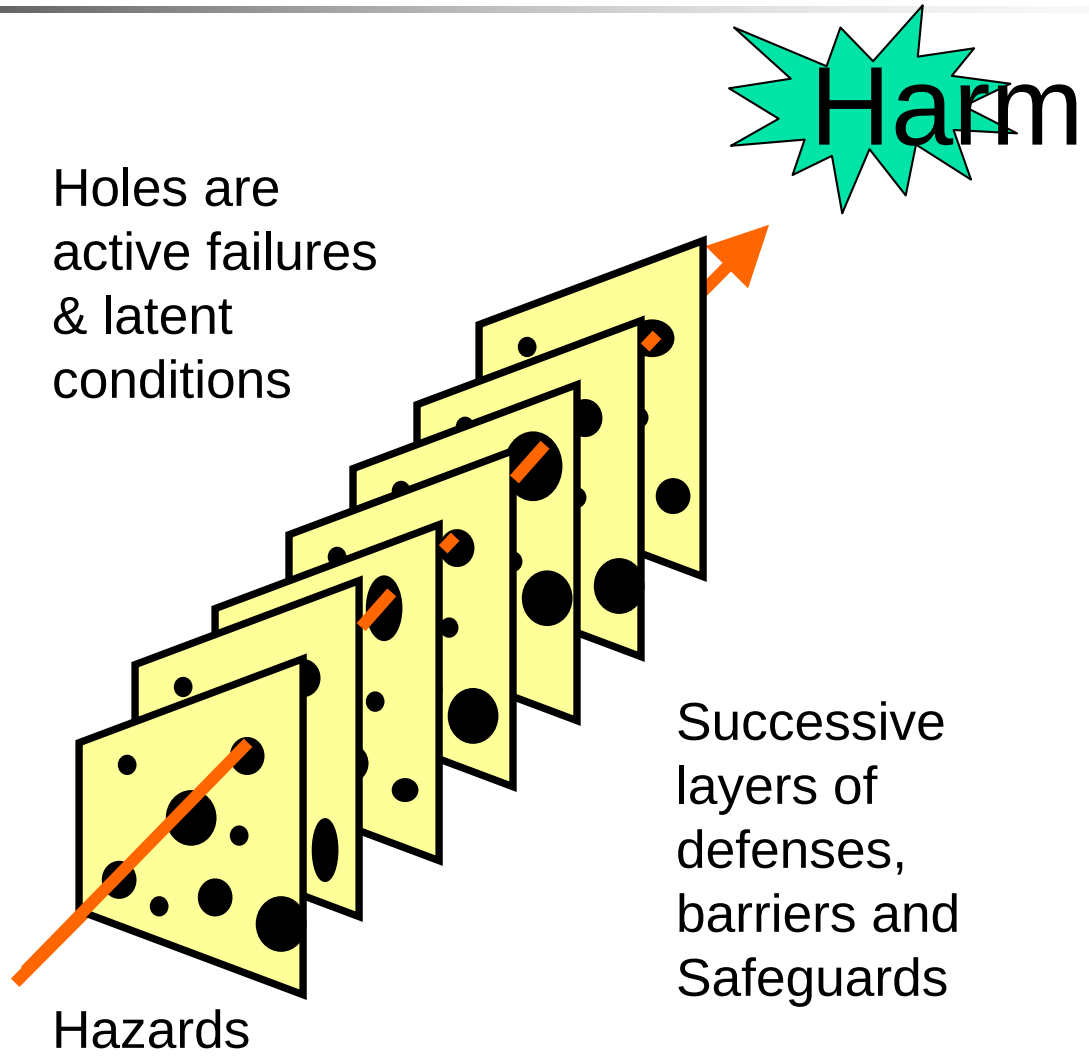
Principles Ideas of HACCP

- Hazard Analysis
  - Flow of current process and preventive measures
- Identify Critical Control Points (CCP)
  - Reduce or eliminate risk
- Establish Critical Limits
  - Process parameters
- Monitor CCP
  - Know and understand capability

Principles of HAACP

- Establish Corrective Action
  - Deviation/Non-conformance
  - Rework the process
- Record Keeping
  - Demonstrate process consistently and control
- Verification
  - Process validation
  - Trending/Testing

Risk Mitigation Decisions



Risk Reduction

- Reduce risk by
  - Severity is always high for Aseptic Processing
  - Increase detection ability
  - Minimizing the probability of occurrence
  - Optimize SOP's
  - Continued process improvement
  - Meaningful training programs
    - Audio
    - Visual
    - Kinesthetic

Residual Risk

- What risk remains after changes and/or modifications are made to the process.
- Is clarification of a process a change or modification
  - What was the risk in the past
  - What is the current process risk
  - Is there a future risk based on the change
  - Can the risk be predicted or is it unforeseeable

Residual Risk

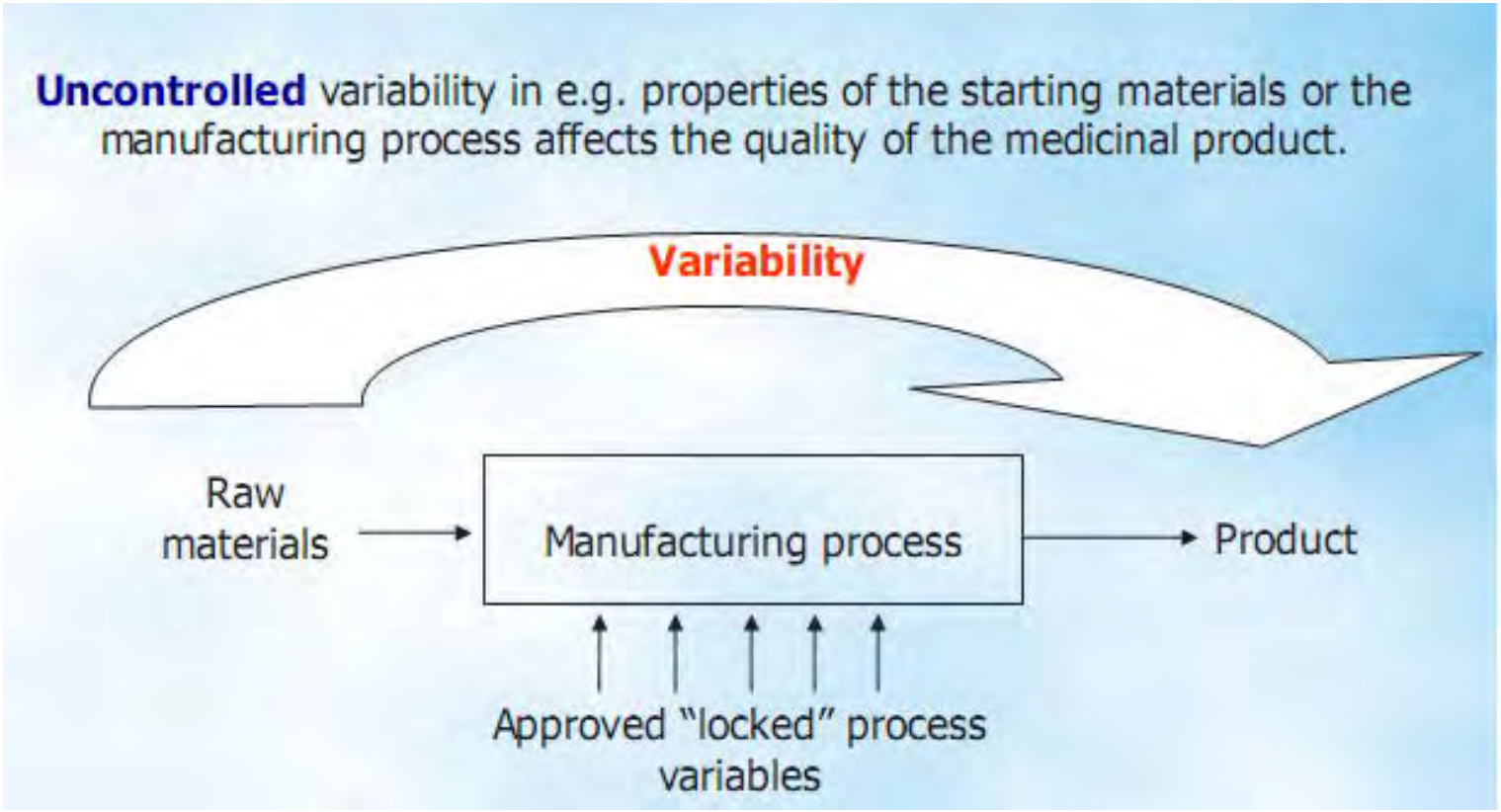
- This may include additional hazards which result form the change or reduction of another “risk”.
- Examples of residual risk
  - Particles due to spraying alcohol
  - Changing from spray to trigger alcohol
  - Gowning sequence
  - Balancing the airflow to fill room returns

Desired State for Pharmaceutical Manufacturing

- Manufacturers have extensive knowledge about critical product and process parameters & quality attributes
- Manufacturers control process through quality systems over life cycle and strive for continuous improvement
- FDA Role: Initial verification, subsequent audits, follow up with process observations

Janet Woodcock, M.D.
Deputy Commissioner/Chief Medical Officer, FDA
Pharmaceutical Quality Initiatives Workshop
March 2, 2007

The Problem is Variability



W. Edwards Demming

Validation & Variation

- Validation is the prediction of an event based on observed conditions
  - Variation = Inconsistency
  - Lack of prediction = Uncertainty of outcome
  - Lack of assurance = Non-compliance

Validation & Variation

- No deviations is the goal however not reasonable or possible
- Deviations and a lack of consistency which indicates unwanted variability
- Many processes have consistent variability
  - Is it due to the process
  - The variability of personnel
  - Cleaning and sanitization
  - Yearly variations

Validation & Risk

- The less a process outcome can be observed, the less certain the outcome
- The more it needs to rely/depend on prediction.
- Validation can add to predictability and certainty to the process.
- Continued assessment of the process is required
- Evaluate the deviations and there relative frequencies

Risk Management

PDA Technical Report No. 44
Quality Risk Management for
Aseptic Processing

Risk Management Cycle TR-44

Risk Management

Final Thoughts
Is the Risk Real or Perceived?