Quality Risk Management ICH Q9 & ISO 14971

Presented by Michael Kerr

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Agenda

- Risk Concept
- QRM Fundamentals
- Regulatory Expectations – Warning Letters / Observations
- Application of QRM

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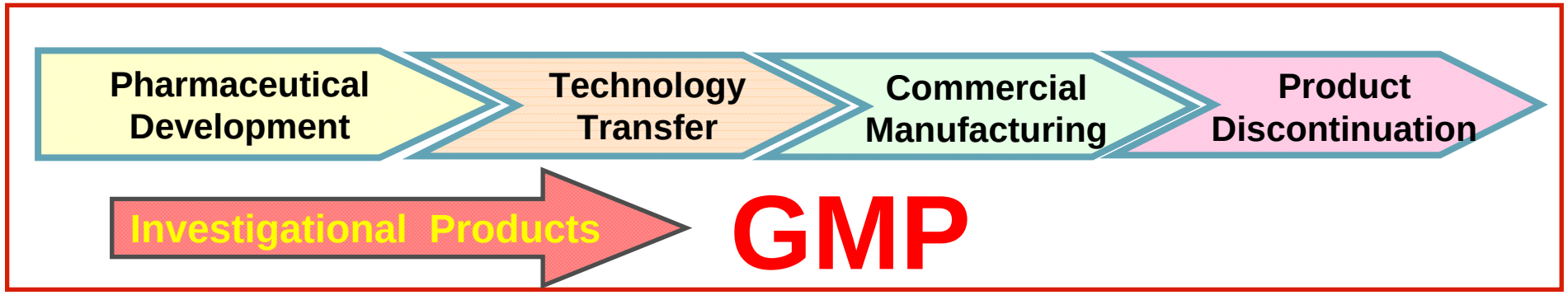
Introduction: Foundation of Risk Assessment – Q8(R), Q9, Q10



Management Responsibilities

PQS Elements

- Process Performance & Product Quality Monitoring System
- Corrective Action / Preventive Action (CAPA) System
- Change Management System
- Management Review

Enablers

- Knowledge Management
- Quality Risk Management

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Primary Tenant of Risk Management in ICH Q9

Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements…

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What is Risk ?

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Some Key Terminology

Harm: Damage to health, including the damage that can occur from loss of product quality or availability. (ICH Q9)

Hazard: The potential source of harm. (ICH Q9)

Hazardous Situation: circumstance in which people, property or the environment are exposed to one or more hazards. (ISO 14971)

Risk: The combination of the probability of occurrence of harm and the severity of that harm. (ISO 14971)

Residual Risk: Risk remaining after risk control measures have been taken. (ISO 14971)

Severity: A measure of the possible consequences of a hazard. (ISO 14971)

Detectability: The ability to discover or determine the existence, presence, or fact of a hazard. (ICH Q9)

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What is a Drug/Device Product Related Risk

"All stakeholders need to understand that the use of a medical device entails some degree of risk." – ISO 14971

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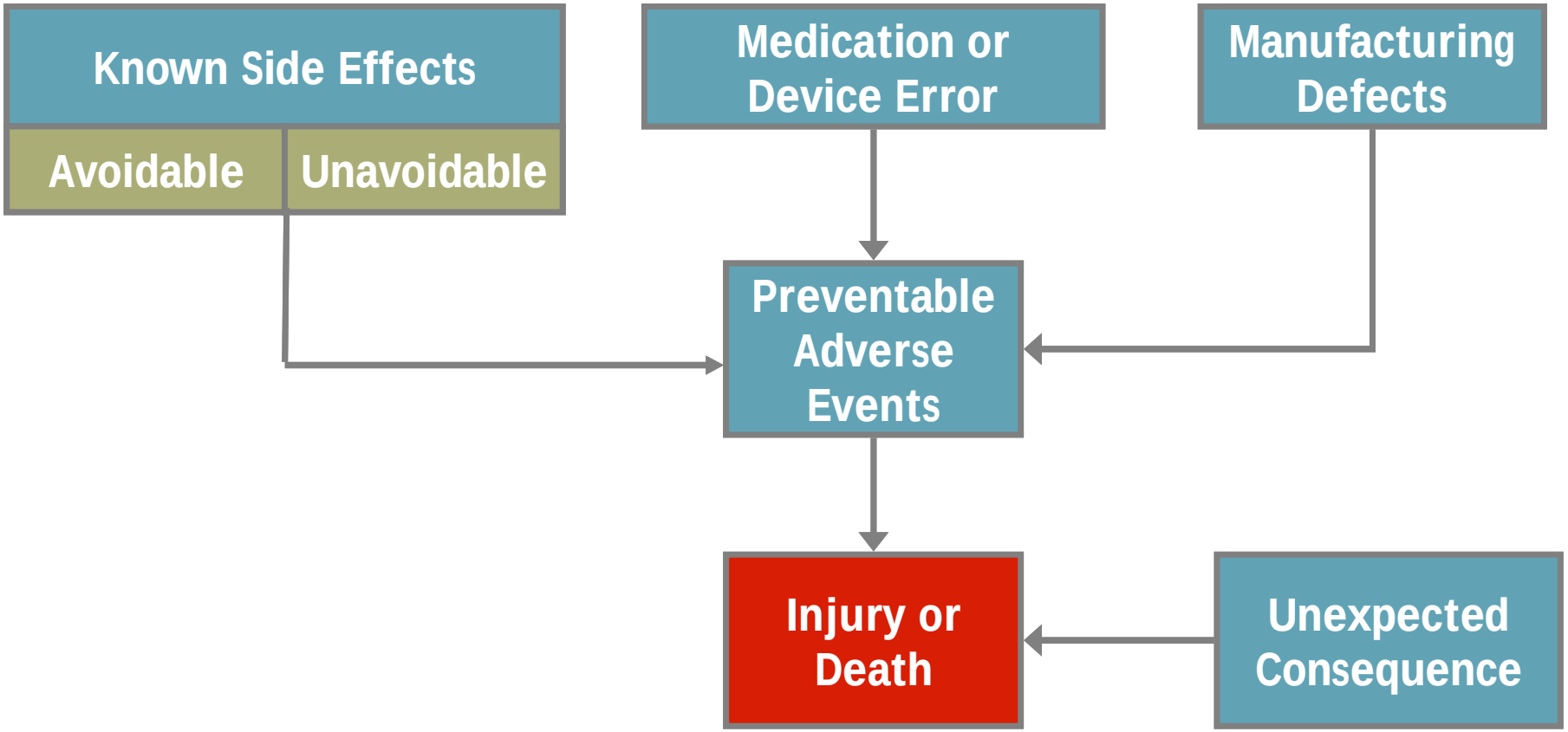
Risk Areas for a Drug / Device Product



Source: adapted from FDA (1999). *Managing the Risks from Medical Product Use.*

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What is Quality Risk Management

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QRM

ICH Q9 (2006)

- "Risk management is a ***systematic*** **PROCESS** for the assessment, control, communication and review of risks to the quality of the medicinal product across the product lifecycle."

ISO 14971 (2007)

- Risk management is the ***systematic*** **APPLICATION** of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling and monitoring risk.

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What are the Benefits:

- Helps reduce overall cost: Supports more qualified decision making in the planning stage
- Promotes quality, through increased efficiency and knowledge transfer, with strong potential to reduce catch-up work done to mediate the effects of poor quality (ie: non-conformances, deviations/investigations, CAPA, rework, scrap, complaints, etc)
- Is an iterative and continuous process where prior risks that became problems are either mitigated or recognised and reviewed in a predictive manner for the future.
- Provides a mechanism for risk communication (formalised vehicle/process) and exposure to management
- Provides a framework to better understand processes, what is critical and why
- Helps provide rationale for not spending time on low risk activities, process events, or systems, rather focusing resources and time on the things that are really important

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QRM – Evolution ISO & ICH

2000

- ✓ ISO 14971: Application of Risk Management to Medical Devices

2003

- ✓ ISO 13485: Medical Devices – Quality Mgt Systems (Reqs for Regulatory Purposes)
- ✓ ISO 14971: Amendment 1: Rationale for Requirements

2005

- ✓ ICH Q9: Quality Risk Management

2006

- ✓ ICH Q9: Quality Risk Management

2007

- ✓ ISO 14971: Application of Risk Management to Medical Devices

2008

- ✓ ICH Q10: Pharmaceutical Quality System (PQS)

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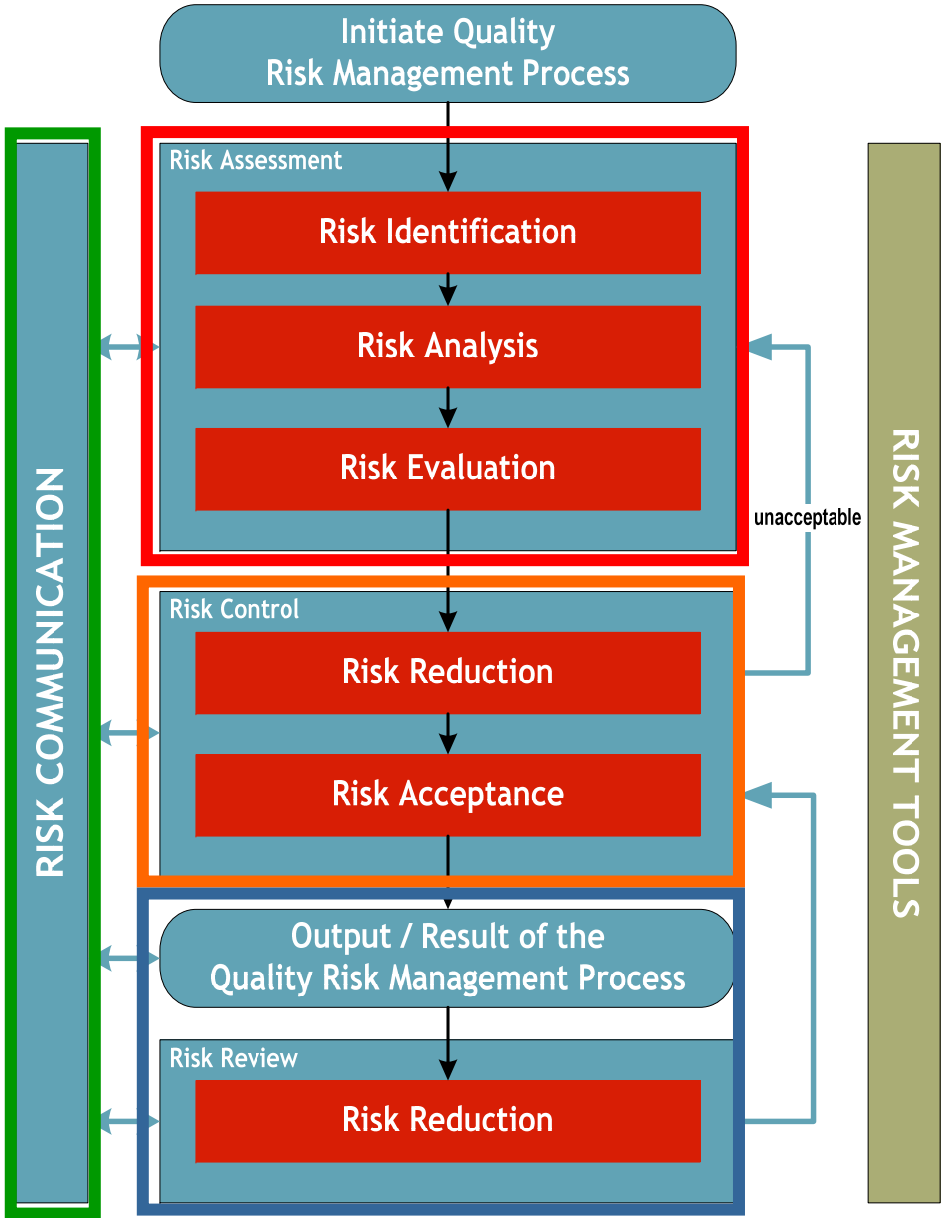
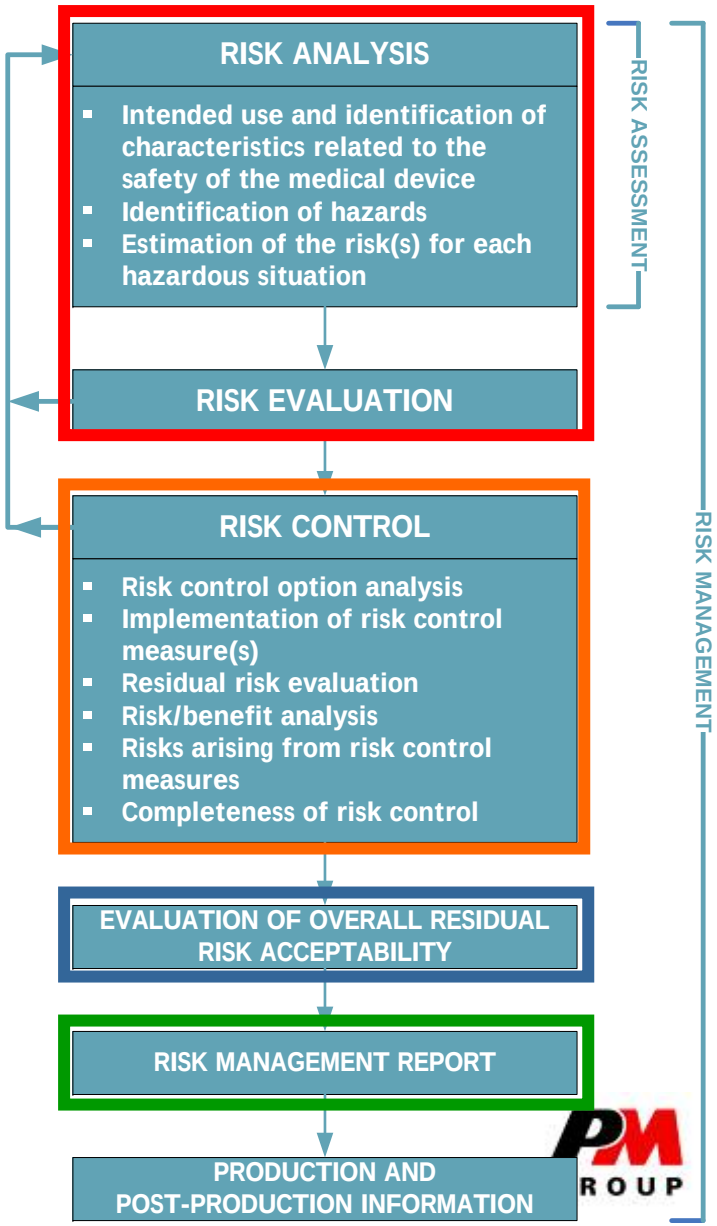
ICH Q9 Vs ISO 14971 QRM Process





ICH Q9 Principles of QRM

- ICH Q9 States that the two primary principles of quality risk management are:
  - The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
  - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

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Recent Warning Letters and Observations

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Observation by French Authorities March 2008

- "There is no risk assessment procedure to evaluate risks related to the products manufactured in the plant (e.g. toxicity, design of facilities…), the equipment used, the qualification / validation needs, or related to judgment when initiating new projects (EU GMP Annex 20)"

Ref : Introduction to ISPE's Risk-MaPP Baseline Guide, Stephanie Wilkins, Pharmaconsult

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Excerpt from South African WHO Audit

- Section C – HVAC Systems / Cross Contamination Observation 4

  "…However, none of the tests were performed in accordance with current recommendations including a risk assessment….."

Ref : Introduction to ISPE's Risk-MaPP Baseline Guide, Stephanie Wilkins, Pharmaconsult

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FDA Warning Letter Excerpts

- Your firm failed to perform a "Root Cause Investigation: Risk Assessment" to determine the impact, severity and safety concerns resulting from the verified root causes of product failure identified in CAPA Plan Worksheet. This assessment is indicated per the CAPA Plan Worksheet and your firm's procedure – W/L 48-11

- Your firm failed to review all aspects of the risk assessment process to determine if other components were lacking, review other risk assessments for similar short comings, and evaluate related procedures and subsystems to determine if they also needed to be addressed in a similar manner. In addition, your firm did not provide evidence of implementation of all of the planned actions. CHI-06-11

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Risk Management – Industry & Regulators

- Currently building experience with Risk management.
- Both will have had bad experiences.
- Important for industry to build confidence of the Regulators in the process.
- Important for individual companies to earn respect in the application of the process.

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Applying QRM

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Sources of Quality Risks

- System Risk (facility & people)
  - e.g. interfaces, operators risk, environment, components such as equipment, IT, design elements
- System Risk (organisation)
  - e.g. Quality systems, controls, measurements, documentation, regulatory compliance
- Process Risk
  - e.g. process operations and quality parameters
- Product Risk (safety & efficacy)
  - e.g. quality attributes: measured data according to specifications

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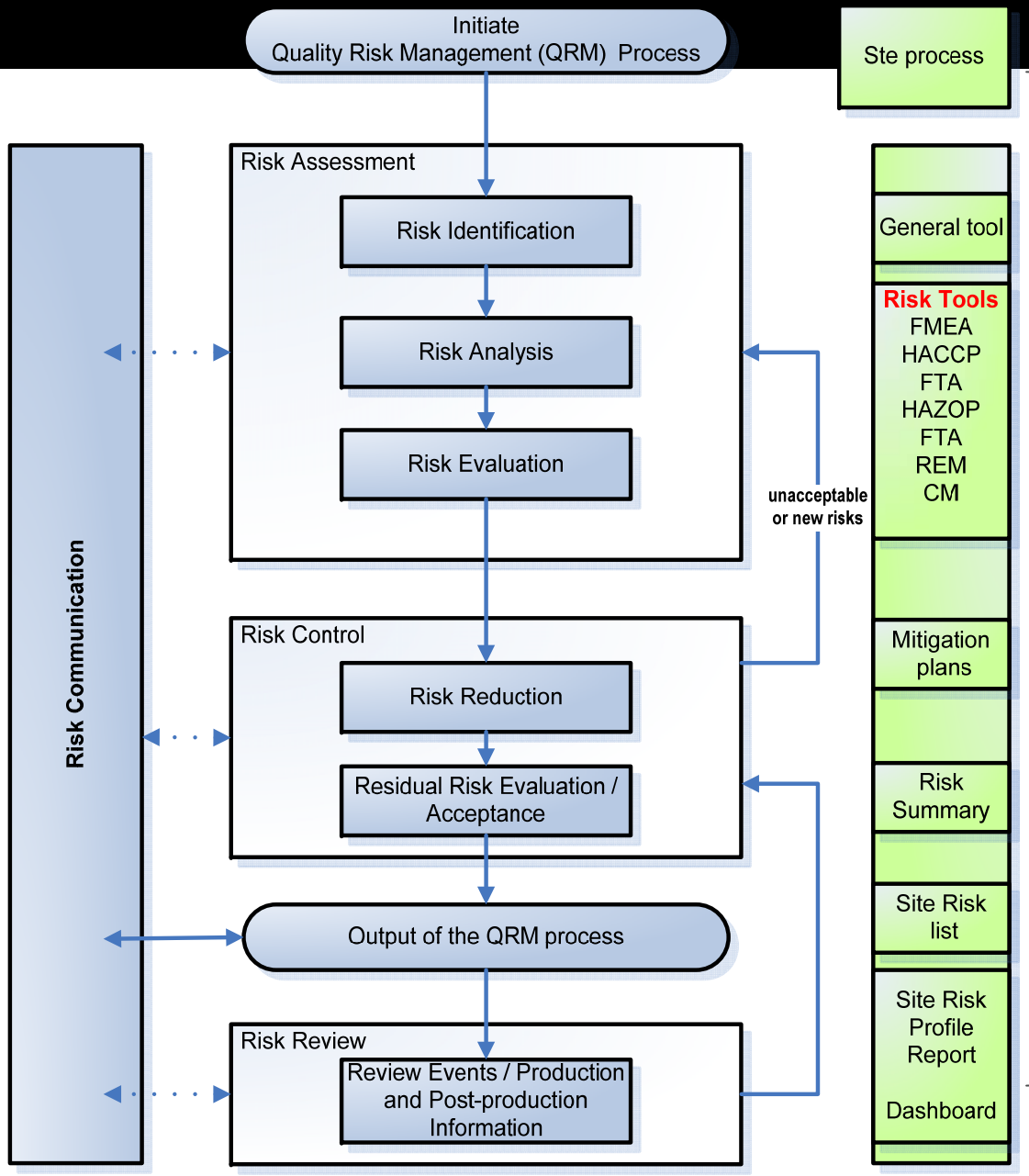
Applied QRM



Life cycle approach

Based on process knowledge

Standardised first step to ensure consistency of approach

Transparent system

Streamlined and iterative

Flexible tool choice depending on scenario

Initiation of a site wide risk register

Automatic roll up of risk from the ongoing RA's to the Risk dashboard

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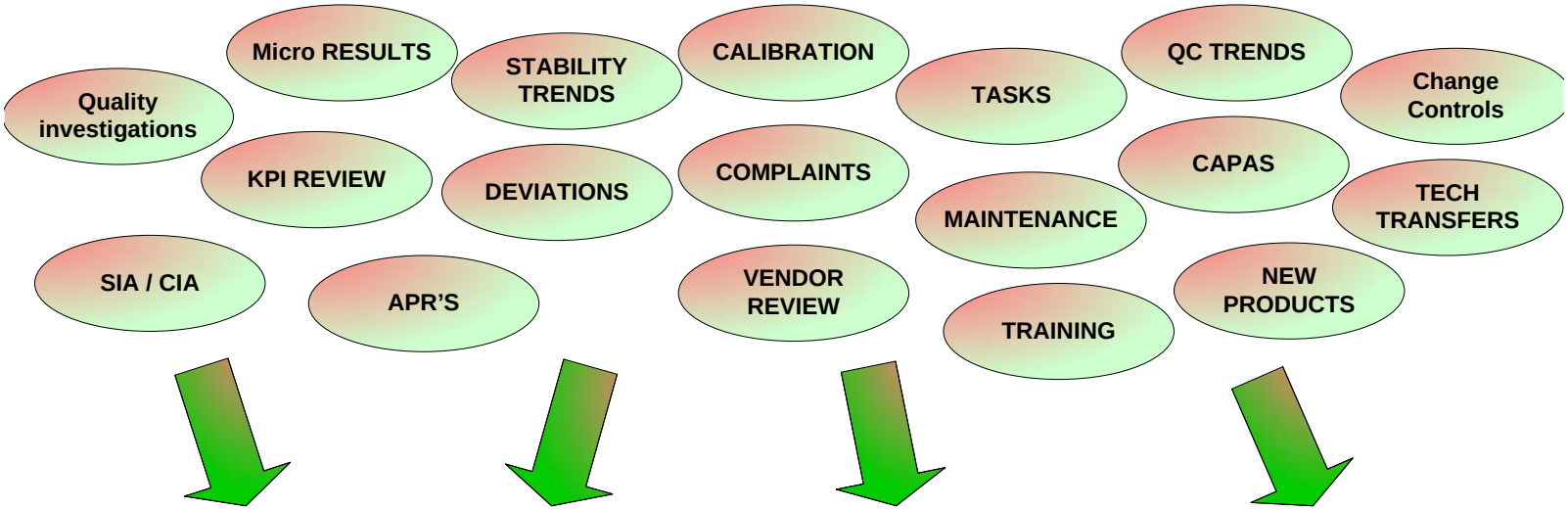
Site Applied QRM Process



SITE

MANUFACTURING P1 GOVERNANCE

MANUFACTURING P2 GOVERNANCE

MANUFACTURING P3 GOVERNANCE

RISK ASSESSMENT-IDENTIFICATION/ANALYSIS/EVALUATION

RISK CONTROL-RISK REDUCTION/RESIDUAL RISK EVALUATION /RISK ACCEPTANCE

RISK REVIEW-REVIEW EVENT /PRODUCTION AND POST PRODUCTION INFORMATION/ REVIEW MITIGATION PLANS

MONTHLY SITE QUALITY COUNCIL
DASHBOARD

PROJECT UPDATE TO RISKS MITIGATION (TRAFFIC LIGHTS)
REVIEW OF NEW RISK SCORING / MITIGATION

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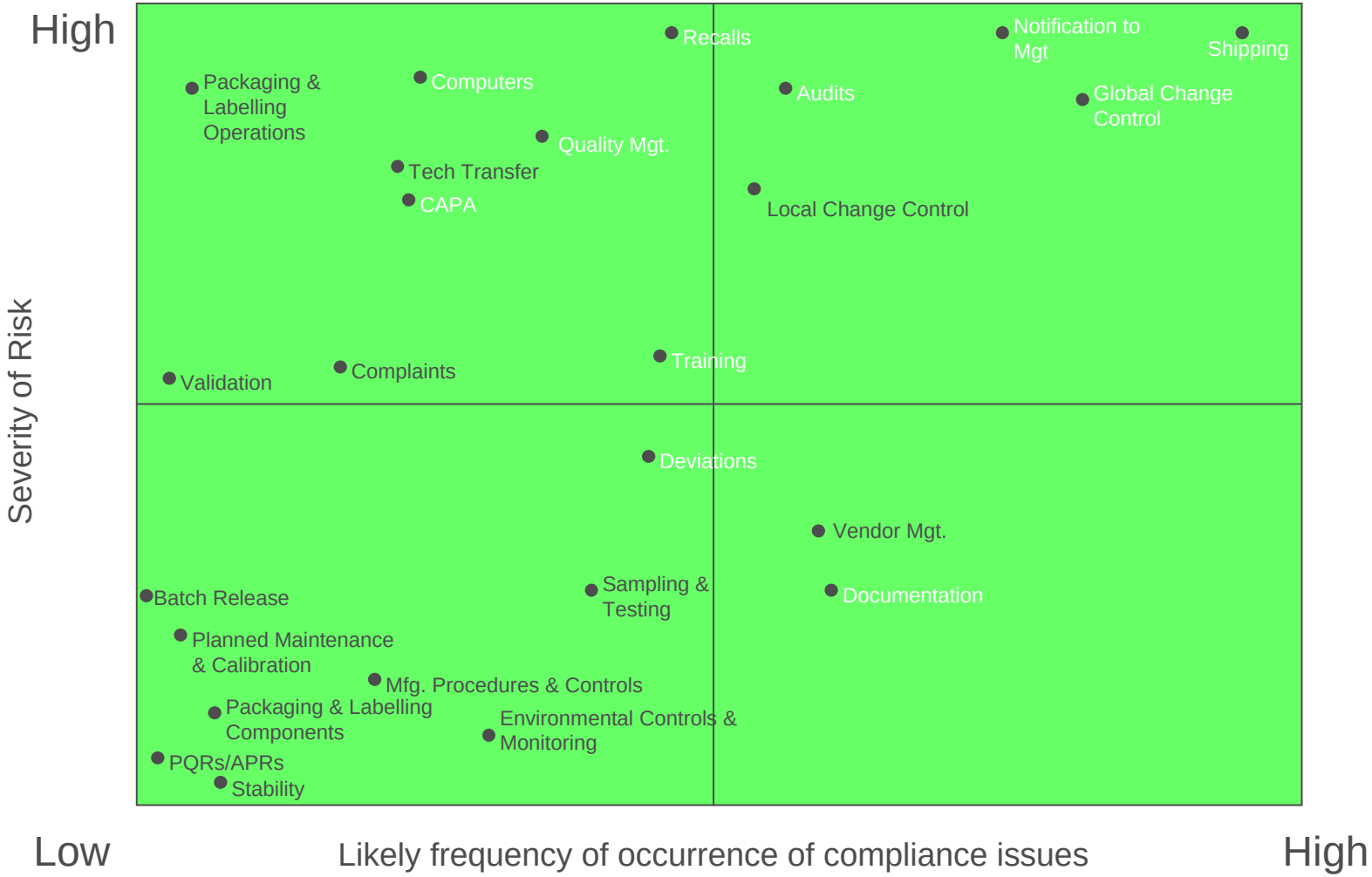
Example of Risk Dashboard



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Identifying the Right Tool - Considerations

‘ It is not always necessary to use formal risk management tools in a QRM process, however in the right circumstances they can be very powerful’

- No single tool or method is appropriate for all cases.
- They require a relatively complete understanding of the process(es) under review.
- They work best when applied in a team environment with range of expertise for various perspectives.

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QRM Tools

1. Basic risk management facilitation methods (flowcharts, check sheets etc.);
   - Flowchart
   - Check Sheets
   - Process mapping
   - Cause and Effect Diagrams (Ishikawa / fish bone)
2. Failure Mode Effects Analysis (FMEA);
3. Failure Mode, Effects and Criticality Analysis (FMECA);
4. Fault Tree Analysis (FTA);
5. Hazard Analysis and Critical Control Points (HACCP);
6. Hazard Operability Analysis (HAZOP);
7. Preliminary Hazard Analysis (PHA);
8. Risk ranking and filtering;
9. Supporting statistical tools

Ref: ICH Q9 Annex 1

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The Tools

- Qualitative
  - Use risk categorisation to assess risk potential, e.g. Risk Checklists
- Quantitative
  - Use data based on scientific understanding to determine probability & impact
  - Use Statistical Techniques or Simulations

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RA Tool Comparison

Tool	Acronym	Formality	Structure	Context
Failure Modes and Effects Analysis	FMEA	Formal	Quantitative	General
Preliminary Hazard Analysis	PHA	Intermediate	Qualitative	General
Hazard Analysis and Critical Control Points	HACCP	Formal	Qualitative	Specific
Fault Tree Analysis	FTA	Formal	Quantitative / Qualitative	General
Hazard Operability Analysis	HAZOP	Formal	Qualitative	Specific

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Adverse Event - Front Line Tool

- Companies used different tools and combinations
  - Brainstorm
  - Fishbone
  - 5 Whys

- ‘Golden Hour’ after an event – data collection, photos, interviews

- Decide if further RA is needed---FTA, FMEA, HACCP

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Adverse Event - Root Cause Analysis

1. Title

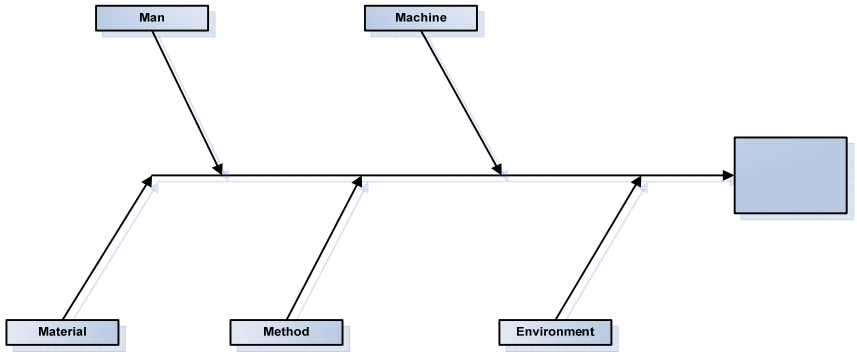
Team Leader **Team Members**

2. Problem Statement (Brief statement clearly describing the problem to be resolved)

3. Objective (Clearly defined target state using graphs, metrics, diagrams)

4. Current Condition (Pictures, Diagram, Pareto, Process Maps, Charts)

5. Root Cause Analysis (Cause & Effect Diagram or 5 Whys?)



6. Proposed Counter Measures (Proposed actions to address each root cause)

7. Improvement plan (How will the new process be implemented

8. Follow Up Actions

Who	What	When

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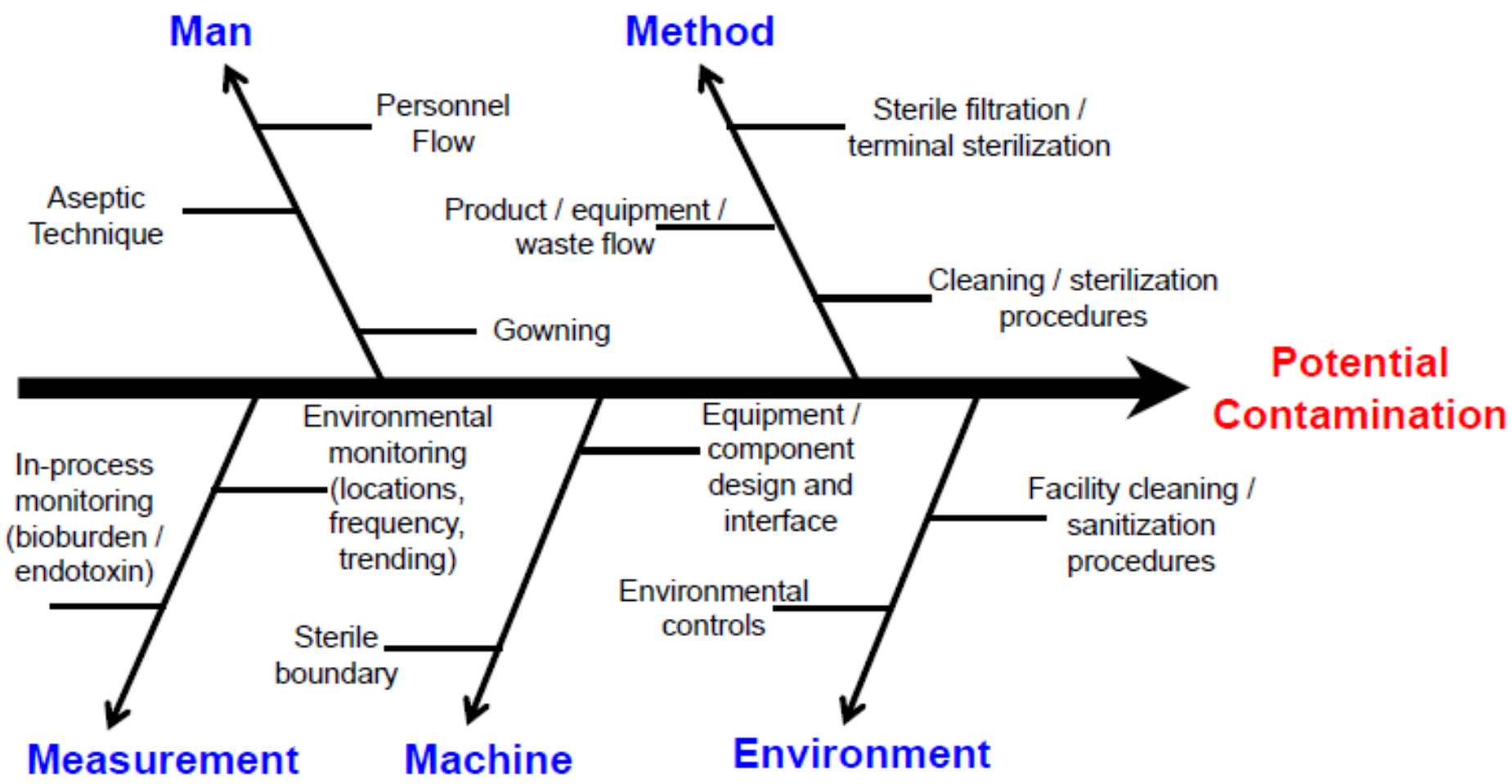
Risk Considerations in Aseptic Processing



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RISK ASSESSMENT							RISK REDUCTION						
Sub Step	**Event (Failure Mode)**	**Effect**	**Severity (S) [1<2<3]**	**Probability (P) [1<2<3<4]**	**Detectability (D) [1<2<3]**	**Risk Factor (S) [1<2<3]**	**Actions: Risk Reduction Strategy**	**Severity (S) [1<2<3]**	**Probability (P) [1<2<3<4]**	**Detectability (D) [1<2<3]**	**Risk Factor (S) [1<2<3]**	**Risk Reduction**	**Comments**
Wet Seving Drying	Temperature	Not meet specificaion of degradation	2	4	1	8	Implement two temperature measures	1	1	1	1	7	Automatically interruption by not meeting range; Temperature monitoring in batch record
Granulation Drying	Water Content	Not meet specification of degradation	2	3	1	6	- Introduce online NIR - Introduce IPC Analytic - Humidity measurement in the exausting air	2 2 2	1 2 1	1 1 2	2 4 4	4 2 2	- Indirect Measurement - Direct Measurement; Time Consuming - Indirect Measurement; Unspecific
Granulation	Kneeding Time	Not meet specification of degradation	3	3	1	9	Reduce personnel fluctuation	3	3	1	9	0	Operator knowledge; depending on power consumption; automatisation not possible at that time
Granulation	Power Consumption	Not meet specification of disolution	3	2	1	6	Try to get to a minimum an optimum of kneeding time	3	2	1	6	0	Depending on kneeding time depending on material properties
Pre Mixing	Mixing time	Not meet specification of content uniformity	3	2	3	18	IPC measure on content uniformity	3	2	1	6	12	Influence on efficacy
Pre-Mixing Granulation	Speed of Adding Water	Not meet specification of disolution and desintegration	3	3	3	27	Analyse (seeving of granulate sieve analysis); use of dosage pumps	3	2	1	6	21	To ge fine appropriate granulate
Pre-Mixing Granulation	Manner of Adding Water	Not meet specification of disolution and desintegration	3	1	1	3	Install spray nozzles	1	1	1	1	2	To get fine appropriate granulate
Granulation	Quality of Excipients	All paramaters have to be re-evaluated	3	4	3	36	Adapt internal specification of physical parameters (e.g. deensity, metability, wetability)	1	2	2	4	32	Contract Supplier
Granulation	Quality of API	All paramaters have to be re-evaluated	3	4	3	36		1	2	2	4	32	Contract Supplier
Overview		**Risk Before Control**			**Max**	**36**	**Risk After Control**			**Max**	**9**	**32**	
					Average	**17**				**Average**	**4**	**10**	
					Min	**3**				**Min**	**1**	**0**	

Hazard Analysis and Critical Control Points (HACCP)

- Structured approach applying technical and scientific principles
- Analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s)
- Considers design, development, production, and use of products

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Hazard Analysis and Critical Control Points (HACCP)

- Looks for physical, chemical, and biological hazards to process
- Requires sufficient process understanding to identify critical control points
- Focus is on lifecycle of product, not just manufacturing process

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From 21 CFR 123.6

Seven steps of HACCP

- List the hazards that are reasonably likely to occur
- List the critical control points for hazards
- List the limits for each CCP
- List the procedures, and frequency for monitoring CCP
- List corrective action plans for deviations from CCP limits
- List the verification procedures
- Provide for a recordkeeping system that documents the monitoring of the CCPs

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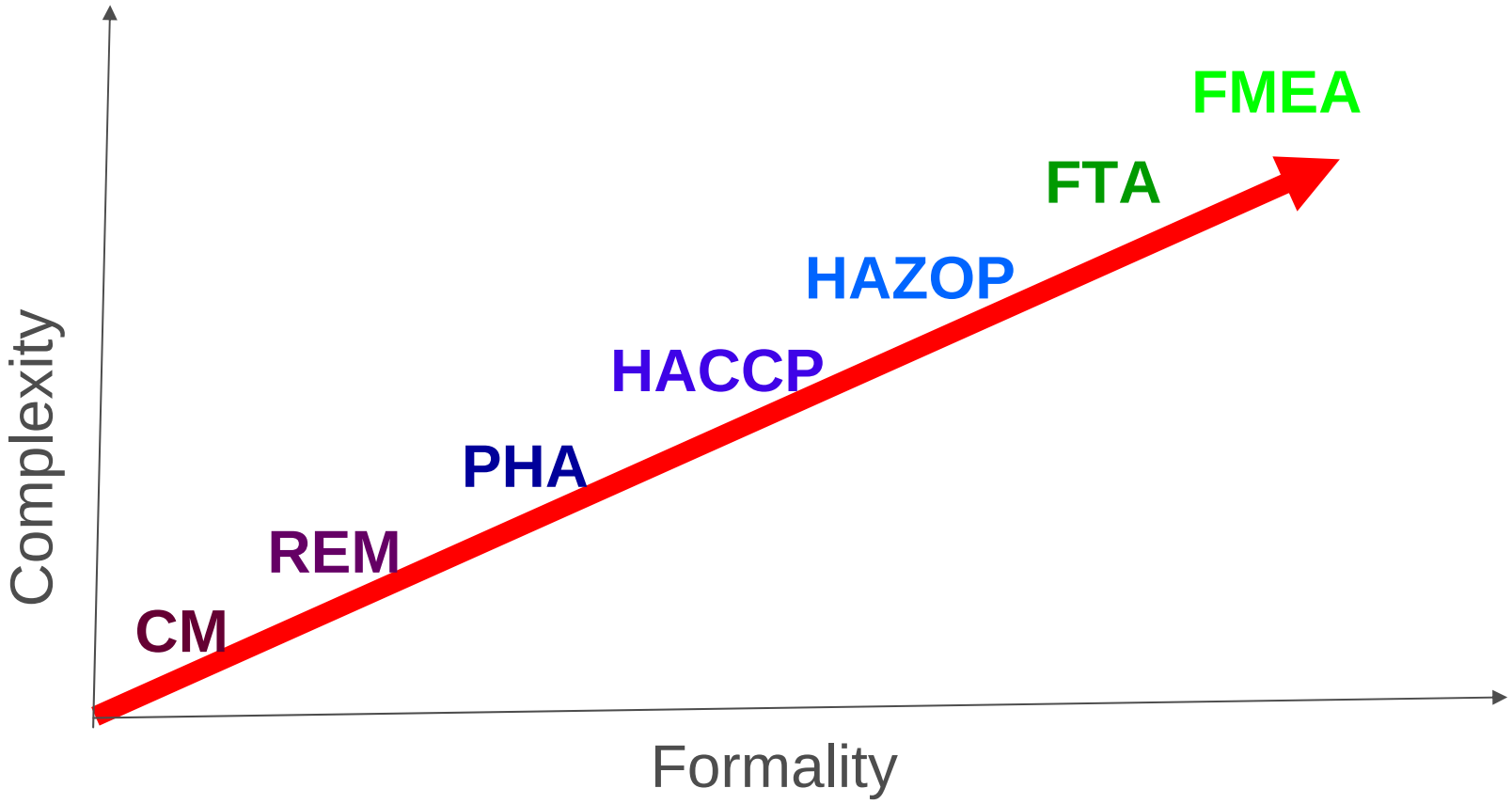
Risk Assessment Tool Formality



A quotation I like

- For any risk management method used in the pharmaceutical industry or any other industry, we must ask, again,

‘How do we know it works?’ If we can’t answer that question, then our most important risk management strategy should be to find a way to answer it and adopt a risk assessment and risk mitigation method that does work.” –

Hubbard, Douglas W. (2009). The Failure of Risk Management: Why It’s Broken and How to Fix It (p. 15).

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Lessons learnt from RA's

- Important to understand the difference between risk assessment (the individual documents) and risk management (the holistic process). Tool is too complex
- No QRM Process / Plan
- Unclear definitions
- Unclear qualitative grading
- Very perspective SOPs for RA that are too complex
- The RA exercise is not done in a timely manner
- The outcome is already decided
- Foundation of process knowledge is not available
- Team is not multifunctional/multidisciplinary
- Stockholm syndrome- follow the crowd….
- Combinations of tools not considered
- The results of the RA are not liked and changed !
- Insufficient Review & Communication
  - Not closing the loop = wasted effort

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To Conclude

- Much similarity between ICH Q9 & ISO 14971
  - Medical Device sector more advanced in implementation of QRM
- Regulatory bodies will expect it
- It helps improve products and processes using an anticipatory approach
- There is an array of tools that can be very powerful used in the right context and combination
- Process doesn’t stop after the Risk Assessment!

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Thank You

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