TECH TRANSFER AND QRM

TIM HOWARD, PE CPIP
VICE PRESIDENT– COMMISSIONING AGENTS, INC

SAAPI Conference
Bytes Conference Centre, Midrand
Friday, Oct 6th, 2017

COMMISSIONING AGENTS, INC.

460+ Agents Global Presence

9 Business Areas

$500M+ Services delivered

150 Active Projects

21 Years Of safety excellence

A global partner in providing professional services to enhance **operational performance** and **reliability**.

GLOBAL IMPACT

- Asset Management & Reliability
- Automation & Information Technology
- BioVoke™ eVLM
- Building Commissioning
- Commissioning & Qualification

LOCAL SERVICES

- Full Scale Operations™
- Human Performance
- Owner's Project Management
- Process & Manufacturing Technologies
- Quality, Compliance, & Regulatory

When you need to meet a higher standard.

What is Technical Transfer?

ISPE

The systematic approach that is followed in order to pass the documented knowledge and experience gained during development and/or commercialization to an appropriate, responsible, and authorized party

ICH Q10

Transfer of product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization

new product transfers during development through manufacturing

transfers within or between manufacturing and testing sites for marketed products

Key References

ICH Q8R2

ICHQ10

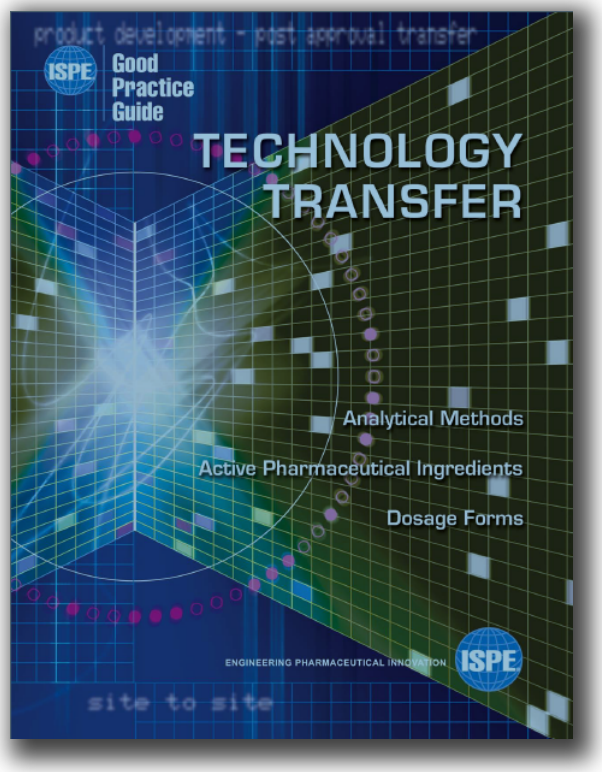
ISPE Tech Transfer Guide 2014

ISPE PQLI guides

WHO guide 2011

EMEA annex 15

Draft annex 12- lifecycle management



Technical Transfer Examples

New product to the market

Limit client risk yet maximize speed to market

Scale-up of an existing process

Creative solutions typically required for implementation

Movement of production to new facility

New can cost less. Like for like expected.

Process improvements

Continual improvement to improve product cost a must

Types of Technical Transfers: Risk Assessment

Each type of Tech Transfer comprises similar risk elements

Sending	Receiving	New Product	Same or Single Market	New or Multiple Market(s)	Existing Production Line	New Production Line	Equivalent Equipment	Equipment Change	>10x Scaleup	Process Change	New Process
Site 1	Site 1	No	Low	Med	NA	Med	Low	Med/High	High	Med/High	High
Site 1	Site 1	Yes	High	High	Low/Med	Med	Low	High	High	NA	High
Site 1	Site 2	No	Low	Med	Low	Med	Low	Med/High	High	Med/High	High
Site 1	Site 2	Yes	High	High	Med	Med	Low	High	High	NA	High

The risk assessment needs to include key cross-functional activities that comprise the boundaries of a TT

Measures of Success of a TT program

Does the approach promote the delivery of working equipment and automation, to achieve smooth transition to full scale operation?

Is the approach efficient in terms of effort (cost) and time (schedule)?

Is the program product/process focused, initiated with Process robustness ?

Will the approach be found acceptable by regulators?

The WHAT – Define Project Scope

Define the Project Scope and establish clear objectives with specific acceptance criteria.

- Proposed Registration and Launch Timings
- Safety Information (MSDS, Fire & Health Hazards etc.)
- Commercial needs (e.g. forecast Volume)
- Cost of Goods
- Tech transfer budget

The WHO – Establish the Team

Appoint a Team Leader and Form a cross functional project team

CORE EXPERTISE: Process Development, Manufacturing Operations - (manufacturing, engineering and maintenance, production QA, QC, Validation)

SUPPORT EXPERTISE: Regulatory affairs, EHS, Medical, Marketing, Supply Chain

The HOW – Establish the Plan

Develop a Comprehensive Execution Plan that captures:

- Goals and timing
- Facility fit and regulatory strategy
- Process tech transfer requirements
- Managing documentation
- Effective Team Communications
- Roles and Responsibilities
- Project schedule and resource requirements & tracking team performance

Documentation Hierarchy

TT Master plan

Subplans

TT Risk Assessment

Process Robustness study

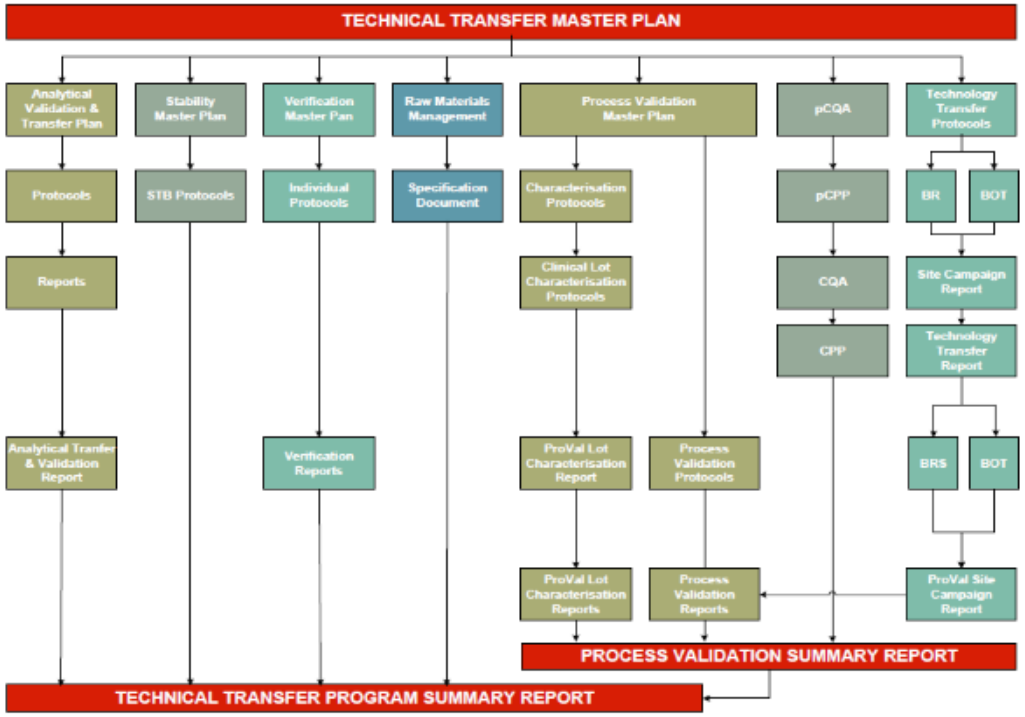
TT SOP/protocols/Templates/reports

CAI Tool Box

- **Program Management Plan**
- **Technology Transfer Plan**
- **TT Project Execution Plan**
- **Lifecycle Phase Checklist**
- **Subordinate plans/Reports**
  - CQV
  - Cleaning
  - Materials Mgt/Control
  - Supply Chain
  - Analytical Methods Validation
  - PQS
- **PM tools**
  - Schedule/Action/Decision logs

Technology Transfer Master plan

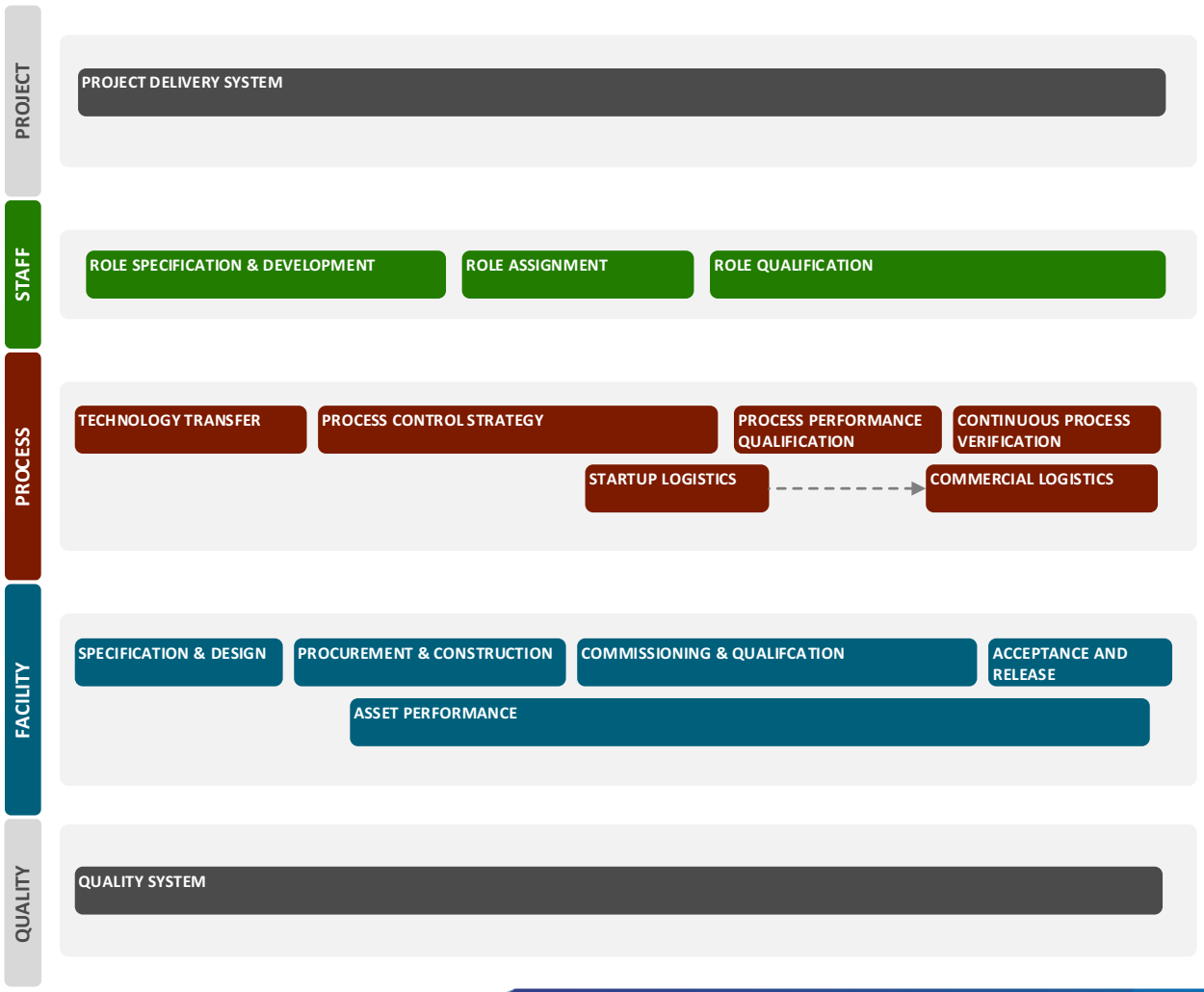
CONTENTS



TT Checklist

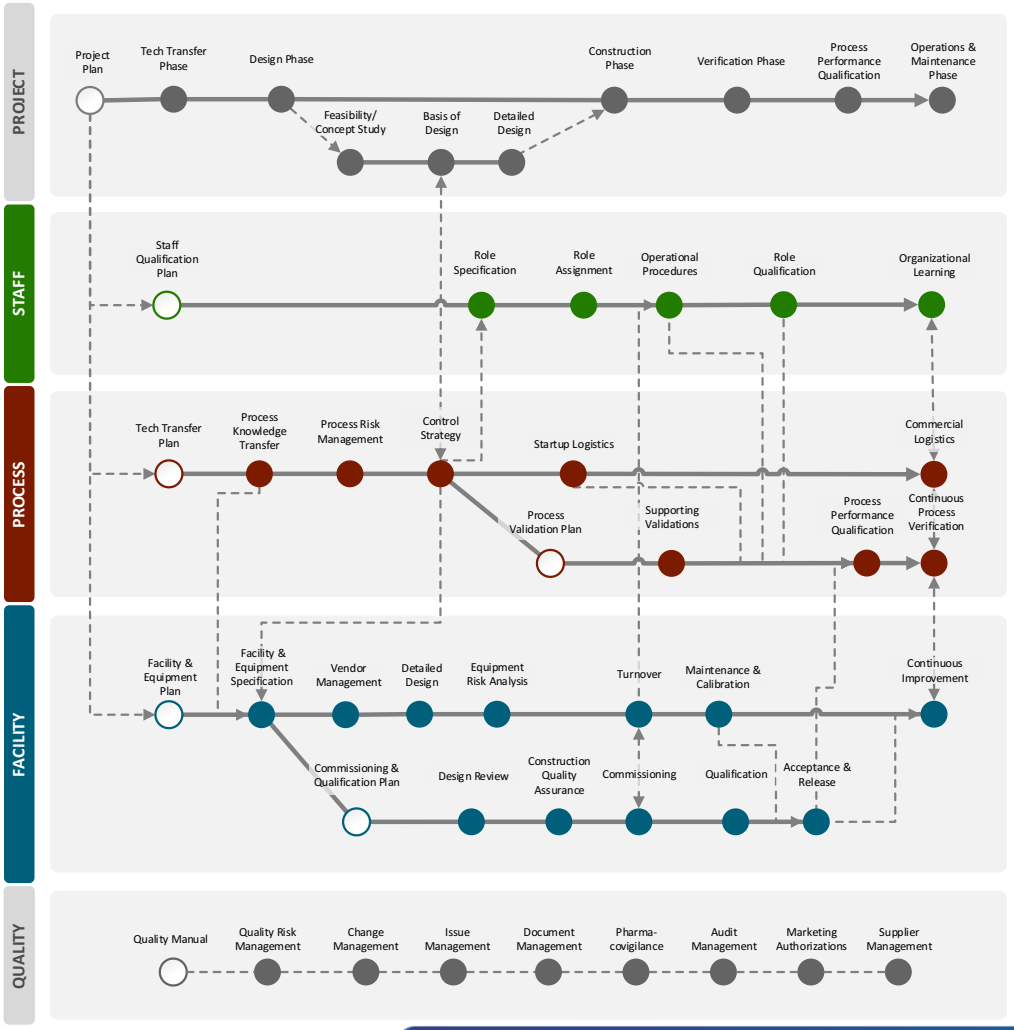
Dev = Development, Mfg = Manufacturing, Eng = Engineering, Reg = Regulatory, QA = Quality Assurance, Anl = Analytical, Val = Validation, Legal = Legal, PM = Project Management, Log = Logistics, EH&S = Environmental, Health, and Safety, Dis = Function
E-E = Existing Drug to Existing site, E-N = Existing Drug to New Facility, N-E = New Drug to Existing Facility, N-N = New Drug to New Facility.

Type	PROJ	Activity	Phase	Dis	Deliverable	Ref	Project
E-E	☐	Technical Development Initial Process Description Initial Product Description Dosage and Delivery Materials (consider European/Japanese/United States Pharmacopoeia or Multi-compendia) Specifications Method Development Instrumentation Needs Process / Product Development Reports Development History Report Manufacturing Monograph	Prior to Transfer or Feasibility	Dev, Mfg, Eng, Reg, QA	Go/No-Go Decision		
E-N	☐						
N-E	☐						
N-N	☐						
E-E	☐	Write Confidential Disclosure Agreement (CDA) Approve CDA	Feasibility	QA, Legal	Approved CDA		
E-N	☐						
N-E	☐						
N-N	☐						
E-E	☐	Evaluate Facility and Utilities Evaluate Equipment Evaluate Process Capability Evaluate Technical Capacity Evaluate Analytical Capabilities Evaluate Regulatory Implications Evaluate Material Logistics	Feasibility	Dev, Mfg, Eng, Reg Anl	Feasibility Assessment Report		
E-N	☐						
N-E	☐						
N-N	☐						
E-E	☐	Assess Quality Systems Assess Prior Regulatory Inspections	Feasibility	QA/Val	Audit Report		



Our Solution.

The Chemistry of Full Scale Operations (FSO)™



Our Solution, in Detail.

The Chemistry of Full Scale Operations (FSO)™

Summary

- **TT subset of Product Realization**
- **Knowledge Transfer is a key element to all TTs**
- **Upfront work to define complexities, resource needs, and understand business/regulatory strategy allows for smoother and more successful TT**
- **Risk management enables a more streamlined lifecycle effort**
- **Solid understanding of company's quality management system essential to defining requirements and flexibility that will be allowed**

ISPE®

QUALITY RISK MANAGEMENT

References

ICH Q9 “Quality Risk Management”

FDA Guidance on Process Validation

ICH Q8 (R2) “Pharmaceutical Development”

ASTM E2500

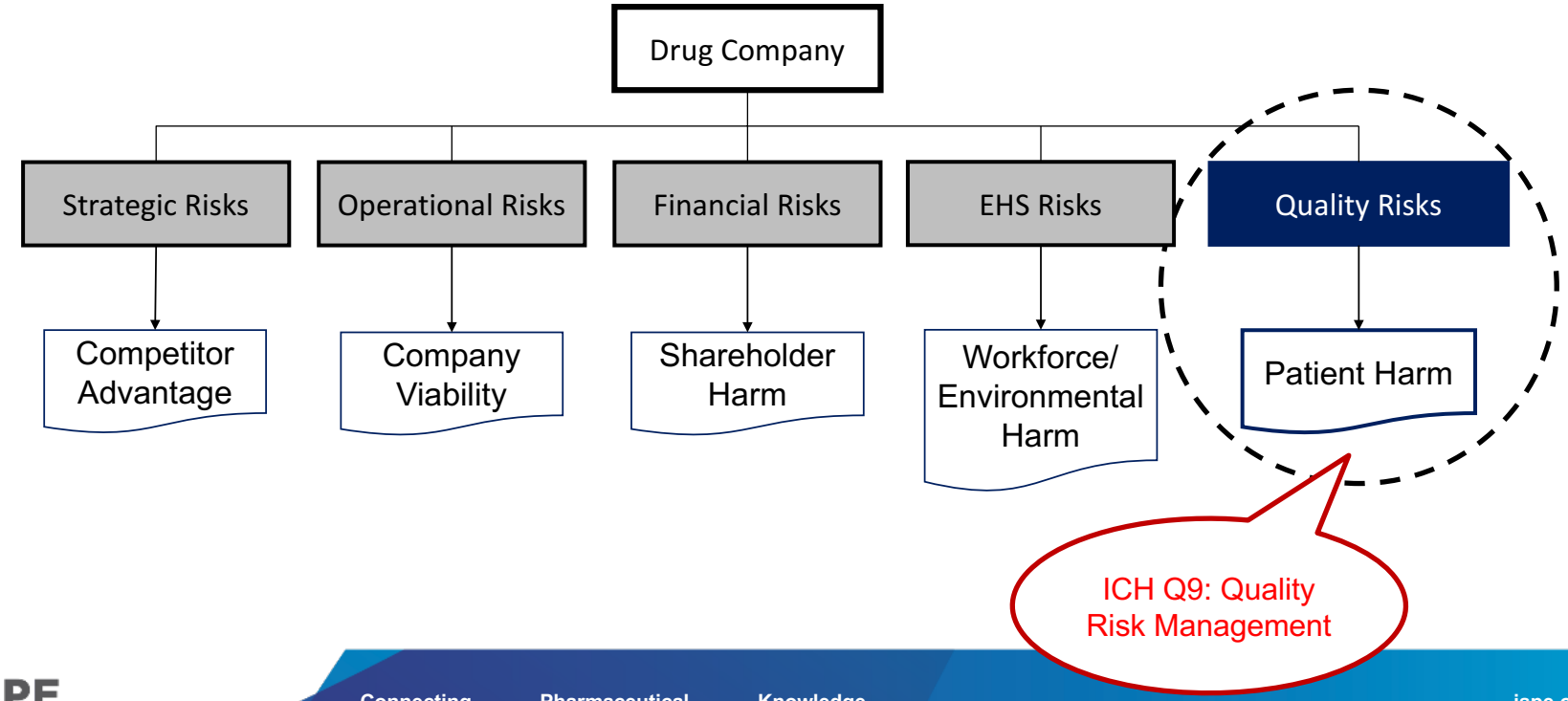
IEC 60812

Analysis techniques for system reliability – Procedure for failure mode and effects analysis (FMEA)

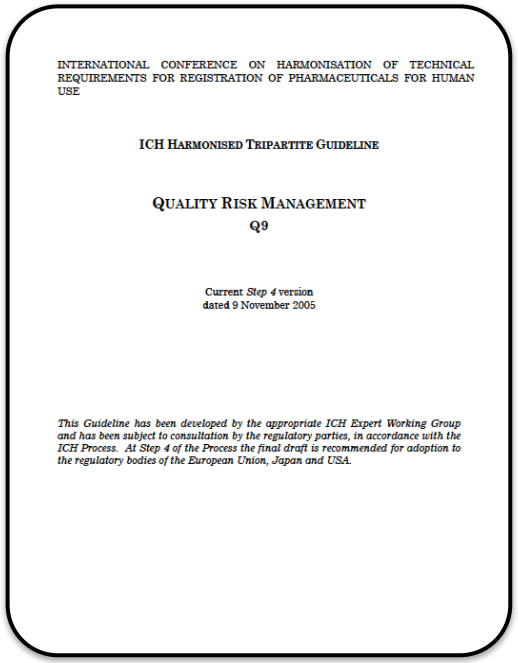
Risk Management is Universal across all Industries

Common Elements	Key Differences
What can go wrong?	Risk criteria
How often does it happen?	Technology involved
How bad are the consequences?	Nature of the hazard
Is the risk acceptable?	Whether the system is static or dynamic

Risk Management In the Drug Industry



Quality Risk Management ICH Q9



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

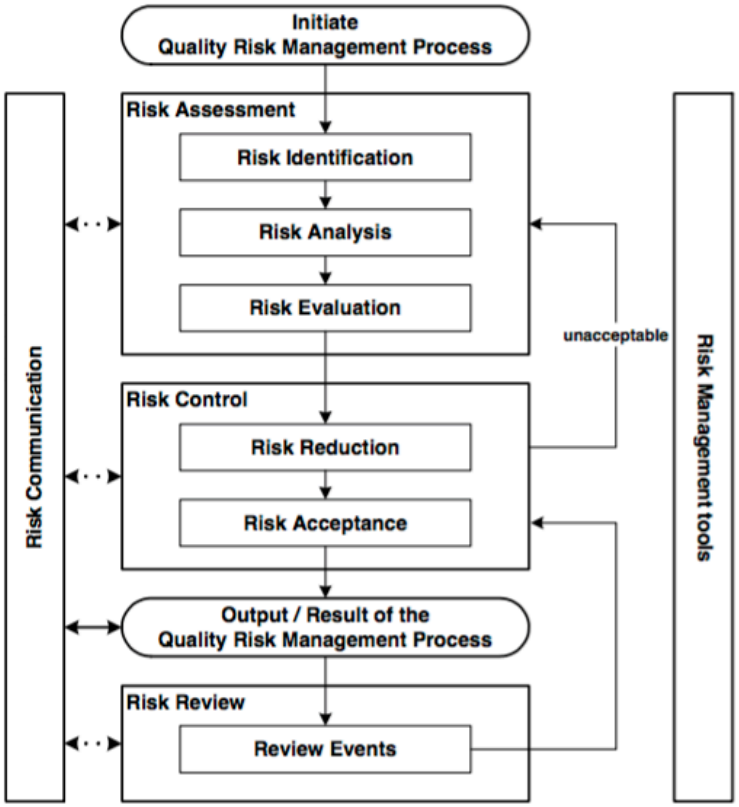
ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Current *Step 4* version
dated 9 November 2005

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Figure 1: Overview of a typical quality risk management process



ICH Q9: Primary Principle #1

“Evaluation of the risk to quality should be based on scientific knowledge (of the product, process and clinical effects) and ultimately link to the protection of the patient”

ICH Q9: Primary Principle #2

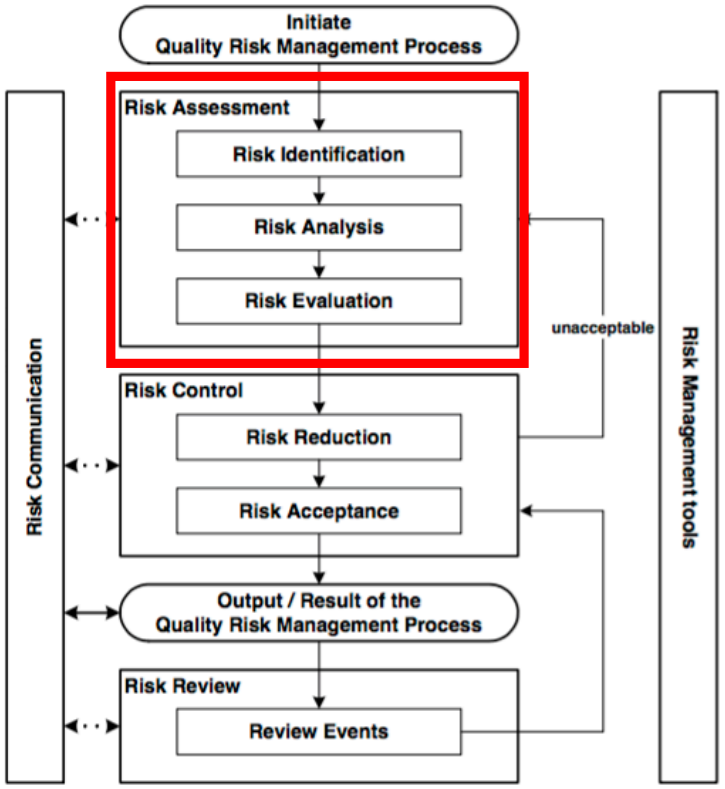
“The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk”

Risk Assessment

Risk Assessments

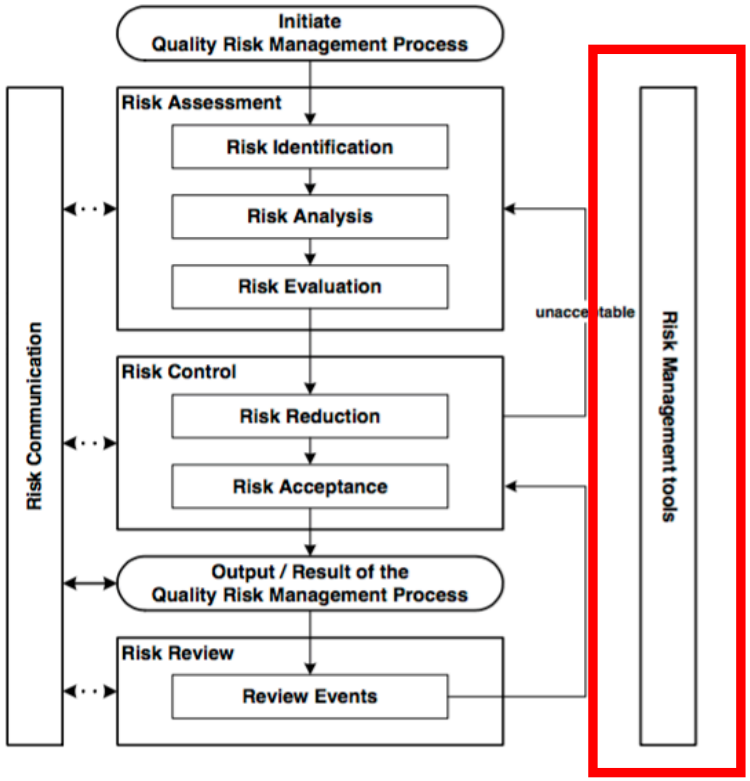
HAZOP
FEMA
FMECA
FTA
HAACP
PHA
Risk Ranking
Statistics

Figure 1: Overview of a typical quality risk management process



Risk Management Tools

Figure 1: Overview of a typical quality risk management process



Tools

HAZOP
FEMA
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Risk Ranking
Statistics

Risk Assessment

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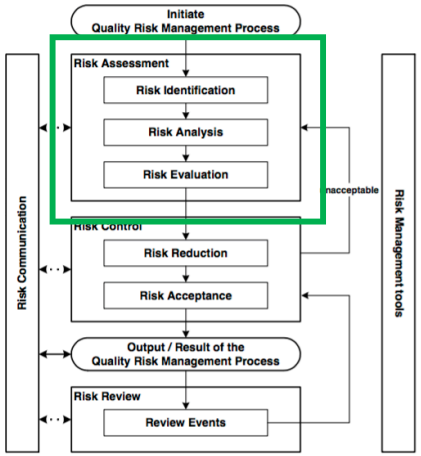
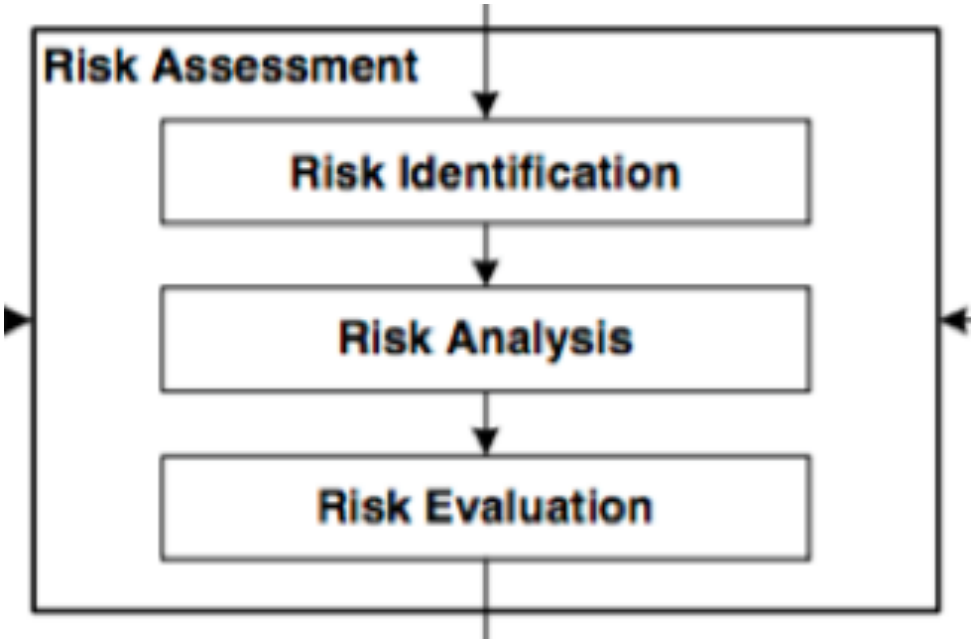




RISK ASSESSMENTS

QRM Tool Selection

Murray, K. and Reich, S.

“Quality Risk Management (QRM) Tool Selection: Getting it Right First Time.”

Pharmaceutical Engineering, July/August 2011, Vol. 31 No. 4.

Risk Assessment Options

Failure Modes Effect Analysis

(FMEA / FMECA)

Fault Tree Analysis

HACCP

Boston Matrix

Ishikawa Diagram (Fishbone)

FMEA / FMECA

Assesses failure modes and looks to reduce impact or occurrence of failure

Relies on robust process understanding

Yields quantitative assessment of risks a risk priority number (RPN)

Methodical in nature, can be time consuming

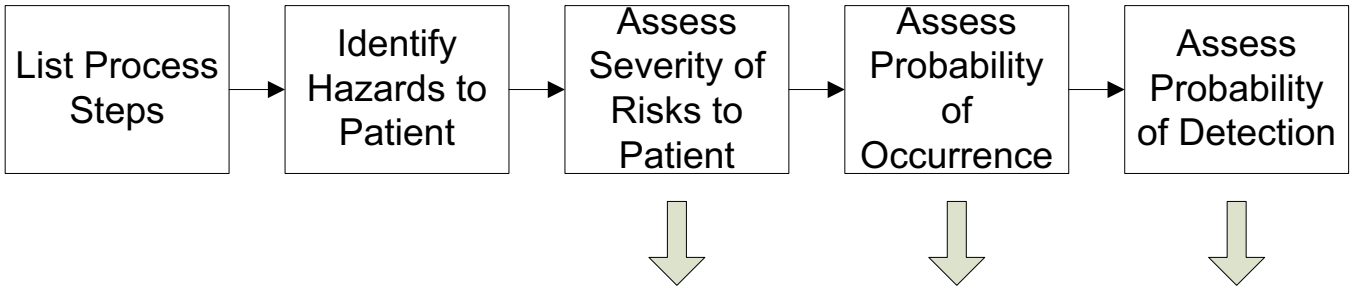
FMEA / FMECA

Typically applied to an equipment or system boundary

Level of effort may not be justified

Use as deep dive for high risk items

Process FMEA Example



List the severity of each hazard listed in previous step. The severity rating is independent of design features or detection mechanisms.

With an understanding of the design features and other risk control mechanisms, assess the probability of occurrence

With an understanding of the detection mechanisms and design features, assess the probability of detection

<u>Critical Aspects</u> = Those design features and functions that serve to reduce probability of occurrence or enhance probability of detection

Scoring Options

Use a 3 to 5 point scale (Quantitative)

1, 3, 5 1, 5, 10 1, 4, 7 10 1,10, 100

Qualitative

Low, Med ,High

Negligible, Low, Med, High, Unacceptable

RPN Limits or Thresholds

Risk is Acceptable or Unacceptable

Grey Zone Suggested

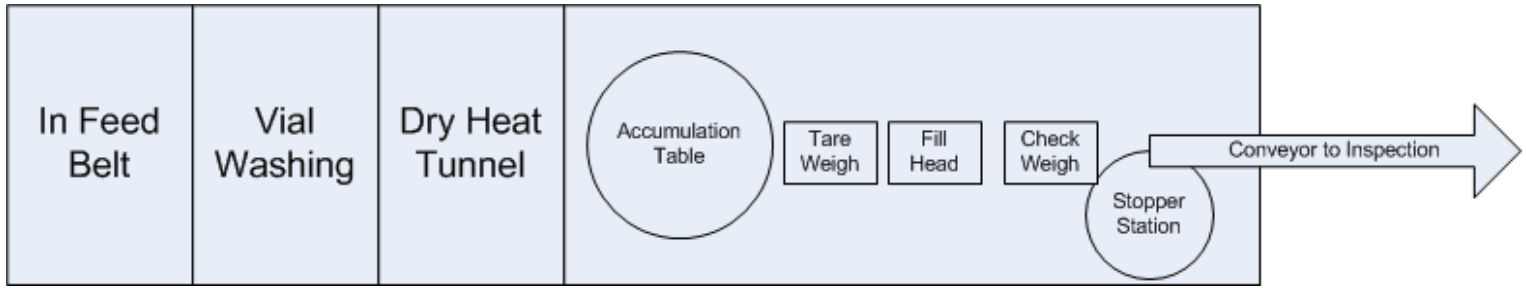
Aseptic Filling Line - Isolator

Isolator Sanitized with VHP

Product Transfer Line cleaned with CIP and sterilized with SIP

Filling Head parts cleaned in Washer and sterilized in Autoclave

Tubing Replaced each lot



Process Steps

Prepare Equipment

Load Vials

Wash Vials

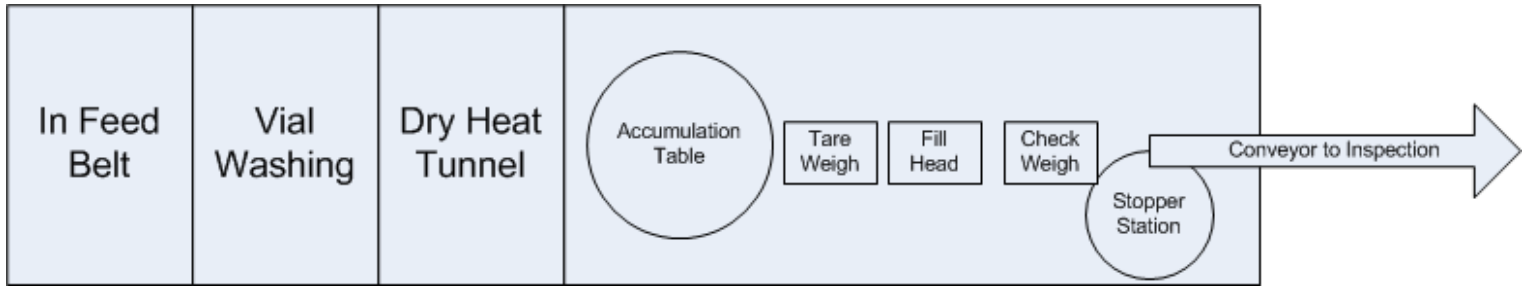
Depyrogenate Vials

Fill Vials

Weigh Vials

Stopper Vials

Convey Vials



Hazards to Patient

Wash Vials

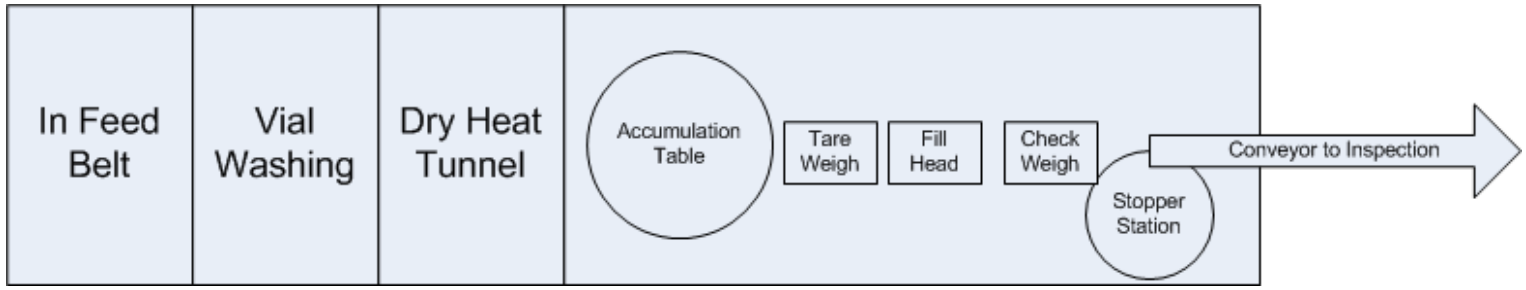
Dirty Vials not adequately Washed resulting in contaminated dose

Contamination from Water or Air ???

Depyrogenation

Vials do not reach time at temperature resulting in endotoxin dose contamination

Contamination from Air???



Example Output

Process Step	Hazard	Severity	Controls	Probability	Detectibility	RPN
Wash Vials	Dirty Vial not Washed					
Depyro Vials	Endotoxin Contamination (Time at temp not reached)					
Depyro Vials	Microbial Contamination from Air					

Example Output (Quantitative)

Process Step	Hazard	Severity	Controls	Probability	Detectibility	RPN
Depyro Vials	Endotoxin Contamination (Time at temp not reached)	5	Automation control of belt speed, temperature control, airflow Alarms associated with belt speed, low temperature, loss of airflow Calibration of instruments	1	1	5

Critical Aspects

Belt Speed Control, Indication, Alarm

Tunnel Temperature Control, Indication, Alarm

Airflow Velocity, Loss of Airflow Alarm

Acceptance Criteria driven by process requirements

Fault Tree Analysis

Assumes a failure has occurred with a process or product

Evaluates sub-process steps and causal effects

Represented pictorially as a logic diagram

May be good for root cause analysis or for assessing impact of multiple factors

Fault Tree Analysis

Graphical methodology that examines combinations of possible events with undesirable results

Human and System Failures

Good for integrated systems analysis, forcing us to think across system boundaries

Intended for assessing designs and processes for risk

Fault Tree Analysis

Start by picking the worst event results and work down to possible causes

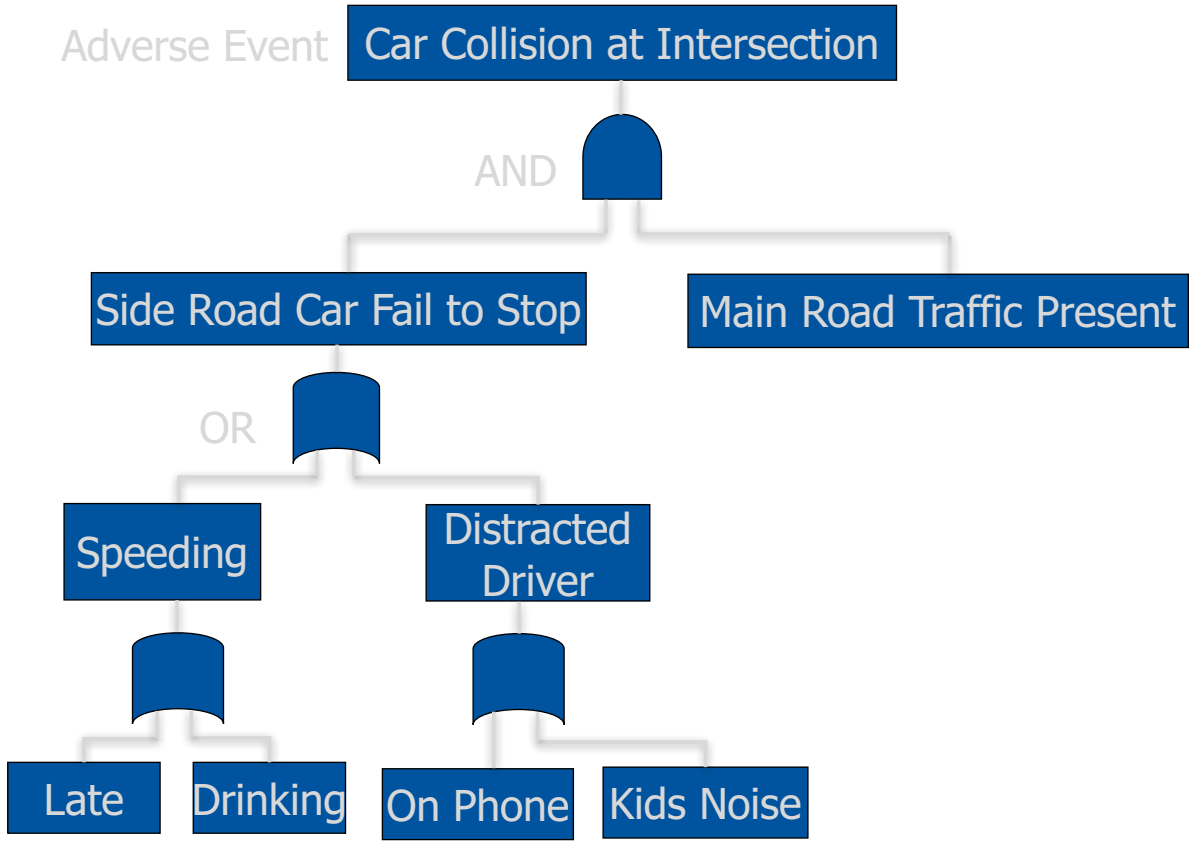
Technique inherently encourages prioritization of events

Uses a set of symbols to depict actions and relationships

= “AND”: combination of events triggers fault

= “OR”: one of several possibilities triggers fault

Standard FTA: Common Example



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

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

From 21 CFR 123.6

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

Boston Matrix

80 / 20 Rule

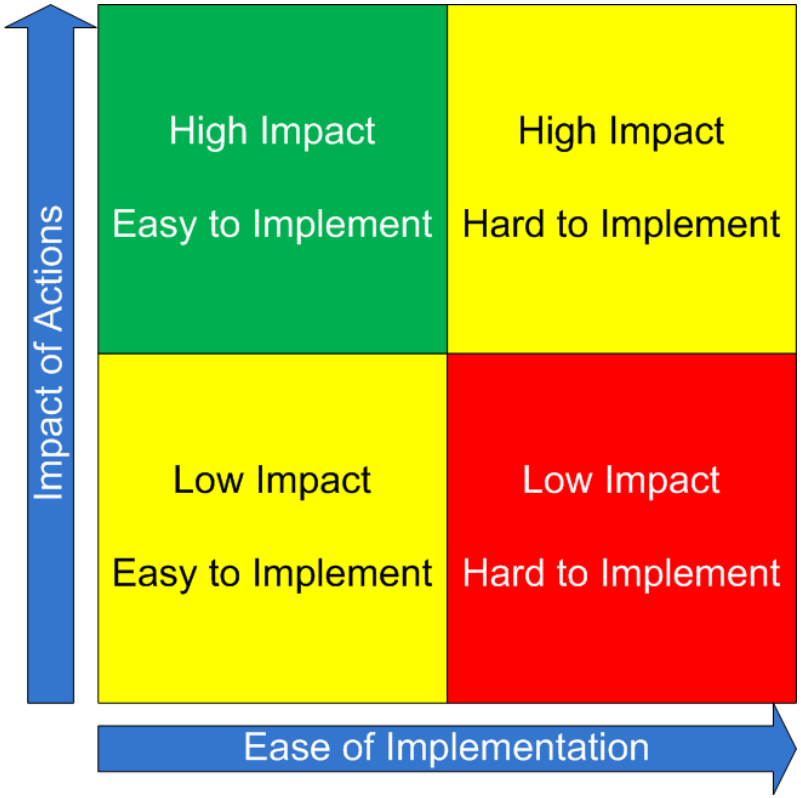
Drive focus to area of most need

Drive focus to actions with most impact

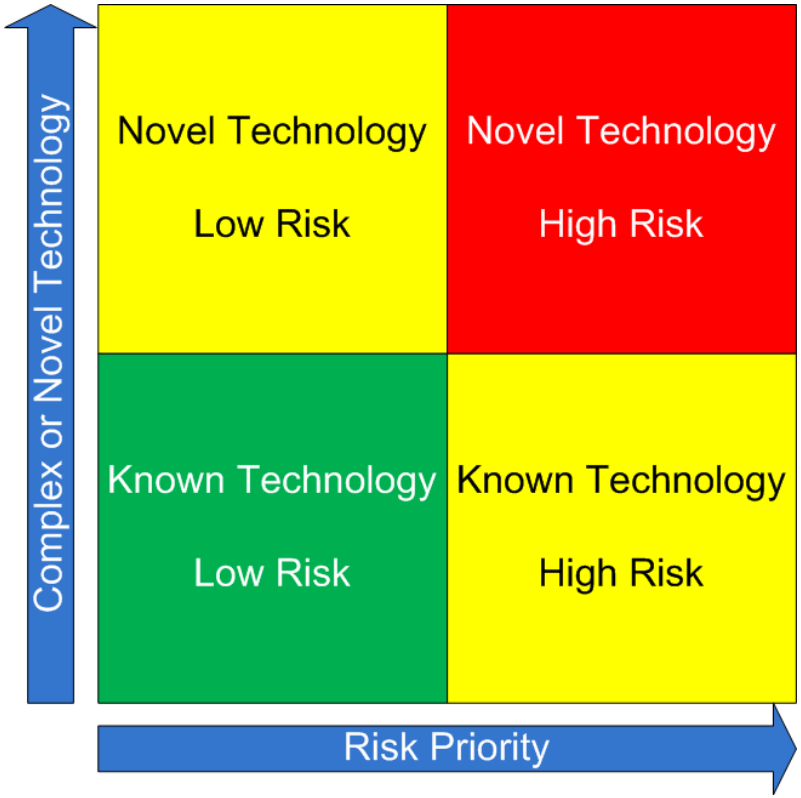
Drives discussion

Documents decisions

Response to Design Review



FAT Planning



Cause and Effect Diagram

AKA: Fishbone or Ishikawa diagram

Widely used for Root Cause Analysis

Used to examine:

Man, Method, Machinery, Materials

Effective when output coupled with another tool

Sample Formulation Process

Formulation Tank CIP/SIP

Buffer Prepared

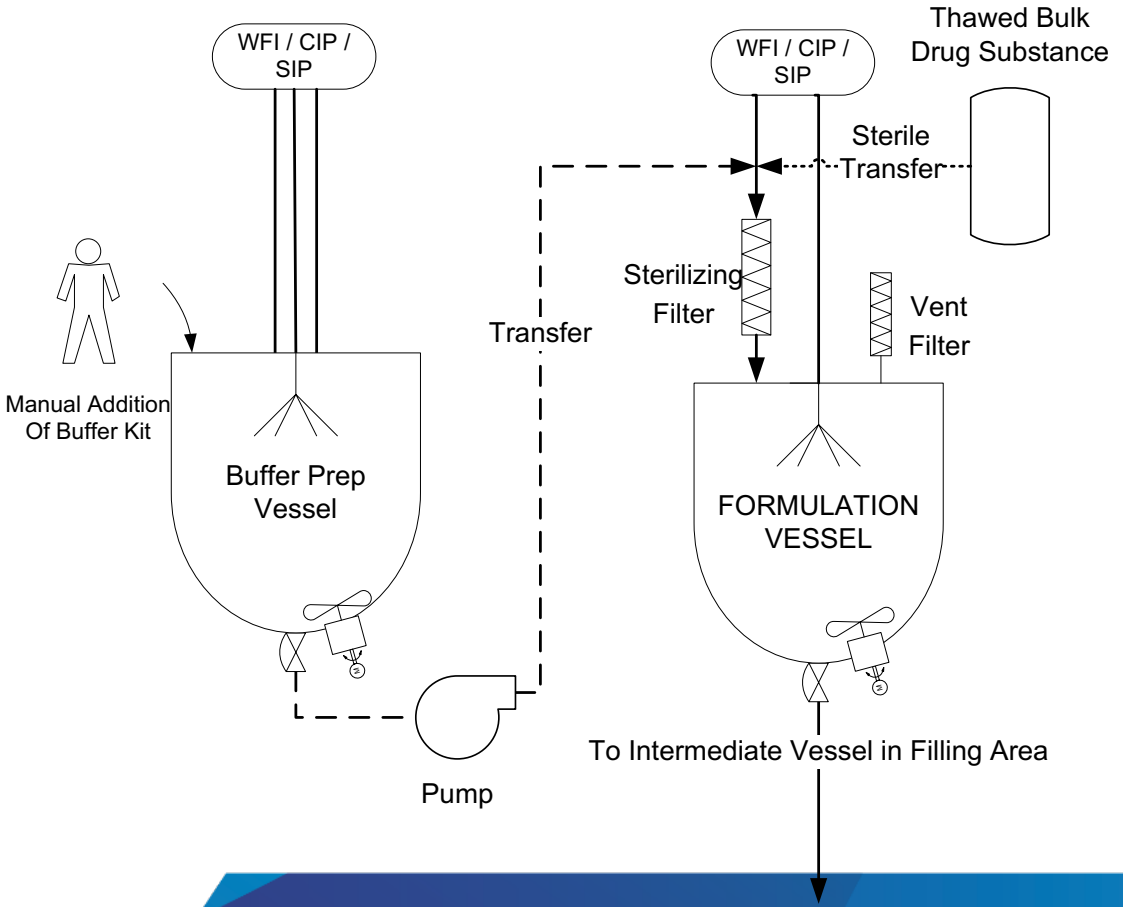
Bulk Drug Substance Thawed

Buffer and Formulation Added to Formulation Vessel

Mixed and Sampled

Transferred to Filling Area

Formulation Process



Hazards to Process

Microbial Contamination

Protein Degrades or Denatures

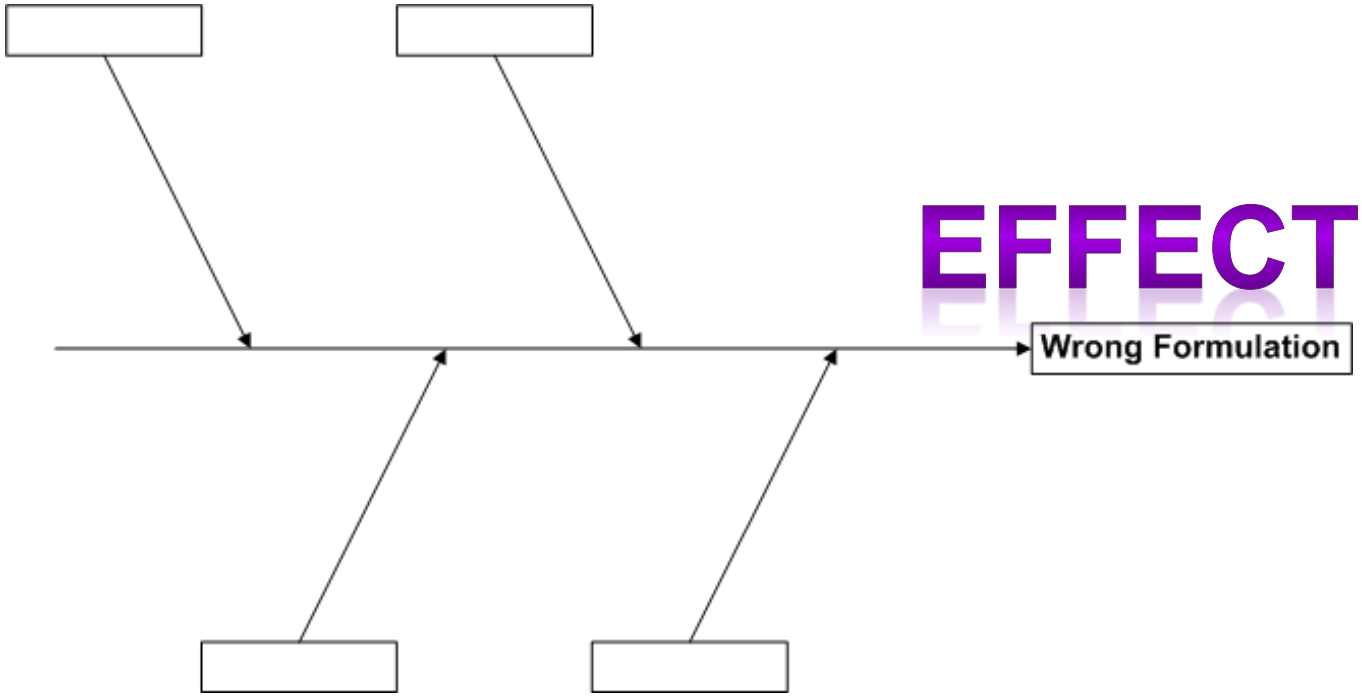
Cross Product Contamination

Wrong Formulation

Endotoxin Contamination

Foreign Material Contamination

Cause and Effect Diagram



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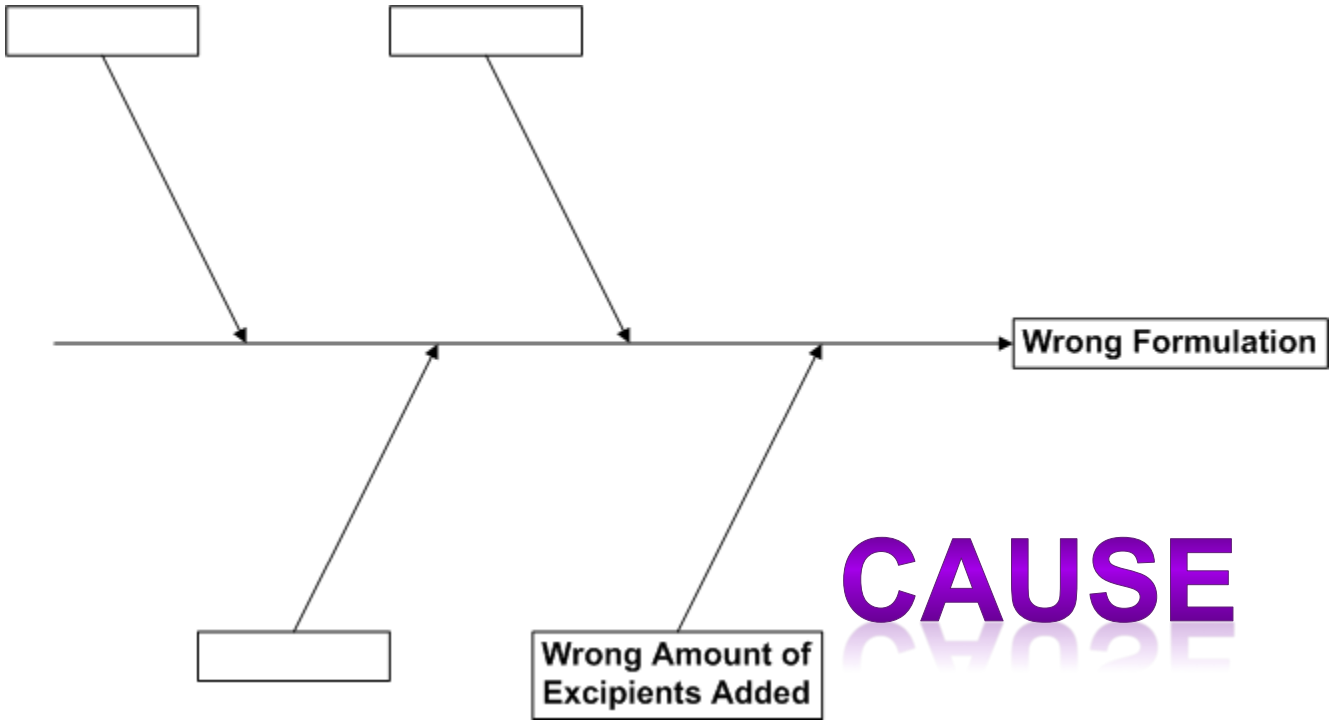

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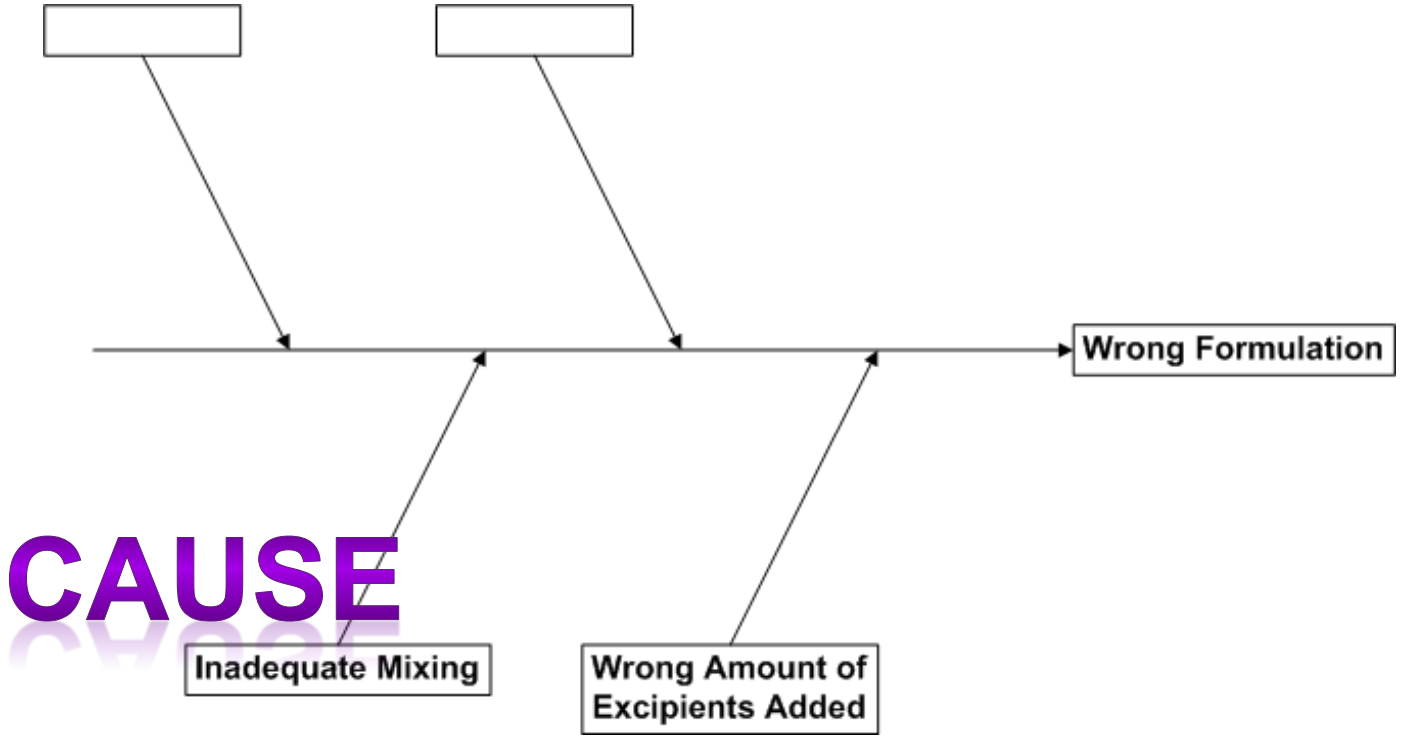

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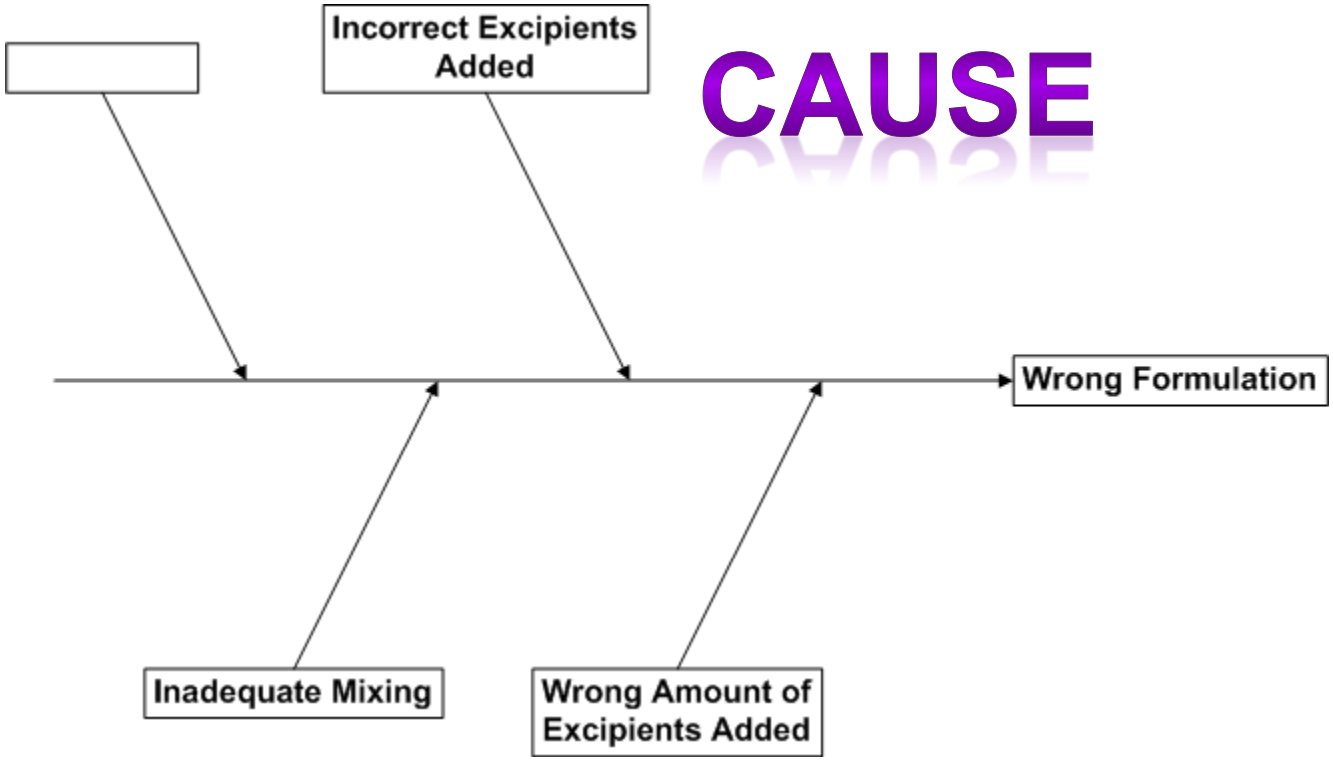

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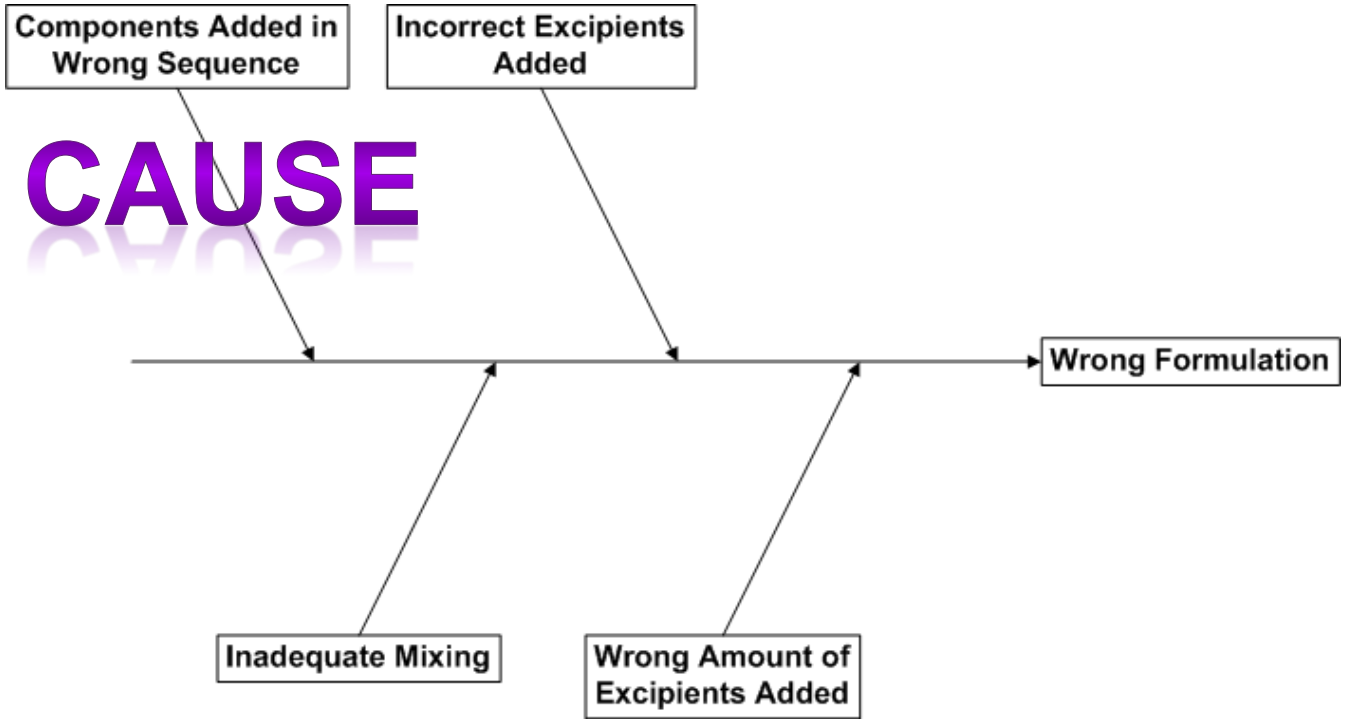

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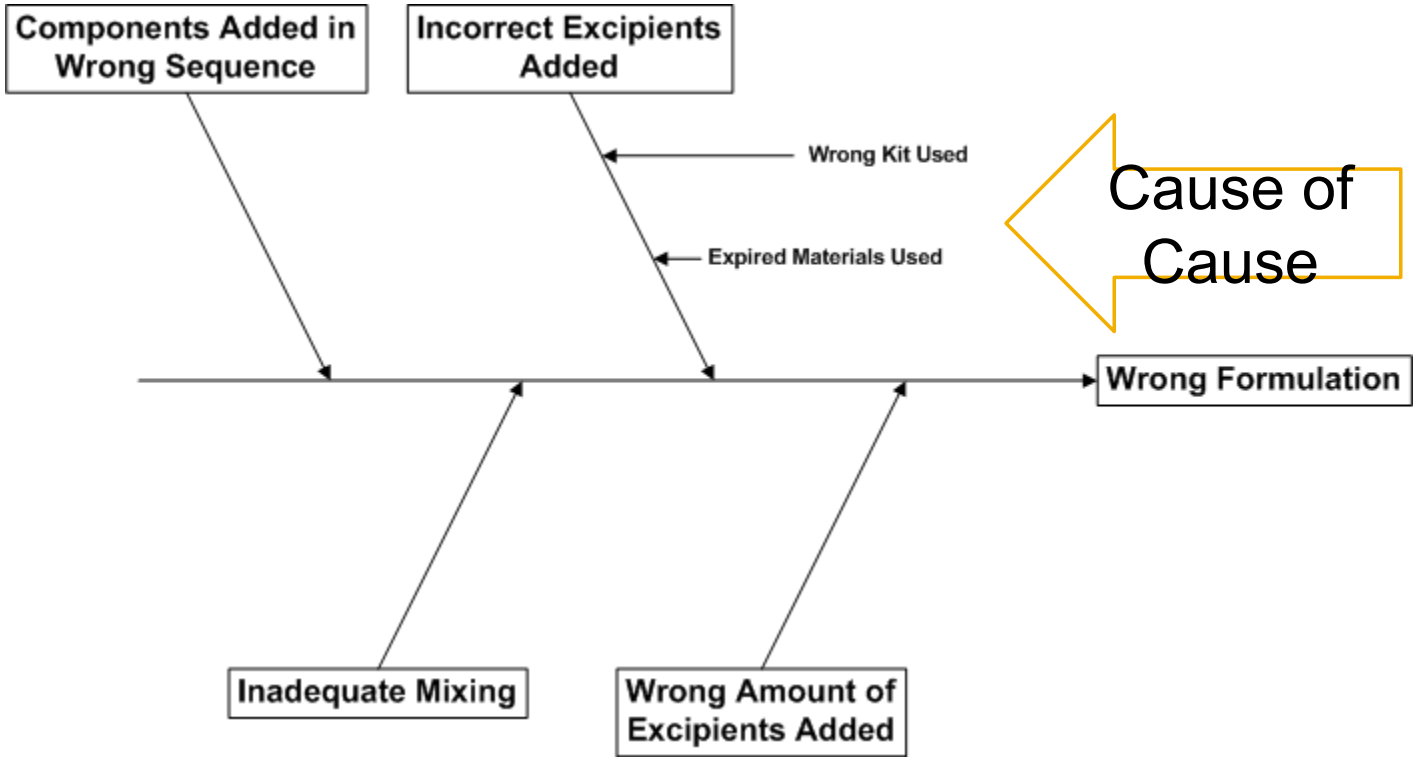


Work Shop

Cause and Effect

Analyze one of the previously identified hazards

Microbial Contamination

Protein Degrades or Denatures

Cross Product Contamination

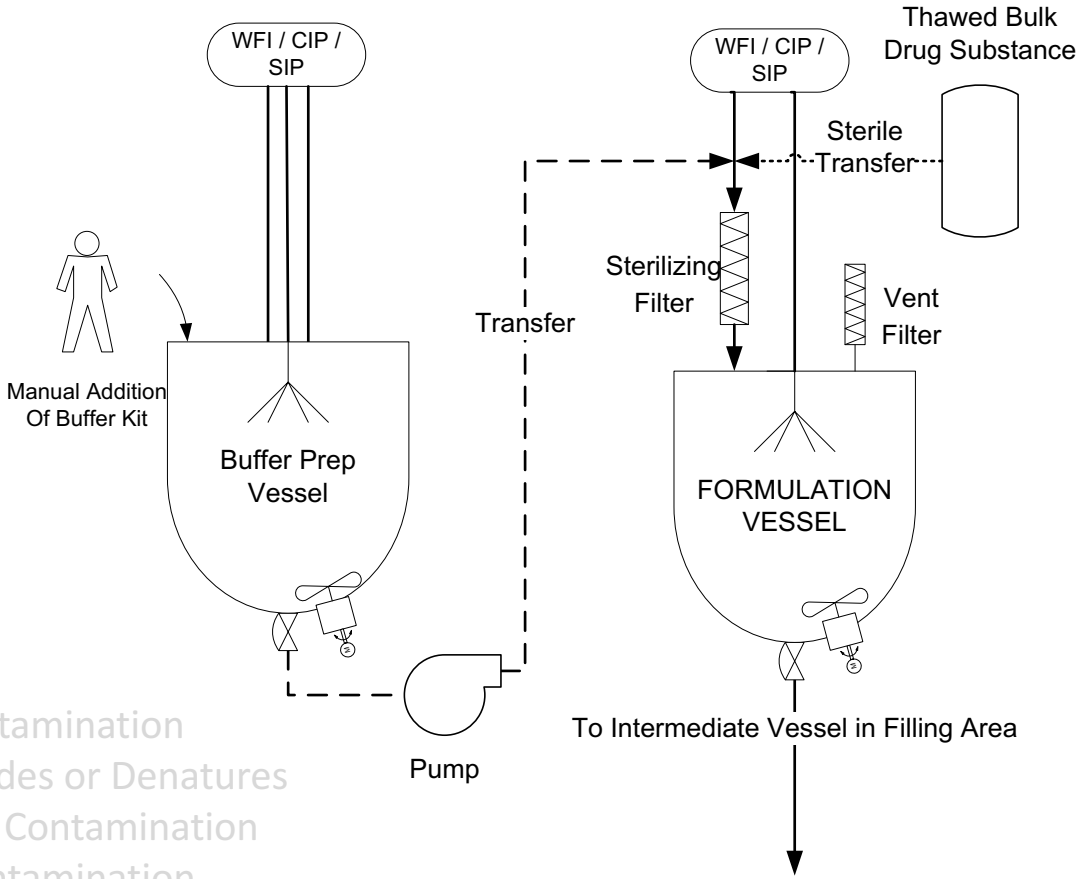
Wrong Formulation

Endotoxin Contamination

Foreign Material Contamination

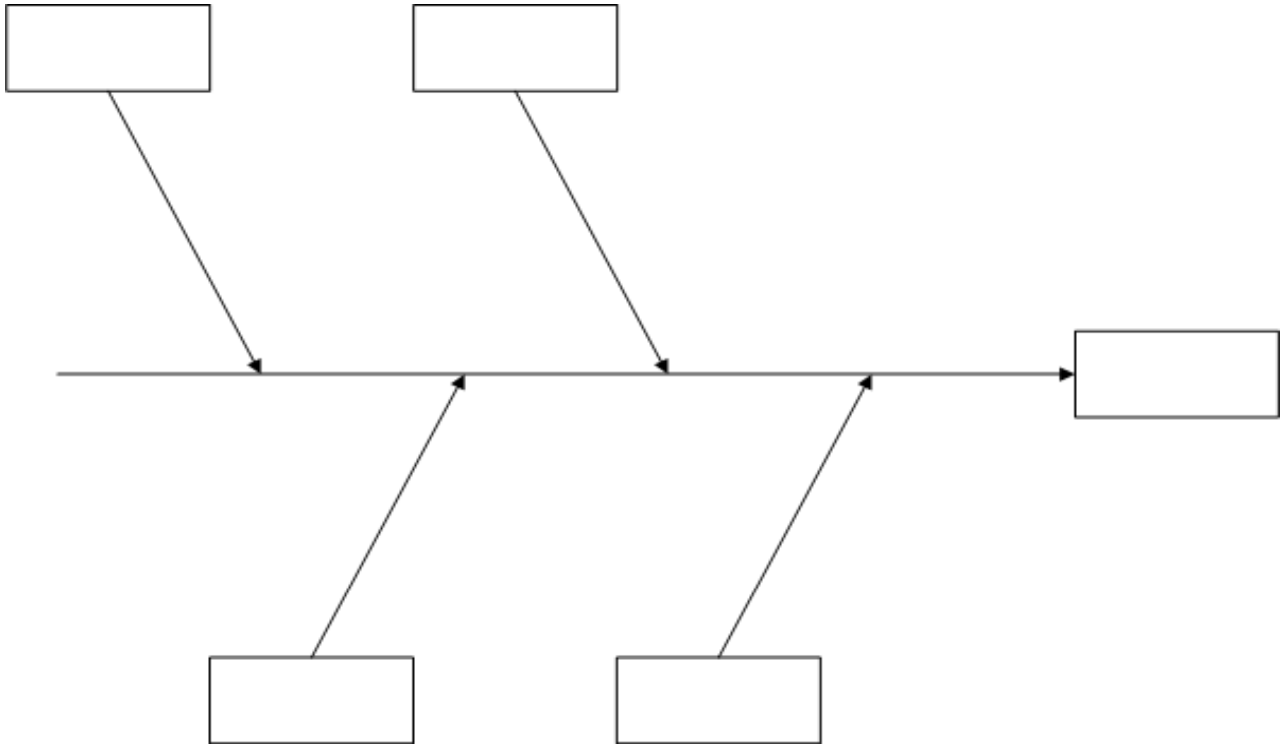
Identify at least three 1st Tier Causes

Identify at least six 2nd Tier Causes



Microbial Contamination
Protein Degrades or Denatures
Cross Product Contamination
Endotoxin Contamination
Foreign Material Contamination

Cause and Effect Diagram



Thank You!

Timothy P. Howard, CPIP, PE
Vice President
Commissioning Agents, Inc.