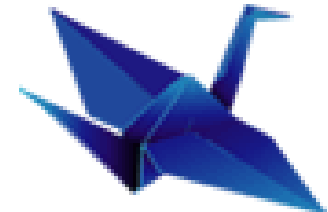


BioIndustry Association

BIA Committee Seminars

London

June 4, 2009

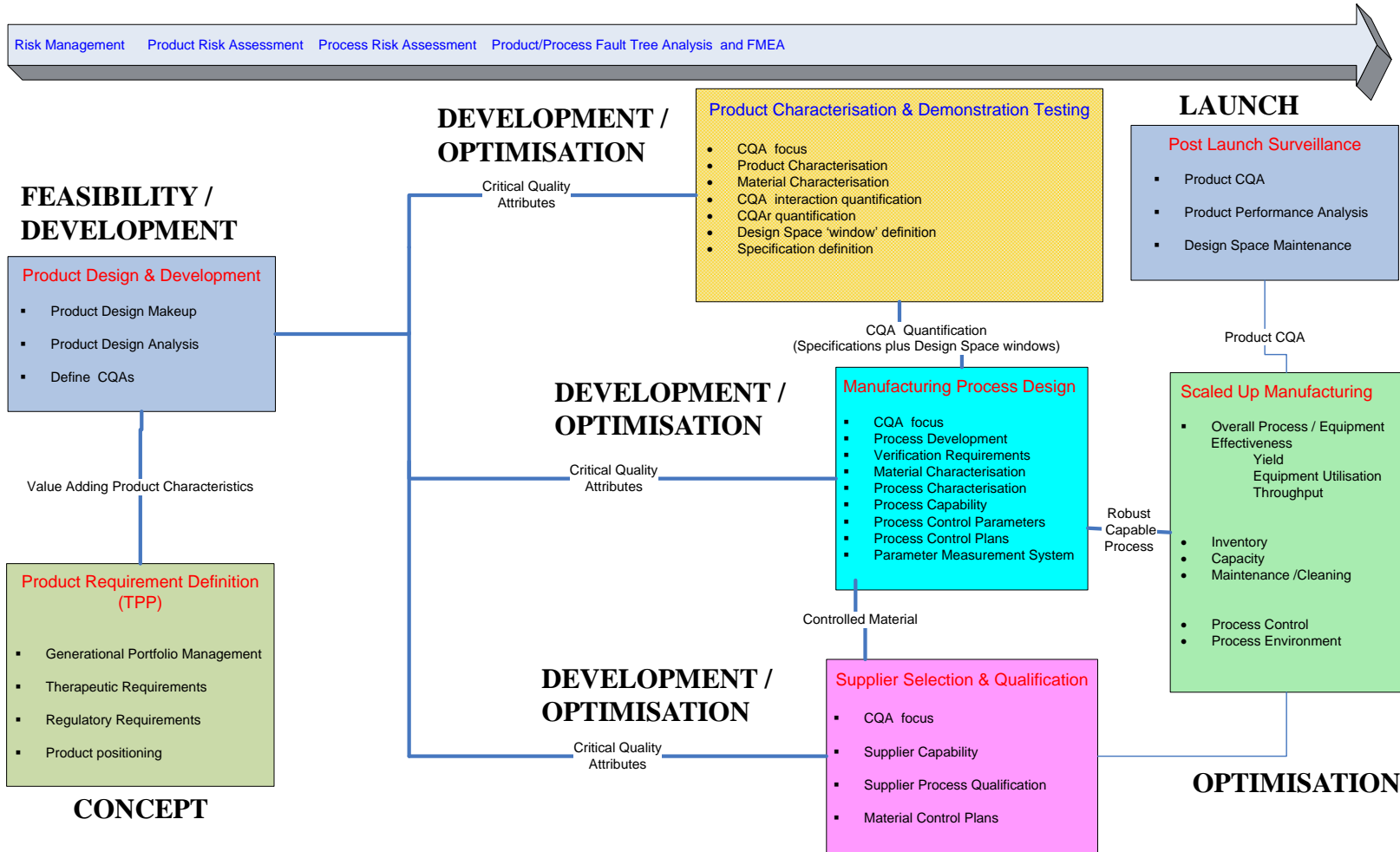


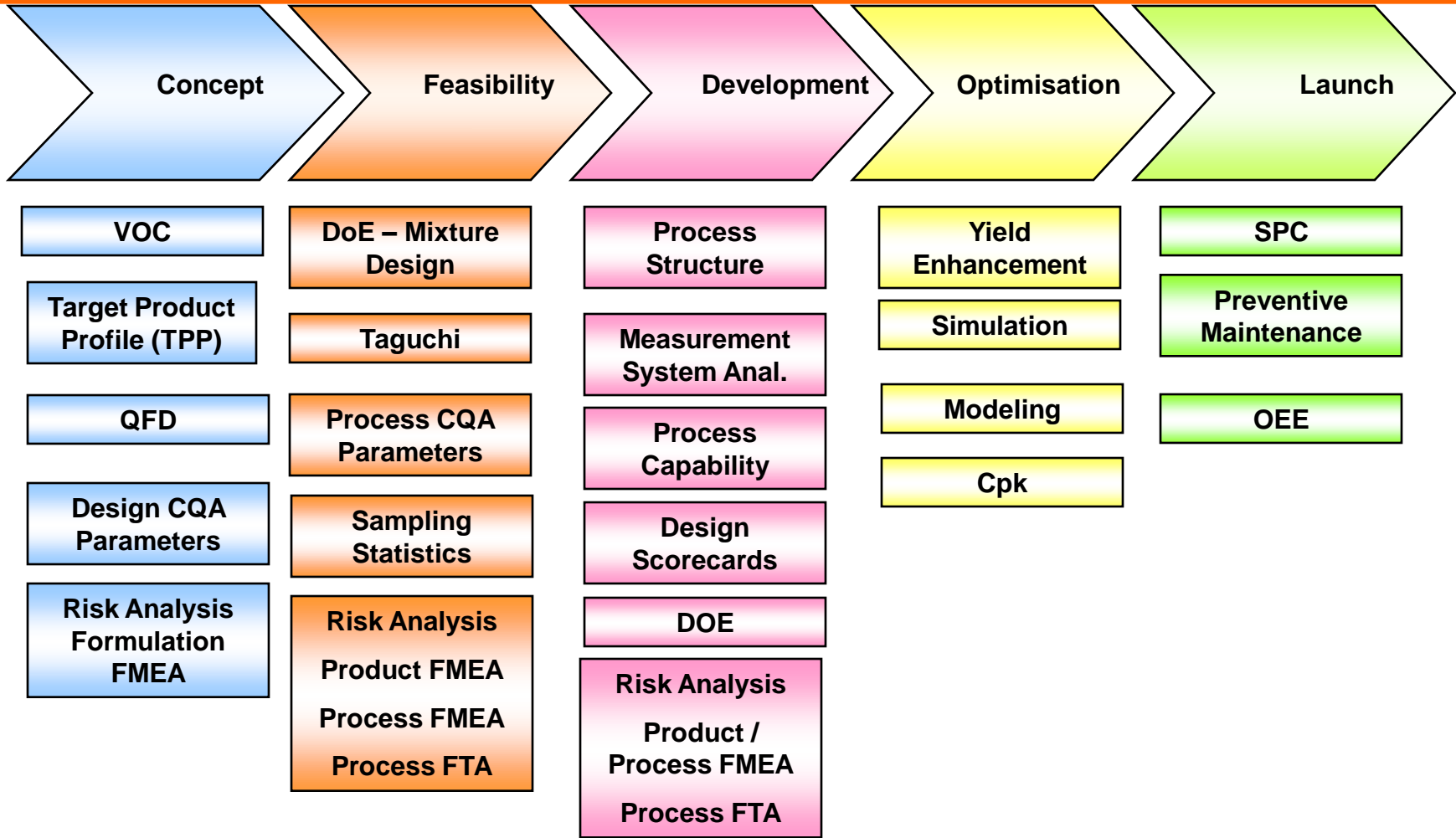
SI ASSOCIATES

TRANSFORMING BUSINESSES, CREATING VALUE

- ❑ **Authorities are establishing modern, risk-based pharmaceutical quality assessment systems to replace current CMC review systems.**
 - ***Knowledge rich submissions***
 - ***Specifications based on product performance requirements***
 - ***Flexibility to operate within the Design Space***
 - ***Focus on robustness and understanding the root cause of variation***
 - ***Identification, understanding and mitigation of risk***
- ❑ **QbD approach aligned with ICH Q8, ICH Q9 & ICH Q10**
- ❑ **Faster New Drug Application (NDA) approval**
- ❑ **Robust product and processes**
- ❑ **Reduced cost of poor quality and improved productivity**

Traditional CMC Submission	Desired State
Quality by Testing and Inspection	QbD – quality assured by well designed & well understood product & process
Data intensive application – disjointed information without “big picture”	Knowledge rich submission – supporting product & process design
Specifications based on process history	Specifications based on product performance requirements
“Frozen process” discouraging changes	Flexible process within design space allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation



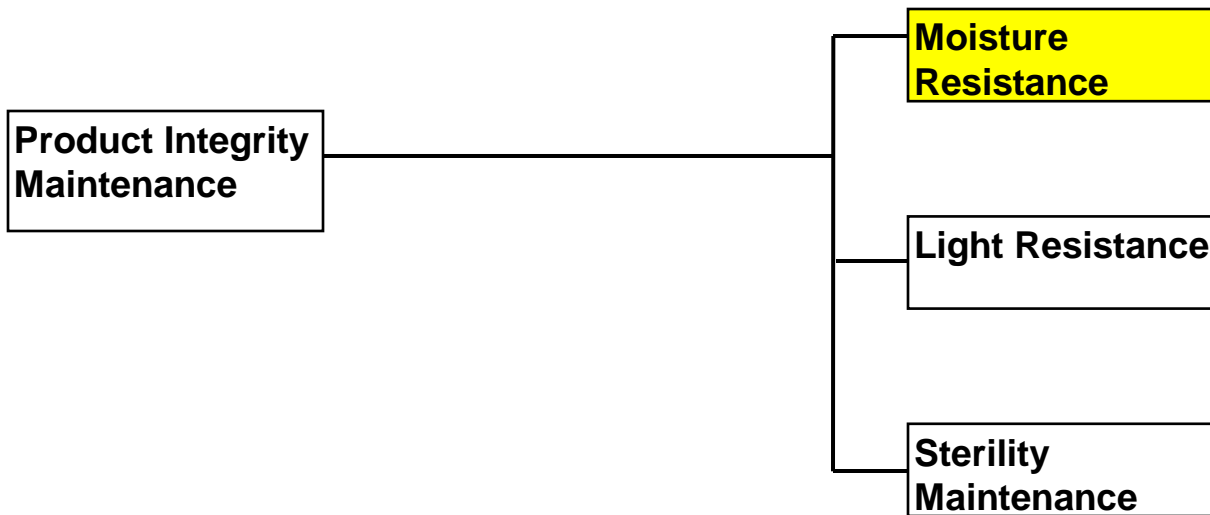


- ❑ **Utilise multi-faceted approach to product characterisation (CQA Focus)**
 - ***Modelling***
 - ***Simulation***
 - ***Experimentation***

- ❑ **Understand & document what product is 'capable of' not what it was *'designed to achieve'***

FUNCTION

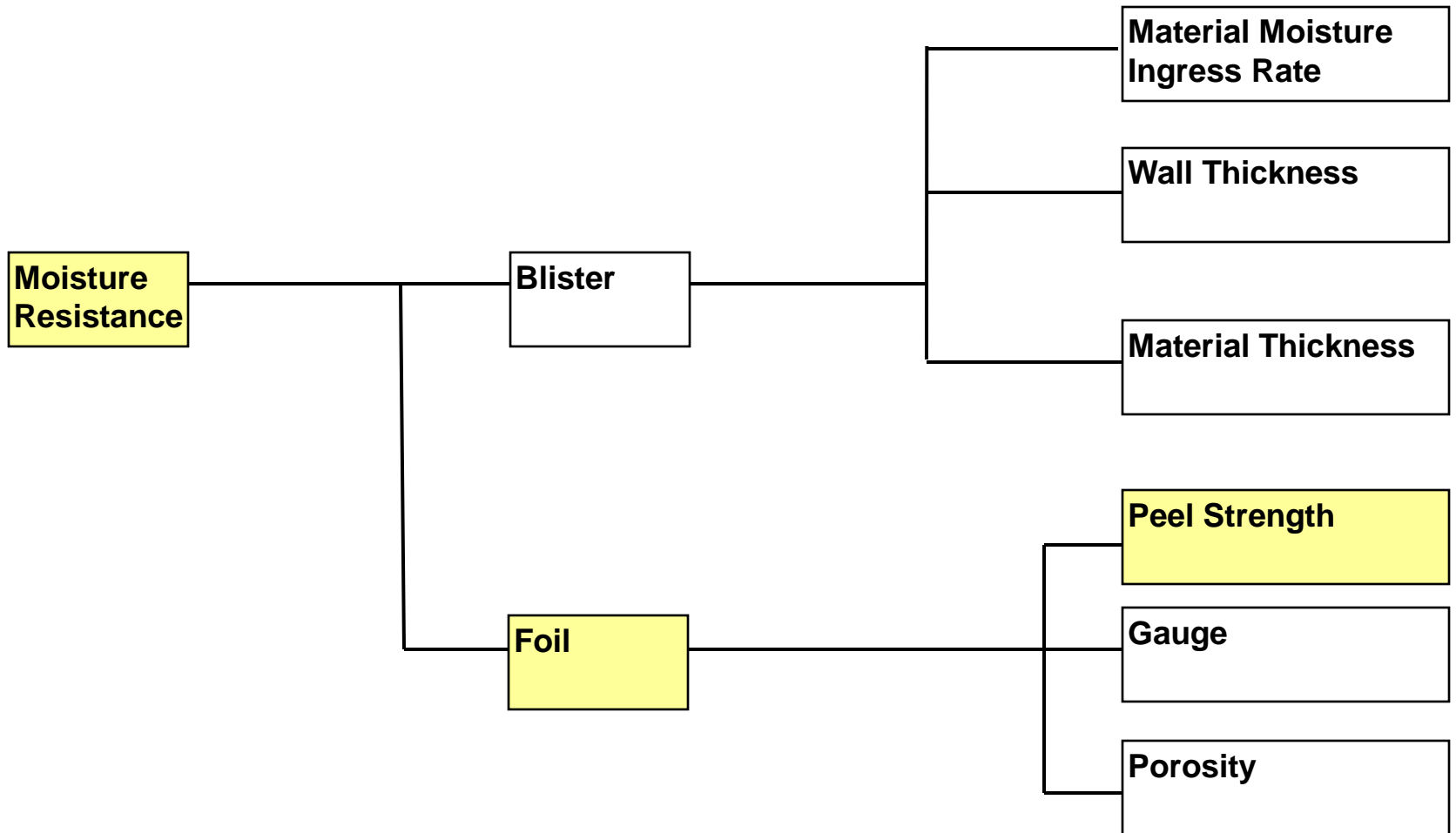
SUB - FUNCTION



SUB - FUNCTION

DESIGN MAKEUP

PRODUCT CQA



- ❑ **Structured process design focusing on delivery of design CQAs**
 - ***Technology re-use minimises the need for new process development***
 - ***Crucial to removing process development risk from launch timelines***

- ❑ **Identification of process CQAs**

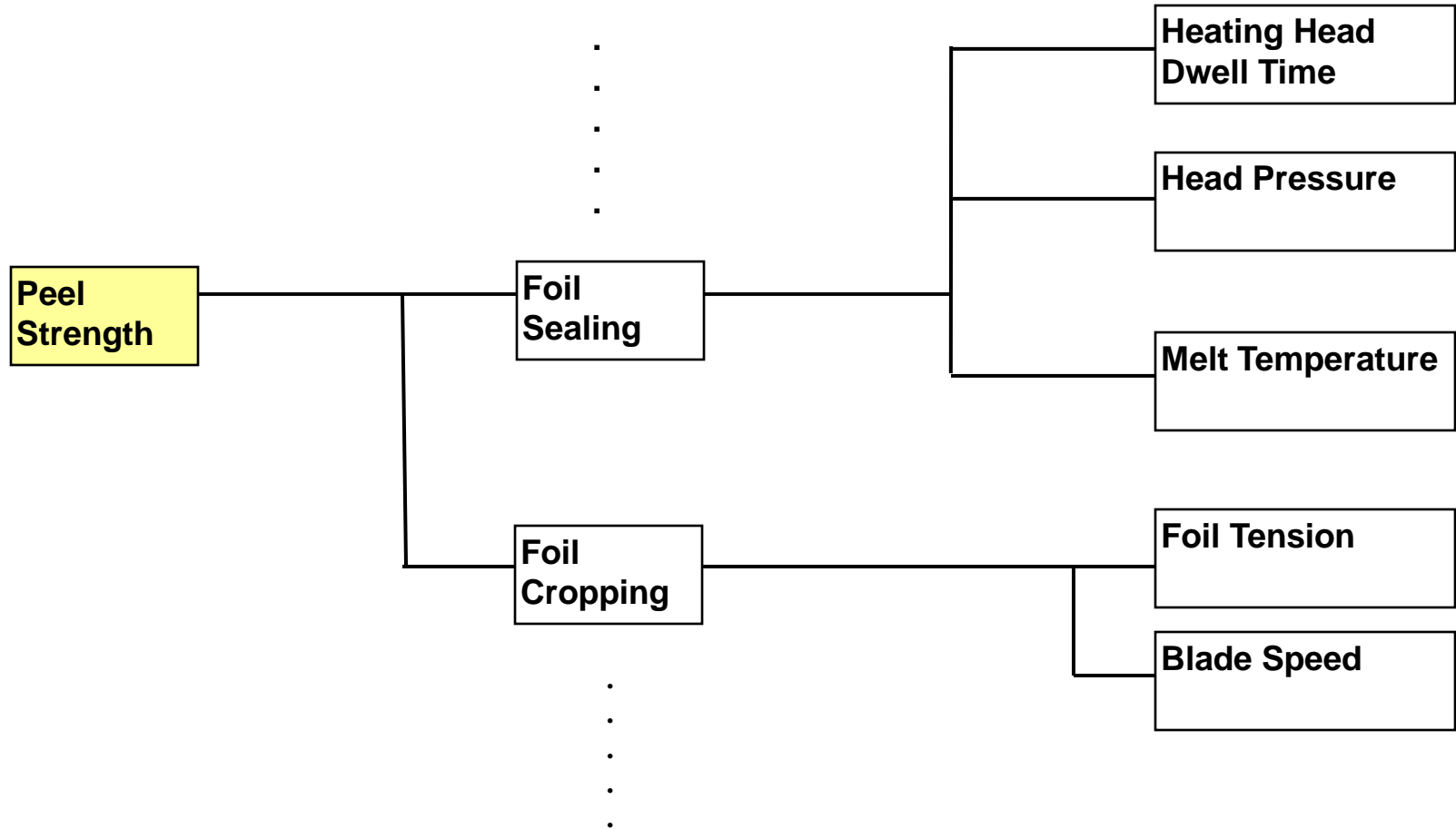
- ❑ **Implements process risk mitigation aspects identified during risk analysis**

- ❑ **Develop control plans**
 - ***Materials***
 - ***In-process***
 - ***Finished product***

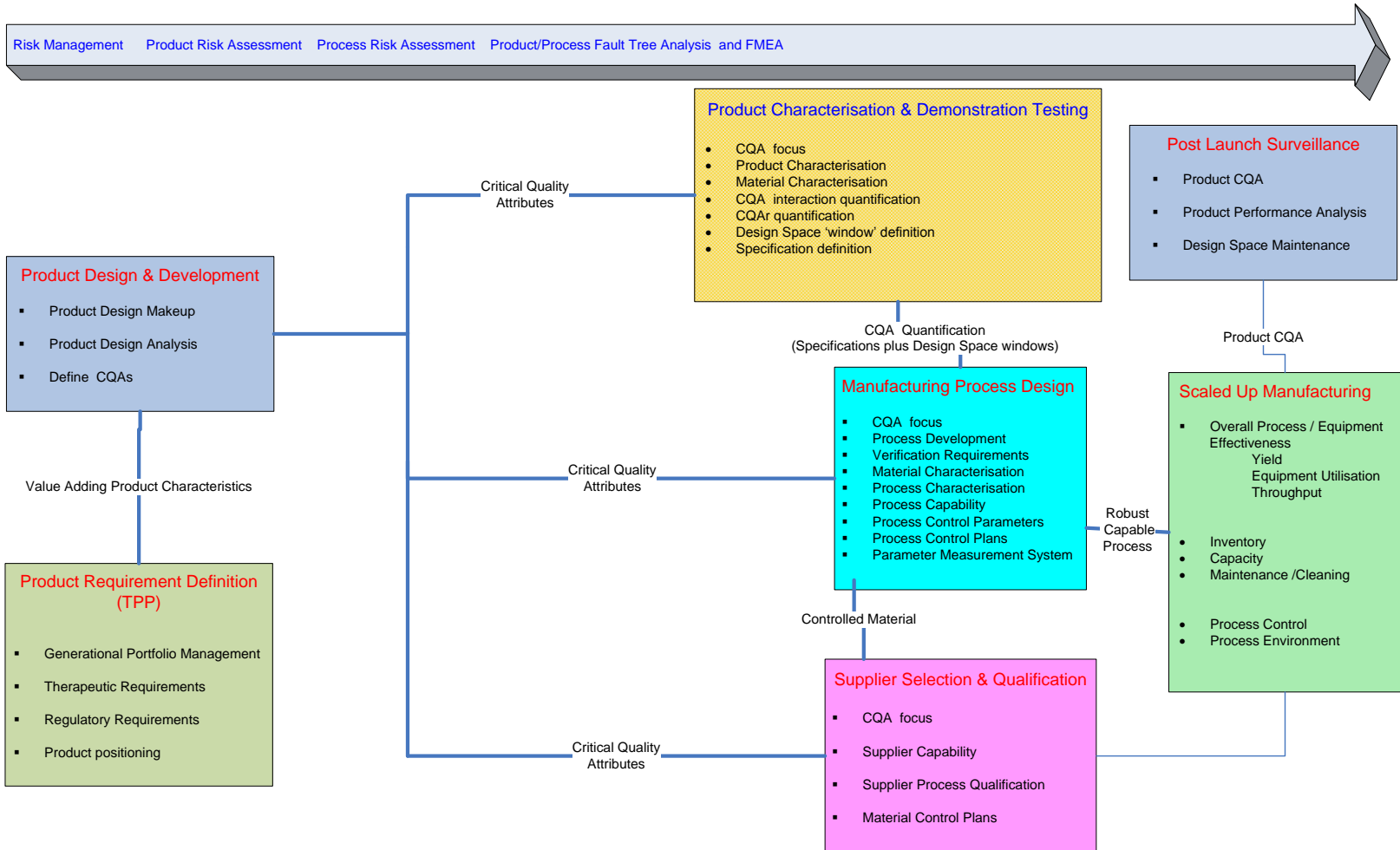
PRODUCT CQA

PROCESS MAKEUP

PROCESS CQA



Structured Risk Analysis - Linkages



- ❑ **Combinational use of**
 - ***Failure Mode & Effects Analysis (FMEA)***
 - ***Fault Tree Analysis***

- ❑ **Builds upon structural functional analysis**
- ❑ **Utilises fault tree analysis techniques to quantify risk and identify risk mitigation elements**
 - ***Introduce incremental Boolean “and” functions to compound error rates and reduce probability of undetected risk***
- ❑ **Uses FMEA techniques to identify failure modes**
 - ***Use as input into FTA***

What is a Failure Mode and Effects Analysis (FMEA)?

S1596/

A structured approach to:

- Identify the ways in which a product or process can fail
- Estimate risk associated with specific failure causes
- Prioritise the actions to reduce risk of failure

- When designing new products, and processes**
- When changing existing designs or processes**
- When platform designs are used in new applications**
- After product, or process functions are defined, but before beginning detailed final design**
- To understand the risk of a project**

- To understand how process steps or key process input variables (KPIVs) relate to risk and to prioritize KPIVS**
- To understand the implementation risks**
- To set the requirements of Control Plans**

- ❑ **Design FMEA**
 - ***Analyses a new process, product design before rollout to understand how it could fail once released***
 - ***Exposes problems that may result in safety hazards, malfunctions, shortened product life, or decrease satisfaction***

- ❑ **Process FMEA**
 - ***Used to improve existing processes to understand how people, materials, equipment, methods, and environment cause process problems***
 - ***Exposes process problems that may result in safety hazards, defects in product or service production processes, or reduced process efficiency***

Product/Design Failure Mode and Effects Analysis

Product/Design Failure Mode and Effects Analysis								Action Results					
Element Function	Potential Failure Mode	Potential Effect(s) of Failure	Potential Cause(s) / Mechanism(s) of Failure	Current Prevention Controls	Current Detection Controls	Detectability	RPN	Recommended Action(s)	Responsibility & Target Completion Date	Actions Taken	Severity	Occur	Detect
1. Describe function provided by element	Manner in which element could fail: cracked, weakened, deformed, leaking etc.	Consequences on other elements or user: unstable, inoperative, impaired, etc.	List every potential cause and/or failure mechanism: incorrect material, improper maintenance, fatigue, wear, etc.	List prevention activities to assure design adequacy and prevent or reduce occurrence.	List detection activities to assure design adequacy and prevent or reduce occurrence.			Design actions to reduce severity, occurrence and detection ratings. Severity of 9 or 10 requires special attention.	Name of organization or individual and target completion date	Actions and actual completion date			
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Severity of Effect:	Occurrence Rating	Detection:	Stakeholder	Effects of Failure	Severity
1. None	1. Remote <.01/1000	1. Almost Certain	User	User Safety Problem	10
2. Very Minor	2. Low - 0.1/1000	2. Very High		Major User Dissatisfaction	8
3. Minor	3. Low - 0.5/1000	3. High		Moderate User Dissatisfaction	6
4. Very Low	4. Moderate - 1/1000	4. Moderate High		Minor User Dissatisfaction	4
5. Low	5. Moderate - 2/1000	5. Moderate	Customer (Manufacturing)	Plant Safety Problem	10
6. Moderate	6. Moderate - 5/1000	6. Low		Possible Product Recall	9
7. High	7. High - 10/1000	7. Very Low		Line Stoppage	8
8. Very High	8. High - 20/1000	8. Remote		Warranty Costs	7
9. Hazardous with warning	9. Very High 50/1000	9. Very Remote		Scrap	7
10. Hazardous w/o warning	10. Very High >100/1000	10. Absolute Uncertainty		Regulatory Penalty	7
				Moderate Rework (<25%)	5
			Plant Dissatisfaction	4	
			Minor Rework (<10%)	3	

Product/Design Failure Mode and Effects Analysis

Element Function	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s) / Mechanism(s) of Failure	Occurrence	Current Prevention Controls	Current Detection Controls	Detectability	RPN	Recommended Action(s)	Responsibility & Target Completion Date	Action Results			
												Actions Taken	Severity	Occurrence	Detectability
1. Moisture Resistance	Failure of Foil Seal	Moisture Ingress	10	Faulty Foil Seal	7	Specification Control	Visual Inspection	8	560	Incorporate Controls in Manufacturing Process					
			10	Damaged Foil	4	Specification Control	Incoming CoA	6	240	Develop SPC regime at Supplier					
			10	Damaged Blister	3	Specification Control	Incoming Visual Inspection	7	210	Sample Inspect					

Severity of Effect:	Occurrence Rating	Detection:
1. None	1. Remote <.01/1000	1. Almost Certain
2. Very Minor	2. Low - 0.1/1000	2. Very High
3. Minor	3. Low - 0.5/1000	3. High
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5. Low	5. Moderate - 2/1000	5. Moderate
6. Moderate	6. Moderate - 5/1000	6. Low
7. High	7. High - 10/1000	7. Very Low
8. Very High	8. High - 20/1000	8. Remote
9. Hazardous with warning	9. Very High 50/1000	9. Very Remote
10. Hazardous w/o warning	10. Very High >100/1000	10. Absolute Uncertainty

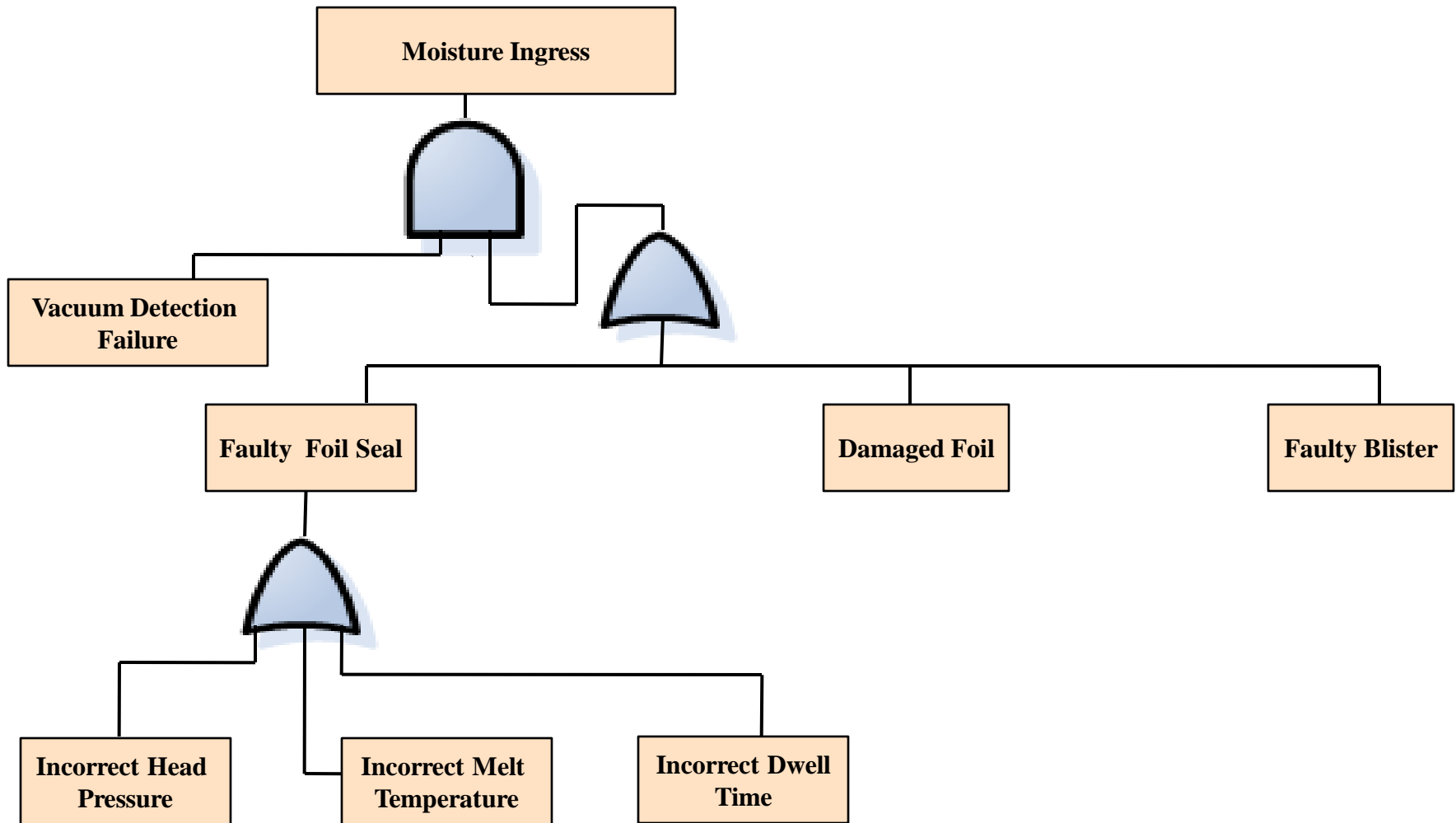
Stakeholder	Effects of Failure	Severity
User	User Safety Problem	10
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	Scrap	7
	Regulatory Penalty	7
	Moderate Rework (<25%)	5
Plant Dissatisfaction	4	
Minor Rework (<10%)	3	

- ❑ **Used to design detailed risk mitigation aspects of a product or process**
 - ***Material***
 - ***Hardware***
 - ***Instrumentation***
 - ***Environment***
 - ***Human***

- ❑ **Based on Boolean Logic analysis**
 - ***Quantifies the 'likely' occurrence of failure or fault***

- ❑ **Determine the process function to be analysed**
- ❑ **Decompose the Top Level into linked Sub Levels**
- ❑ **Construct the logical connections**
 - ***AND & OR functions***
- ❑ **Decompose the Sub Levels further until lowest level events are identified**
- ❑ **Quantify the Top Level probability**

- Assess acceptability of Top Level probability**
- Identify additional failure redundancy 'chains' if top level probability is not acceptable**



- ❑ **QbD represents the way ahead**
- ❑ **Systematic linkage from Patient Need to Product Performance through TPP**
- ❑ **It is a signposted route to the adoption of Design Space approaches that enables**
 - ***Improved management of Quality***
 - ***Reduced Risk/Liability***
 - ***Better yields and efficiencies***
 - ***Quicker Time to Market***

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