YPSOMED
SELFCARE SOLUTIONS

The Device Perspective of Quality in Manufacturing

June 7, 2005

Quality in Manufacturing: Device Perspective

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Agenda

- Scope of Presentation
- Background, Introduction
- Impact of Poor Quality
- Main Influences on Quality
- Tools and Methodology
- Summary
- Discussion / Questions

Scope

Context of Presentation

- Medical devices for drug delivery: stand alone or combinatorial products
- Quality from perspective of management / business

Background: Ypsomed

- Medical device design and manufacturer
- Focus on self-injection devices for therapeutic large molecules e.g. peptides, MCAs
- 19 years old
- $200 million annual turnover; 850 employees
- Publically traded on SWX; market cap. $1.1 billion

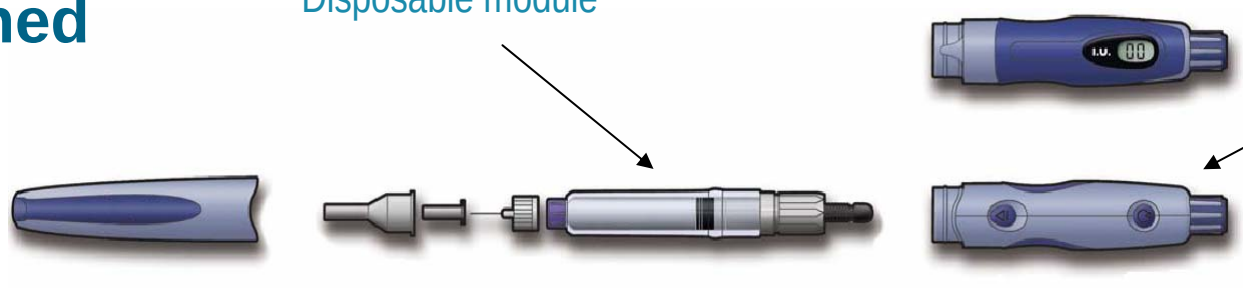
- > 3 million devices with lifetime > 2 years (20-40 parts)
- > 50 million disposable devices with lifetime 5 – 15 days (7 – 10 parts)
- >150 million sterile single use devices (5 parts)

Background: Ypsomed – Product Examples

Combined

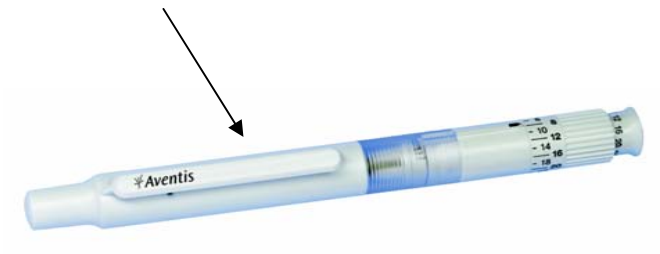
Disposable module

Dialing unit

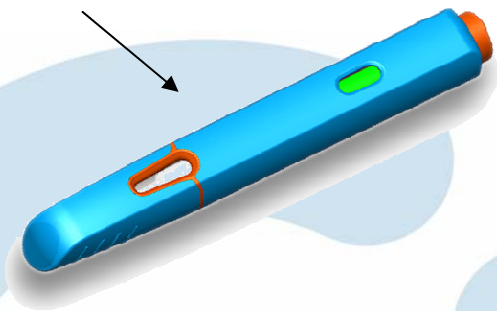


OptiClik Animation

Disposable prefilled pen



Disposable auto-injector



510k

Reusable pen

Quality and the Value Chain

Example: injectable biotech drug
prefilled syringe or cartridge
safety or self-injection device

- Annual cost of drug in treatment: $20‘000
- Other associated treatment costs: $10‘000
- Annual cost of devices: $ 250

- Cost of handling one device complaint: $1000‘s

Impact of Poor Quality

company	POTENTIAL IMPACT ON			
	direct costs	liability	reputation	sales
Pharma / Biotech	+++++ (1)	++	---	----
Device	+++ (2)	++++	--	--

(1) complaint handling, lost drug, lost market, administration
(2) guarantees, complaint handling, corrective action

Massive Increase in Quality Demands

- Convergence of expectations for medical devices and drug product
- Traceability requirements increased back through several layers of suppliers
  → higher performing QA systems required
- Post market surveillance and corrective action expectations increased
- Cost and risk of complaints has increased
  → increased liability risk
- Vigilance of pharma and biotech industry has increased
  → realisation of vulnerability to quality issues in devices

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Two aspects of quality

quality in	measured by	timeframe of impact
Design	- patient complaints on handling / ease of use - internal wastage - product failure on market	- immediately patient has product - during production - late in lifecycle of product
Manufacturing	- internal wastage - product failure on market	- during production - late in lifecycle of product

Quality of Design

Perhaps the single most important factor in quality in manufacturing is the quality of the design

Determined by:

- Simplicity → remove unnecessary complexity
- Robustness → account for variability on manufacturing
- Manufacturability
- Well specified product and process

Manufacturing aspects are an integral part of medical device design

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Design - Quality

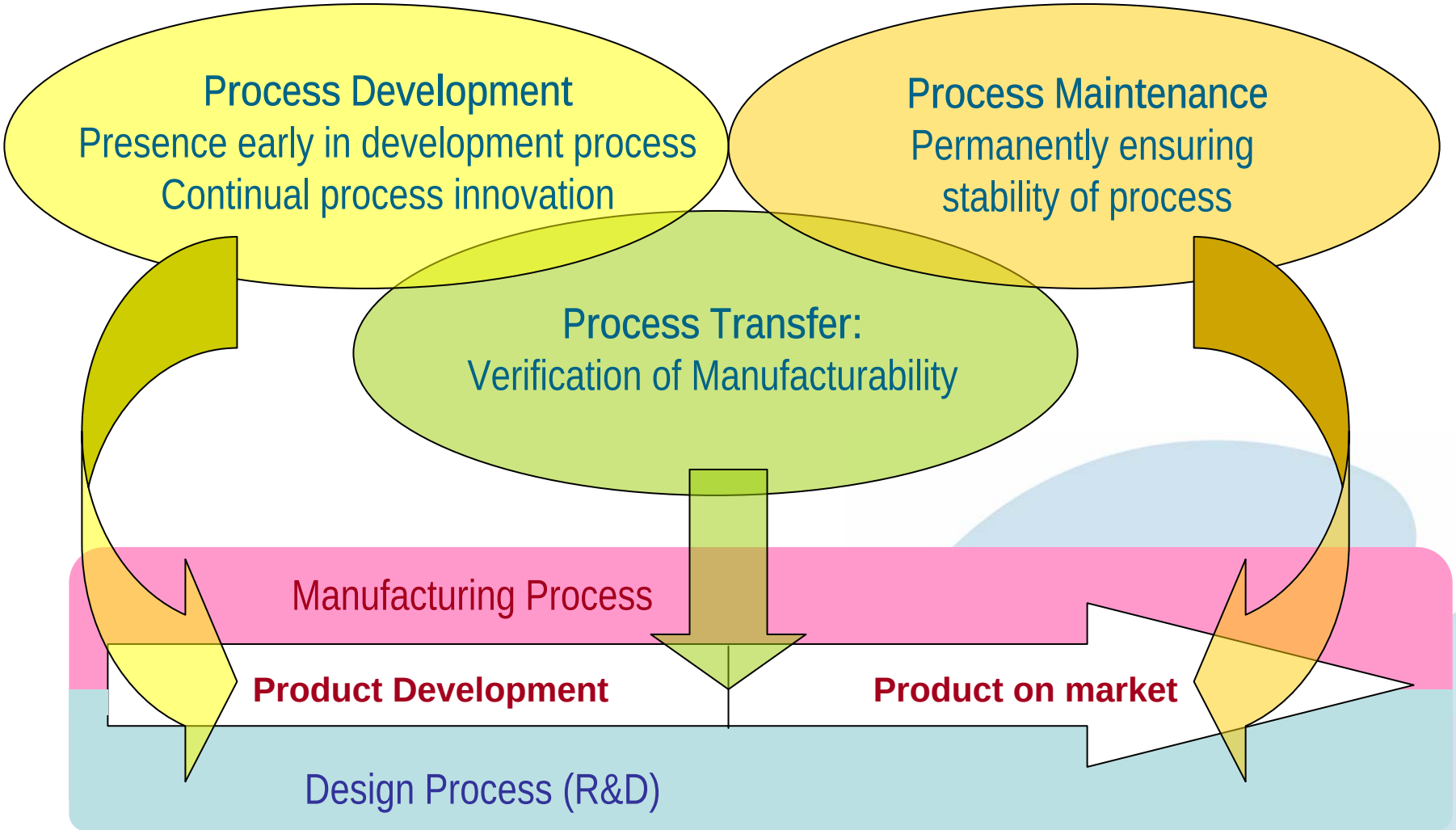
Specification of Product and Components

In my experience, most quality problems in manufacturing arise from insufficiently or poorly specified products, components or raw materials rather than a poorly executed manufacturing process

→ focus on specifications
(a verification / validation to incomplete specifications is useless)
→ understand supplier processes well enough to specify product
→ audit suppliers frequently

Device Perspective of Quality in Manufacturing, 7th June, 2005, Princeton. M.S.E.Robin

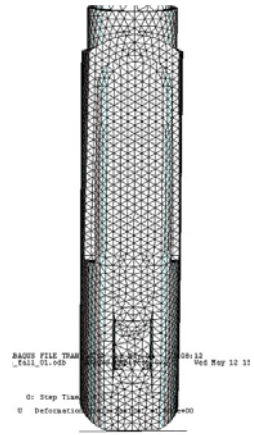
Design Development & Maintenance Process



Design - Tools

- CAD / Kinematic animations
- Finite Element Analysis
- Mold Flow
- Tolerance Analysis
- Risk Analysis
- Design FMEA
- Process FMEA
- Mishandling analysis and studies

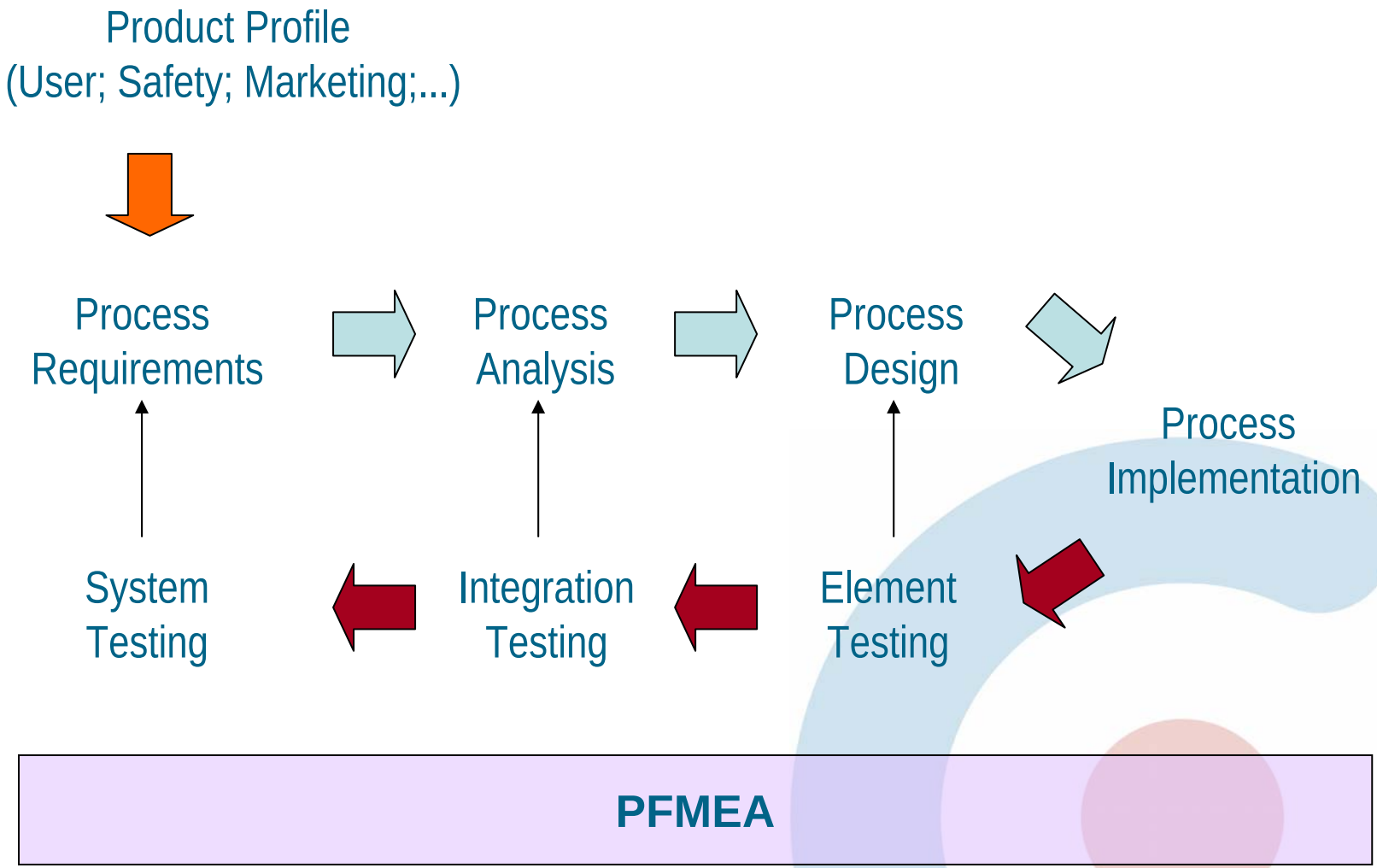
Auto-Injector Easy cutout



Specifications of components and product; validation and IPC parameters

Risk of damaging product during manufacturing → assembly processes, transport, automation
Process verification and validation parameters

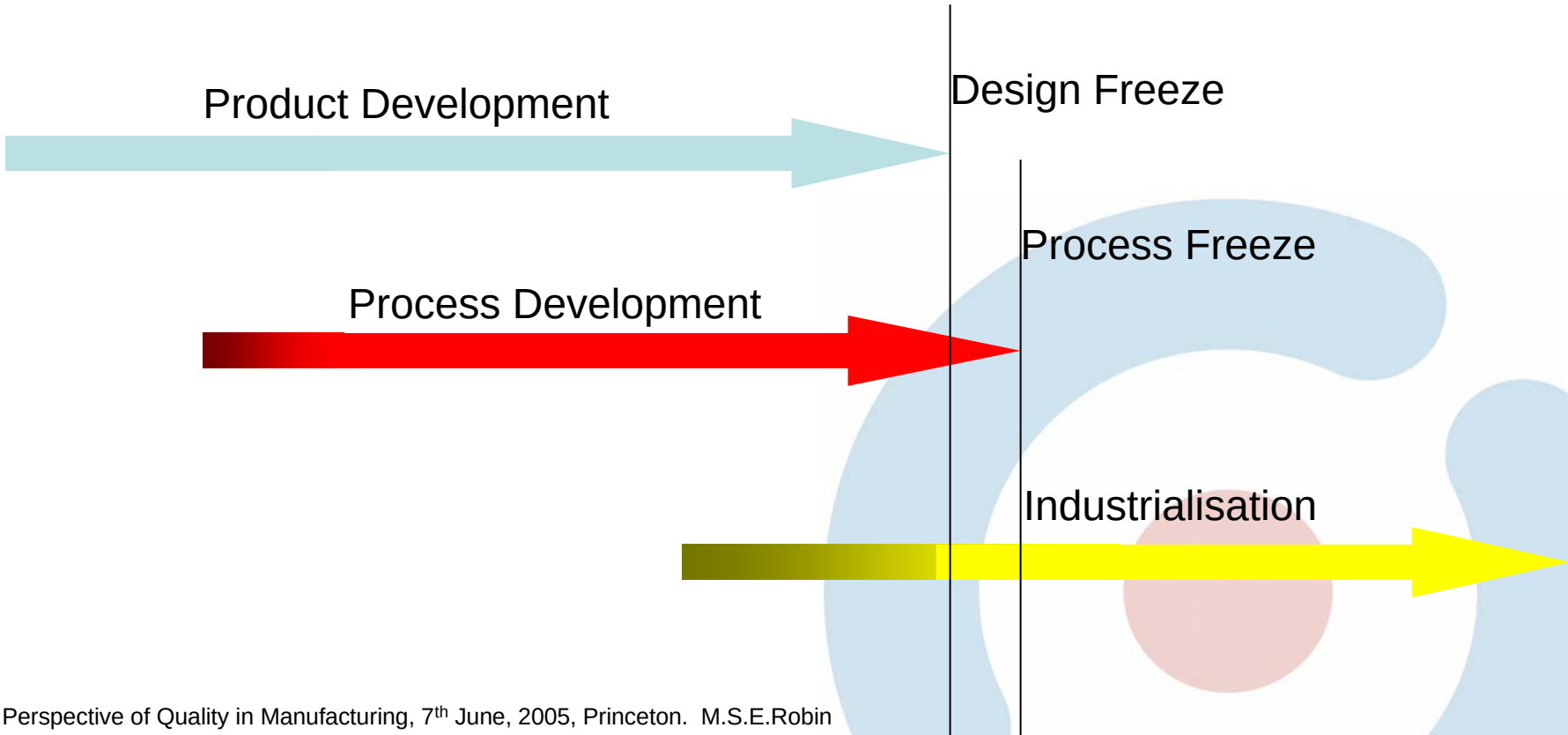
Design – PFMEA Procedures



Design – Release

Management and technical reviews

Key quality decision points
- delay if insufficiently specificed or not robust



Manufacturing – Difference to APIs

- API / chemical quality control:
  → characterisation of raw materials possible
  → focus on ensuring homogenicity of solution, powder etc. → assay analysis etc.
  → by definition then 100% of batch is released

- Medical device quality control
  → complete characterisation of components hardly possible – but key is sufficient specification
  → focus on consistency of process parameters, key dimensions, elasticity parameters etc.
  → in addition need to identify individual deviations
  → thousands or millions of individual devices, tests often destructive
  → by definition release of batches through statistical confidence levels

Manufacturing – Testing strategies

- Statistical in-process control (IPC)
  Example: injection moulding

  → tools will degredate
  - focus on identifying that moment
  - regular sampling
  - cavity separation to ensure isolation of problem

  → numerous environmental parameters will influence dimensional and rheological characteristics of plastics
  - environmental monitoring
  - statistical IPC of dimensional parameters
  - intervention levels

Manufacturing – IPC

- Example of IPC

Manufacturing – Testing Strategies

- Design testing into product

→ every product must function, but virtually impossible to test each individual product unless designed into product

→ these must be integral part of the design

Manufacturing - Designing Testing into Product

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Example: Disposable Pen assembly

- torque tests carried out as pen initial dose set
- dosing and resistance tests carried out as pen assembled (extra doses designed into pen !!)
- printing verified to 100% with cameras

video sequence OptiSet

Manufacturing - Designing Testing into Product

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Example: Electronic Products

Possibility of self testing

- self-testing as device starts up
- monitoring of forbidden configuration changes
- diagnostic features to allow failure analysis
  if product malfunctions and returns from market
- secondary circuits which monitor functioning

simulation electronics

Manufacturing – 100% Testing

- 100% Testing may be appropriate

  In electronics, challenge is low component yields, poor quality systems in supplier industry, sensitivity of manufacturing processes and complexity of devices

  → chips have low yields and show frequent deviations
  - 100% testing of chips

  → components supplied on rolls from industry without medical device industry standards, incorrect labelling possible
  - 100% testing of individual rolls
  - 100% testing of each complete circuit board

  → functionality of final product could be damaged in manufacturing process (ESD)
  - 100% test of final product

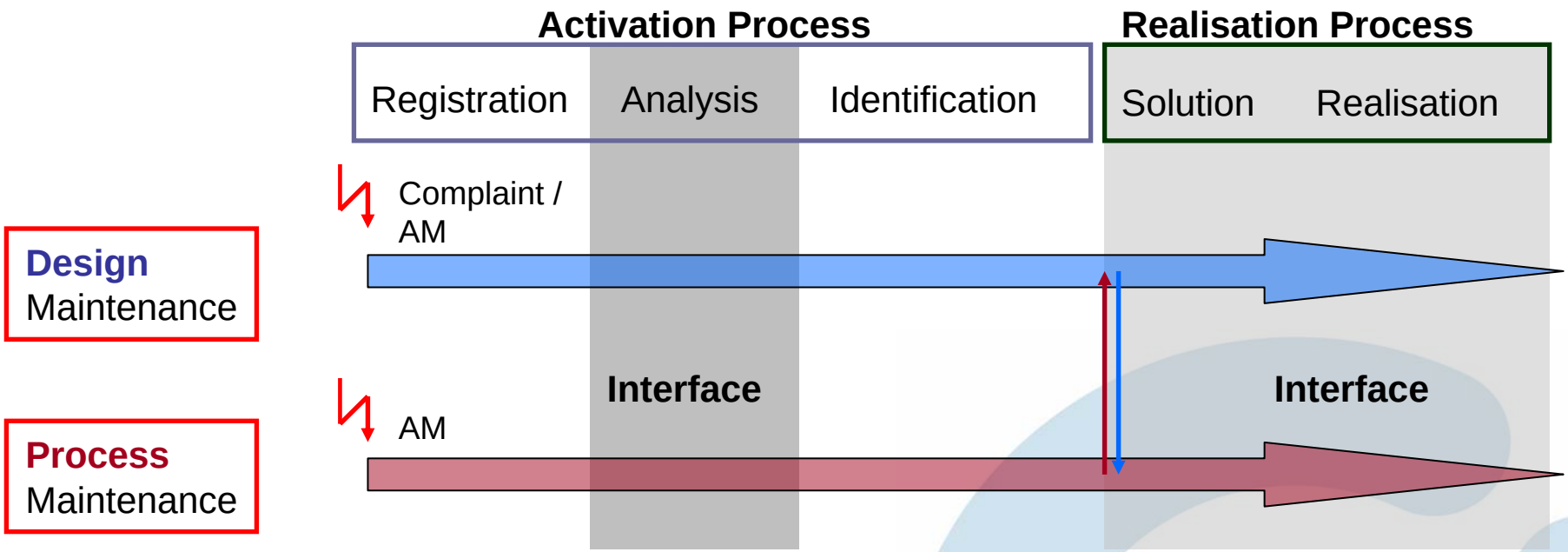
Manufacturing – Post Market Surveillance

- Market feedback will usually indicate manufacturing or design risks: it is important to react before a major quality issue occurs

  - trending is insufficient, action on findings required
    → product improvement teams
    → complaint reduction targets
    → waste reduction targets
      - waste as an indication of defect potential

  - react to single complaints or deviations, don‘t wait for an accumulation as it is probably too late then
    → maintain design team into post-market surveillance period

Manufacturing – Post Market Surveillance



Ensuring Quality in Manufacturing

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Summary

- Prevention
  - → well specified products and raw materials
  - → good control over suppliers (understand their processes)
  - → good, robust design
  - → well thought out, robust process
  - → zero tolerance of weaknesses, delay launch if required

- Monitoring
  - → In-process control strategies
  - → Consider and design in 100% testing

- Correction
  - → Market vigilence and corrective action