Managing Change in Manufacturing

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PQRI/FDA Process Drift Conference,
Maryland, Washington DC
1st – 3rd December 2010

sanofi aventis
Because health matters

King Henry VIII – Flagship ‘Mary Rose’

- Launched 1509
- Numerous ‘improvements’
  - More guns (and ports)
  - Heavier guns
- Sunk 1545
  - Fighting the French!

Managing Change in Manufacturing

- Link to ICH Q10
- Types of Product and Process change
- Importance of knowledge to effective change management
- Consider another high tech industry
- Key Messages

Product Lifecycle (ICH Q10)

ICH Q10 Pharmaceutical Quality System

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Discontinuation

Investigational products

GMP

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

Change Management

- **Changes *WILL* happen throughout the product lifecycle**
  - Proactively **due to business or technical reasons**
    - Part of continual improvement initiatives
  - Reactively **driven as part of CAPA**
    - Due to deviations, OOS, batch rejections

- **The Pharmaceutical Quality System must include a *robust* change management system**
  - **Use of knowledge and Quality Risk Management**

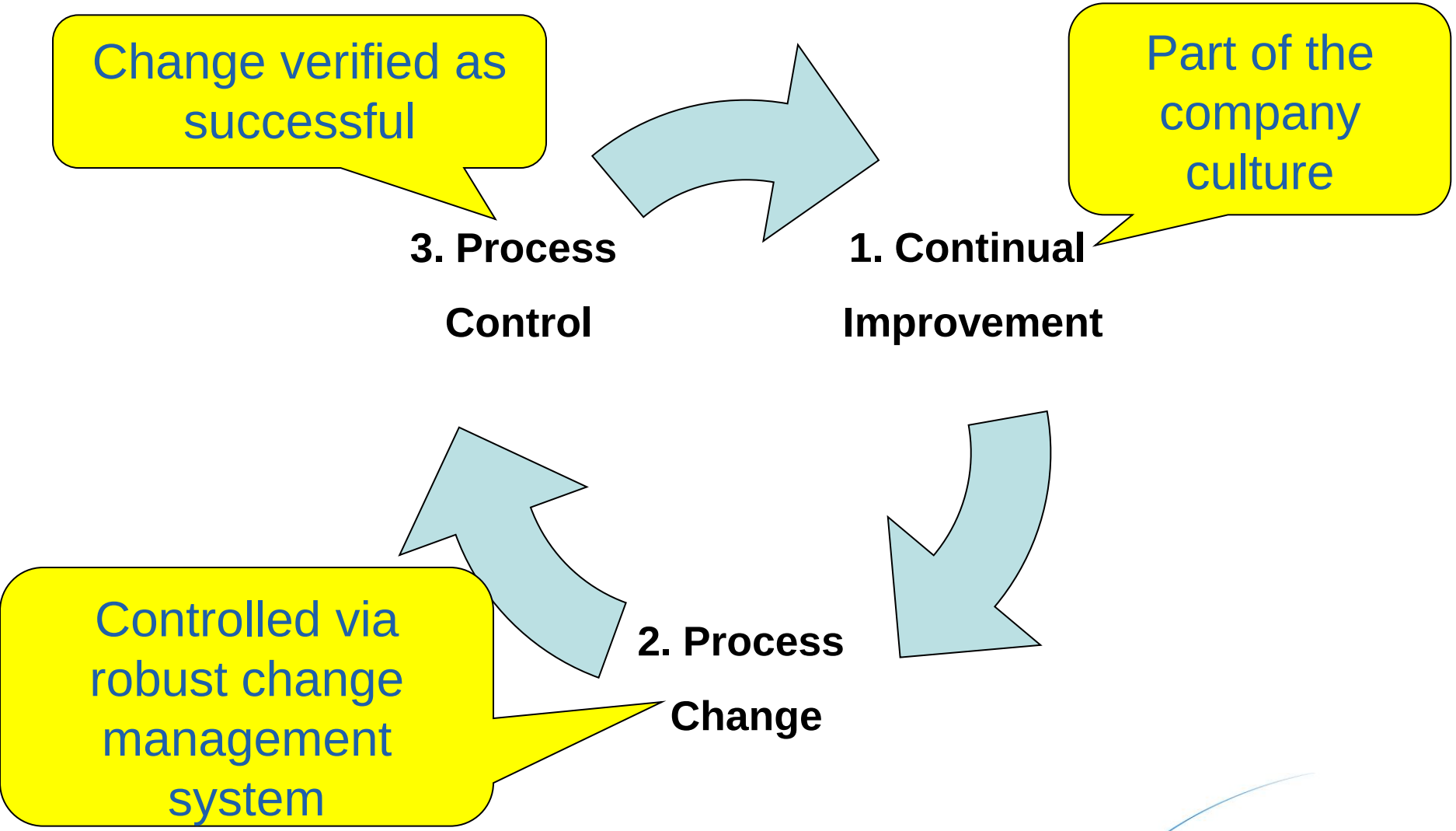
Changes - Forced or Voluntary ?

- Some things <u>must be</u> changed – where we have no option
  - Supplier stops trading
  - Customer complaints
- Other things <u>can be</u> changed – where we do have an option
  - Equipment modernisation / Software upgrade
  - QC test method improvement
  - Continual improvement initiatives
- We always need to consider the risk versus benefit of each change
  - But the biggest risk by far is an uncontrolled change
  - Small changes do not always equal low risk

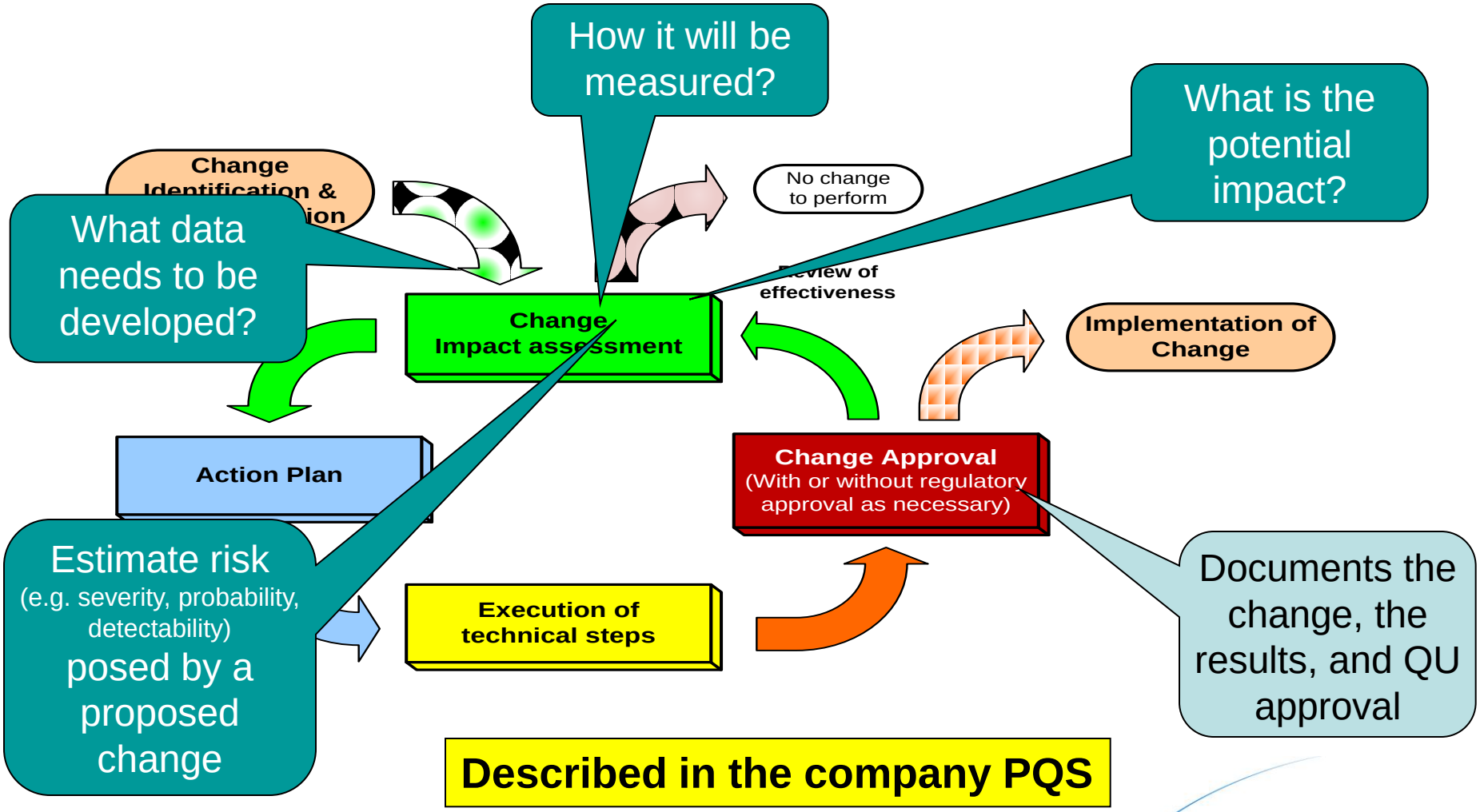
Types of Product and Process Change

Nature of Change	Controlled Change	Uncontrolled Change	Managed through formal change control system
Product Change (e.g. excipient supplier change)	√		√
Process Change (e.g. equipment upgrade)	√		√
Unnoticed change - process drift (over time period or number of batches)		√	
Uncontrolled change (e.g. fraud, accident, or error)		√	

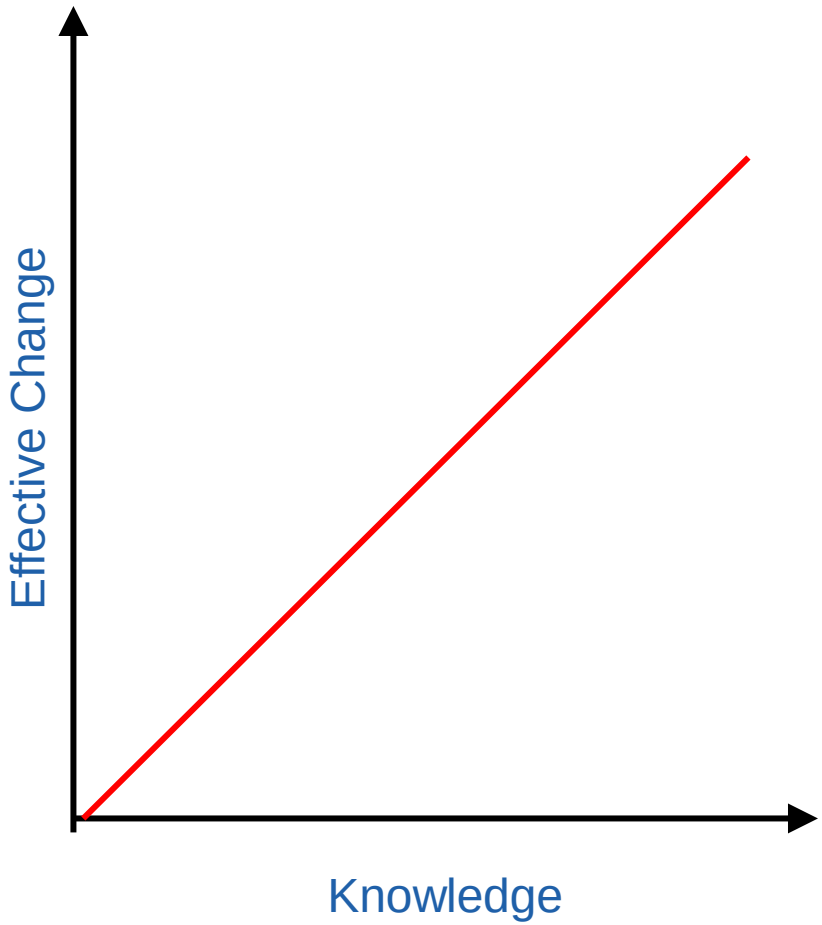
Continual Improvement and Change Management



Typical Change Management Process Map

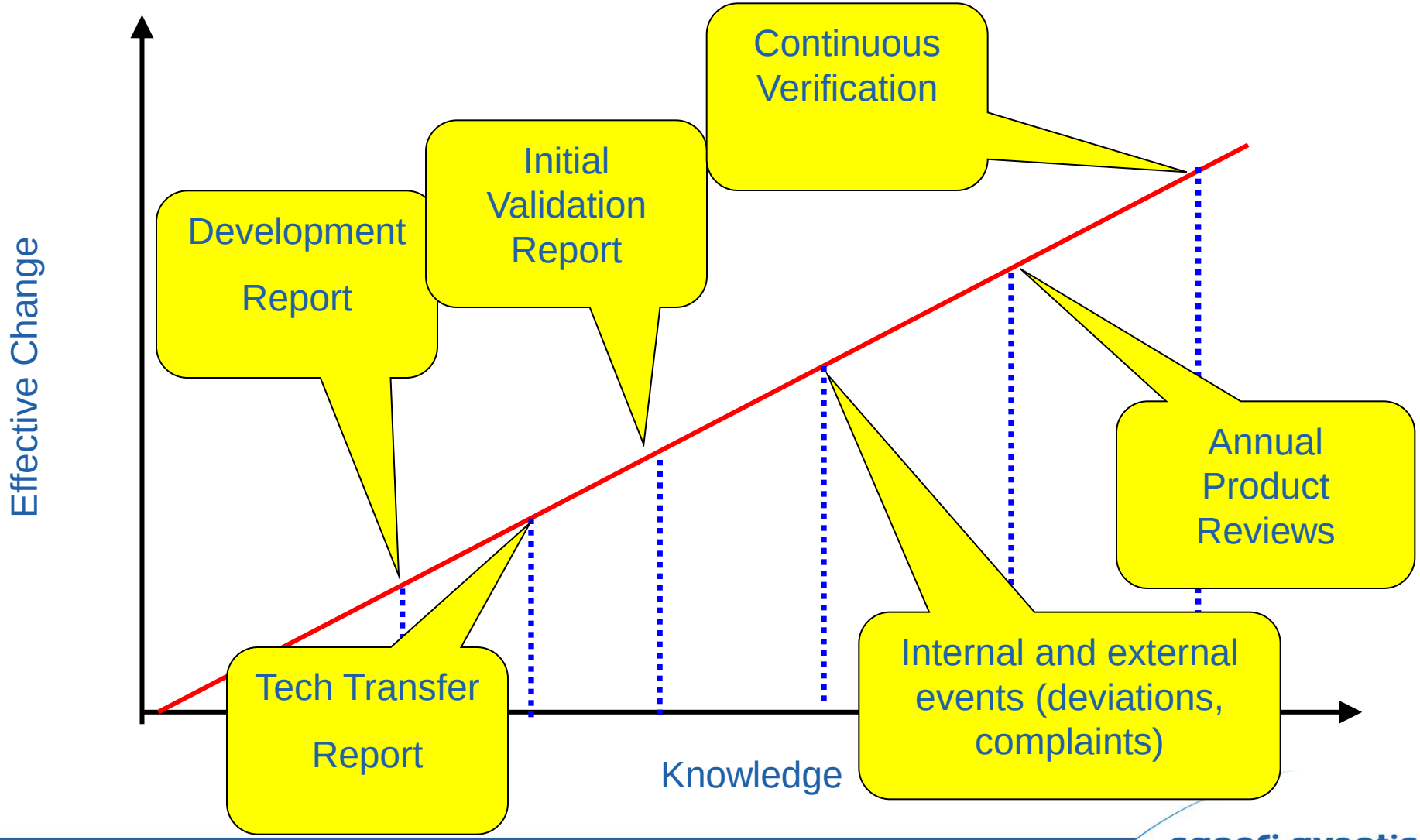


Change Management: Importance of Knowledge



- **Increased knowledge increases chances of successful change**
- **Increased knowledge comes from**
  - **Experience!**
  - **Increased Product Understanding**
  - **Increased Process Understanding**
- **But how do we systematically capture such product and process understanding?**

Change Management: Importance of Knowledge

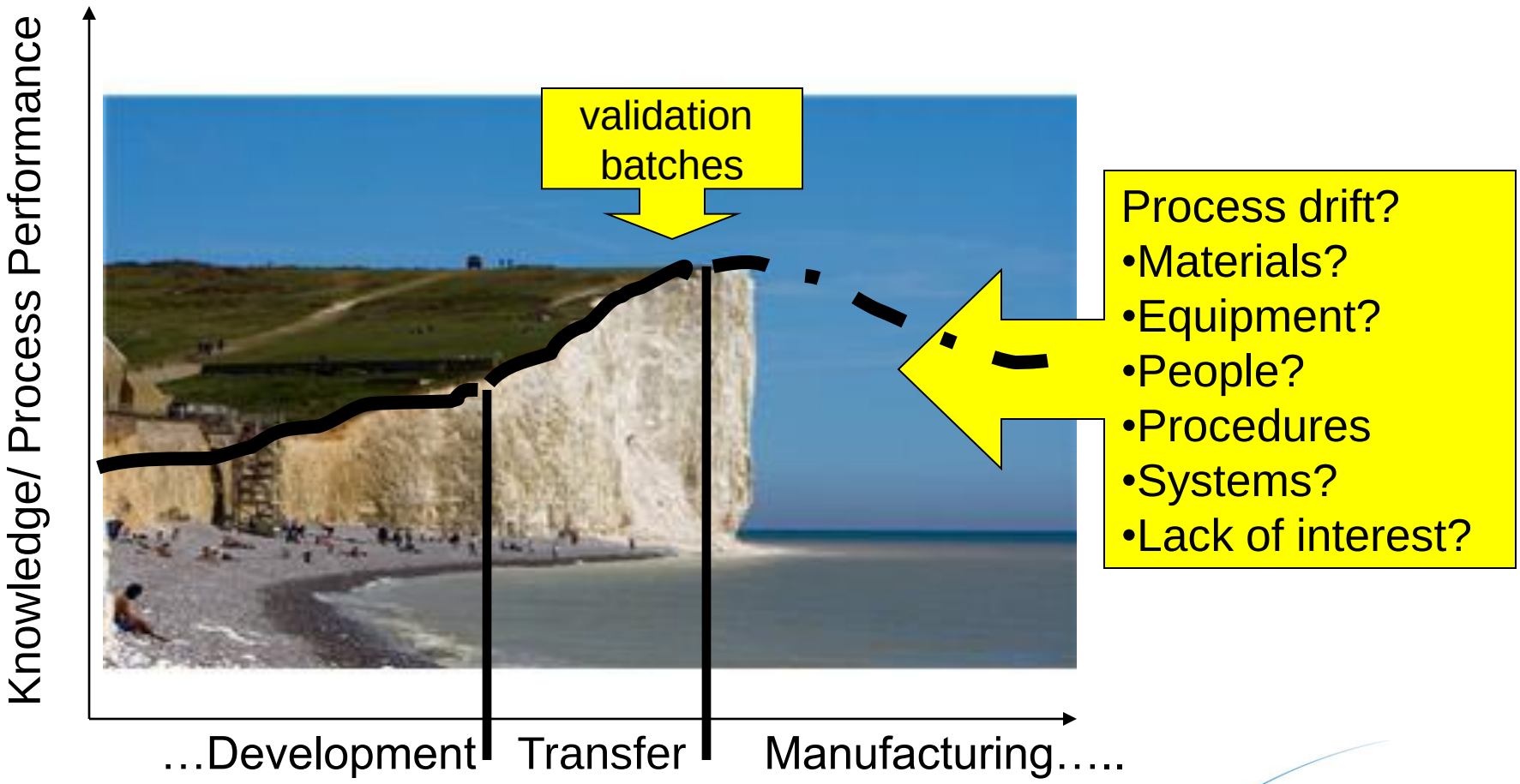


Change Management: Importance of Knowledge

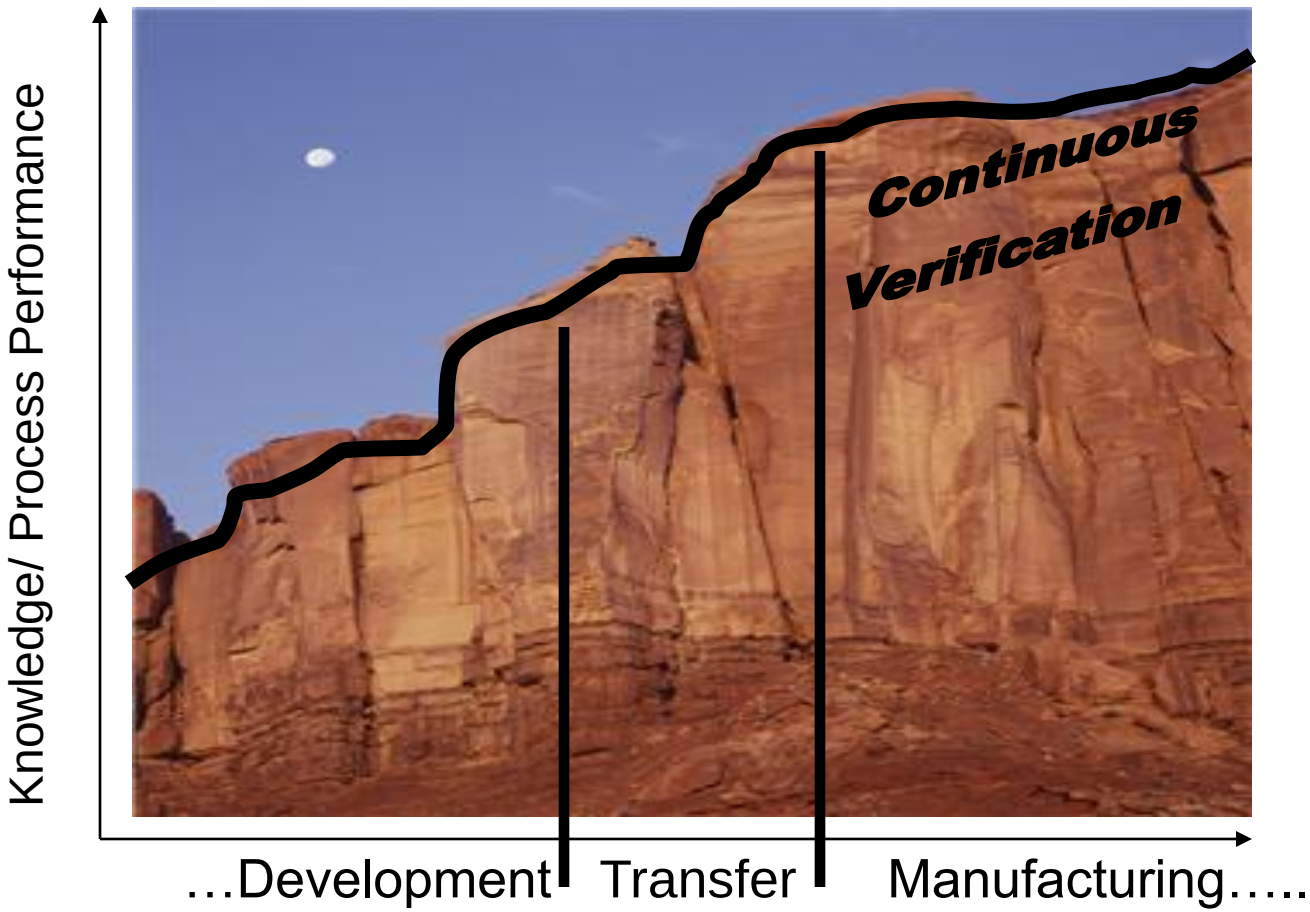
- But these key pieces of data
  - Need to be available to the manufacturing site
  - Used as reference data when assessing changes

- The people need to be trained and educated as appropriate for their daily work
  - On the most recently available knowledge
  - …and the background/reasons for changes

Change Management: Traditional Process Validation



Change Management: Continuous Verification

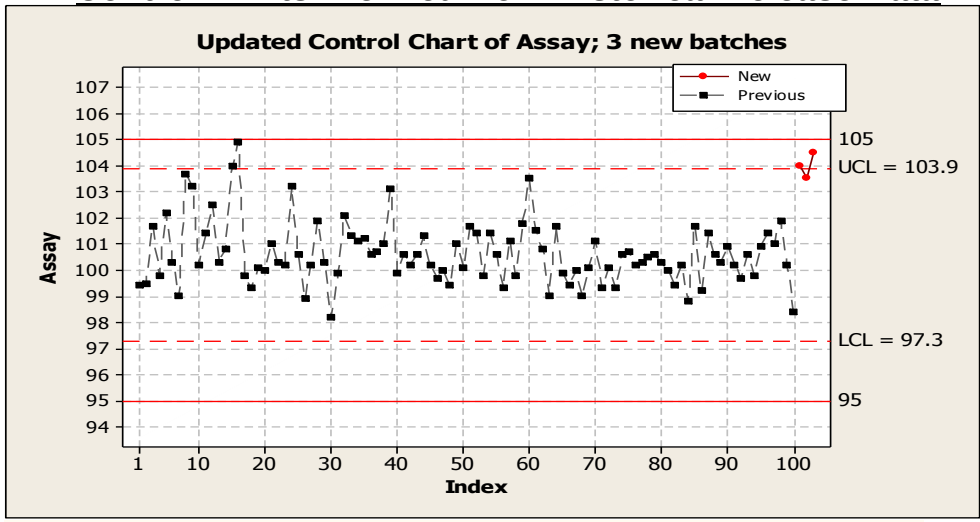


- More batch data
- Trend monitoring
- More knowledge

Continuous Verification: Process Monitoring

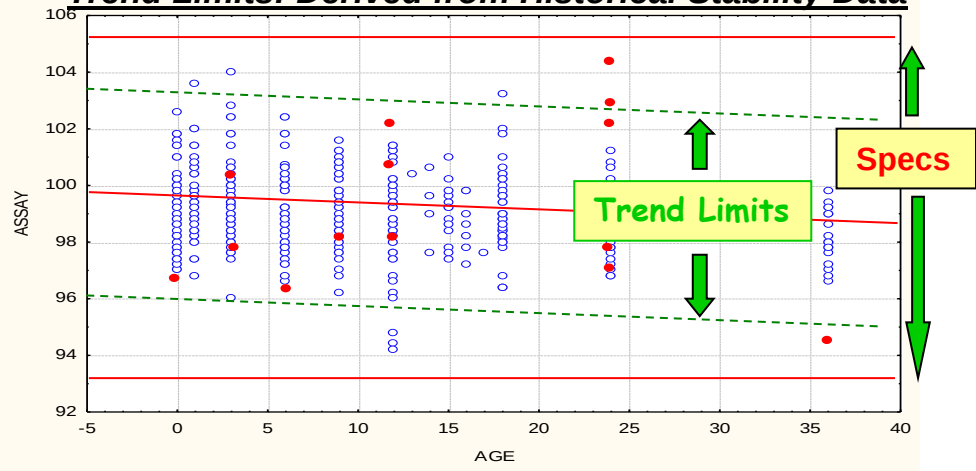
- **Process Tracking and Trending**
  - Address trends before they become problems
  - Verify changes are successful

Control Limits: Derived from Historical Release Data



- **Product Quality Monitoring**
  - Analyze critical process parameters & critical quality attributes in the control strategy
  - Reduce sources of variation
    - If it brings quality improvement

Trend Limits: Derived from Historical Stability Data



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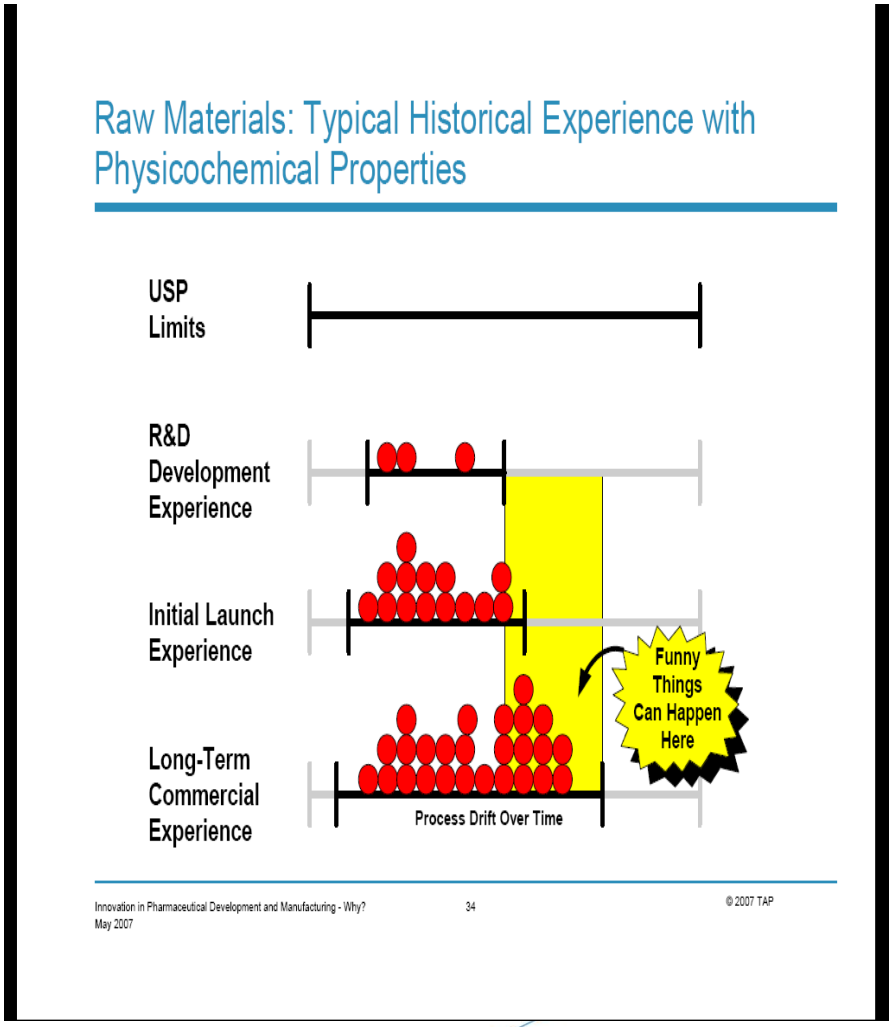
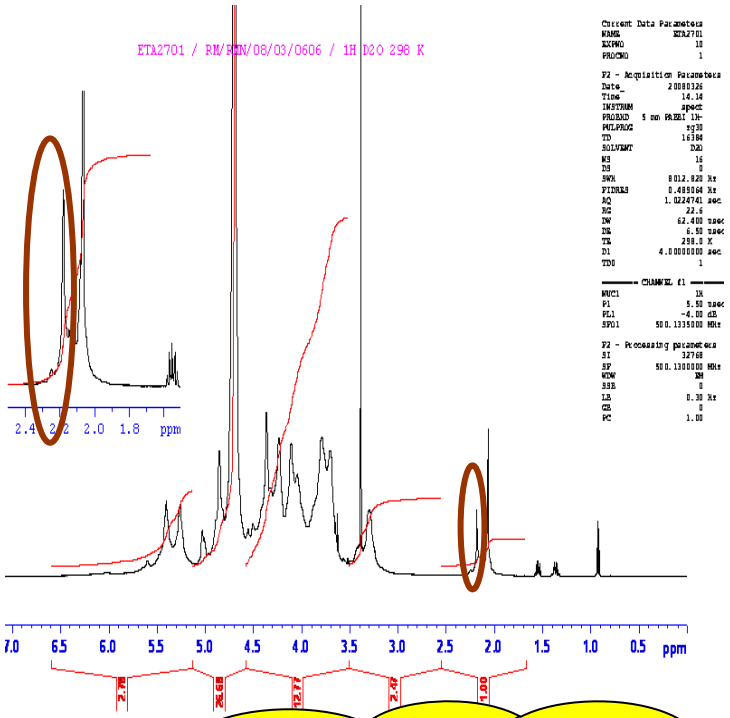
Example of Uncontrolled Change – Unnoticed Process Drift

- Raw Material variability is one major of pharmaceutical process variation
- Can give rise to process variation – even if raw material is within the agreed specification limits
- This 'natural variability' needs to be understood and controlled



Example of Uncontrolled Change – Fraud/Malpractice

- Fraudulent change of raw material (glycerin, heparin, etc)
  - Improved fingerprinting of high risk susceptible raw materials
  - Supplier audits and controls
- Operator decides to wash machine parts at higher temperature 80ºC instead of 50ºC for a shorter time period without change control
  - Thought he was doing continual improvement!
  - His heart was in the right place!



Always ask: Technical, System, or Management issue

Example of Uncontrolled Change – Accident or Error

- Accident/Errors Examples
- Operator accidentally drops scissors into the product during processing
  - First time using a new isolator
  - Process design had not been thought through
- Operator accidentally selects wrong cleaning cycle
  - Master batch record updated as part of change
  - New cycle entered into CIP as part of change
  - …but old cycle was not deleted

Nailing Down the Processes

- Need to ‘nail down’ process to avoid changes via accident or error
- Remove possibility for process parameters to be changed by malpractice, accident or error
  - e.g. machine parts washer
- Use of FMEA when considering process design, process changes
  - e.g. scissors in product,
- Need to train everyone on change control procedure
  - Good change control will be as good as the training and education
  - Include training on serious consequences of uncontrolled change
  - Build it into the culture of the company/site

NASA Space Shuttle Program Process Control Standards & Practices Handbook

- **40 pages mention 'change' 58 times!!**

- ***Standard 1:*** *Detect and eliminate process variability and uncoordinated changes.*
  - Implement methods for early detection of changes in materials, parts, or assemblies

- ***Standard 3:*** *Understand and reduce process risks*
  - Understand potential risk when a change is implemented

NASA Space Shuttle Program Process Control Standards & Practices Handbook

- ***Standard 6:*** *Promote process control awareness. Understand and report changes.*
  - Document process for reporting changes to processes, materials, methods, etc. to the appropriate individuals for analysis and potential impacts

- ***Standard 7:*** *Identify and evaluate changes to equipment and environment.*
  - Identify the baseline and manage and control any changes to that baseline
  - Analyze changes for potential impacts to risk, safety, etc.
  - Ensure changes are coordinated, reviewed, and approved by authorized individuals
  - Maintain documentation of changes

Summary: *Management culture is key to effective change control*

Managers must lead by example

- ***Create and maintain strong change control system and culture***
  - *Management support for problem identification, reporting, and continual improvement*
- ***People must be trained <u>and educated</u> on the change control system***
- ***Ensure QRM tools used as part of the change control when appropriate***
- ***Nail down process to avoid change by accident or error***
  - *Are issues technical, system, or management related*

Summary: *Knowledge is key to effective change control*

People must systematically obtain and utilise the knowledge available to them as part of change control

- ***To make the best judgements of risk (QRM)***
  - *Small changes do not always equal low risk!*
- ***To be able to demonstrate scientific and logical justification***
- ***And to continually add to the product and process knowledge***

Thank you for your attention

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