

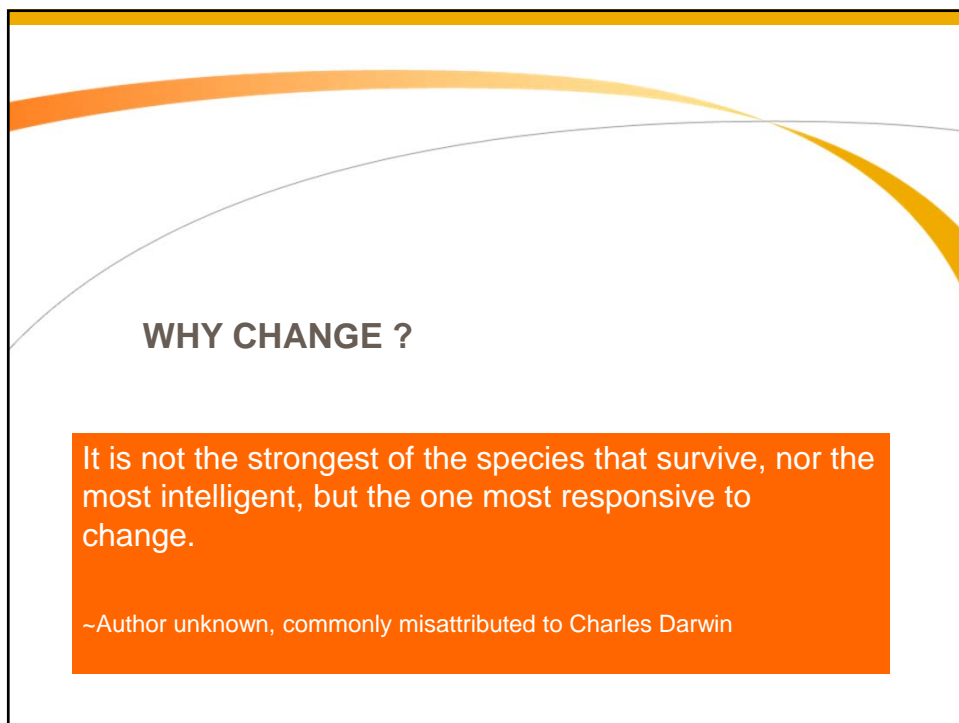


**ICH Q10 and Change Management:  
Enabling Quality Improvement**

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**Overview**

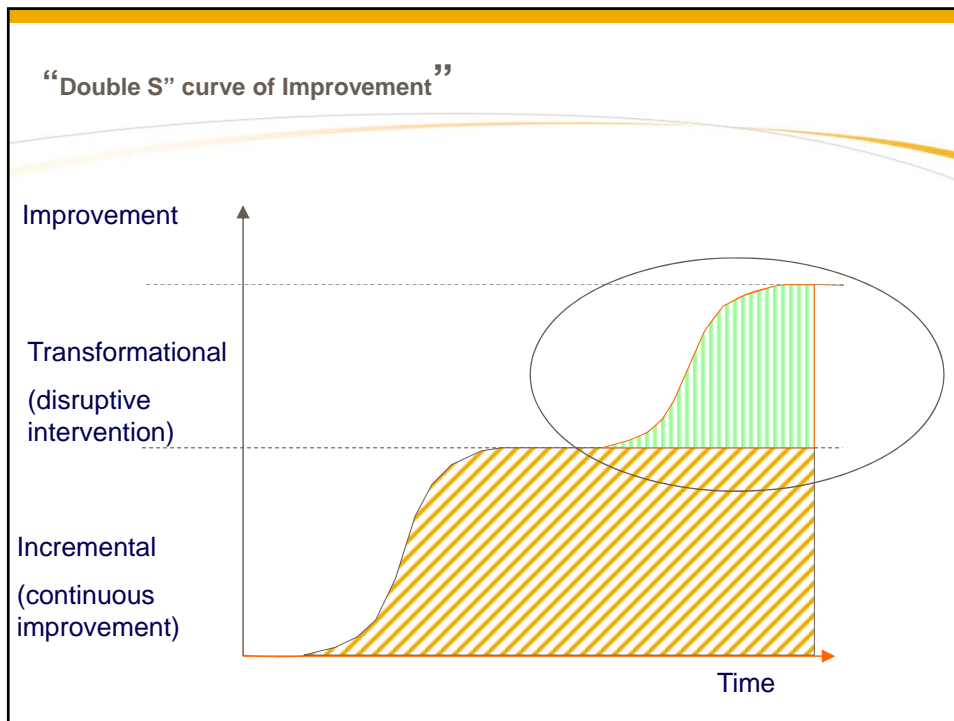
- Drivers for Change
- ICH Q10 and Change Management
- Implementation of ICH Q8, Q9 and Q10
- Case Studies
- Management Responsibility
- Considerations and Opportunities
- Summary



**Operations in Pharmaceuticals Compare Poorly to Other Industries**

*The pharmaceutical industry lags similar industries in key measures of operations performance, most notably in overall equipment effectiveness, labor value-add time and direct/indirect labor ratio, McKinsey's Ted Fuhr told the recent CDER on CMC conference in Bethesda, Md. Many of the shortcomings reflect poor quality practices and represent cost savings opportunities for the quality by design paradigm. Estimates are from McKinsey Operations Practice.*

Measure	Pharma	Automotive	Aerospace	Computer	Consumer Packaged Goods
Overall equipment effectiveness	10% to 60%	70% to 85%	50% to 70%	80% to 90%	70% to 90%
Annual productivity improvement	1% to 3%	5% to 15%	5% to 10%	1% to 3%	5% to 15%
First-pass yield – zero defects	60%	90% to 99%	70% to 90%	90% to 99%	90% to 99%
Production lead times in days	120 to 180	1 to 7	7 to 120	5 to 10	3 to 7
Finished goods inventory in days	60 to 90	3 to 30	3 to 30	5 to 50	10 to 40
Labor value-add time	20%	60% to 70%	60% to 70%	60% to 70%	60% to 90%
Direct/indirect labor ratio	1:1	10:1	10:1	10:1	10:1



## ICH Q10 and Change Management

### ■ Change Management

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes (ICH Q10)

- The scope of change management is much broader than change control, which was typically applied to one change at a time
- Change management includes the oversight and management of the entire portfolio of changes and the change process, including all the components of change control
- In a Pharmaceutical Quality System (PQS) developed according to Q10, change management applies across the entire product lifecycle

## Change Management System

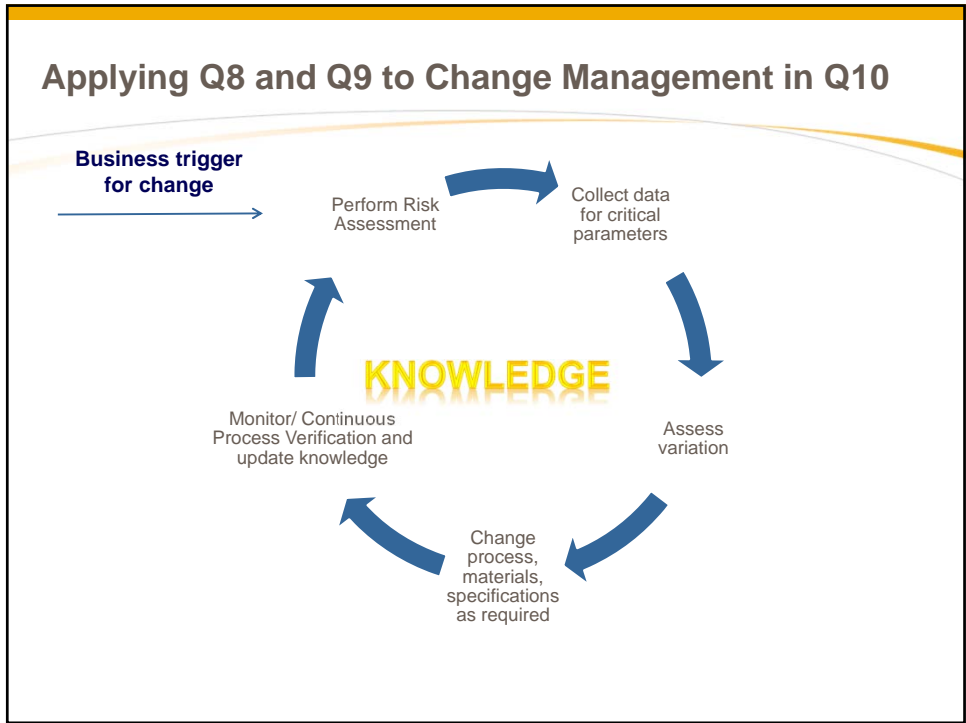
- A company should have an effective change management system in order to evaluate, approve and implement changes
- The change management system should include the following :
  - Quality risk management should be utilised to evaluate proposed changes; The level of effort and formality of the evaluation should be commensurate with the level of risk;
  - Proposed changes should be evaluated relative to the marketing authorisation, including current product and process understanding and/or design space, where established;
  - Expert teams, with appropriate expertise and knowledge, should evaluate proposed changes;
  - An evaluation of the change should be undertaken after implementation to confirm the change objectives were achieved.

## ICH Q10 and Continual Improvement

- Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities (ICH Q10)
- **Facilitate Continual Improvement**
  - To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently (ICH Q10)
- Key enablers
  - Quality risk management
  - Knowledge management

## Opportunities from implementing Q8, Q9 and Q10?

- Product and process understanding, the use of quality risk management principles, supported by the implementation of an effective PQS ( i.e. applying ICH Q8, ICH Q9 and ICH Q10 principles) provides the opportunity to:  
***optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement (ICH Q10)***



### “Straightforward” Excipient Supplier Changes ?

Case Study 1

New Excipient supplier delivered material to agreed specification

Excipient manufacturing process allowed addition of mineral oil to bring batches into specification

Criticality of replacing catalyst to control hydrogenation not recognised

**Impact on Drug Product**

Surface of API fluoresces due to surface peroxidation

**Control Strategy**

Tighter control of additions of mineral oil and manufacturing process

Enhanced GC test performed by supplier and reviewed by Site prior to shipment

## Case Study 2

**Fermentation Product Impurity control****Problem :**

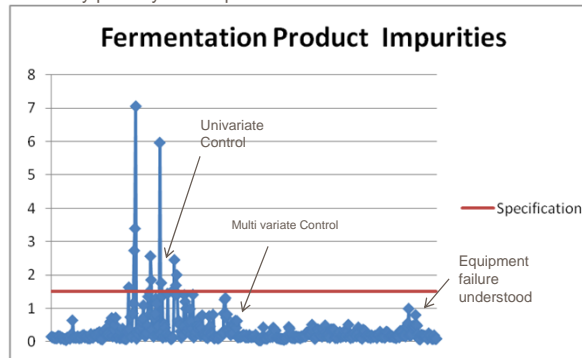
- Fermentation product producing high levels of impurity restricting supply of critical medicine
- Multiple potential root causes.
- Initial univariate root cause solution only partially solved problem.

**Solution**

- Identification of interaction between rape seed oil quality (fermentation), Crystal Form (Extraction Process) and Extraction equipment mechanical force (Equipment)
- Controls put in place to tackle all three causes

**Which Tools used?**

- Complex Root Cause Analysis using modified Britest tools Process via Metabolic Pathway and Mechanism Map,
- True root causes verified in controlled conditions using classical experimentation
- **Benefit – Failure rate reduced from 15% to zero,  
No impurity levels > 0.6% for five years,  
Reduction in hidden factory investigations, confidence in process.**

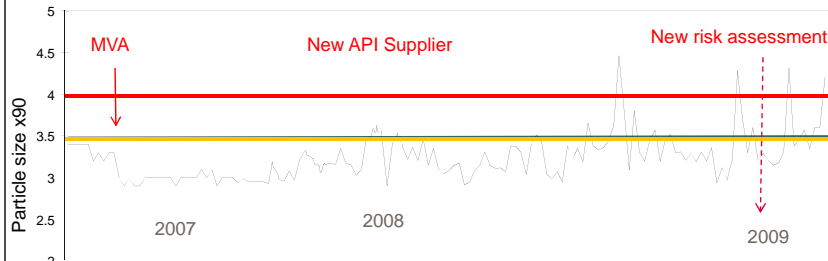


## Case Study 3

- High Cost of Waste and risk of stock out for life-saving medication
- Complex system that is inherently close to the edge of failure with respect to its propensity for API aggregation
- Very subtle changes in raw material properties and processing parameters can result in aggregation
- Internal & external experts advised the root cause of the aggregation failure is inherent and linked to the formulation

Process History

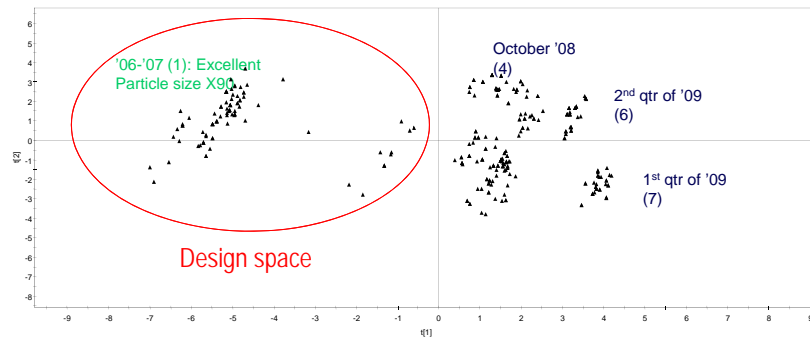
Risk assessment and MVA of process and input parameters used to optimize performance in 2007



From October 2008, 5 batches failed the  $x_{90}$  particle size specifications and 13 batches were atypical

Root Cause Analysis

- Expand MVA data set to develop functional specifications
- Engage excipient suppliers in root cause analysis

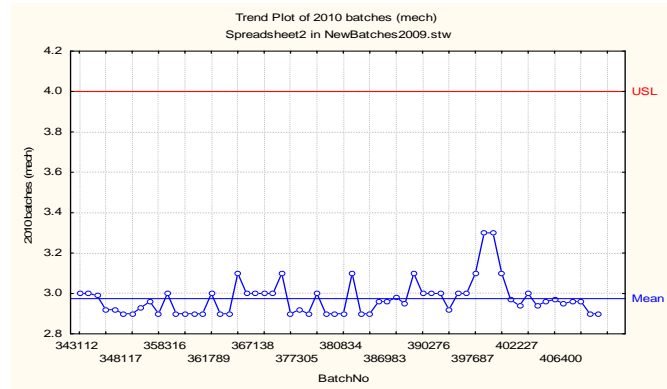


Expanded model shows that shifts in particle size are 80% due to changes in API & raw materials. The objective is to manipulate process variables and raw material to bring process back to Design Space (DS).



**Results of Corrective Actions**

Results following Improvements to Functional Specifications



Mean = 2.97  $\mu\text{m}$   
PpK > 2

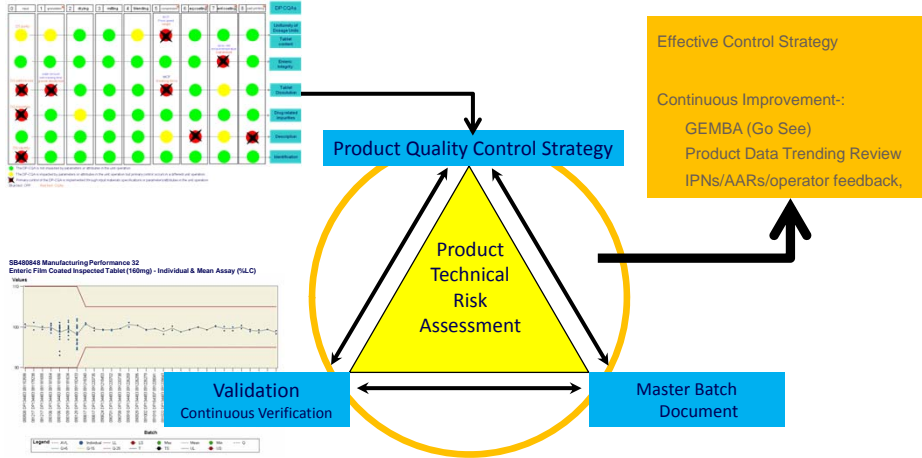
## ICHQ10 and Management Responsibility

Management should -:

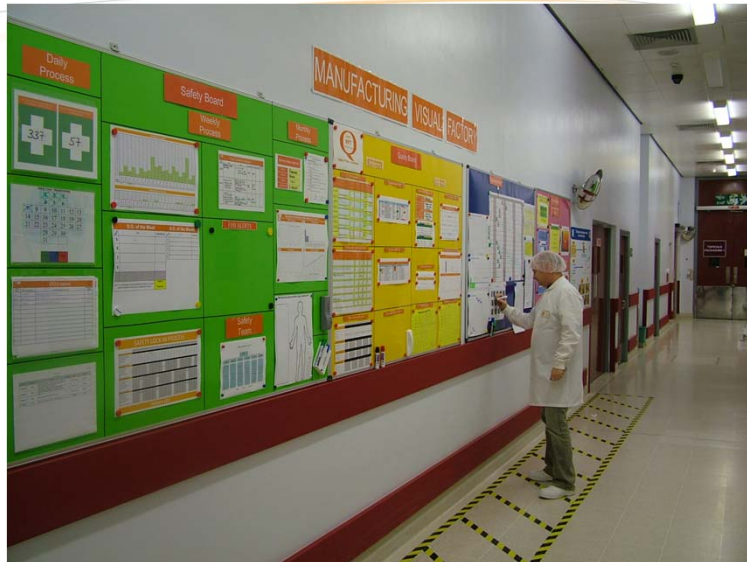
- *Participate in the design, implementation and monitoring of the pharmaceutical quality system*
- *Ensure a timely and effective communication and escalation process exists to raise Quality issues to the appropriate levels of management....*

## How to translate QbD “Effective Control Strategy on the shop floor”

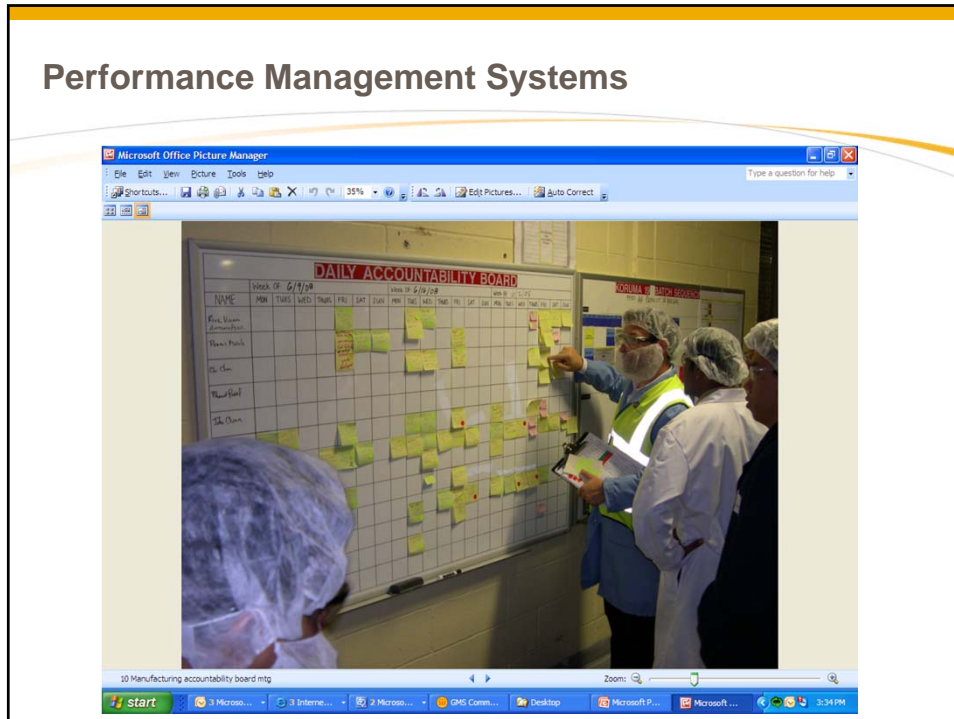
- A major part of execution is the **Batch Document**
  - It should be articulated into an effective set of instructions, SOPs , guides ... leading to:  
**A clearly understood Control Strategy at a level where the product is made**



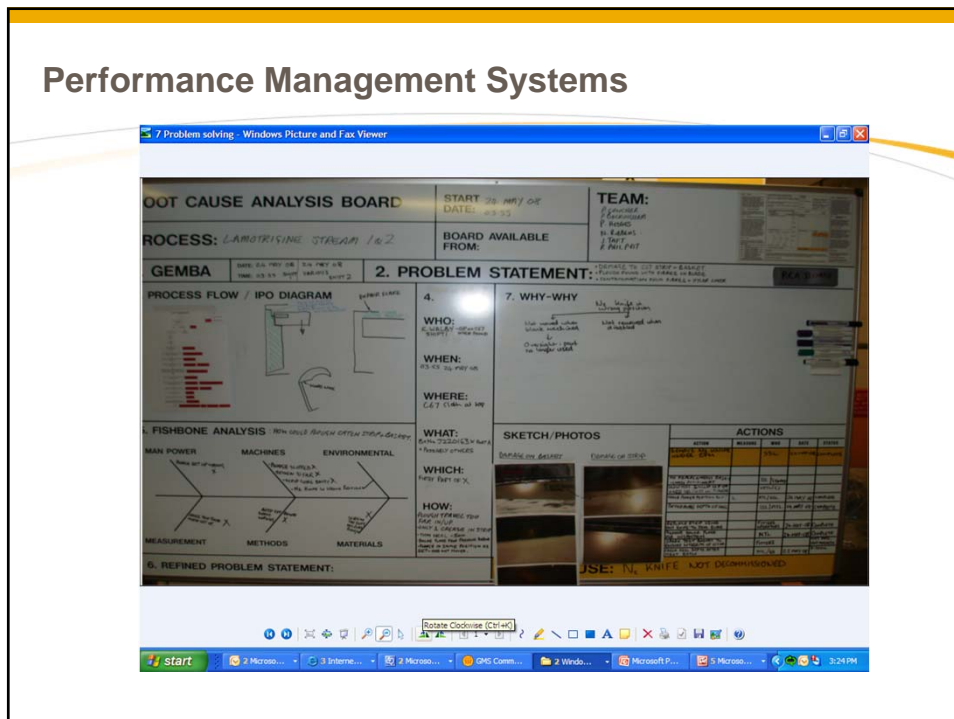
## Performance Management Systems

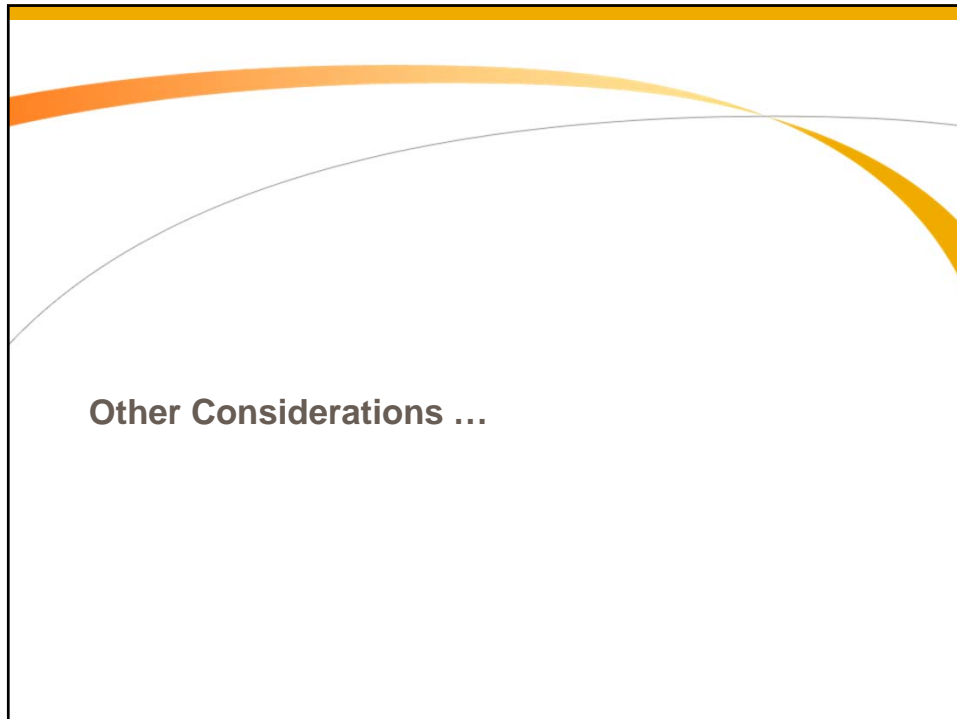


## Performance Management Systems



## Performance Management Systems





**Regulatory Challenges to Implement Changes**

- Lack of a harmonised regulatory system for managing post-approval changes
  - EU vs US vs Japan vs ROW
- 'Registered detail'
  - not a common agreement of what constitutes 'registered detail' and what we need to change via a variation
- Leads to different requirements and timelines for approval, and different types of variations
  - Particularly challenging when trying to manage manufacturing changes globally

## Opportunities

- Implementing Q8, Q9 and Q10 provide opportunities to **optimise science and risk based post-approval change processes** to maximise benefits from innovation and continual improvement
- Legacy products are also improved under the ICH Q10 change management system over the lifecycle
- Q8, Q9 and Q10 are moving Industry and Regulators in the right direction
- Are we realising opportunities or obtaining benefits as quickly as we should ?
  - How can we facilitate this?

## Summary

- Drivers for Change
- ICH Q10 and how change can be supported
- Implementation of ICH Q8, Q9 and Q10
- Case Studies
- ICH Q10 and Management Responsibility
- Considerations and Opportunities

## Acknowledgements

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Life is change, growth is  
optional, choose wisely !

Q&A