Implementation of ICH Q8, Q9, Q10

Manufacturing Implementation and the Pharmaceutical Quality System

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Introduction

- Moving through the product lifecycle
  - Development into Commercial Manufacturing site
  - ‘smooth transition’ – continuation of product and process learning
- Manufacturing role will be simplified by a well developed product
  - More product and process knowledge

Introduction

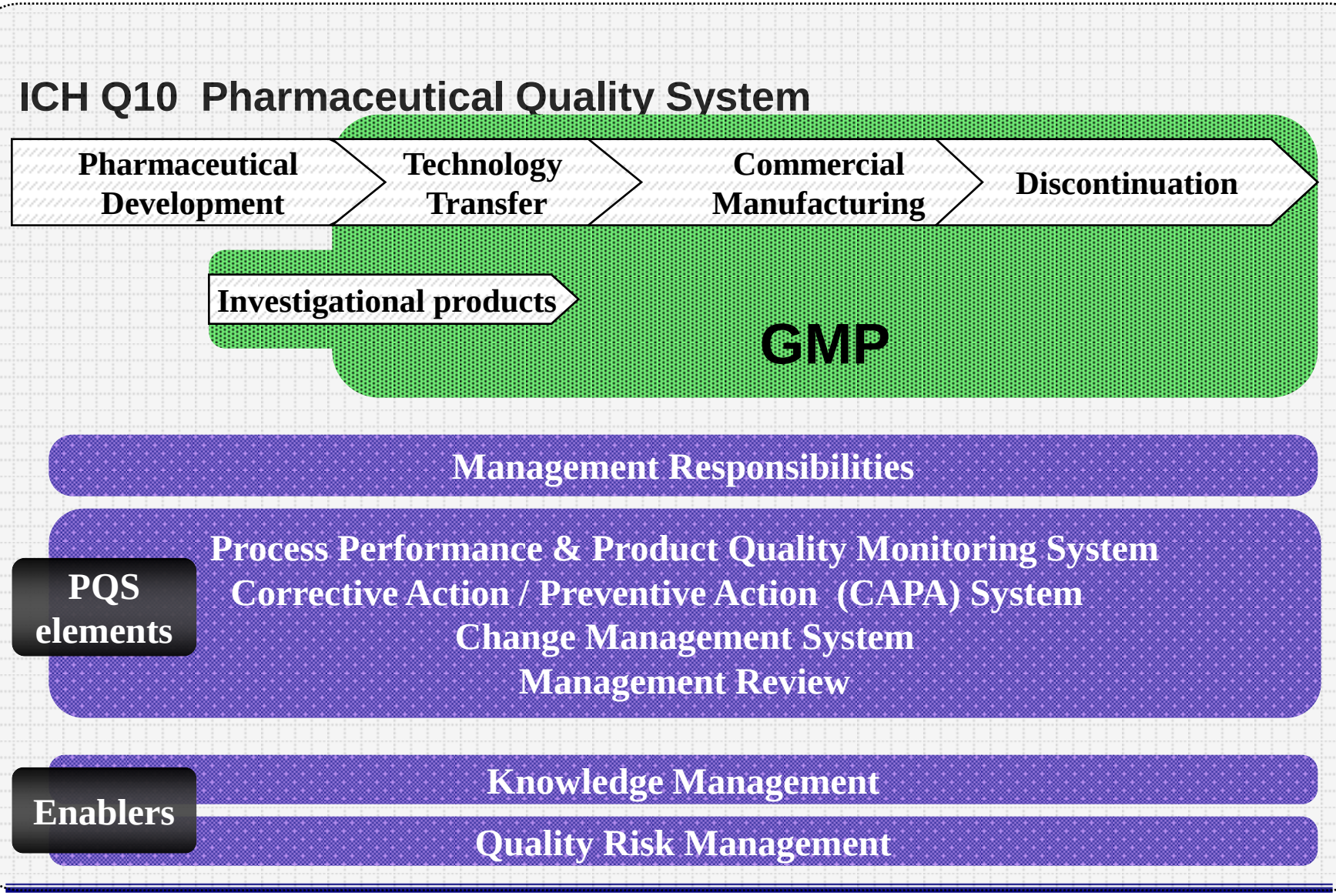
- Manufacturing still have a key role to play
  - Using that knowledge gained during development
  - Using current site knowledge (e.g. similar products)
  - Building on that knowledge through transfer, validation, and commercial manufacturing activities
  - Feedback of that knowledge to Development

- Will consider the PQS in this presentation
  - And how it can help ‘drive’ the product through the lifecycle

Manufacturing Implementation and PQS considerations

- **Pharmaceutical Quality System**
- Scale-up and Technology Transfer
- Process Validation
- Change Management and Continual Improvement
- Quality Unit (QA/QC) and Batch Release

Manufacturing Implementation and PQS considerations



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Scale up and Technology Transfer

- Creates a unique opportunity to jointly learn more about product and process (development/manufacturing)
  - Needs to be properly planned
    - Use development knowledge
    - Involve the correct people (knowledge and training)
    - Ensure enough time
    - Use QRM to identify risks of next scale up
    - Tests the documentation (master batch record, SOP's)

- Technology Transfer must ensure that the
  - Process works in practice (facility, equipment)
  - Control strategy works in practice
    - Proving Predictive models work at increased scale
    - Real Time Release Testing data can be used with confidence

Case Study: Drug Product Manufacturing Process

2.3.P.3.3 Manufacturing Process

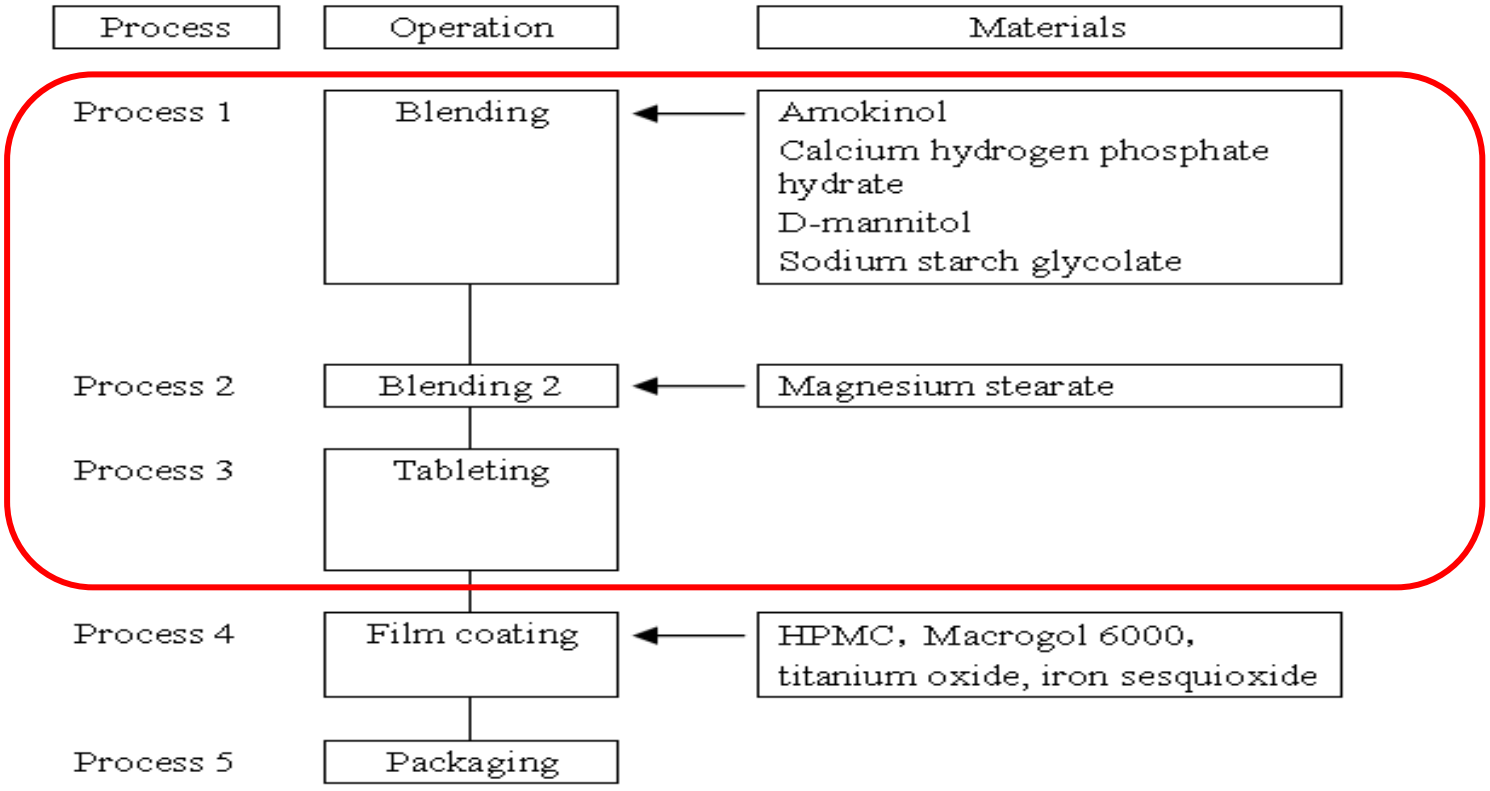


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

Focus of Story

Drug Product Process Scale-up

Case Study Focal Steps – Blending and Tabletting

- Early Clinical Development – Liquid-filled capsules
- Phase 3 Scale – 50,000 units (made in Development)
  - Technology Transfer to Production Begins
- Verification of Predictive Model
- Scale at time of Submission 200,000 units (made in Manufacturing plant)
- QRM Evaluation for next scale-up (?)
- Desired Commercial scale – 1,000,000 units (Planned for Commercial Plant(s)

Predictive Model Verification

- Predictive Models proposed and utilized during Development phase
- Laboratory testing for dissolution and compressed tablet CU is performed:
  - During Tech Transfer to evaluate and confirm predictive Model at pilot and commercial scale at site of manufacture
  - Confirmatory Laboratory testing for dissolution and compressed tablet CU compared to values calculated by model for initial commercial batches (e.g. the first 10 batches)
- Review Development, Process Validation, and Commercial scale batch data to analyze and refine predictive model
- Periodic confirmatory testing of commercial batches

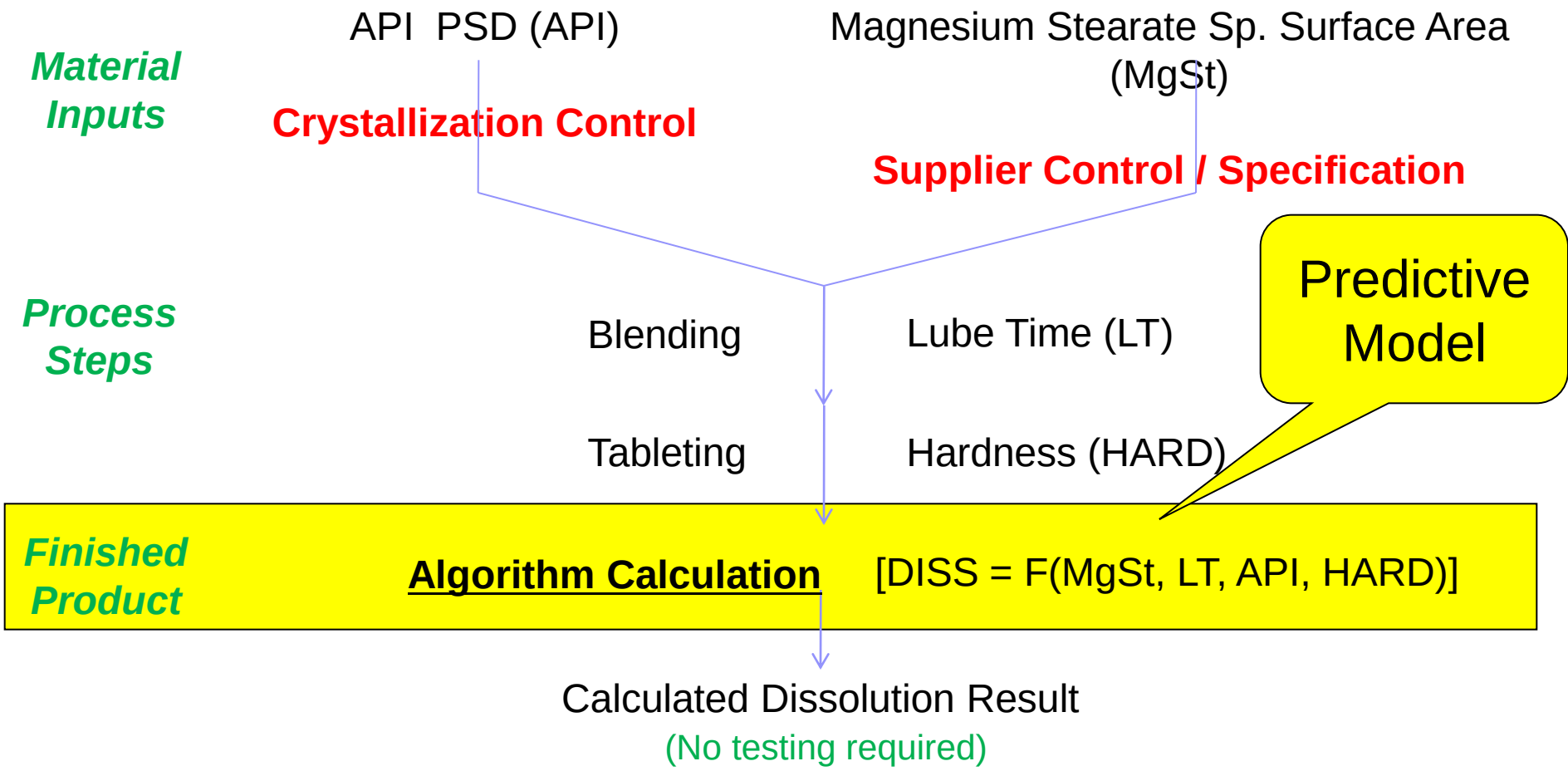
Control Strategy

Finished product is not tested by QC lab for assay, CU and dissolution

- **Input materials** meet specifications and are routinely tested for their critical attributes
  - API: Particle Size Distribution
  - Magnesium stearate: specific surface area
- **Assay calculation**
  - Verify (API assay of blend by HPLC) X (tablet weight)
  - Tablet weight by automatic weight control (feedback loop)
    - For 10 tablets per sampling point, <2% RSD for weights
- **Content Uniformity**
  - On-line NIR criteria met for end of blending (blend homogeneity)
  - Tablet weight control results checked
  - Compression force monitored and in range

- **Dissolution** **(See next slide)**
  - Predictive model using input and process parameters for each batch calculates dissolution meeting acceptance criteria
  - Input and process parameters used are within the filed design space

Dissolution: Control Strategy



Note: Use of algorithm potentially allows process to be adjusted for variation in API particle size, for example, and ensure dissolution performance.

Example

Predictive Model for Dissolution

Prediction algorithm:

$$Diss = 108.9 - 11.96 \times API - 7.556\times10^{-5} \times MgSt - 0.1849 \times LubT - 3.783\times10^{-2} \times Hard - 2.557\times10^{-5} \times MgSt \times LubT$$

Factors include: API PSD, magnesium stearate specific surface area, lubrication time, tablet hardness

Confirmation of model

	Batch 1	Batch 2	Batch 3
Model prediction	89.8	87.3	88.5
Dissolution testing result	92.8 (88.4–94.2)	90.3 (89.0-102.5)	91.5 (90.5-93.5)

No failures. Verify model in production scale to determine if it provides suitable and sufficient surrogate to replace direct measurement of the critical product attribute (dissolution). **The model will be maintained within the PQS**

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- **Process Validation**
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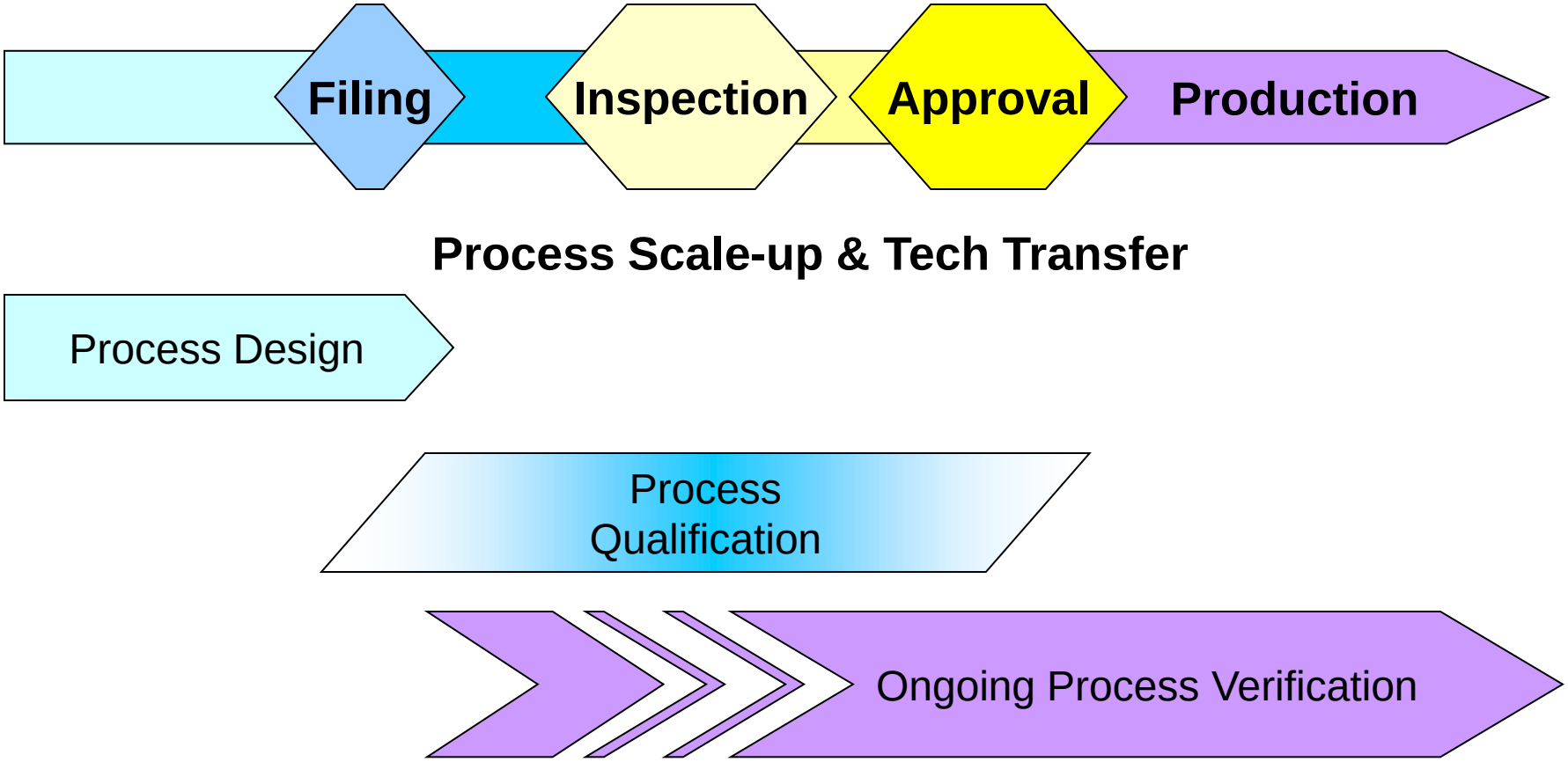
Process Validation

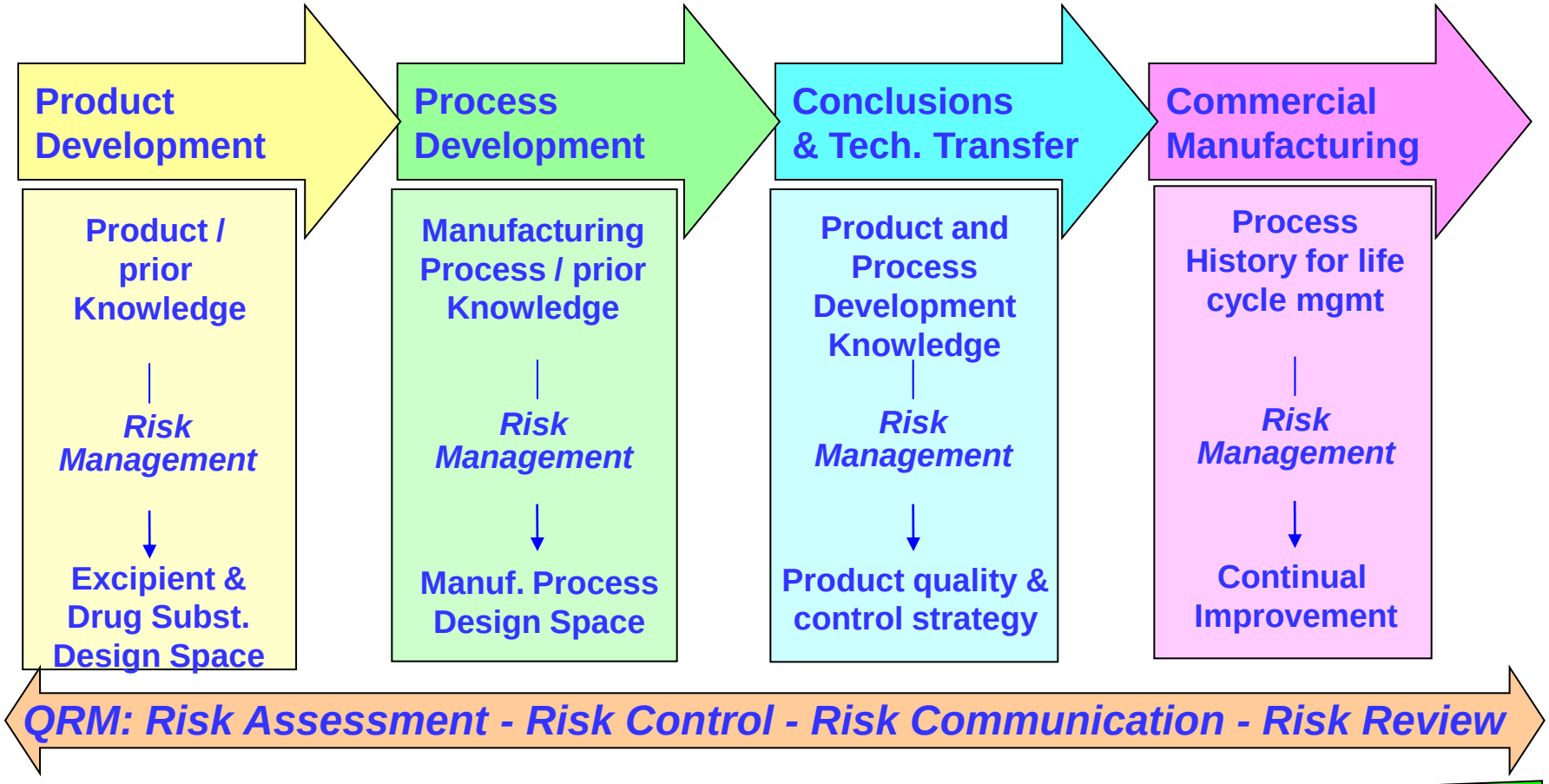
- Helps to build confidence in the product and process

- Consider new approach to process validation
  - No longer a one-off exercise (i.e. 3 validation batch approach)
  - Process Validation starts earlier in the product lifecycle
  - Continues throughout the remainder of the product lifecycle
  - Focus more on the critical parts of the process
    - Use of Development knowledge
    - Use of Process monitoring data
    - Use of QRM tools (e.g. FMEA)
    - Use of statistical process capability and control analysis

Process Validation Lifecycle



Role of Quality Risk Management in Process Validation



Ongoing Process Verification

Continual process verification

- Can be established by placing process monitor/evaluation tools at appropriate manufacturing steps based upon thorough product and process understanding
- Can be built in process validation protocols for the
  - initial commercial production
  - manufacturing process changes
  - continual improvement throughout the product lifecycle.

Manufacturing Implementation and PQS considerations

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- **Change Management and Continual Improvement**
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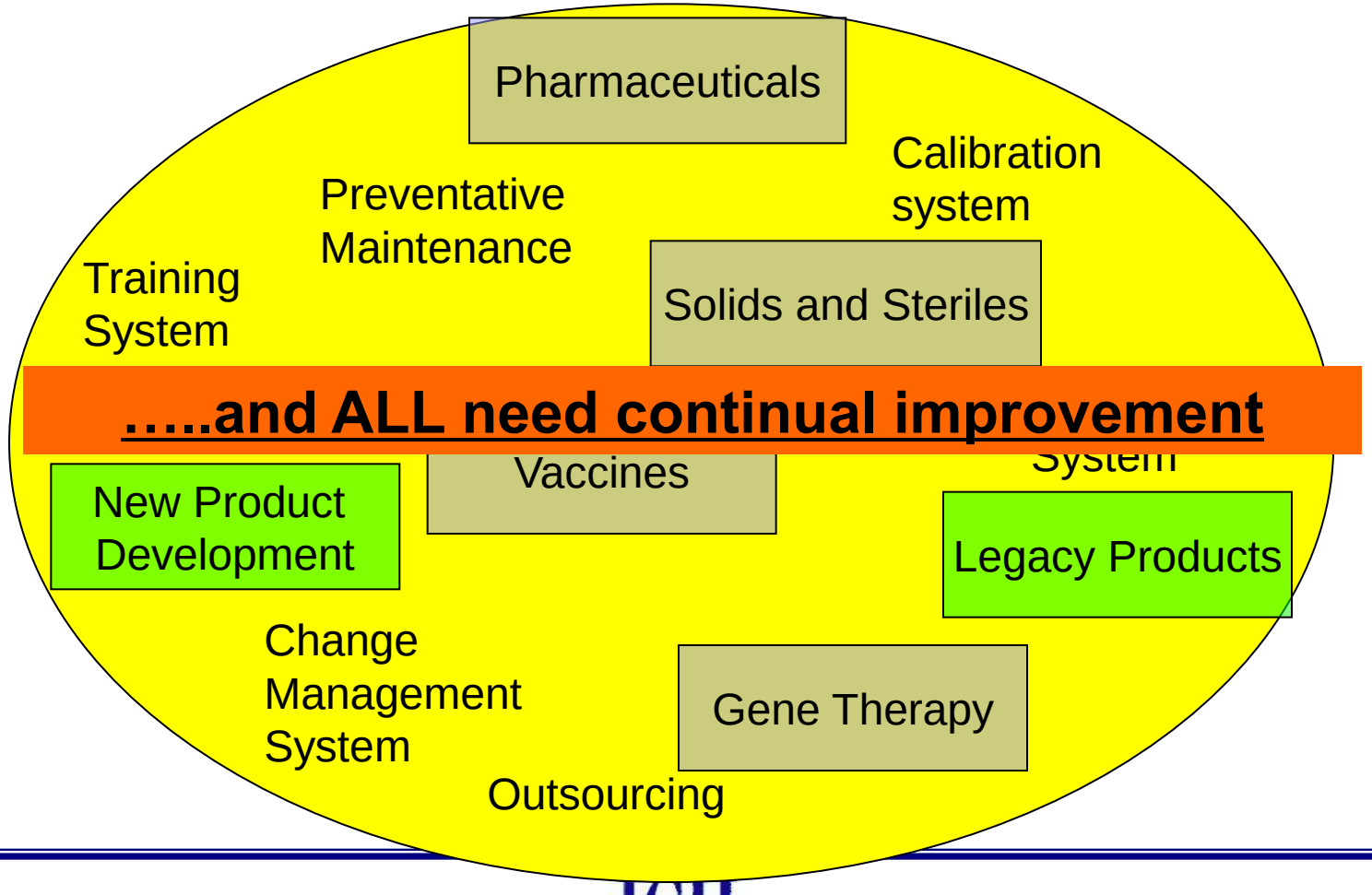
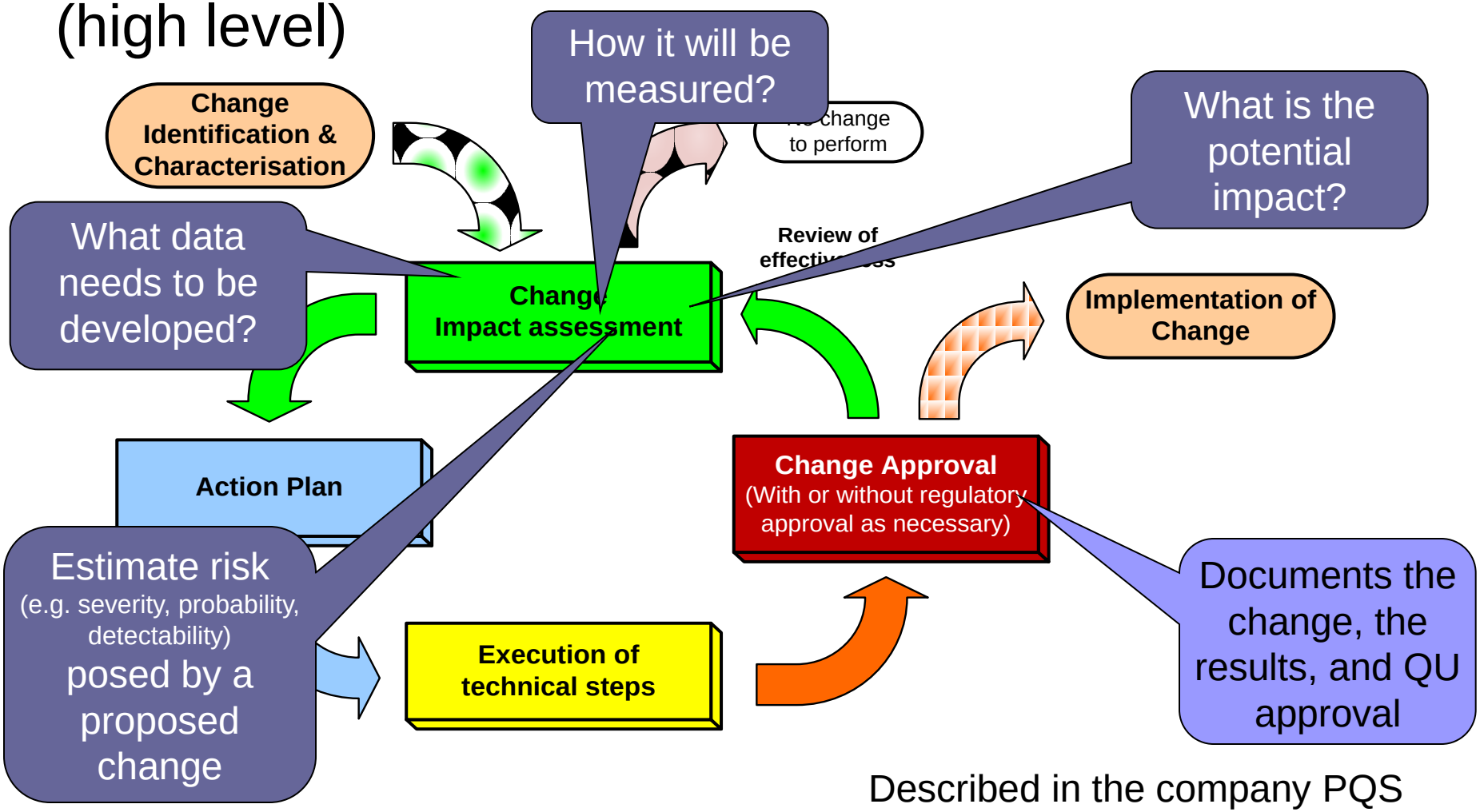
Change Management and Continual Improvement

- Changes *WILL* happen throughout the product lifecycle
  - **Proactively** due to business or technical reasons
    - Part of continual improvement initiatives
      - e.g. new supplier, batch size change, new equipment
  - **Reactively** driven as part of CAPA
    - Due to deviations, OOS, batch rejections
- The PQS must include a *robust* change management system
  - Use of knowledge and Quality Risk Management
- Continual Improvement must be part of our daily working lives
  - Helped by data (e.g. trend data, Statistical Process Control)
  - Driven by people - as part of the culture!

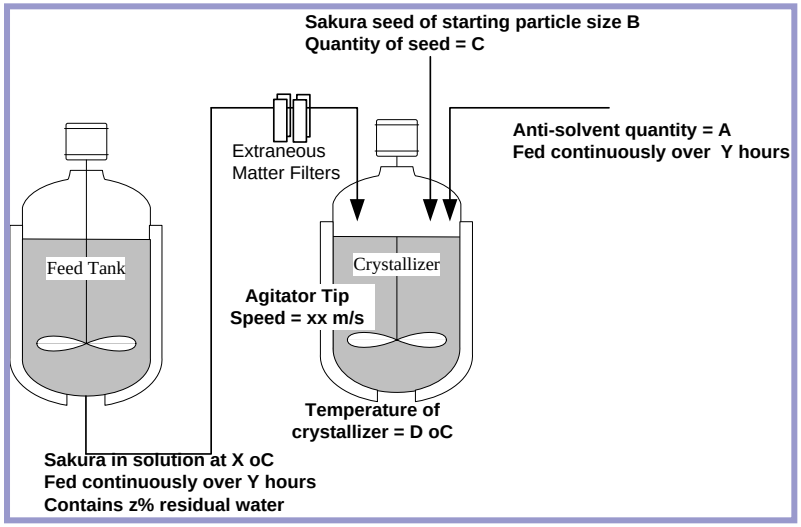
Different Types of Products, at Different Stages of Lifecycle
All need 'relevant' supporting processes, managed by PQS



Typical Change Management Process Map (high level)



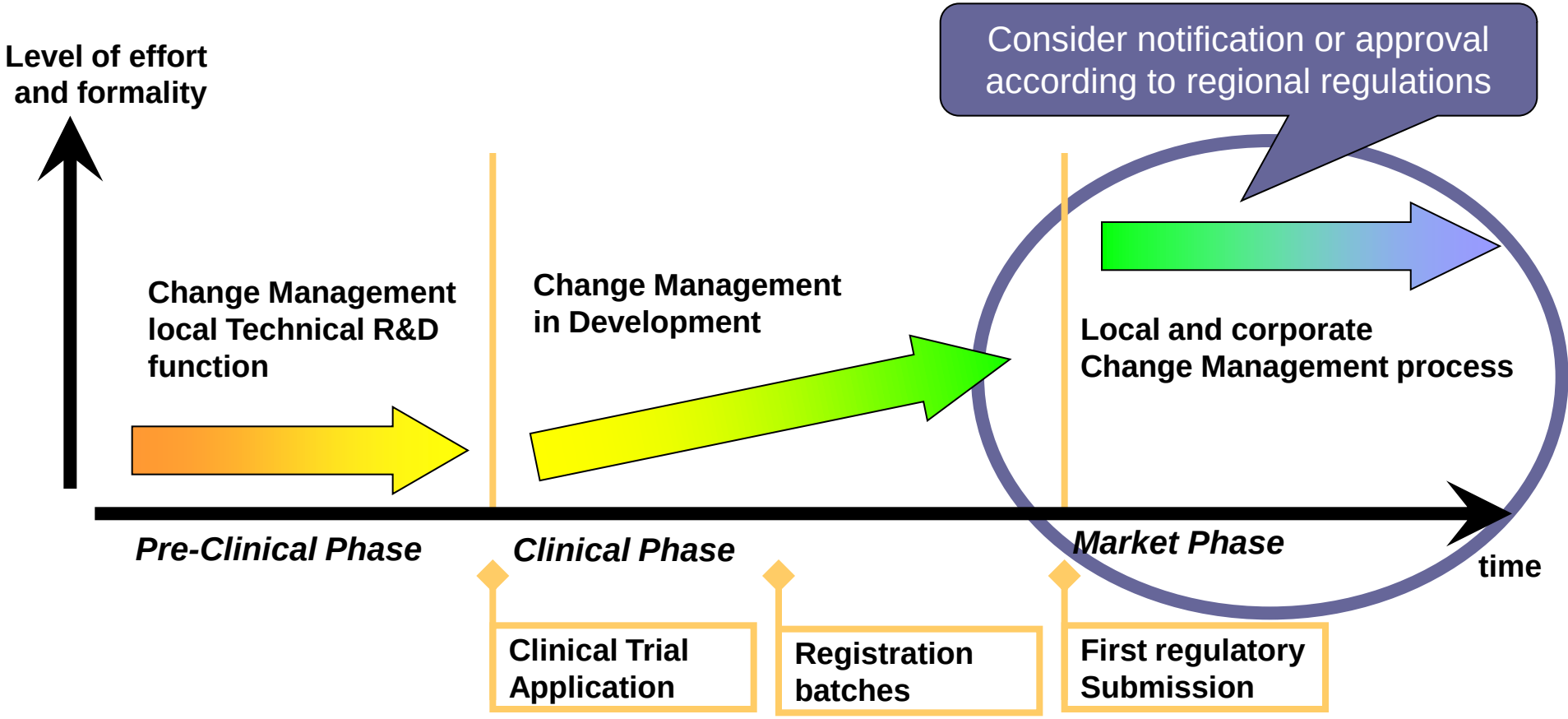
Change Management



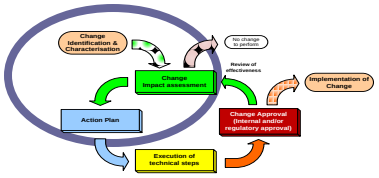
- **What happened?**
  - Over time the seed characteristics changed
- **Available knowledge**
  - Seed characteristics has an influence on the Particle Size distribution
  - The Control Strategy provides guidance:

CQA	Unit Operation	Parameter	Design Space	Comments
Particle Size	Crystallization	Agitation	1.1 to 2.5 m/s	Quality system should ensure changes in agitator size result in change to speed setting

Different Change Management approaches over the Life Cycle



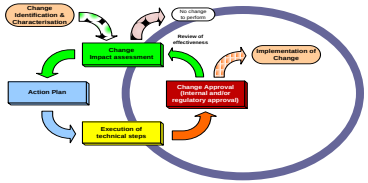
Change Management Process



- **Verification by Quality Management**
  - Consider Technical Regulatory Filing
  - Link to Knowledge Management
    - Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components.
    - Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; deviations, customer complaint, returns, CAPA and OOS's assessments; continual improvement; and *change management* activities.

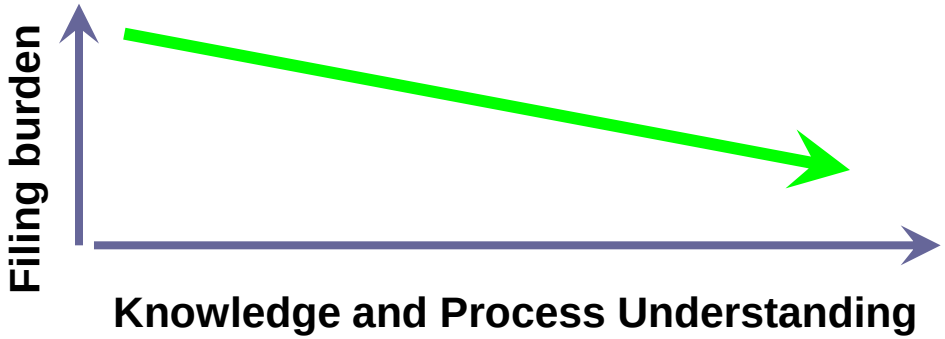
Based on ICH Q10, Pharmaceutical Quality Systems

Change Management Process



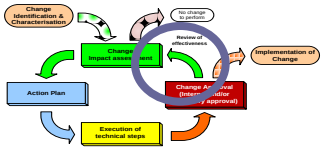
Quality Management will:

- Verify if proposed change to operating range is within design space
- Utilise Knowledge and Process Understanding



- Ensure Manufacturing can perform the change without prior notification of health authorities
  - Critical process parameters within design space
  - Non-critical process parameters

Change Management process



- **Confirmation of successful change: e.g.**

- **Process Validation**
  - Can be operated as a lifecycle monitoring i.e. 'Continuous Process Verification'

- **Annual Product Review (APR)**
  - The effectiveness of the change is demonstrated

Further elements of the PQS

Continual Improvement of the Product

Inputs

- Manufacturing Experience
- Deviations / CAPA
- Performance Monitoring
- Customer Complaints
- Management Reviews
- Material Variance

Continual Improvement

Lifecycle Adjustment

- Readily achieved as part of routine feedback
- Require permanent & substantial process/facility design to improve original concept

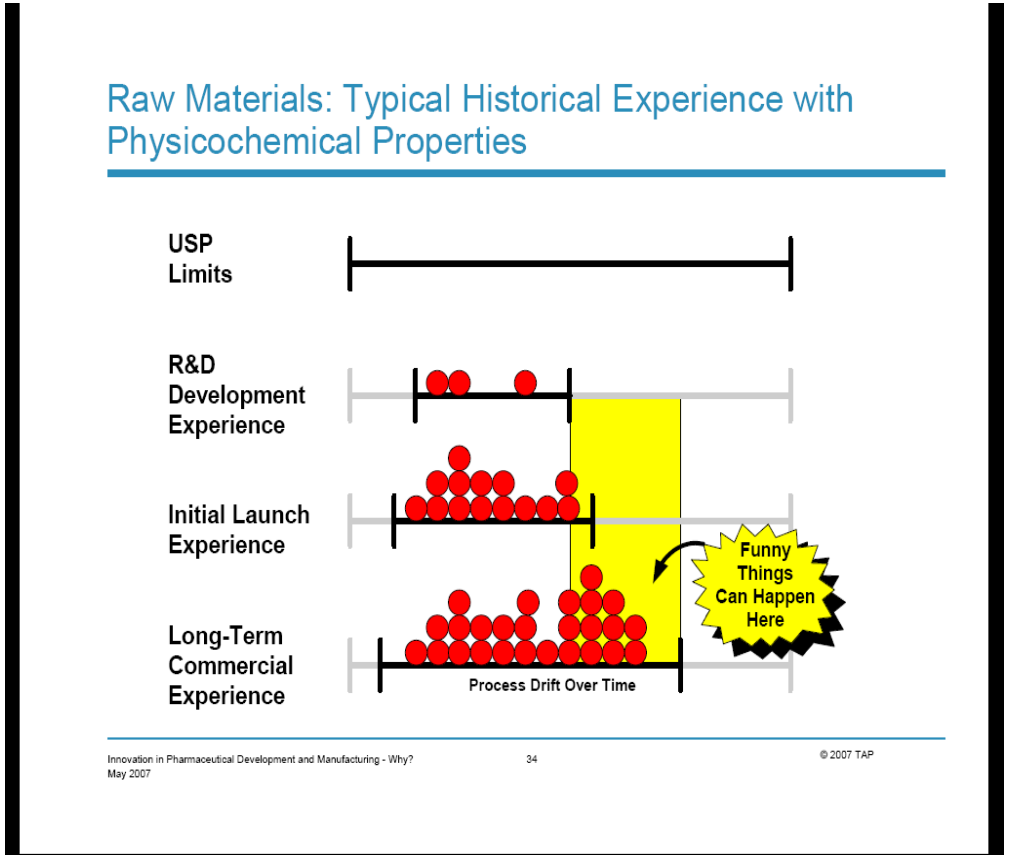
Expanded Body of Knowledge

Feed Forward

Feedback

Lifecycle Management

Change Management and Continual Improvement of the Product



[Jean-Marie Geoffroy, May, 2007]

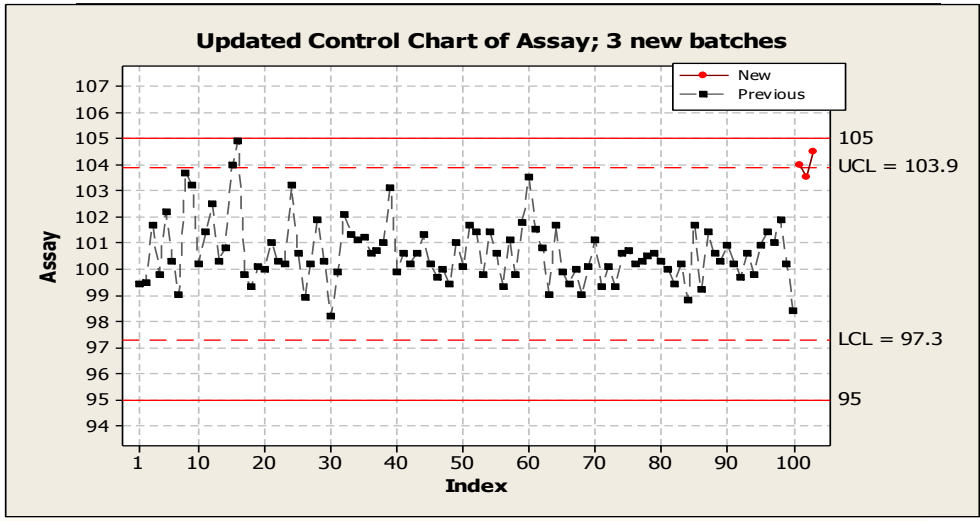
Raw Materials

- Can be one major source of process variation – even if within the agreed specification limits
- Commercial manufacturing experience will increase our understanding of such raw material batch to batch variation over time
- Case study example:
  - Magnesium Stearate Specific Surface Area

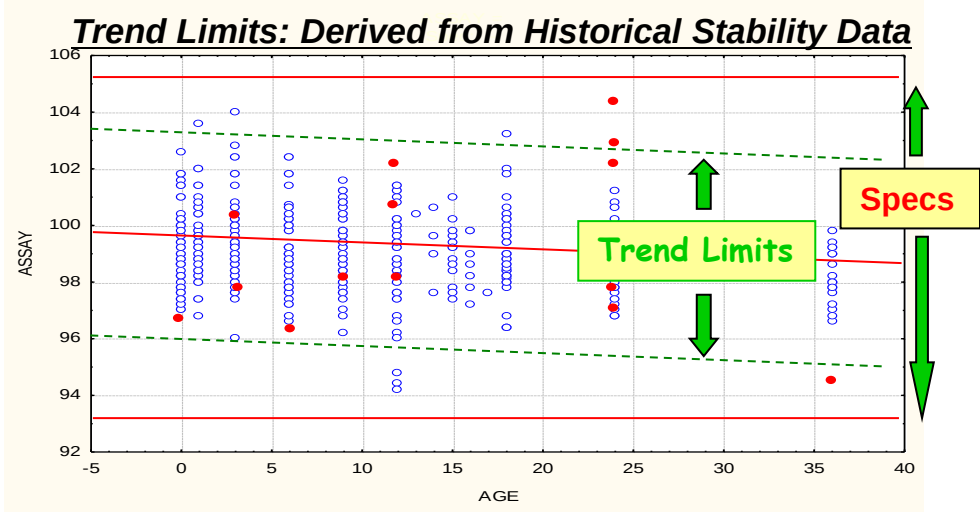
Continual Monitoring

- Process Tracking and Trending
  - Statistical Process Control
  - Address trends before they become problems
- Product Quality Monitoring
  - Analyze parameters & attributes in the control strategy
  - Reduce sources of variation

Control Limits: Derived from Historical Release Data



Trend Limits: Derived from Historical Stability Data



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- **Quality Unit (QA/QC) and Batch Release**

Quality Unit (QA/QC) and Batch Release

- The role of the Quality Unit does not change generally with respect to Batch Release just because of Design Space, Real Time Release Testing, etc.

- Will consider some specific aspects that the Quality Unit may need to consider as part of their role
  - e.g. Real Time Release Testing

Manufacturing Quality Unit Oversight

- Lifecycle Responsibility - Cross functional with commercial/R&D
- Modifications of site PQS to ensure alignment with enhanced development approach (e.g. design space, RTR testing)
- Key development information (knowledge) must be available to manufacturing sites (e.g. predictive models, design space)
- Continual Improvement in the Commercial part of the Lifecycle
- Maintenance and use of the Design Space and Control Strategy
- Use of Risk Management within the Quality System
- Clear traceability between CQA's, CPP's, specifications
  - Development  Production

Supplier and Outsourced Manufacturing Activities

- Increasing trend for industry to use outsourcing
  - Industry may outsource

…….but they can never outsource their responsibilities and and accountability!

- Company PQS must ensure appropriate control of:
  - Suppliers
    - Active Pharmaceutical Ingredients, Excipients
    - Other GxP related materials (e.g. cleaning materials)
  - Third party contractors
    - Manufacturing, Packaging, Distribution, Transportation
- PQS must consider selection and assessment, responsibilities, communication, ongoing monitoring, reviewing performance, and verifying supply chain

Real Time Release Testing versus QC Testing

- Need to ensure the same degree of confidence in the Real Time release testing as 'traditional' Quality Control laboratory testing, for example:
  - Responsibilities clearly defined
    - Routine maintenance and calibration (e.g. NIR)
    - Reporting deviations
  - Qualification and Validation
    - Qualification of test equipment (e.g. NIR)
    - Validation of analytical testing method
    - Validation of any data handling software and summary reporting (e.g. statistical software)

RTR Testing: Batch Release Considerations

- In line with marketing authorisation requirements?
- Sample sizes?
- Samples taken how frequently?
- Samples representative of the process? (e.g. tablet weight from each compression head)
- Data statistically analysed and reported correctly?
- What constitutes an RTR testing deviation (e.g. testing equipment failure), and how will it be handled under the quality system?

Conclusions

- **Scale up and Technology Transfer**
  - Scale-up of manufacturing processes and controls must confirm and support final design space
  - Proof of concept and adaptation of Control Strategy for commercial applicability
- **Process validation**
  - Over the lifecycle rather than a one time event
  - Confirms predictive models at full scale
  - Incorporates QRM Principles and Knowledge Management
  - Part of PQS at commercial manufacturing site

Conclusions (continued)

- **Change Management**
  - Need to consider development information
  - Changes within the design space can be managed internally without prior regulatory notification
  - Changes to Non-Critical process parameters can be managed internally without prior regulatory notification

- **Continual Improvement of the product**
  - Proactive use of trended data
  - Feed expanded knowledge back to Development

Conclusions (continued)

- **Quality Unit and Batch Release**
  - Use of Risk Management within the Quality System
  - Lifecycle responsibility with Cross functional alignment with commercial/R&D
  - Ensure alignment of the site PQS with enhanced development approach (continual improvement of the PQS itself)
  - Maintenance and use of the Design Space and Control Strategy, and predictive models

Key elements for manufacturing

Implementation of an enhanced development approach in a PQS should consider especially

- Scale up and Technology Transfer
- Process validation
- Change Management
- Continual Improvement
- Quality Unit and Batch Release