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

ICH

Disclaimer

The information within this presentation is based on the ICH Q-IWG members expertise and experience, and represents the views of the ICH Q-IWG members for the purposes of a training workshop.

ICH

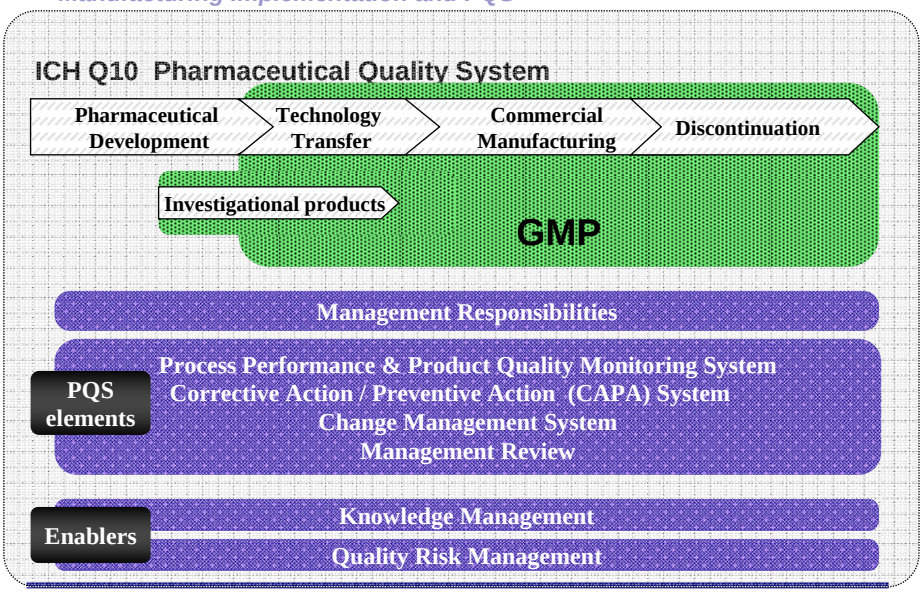
Introduction

- 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

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



- Pharmaceutical Quality System
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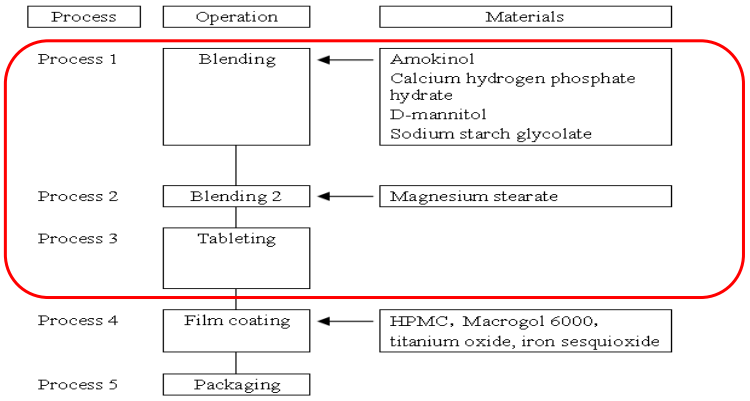
Scale up and Technology Transfer

- 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



Focus of Story

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

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

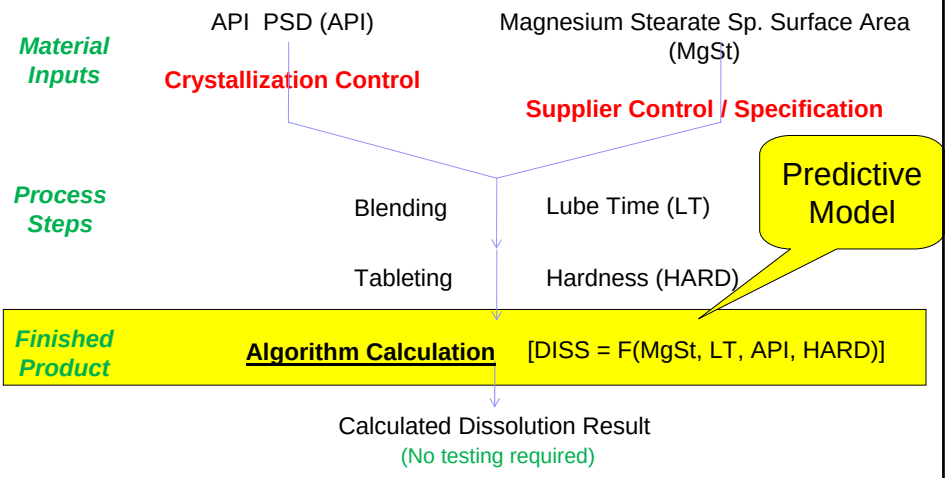
- Predictive Models proposed and utilized during Development phase
- Laboratory testing for dissolution and compressed tablet CU is performed:
  - During Tech Transfer to evaluate and confirm predictive Model at pilot and commercial scale at site of manufacture
  - Confirmatory Laboratory testing for 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**

- Pharmaceutical Quality System
- Scale-up and Technology Transfer
- **Process Validation**
- Change Management and Continual Improvement
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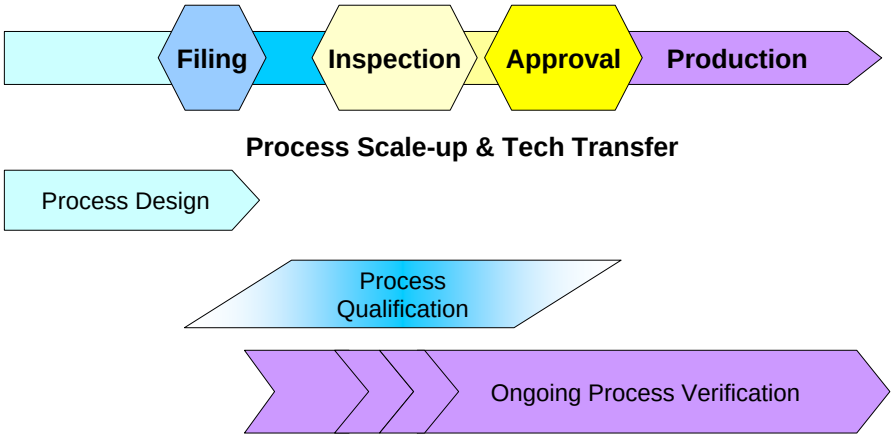
Process Validation

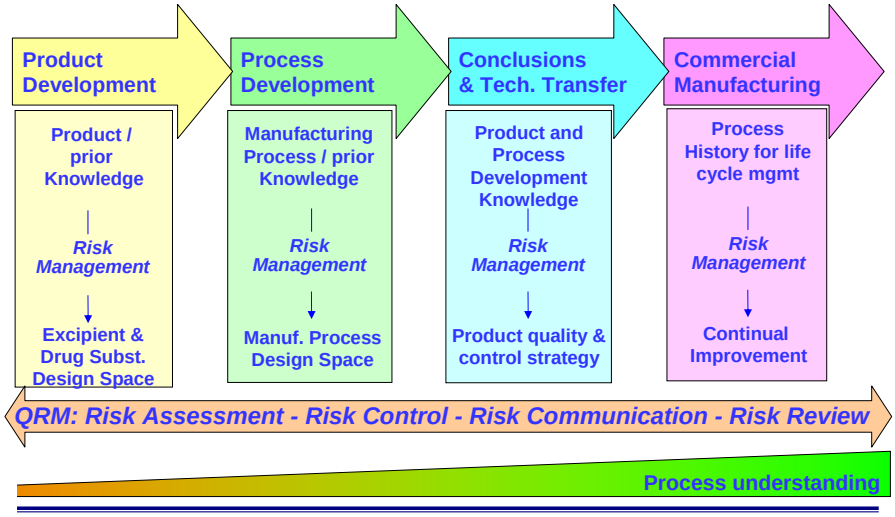
- Helps to build confidence in the product and process

- 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.

- Pharmaceutical Quality System
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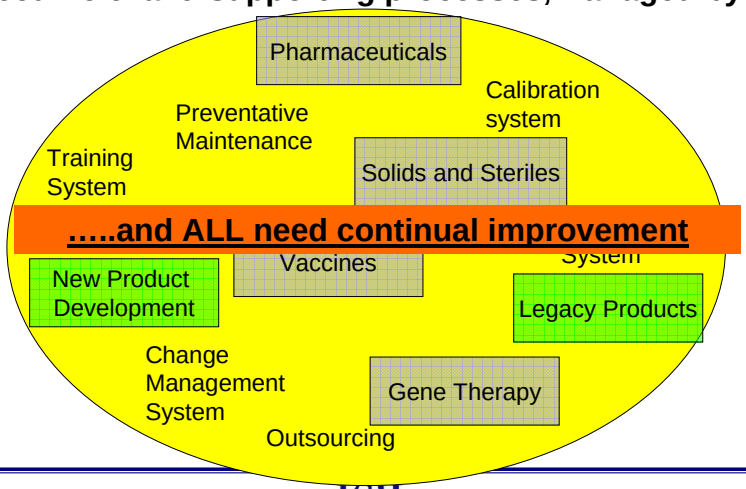
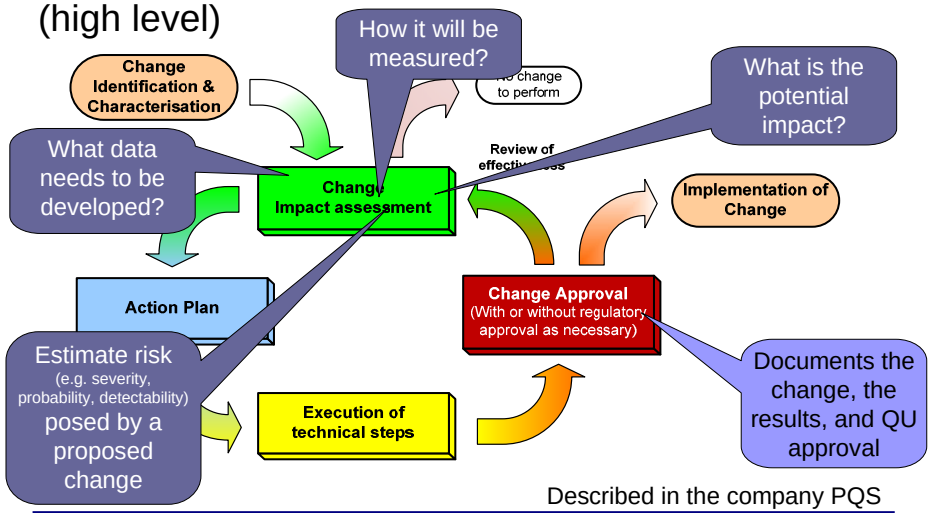
Change Management and Continual Improvement

- 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

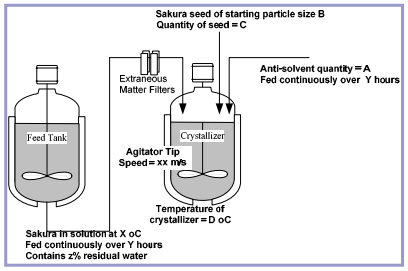


Typical Change Management Process Map (high level)



Described in the company PQS

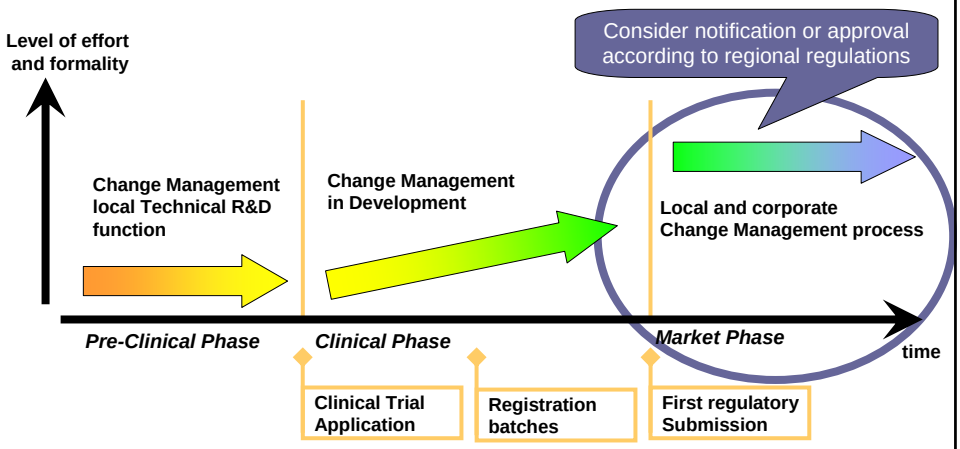
Change Management



- **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

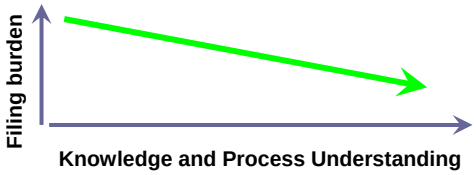
- **Verification by Quality Management**
  - Consider Technical Regulatory Filing
  - Link to Knowledge Management
    - Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components.
    - Sources 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

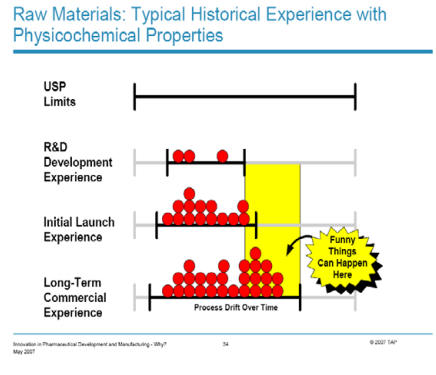
Expanded Body of Knowledge

Feed Forward

Feedback

Lifecycle Management

Change Management and Continual Improvement of the Product



[Jean-Marie Geoffroy, May, 2007]

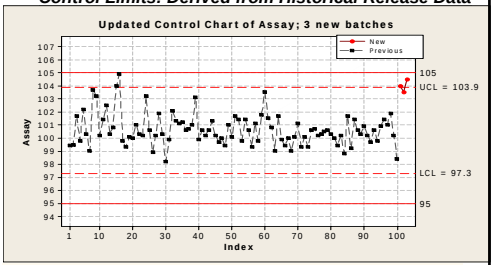
Raw Materials

- 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

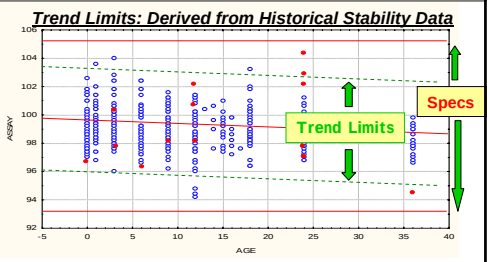
Continual Monitoring

- 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

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