Pharmaceutical Quality Systems (ICH Q10) Conference

A Practical Approach to Effective Lifecycle Implementation of Systems and Processes for Pharmaceutical Manufacturing

October 4-6, 2011 | Crystal Gateway Marriott | Arlington, Virginia
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Welcome

P6: A Regulatory Perspective on Knowledge Management and Quality Risk Management :

- European GMP Directives have always mandated that Pharmaceutical Companies should have a robust pharmaceutical assurance system and Regulators have long recognised the importance science-based risk management.

- ICH Q10 deliberately brings to the forefront the critical area of risk and knowledge management within the Pharmaceutical Quality System (PQS) and reinforces the importance in establishing and maintaining a companywide quality system. Understanding sources of variation and controlling these on a risk basis was recognized by Deming 50 years ago.

- In his presentation Mr Thrussell will discuss why regulators consider this so important and how use of robust risk and knowledge management can drive operational excellence and allows tangible quality-business synergies to be reaped by “learning organisations” that proactively seek out sources of variability through daily vigilance and take advantage of contemporary technological solutions to improve product quality.

- This presentation is based upon the slides used by Tara Gooen, Team Leader, Office of Compliance FDA/CDER Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality at the PQS Washington Conference.

P6: A Regulatory Perspective on Knowledge Management and Quality Risk Management

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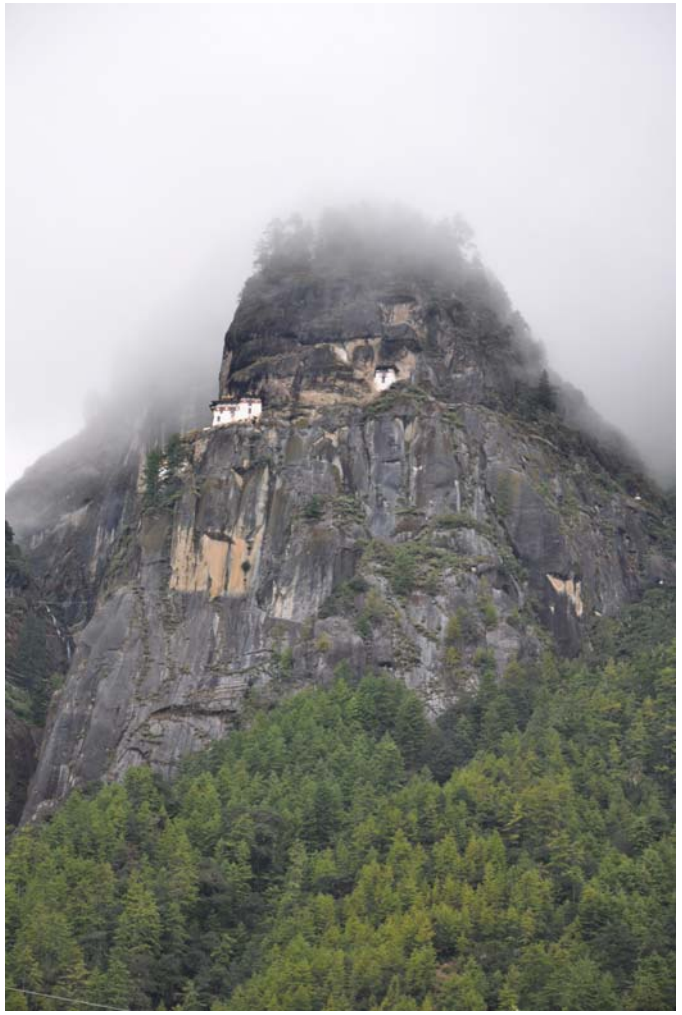
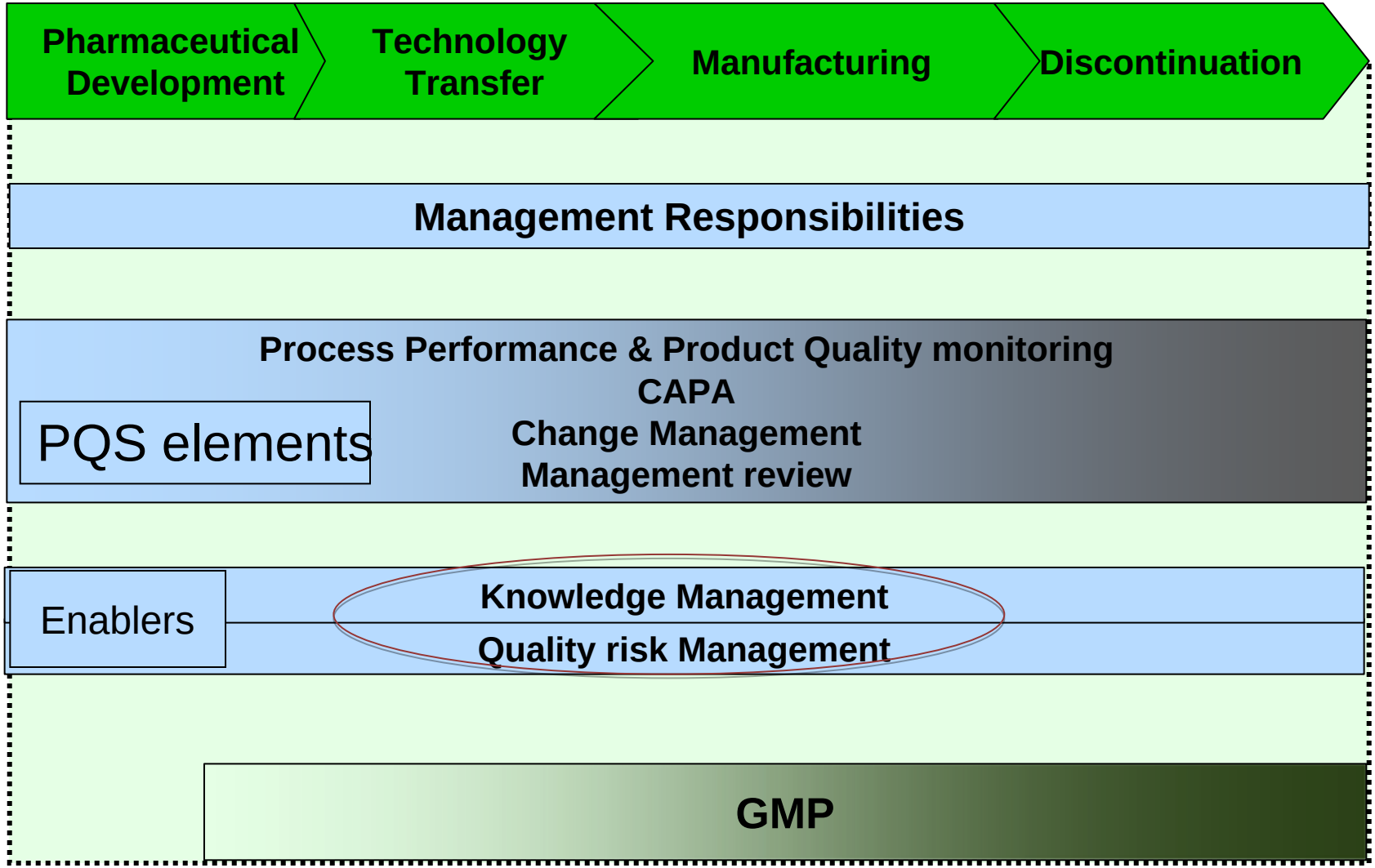
Information is not knowledge.
Let's not confuse the two.

- W. Edwards Deming

We are drowning in information but starved for knowledge.

- John Naisbitt




Pharmaceutical Development
Technology Transfer
Manufacturing
Discontinuation
Management Responsibilities
Process Performance & Product Quality monitoring
CAPA
Change Management
Management review
PQS elements
Enablers
Knowledge Management
Quality risk Management
GMP

- The "risk" concept not new: mentioned 90 times and in 20 different documents in EU GMP legislation and guidance

- Has always been part of operations, development, troubleshooting and investigations
  - What is new is more systematic approaches being used
  - More proactive use
  - More proportionate use

- Risk assessment and management tools are well described in ICH Q9
  - In terms of areas of applicability for the developer
  - AND for the regulator
    - Risk based assessment
    - Risk based inspection

- PIC/s Guidance to inspectors on the inspection of QRM

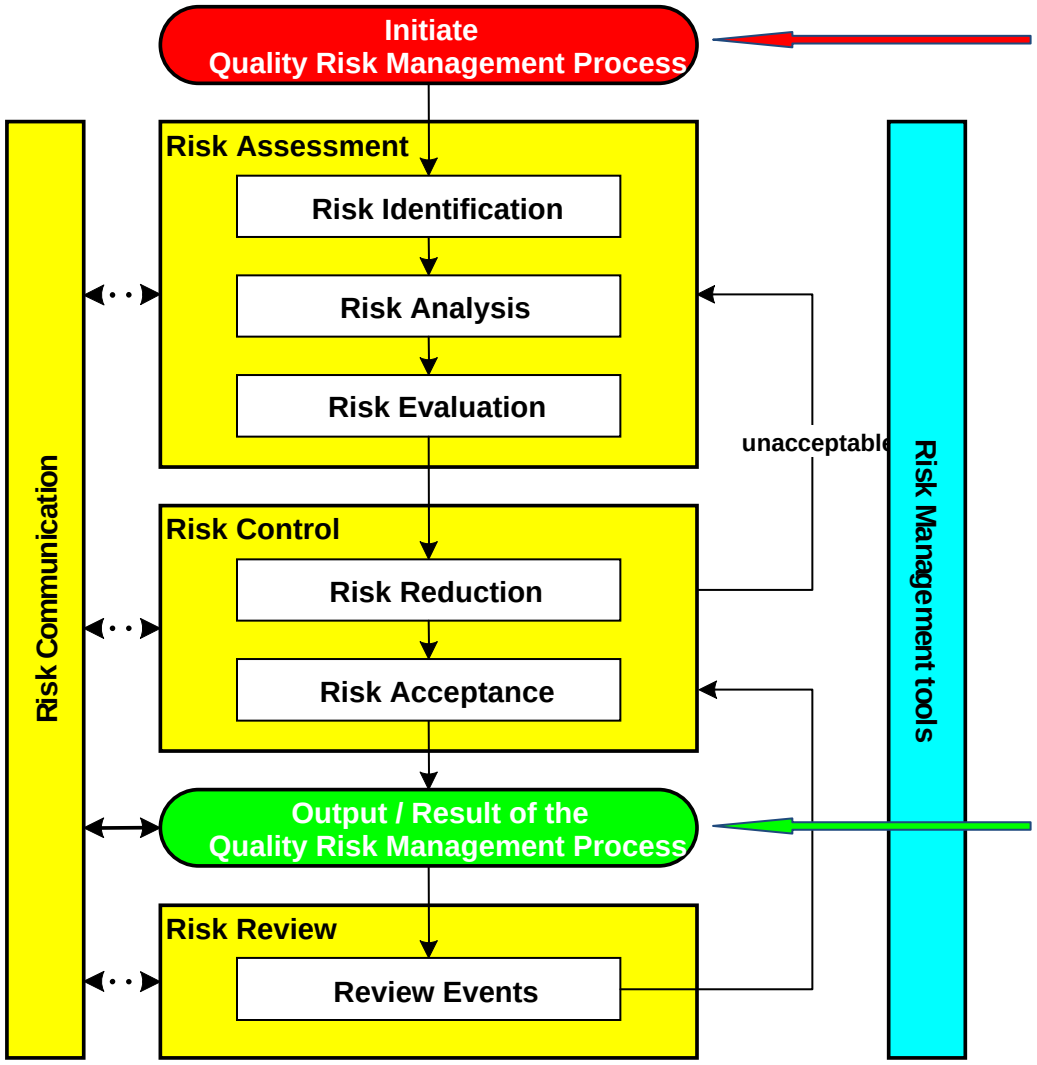
Risk management use in other areas by regulators

- medical devices: since early ’90s, e.g. ISO 14971 ‘Application of risk management to medical devices’
- pharmacovigilance: risk management plans – 3 to 153 pages, used to extend knowledge on safety or change warnings/dosage/excipients, withdraw from market
- inspection of source plasma sites for blood products

Regulatory changes – UK: Hampton Report

- 'Reducing administrative burdens: effective inspection and enforcement', March 2005
- Executive summary:

"Risk assessment should be comprehensive, and should be the basis for all regulators' enforcement programmes. Proper analysis of risk directs regulators' efforts at areas where it is most needed, and should enable them to reduce the administrative burden of regulation, while maintaining or even improving regulatory outcomes."



Define problem, assemble information, team and timeline

Choice of internal procedure or risk management tool - Q9 process (shown), FMEA, HACCP etc

Link to company's QS

QRM fundamentals – application

- A structured, scientific decision-making process about risks to product quality - and therefore to patients
- Common language and processes
- Across all stages of product lifecycle

- However …. formality is not always necessary:
  - practical knowledge and internal procedures (e.g. SOPs) will be appropriate
  - define level where formal (QRM) or other processes apply
  - “horses for courses”

- Development
  - Quality Risk Management & Knowledge Management
- Tech Transfer
  - Quality Risk Management & Knowledge Management
- Manufacturing
  - Quality Risk Management & Knowledge Management
  - Continual Improvement

…a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components

…a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle

ICH Q10, Q9

- Development
  - Quality Risk Management & Knowledge Management
- Tech Transfer
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- Processes for pharmaceutical development (Q8 or equivalent) are key linkages to product realization within the Pharmaceutical Quality System

- Q8 provides for robust development and understanding that serves as the basis for continual improvement

- Product
- Manufacturing Process
- Equipment
- Facility
- Utilities
- Raw Materials
- Containers
- Transport
- Manufacturing Yield
- Batch Reject Rates

So when things start to go wrong what has happened?

- Management processes have failed!
  - Risk identification may have failed!
  - Identification of emerging or changing risk may have failed
  - Communication of the risk or changing risk has failed!
  - Investment in systematic risk and quality management has failed!
  - Inadequate knowledge or a failure to leverage existing knowledge!

Knowledge management and the communication of the risk or changing risk has almost certainly failed!

- Development
  - Quality Risk Management & Knowledge Management
- **Tech Transfer**
  - **Quality Risk Management & Knowledge Management**
- Manufacturing
  - Quality Risk Management & Knowledge Management
  - Continual Improvement

- "To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes."

- "A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas

ICH Q10

Building knowledge…

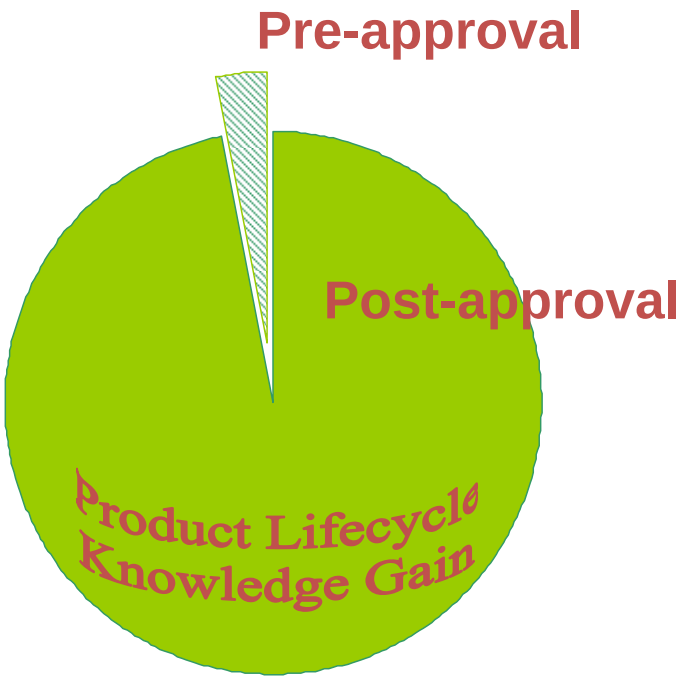
Development

"Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy."

ICH Q10 – Technology Transfer

Building Knowledge…
Monitoring and Adaptation

- Process performance and product quality monitoring systems for each product
- Management review of process performance and product quality
- *Corrective action* and *preventive action* (CAPA) system
- Change management system



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CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

- PQS Elements
  - Monitoring
  - Corrective/Preventive Actions
  - Change Management
  - Management Review

Managing Knowledge: Out of Specification, deviations and process failures

OOS results may indicate a flaw in product or process design

- Lack of robustness in product formulation
- Inadequate raw material characterization or control
- Substantial variation introduced by one or more unit operations of the manufacturing process
- Combination of these factors

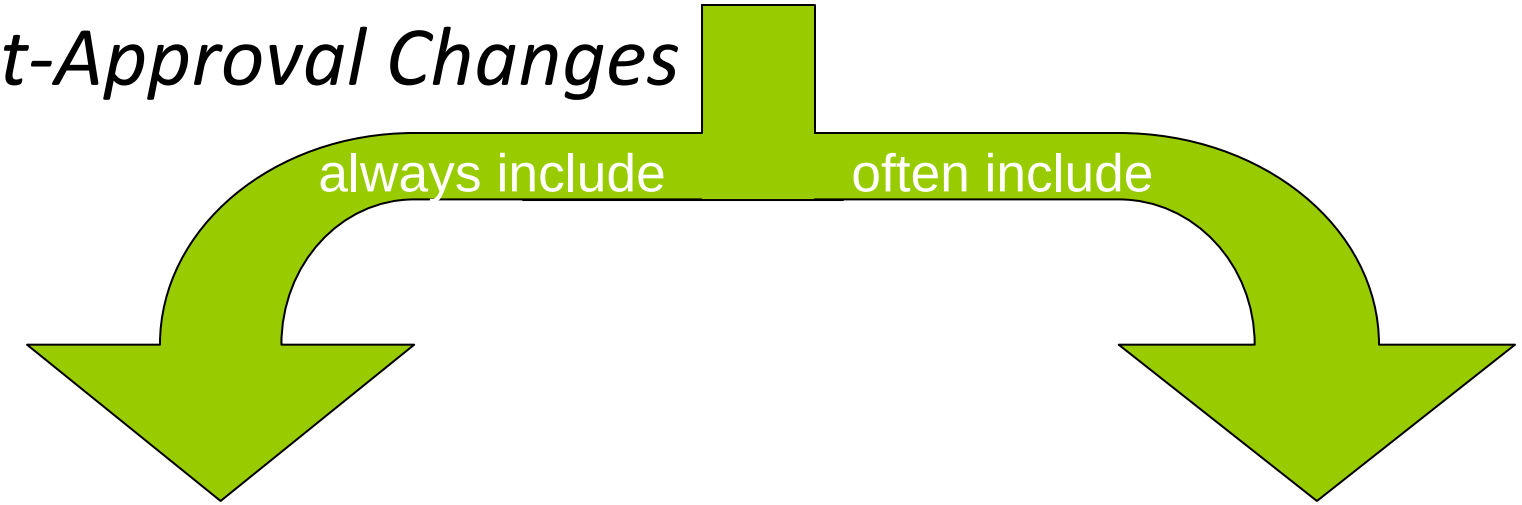
In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality

FDA Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (Oct 2006)

Importance of root cause investigations and risk management

Managing Knowledge…

Post-Approval Changes



On-Site CGMP Oversight

- Change control system
- Authority inspection of quality system, including the change control system

Filed CMC Submission

- Vartiations and notifications
- PAS
- CBE
- AR
- Special report (immediate notification)

- Enablers of a Pharmaceutical Quality System:
  - Quality Risk Management
    - Knowledge and understanding of product, process and materials
    - Design of facilities, equipment and processes
  - Knowledge Management
    - Proactive, rather than reactive
    - Based on modern manufacturing and control science

- Knowledge Should Be:
  - Managed, rather than merely gathered
  - Evaluated by management
  - Managed to facilitate continual improvement

Knowledge is no guarantee of good behavior, but ignorance is a virtual guarantee of bad behavior.

Martha Nussbaum