What Quality Systems mean to Regulators and how Regulators expect Management to oversee the System

Synopsis:

- European GMP Directives have always mandated that Pharmaceutical Companies should have a robust pharmaceutical assurance system and Regulators have long recognised the importance of there being companywide quality culture and an effective PQS assuring a state of control and driving improvement. ICH Q10 builds upon this philosophy by giving clear guidance on the elements and enablers of a robust QMS benefiting Industry and consumers when underpinned by science-based risk management throughout the lifecycle.

- ICH Q10 deliberately brings to the forefront the critical area of management responsibility within a Pharmaceutical Quality System (PQS) and reinforces the importance of senior management in establishing and maintaining a companywide quality culture and an effective PQS that assures a state of control and drives improvement. Deming recognized this 50 years ago, and it subsequently became a key part of the ISO 9000 series of Quality Management standards and more recently is reflected in Q10.

- In his presentation Mr Thrussell discusses why regulators consider this so important and how a strong Quality System protects patients but also drives 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.

What the QS means to Regulators and how Management should oversee the system

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Objectives of this Presentation

To illustrate why regulators look for an effective QS during their interactions with companies and

To provide an insight as to how inspectors look at the management responsibility in the context of the establishment and maintenance of a robust system

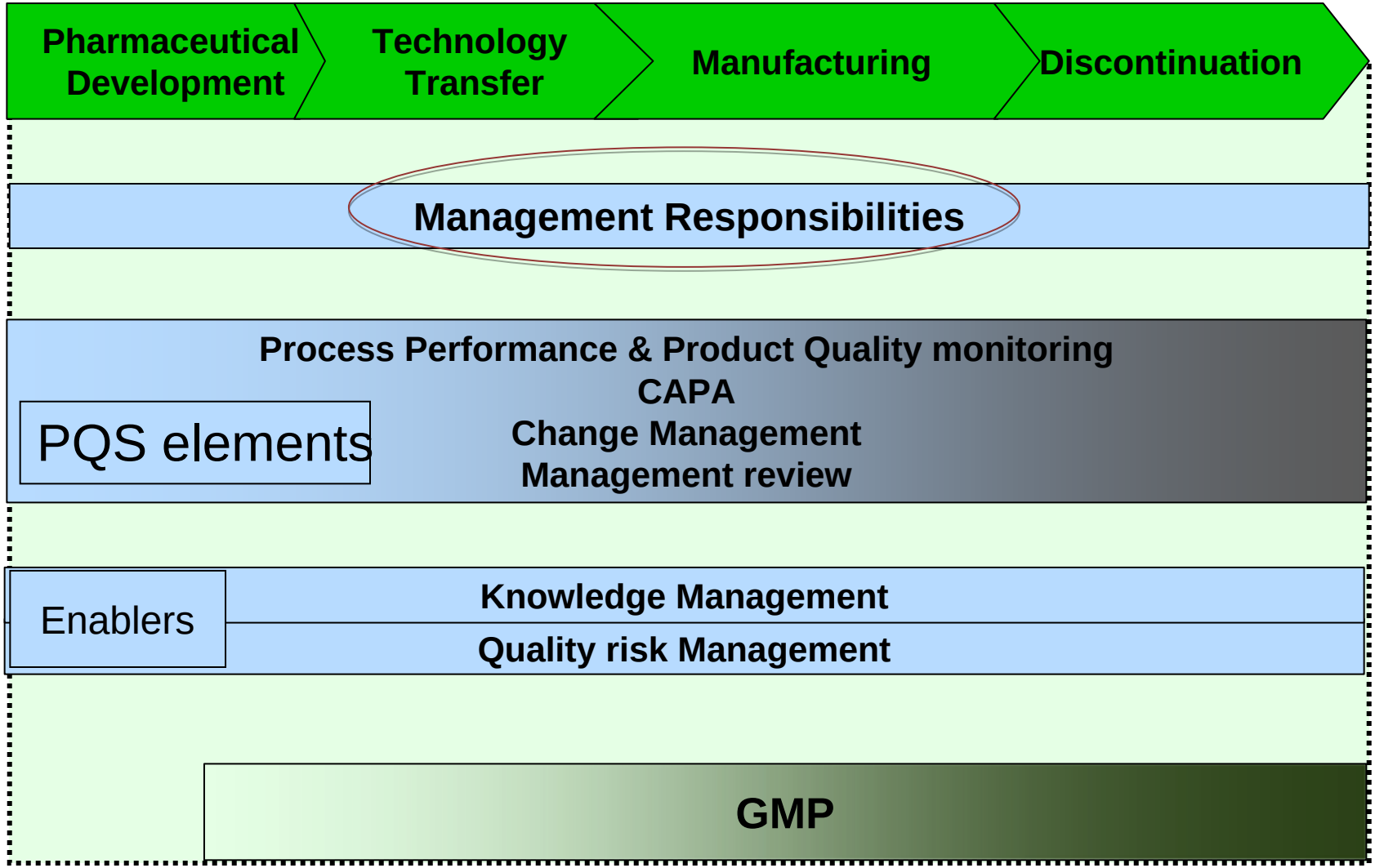
ICH Q10 (Management responsibility) … :

‘Leadership is essential to establish and maintain a companywide commitment to quality and for the performance of the pharmaceutical quality system’

ICH Q10 Management commitment(2.1)

- Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives and that the roles, responsibilities, and authorities are defined, communicated and implemented throughout the company

……*The concept of corporate governance*


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

GMP: assuring the consistency of quality

- Since the establishment of GMP the prime objectives set out in EU directives and guidance has been to:
  - Ensure that products are manufactured batch upon batch, year upon year, to the appropriate and consistent quality standards and in accordance with regulatory requirements by requiring that there be a pharmaceutical quality system.
    - HAVING A QMS IS NOT NEW!
  - Require Marketing Authorisation holders to regularly review their products and their manufacturing processes to ensure that they keep up to date with scientific and technological progress
    - CONTINUAL IMPROVEMENT HAS ALWAYS BEEN A REQUIREMENT!

Current regulatory view of quality management

- an effective QS is already mandated by EU GMPs and most of the accepted common elements of an effective QS are already required by EU GMP
- inspections have always included an assessment of company QSs
- It has always been recognised that the Quality Culture of a company and the robustness of its QMS was important
- "risk" concept not new: mentioned 90 times and in 20 different documents in EU GMP legislation and guidance
- "unless otherwise justified" concept frequently used in both GMP and quality guidelines

But not necessarily a lifecycle approach and some elements not adequately emphasised

MHRA GMP Inspections: April – December 2010

- Critical deficiencies
  15
- Major deficiencies
  510
- Serious deficiencies per inspection
  2.26

- Top 10 categories:
  - Investigation of anomalies
  - Quality management
  - Change control
  - Validation master plan
  - Corrective/preventive action
  - Complaints and product recall
  - Documentation
  - Equipment validation
  - Product quality review
  - Out-of-specification investigations

Why do inspectors already look at an organisation's QMS and QRM programmes during inspections?

- ***Looking at how companies react when things go wrong or are changing and are under pressure is a major diagnostic indicator of the robustness of the scientific and organisational integrity of a company's operations***
  - Do they investigate to improve knowledge or simply build arguments for release of product
  - Quality of investigations- appropriateness of depth of investigation
  - Reactive rather than proactive usage of knowledge
  - Quality is everyone's responsibility – Is this true when things go wrong?
  - Is the company a learning organisation? And where is it on the learning curve?

Quality management finding - Investigations

- The quality of investigations performed, with particular reference to complaints, rejects, deviations and out-of-specification data, was not of the required standard to consistently identify the root cause of the issue and suitable CAPAs, including a robust assessment of the impact of the findings on other batches or systems

- Risk assessment and categorisation were weak with the lowest impact risk appearing to be selected for every investigation. The change control system was not used despite a number of significant changes having taken place (e.g. new isolator)

Investigation of anomalies

- Investigations often lacked detail and adequate consideration of related issues, for example:
  - investigation (XXX) lacked adequate justification for invalidation of the original corrective action, and lacked consideration of training issues identified by subsequent investigations
  - investigation (XXX) did not adequately detail the events involved in a cleaning sampling failure and did not sufficiently support the assumption was invalid
  - out of trend into a cleaning conductivity sample failure did not lead to a full investigation into the CIP process, even though it was decided to re-run the CIP cycle

Investigation of anomalies

- There had been no deviations raised to formally investigate and record the impact on XXXXX vaccines identified as having been exposed to minus 5 degC in one of the recent ambient temperature shipping studies from USA product to the EEA

- A significant number of deviations had been recorded for errors in the packing record and label generation processes, yet there was no recognition of this trend and as a result there had been no concerted root cause analysis and CAPA identified

- Overall the investigation reports into deviations and OOS did not follow a logical process and lacked detail in the documentation of all the actions and justifications taken during the investigation

Quality management – change management

- Provisions for the management of change are insufficiently robust as exemplified by:
  - no change control was raised for the replacement of XXXX
  - no change control was raised for the replacement of the generator and the temporary provisions for sanitisation were not defined and agreed in the deviation report nor were temporary SOPs written
  - change control is not used as part of the artwork revision procedure
  - The introduction of the third shift was not recognised as a change within the change management process

Quality management finding - Audit and Reviews

- Control of the quality management system was deficient in that:
  - the PQR report did not review all of the items detailed in the procedure, e.g. technical agreements and equipment validation status
  - There was a lack of evidence that the results of the PQR had been effectively communicated to the QPs and senior management
  - Inadequate resources were not available to complete the review programme in a timely manner or to cover the scheduling and performance of self-inspection despite this being a commitment from the last inspection

Quality management – change management

- Change control ( ) for the change of material from X to Y did not include a detailed list of required actions before authorisation to use in commercial batches:
  - there was no statistical or other capability comparison between the two raw materials or the finished product produced from each
  - product X was manufactured and released to European markets before documented verification was received that there was no regulatory impact
- There were no data or justification to support the decision not to revalidate the process following the change

So why these observations today in 2011?

- We all know having a good QMS is logical !

- We all know that any company would be foolishly shortsighted not to be following the basic elements of a robust QMS such as are outlined in Q10 and other similar model systems

Inspectors know this, Regulatory Authorities know this, and Companies……

So when things start to go wrong what has happened?

- Management processes have failed!
  - Risk identification may have failed! Resources?????
  - Identification of emerging or changing risk may have failed
  - Communication of the risk or changing risk has failed!
  - Investment in 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!

……. And Senior Management has failed!

Important PQS Elements

- Systematic Process Performance and Product Quality Monitoring
  - A monitoring system to ensure a state of control is maintained
  - The monitoring system should use QRM
  - Identify sources of variation (Deming…….. 50s!!!!!!!)
  - Include feedback from internal and external sources
  - Provide knowledge to enhance process understanding
- CAPA methodologies should result in improvements and improved understanding and knowledge not just data!
- Change management NOT Change control!
- Management review of process and product performance and quality

Culture of reporting of anomalies and expecting improvement alongside compliance!

Perceptions of both the industry & its regulatory environment:

- Regulatory processes inflexible – Strict compliance focus. Post marketing change can be complex and time consuming - It's a big world!
- Risk averse compliance focus with non-science or non risk-based regulations and guidance – lack of risk appetite from both companies and the regulators.
- Pharmaceutical manufacturing is not fully utilizing modern manufacturing technologies and quality management.
- Toleration of the status quo, conservatism & innovation with improvement stifled and risk management not fully utilised. Approaches – fear of asking the regulators and yes, perhaps some regulators (individually and collective behaviour) not being as open as really necessary
- Tell only the minimum necessary and wait until you are asked mentality

So what are the likely discriminators and signs of the exercise of management responsibility?

Demonstrable signs of a true quality culture and quality leadership

- Price of non-conformance known and measured
- Processes mapped and well understood and monitored – metrics are understandable but challenging
- Tools such as lean and 6 sigma demonstrably in place
- The visual factory!
- Substantive Global Quality standards
- Robust escalation measures in place

So what are the likely discriminators and signs of the exercise of management responsibility?

Demonstrable signs of a true quality culture and quality leadership:

- Quality objectives from top to bottom of the organisation
- Quality council/networks/infrastructure
- Senior management the walk the talk
- A prospective openness in engagement with regulators as the organisation knows its issues and has plans to deal with them
- Excellence with humility and vision
- Adoption of targeted tools for better process understanding
- Not talking too much about quality and compliance! They understand what is the “right thing” and do it naturally so don’t have to worry about compliance!

SO WHAT DO WE NEED TO DO? …….Change cultures and manage to succeed!

- In the face of competing pressures - Senior management and management commitment to
  - Development and maintenance of the quality system
  - Provide the leadership needed for the successful functioning of the quality system
  - Adequate provision of resources - ensuring assigned authorities and responsibilities support production, quality, and management activities
  - Encourage internal communication on quality issues at all levels of the organization (QU, R&D, RA, manufacturing, etc.)
  - Ensure that there are Informed scientific decision-making processes with the participation of key components of the organization using product and process knowledge and risk management tools

Management Responsibilities

- Senior management commitment
- Development and maintenance of the quality system
- Provide the leadership needed for the successful functioning of the quality system
- Adequate provision of resources
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