ICH Q10
Pharmaceutical Quality System
- A GMP inspector’s perspective

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Presentation overview

• How does Q10 fit the new paradigm.

• Desired outcomes Q10 alone and Q8, Q9, Q10 together, for both Industry and the Regulator

• Overview of ICH Q10. Summary and content.

• Perceived benefits from implementing a Q10-like QMS

• Why is the Pharmaceutical Quality System of such interest to Inspectors?

• Current EU and National positions and initiatives

• Concerns and challenges to successful outcomes
Current regulatory and external environment

PWC report 2001

Low Process Capability in Manufacturing
- Low utilisation levels (15% in some cases)
- Scrap and rework at 5-10% is accepted
- Time to ‘effectiveness’ is not challenged
- Cost of Quality > 20%

‘You need to improve…..other high-tech industries have achieved enormous product gains in manufacturing in the last 25 years. We should expect nothing less from the Pharmaceutical Industry.’ Mark McLellan ex FDA Commissioner
Current regulatory and external environment

IBM report 2005 ‘The metamorphosis of manufacturing’

- On time supply 60-80%
- Right First Time 85-95%
- Process control level 1 to 2
- 2.5 sigma processes
- QbD and Continual Improvement controlled within an effective QMS could give 4.5 sigma processes with potential cost benefits of >$10 billion a year
Current regulatory and external environment

- Perceptions of both the industry & its regulatory environment:
  - Regulatory processes inflexible – Strict compliance focus
  - Innovation and improvement stifled
  - Risk averse compliance focus with non-science or non risk-based regulations and guidance – lack of risk appetite
  - Toleration of the status quo
  - Cost pressures for industry and regulators
    - Margins / resources reduced
    - Drive for better efficiency
    - Manufacturing expenses exceed R&D investment

- Pharmaceutical manufacturing is not fully utilizing modern manufacturing technologies and quality management approaches

- Pressures on both Regulators AND Companies for a change in approach
The vision. Systems that.....

- **Leverage knowledge** and encourage a preventive action culture, which ensures that actions are taken before a problem / issue arises.

- **Improve quality monitoring and review** (e.g. existing and PAT tools, data evaluation, statistical process control and process capability measurements), which form the basis for continual improvement of processes.

- Provide **greater assurance** that there is **no unintended consequence** as a result of continual improvement activities.

- Are **widely accepted** globally.
The ‘desired state’…………

‘A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight’

- Manufacturers have extensive product and process knowledge
- Manufacturers strive for continual improvement
- No manufacturing supplements needed
- The regulator’s role is verification and subsequent auditing of QS
- Adjust level of regulatory scrutiny commensurate with patient risk
- Use limited resources to focus on more important issues

FDA – Janet Woodcock et al
What’s the current regulatory and external environment that the Inspector works in?

GMPs are a widely accepted as being a critical element of an effective Pharmaceutical Quality System but:

Regional GMPs do not currently apply across the whole life cycle but:

- GMPs do provide guidance on manufacture and control of pharmaceutical products
- GMPs do provide guidance on most of the essential elements of a Quality Assurance System
- GMPs address CAPA but not proactive continual improvement
- GMPs touch on management responsibilities

GMPs do not fully address the systems needed to bring a quality product to market and fully manage post marketing change.

We do GMP – but what have we to learn from ISOs?
ICH Q10 Pharmaceutical Quality System

- Complements existing GMPs (GMP = not a full QS). QMS required by GMP do not cover the full life cycle. Links development and manufacturing through product lifecycle

- Facilitates application of ICH Q8, Q9

- Facilitates continual improvement in pharmaceutical manufacturing

- Is based on ISO 9000 structure with a pharmaceutical context emphasis on:
  - Management responsibilities
  - Improvement of QS
  - Improvement of Product Quality over Lifecycle

- Facilitates ‘appropriate regulatory scrutiny’
  - Post approval change & Inspections
Quality will be driven by science throughout the product life cycle.

Holistic use of knowledge generated during the development and manufacturing life cycle.

Quality Management System with decision making based on science and risk management principles.

Quality by Design

Continual Improvement

Product Life Cycle
ICH Q10 Content and structure

- Scope includes drug substance and drug product
- Uses familiar ISO terminology, structure and concepts as a starting point & provides a pharmaceutical context for the terms and elements
- Life cycle focus – starting in Development, during Technology Transfer and throughout Commercial Manufacture to Product Discontinuation
ICH Q10 Pharmaceutical Quality System

Pharmaceutical Development → Technology Transfer → Commercial Manufacturing → Product Discontinuation

Investigational products

GMP

Management Responsibilities

Process Performance & Product Quality Monitoring System
Corrective Action & Preventive Action (CAPA) System
Change Management System
Management Review

PQS elements

Knowledge Management
Quality Risk Management

Enablers
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

• Encourage internal communication on quality issues at all levels of the organization (QU, R&D, RA, manufacturing, etc.)

• Ensure assigned authorities and responsibilities support production, quality, and management activities

• Ensure that there is Informed decision-making processes with the participation of key components or the organization using product and process knowledge and risk management tools
How will Q10 be used?

• As a model for an effective QMS
  • Doesn’t it make excellent good sense anyway. Might then Inspectors be looking for a system like Q10

• Demonstrate an effective quality system to regulatory authorities – most frequently during inspections

• A Q10 site would be considered lower risk as it would have effective systems in place to:
  - Identify what is critical to quality
  - Establish appropriate controls
  - Assess and mitigate the risk of quality failures
  - Implement continual improvement changes to avoid future failure
  - Have robust systems for oversight and re-evaluation

• The intensity of regulatory oversight should be commensurate with the level of risk from degree of product & process understanding, QRM and PQS present
  - Post-approval changes
  - Inspection depth and frequency
### how might industry and regulators use Q 10 with Q8 & Q9?

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<tr>
<th>Scenario</th>
<th>Potential Opportunity</th>
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<tr>
<td><strong>1. Comply with GMPs</strong></td>
<td>Compliance – status quo</td>
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<td><strong>2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g. ICH Q9 and ICH Q10).</strong></td>
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ICH Q10 Benefit potential (General)

- Demonstrates industry and regulatory commitment to robust quality systems and technical innovation and enhance assurance of consistent availability of medicines around the world.
- Harmonizes the concept of pharmaceutical quality systems for industry between the three regions
- Enables the potential benefits from ICH Q guidelines for industry and regulators
- Encourages industry to improve manufacturing processes thus reducing undesired variability and leading to a more consistent product quality, improved process robustness and more efficiency
ICH Q10 Benefit potential for product quality & GMP

- Facilitates innovation and continual improvement throughout the whole product life cycle
- Provides the link between development and manufacturing to ensure systems are in place for knowledge management
- Helps to ensure and give confidence that the correct decisions are made by industry to manage changes, both within and outside the design space
- Facilitates strong management leadership & commitment to quality
- Encourages a science- and risk-based approach to quality decisions
Q10 Potential Benefits to product quality & GMP

- Encourages a preventive action culture, which ensures actions are taken before a problem / issue arises

- Driver for improvement quality monitoring and review (e.g. data evaluation, statistical process control and process capability measurements), which form the basis for better product knowledge and continual improvement of processes

- Ultimately providing greater assurance there is no unintended consequence as a result of continual improvement activities
Q10 Potential Benefits (Cost Benefits)

- Improved process performance
  - A reduction in the costs of internal failures (rejects, reworks, reprocessing and investigations) as the quality systems guideline drives improvement
  - A reduction in the costs of holding duplicate stock and operating multiple processes as improvements and changes are made more effectively across all regions
  - A reduction in the costs of preparing / reviewing certain regulatory submissions
What would success look like?

- Industry would be able to operate effectively globally with decreased complexity within the supply chain

- We would have a more 'flexible’ regulatory environment encompassing small and large molecules

- Mutual acceptance of technical and compliance standards

- Demonstrable successes from global submissions
  - Both NCE and biotech

- An ability to effect continual improvement, new technologies, new approaches - in an empowered way
Why do EU inspectors already look at an organisation’s QMS and QRM programmes during inspections?

• *Looking at how companies react when things go wrong 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
- Quality is everyone’s responsibility – Is this true when things go wrong?
EU Position

- Many of the principles expressed in ICH Q8, Q9 and Q10 are not new but have a new look & now have stabilised definitions between the 3 ICH regions
- EU MA application procedures have always allowed for a company to demonstrate its knowledge and process for a product’s development
- An effective QMS is already mandated by EU GMPs and most of the accepted common elements of an effective Q10 like QS are already required by EU GMP.
- Risk management is implicit in the current GMP guide has but been made more explicit with the recently added text to Chapter 1.
- Assessments & inspections conducted into company risk assessments, QSs for many years but looking at QRM processes is newer.
- What is however new is the life cycle approach and it is clear that parts of EU GMP are always not well aligned with Q10

EU GMP guide needs to be updated to better harmonise principles that are already mandatory. Q10 will be integrated as a new annex. But we must NOT loose what has served well for many years

Work has already commenced to look at Chapter 1, 2 & 7 to identify proposed changes.
Regulatory changes – EU: Variations Regulations

• “Better regulation of pharmaceuticals: towards a simpler, clearer and more flexible framework on variations”
  - focus on the changes having a genuine impact on quality and further reduce the overall number of variations
  - regulatory action classified according to relative risk
  - applies to Community and National Licences
  - design space optional but encouraged
  - continuous improvement encouraged
  - Type 1A - do and tell procedures: annual reporting or immediate notification (admin procedures)
  - Type 1B by default
Challenges and opportunities

- How do we achieve harmonised understanding, and then implementation across the regions?

- What does this all mean for those other than big pharma?
  - These are most of our inspections?

- Trust and culture change:
  - Clear understanding of stakeholders needs and options
  - Trust and openness in working and learning together
  - Culture change:
    - Overcome internal conservatism and ‘silo’ thinking
    - Organisational change management – resistance to change, new competencies needed

- New ways of working particularly with assessors. In the EU the locus of some work will shift but what, how much and when?

- Working with other GMP Inspectorates – e.g. pilot API programme
**Desired goal – similar outcomes of inspections**

- How will inspections in the new paradigm differ from inspections where products are developed and manufactured using traditional approaches?

- What will an inspection look like in a Q8, 9 and 10 environment?

- Why and how to demonstrate implementation of Q10?

- How to verify compliance with Q10 in the product lifecycle? Will there be Q10 certification? Must it be applied to the global organisation?

- Inspectional expectations at the different steps of the product lifecycle, especially with regard to development activities
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Abbreviations

- QRM: Quality Risk Management
- Q8: ICH draft guideline - Pharmaceutical Development, Quality by Design
- Q9 ICH draft guideline - QRM
- Q10 ICH draft guideline - pharmaceutical quality system
- QS Quality Systems
- CAPA Corrective and preventive action
- EM Environmental monitoring
- IMP Investigational Medicinal Product
- PSF Product Specification File
- CTA Clinical Trial Authorisation
- MAA Marketing Authorisation Application