WCC PDA Dinner Meeting Jan 2012

ICH Q10 - Pharmaceutical Quality System

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Your Presenter

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- 30+ years Pharma experience
- Manufacture, Quality, Supply
- Senior Global Roles
- EU Industry Topic Lead ICH Q10 EWG

Discussion Topics

- Why do we need a 'modern effective PQS'?
- Where are we currently?
- Q10 Key elements
- Regulators Views
- Implementation
- Q&A

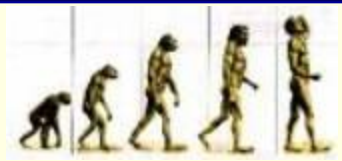
Why do we need a 'Modern Effective PQS'?

- Good business practice!
- Significant changes in external business environment
  - Fewer new products/'blockbusters'
  - Reduced margins/greater competition/low-cost sources
  - Focus on efficient, effective organizations, lean processes
  - Global Economy
- Pharmaceutical industry is still way behind other industries in Quality Management philosophies/practices
  - Marketed products ARE safe and efficacious
  - BUT costs of quality are high
  - Often reactive, not designed-in/preventative

Why do we need a 'Modern Effective PQS'?

- Historically innovation and improvement are constrained
  - Inflexible regulatory environment
  - Focus on Compliance, not Science and Risk-Based approach
  - Industry margins didn't provide drive for change
- GMPs do not provide a 'full modern' Quality System
  - Originated in 1970s – only incrementally added to
  - ISO Quality Management thinking not embedded
  - Need to be complemented

Where are we Currently?



- Evolution of regional GMPs 1970s -
- Evolution of ISO 9000 approaches 1980s -
- FDA 21st Century initiative 2002 -
- ICH Quality Vision / Q8, Q9, Q10 2003 -
- FDA Quality Systems guide 2006 -
- ICH Q10 Pharmaceutical Quality System 2008
- Q10 Implementation journey.....

What is the Purpose of Q10?

- ICH Q10 aims to promote a paradigm shift from discrete GMP compliance procedures at each stage of the product lifecycle to a comprehensive quality systems approach over the lifecycle of the product

ICH Q10 - Pharmaceutical Quality System

- The objective is to:
  - Achieve product realisation
  - Establish and maintain a state of control
  - Facilitate continual improvement

Q10 - Structure

1. Pharmaceutical Quality System
2. Management Responsibility
3. Continual Improvement of Process Performance and Product Quality
4. Continual Improvement of the PQS
5. Annexes
    1. Potential opportunities to enhance Science and Risk Based Regulatory Approaches
    2. Q10 Model Diagram

ICH Q10 - Pharmaceutical Quality System

Implementation of Q10 should facilitate:

- Innovation and continual improvement throughout the product lifecycle; and
- Strengthen the link between pharmaceutical development and manufacturing organisations

Q10 - Scope

- Applies to systems supporting the development and manufacture of pharmaceutical drug substances (API) and drug products, including biotechnology and biological products, throughout the product lifecycle
- Both newly developed and existing products fall within the scope
- Apply in a manner appropriate and proportionate to the stage of lifecycle

Q10 and Regional GMPs

Q10 will:

- Augment existing GMPs with specific PQS elements and management responsibilities
- Encourage science and risk based approaches
- Be used together with existing GMPs
- Cover all stages of the product lifecycle as defined (beyond GMPs)

Q10 and Regulatory Approaches

- Regulatory approaches for a specific product or manufacturing facility should be commensurate with:
  - The level of product and process understanding
  - The results of quality risk management
  - The effectiveness of the PQS

Q10 - Enablers

- The enablers provide the means for science and risk based decisions related to product quality through the lifecycle
- Knowledge Management
  - Manage knowledge from development through commercialisation to discontinuation
- Quality Risk Management (Q9)
  - Proactive approach to managing risks to quality

Q10 Pharmaceutical Quality System (PQS)

- Design and Content considerations are:
  - PQS should be well structured and clear / consider complexity of organisation
  - The elements of ICH Q10 should be applied in a manner that is proportionate to each of the product lifecycle stages
  - Outsourced activities / purchased materials should be within the scope of the PQS
  - Management responsibilities should be identified
  - The PQS should include process performance and product quality monitoring, corrective and preventive action, change management and management review
  - Performance indicators should be identified and used to monitor the effectiveness of the PQS

Q10 - Quality Manual

- A Quality Manual (or equivalent) should be established and should contain the description of the pharmaceutical quality system; including:
  - The quality policy
  - The scope of the pharmaceutical quality system
  - Identification of the processes within the PQS, as well as their sequences, linkages and interdependencies
  - Management responsibilities within the PQS

So What are the Key Elements?

- GMPs
- Management Responsibility
- Continual Improvement
  - Products and Processes
  - PQS itself
- Quality Risk Management
- Knowledge Management
- Lifecycle approach
- Opportunities for science-based and risk-based regulatory approaches

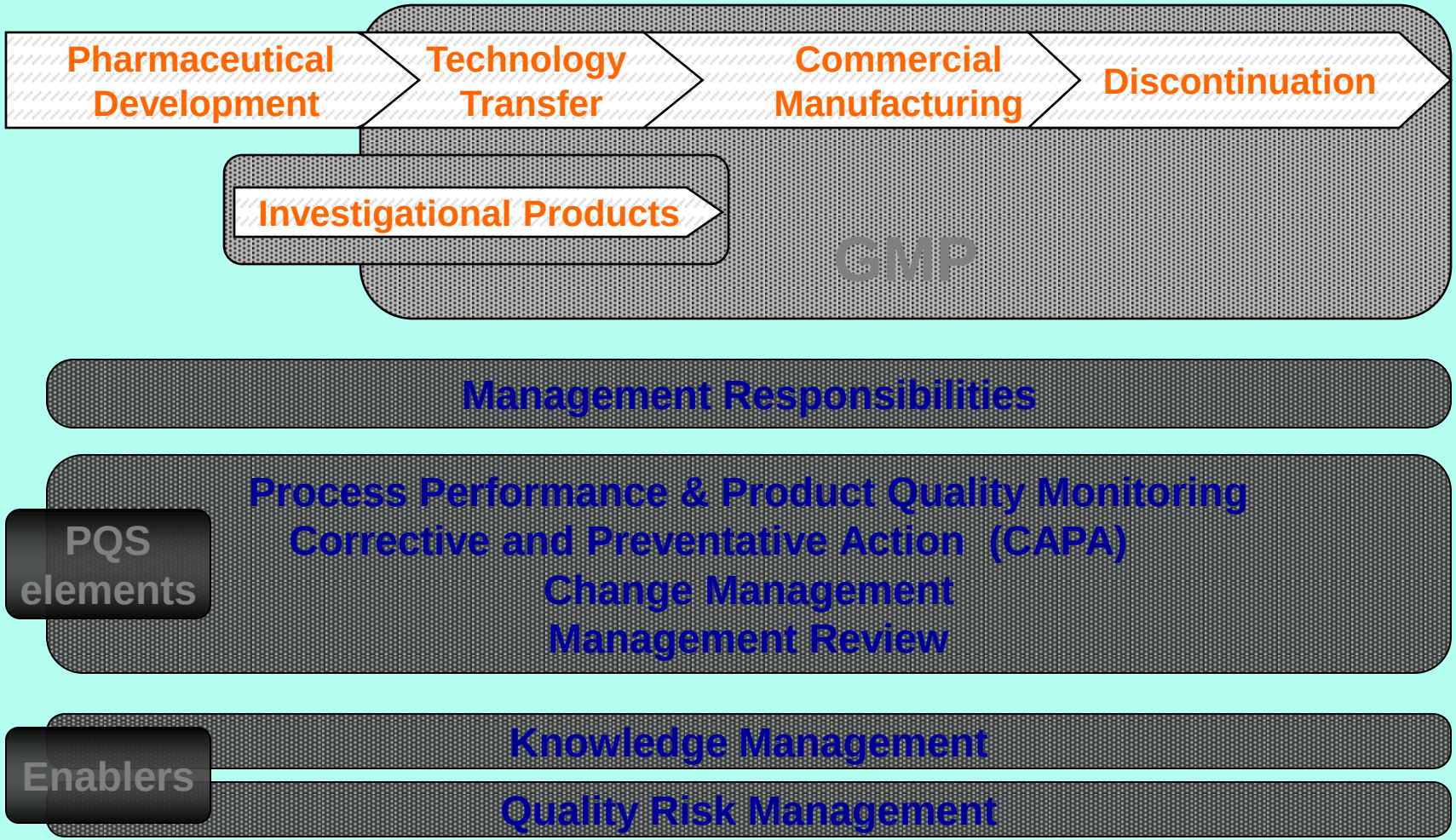
So what are the Key Elements?

	GMP	ISO 9000	FDA QS	Q10
GMPs	✓ ✓		✓ ✓	✓ ✓
Management	✓	✓ ✓	✓ ✓	✓ ✓
Continual Imp		✓ ✓	✓ ✓	✓ ✓
QRM		✓	✓ ✓	✓ ✓
Knowledge		✓	✓ ✓	✓ ✓
Lifecycle		✓	✓ ✓	✓ ✓
Opportunities			✓ ✓	✓ ✓

Lifecycle Approach

- A Modern PQS needs to be holistic and cover the product lifecycle
  - Design and Development
  - Manufacturing
  - Withdrawal
- Challenges and removes some traditional organisational silos
  - Within Industry
  - Within Regulatory Agencies
  - With outsourcing partners

ICH Q10 Pharmaceutical Quality System



Management Responsibilities

- Essential component
- Not just about compliance
  - Visible leadership to establish and maintain a company wide culture and commitment to Quality and improvement
  - Monitor performance of the PQS and act
  - Internal and Outsourced activities
- Quality cannot be owned by the Q Unit
  - Management is accountable
  - But independent assessments / audits are key

Management Responsibilities

- Clear roles, responsibilities and governance processes are essential
  - Quality Policy – standards and direction of organisation
  - Quality Planning – convert into objectives / plans
  - Resources - allocations and competence
  - Communication – Q items to appropriate audiences
  - Management Reviews
    - Product and Process performance
    - PQS performance

Management Responsibilities

- Management of Outsourced Activities and Purchased Materials
  - PQS must extend to the control and review of these activities
  - Pharmaceutical firm (Management) is ultimately responsible to assure processes are in place

Management Responsibilities

- Management of Outsourced Activities and Purchased Materials
- Processes must be in place to:
  - Assess suitability of contractors / suppliers before use
  - Ensure use of approved suppliers and a defined supply chain
  - Define responsibilities and communication processes for quality related activities
  - Review performance and make improvements

Continual Improvement

- Monitoring of product quality and process performance
- CAPA
- Change Management
- PQS itself

Continual Improvement

- CAPA System
  - Investigation of non-conformances

    e.g. deviations, rejections, complaints, recalls, observations from audits and inspections = reactive

    e.g. feedback from trends = proactive
  - Structured investigations to seek root cause
  - Use QRM to ensure degree and formality is commensurate with level of risk
  - Should result in enhanced knowledge and improvement
  - Not just reacting to non-conformances
  - Focus on preventative actions
  - Need effective tracking / follow up processes

Continual Improvement

- Change Management System
  - Change can be good!
  - Proactively driven by outputs from monitorin trending / improvement / innovation
    - Not just by reacting to problems
  - Use expert teams and knowledge to evaluate and set success criteria
  - Use QRM commensurate with level of risk
  - Consider impact on regulatory filings
  - Undertake in timely and effective way and track
  - Assure no unintended consequences
  - > Self management by competent manufacturers

Continual Improvement

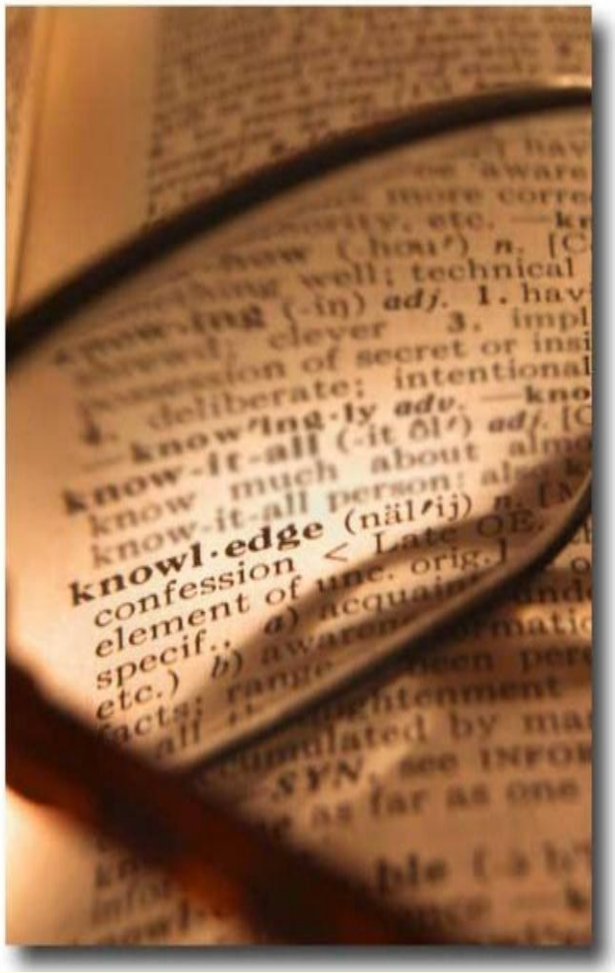
- Product Quality and Process Performance Monitoring System
  - Use knowledge, QbD, Product and Process understanding and QRM to set Control Strategy
    - What and when to monitor / measure / test
    - Based on critical product quality attributes and critical process parameters to deliver them
  - Confirm and maintain a state of control
    - Feed-back and Feed-forward loops
  - Reduce and control variation to appropriate levels
  - Drive continual improvement
  - Continual verification

Quality Risk Management (Q9)

- Essential integrated part of PQS – 2 key principles
  - The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
  - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk
- Proactive use to identify and control risk
- Support decisions through lifecycle
- Integrate into key parts of PQS
  - e.g. change management, CAPA, GMPs - Validation, etc
- Help set meaningful specifications / CPPs to ensure product CQAs are met

Knowledge Management

- Systematic and lifecycle approach to acquiring, analysing, storing and disseminating knowledge on products, processes, components…
- Provides the basis for science and risk-based approaches in the PQS
  - Product and process development
  - Manufacturing
  - Change management
  - Continual improvement



So How does Q10 'fit in' ?

- Product of ICH is Guidelines
- ICH members (including FDA) are obliged to implement after the step 4 sign-off
- FDA have published as FDA Guidance via the Federal Register
- Q10 reflects FDA's current thinking on Pharmaceutical Quality Systems = c-GMP

European Regulator Views

- **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!

European Regulator Views

- **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

European Regulator Views

- **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

FDA Regulators Views

- Based on inputs by
  - Steven Lynn
  - Rick Friedman
  - (Joe Famulare)
  - Rebecca Rodriguez
  - Monica Caphart
  - (Moheb Nasr) / Christine Moore

FDA Regulators Views

- Voice of the Customer: Quality should be customer-focused
  - e.g., what type of patient may receive this drug? what is the intended use of the ingredient?
- Quality is achieved (and consumer risk minimized) by a robust Quality System. This requires Senior Management Commitment.
- In a strong quality system, senior management recognizes and leads with the philosophy that:
  - *a proactive, preventative paradigm must be ingrained in the organization's daily operations*
  - *robust supplier relationships and neural networks are essential to limit variability in materials and processes.*

FDA Regulators Views

- Support and Ownership of Quality Goes Beyond the Quality/Compliance Units
- A Culture of Quality Yields Many Benefits:
  - Enhanced Process Stability Drives Productivity and Performance.
  - Prevention Reduces Compliance Risks and Costs.
  - Best Plants have Fewer Significant Complaints and Investigations and Therefore More Efficient QA Release of Batches.
  - Protection of Brand.

FDA Regulators Views

- Evaluation activities are key
  - Data trending
  - Internal Audits
  - Preventative actions
  - Quality Risk Management

FDA Regulators Views

- ICH Q10 and ICH Q8 linkage
  - Processes for pharmaceutical development (ICH Q8 or equivalent) provide key linkages to product realisation within the PQS
  - ICH Q8 provides the process understanding that serves as the basis for continuous improvement

FDA Regulators Views

- ICH Q10 and ICH Q9 linkage
  - The PQS should encourage and facilitate the use of QRM (ICH Q9) throughout
  - The design and application of processes within the PQS should be based on QRM principles and methods

FDA Regulators Views

- **Words/Concepts you will hear frequently**
  - Quality Culture
  - Business Case for Pharmaceutical Quality
  - Variability Reduction / State of Control
  - Innovation
  - Root Cause
  - Lifecycle
  - Management Responsibility
  - Control Charts
  - Process performance / process capability
  - Preventive and Proactive (vs. reactive)

FDA Regulators Views

- **The Business Case**
- **GMP is Good Business Practice**
  - PQS further aligns GMP with basic business goals of process predictability (e.g., Right First Time) & product dependability
- **Deming's Chain reaction:**
  - Reduce Variability ☐ Improve Quality ☐Decrease Costs (rejected goods, etc.) ☐ Better Products and Productivity…. ☐ More Competitive
- **Measuring Performance is Good Business**
  - Gap vs. Standard: Identifying performance gaps and promptly correcting root causes is good business

FDA Regulators Views

- FDA Responses
  - 'cGMP for 21st Century' initiative
  - CDER and CBER QbD schemes
  - Proposed changes to Post-Approval regs
  - Implemented ICH Q guidelines
  - New Process Validation guidance
  - And more to come …

Some Implementation Questions

- What is different to our previous QS approach?
  - A list of SOPs and GMP has never been a QMS!
  - Q10 goes beyond GMPs with an ISO approach
  - It covers the Product Lifecycle
  - It introduces some ‘new’ expectations and ‘beefs up’ several others
  - It introduces concepts common in other industries
    - Design, Continual Improvement, Statistics, Process Capability, Knowledge Management, Risk Management..

Some Implementation Questions

- Where are we in Implementation?
  - Wide range of variability across industry sectors and companies
  - Well advanced – Partial – Pilot – Not started – Waiting to be told by FDA…..
  - One size does not fit all business models!
    - Integrated, Outsourced, Virtual, Large, Small, ….

Some Implementation Questions

- PDA 2011 Survey
  - Cost savings from Q8-10?
    - 36% Yes, 23% No, 41% Don't know
  - Downturn in deviations?
    - 52% Yes, 48% No
  - Calculate Cost of (Poor) Quality?
    - 38% Yes, 62% No

= If you don't measure how can you improve?

Some Implementation Questions

- What implementation strategies are seen?
  - Must have top level, cross-functional support
  - Cannot be driven by Quality alone
  - Business Case to drive need
  - Gap analysis and Process mapping
  - Start small – use QRM to identify key gaps and break down the 'elephant' bit by bit
    - E.g. CAPA, Management Reviews, …..
  - Few start from scratch (maybe Mergers)
  - Don't wait for FDA to tell you……..

Some Implementation Questions

- How have firms changed their Quality Manual?
  - Q10 accepts Quality Manual or equivalent…
  - Some firms have an integrated Quality Manual
  - Others have ‘descriptions’ of how their key Q Business processes fit together in PQS
  - Remember – not just a list of SOPs or just GMP
    - Tech Transfer, Pharm Dev, KM, QRM, …….

Some Implementation Questions

- Are firms doing CAPA effectiveness checks?
  - Not well ! Retrain Operator and update SOP……
  - Need to understand CAPA
    - C = CORRECTIVE (to stop a re-occurance)
    - P = PREVENTIVE (to stop happening in first place)
  - We have been / are still mostly reactive to problems, rather than preventive
  - Apply QRM to triage level of risk / degree of investigation / number of actions / how to measure effectiveness
  - Monitor - as appropriate to specific action

Some Implementation Questions

- What Q10 related 483s are appearing?
  - 483s have to refer to legal CFR / FD&C Act
  - FDA guidances are written to reflect c (current) GMP
  - So may not see direct references…..
  - We are seeing increases in some key areas
    - Corporate and Management oversight
    - Quality unit is inadequate in that ……
    - Deviation and Complaint CAPA effectiveness and investigations
    - Out of control processes

Some Implementation Questions

- Any more Questions ??
- THANK YOU FOR INVITING ME

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