Industry Perspective on ICH Q10

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Industry and Health Authorities Have Similar Challenges

How do we bring new products to market quickly while maintaining patient safety?

How do we set meaningful product specifications (i.e., set the Design Space)?

How do we facilitate continuous improvement?
Regulators regulate regionally. Manufacturers commercialize globally.

Multiple regional regulations governing CMC and manufacturing changes are not harmonized--each region (US, EU, Japan, China, Korea, others) has unique regulations.

Differences include review cycles, data requirements, regulatory filing mechanism for same change and interpretation of same data.

Result is resistance to change and logistical hurdles that could be avoided.
Why harmonized standards for CMC and Quality Systems?

Product A

Submitted and reviewed

A1 A2 A3 A4

Process Improvement proposed & submitted

A5 A6 A7

Change submitted

Change requested by authority

Time

One CMC dossier

Differences in specs, in-process controls, shelf life = 4 “products”

2 processes running 3-5 “products”

Logistical nightmare
Why harmonized standards for CMC and Quality Systems?

Change in API which affects 3 formulations

A logistical impossibility !!!
Current GMP Process

Process Responses
(Measurements)

Raw Material → Process Variables
(Knobs or Controller Set Points)

Any Variability Here

Optimized and set during development
Controlled as closely as possible during production

Adjust Process Variables in Response to Process Measurements

Shows Up Here

Product

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Product
21st Century GMP Approach

Add PAT to Measure Raw Material Attributes

Adjust Process Variables in Response to Raw Material Attributes

Add PAT to Measure Product Quality Attributes

Adjust Process Variables in Response to Product Quality Attributes

Combination of Feed Forward and Feedback Control of Process Parameters Provides even Greater Control of Critical Quality Attributes
Adjustment of Process Variables Based on Product Measurement Minimizes Product Variability by Allowing the Process to Compensate for Variability
What does Q8, Q9 and Q10 do for us?

Q8 provides guidance on Quality by Design and identification of what is Critical to Quality – for submission to authorities

Q9 outlines the Quality Risk Management approach across the lifecycle of a product – for both industry and authorities

Q10 provides guidance on the Quality System framework needed to augment the GMP regulations and enable continual improvement – of process understanding and capability

- To enhance quality assurance
- To assure product availability
What does Q8, Q9 and Q10 do for us?

Encourages us to:

Design quality into the manufacturing process – for new products

Understand what is critical to quality – for new and existing products

Continually enhance product and process understanding – for new and existing products

Continually improve process capability – for new and existing products
Process Control and Capability Cycle

Development History

Integrated Validation Master Plan
- process • product • systems

Technology Transfer

Qualification

Validation

Execute & Monitor

Technical Evaluations
- process • product

Countermeasures
- process • product

Quality (GMP) Evaluations
- quality systems

Countermeasures
- quality systems

Site Quality Plan
A Paradigm Shift

Product development is not a static activity – we need to assimilate knowledge gained over the product life cycle

Product specifications should be set based on process understanding, process capability and representative data

This Is NOT a New Concept
Previous Industry Comments to Proposed FDA “Low Risk” Manufacturing Changes

Risk is **NOT determined by:**

- Time on market
- Complexity (at least not *a priori*)

Risk **IS determined by:**

- Understanding of the manufacturing process
- Having adequate controls

PhRMA comments to Pharm Sci AC 2001
Most products can be low risk. Need appropriate “modern” controls and understanding of the manufacturing process for API and product.

Current compendial monographs do not provide such a set of modern controls.

Need cGMP compliance

Workshop Summary, Massa et al to Chiu, 8/8/01
Define the type of activities which a manufacturer may take, using risk management processes (Q9) when appropriate, to
– monitor and evaluate quality of products, processes and systems appropriately
– make and manage improvements/changes appropriately

In order to demonstrate that Industry understands the manufacturing process, controls the process appropriately and can manage post-approval changes effectively based on product and process knowledge (Q8).

To create a guideline against which these aspects of a manufacturer’s quality systems can be inspected.

ACPS 7/20/04
The body of knowledge available for a specific product and process, including critical-to-quality product attributes and process parameters, process capability, manufacturing and process control technologies and the quality systems infrastructure

PhRMA Quality Leadership Committee
Low (Lower) RISK generally associated with:

- Lower complexity
- Higher robustness
- Higher process capability
- Manufacturing technologies that mitigate risk
- Existence of adequate quality systems infrastructure

PhRMA Quality Leadership Committee White Paper
Relationship between science, risk management and the regulatory process

- **Reduction of risk by good design and control strategies**

- **Low complexity, robust process, high capability effective Q systems**

**Manufacturing Science**

**More**

**Less**

**RISK**

**Regulatory Process Category**
- III- High
- II- Medium
- I- Low
ICH Q10 is not intended to create any new expectations beyond current regulatory requirements

Consequently, the content of ICH Q10 that is additional to current GMP requirements is optional
ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle.
Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.
ICH Q10 Pharmaceutical Quality System

A quality system can provide the necessary framework for implementing quality by design, continual improvement, and risk management in the drug manufacturing process.
Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization.
What does the Pharmaceutical Quality System consist of?

- GMPs
- Knowledge management
- Risk management system
- Process performance and product quality monitoring system
- Change management system
- Corrective and Preventive Action system
- Management review and continual improvement
Pharmaceutical Quality System

Elements

- Management Review
- Change Management
- Corrective Action and Preventive Action
- Process Performance and Product Quality Monitoring

Enablers

- Knowledge Management (Q8)
- Quality Risk Management (Q9)

The Foundation

GMP Compliance Systems
The Benefits:

Better process understanding leads to more robust process and less product variability

- More robust process leads to consistent production/less waste
- Less waste leads to lower inventory

Process understanding leads to better knowledge of the product and the process

- Better knowledge leads to shared understanding of critical attributes with regulators
- Shared understanding leads to increased trust between industry and regulator
The Benefits:

Monitoring the process and its performance leads to an ability to understand the process better and make continual improvements

- Use modern techniques to understand process variability and capability better
- Root Cause Analysis leads to prevention of repeat errors
- Corrective Action leads to Preventive Action
The Benefits:

Better process understanding and a good change management system leads to the manufacturer being able to make changes without undue oversight

- Consider whether the change is within what is registered
- Impact of change must be based on scientific- and risk-based evidence
- Company system must be multi-disciplinary, robust and well controlled
We all have to start somewhere . . .
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