Regulatory Aspects of Pharmaceutical Development and Manufacturing in the 21st Century – FDA Perspective

Moheb M. Nasr, PhD
ONDQA/CDER/FDA

Cortona Conference on QbD/PAT

Cortona, Italy
September 20, 2010
Outline

• Status of Pharmaceutical Manufacturing
• FDA 21st Century Initiative
  – Recent ICH Quality Guidances
• Implementation of QbD
• Progress and Challenges
  – What has QbD Delivered So Far?
  – Adaptation of new technologies
  – What Should QbD Deliver in the Future in a Globalized Industry?
• Ongoing Research and Future Innovation
  – Cortona Conference
• Concluding comments
Status of Pharmaceutical Manufacturing

• Adequate and sufficient quality
  – Several cost effective therapy options available
• High manufacturing cost
  – Low efficiency and considerable waste
  – Strong reliance on regulatory oversight
  – Low factory/equipment utilization rate
  – Frequent manufacturing failures and product recalls
• Lack of coordination/integration among key business units (R&D, manufacturing, quality, regulatory, etc.)
• Slow to innovate and embrace new technologies
• Increase reliance on outsourcing
FDA 21st Century Initiative

Objectives:

♦ Encourage the early adoption of new technological advances by the pharmaceutical industry

♦ Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches

♦ Encourage implementation of risk-based approaches

♦ Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science

♦ Enhance the consistency and coordination of FDA's drug quality regulatory programs
FDA and ICH Guidance

Sept 2004
Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Sept 2006
Guidance for Industry
Quality Systems Approach to Pharmaceutical CGMP Regulations

Nov 2005 & Nov 2008
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH Harmonised Tripartite Guideline
Pharmaceutical Development (Q8(R2))
Current Steph 3 version dated August 2008

November 2005
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH Harmonised Tripartite Guideline
Quality Risk Management (Q9)
Current Step 3 version dated 8 November 2005

June 2008
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH Harmonised Tripartite Guideline
Pharmaceutical Quality System (Q10)
Current Step 3 version dated 4 June 2008

April 2009 & Ongoing

Guidance for Industry
Process Validation: General Principles and Practices

Draft Guidance
This document is draft & being developed for consultative purposes only
Recent ICH Quality Guidances –

• Pharmaceutical Development - Q8(R2)
  – Describes good practices for pharmaceutical product development
  – Introduces concepts of design space and flexible regulatory approaches
  – Introduced and elaborated on QbD concepts
Quality by Design

- Process Parameters
- Process Understanding
- Process Design (Unit operations, control strategy, etc.)
- Process Performance (Cpk, robustness, etc.)
- Continual Improvement
- Quality Control Strategy (Desired clinical performance)
- Product Knowledge
- Product Design (Dosage form, excipient selection, stability, etc.)
- Product Quality Attributes

Quality by Design
Linking Process - Product - Patient

- Patient
- Product
- Process

Clinical Outcome

Critical Quality Attributes

Material Attributes & Process Parameters
Example QbD Approach - Q8(R2)

- Quality Target product profile (QTPP)
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement
Recent ICH Quality Guidance (cont.)

- **ICH Q9 – Quality Risk Management**
  - Describes a systematic process for the assessment, control, communication and review of quality risks
  - Applies over product lifecycle: development, manufacturing and distribution
  - Includes principles and examples of tools for quality risk management

- **ICH Q10 – Pharmaceutical Quality Systems**
  - Describes systems that facilitate establishment and maintainence of a state of control for process performance and product quality
  - Facilitates continual improvement
  - Applies to drug substance and drug product throughout product lifecycle
Quality Risk Management Process - Q9

- Initiate Quality Risk Management Process
  - Risk Assessment
    - Risk Identification
    - Risk Analysis
    - Risk Evaluation
  - Risk Control
    - Risk Reduction
    - Risk Acceptance
  - Output / Result of the Quality Risk Management Process
  - Risk Review
    - Review Events

Process Development
Control Strategy Development
Continual Improvement
(PQS) ICH Q10

Management Responsibilities

Process Performance & Product Quality Monitoring System
Corrective Action / Preventive Action (CA/PA) System
Change Management System
Management Review

Enablers
Knowledge Management
Quality Risk Management
ICH – Where do we go from here?

• ICH Quality Implementation Work Group (Q-IWG)
• ICH Q11 – Drug Substance
• ICH Q 3(D) - Heavy Metals
• ICH M7 – Genotoxic Impurities
ICH Q-IWG

- Q&A doc:
- Case studies and collaborative efforts
- Training workshops
  - How Q8, Q9 and Q10 should work together
  - June 2-4, 2010 – Tallinn, Estonia
  - October 6-8, 2010 – Washington, DC
  - October 25-27, 2010 – Tokyo, Japan
ICH

The ICH Quality Implementation Working Group (Q-IWG) Presents

Official Integrated Implementation Training Workshops for ICH Q8, Q9 and Q10

6-8 October 2010
Bethesda North Marriott
Washington DC, USA
ICH Quality Implementation Workshop

- Workshop features:
  - How Q8, Q9, and Q10 can benefit pharmaceutical development, manufacturing, regulatory assessment, scale up to commercial operations and GMP-inspection
  - A case study demonstrating opportunities for using the combination of Q8, Q9, and Q10
  - Discussions to develop solutions to implementation challenges
  - Interaction between regulators and industry experts
  - Four specialized breakout discussions covering Design Space, Control Strategy, Pharmaceutical Quality System, and Quality Risk Management
    - Participants will attend each discussion
ICH Quality Implementation Workshop

- Feedback from the workshops will be used by the ICH Q-IWG to further facilitate harmonized implementation of ICH Q8, Q9 and Q10.

- The final workshop materials and outcomes will be presented to regulators and industry in the three ICH regions and will be made available to other regions as well.

- The workshop material is intended to be used for internal training purposes by industry and regulators.
Demystification of QbD

• QbD is a systematic approach to pharmaceutical development and manufacturing using:
  – Modern scientific and quality risk management (QRM) principles
  – Quality control strategies based on product and process understanding

• Development and manufacturing information to be included in regulatory submissions

• Regulatory decisions must be based on scientific and QRM principles
Implementation of QbD in FDA Human Drug Programs

• Office of New Drug Quality Assessment (ONDQA)
  – 2005 CMC Pilot program
  – QbD Implementation Outside the CMC Pilot

• Office of Biotechnology Products
  – 2008 Biotechnology Pilot Program

• Office of Generic Drugs
  – Question Based Review (QBR)
ONDQA - Findings from CMC Pilot Program

• Provided valuable experience for industry and FDA in implementing QbD
  – Elements of QbD in submissions
    • Risk assessments
    • Design spaces
    • Proposals for flexible regulatory approaches
  – Risk-based regulatory decisions were enabled
• Learning has been incorporated into ICH Q8R
• Refinement of concepts still ongoing
ONDQA - Modern Control Strategies in Recent QbD Applications

• Translating process understanding into effective controls
  – On-line and in-line measurement instruments
  – Effective sampling strategies
  – Feed-back and feed-forward control systems

• Modern manufacturing approaches
  – Lean manufacturing and real-time release testing
  – Continuous manufacturing

• Continual Improvement
  – Maintenance and update of process and analytical models
  – Utilization of process data to update control models (e.g., Multivariate statistical process control)
  – Knowledge retention and risk management updates
Control Strategy Example - Real Time Release Testing (RTRT)

- **NIR Monitoring**
  - Blend Uniformity

- **Laser Diffraction**
  - Particle Size

- **NIR Spectroscopy** (At-Line)
  - Identity
  - Assay
  - API to Excipient ratio

**Raw materials & API dispensing**
- Specifications based on product

**Processes**
- Dispensing
- Blending
- Sifting
- Roller compaction
- Tablet Compression
- Pan Coating
ONDQA - Recent QbD Experiences

• Number of QbD meetings and applications have been increasing
• Applications containing QbD elements, outside of pilot
  – 15 NDAs
  – 20 INDs
  – 6 supplemental NDAs
• New proposals containing challenging regulatory approaches
• Additional experience is helping to harmonize review approaches and regulatory decisions
QbD in Biotechnology

- Mock case studies developed
- OBP Pilot Program
  - FR Notice July 2, 2008
  - To consider quality-by-design (QbD) approaches to unit operations in supplements (10) as well as original applications (5)
  - To explore the use of protocols submitted under (21 CF 314.70(e) and 601.12(e))
  - 5 applications accepted (3 full BLA, 2 Supplements)
    - more under consideration
Generic Drug Quality Assessment

• OGD has developed a question-based review (QbR) for quality evaluation of generic drug applications

• Several Industry/OGD workshops
  – goal to move toward a common understanding of QbD for generics

• Agreement to address MR dose forms (formulation and manufacturing process)
  – ANDA submission requirements for MR products may change in the future
What has QbD Delivered So Far?

• Focus on systematic pharmaceutical development
• Utilization of formal quality risk management in pharmaceutical development, control strategy, change control and **regulatory processes**
• Collaborative scientific interaction between manufacturers and regulators
• Harmonization and collaboration among global regulators
• Opportunities for pharmaceutical innovation (continuous manufacturing, RTRT, PAT tools, etc.)
• Flexibility in manufacturing and operations
What has QbD Delivered So Far? – Cont.

- Identification of some scientific and regulatory gaps (analytical, modeling, biopharm, characterization, etc.)
- Effective collaboration between CMC and clinical reviews
- Improved interactions between review and inspection
- More diverse and high quality reviewers on board
- Changes in the review process and the interaction with industry
- Development of QMS for CMC review
Adaptation of New Technologies

• QbD paradigm supports adaptation of new technologies and development approaches
  – Better/more utilization of DOEs and QRM
  – Chemometric based methods for real time determinations of tablet potency
  – Multivariate models as surrogates for traditional release tests (e.g. dissolution)
  – Multivariate models for statistical process control
  – Advanced analytics and process controls (PAT)
  – Continuous manufacturing in lieu of batch processing
Example: Real Time Determination of Tablet Potency

- **Blend Uniformity** determined by on-line NIR
  - Adjustable blending time
  - Fast response

- **Tablet CU** determined during compression
  - On-line measurement of active content by NIR
  - Fast turn around
  - Fully automated
  - Corrective action feasible
Example: Multivariate Model for Predicting Dissolution

Qualitative Assessment by PCA

Manufacturing Data

Quantitative Prediction by PLS
Example: Multivariate Model for Statistical Process Control

- MSPC (Multivariate Statistical Process Control) model for a unit operation e.g. compression
  - Built from multiple batch data
  - All batches had acceptable quality product

- New batch data projected onto the MSPC model to demonstrate conformance
Conceptual Example of Continuous Manufacturing

- Continuous Blending
  - Receiving
  - Continuous Granulation
    - Particle Size Distribution
    - Weight & Hardness
  - Continuous Blending
    - Concentration & Uniformity (Multi-component)
  - On-line Assay
  - Real-time Release Testing

- Continuous Film Coating
  - Dissolution Model (release)
  - Digital Imaging
ONDQA/FDA Sponsored Research on Microreactors

• Joint research with CPAC (Center for Process Analytical Chemistry), University of Washington, Seattle and Corning
  – Funded by the FDA
  – Initiated in November, 2008
  – Also utilize CPAC’s New Sampling/Sensor Initiative (NESSI)
• Goal of this project is to enhance our understanding of continuous manufacturing and microreactors
• Potential benefits include:
  – Improved reactor design
  – Effective sampling and online analytics,
  – Robust control strategy
  – Ultimately lead to increased process understanding and manufacturing efficiency
More Research Opportunities

- Development of additional PAT tools for feed-back or feed-forward control
- Models to describe and/or predict underlying physico-chemical phenomenon within each process in drug product manufacturing
- Methodologies for robust scale up/down of pharmaceutical processes
- Defining representative sampling to consistently assure product quality over time
  - Location of sampling probes
  - Sample size and sampling frequency
Regulatory Perspective on Innovation

- There are no regulatory hurdles for implementing innovation in pharmaceutical manufacturing
  - **There is a lack of experience and fear of the unknown**
- FDA actively involved in harmonizing regulatory approaches for evaluating novel concepts – internally and externally
- FDA supports the implementation of new concepts and technologies using a science and risk-based approach
  - Recommend early and frequent discussion with Agency before implementation
What Should QbD Deliver in the Future in a Globalized Industry?

• Higher assurance of pharmaceutical quality
• Fewer recalls, batch rejections and un-necessary enforcement actions
• Performance based specification
• Better utilization of resources
• Harmonized global regulatory processes (review and inspection)
  – Transparency in regulatory processes
• More flexible regulatory approaches
• Enhanced innovation (new dosage forms, manufacturing processes and analytical techniques)
• Ability to adjust to market demand on short notice (necessary medication, counter measures, epidemics, etc.)
Cortona Conference

• A unique learning opportunity:
  – FDA and EU regulatory approaches
  – Green processing
  – Continuous processing
  – PAT, RTRT, on-line measurement and control
  – Sampling consideration and data handling
  – QbD implementation in analytics, generics, bio-processing
  – Modern analytical technologies
Cost and Benefit of QbD

**Investment** (development, organizational planning, etc.)

**Old Paradigm**
- Empirical development approach
- Quality by testing & inspection
- Frozen process with reactive changes

**Desired State**
- Quality by design development
- Flexible process & continuous improvement

**Decreased Expenses and Savings** (manufacturing and compliance costs)

QbD Implementation Progress

- Initiate QbD Efforts
- QbD Fully Realized
The Desired State:
A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight (JW, 2005).

Quality Risk Management (ICH Q9)

2010

ICH-Quality IWG

Quality by Design Highway

Product and Process Understanding (ICH Q8R2)

Pharmaceutical Quality Systems (ICH Q10)

The Desired State
Concluding Comments

• Implementation of QbD is progressing well
• There is a need to address remaining gaps and to encourage innovation and new technologies
• Opportunities for global harmonization of regulatory processes (review and inspection)
• Need to establish “new” metrics to evaluate regulatory success and compliance
• Regulatory processes need to adjust to QbD realities
Thank you!

Questions, comments, concerns:
NewDrugCMC@fda.hhs.gov