A Regulatory Perspective on the Current and Future State of Pharmaceutical Quality

International Conference on Drug Development
Austin, TX
Feb 26, 2013

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Outline

• Background on quality
• Quality today
  – New drugs and QbD
  – Legacy drugs and shortages
• Current and future challenges for quality
• Potential next steps for industry and regulators
What is Quality?

The Patient Cannot "See" Quality

Which milk is subpotent?

Which drug is subpotent?

High Concentration

Low Concentration
Expectations for Quality

Patients and caregivers assume that their drugs:
• Are safe
• Are efficacious
• Have the correct identity
• Deliver the same performance as described in the label
• Perform consistently over their shelf life
• Are made in a manner that ensures quality
• Will be available when needed
What is Pharmaceutical Quality?

- The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength and purity (ICH Q6A).
- The degree to which a set of inherent properties of a product, system or process fulfills requirements (ICH Q9).
Linking Process - Product - Patient

- Patient
- Product
- Process

Quality Target Product Profile
Critical Quality Attributes
Material Attributes & Process Parameters
Surveying the Landscape

- Slippery Slope
- Fully Developed
- Wilderness
Pharmaceutical Quality Today

• Many companies are widely adopting Quality by Design (QbD) approaches for pharmaceutical development for **new products**
  – Growing evidence that QbD in development decreases product variation and is good business practice
  – Increasing use of QbD in generic and biotech companies

• American public is facing unprecedented drug shortages
  – Many due to quality related issues of ‘legacy’ products
  – Manufacturing problems are not a new issue
FDA Initiatives: “Pharmaceutical Quality for the 21st Century”

– In 2002, FDA identified a series of ongoing problems and issues in pharmaceutical manufacturing using traditional approaches

– Internal and external assessment found:
  • Pharmaceutical manufacturing HIGHLY regulated compared to food, chemical, etc
  • Cost of cGMP compliance very high
  • Process efficiency and effectiveness were low – high waste and rework
  • Level of technology lower than comparable industries
  • Reasons for manufacturing failures were not understood

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
The Desired State

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

Janet Woodcock, M.D.
Pharmaceutical Quality Assessment Workshop
October 5, 2005
Quality Related Guidance and Initiatives

**Initiatives**
- Critical Path Initiative
- 21st Century Initiative Final Report
- ONDQA CMC Pilot Program
- OGD QbR Announced
- ICH IWG formed
- OBP Pilot Program
- EMA-FDA QbD Pilot Program

**Guidance/Documents**
- PAT Guidance
- ICH Q8 Finalized
- ICH Q9 Finalized
- Quality Systems Guidance Finalized
- ICH Q10 Finalized
- ICH Q8(R1) Finalized
- ICH IWG Q&A’s
- Process Validation Guidance Finalized
- ICH IWG Points to Consider
- ICH Q11 Finalized

- Guidance on Residual Drugs In Transdermal and Related Drug Delivery Systems - Final
- Tablet Scoring, Nomenclature, Labeling, and Data for Evaluation - Draft
- Size of Beads in Drug Products Labeled for Sprinkle - Final
This article presents the results of a survey conducted by the ISPE United Kingdom/Ireland PAT COP.

The Business Benefits of Quality by Design (QbD)

by Theodora Kourtı and Bruce Davis

Introduction

The business case for Quality by Design (QbD) was a hot discussion topic during a meeting of the Process Analytical Technology Community of Practice United Kingdom/Ireland (PAT COP UK/IR). The discussion concluded with a plan to conduct a survey that would aim to gather actual experiences, examples and candid industry opinions on the business benefits of QbD. The questions one questionnaire. Written answers also were produced for the telephone interviews and these were approved by the interviewees. Interviewees were from development, manufacturing and regulatory while the companies range from large and small, both small molecule and biotech.

In total, we received 15 completed questionnaires from 12 companies. The responses were received between November 2010 and September 2011. The companies agreed to have their

• Survey of 12 companies on their experiences with QbD and their opinions of QbD

Pharmaceutical Engineering, July/Aug 2012, 32(4), 1-10
Business Benefits of QbD

- Improvement in Product Quality and Product Robustness/Reproducibility
- Improved Development Capability, Speed and Formulation Design
- Cost Reduction Benefits
- Yield Increase
- Fast and Reliably to Market
- Increased Process Capability; Reduced Atypicalcs
- Reduced Impact of Raw Material Variability
- Improved Product Stability
- Improved Scale Up Efficiency/Speed

Industry Perspective on “The Future of QbD”

• “QbD will become the norm”
• “The value of QbD principles is clear and will continue to be integrated into the product development processes.”
• “QbD is already expanding its scope into new paradigms such as RTRT, continuous quality verification, analytical QbD, lean stability approaches and others. We expect this trend to continue.”
• “QbD will continue to grow and become more embedded as it is applied more in production we will get better at it. We will use more prior knowledge and more risk-based approaches.”

QbD Status

• QbD has been widely adopted by innovator pharmaceutical manufacturers for new products
  – Increasing use in biotech and generics
• QbD has delivered to date:
  – Realization of the advantages of science and risk based approach in pharmaceutical development, manufacturing and regulatory review
  – Demonstrated increases in product quality and manufacturing efficiency
  – Some flexibility for lifecycle management
  – Platform for scientific discussion and collaboration between industry & regulators and amongst regulators
Additional Opportunities
- Remaining Challenges for QbD

• Expansion of QbD approaches to more legacy products, generic drugs and biotech products
• Easing post-approval change reporting requirements through use of risk based assessments
  – Applicable to both newer and older products
• Developing scientific methodologies to establish clinically relevant specifications
  – Especially for bioavailability
• Clarifying regulatory expectations for quality systems
  – Including change management and knowledge management
• International harmonization
Drug Shortages and Recalls

• Recent issues have placed a strong focus on the importance of quality of drugs
• The general public is experiencing shock and disbelief at current situation
• Has received extensive media and Congressional attention
• Current efforts for drug shortages are short term and not truly preventive
• Most of the recent high profile recalls, drug shortages, etc can be traced to failure of the firm’s QMS
• The subsequent problems have led to lost revenue, damaged reputation, lost jobs, and in some cases possible loss of the company

Drug Shortages in 2011

2011 US Drug Shortages by Dosage Form

- Dermal/transdermal: 18%
- Inhalation: 2%
- Injectable: 2%
- Oral suspension solution: 2%
- Suppository: 1%
- Tablet/capsule: 1%
- Other: 3%

N = 251

2011 US Drug Shortages by Reason for Shortage

- Packaging component problems: 46%
- Delays/capacity issues: 12%
- Discontinuation: 10%
- Increased demand: 6%
- Loss of manufacturing site: 6%
- Other/unknown: 19%
- Quality issue: 1%

N = 251

Barriers to Quality – “Legacy” Products

• Little incentive to upgrade facilities, processes, or knowledge to existing approved products
  – Perceived as low return on investment
  – Market does not reward quality
  – Perceived low enforcement threat for medically necessary drugs

• Regulatory post-approval requirements are a barrier to change
  – Cost and complexity of handling changes for multiple markets
  – Fear of discovering a previously unknown issue

• Lack of “Quality Culture”
  – Manufacturing objectives targeted to meet compliance requirements, versus meeting patient expectations
  – Can lead to short sighted decision making
How do we get to “Desired State” – Industry?

• Commitment to quality, including:
  – Establishing effective pharmaceutical quality systems
  – Maintaining, and modernizing as needed, equipment and facilities
  • Adopt a “Quality Culture”
    – Stress importance of product quality from the top down
    – Decision making with end-user / patient in mind
  • Proactively monitoring products and processes using risk-based approaches and modern analytical methods
• Anticipate supply problems
  – Arrange for additional manufacturing capacity
  – Develop alternate supplies of components
• Invest in quality and continual improvement
  – Quality can pay for itself!
“Culture of Quality”

• “An environment where each and every person understands and embraces their responsibility for protecting product quality and patient safety” (Mary Oates, ISPE CGMP Conference, June 2012)

• Potential characteristics of a quality culture:
  – The organization and management have clear, visible and demonstrated support of product quality
  – Decisions are made with patient needs in mind
  – Investments are made supporting product quality
  – Continual improvement is encouraged
Pharmaceutical Quality System Elements

Traditional CAPA – Reactive Approach

Product Performance & Product Quality Monitoring Systems
Corrective & Preventive Actions (CAPA)
Change Management Systems

Continual Improvement – Proactive Approach

Product Performance & Product Quality Monitoring Systems
Corrective & Preventive Actions (CAPA)
Change Management Systems
Multivariate Statistical Process Control

Multivariate Statistical Process Control (MSPC)
- Advanced monitoring methodology
- Looks at relationships between a large number of process variables
- Flag atypical or previously unseen operation
- Applicable to new and legacy products
- Outliers do not mean a failed batch but trigger investigation
- Growing examples of “saved” batches due to MSPC
“Large N” Sampling Plans

- Traditional sampling for content uniformity (ICH UDU / USP <905>) uses a small sample size (10 or 30 tablets)
- Wide “operating curve” can lead to erratic results for products of marginal quality
- Larger sample sizes provide higher confidence in quality and clearer picture of process capability
- EDQM chapter published in 2012; FDA is currently evaluating this methodology
How do we get to the “Desired State” – Regulators?

• Improved efficiency of regulatory oversight
  – Clear manufacturing expectations and consistent consequences
  – Provide additional guidance on manufacturing expectations and quality standards, as needed

• Differentiate between manufacturers based on quality
  – Degree of regulatory scrutiny more proportional to product and manufacturing risks
  – Develop pharmaceutical manufacturing metrics
  – Provide market rewards for quality?

  "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," Woodcock and Wosinska, Clinical Pharmacology and Therapeutics, V. 93(2), Feb 2013

• Ease post approval change reporting to support continual improvement
  – Incorporate risk-based approaches into regulatory framework
  – Work toward harmonization and coordination with other regulatory authorities
How FDASIA Can Help Quality

- The FDA Safety and Innovation Act of 2012 (FDASIA) contains several provisions that can help aid regulators to enhance quality and efficiency
  - Sections 701-704 – Registration of domestic drug establishments, foreign establishments. Identification of drug excipient information and electronic system for registration and listing
  - Section 705 – Risk-based inspection frequency - considerations including: compliance history, recall history, risk of drugs, last inspection, foreign inspections
  - Section 706 – Records for inspection - ability to request manufacturing site records or other information prior to inspections or in lieu of an inspection
  - Section 712 – Recognition of foreign government inspections
  - Section 1001 – Discontinuation or interruption in production of life-saving drugs
  - Section 1136 – Electronic submission of applications
Additional Challenges for Quality Review Under FDASIA

• Section 901 – Fast Track Drug Products
  – Facilitate development and expedite the review of drugs for the treatment of a serious or life-threatening disease or condition that demonstrates the potential to address unmet medical need

• Section 902 – Breakthrough Therapy Drugs
  – Expedite the development and review of a drug for serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
    • Provide timely advice and interactive communication with the sponsor regarding the development of the drug to ensure that the development
    • Provide a collaborative cross disciplinary review utilizing senior managers and experienced review staff, as appropriate

• Section 905 – Risk Benefit Framework
  – Implement a structured risk-benefit assessment framework in the new drug approval process and regulatory decision making
Challenges for Expedited Reviews

• Alignment of CMC development and manufacturing timelines with the clinical development program
  – Consideration of manufacturing scale
  – Coordination with contract manufacturers, as needed
  – Early availability of manufacturing sites for inspection
• Coordination of CMC development program and submissions
  – Recommend early communication between Sponsor and Agency
  – Involve both review and compliance staff to facilitate review and inspection timing
  – Recommend earlier submission of product quality information for review and inspection planning
• Accelerated manufacturing development program likely with less information than typically available
  – May warrant a risk-benefit assessment regarding risk of less CMC information vs. patient benefit (e.g., less stability data)
Proposed Office of Pharmaceutical Quality

• Combines components of current CDER Office of Pharmaceutical Sciences and CDER Office of Compliance
• Intended to provide better alignment between all quality functions (review, inspection, research)
• Focus areas for new office:
  – Integrated approaches for review and inspection
  – Risk based approaches to review and inspection
  – Efficiency and risk-based work prioritization
  – Modern regulatory science approaches (e.g., clinically relevant specifications, statistical sampling)
Conclusions

• A wide spectrum of pharmaceutical quality exists today
  – Many newer products have a high level of product and process understanding and process control through QbD
  – Many older products have had quality issues leading to drug recalls and shortages
  – Most products and firms are somewhere in between

• Both industry and FDA have work to be done to reach the “Desired State”
  – Industry needs to commit to quality through investment, culture changes and proactive thinking and actions
  – Regulators need to provide clear and consistent messages and use sound science and risk based approaches
  – Both industry and regulators need to pursue international harmonization

• FDASIA and CDER’s restructuring of quality functions hold promise for moving forward
Thank you!

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