Quality by Design –
FDA Lessons Learned and Challenges
for International Harmonization

International Conference on Drug Development
Austin, TX
Feb 28, 2012

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Outline

• Introduction to Pharmaceutical Quality by Design (QbD)
• Update on QbD Implementation within CDER’s Office of New Drug Quality Assessment (ONDQA)
• Global harmonization activities – ICH and FDA-EMA Parallel Assessment Pilot
• Concluding Comments
Background on Pharmaceutical Quality by Design (QbD)
Quality by Design Definition

- Systematic approach to pharmaceutical development and manufacturing
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

From ICH Q8(R2)
Quality by Design Definition

The definition of QbD does NOT discuss:

• Design space
• Regulatory flexibility (e.g., Real Time Release Testing)
• Protocols

*The higher level of understanding obtained through QbD facilitates flexible regulatory approaches*
Advantages of QbD

• Higher level of product and process understanding, which can lead to
  – Increased success rate in development and manufacturing
  – Increased process robustness, less manufacturing deviations and failed/reworked batches

• Potential regulatory flexibility, which can lead to
  – Ease of post approval changes for movements within an approved design space
  – Real time release testing (RTRT) resulting in lower analytical testing costs, lower cycle times, etc.
Regulatory Experience with QbD
ONDQA’s CMC Pilot Program

• Initiated in July 2005
• Objectives
  o To provide participating firms an opportunity to submit CMC information demonstrating QbD
  o To enable FDA to implement new QbD concepts
• Status Complete
  o 9 original and 2(3) supplemental NDAs accepted
  o 11 approved, 1 withdrawn (for non-CMC reasons)
• Provided valuable experience for industry and FDA in implementing QbD
  o Elements of QbD in submissions
  o Risk-based regulatory decisions were enabled
• Learning has been incorporated into ICH documents
New Drug QbD Containing Submissions
Trends in Applications and Meetings

• QbD concepts are frequently crossing into “non-QbD applications”
  – Applications include more development information
  – Many applications include “enhanced approaches”, e.g., risk assessment, without asking for additional flexibility

• QbD approaches are being applied to newer areas
  – Analytical methods
  – Container closure

• Increased interest in RTRT, continuous manufacturing, and biopharmaceutics approaches to QbD
ONDQA QbD Review Status

• The number of QbD containing applications has been increasing over the past 6 years
• “Standard” QbD approaches (e.g., defining CQAs, quality risk assessment, design space) have been fairly well fleshed out by applicants and reviewers
• More experience is still needed to standardize approaches for more complex concepts (e.g., RTRT, continuous manufacturing)
Internal Support of QbD within ONDQA

- ONDQA’s QbD Steering Committee established
- Internal searchable database for tracking QbD elements in submitted applications launched
- QbD CMC Lead position established
- Extensive QbD Training (small and large group)
- Established “QbD Liaison” – mentoring role
- Increase in reviewer participation in inspections
- Development of internal guidelines on review considerations for QbD aspects
- Collaborative research between ONDQA and academia on QbD and PAT focused topics
QbD in OGD and OBP

• Office of Biotechnology Products
  – Mock case studies developed
  – OBP Pilot Program for QbD approaches
    • 5 applications accepted (3 full BLA, 2 Supplements)
  – One QbD containing application to follow the same pathway as the small molecule EMA-FDA pilot

• Office of Generic Drugs
  – Draft case studies published
    • Immediate release tablets, modified release tablets
  – Revision of Question Based Review (QBR) templates to include QbD elements, ongoing

• Increased efforts to work collaboratively across review offices
“State of QbD”

Disclaimer: Includes my general impressions based on individual discussions, conference presentations, various reports

• The science and risk based approaches in QbD are being embraced by most innovator pharma companies for development
  – Often, the enhanced knowledge is not used to justify “regulatory flexibility” in the application
  – Experience has proven to improve product quality, process robustness and operational costs

• Some other companies starting to adopt QbD, including some generics and biotech companies
Remaining Challenges for QbD

• A pathway for risk based assessment to ease post-approval change requirements
• Establishing clinically relevant specifications, especially for bioavailability
• Clarifying quality systems expectations for change management
• Alignment of “old” ICH guidelines with new quality paradigm
• International harmonization
Advances and Challenges in International Harmonization
Global Regulatory Environment and QbD

• Enhanced development approach from QbD should not be problematic in the global regulatory environment

• Opportunities for flexibility regulatory approaches might not be available in all regions, e.g.,
  – Acceptance of design space approach
  – Agreement on PAT and/or RTRT approaches
  – Establishing clinically relevant specifications

• Further collaboration, communication and education may be needed
ICH Quality Implementation Working Group

Achievements Summary

- Published 45 Q&As related to ICH Q8, 9, 10
- Published ‘Points to Consider’ documents
  - Criticality of Quality Attributes and Process Parameters
  - Control Strategy
  - Level of Documentation in enhanced (QbD) Regulatory Submissions
  - Process validation/continuous process verification
  - Role of modeling in QbD
  - Design space
- Training provided in all US, Europe, Japan, Asia, Canada
- IWG work completed in 2011
FDA Efforts in International Collaboration (Outside of ICH)

- FDA-EMA Parallel Assessment Pilot
  - Set up a pathway for knowledge sharing between FDA/ONDQA and EMA reviewers/assessors
  - Ensure consistent implementation of ICH guidelines

- Pharmaceutical Inspection Cooperation Scheme (PIC/S)
  - Collaboration between regulatory agencies on pharmaceutical inspection and training

- CDER Forum for International Drug Regulatory Authorities
  - Training and information exchange forum for non-US pharmaceutical regulators
  - Typically offered twice per year; no registration fee
FDA-EMA Parallel Assessment Pilot

- Announced March 2011
  [link to program details]

- Overall objectives of this program:
  - Ensure consistent implementation of ICH guidelines
  - Establish a pathway for EU and FDA knowledge sharing on QbD containing application
  - Facilitate existing collaborations between FDA-EMA on inspections
  - Provide opportunities for joint training
  - Initiate a forum for harmonizing review approaches
Parallel Assessment Pilot - Scope

• Applicable to applications including QbD and/or Process Analytical Technology (PAT) elements
  – Biotech products and priority review applications excluded

• Parallel Assessment Pathway
  – NDA/MAA or sNDA/Type II Variations
  – Requested by applicant/sponsor
  – Submitted concurrently to both agencies

• Consultative Advice Pathway
  – Applications submitted to only to one agency
  – Can be initiated by EMA or FDA

• Scientific advice/CMC meetings
  – Handled as “EMA-FDA Parallel Scientific Advice”
Parallel Assessment Pilot – Submission Process

• Request to participate
  – Applicants submit request for participation to both agencies ≥ 3 months prior to anticipated submission date
  – Include a brief description (< 5 pages) of QbD elements
  – EMA & FDA joint determination of acceptance within 30 days of request

• Submission Process
  – Standard EMA and FDA submission requirements apply
  – Submission should reference the pilot in the cover letter
  – Applicant provides a letter allowing sharing of trade secret and confidential information between agencies
Parallel Assessment Pilot – Review Process

• Separate reviews conducted by each agency with information exchanges during review cycle
• Pre-established timelines for agency meetings and information sharing during review cycle
• **No change in statutory review timelines**
• Independent communication of questions to applicant, using existing processes
  – Strive for common List of Questions/ Information Requests
• Lessons Learned meeting between agencies after conclusion of the parallel assessment
Parallel Assessment Pilot – FDA Timelines

- **NDA Receipt**
  - Initial Telecon to discuss review and inspection
  - Exchange Draft Reviews and Questions
  - List of Questions/Information Requests Sent to Applicant

- **Exchange Comments, Discuss IR/LoQs via Telecon**

- **Applicant Response**
  - Exchange Comments, Discuss Deficiencies via Telecon
  - Complete & Exchange Review of Applicant Responses

- **Midcycle Meeting**
  - Primary Review Completion
  - Target Action Date

- **Post Action**

- **EMA-FDA Lessons Learned Telecon**

**FDA GRMP Timelines (no later than)**
- Filing Meeting
- 74 Day Letter
- Midcycle Meeting
- Primary Review Completion

**Review Month (Standard)**
- 1
- 2 3
- 4 5 6 7 8 9 10

**Target Action Date**
Parallel Assessment Pilot – Goals and Status

• Parallel Assessment
  – Target of at least 3 applications by March 2014
  – Currently one submitted, one accepted
    • Application will include Japanese regulators as observers
  – Several additional informal inquiries

• Consultative advice
  – Target of at least 4 applications by March 2014
  – One biotech product submitted to Office of Biotech
    Products will use the consultative advice format

• Applications still being accepted
FDA-EMA Initial Discussion Points

• In July 2011, a team from ONDQA visited EMA to discuss QbD topics, including anticipated challenges for parallel assessment

• Topics discussed included:
  – Level of detail in QbD containing applications
  – Verification of models for real time release testing (RTRT) and in-process Near Infrared (NIR) spectroscopy analytical methods
  – Strategies for scale-up and verification of design space
  – Post approval change protocols
  – Large sample size acceptance criteria
Conclusion

• QbD has delivered to date:
  – Realization of the advantages of science and risk based approach in pharmaceutical development, manufacturing and regulatory review
  – Opportunities for pharmaceutical innovation (RTRT, PAT, continuous manufacturing, etc.)
  – Some flexibility for lifecycle management
  – Platform for scientific discussion and collaboration between industry & regulators and amongst regulators

• Challenges/Opportunities remain
  – Modernizing our regulatory structure to fully embrace science and risk based approaches from QbD
  – International harmonization
Thank you!

Questions, comments, concerns:
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