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

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

Christine M. V. Moore, Ph.D.
Acting Director
Office of New Drug Quality Assessment
(ONDQA/OPS/CDER)

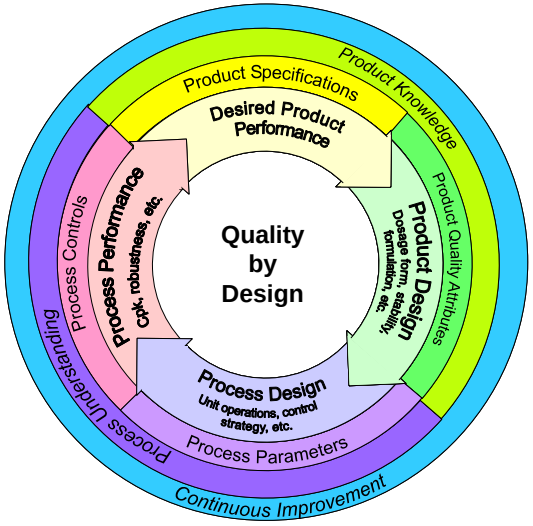
Outline

- 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

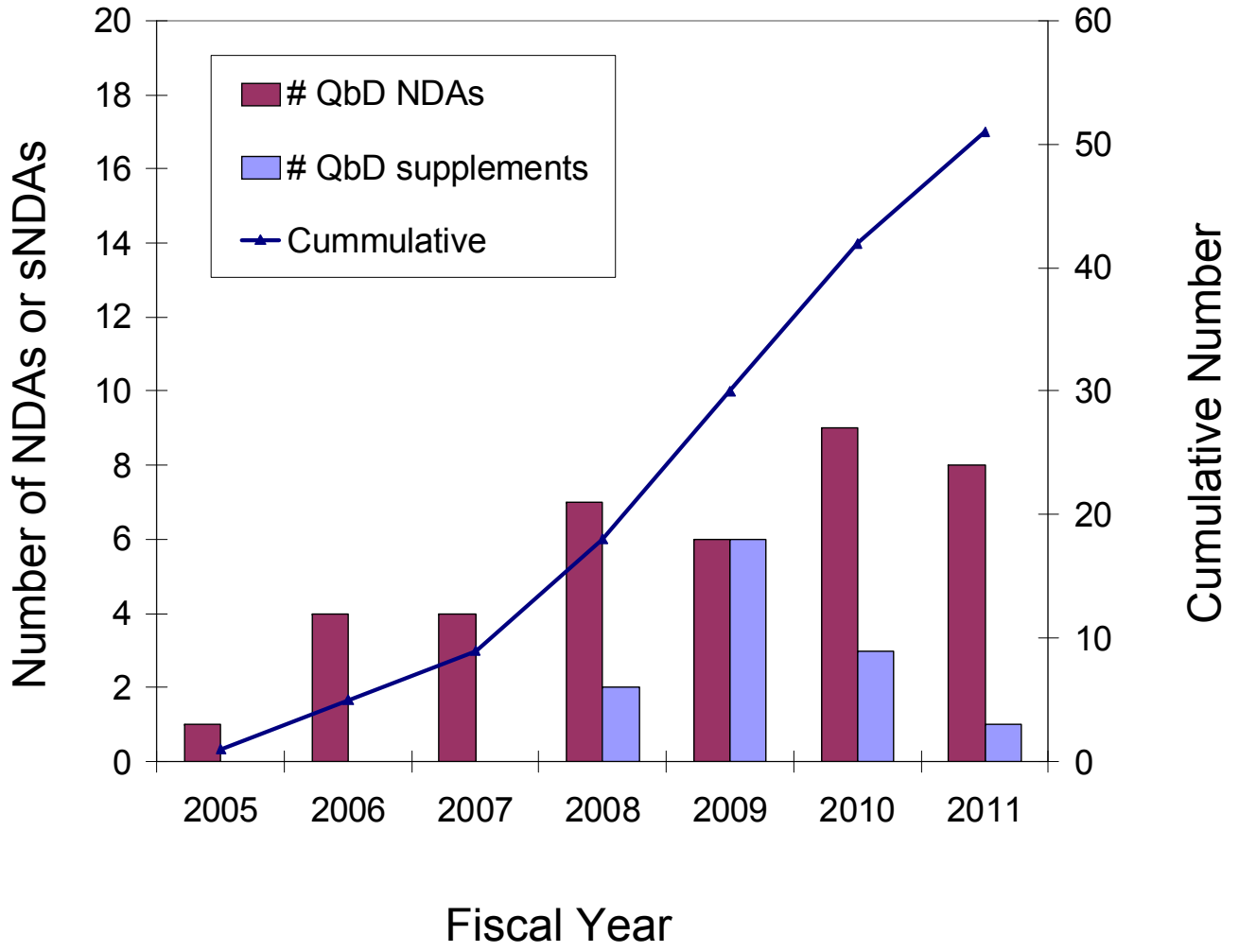
- Higher level of product and process understanding, which can lead to
  - Increased success rate in development and manufacturing
  - Increased process robustness, less manufacturing deviations and failed/reworked batches
- Potential regulatory flexibility, which can lead to
  - Ease of post approval 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
  - To provide participating firms an opportunity to submit CMC information demonstrating QbD
  - To enable FDA to implement new QbD concepts
- Status Complete
  - 9 original and 2(3) supplemental NDAs accepted
  - 11 approved, 1 withdrawn (for non-CMC reasons)
- Provided valuable experience for industry and FDA in implementing QbD
  - Elements of QbD in submissions
  - 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

Additional Opportunities ~~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
  http://www.fda.gov/downloads/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/UCM259808.pdf
- 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”

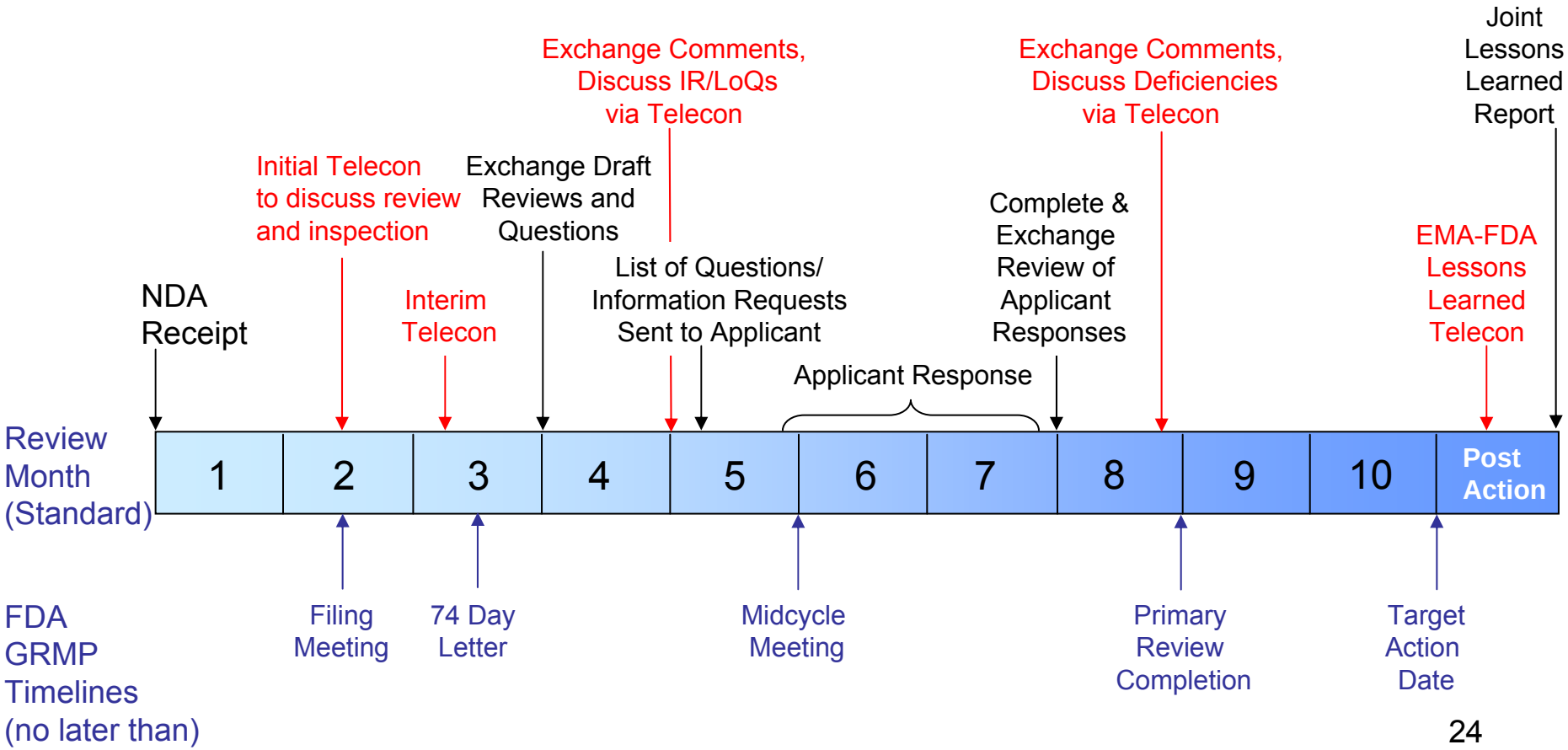
Parallel Assessment Pilot – Submission Process

- 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



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 inquires
- 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:

NewDrugCMC@fda.hhs.gov