FDA Reflections on Joint Regulators/Industry QbD Workshop

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Overall Workshop Impressions

- Great format with regulators and industry
  - Good participation of all
- Impressive transparency
- Much progress with QbD implementation

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HOW
Should I Do QbD?

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Main Themes and Concerns

- Classifying criticality
- Level of detail in process description
- Design space verification
- Level of detail in risk assessments
- How to change non-CPPs
- How to summarize control strategy

Discussed In EMA-FDA Q&As

Related to Post-Approval Change

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Unclear Definitions

- Non-CPP (not defined in ICH)
  No potential to affect CQAs:
  - for any range?
  - within ranges studied?
  - within statistical significance?
- Proven acceptable ranges (PARs)
  - Definitions other than ICH
  - How are they being used?
- Model maintenance
  - OOS vs OOT
- Regulatory commitments
  - What is filed?
  - How changes are reported?

Related to Post-Approval Change

Thoughts on Post-Approval Change

- FDA is exploring “Regulatory Commitments”
- Comparability Protocol guidance is being revised
- EMA-FDA Pilot “Phase 2” being considered
- Proposed FDA reorganization of drug quality units (Office of Pharmaceutical Quality)

What do regulators need?

EMA-FDA QbD pilot

Aim

- Allow EU and US assessors exchange their views on the implementation of ICH Q8-10 using actual applications and **facilitate harmonisation**
- **Share knowledge** gained with the EU network and Industry through lessons learnt
- Japan joined as an observer

Scope

- Submissions that include an enhanced approach to pharmaceutical development leading to the use of at least one of the following:
  - Design space,
  - PAT tools for control,
  - Continuous process verification,
  - Models to support real time release testing,
  - **continuous processes**
  - **post-approval regulatory flexibility**,

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103621.pdf
http://www.fda.gov/downloads/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/UCM259808.pdf

EMA-FDA QbD pilot

Two options:

Parallel assessment: 1 application complete	• The application is submitted to both agencies at about the same time, for MAAs/NDAs for **parallel evaluation** by both agencies
Consultative advice: Several ongoing	• The application is submitted to either EMA or FDA and the agency doing the evaluation requests to obtain **consultative advice** from the other agency
Type of products:	• **Chemicals** • There are some informal interactions on biologicals as well.

EMA-FDA Pilot for QbD – Progress to Date

- Applications in program
  - 1 parallel assessment complete, another accepted
  - 5 consultative advice
  - 1 biotech product that followed the consultative advice pathway
- Meetings
  - Multiple teleconferences on applications and on general topics
  - 3 face-to-face meetings
- Communications
  - 2 sets of Q&As published, others being developed
  - Many conference presentations
- Japanese participation
  - Parallel assessment application and in multiple meetings
- Considering extension of pilot beyond March 2014

EMA-FDA QbD Pilot Question & Answers

- Two sets of Q&As have been published jointly as a result of the pilot (8/20/13 and 11/4/13):

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148215.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500153784.pdf

- Topics include:
  - Expectations for Quality Target Product Profile (QTPP)
  - Expectations for Critical Quality Attributes (CQAs)
  - Classification of criticality in 3 tiers (e.g., Key Process Parameters)
  - Expectations for the manufacturing process description
  - Use of QbD for analytical methods (e.g., Analytical Target Profile (ATP) and Method Operational Design Ranges (MODR)
  - Design space verification

EMA-FDA Pilot Q&A - Design Space Verification

Design Space Verification Definition	Demonstration that the proposed combination of input process parameters and material attributes are capable of manufacturing quality product at commercial scale
Initial Design Space Verification	• Design space typically developed at laboratory or pilot scale • Often initial commercial scale demonstration of design space solely at or near target/normal operating ranges (NORs) • Not necessary to repeat all lab/pilot experiments at commercial scale
Design Space Verification Protocol	• Definition of the potential scale-up risks • List of unverified scale-dependent parameters • Discussion of control strategy related to scale-up risks • Description of any additional controls

Differences:

- EMA recommends a design space verification protocol be submitted in Section 3.2.R
- FDA recommends a design space verification protocol be maintained at the manufacturing site, and that a high level description be provided in the application

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500153784.pdf

EMA-FDA Pilot – Next Steps

- We are considering extending the pilot to gain additional experience in harmonized approaches
- We expect to additionally consider:
  - Continuous manufacturing
  - Use of protocols for post-approval change flexibility

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Proposed CDER Quality Reorganization

- FDA-CDER is proposing a reorganization that will consolidate our quality functions into a single, focused office

  OPQ Mission: The Office of Pharmaceutical Quality assures that quality medicines are available for the American Public

  OPQ Vision: The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality

The "Desired State"

A maximally agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drug product without extensive regulatory oversight

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OPQ Value Statements

- Put patients first by balancing risk and availability
- Have one quality voice by integrating review and inspection across product lifecycle
- Safeguard clinical performance by establishing scientifically-sound quality standards
- Maximize focus and efficiency by applying risk-based approaches
- Strengthen the effectiveness of lifecycle quality evaluations by using team-based processes

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OPQ Value Statements (cont.)

- Enhance quality regulation by developing and utilizing staf expertise
- Encourage innovation by advancing new technology and manufacturing science
- Provide effective leadership by emphasizing cross-disciplinary interaction, shared accountability and joint problem solving
- Build collaborative relationships by communicating openly, honestly and directly

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OPQ – Proposed Structure

- Office of Biotechnology Products
- Office of New Drug Products
- Office of Lifecycle Products
- Office of Process and Facilities
- Office of Surveillance
- Office of Operations
- Office of Policy
- Office of Testing and Research

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OPQ – Changing the Paradigm

- Greater utilization of staff expertise
- Full integration of process review and pre-approval inspection
- Integration of risk assessment into regulatory work products and decision making
- Surveillance function

Goal – More efficient and effective organization

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Thank you!

Questions, comments, concerns:

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