An FDA Perspective on Post-Approval Change Management for PAT and RTRT

IFPAC 2015
January 26, 2015

Christine M. V. Moore, Ph.D.
Acting Director, Office of Process and Facilities
FDA/CDER/OPQ

Post-Approval Changes for PAT and RTRT

• Where have we been?
• Where are we now?
• What are the roadblocks?
• What are the potential paths forward?

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 Quality Related Guidance and Initiatives

Initiatives

Guidance/Documents
Current Status of QbD (my observations)

- Science and risk based approaches in QbD are being embraced by many companies for development.
- Focus has been on enhanced product and process understanding rather than advanced manufacturing controls.
- Often the enhanced knowledge is not used to justify “regulatory flexibility” (e.g., design space, RTRT, protocols).
- Little advancement in achieving “true continual improvement”.

Current Status of PAT and RTRT (my observations)

- PAT is rarely used for regulatory control of manufacturing operations.
  - Increased interest with advent of continuous manufacturing.
- PAT occasionally used for process monitoring and trending.
  - For example, multivariate statistical process control (MSPC).
  - Often not filed in application, difficult to determine rate of adoption.
- RTRT implementation has seen very limited usage.
“True Continual Improvement”

• In order to reach “the desired state” we need to have a risk-based regulatory framework that:
  – Allows manufacturers to readily make changes under their quality system with little or no regulatory pre-approval
  – Provides confidence to the regulators that firm is making good decisions and that quality product will be available to the public, over the product lifecycle

• Will facilitate adoption of new technologies
  – For example: PAT, RTRT, continuous manufacturing

What are some hurdles to “true continual improvement”?

• Lack of clarity for regulatory notification of changes
• Regional differences for reporting changes
• Different timing for approval of changes from multiple health authorities
• Costs of filing changes
• Perceived regulatory risks
Potential Paths Forward

• Clarify what changes need to be reported
  – “Regulatory Commitments” / “Established Conditions”
• Establish a customizable system for risk-based change reporting
  – Change protocols
  – Post approval change management plans
• Clarify the infrastructure needed to effectively implement continual improvement
  – Risk management
  – Knowledge management

ICH Q12 Scope

• “ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”
  – Concept paper endorsed September 2014
• Products to be included:
  – New and approved drugs
  – Chemical, biotechnological and biological products
  – Each region would determine applicability to generics
• Proposed timeline:
  – Step 2 document by mid-2016
Q12 Issues to be Resolved

- Pharmaceutical Quality System aspects
  - Risk-based change management system
  - Expectations for lifecycle knowledge management
- Regulatory Dossier
  - Explore harmonized approach to “regulatory commitments”.
  - Delineate appropriate level of detail in dossier
- Post-Approval Change Management Plans and Protocols
  - Introduce and establish criteria for post approval change management plans concept & criteria
  - Encourage QbD as a foundation for post approval change management

Risk and Knowledge Management

- Risk and knowledge management are the cornerstones of an effective change management system
- These are discussed in Q10, but additional clarity needed
  - Clear expectations will boost regulator’s confidence and trust in the PQS and ability of the firm to manage changes
- Clear expectations will facilitate proposals for ‘operational flexibility’
  - Based on enhanced product and process understanding and the pharmaceutical quality system
  - Will help lower barriers for continual improvement and innovation to novel manufacturing technologies and PAT
"Regulatory Commitments"

- The ICH regions (US, EU, Japan) currently differ in their interpretation of "regulatory commitments and how this information relates to change reporting"
  - Some information in dossier is "supportive information" to aid in review
- Defining "regulatory commitments" will:
  - Encourage companies to provide appropriate level of detail and information sufficient for regulatory assessment
  - Clarify regulatory filing requirements during the commercial manufacturing phase of the product lifecycle
  - Potentially reduce post approval filings and ease continual improvement
  - Increase transparency of change management approaches

Why do we need "Regulatory Commitments"?

- Allow for more effective post-approval change management
  - Focus on high risk areas of the product and process
  - Reduce /or eliminate regulatory focus on well justified or demonstrated low risk areas
- Promote "knowledge rich" submission
- Facilitate innovation and continual improvement over the lifecycle
- Strengthen quality assurance and reliability of supply
- Provide the FDA pathways more efficiently regulate post-approval changes in a risk-based fashion
Post Approval Management Plans

• “Post approval management plan” not yet defined
  – Could contain elements of “regulatory commitments” and/or change protocols
• Provide a common platform for summarizing approaches to post-approval changes, with potential to
  – Enable reduced reporting categories of post-approval changes
  – Ease coordination with multiple health authorities
  – Achieve early agreement on change plan from regulators
  – Allows multiple changes or repetitive implementations of a specific change

Change Protocols - Advantages

• Allow for reduced reporting categories of post-approval changes
• Enable faster distribution of product after a manufacturing change
  – Eases coordination with multiple health authorities
• Achieve early agreement on change plan from regulators
• Allow multiple changes or repetitive implementations of a specific change
• Currently implementable under 21 CFR 314.70(e)
Current Status of Protocols

- Both EMA and FDA have regulations for protocols that can reduce reporting categories
- EMA and FDA have an ongoing pilot for “Parallel Assessment” or “Consultative Advice” for QbD containing applications
- FDA and EMA pilot extended to April 2016
  - Focus on protocols for flexibility of post-approval changes and new technologies

FDA Efforts Forward

- Participation on ICH Q12
- Included on CDER 2015 Priority Guidance Agenda:
  - Established Conditions: Reportable CMC Changes for Approved Drugs and Biological Products
  - Development of Near Infrared (NIR) procedures
  - Comparability protocols for Approved Drugs: Chemistry, Manufacturing and Controls Information
- Continuation of FDA/EMA pilot on QbD
- Establishment of the Office of Pharmaceutical Quality
Could “regulatory commitments” and post approval change management plans/protocols be beneficial for PAT and RTRT post-approval changes?

Absolutely yes!

• However, very little experience to date with implementation
• FDA and EMA are encouraging “trailblazing” companies to explore this area through the EMA/FDA QbD Pilot

CDER Office of Pharmaceutical Quality

Centralize quality drug review—creating one quality voice by integrating quality review, quality evaluation, and inspection across the product lifecycle

Consistent quality standards and risk-based approaches

“One Quality Voice”
Office of Process and Facilities (OPF)

- OPF ensures that quality is built into manufacturing processes and facilities over the product lifecycle.
- OPF will use risk-based approaches for efficient assessment of the following application-related aspects:
  - Manufacturing facilities, processes, and controls for certain drug substances and intermediates, and for all ANDA and NDA drug products.
  - Microbiological aspects for drug substances and drug products.
  - Facility and manufacturing process suitability for commercial manufacturing and consistency with the principles of CGMP.
- Additionally, OPF will partner with other offices internal and external to OPQ to establish standards for OPF-related review and inspectional activities.

OPF Interfaces

- Office of Process and Facilities
- Office of Lifecycle Drug Products
- Office of New Drug Products
- Office of Biotech Products
- Office of Regulatory Affairs
- Office of Compliance
- Office of Testing and Research
- Office of Program and Regulatory Operations
- Office of Policy for Pharm Quality
- Office of Surveillance
- Office of Lifecycle Drug Products
Summary

- Broad implementation of QbD, PAT and RTRT has been hampered by limited ability to make post approval changes and achieve “true continual improvement”
- Q12 promises pathways forward to enhance flexibility and ease of post-approval changes, through elaborating on:
  - Expectations for knowledge and risk management
  - How to define what needs to be reported, if changed
  - Protocols/post approval management plans
- FDA is willing to work with companies interested in exploring protocols for post approval changes
  - Could be inclusive of PAT and/or RTRT applications

Thank you!

Questions, comments, concerns:

CDER-OPQ-Inquiries@fda.hhs.gov