OPQ’s Lifecycle Approaches

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Presentation Outline

1. What Lifecycle Management Means to OPQ

2. OPQ’s Lifecycle Approaches
   a. Review Space
   b. Facilities
   c. Other Aspects

3. OPQ Initiatives/Tools for Lifecycle Management
   a. Overview – Integrated Quality Assessment (IQA)
   b. Risk Assessment, Management, and Communication
   c. ICH Q12 and Comparability Protocols

4. Summary/Conclusions
1. What Lifecycle Management Means to OPQ
1. What Lifecycle Management Means to OPQ

Lifecycle Management

Ensures medicines of consistent quality are available to the American public

Proactively prevents drug shortage situations
1. What Lifecycle Management Means to OPQ

Office of Pharmaceutical Quality (OPQ)

Promotes a lifecycle approach to product quality

Integrates

1. Functional areas
2. Data
3. Processes

Drug Product Knowledge Base
1. What Lifecycle Management Means to OPQ

- Apply knowledge about quality issues gained from the evaluation of the innovator product to the evaluation of the generic, as appropriate.

- Systematically document risks to product quality and utilize that information for assessing post-approval changes throughout the product’s lifecycle.
Building the Knowledge Base - OPQ’s Holistic Approach

• The drug product lifecycle can be divided into 4 phases based on the natural progress of product development.
  – OPQ focuses on the entire drug product line with an emphasis on knowledge sharing
1. What Lifecycle Management Means to OPQ

- The alignment of application review responsibilities across the various OPQ sub-offices:
  - Maximizes knowledge sharing and enhances decision making during the quality assessment.
  - Provides a bridge between brand and generic that helps ensure uniform and consistent standards and safeguards overall drug product quality.
2a. OPQ’s Lifecycle Approaches

Review Space
2a. OPQ’s Lifecycle Approaches – Review Space

**Immediate Office**
Director: Michael Kopcha
Deputy Director: Lawrence Yu

**Office of Program and Regulatory Operations**
Director: Giuseppe Randazzo

**Office of Policy for Pharmaceutical Quality**
Director: Ashley Boam

**Office of Biotech Products**
Director: Steven Kozlowski

**Office of New Drug Products**
Director: Sarah Pope Miksinski

**Office of Lifecycle Drug Products**
Director: Susan Rosencrance

**Office of Surveillance**
Acting Director: Sarah Pope Miksinski

**Office of Testing and Research**
Director: Lucinda Buhse

**Office of Process and Facilities**
Director: Robert Iser

**OPQ – Structured for Lifecycle Management**
2a. OPQ’s Lifecycle Approaches – Review Space

Review Functions within the Office of New Drug Products (ONDP)

• Responsible for product quality aspects* of NDAs which become the reference listed drug (RLD) for future generics.

• Begins building the knowledge base for the drug product line, which is expanded as ANDAs are submitted for the associated generic.

* Formulation, product design, clinically relevant specifications, and controls strategy related product attributes.
Review Functions within the Office of New Drug Products (ONDP)

- Also responsible for aspects of the ANDA, including:
  - Supporting DMFs (Drug Master Files) for the drug substance.
  - The biopharmaceutics sections of ANDAs* (i.e., dissolution aspects which link the clinical evaluation of the RLD with bioequivalence determinations for the generic).

* Also perform biopharmaceutics review for NDAs
Review Functions within the Office of Lifecycle Drug Products (OLDP)

- Responsible for product quality aspects of ANDAs, including formulation, product design, clinically relevant specifications, and control strategy related to product attributes.

- Generally leads the quality assessment of post-approval change supplements for brand (NDAs) and generic (ANDAs) and serves as the centralized home office.

Office of Lifecycle Drug Products
Director: Susan Rosencrance
Review Functions within the Office of Lifecycle Drug Products (OLDP)

• Centralizing the management of supplements within a single OPQ sub-office has a number of benefits:
  – Provides a uniform, consistent approach to post-approval changes; and promotes parity in the regulatory oversight of brand and generic drug products.
  – Provides a home-office that makes it easily manageable for all stakeholders; OND, OGD and Industry know who to contact when questions arise.
  – Agency receives approximately 5,000 supplements annually; need a system that can handle high-throughput efficiently; a centralized home office provides the right environment.
2a. OPQ’s Lifecycle Approaches – Review Space

Review Functions within the Office of Lifecycle Drug Products (OLDP)

- Knowledge flow/sharing is maximized through OLDP’s organizational structure.

- Knowledge about the brand drug gained during the post-marketing phase is continuously expanded, documented, and shared allowing for well-informed decision making during the quality assessment of generics in that same drug product line.
2a. OPQ’s Lifecycle Approaches – Review Space

Review Functions within the Office of Lifecycle Drug Products (OLDP)

OLDP Immediate Office

Division of Post-Marketing Activities I (NDAs)

Division of Post-Marketing Activities II (ANDAs)

Division of Immediate Release Products I
Division of Immediate Release Products II
Division of Modified-Release Drug Products
Division of Liquid-Based Drug Products

ANDA Pre-Marketing
2a. OPQ’s Lifecycle Approaches – Review Space

Review Functions within the Office of Process and Facilities (OPF)

Office of Process and Facilities
Director: Robert Iser

• Responsible for the quality assessment of the manufacturing process, facilities, and microbiological aspects of all application types (brand and generic).

• Maximizes knowledge sharing/flow between the field and review functions allowing for well informed decision making on complex manufacturing technologies.
OPF effectively and efficiently leverages its complementary expertise in process engineering and controls, quality microbiology, facility aspects and CGMPs, in the assessment of all manufacturing aspects of regulatory submissions in order to provide consistent and comprehensive approvability decisions over the product lifecycle.

**Enablers**

- Robust *training* programs
- Agreed upon quality assessment *standards*
- *Processes and procedures* that clearly link our assessment to risk
- Open and seamless *communication* within OPF and with our stakeholders
- Full *awareness* of issues related to and impacting OPF assessment roles
- *Decisions* that are data driven and based in current science
- *Transfer of knowledge over the product lifecycle (and over the entire supply chain)*
2b. OPQ’s Lifecycle Approaches

Facilities
2b. OPQ’s Lifecycle Approaches – Facilities

One Quality Voice - Inspection Management & Facility Assessment

OPF – Facility Assessment for pending applications & product specific pre- and post-approval inspections

OS – Risk Based Site Selection for Surveillance Inspections & Quality Intelligence

OMQ* – Focus on surveillance CGMP inspections, distributed drugs & enforcement actions

ORA – Inspectorate for all inspection types (PAI, post-approval, Surveillance & For Cause)

* OMQ is part of CDER’s Office of Compliance
Risk Based & Lifecycle PAI Determination

- Profile class unacceptable or not updated
- 2, 3, 4 trigger
- Challenge to state of facility control (e.g., many products)
- High Risk API (Derived from animals or different use)
- Substantially different API or FDF process at facility
- Narrow Assay Range (NTI) or titrated dose

PAI Triggers

- Named in application for the 1st time
- 1st application filed by the applicant
- First ANDA for an approved drug
- NME (not applicable to ANDAs)

**Priority** PAI Criteria per current CPGM 7346.832
2b. OPQ’s Lifecycle Approaches – Facilities

Risk Based & Lifecycle PAI Determination

• Not all priority criteria automatically trigger a PAI

• IQA team assessment of risk factors outside of priority criteria in to final decision
  – **Product Risk Factors**
    • Known issues with the RLD
    • Intended patient population
    • Breakthrough therapy or drug shortage
  – **Manufacturing Process Risk Factors**
    • Complex manufacturing process
    • Lack of development data or detailed manufacturing instructions
  – **Facility Risk Factors**
    • Inspectational history for relevant operations in application
    • Product quality defect signals (e.g., FARs, Recalls)
2b. OPQ’s Lifecycle Approaches – Facilities

Risk Based & Lifecycle Post-Approval Inspections

• Post Approval Audit Inspections Compliance Program (7346.843)

• Provide continuing inspection coverage of products marketed under a recently approved application

• Monitor for changes in the production and control practices that occur after approval (6-24 months)

• Coverage is based on reason for inspection (e.g. pre-approval inspection, PPQ concerns, past history)

• Trend towards an increase in post-approval inspections as a part of *OPQ’s lifecycle approach to quality assessment* – (Note: CPGM is a pre-OPQ version)
2b. OPQ’s Lifecycle Approaches – Facilities

Risk Based & Lifecycle Post-Approval Inspections

- No PAI on original submission
- Deficiencies found on PAI that did not yield WH
- Corrective Actions “promised”
- Stage 2 – PPQ not complete
- History of PAI findings / post-approval reports (FARs, etc.)
- Complex Process / Residual Risk
- First application for facility / new profile class

Post-Approval Inspection “Triggers”
2c. OPQ’s Lifecycle Approaches

Other Aspects
2c. OPQ’s Lifecycle Approaches – Other Aspects

Office of Testing & Research (OTR) Activities

- Method Verification Program
- Research to support quality, manufacturing, pharmaceutical equivalence, and immunogenicity evaluation of complex drug substances and products
  - Complex mixtures, peptides, drug-device combination products (e.g., orally inhaled and nasal products and transdermals), products containing nanomaterials, complex solid oral formulations, etc.
- RLD and ANDA physicochemical comparisons
  - Dissolution, particle size, structural analysis, and impurity profile identification, etc.
- Profile sample comparisons from bioequivalence clinical trial inspections
2c. OPQ’s Lifecycle Approaches – Other Aspects

Office of Testing & Research (OTR) Activities

• **ANDA Evaluation and Approval**
  – Develop scientific approaches and methods to support OPQ’s evaluation of pharmaceutical equivalence and product quality, as well as OGD’s evaluation of bioequivalence
  – Assess the validity of methods and data in ANDAs

• **Standards, Guidance, and Policy Development**
  – Develop methods and generate data to support generic drug product specific guidance and general quality guidance
  – Establish standards for product quality and pharmaceutical equivalence
  – Generate data to support policy and Agency’s response to Citizen Petitions

• **Response to Public Health Issues**
  – Support post-marketing quality monitoring
  – Address quality-related safety issues raised in adverse event investigations
3a. OPQ Initiatives/Tools for Lifecycle Management

Overview – Integrated Quality Assessment (IQA)
3a. OPQ Initiatives/Tools for Lifecycle Management

Overview – Integrated Quality Assessment (IQA)

• To best perform the assessment of drug products, OPQ has developed, piloted, and/or placed into practice a series of quality oversight tools

And more tools are still under development.....
3a. OPQ Initiatives/Tools for Lifecycle Management

Overview – Integrated Quality Assessment (IQA)

- These tools are generally applied to both brand and generic products to ensure parity.
An IQA approach is used for application review and pre-approval inspections for a more informed evaluation, whereby experts in all disciplines work together to generate an integrated quality assessment/decision based on risk, knowledge, and impact to consumer.

- Drug substance
- Drug Product
- Process
- Facility
- Microbiology
- Biopharmaceutics
- ORA Investigators
Maximizes each team member’s expertise and provides a risk-based and patient focused quality recommendation;

Team led by:

- Application Technical Lead (ATL); and
- Regulatory Business Process Manager (RBPM)
3b. OPQ Initiatives/Tools for Lifecycle Management

Risk Assessment, Management, Communication
Risk Assessment, Management, Communication

- Risk assessment is a critical component of the team-based review process.
  - OPQ employs a formal risk assessment to define the scope and extent of the integrated quality assessment.
  - The risk assessment increases the efficiency and effectiveness of the integrated quality assessment (IQA) by focusing review on the critical areas and potential failure modes that pose risks to patients.
3b. OPQ Initiatives and Tools for Lifecycle Management

Risk Assessment, Management, Communication

**Past:** Informal risk assessments

**Present:** Formal risk assessment for individual applications

**Future:** Drug Product Quality Dashboard

**Risk Rating Table**

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H = High Risk
M = Moderate Risk
L = Low Risk

**Present:** Formal risk assessment for individual applications

**Same Drug Product**

- Requires less emphasis by reviewer/investigator
- Requires more regulatory scrutiny by reviewer/investigator

**Future:** Drug Product Quality Dashboard

- ANDA x
- NDA
- ANDA y
3b. OPQ Initiatives and Tools for Lifecycle Management

Risk Assessment, Management, Communication

A unified risk evaluation framework for all drug products (brand and generic) that integrates the risk assessment with the existing drug product knowledge base.
Risk Assessment, Management, Communication

**Drug Product Quality Dashboard**

- Provides a risk profile and ranking of a drug product’s critical quality attributes (CQAs) during the pre-marketing phase.
- May also include information on the manufacturing site and quality system.
- Utilized in the post-marketing phase to assess proposed changes and the associated risks to product quality.
3b. OPQ Initiatives and Tools for Lifecycle Management

Risk Assessment, Management Communication

- Provides a comprehensive summary of the current state of quality for all approved NDAs/ANDAs of a particular drug product.
- Effective for lifecycle management as it signals high-risk areas that require close monitoring.
- Unique for each drug product and each manufacturer potentially allowing for individualized regulatory oversight of post-approval changes.
Is there a history of manufacturing risks at this facility that impact the application?

What are the manufacturing risks associated with the proposed unit operations in the application?

Is there limited knowledge about the manufacture of this product?

What’s the connection between manufacturing and clinical efficacy and patient safety?
3c. OPQ Initiatives/Tools for Lifecycle Management

ICH Q12 and Comparability Protocols
ICH Q12 –
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Scope:
• Applies to pharmaceutical products, including marketed chemical, biotechnological and biological products

Objectives:
• Best practices for management of post-approval CMC changes
• Emphasis on risk-based approaches (compliments ICH Q8 - Q11)
• Facilitates regulatory flexibility
• Increased transparency (e.g., better understanding of product development approaches in submissions)
• Increased predictability (e.g., clarity on post-approval change management)
• Better allocation of resources
• Supports innovation and continual improvement

3c. OPQ Initiatives and Tools for Lifecycle Management
3c. OPQ Initiatives and Tools for Lifecycle Management

ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

• Post Approval Change Management Protocols (PACMPs) a regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change
• An approved PACMP provides an agreement between the firm and the regulatory authority
• Some regions have a good deal of experience with PACMPs (aka Comparability Protocols) & some regions do not
• Q12 will include sections of PACMPs, types & illustrative examples

Note – Concepts very consistent with FDA draft Guidance on Comparability Protocols
3c. OPQ Initiatives and Tools for Lifecycle Management

ICH Q12 and Comparability Protocols

Comparability Protocols - Chemistry, Manufacturing, and Controls Information

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2003

Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2016
ICH Q12 and Comparability Protocols

• Little historical practice for comparability protocols in the generic space.

• The Comparability Protocols submitted in ANDAs were often:
  - Too general;
  - Lacked information to demonstrate product and process understanding;
  - Lacked a risk assessment.

• Often applicants were asked to withdraw these protocols, but with the issuance of the 2016 draft guidance there are renewed efforts for active review and using comparability protocols as lifecycle management tools.
4. Summary/Conclusions
4. Summary/Conclusions

Good lifecycle management with effective leveraging of the knowledge base enriches the quality assessment process, streamlines the evaluation of post-approval changes, enhances regulatory flexibility, and promotes continuous improvement.

Application Lifecycle Management

OPQ provides unique opportunities for building and using an integrated knowledge base that allows for quick, informed decisions during all stages of a product’s lifecycle.
• This unique paradigm in OPQ allows for:
  – Clearer identification of product risks for more informed decision making
  – Quickly addressing quality problems
  – Overall efficiency improvements
  – Greater parity in the regulatory oversight and quality assessment of brand and generic drugs
  – Reduced regulatory oversight and increased operational flexibility in the commercial manufacturing phase
4. Summary/Conclusions

A lifecycle approach to drug product quality leads to enhanced transparency, understanding, and trust between regulators and industry.

Promotes product improvements

Ensures a continuous supply of quality drug products

WiN WiN

A win for everyone, especially the patient
THANK YOU!