Lifecycle Management considerations as it includes changes throughout the lifecycle of the product

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Outline

- Lifecycle management of drug products
- Type of post-approval changes
- Enablers of post-approval changes
- Conclusion

OPQ Focus on Lifecycle Management

OPQ

Emphasizes a lifecycle approach to product quality using knowledge management

Monitor the state of quality for all regulated manuf. Sites and drug product

Ensures medicines of consistent quality are available to the American public

Proactively prevents drug shortage situations

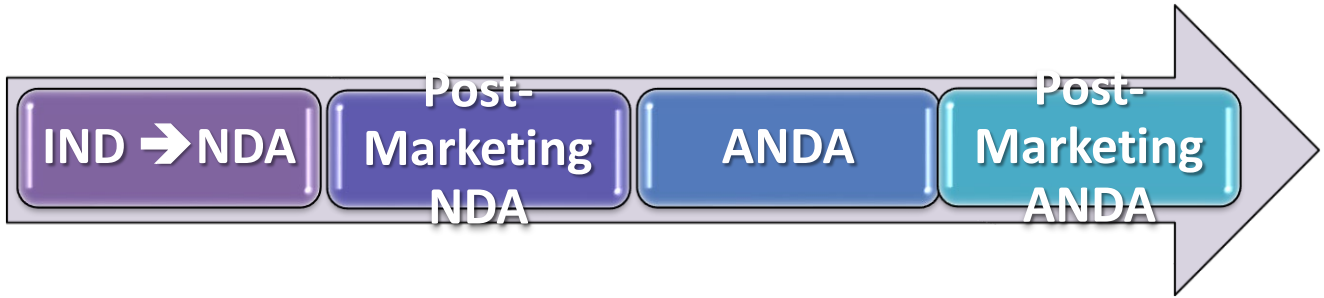
Enhances parity between brand and generic products

OPQ Focus on Lifecycle Management

OPQ's Holistic Approach

The product lifecycle can be divided into 4 phases based on the natural progress of drug product development.

Focus is given to the entire drug product line with an emphasis on knowledge sharing



Why Post-Approval CMC Changes?

- Continuous improvement
  - Product optimization
  - Incorporating a new technologies
  - Process improvement
- Regulatory Requirements/Commitments
- Product quality issues
- Business reasons
- Supply and demand

Typical Post-Approval CMC Changes

Drug substance

- New manufacturing site
- New supplier for regulatory starting materials
- Route/method of synthesis
- Manufacturing process
- In-process controls and/or drug substance specifications
- Retest period

Typical Post-Approval CMC Changes

Drug product

- New manufacturing site
- Manufacturing process and/equipment
- Formulation
- Container/closure system
- Device/ device material change in drug-device combination products
- Specifications
- Shelf-life
- Introduction of new strengths

Regulatory basis for Post-approval Changes

21 CFR 314.70

- § 314.70 Supplements and other changes to an approved application.
- The applicant must notify FDA about each change in each condition established in an approved application

Classification of CMC Changes

- Major changes (Prior Approval Supplements)
  - Cannot be implemented until approved
- Moderate changes (Changes Being Effected in 30 Days Supplements)
  - Can be implemented 30 days after submission at the applicants own risk
- Minor changes (changes being effected in 0 days supplement or Annual report
  - Can be implemented immediately upon receipt by FDA

Type of Supplements

- Efficacy supplement
  - New indication
  - Changes in the dosing regimen
  - Safety Changes (precautionary statements/Blackbox warning/new contraindications)
  - Addition of dosing information for special population
- Labeling supplements
  - Changes in the approved labeling, including prescribing information, immediate container and carton labels, medication guide, etc.
- CMC supplements
  - Changes in the drug substance and/or drug product manufacturing, analytical changes, site changes etc..

Enablers of Lifecycle Management

- Comparability protocols
- Post-approval change management protocol (PACMP) (ICH Q12)
- Emerging technology

Comparability Protocols

- A ***Comparability Protocol*** is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC post-approval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product (i.e., product quality).

Agency definition in draft guidance published April 2016

Comparability Protocols

- An optional way to manage post-approval changes [21CFR314.70© and 21 CFR 601.12(e)
- Can be used to implement a CMC post-approval change
- Facilitates post-approval changes and drug product lifecycle management
- Useful for drug products with accelerated manufacturing development
- Reporting category for implementation of CP may be downgraded depending on the product and process knowledge, risk assessment, and the controls strategy.

Comparability Protocols

- Can be submitted in the original applications (NDA, ANDA, and BLA) and in supplements
- Submitted post-approval, submission of a PAS is required.
- Can be submitted for one or more changes
- Can be submitted to cover an identical change(s) that affects multiple applications
- Can be for one-time change(s) or be used repeatedly for a specified change over the life cycle of a product

Comparability Protocols

When submitting a comparability protocol, consider:

- Effective use of knowledge and understanding of the product and manufacturing process
- A robust control strategy
- Risk management
- An effective pharmaceutical quality system

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

- Scope:
  - Applies to pharmaceutical products, including marketed chemical, biological and biotechnological products
- Objectives:
  - Best practices for management of post-approval CMC changes
  - Emphasis on risk-based approaches (compliments ICH Q8-Q11)
  - Facilitates regulatory flexibility

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

ICHQ12 contains the following fundamental tools and enablers to support a harmonized lifecycle management:

- Established Conditions (EC)
- Product Lifecycle Management (PLCM)
- Post-Approval Change Management Protocols (PACMP)
- Pharmaceutical Quality Systems (PQS)

Established Conditions (ICH Q12)

- Elements in an application considered necessary to assure product quality
- Legally binding when submitted and approved in the application
- Can be submitted in the original application or post-approval
- If submitted post-approval, submission of a PAS is required.
- Established conditions should be justified.
- PLCM should list proposed established conditions and filing categories for making changes.
- Filing categories could be other than that required by existing regulations and/or guidances
- Any change to ECs necessitates a submission to the regulatory authority

Post-approval Change Management Protocol (PACMP)

- Also known as “comparability protocols”
- 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

Post-approval Change Management Protocol (PACMP)

- Outline future change(s) to be made
- Tests, studies, etc. to be conducted to verify acceptability of change
- Proposed reporting category; often reduced compared to existing guidance and regulation.

Emerging Technology

What is Emerging Technology?

- Technology with the potential to modernize the body of knowledge associated with pharmaceutical development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences, due to its relative novelty

- Innovative or novel product, manufacturing process, or analytical technology subject to quality assessment (including review and inspection)

Emerging Technology

- Emerging technologies for small molecules
  - Continuous manufacturing of drug substance
  - Continuous manufacturing of drug product
  - Model-based control strategy for continuous manufacturing
  - Continuous aseptic spray drying
  - 3D printing manufacturing
  - Ultra long-acting oral formulation
- Emerging technologies for biological molecules
  - Controlled ice nucleation for lyophilization processes
  - Advanced process control: predictive modeling for process monitoring; close loop bioreactor control; feed forward impurity control

Changes to Container Closure Systems Inhalation Drug Products

- Inhalation drug products
  - Metered dose inhalers (MDIs)
  - Dry powder inhalers (DPIs)
  - Nasal spray
  - Inhalation solutions and suspensions

Container Closure System for Drug Device Combination Products

- Inhalation drug products
  - Propellant-based inhalation and nasal aerosols
    - Metered dose inhalers (MDIs)
    - Dry Powder inhalers (DPIs)
  - Non-propellant-based inhalation products
    - Nasal spray
    - Inhalation solutions and suspensions

Suitability of Container Closure System

- Compatibility with the drug product formulation (leachables)
- Performance (dose delivered)

Changes Over the Lifecycle of Drug Product

- Change in the components of drug product container closure system
- Changes in the device components

Factors Affecting Safety and Efficacy of Drug Products

- Materials used for fabrication of device and container closure systems
  - Leachables (safety and effectiveness)
  - Aerodynamic performance (delivered dose and aerodynamic particle size distribution (APSD) by surface properties of device part
  - Drug particle surface interactions (adhesion) affecting delivered dose and APSD
  - Biocompatibility

Meetings with FDA

- Types of meeting
  - Type A
    - Granted within 30 days
  - Type B
    - Granted within 60 days
  - Type C
    - Granted within 75 days

Relevant FDA Guidances

- Guidance for Industry: Changes to an Approved NDA or ANDA, 4/8/2004
- Guidance for Industry: Changes to an approved NDA or ANDA, Questions and Answers, 1/1/2001
- Guidance for Industry - Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry, September 2017
- Guidance for Industry - Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Guidance for Industry, MAY 2021
- Guidance for Industry – Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation, July 2002

Conclusion/Summary

- Application of ICH Q12 and emerging technologies enable enhancement of product quality and continual improvement of product manufacturing process and controls throughout the product lifecycle.
- Effective use of knowledge management and product and process understanding along with a robust control strategy, risk assessment, and pharmaceutical quality system are essential for regulatory flexibility throughout the drug product lifecycle management.

Thank You!