Overview of post-approval Chemistry, Manufacture, and Controls (CMC) changes to NDAs

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Post-approval CMC Changes

- Are there any post-approval reporting requirements for NDAs?
- Can I make changes post-approval without notifying the Agency?
- If I have to notify, how do I notify?

Post-approval CMC Changes

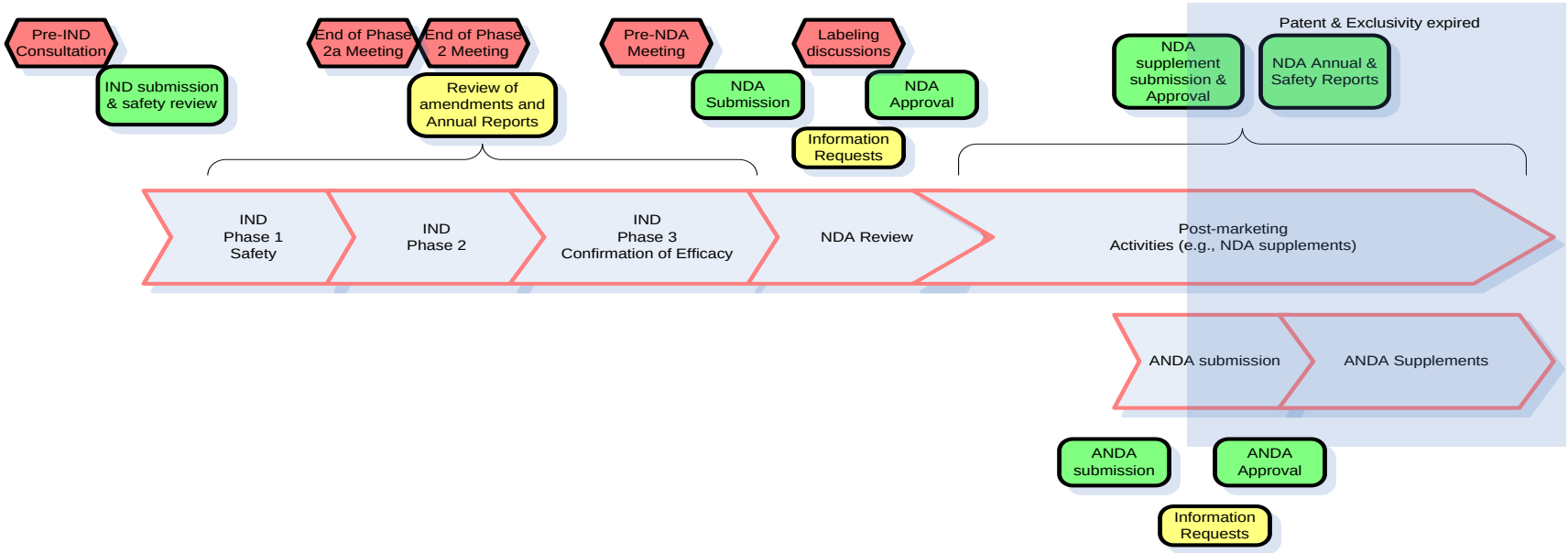
- What information and data will I have to provide to support the change?
- Where do I find information to make CMC changes postapproval?
- Are there any resources/guidances available that I can refer to make a change?

Learning Objectives

- Describe regulations and guidances for making post-approval CMC changes, including ICH Q12 and comparability protocols.
- Cover type of submissions to FDA for post-approval changes
- Discuss opportunities available for seeking guidance from FDA.

Lifecycle Management of NDAs

Drug lifecycle



Reporting Requirements for an Approved Application

Postmarketing Reporting Requirements for an Approved Application

21 CFR 314.70(a)(1)(i)

- Changes to an approved NDA

Postmarketing Reporting Requirements for an Approved Application

21 CFR 314.80 and 314.81 and Section 505(k)

- Adverse drug experience
- Field alert reports
- Annual report
- Other reporting

CMC Changes to an Approved NDA

21 CFR 314.70(a)(1)(i)

- Notification of each change in each condition established in an approved application (There are some exceptions).
- Notify FDA of the change in a supplement or in the annual report to the application.

CMC Changes to an Approved Application – contd.

21 CFR 314.70(a)(2)

- The applicant of an approved application must assess the effects of the change before distributing a drug product made with a manufacturing change (section 505 of the act)

Guidances

Guidance for Post-Approval CMC Changes

- Guidance for Industry: Changes to an Approved NDA or ANDA, 2004
- Scale-Up and Post-Approval Change (SUPAC) Guidances
- ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Guidance for Post-Approval Changes – contd.

- Comparability Protocol
- Continuous Manufacturing
- Emerging Technology

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Guidance for Industry

Changes to an Approved NDA or ANDA

U.S. Department of Health and Human Services Food and Drug Administration

Center for Drug Evaluation and Research (CDER) April 2004

CMC

Revision 1

Guidance for Post-Approval CMC Changes

Guidance for Industry: Changes to an Approved NDA or ANDA, 2004

- Recommends reporting categories for various changes
- Covers both drug substance and drug product

Guidance for Post-Approval CMC Changes – contd.

Guidance for Industry: Changes to an Approved NDA or ANDA, 2004

- Does not recommend specific information to be developed to assess the effect of the change

Guidance for Post-Approval Changes – contd.

Recommends reporting categories for:

- Components and composition
- Manufacturing sites
- Manufacturing process (including change in synthetic route for API)

Guidance for Post-Approval Changes – contd.

Recommends reporting categories for:

- Specifications
- Container closure system
- Labeling
- Miscellaneous changes (stability protocol, comparability protocol, change in shelf life)
- Multiple related changes

Guidance for Post-Approval Changes – contd.

Challenge Question:

A company wants to add a site to manufacture their drug X in the same city at a different location. Should they:

A. Add the site, start manufacturing and distribute the product?
B. Notify the FDA by submitting a supplemental application to the NDA?
C. Manage the addition under their pharmaceutical quality system?
D. Call FDA and let them know about the addition?

SUPAC Guidances

SUPAC Guidances

- SUPAC-IR for Immediate-Release Solid Oral Dosage Form
- SUPAC-MR for Modified Release Solid Oral Dosage Form
- SUPAC-SS for Non-Sterile Semisolid Dosage Form
- SUPAC: Manufacturing Equipment Addendum, 2014

SUPAC Guidances – contd.

Provide recommendations for postapproval changes to:

- Components and composition
- Manufacturing site changes
- Changes in batch size (scale-up or scale-down)
- Manufacturing (equipment and process)

SUPAC Guidances – contd.

Define:

- Level of change based on risk (Level 1, Level 2, and Level 3)
- Recommend CMC tests for each level of change
- *In-vitro* dissolution tests and/or *in vivo* bioequivalence tests for each level of change
- Documentation that should support the change and filing category

SUPAC Guidances – contd.

Challenge Question:

A company wants to change the composition of their immediate release tablet drug product. Which FDA guidance should they refer to?

- SUPAC MR
- SUPAC SS
- Changes to an approved NDA or ANDA
- SUPAC IR

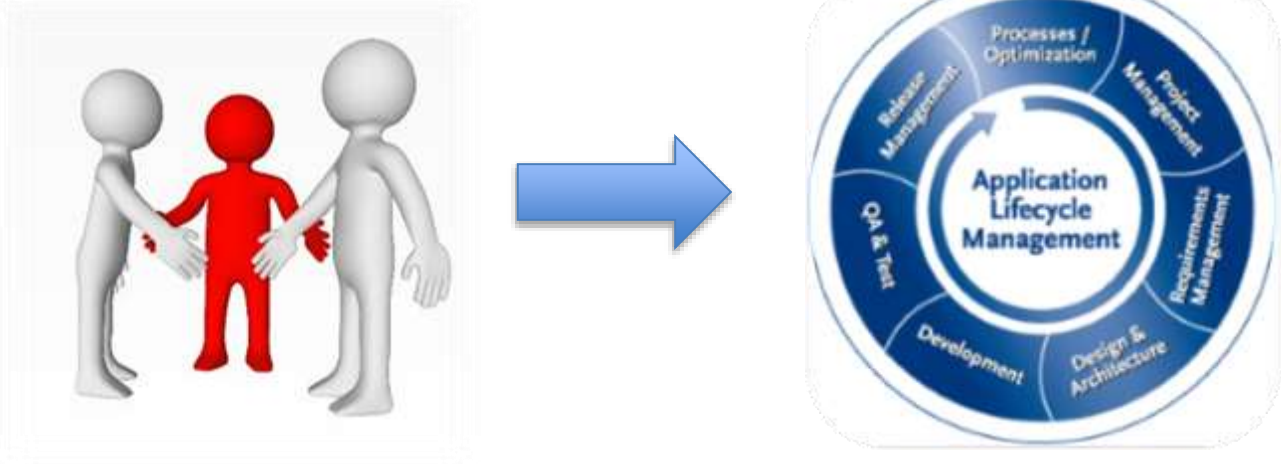
Comparability Protocol

Comparability Protocol

- Provides another means of managing post-approval changes.
- A Comparability Protocol (CP) 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 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*

Basic Facts about Comparability Protocols (CPs)

- Agency approval of the submission containing the CP provides the applicant with an agreed-upon plan to implement the change.



Comparability Protocol

What should be included in a CP?

- Description of and rationale for the proposed change(s)
- Specific tests and studies to be performed
- Acceptance criteria to be achieved

Comparability Protocol

What are the benefits?

- Facilitates the subsequent implementation and reporting of the change specified in the CP,
- Can result in moving the product into distribution sooner than if a protocol were not submitted.

Comparability Protocols

What are the benefits - contd?

- Changes can be made repeatedly over the life cycle of the product, or can be a one time change.
- Potential reduced reporting category for implementation of a CP.

Comparability Protocol

- Can be submitted in original application (NDA, ANDA, and BLA) and in supplements (PAS)
- Can be submitted for one or more changes
- Can be submitted to cover an identical change(s) that affects multiple applications

Comparability Protocols

Challenge Question

Can you submit a comparability protocol for the manufacturing process and packaging components?

- Yes
- No

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

ICH Q12

- Provides a framework to facilitate the management of post-approval changes in a more predictable and efficient manner.
- Describes tools and enablers to manage many CMC changes effectively.
- Could result in fewer submissions of supplements to NDAs.
- Applies to both drug substance and drug product.
- Encourages innovations and continual process improvement.

ICH Q12

Fundamental tools and enablers to support harmonized lifecycle management:

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

Established Conditions (ECs)

- Elements in an application considered necessary to assure product quality
- Legally binding when submitted and approved in the application
- Any change to ECs necessitates a submission to the regulatory authority
- Can be submitted in the original NDA or post-approval.

Supportive Information

Supportive information (non-established conditions)

- Conditions other than the established conditions
- Managed under company's pharmaceutical quality system
- No need for regulatory approval prior to implementation.

Established Conditions – FDA Experience

- Announced established condition pilot in February
- Accepted 9 applications (NDA, ANDA, and BLA)
- Approved for few products
- Approved for both drug substance and drug product

Emerging Technology Program

Emerging Technology Program

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 Program

Program Objectives:

- To serve as a centralized location for external inquiries on novel technologies
- To provide a forum for firms to engage in early dialog with FDA to support innovation
- To ensure consistency, continuity, and predictability in review and inspection
- To identify and evaluate potential roadblocks relating to existing guidance, policy, or practice
- To help establish scientific standards and policy, as needed

Emerging Technology – FDA Experience

With small and large molecules

Examples:

- Continuous manufacturing
- 3D printing
- Continuous aseptic spray drying
- Ultra long-acting oral formulation
- Closed aseptic filling system
- Controlled ice nucleation for lyophilization (biological molecule)

Continuous Manufacturing

What is continuous manufacturing?

- In a continuous manufacturing process, a drug product is manufactured continuously starting from active and inactive ingredients to the final product without any stop during manufacturing.
- Does not require large equipment or large space.
- Batch size can be increased or decrease without changing the equipment.

Continuous Manufacturing – FDA Experience

- Approved for a few products
- Approved for both the drug substance and drug product
- Approved for a semi-continuous manufacturing

Emerging Technology

The Agency encourages introduction of emerging technologies

CMC only meeting requests during development of new technology for approved NDAs greatly facilitate first cycle approval.

Contact Emerging Technology Team (CDER-ETT@fda.hhs.gov)
Refer to the September 2017 ETT guidance "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization."

Emerging Technology

Guidance:

- Guidance for Industry: Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization
- Guidance for Industry: Quality Considerations for Continuous Manufacturing

Guidance from FDA

- Meetings with FDA
  - Type A
  - Type B
  - Type C
- Contact the review division
- OPQ inquiry box (CDER-OPQ-Inquiries@fda.hhs.gov)

Summary

The Agency seeks to promote continuous improvement in drug product quality and encourages good lifecycle management:

- Follow regulations for making CMC changes to approved NDAs and for reporting requirements.
- Refer to available guidances for filing categories and information and data requirements to support the change.
- If needed, contact the Agency for further guidance.

Closing Thought

Prior to making any decisions for changes to the approved NDA, refer to the regulations and available guidances for recommendations and requirements for those changes. This will help in submitting a better submission to the Agency and will help Agency in the review and approval of the submission.

Thank You

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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