Regulatory Education for Industry (REdI)
Spring 2015

FDA SMALL BUSINESS AND INDUSTRY ASSISTANCE

REdI Conference

Hasmukh B. Patel, Ph.D.

Director (Acting)
Division of Post Marketing Activities I
OLDP/OPQ/CDER/FDA

September 30, 2015

An Overview of Post-Marketing Activities for NDAs

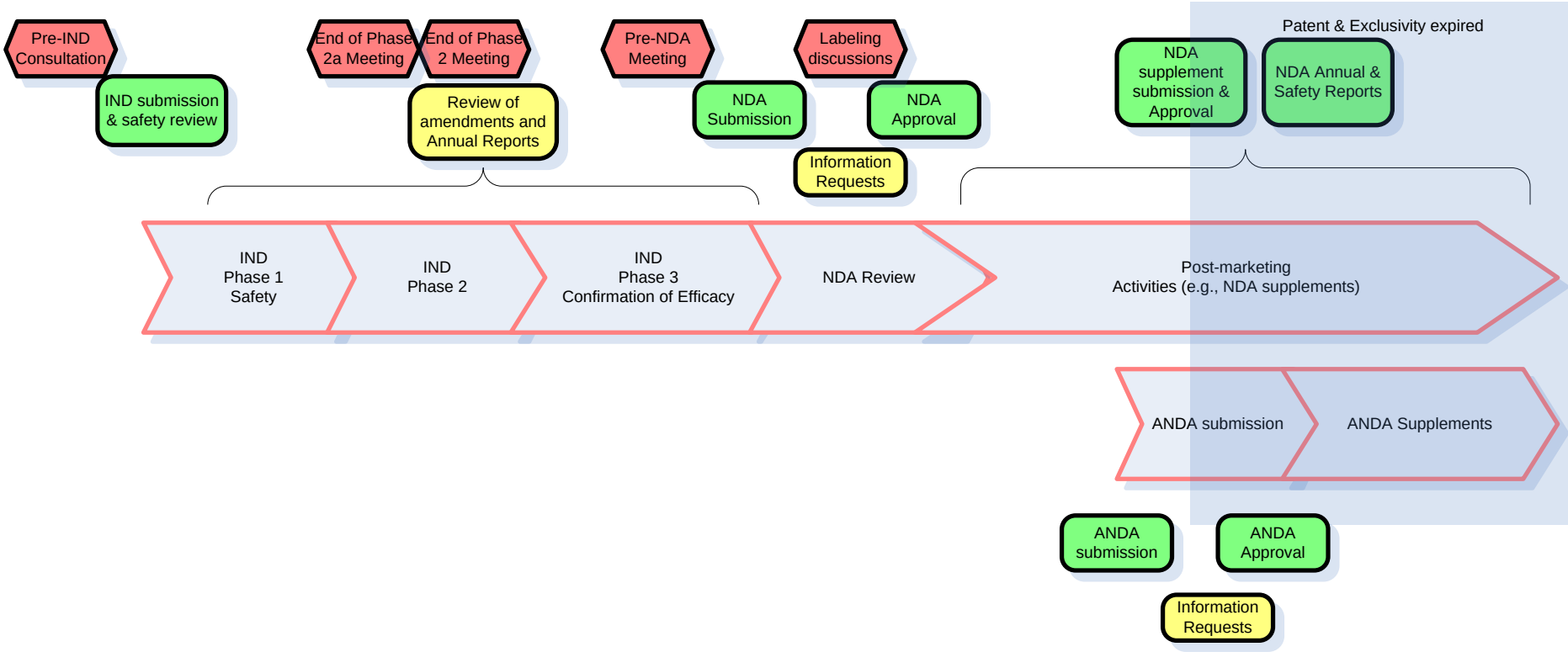
Redl Conference

September 30, 2015

Outline

- Post-marketing requirements for NDAs
- Post-approval changes
- Comparability protocols
- Application of Quality by Design (QbD)
- Drug Shortages
- Product quality issues

Lifecycle Management of NDAs



Life Cycle Management of NDAs

- Are there any post-approval requirements for NDAs?
- Can changes to an approved NDA be made?
  - What are the requirements?
  - What changes can be made?
  - How can the changes be made?
  - What information and data should be submitted?

Post-marketing Studies and Clinical Trials

- Studies conducted after NDA approval
- Agreed upon between the applicant and FDA
- Intended to further refine the safety, efficacy, or optimize use of the drug
- To ensure consistency and reliability of the product quality

Post-Marketing Studies and Clinical Trials – contd.

- **Post-marketing requirement (PMR)**
  - **Required post-marketing studies or clinical trials the applicants have agreed to conduct (Section 505(o) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 CFR subpart H)**
- **Post-marketing commitment (PMC)**
  - **Studies and clinical trials the applicants have agreed to conduct, but not required (Section 506B of the Act).**

Post-Marketing Requirement (PMR)

Required for all studies and clinical trials

- **For assessing or identifying a "serious risk" at the time of approval or after approval if FDA becomes aware of new safety information.**

Post-Marketing Requirement (PMR) – contd.

Reporting requirements

- **A timetable of completion**
- **Periodic reports on the status of the study, including whether any difficulties in completing the study**
- **Periodic report on the status of the clinical trial**

Post-Marketing Commitment (PMC)

- Not considered as meeting the statutory purposes in 505(o)(3)(B) and so not required.
- For drug and biologic quality studies , including manufacturing, stability, and immunogenicity studies that do not have a primary safety endpoint
- The applicant has agreed with FDA to conduct.

Post-Marketing Requirements - Other

- Risk evaluation and mitigation strategies (REMS) Required under certain circumstances (Sections 505-1 and 505(o)(4) of the Act)
- Safety related labeling changes (SLC)
- Pediatric studies (21CFR314.55)
  - Assessment required for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration
  - To assess the safety and effectiveness of the drug product for the claimed indications
  - For all relevant pediatric subpopulation

Post-Marketing Reporting Requirements

Reporting requirements as per 21 CFR 314.80 and 314.81 and Section 505(k)

- **Adverse drug experiences**
  - **Any adverse event associated with the use of the drug in humans, whether or not considered drug related**

Post-Marketing Reporting Requirements – contd.

Reporting requirements as per 21 CFR 314.80 and 314.81 and Section 505(k)

- **Field alert reports**
  - **Within 3 working days of receipt by the applicant**
  - **Drug product quality issues**
  - **Incidents causing the drug product or its labeling to be mistaken for, or applied to, another article**

Post-Marketing Reporting Requirements – contd.

Reporting requirements as per 21 CFR 314.80 and 314.81 and Section 505(k) - contd.

- **Annual report**
- **Other reporting**
  - **Advertisements and promotional labeling**
  - **Special reports**
  - **Notification of discontinuance**
  - **Withdrawal of approved drug product from sale**

Changes to an Approved Application

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

- **The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (There are some exceptions).**
- **Depending on the type of change, the applicant must notify FDA about the change in a supplement or by inclusion of the information in the annual report to the application.**

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)**

Reporting Categories for Post Approval Changes

- **Major change - Prior approval (PA) supplement**
  - **A substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety and effectiveness of the drug product**
  - **Review timeline 4 months**
  - **Expedited review request can be made if there is a public health need (drug shortage) or hardship on the applicant**

Reporting Categories for Post Approval Changes –contd.

- **Moderate change – Changes being Effected in 30 days (CBE-30) or Changes being Effected (CBE-0) supplement**
  - **A moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety and effectiveness of the drug product**
  - **Review timeline 6 months**

CBE-0: Moderate changes for which distribution can occur when FDA receives the supplement.

Reporting Categories for Post-Approval Changes – contd.

- **Minor change – Annual Report (AR)**
  - **Minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety and effectiveness of the drug product**

Types of Supplements

- **Efficacy supplement**
  - **To make one or more changes in the labeling**
  - **Add or modify indication, revise dose or dose regimen, new route of administration, make a comparative efficacy claim in naming another drug product**
- **Labeling supplement**
  - **Changes in the approved labeling**
- **Chemistry, Manufacturing, and Controls (CMC)**
  - **Changes in the API and drug product CMC**

Guidance for Post-Approval 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**
- **Does not recommend specific information to be developed to assess the effect of the change**

Guidance for Post-Approval Changes – contd.

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

Recommends reporting categories for

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

Guidance for Post-Approval Changes – contd.

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

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.

Scale-Up and Post-Approval Change (SUPAC) Guidances: SUPAC-IR, SUPAC-MR, and SUPAC-SS

- **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

SUPAC Guidances 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

SUPAC Guidances 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**

Assessing the Effect of Manufacturing Changes

- Compare the product before and after the change – are the test results equivalent?
- Side by side comparison of each and every step where applicable
- Conformance to approved specifications

Assessing the Effect of Manufacturing Changes – contd.

- **Additional testing (recommended when appropriate)**
  - **New impurity or an impurity above a previously qualified level – need for toxicology studies?**
  - **Bioequivalence when required under 21 CFR Part 320 (multipoint and/or multimedia dissolution profiling and/or an *in vivo* bioequivalence study)**

Supplement - Examples

Manufacturing site changes for

- **API and drug product**
- **Release and stability testing of the API and drug product**
- **Specific tests of API and drug product (e.g., sterility testing for drug product)**
- **Packaging of drug product**

Supplement – Examples (contd.)

Manufacturing site change for drug product (including contract facilities)

- **Are there other changes in addition to the site change?**
- **No - is the site a new site never inspected by FDA?**
  - **Yes, submit a prior approval supplement.**
  - **No - does it have a current GMP status for the type of operation to be performed?**
    - **Yes, submit a CBE-30 supplement.**
    - **No, submit a PA supplement.**

Supplement – Examples (contd.)

Manufacturing site change for drug product (including contract facilities) – contd.

- **If there are other changes in addition to the site change such as equipment, process, etc., filing category will depend on the changes (major or minor) and on the impact of those changes on the product quality**

Supplement – Examples (contd.)

Manufacturing site change for drug product (including contract facilities) – contd.

- **Make sure the manufacturing site(s) is ready for inspection at the time of supplement submission.**
- **Provide correct information on the site(s) such as function (of each site if multiple sites), FEI, contact person, address, and GMP status, if any.**
- **Assess the effect of the manufacturing site change on the product quality**

Supplement – Examples (contd.)

Manufacturing site change for drug product (including contract facilities) – contd.

- **Test documentation**
  - **Batch release data**
  - **Stability data**
  - **Additional test data demonstrating that the product before and after the change is equivalent**
  - **Product specific data, if applicable**

Refer to appropriate guidances

Other CMC Post-approval Changes

- Additional dosage form(s)
  - Tablets, extended release product, modified release product, capsules
- Additional strengths
- Additional fill volumes for liquids
- Additional packaging presentations
- Lyophilized formulation to a liquid formulation
- Vial presentation to pre-filled syringes
- Changes outside approved design space and control strategy

Action on supplements

- Approval
- Complete response
  - List deficiencies in the supplement
  - For PA, requires approval for implementation
  - For CBE-30 and CBE-0, drug product manufactured using the proposed change can be distributed unless FDA orders the applicant to cease distribution. However, the applicant should resolve all deficiencies in the letter.

CR letter deficiencies

Common CR deficiencies:

- **GMP issues with the site**
- **DMF not adequate**
- **For sterile products, microbiology related issues**
- **Qualification of new impurity(ies) or of impurities above the qualified levels in the original NDA**
- **Justification for the proposed limits for tests in the specification**
- **Stability data for the proposed changes**
- **Sufficient details of the analytical methods used**

Meetings with FDA

Type of meetings with the Agency

- **Type A**
  - **Needed to help an otherwise stalled product development (dispute resolution)**
  - **within 30 days**
- **Type B**
  - **Pre-IND, End of Phase 2 and 3, Pre-NDA**
  - **Within 60 days**

Meetings with FDA – contd.

Type of meetings with the Agency

- **Type C**
  - **Regarding the development and review of a product**
  - **Within 75 days**

Comparability Protocol

A well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product.

Comparability Protocol

- Describes the changes covered under the protocol
- Specifies the tests and studies to be performed (analytical procedures and acceptance criteria).
- The submission of a comparability protocol is optional.
- PA Supplement
- CBE-30 supplement for implementation of the protocol (one category lower)

Comparability Protocol – contd.

Type of changes proposed in a comparability protocol

- **Manufacturing site change for API and Drug Product**
- **Formulation**
- **Container/closure system**
- **Manufacturing process**
- **Changes outside approved design space and control strategy**
- **Continuous manufacturing process**

Application of QbD

Establish a design space and control strategy

- **Design space for unit operations in the manufacturing process**
- **Control strategy and Real Time Release Testing (RTRT)**
- **PA supplement**

Application of QbD – contd.

Changes to approved design space and control strategy

- **Changes to design space for unit manufacturing operations**
- **Changes to control strategy**
- **Submission of a comparability protocol or a PA supplement**
- **CBE-30 supplement or annual report for implementation of the design space and control strategy**

Other post-approval activities

- Drug shortages
  - For medically necessary product
  - Shortages due to quality and manufacturing issues
- Product quality issues
  - Not meeting specifications
  - Particulates in the product
  - Compatibility with container closure system or devices used to administer

Drug Shortages

Medical necessity

"A medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug, available in adequate supply, that is judged by medical staff to be an adequate substitute."

Expedited reviews for prior approval supplements submitted to address drug shortages

Drug shortages

Drug shortages – causes

- **Sterility: Bacterial and fungal contamination**
- **Particulates: Glass, metal or fiber in vials**
- **Crystallization: Drug may form crystals**
- **Precipitates: Reaction between drug and container or diluent**
- **Impurities: Can be toxic**
- **Degradant: Lead to less effective drug product**
- **Equipment breakdown**
- **Natural Disasters**

References

Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

References

Changes to an Approved NDA or ANDA

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf

CMC Postapproval Changes to be Documented in Annual Reports,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217043.pdf

SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070636.pdf

References

SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf

SUPAC-SS: Nonsterile Semisolid Oral Dosage Forms: Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070930.pdf

SUPAC: Manufacturing Equipement Addendum

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346049.pdf

References

Comparability Protocols – Chemistry, Manufacturing, and Controls, draft

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070545.pdf

Formal Meetings Between the FDA and Sponsors or Applicants
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

Guidance for Industry: Q3A (R) Impurities in New Drug Substances

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf.

References

Guidance for Industry: Q3B (R2) Impurities in New Drug Products

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf

Thank You!

Questions????

Please complete the session survey:

surveymonkey.com/r/DRG-D2S6