Case Study: Supporting Post-approval Changes Based on Product and Process Understanding

Yihong Qiu, Ph.D.
Research Fellow
Abbott Laboratories

Outline

- Introduction
  - Product/Process Changes and Justification
    - Regulatory guidelines
    - Product and process understanding
    - Role and utility of In Vitro-in Vivo Relationship (IVIVR)
- Case Studies
  - DR Tablet
    - Multiple related changes
  - ER Tablet
    - Specification change
  - ER Tablet
    - Site, Formulation changes, Quality control
- Summary
Introduction

- Pharmaceutical products rarely remain unchanged throughout product lifecycle

  Drug substance; Raw materials; Composition; Shelf-life; Process; Equipment; Site; Packaging; Specifications; Test methods, etc.

- Assess and understand the effect of changes on product quality and performance. Provide supporting data and justification for the changes in regulatory filing

Requirements and expectations

- Studies need to be conducted to understand and demonstrate the effect of changes
  - Assess the effect of post-approval changes on the identity, strength, quality, purity and potency, and ensure a safe and effective product
  - Assess the level of risk posed by changes
  - Demonstrate that products manufactured prior to and subsequent to a change are equivalent
  - Make and report changes to an approved application and meet requirements
    - Comply with requirements for appropriate reporting category
    - Use comparability protocols to save time and effort by reducing reporting requirements and streamlining processes
  - Determine the extent of validation needed for post-approval changes and meet the regulatory requirements
Introduction

- Justifying changes (FDA) / variations (EMA)

(I) Guidance of regulatory agencies

- FDA, EMA (EMEA), Health Canada, MHLW, SFDA, ANVISA,…
  - Major changes: Substantial potential to have an adverse effect (FDA)
  - Moderate changes: Moderate potential to have an adverse effect (FDA)
  - Minor changes: Minimal potential to have an adverse effect (FDA)

- Reporting categories
  - FDA
    - Annual Report (AR)
    - Changes-Being-Effected (CBE); Changes-Being-Effected-in-30-Days (CBE-30)
    - Prior Approval Supplement
  - EMA
    - Type 1A, Type 1B and Type II

Examples of Regulatory Guidance

- FDA
  - IVIVC-MR (1997)
  - IR-Dissolution (1997)
  - SUPAC-Addendum (1999)
  - BCS/Biowaiver (2000)
  - Changes to Approved NDA/ANDA (2004)

- EMA
Introduction

- Justifying changes (FDA) / variations (EMA)
  
  (II) Product and process understanding

  Use our knowledge
  
  - Design and operating principles of both product and manufacturing process
  - Characteristics of API and excipients
  - Development and production history/experience

  Evaluate potential impact
  
  - Product quality, in vitro and in vivo performance, risk to patients

  Provide justification
  
  - Based on scientific assessment of the changes and associated risk

Introduction

- Justifying changes (FDA) / variations (EMA)
  
  (II) Product and process understanding

  - Assessing the effect of changes on the identity, strength, quality, purity, or potency of the drug product that may be related to the safety or effectiveness of the drug product

  - Focus: Two most critical product quality and performance attributes linked to safety and efficacy
    - Stability
    - Bioavailability

  - Solid dosage forms
    - API, formulation, process, packaging, etc. ⇒ In vitro dissolution ⇒ In vivo dissolution ⇒ Bioavailability
    - An important tool for providing clinical linkage to in vitro drug release: In vitro-in vivo relationship (IVIVR)
**Linking *In Vitro* and *In Vivo* Performance**

**In vitro vs. in vivo data**

- **In vitro test** (e.g., drug release)
- **In vivo drug release and absorption** *In the GI tract*
- **In vivo response** (e.g., PK profiles)

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**In Vitro and In Vivo Relationship** *(IVIVR)*

- **Quantitative (IVIVC)**
- **Non-quantitative (e.g., rank order)**
- **None**

**In vitro test**

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**In vivo PK**

- **(I) Predictive** (*= or ≥ 1:1*)
- **(II) Rank order**
- **(III) Under- or non-discriminative**
- **(IV) Over-differentiating**

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**INTERPHEX 2012**
May 1-3, 2012
Title – Date – Javits Center – New York, NY
Utility of IVIVR

- With a validated IVIVC
  - Establish *in vitro* dissolution as one of the most important CQA
    - Serve as a critical tool for product and process understanding
    - Predict and control *in vivo* performance within the life cycle of a product
  - Prior to product filing
    - Guide formulation and process design
    - Facilitate application of QbD principles in product development
    - Aid scale-up, optimization and risk management
    - Assess and define CPP, design space, risks, control strategy, etc
    - Justify meaningful specifications for regulatory submission
  - Post-approval
    - Planned or unintentional changes/variations of raw materials, composition, process, site or equipment
      - Ensure consistent quality and performance of commercial products
      - Reduce regulatory burdens via biowaiver

- Without a validated IVIVC
  - With non-quantitative IVIVR
    - Understand *in vitro* and *in vivo* behaviors and define relationship based on the knowledge of API, product, process and test method
    - During development
      - Support formulation and process screening and understanding
      - Justify biorelevant specifications
    - Post-approval
      - Assess and justify changes

- No IVIVR
  - *In vitro* dissolution: Just a physical test for QC
Case Studies
(within and outside guidance)

- Justify changes of composition, process, equipment, site, specification
- Set meaningful dissolution specification and control product quality
- Biowaiver

Case Study #1: A Delayed-Release Tablet

- Drug and Product
  - BCS I/II, Narrow therapeutic index
  - Enteric coated tablets (HP-55; solvent based)
    - Strength: High, medium and low
    - Process: Wet granulation and pan coating
- Background
  - On the market for > 20 yrs.
  - Manufacturing site transfer
    - PAC: Multiple related changes: Site/Composition/Process/Equipment
- Objectives
  - Understand potential impact on product quality and performance
  - Justify a biowaiver
Case Study #1: A Delayed-Release Tablet

– Summary of Changes
  • Component: Ink for printing
  • Processing/Equipment (SUPAC L-3)
    ▪ Low-shear planetary mixer/oven drying => high-shear Single Pot Processor (SPP)
    ▪ Granulation and coating solvents (EtOH => IPA; grade)
    ▪ Slightly different total solids content of coating solution
    ▪ Low strength: Perforated coating pan => a conventional pan and the smaller batch size
  • Site (SUPAC L-3)

– Approach
  • Review of product and manufacturing history
    ▪ Product licensed and manufactured in various markets
      • Formulation for various markets: Same
      • Process: Slight variation due to local equipment availability
      • Specifications, in-process control and test methods: Same
    ▪ Consistent product quality and robust manufacturing for >20 yrs

– Approach (Cont’d)
  • Comparison of product performance
    ▪ Tablet Characteristics: All tablets met the established acceptance criteria (potency, content uniformity, acid resistance, hardness and physical inspection, etc.)
    ▪ In Vitro Drug Release
      • Two lots for each of the three strengths from both sites
      • Testing at 4 pH values to evaluate effective enteric protection and subsequent drug release
    ▪ In Vivo Performance
      • Evaluate potential impact of the changes: (1) In vivo BE study or (2) IVIVC
      • No-quantitative IVIVR: Explore a range of in vitro drug release that demonstrates acceptable in vivo performance
Case Study #1: A Delayed-Release Tablet

- **In Vivo Performance (Cont’d)**
  - A previous BE study of the US product was used to investigate IVIVR
    - A single dose, fasting, 3-way crossover study (n=15)
    - Mapping in vitro drug release
      - Tablets studied differ in granulation solvent, rate-controlling polymer, coating solvent and processing parameters
      - Two different formulations containing varying amounts of rate-controlling polymer (10% vs. 14%) with fast and slow drug release are bioequivalent
      - Drug release of the tablets from the new site are within the region of bioequivalence

- **Justification of a Biowaiver**
  - **Drug properties**
    - Stable, soluble and permeable. > 90% BA demonstrated with both DR and ER tablets in multiple biostudies
  - **Formulation**
    - The tablet core consists of high loading of the soluble active, and hydrophilic excipients, resulting in rapid drug release upon dissolution of the enteric coating
    - The enteric polymer has a long history of proven performance. Changes are unlikely to result in changes in functionality of the core composition and the enteric coating
    - The *in vivo* performance remains unaltered when more significant changes in core and coating compositions were made
  - **Processing**
    - Major changes: Low shear to high shear granulation and drying => did not lead to changes in subsequent tablet processing or product quality attributes
    - A long history of manufacturing the same product using high shear granulation and fluid-bed drying in other markets that showed consistent in vivo performance
Case Study #1: A Delayed-Release Tablet

- Justification of a Biowaiver (Cont’d)
  - **Product characteristics**
    - Tablets met the same specifications and in-process tests: Unchanged stability and functionality
    - *In vitro* drug release test: More sensitive and discriminating than the *in vivo* test
  - **Pharmacokinetic and safety/efficacy considerations**
    - Risks to patients are assessed by analyzing different theoretically possible scenarios based on knowledge of the API and related products
      1. If enteric protection is either inadequate or compromised
      2. If enteric coating does not dissolve quickly in the proximal bowel
      3. If the core tablet does not disintegrate and dissolve following dissolution of the enteric coating in the small intestine
      4. If a combination of “Scenarios # 2 and #3” occurs
  - **Outcome:** Biowaiver granted

Case Study 2: A FDC Extended-Release Tablet

- Drug and Product
  - API’s: BCS I; stable
  - A FDC bi-layer tablet: IR + ER matrix; Wet granulation
- Background
  - Multiple strengths available worldwide for > 25 yrs
    - Different specifications, test methods, packaging, etc. depending on the markets, for example
      - Dissolution specifications differ between dosage strengths
      - Dissolution specifications differ among approved commercial markets
      - *An out of specification value in one market may be within specification in other markets*

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Strength Q(1hr)</th>
<th>Q(2hr)</th>
<th>Q(3.5hr)</th>
<th>Q(4hr)</th>
<th>Q(5hr)</th>
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</tr>
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</table>
Case Study 2: A FDC Extended-Release Tablet

- Objective
  • Harmonize dissolution specifications
    ▪ Align dissolution specifications with current regulatory standards
    ▪ Propose dissolution limits based on historical *in vivo* data
  • Harmonize product expiry period
    ▪ Align expiry period for all dosage strengths based on revised dissolution specifications and historic stability performance

- Justifying or Changing Specification for ER products
  • Biostudy study
    ▪ Setting dissolution limits: ±10% of the pivotal biolot without IVIVC (FDA, EMA)
    ▪ Changing/widening spec: Bioequivalence (BE) study
  • IVIVC
    ▪ Supporting spec setting or change, and risk assessment
  • IVIVR
    ▪ Also useful in supporting spec setting or change

Case Study 2: A FDC Extended-Release Tablet

- Understanding Product Design and Performance
  • Different strengths
    ▪ Qualitatively the same in compositions
    ▪ Share the same drug release mechanism and manufacturing process
    ▪ A range of *in vitro* dissolution profiles observed
  • *In vivo* performance of high and low strengths
    ▪ Bioequivalent to the reference products with proven efficacy and safety
Evaluation of *In Vitro* and *In Vivo* Data

**In vivo** data
- Historical multiple-dose bioequivalence studies in the regulatory submission documents
  - **US NDA;** *n* = 2 x 50 (1995); *High and low strengths*
  - **EU filing: Middle strength**
    - #1: *n* = 4 X 24; (1993)
    - #2: *n* = 30; (1996)

**In vitro** data
- COA’s of clinical lots

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**Case Study 2: A FDC Extended-Release Tablet**

Assessing Scattered Plots of *In Vitro* and *In Vivo* Data
- Explore a dissolution region where bioequivalence had been shown
  - Compare dissolution values at each time interval, *Q*(*t*) with *C*<sub>max,ss</sub> and AUC, for the lowest and highest strengths to assess IVIVR

(a) Study TV-4-CP (120 and 240 mg) : *C*<sub>max,ss</sub> vs. *Q*(*t*)
(b) Study TV-4-CP (120 and 240 mg): AUC vs. *Q*(*t*)

*Within the dissolution range of the biobatches, both *C*<sub>max,ss</sub> and AUC, appear to be insensitive to the dissolution rate (lacking a trend)*
Case Study 2: A FDC Extended-Release Tablet

Mapping Dissolution Range/Space

- Compare bioequivalence parameters (ratio of $C_{\text{max,ss}}$ and $\text{AUC}_{\tau}$) with $Q(t)$’s to define a dissolution space in which bioequivalence can be assured

- Within the range studied, both highest and lowest strengths used in the pivotal study have been shown to be bioequivalent to the reference products

(a) Study TV-4-CP (120 and 240 mg):
Ratios of $C_{\text{max,ss}}$ and $\text{AUC}_{\tau}$ vs. $Q(t)$

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<th>54.0</th>
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<td>$F(C_{\text{max}})$ or $F(\text{AUC})$</td>
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Justification of Revised Specification

Dissolution Mapping
- Results from Pivotal Study
- Supported by data of the middle strength

Additional Evaluation and Considerations
- Understanding API properties
- Understanding product and process
  - Product design, material properties, release mechanism, interactions, prior knowledge
- Understanding in vitro test method and product performance

Conclusion
- The in vitro test is over-discriminating
- Observed difference/variability in drug release
  - Inherent variability of the material/product
  - Artifact of the test method
  - Minimal potential to have in vivo impact within the mapped dissolution range
- Specification limits require harmonization to meet current regulatory expectation
Original vs. New Dissolution Specifications

- **Specification Change**
  - Modify and harmonize dissolution specifications to align limits with the in vivo performance and current regulatory expectation
  - Regulatory guideline, release kinetics and duration

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Strength</th>
<th>Q(1hr)</th>
<th>Q(2hr)</th>
<th>Q(3.5hr)</th>
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- **Outcome**
  - Approved by regulatory agencies in ICH countries

Case Study 3: An Extended-Release Tablet

- **Drug and Product**
  - API: BCS I/II; NTI
  - ER tablets
    - Strength: 500 mg and 250 mg
    - Process: Wet granulation

- **Background**
  - Near zero-order in vivo absorption for \( \approx 20 \) hrs
  - A validated IVIVC established during development

- **Objectives**
  - Development: Setting dissolution specification
  - Post-approval: Biowaiver for Site change
  - Production: Quality control
• Level A IVIVC Established
  – Model Validation and Prediction
  • Six different formulations
    ▪ Modeling and internal validation:
      Three formulations
    ▪ External validation: (1) two variants of commercial formulation (2) new formulation (strength) (3) commercial batch

![Graphs showing % Released vs Time and Plasma VPA Concentration vs Time for different study conditions](image)

Applications
(I) Setting Dissolution Specification
  – Proposed spec limits based on the pivotal biobatch
    – Evaluate using IVIVC
  – Statistical Assessment
    – Review of all R&D data including stability data (> 1400 tablets)
      • Variability
    – Evaluation of Future Commercial Manufacturing
      • Monte Carlo simulations: Computer script randomly samples 10,000 groups of 6 tablets
        – Tests against proposed specifications to calculate:
          Rates of passing L1, L2, and L3
        – Assess probability of batch failures
    – Results confirmed in commercial production (8 years)
Case Study 3: An Extended-Release Tablet

(II) Biowaiver
- Qualify a second manufacturing site
- Development of a new strength (formulation)

(III) Control of commercial product quality
- 2 yrs after product launch (> 100 batches manufactured)
  - Trending in dissolution performance observed and investigated
    - Root cause: Unexpected changes in one of the critical variables (material, composition, processing)
    - Timely identification and resolution of the problem (additional controls put in place)
- IVIVC method: Predictive of in vivo absorption
- Conventional method (SIF, pH6.8): very low variability, non-discriminating

Summary

- Supporting Post-approval Changes
  - Regulatory Guidance
  - Understanding and Control of Drug Substance, Product and Manufacturing Process
    - Within and outside of guidance scope
    - IVIVR: an important tool
      - Link in vitro quality attributes with in vivo performance
      - Facilitate product and process understanding (QbD)
      - Facilitate setting meaningful spec, risk assessment and control (QbD)
      - Support biowaivers for changes and offer opportunities for regulatory flexibility
Summary

- IVIVR
  - Quantitative IVIVR (IVIVC): A critical tool for linking *in vitro* quality attributes with *in vivo* performance and facilitating product and process understanding and changes
  - Non-quantitative IVIVR: May also be useful for supporting changes in product, process, specification, etc. especially when combined with the knowledge of API, product, test method and their interplays

- Case studies
  - Successful application of quantitative and non-quantitative IVIVR combined with product/process understanding
    - Justifying specification change/harmonization
    - Support biowaiver for multiple related changes

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Development and Application of IVIVR

- Understanding the influence of API, formulation/process, test method and condition, GI environment and their interplays on in vitro and in vivo behaviors/performance of a dosage form.

In vitro performance & Test method(condition)

PK performance & Biopharmaceutics, Biologic/physiological factors

Product design (Composition, Properties of components, Dosage form and process factors)

Interplay

In vivo

Biopharmaceutics: The study of the relationships between physical and chemical properties, dosage form, and administration of a drug and its activity in humans and animals

Illustration: Level A IVIVC

In vitro drug release

Observed or predicted Cp profiles

Biostudy

Deconvolution

IVIVC model

Modeling relationship

Convolution

(1) Validation

(2) Prediction

(3) Validation

Disposition Function

IV or IR Cp profiles

Estimated in vivo input

Validation

Prediction

Validation

Convolution

IVIVC model

Modeling relationship

Biostudy

Deconvolution

Observed or predicted Cp profiles

In vitro drug release

In vitro

In vivo