Case Studies of In vivo Pharmacokinetic Bioequivalence Study to Support SUPAC Changes for Solid Oral Drug Products

Hongling Zhang, Ph.D.
Division Director
Division of Bioequivalence II (DB II)
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (USFDA)

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Outline

- Overview of SUPAC Changes with in Vivo BE Recommendations
- General Considerations for in Vivo BE Study Design to Support SUPAC Changes
- Case Studies with Special Considerations
- Summary

SUPAC Guidance for Solid Oral Drug Products

- 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 (November 1995)
- 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 (September 1997)
- Information contained in the SUPAC documents:
  - The level of change
  - Recommended chemistry, manufacturing, and controls tests for each level of change
  - In vitro dissolution tests and/or in vivo pharmacokinetic (PK) bioequivalence (BE) tests for each level of change
  - Documentation to support the change

Overview of SUPAC Changes with In Vivo PK BE Recommendations

Change	Levels	Recommendation with In Vivo PK BE Study
Components and Composition	1, 2, 3	>Level 1 Change for Narrow Therapeutic Index (NTI) drugs >Level 1 Change for low solubility/low permeability IR drugs Level 3 Change for immediate-released (IR) and modified-released (MR) drug products
Manufacturing Process	1, 2, 3	Level 3 Change for IR and MR drug products
Manufacturing Site Change	1, 2, 3	Level 3 Change for MR drug products

General Considerations for in vivo PK BE Study

- Comparing the post-change product to the reference standard (RS)
- In vivo studies may be waived in the presence of an established in vitro/in vivo correlation
- Typically, the type of study recommended is in alignment with product-specific guidance (PSG) recommendation
- There are exceptions

Case Study 1

Drug Product: ER Capsules, 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg

PSG Recommendations: Fasting, fed, and fasting sprinkle studies on the 100 mg strength; fasting study on the 10 mg strength

Agency's Recommendation for In Vivo BE study to support level-3 SUPAC change: Fasting study on the 100 mg strength only

Rationale: Test product is manufactured from a common blend – the strengths differ only in the number of encapsulated beads containing the active moiety and thus the SUPAC change should impact each strength similarly

Case Study 2

Drug Product: ER Tablets, 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, and 300 mg

PSG Recommendations: Fasting and fed studies on the 200 mg strength; fasting study on the 50 mg strength

Agency's Recommendation for In vivo BE study to support SUPAC changes: Fasting study on the 50 mg strength and a fed study on the 200 mg strength

Rationales:

- PK linearity was not directly established
- Some strengths of the test products were not proportionally formulated

→ Two BE studies

- Tlag differences were observed in fed BE studies submitted in ANDAs for the same drug product which were deemed as a concern for demonstration of BE

→ Fed study on 200 mg strength

Case Study 3

Drug Product: IR Tablets**,** 1 mg, 2 mg, 5 mg, and 10 mg

PSG Recommendations: Fasting and fed studies on 2 mg strength

Agency's Recommendation for In vivo BE study to support SUPAC changes: Fasting and fed studies on 2 mg strength

Rationales:

- The product was reintroduced with multiple changes after being discontinued for over 10 years
- The multiple changes included new manufacturing site and new manufacturing process
- Lack of pre-change drug product for comparison

Summary

- In SUPAC IR Guidance and SUPAC MR Guidance, BE recommendations to support SUPAC changes are based on drug product properties (MR, NTI, etc.) and the degree of change (minor, moderate, and major)

- In general, one in vivo BE study, i.e., a fasting BE study on bio-strength, is recommended to support major SUPAC changes, unless the PSG recommends fed study only for the specific drug product

- In some cases, more than one in vivo BE study are recommended by considering PK linearity, formulation design of the drug product, as well as the overall SUPAC changes

- Applicants may solicit advice from the Agency on the BE study design, if needed, through a controlled correspondence.

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