Bioequivalence Recommendations in Support of Level 3 Formulation Changes to Complex Topical Products: Considerations and Case Studies

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Changes in complex products

Background

SUPAC guidance recommendations 1995-1997

- Immediate release product 1995 (SUPAC-IR)
- Modified release products 1997 (SUPAC-MR)
- Topical semisolid products 1997 (SUPAC-SS)

Current Status

- Recent advances in bioequivalence (BE) recommendations (e.g., those in product-specific guidances) for complex products.
- In vitro characterization-based approaches are recommended for complex topical products when there are no formulation differences between the test product and reference standard product (e.g., qualitatively (Q1) and quantitatively (Q2) the same) and have the same physicochemical and structural (Q3) attributes (comparative Q1/Q2/Q3).
- There is rise in number of complex generic drug product approvals in recent years
- How can modernized BE recommendations be applied to support changes in complex products?

SUPAC-SS and Topical semisolid products

SUPAC-SS level 3 components and composition change:

- Addition of a new excipient or deletion of an existing excipient
- More than 10% change in approved amount of an individual excipient
- Likely to have a significant impact on formulation quality and performance.
- In vivo bioequivalence documentation is recommended to support these changes.
- Cases with level 3 formulation changes were identified in which an in vivo BE study is recommended per SUPAC-SS but only in-vitro approaches were proposed.

Case 1 Topical cream

- **Formulation Change: Addition of edetate disodium (EDTA) during review cycle**
- The applicant submitted adequate in vivo vasoconstrictor assay (VCA) study to support the proposed product.
- A revised formulation containing EDTA as a chelating agent was submitted in response to a drug product quality deficiency during the review cycle.
- **Risk evaluation: Low**
  - Adding the proposed amount of EDTA was not expected to alter the solubility of the API in the formulation and thereby the thermodynamic activity/ bioavailability of the active ingredient from the formulation.
- A **modified characterization-based approach** was deemed acceptable, supported by:
  - **Q3 comparison** - Physicochemical and structural similarity between test products with and without EDTA
  - **IVRT** – Equivalent release rate between test products with and without EDTA

Case 2 Topical spray

- **Formulation Change: Addition of citric acid anhydrous**
- PAS Submitted: **Addition of citric acid anhydrous** as an acidifying agent to improve stability.
- The change was **not expected to alter API solubility or systemic/local bioavailability** and was considered acceptable without additional in vitro or in vivo BE studies, taking into account:
  - Dosage form complexity (solution)
  - Original in vivo study as a scientific bridge between the RLD and post-change product
  - Anticipated impact of the new excipient
  - Adequate drug product quality

Case 3 Suppositories for rectal use

Formulation Change - Reduction of antioxidant

- The applicant conducted adequate **single-dose, fasting in vivo BE study** per PSG recommendation.
- In the original submission, levels of **Butylated Hydroxyanisole (BHA)** and **Butylated Hydroxytoluene (BHT)** were deemed unacceptable from a **safety perspective**, prompting reformulation.
- The reduction of BHA/BHT constituted a **Level 3 change per SUPAC-SS guidance***.
- Considering the small mg/unit change, information available to the Agency the applicant was offered **a biowaiver pathway**, contingent on:
  - In vitro dissolution comparison (pre- vs. post-change)
  - Evidence that the BHA/BHT reduction does not affect drug absorption
  - Confirmation of no other changes to the exhibit batch

*In the absence of SUPAC guidance for suppositories, considering the semisolid properties of the drug product, scientific principles outlined in the SUPAC-SS guidance were used to assess changes.

Summary: Risk-Based BE Strategies to Support Complex Product Changes

- The Agency applies a **risk-based, case-by-case framework** based on:
  - Complexity of the drug product
  - Function and magnitude of the excipient change
  - Anticipated impact of the proposed change on product performance
- Scientific thinking for post-approval products outlined in the SUPAC guidance documents may be used to support pre-approval changes also, provided all recommended BE studies on the pre-change product are acceptable.
- SUPAC guidance documents detail current recommendations for certain product types and provide a useful scientific framework for both post-approval and pre-approval changes. However, applicants may propose alternative approaches to support product changes if scientifically appropriate.

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