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Scientific Foundations for Development of Generic MR Oral Products

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April 18, 2024

FDA/PQRI Workshop - Challenges and Opportunities for Modified Release Oral Drug Product Development

A Forum for Stakeholder Engagement

Workshop Goal

- Clarify the scientific foundation for “strength waivers” for Modified Release (MR) oral products
  - FDA does not waive BE studies for additional strengths of MR products
  - FDA makes a determination of BE for each MR strength based on in vitro data: 21 CFR 320.24(b)(6)

- Build a foundation for better guidance on this question

Patient Centered

- Having multiple strengths available for MR products is patient-centric
  - Allows the optimal dose to be prescribed
  - Convenience of one unit with the optimal dose

Expectations for a Product Line

- An NDA supplies 100 MG, 50 MG and 25 MG tablets
  - Default expectation is “Consistent bioavailability across strengths”
  - If this is not true, it should be in the label supported by the facts of the deviation

Consistent Bioavailability Across Strengths

- Same (bioequivalent) drug exposure from
  - 1 x 100 MG tablets
  - 2 x 50 MG tablets
  - 4 x 25 MG tablets

Strength not Dose

- I said “Consistent bioavailability across strengths” not “Consistent bioavailability across dose”
- Some active ingredients have non-linear pharmacokinetics
  - A property of the molecule not the formulation

Old FDA Guidance for MR

- From 2000:
  - "For extended-release tablets, when the drug product is in the same dosage form but in a different strength, is proportionally similar in its active and inactive ingredients, and has the same drug release mechanism, an in vivo BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an in vivo study only on the highest strength. The drug products should exhibit similar dissolution profiles between the highest strength and the lower strengths based on the f2 test in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8). The dissolution profile should be generated on the test and reference products of all strengths."

BE: bioequivalence

Current Guidance (for ANDAs)

- The test product includes the same excipients for different strengths and the ratios of drug and excipients among different strengths of the test product is **justified and appropriate for the drug release mechanism of the test product** (e.g., drug and excipients of different strengths can be either proportional or not proportional in quantity).
- The additional strength of the test product has the same drug release mechanism as the strength of the test product that underwent an acceptable in vivo BE study compared to the reference product.
- Dissolution testing of all strengths is acceptable. The drug products should exhibit similar dissolution profiles between the strength on which the BE testing was conducted and other strengths, based on the similarity factor (f2) test or other appropriate statistical approaches (e.g., a multivariate model independent approach or a model dependent approach) in at least three dissolution media (e.g., a pH of 1.2, 4.5, and 6.8).

The Change

- From “proportionally similar” to “justified and appropriate for the drug release mechanism”
- Today we begin a deep dive into “justified and appropriate for the drug release mechanism”
- This is the scientific foundation for strength waivers!

Proportionality is Fine for Immediate Release

- If a dosage form rapidly dissolves, then for proportional formulations
  - 1 x 100 MG
  - 2 x 50 MG
  - 4 x 25 MG
- All results in the same dissolved contents in the in vivo environment

Proportionality for MR

- For MR products the dosage form controls the release
- Many different mechanisms
  - Osmotic pumps
  - Matrix tables
  - Coated tablets
  - Coated beads
- Surface area to volume ratios are different

Hypothetical Example

- 100 MG: 90% drug 10% coating
  - Surface Area: 104 units
  - Coating thickness: 0.09 units
- 4x25 MG: 90% drug 10% coating
  - Surface Area: 165 units
  - Coating thickness: 0.06 units

Real Example

- Bupropion Extended-Release Tablets RLD
  - 300 MG dose => total weight 360 MG
    - Non-drug total 60MG
  - 150 MG dose => total weight 191MG
    - Non-drug total 41MG
- Bupropion Extended-Release Tablets ANDA
  - 300 MG dose => total weight 795.6 MG
    - Non-drug total 495.6MG
  - 150 MG dose => total weight 397.8 MG
    - Non-drug total 247.8 MG

RLD: reference listed drug

Real Example: Consequences

- FDA approved the ANDA based on 150MG BE study and waiver of 300MG
- FDA later conducted its own BE study on the 300MG ANDA and the study did not demonstrate BE
  - The ANDA product did not provide consistent bioavailability across strength
    - But it was proportionally formulated

Future State

- Scientifically sound scaling principles for each modified release mechanism
  - Establishment of community best practice
  - All have an interest in a common pharmaceutical science foundation that leads toward “consistent bioavailability across strengths”

Future State

- Interpretation of dissolution data from MR products
  - For strength waivers: Goal is measuring consistency across strengths from same manufacturer
    - Is bio-relevance or IVIVC critical?
  - In vivo products are exposed to a sequence of pH environments
    - Is it important to include this in the core dissolution data set?

Future State

- Important role of physiologically-based pharmacokinetic (PBPK) models of drug absorption
  - PBPK models can describe the non-formulation aspects: non-linear PK, solubility, permeability, transporters
  - Sensitivity of drug exposure to **in vivo dissolution rate** can drive risk-assessment and level of control/similarity that are appropriate

Conclusion

- Everybody wants consistent product performance across strengths
- Build the pharmaceutical science foundation to do this
  - Mechanism based formulation scaling
  - Optimal use of dissolution data
  - Integration with PBPK models that describe the overall integration of formulation and physiology


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