Modeling to Support Relaxation of Compositional/Microstructural Criteria to Qualify for Streamlined Bioequivalence Approaches

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Streamlined bioequivalence (BE) approaches

- FDA currently allows for streamlined BE approaches if certain narrow compositional/microstructural criteria are met
- BCS Class 3 biowaivers
  - *in vitro* dissolution-based
  - Avoids the need to perform *in vivo* (pharmacokinetic) BE studies
  - Especially helpful for toxic drugs requiring BE studies in patients
- "*In vitro* only" BE pathways
  - Available for some complex, locally-acting drug products
  - Avoids the need to conduct lengthy, expensive clinical endpoint BE studies in patients
  - Growing number of product-specific BE guidances for complex, locally-acting drug products describe *in vitro*-only BE approaches

BCS class 3 (highly soluble, poorly permeable) oral drug product biowaivers

- Must be very rapidly dissolving (≥ 85% dissolved in 15 minutes)
- Test product must have same excipients as reference product except for changes in the technical grade
- Quantitatively similar to the reference product:
- Test-reference differences in excipient content, expressed as percent (w/w) of the total formulation less than or equal to the following percent ranges:
  - Filler (± 10%)
  - Disintegrant, Starch (± 6%)
  - Disintegrant, Other (± 2%)
  - Binder (± 1%)
  - Lubricant, Calcium or Magnesium Stearate (± 0.5%)
  - Lubricant, Other (± 2%)
  - Glidant, Talc (± 2%)
  - Glidant, Other (± 0.2%)
  - Film Coat (± 2%)
- The total additive effect of all excipient differences should not be more than 10 percent.
- Some other conditions, e.g. NTI drugs, combination products, absorption through oral mucosa, etc.

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, December 2017

In vitro-only BE approaches for complex, locally-acting drug products

- Must typically be Q1/Q2/Q3 to the reference product
- Q1 – qualitatively the same as reference product
  - Same excipients, no additions, subtractions, or substitutions (some exceptions)
  - Must use same grades of certain key excipients
- Q2 – quantitatively the same as reference product
  - Each excipient must be present in the "same" amount as in the reference product
  - "Same" defined as ± 5% of the amount present in the reference product
- Q3 – same microstructure (arrangement of matter) as reference product
  - Direct (particle size, XRD, etc.) and indirect/performance (rheology, IVRT, etc.) measures of 3D architecture
  - "Same" defined on a case-by-case basis, taking lot-to-lot variability of the reference product into consideration

Compositional/microstructural requirements to qualify for streamlined BE can be challenging

- Difficult to quantitate even some simple excipients to the very narrow quantitative limits required
- Difficult to quantitate and determine grade of some excipients (especially heterogeneous polymers) in reference product with very high accuracy and grade certainty
- May be difficult to develop complex manufacturing process that reproduces reference product microstructure/performance characteristics closely
- May need to be intentionally different from reference product composition to avoid patent infringement
- Reverse engineering may detect amount of an excipient different from amount used in reference product master formula
  - If reference product manufacturing process depletes or enriches the content of an excipient, finished dosage form may have more or less of that excipient than was used in the compounding process
  - Some excipients may have high and variable moisture content, making it impossible to accurately deduce amount used in reference product compounding from reverse engineering analysis
- Opaque Q1/Q2 letter responses from FDA
  - FDA must protect reference product confidential info – limited to yes/no answers to Q1/Q2 inquiries
  - Multiple Q1/Q2 letter cycles with 3 proposed formulations each

Dilemma

- Streamlined BE approaches have, in principal, been welcomed by the industry, however:
- Meeting compositional/microstructural requirements can be so challenging that sponsors frequently abandon streamlined BE pathway and follow traditional BE approaches:
  - Conduct human BE studies for BCS class 3 drugs
  - Conduct clinical endpoint BE studies for locally-acting drug products
- Sponsors sometimes also shy away from developing their own novel streamlined BE pathway for similar reasons
- Dilemma between extreme BE approaches with too much or too little sensitivity
  - Current compositional/microstructural criteria are extremely narrow (conservative) due to lack of understanding of relationships between these criteria and clinical effect (i.e., they are too sensitive to product differences that may be clinically irrelevant)
  - Clinical endpoint BE studies are extremely insensitive even toward product differences that may be clinically relevant

Opportunities

- Significant opportunities exist to apply modeling methods to justify relaxation of existing narrow compositional/microstructural requirements to qualify for streamlined BE pathway
- Many reference product drugs are locally-acting drugs and have no (or few) approved generics, at least in part because of the difficulties in qualifying for streamlined BE pathways
- Opportunity to facilitate the development of generics by relaxing the compositional/microstructural criteria to qualify for streamlined BE approaches, using modeling methods to probe the effect of deviations from narrow compositional/microstructural criteria on expected product performance *in vivo*
- Developing such modeling approaches should be an important GDUFA FY 2021 research priority, because the results of such research would act directly to remove major impediments to the development of the most-needed generics

Thank-you!

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