Considerations for Bioequivalence Bridging Studies to Support Pre- and Post-Approval Changes in Orally Inhaled and Nasal Drug Products

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Outline

- Background information
- When, why, and what BE bridging studies may be needed
  - Case studies
- Considerations in conducting BE bridging studies
- Tips for submitting BE bridging studies
- Conclusion

Background Information

- Changes in the drug product may occur after BE studies are completed, before or after ANDA approval.
- No Scale-Up and Post-Approval Changes (SUPAC) guidance is available for complex generics such as orally inhaled and nasal drug products (OINDPs).
- From a BE perspective, recommendations for bridging studies needed for pre-approval changes (after BE studies are completed using pre-change test product) and post-approval changes are generally the same.

When and Why BE Bridging Studies May Be Needed

- According to the product specific guidances (PSGs) for generic OINDPs, in vitro, pharmacokinetic (PK), pharmacodynamic (PD), and/or comparative clinical endpoint bioequivalence (BE) studies are typically recommended.
- For in vitro, PK, PD, and comparative clinical endpoint BE studies, prefer to use test batches that represent the proposed to-be-marketed product.
- However, changes in the drug product (e.g., in device, formulation and manufacturing) may occur after BE studies are completed, before or after ANDA approval.
- Depending on the specific change, bioequivalence between the post-change test product and the reference listed drug (RLD) may be established by
  - Repeating the complete set of BE studies recommended in the PSG between the post-change test product and the RLD/reference standard (RS)
  - Conducting in vitro or in vivo BE bridging studies (i.e., typically a subset of the studies recommended in the PSG) between the post-change test product and the RLD/RS product.

Examples of Changes

- Device
  - Change in material in metered dose pump of nasal spray product
  - Incorporation of dose counter
  - Change in dip tube length for nasal spray product
- Manufacturing process
  - Change in filling instrument
  - Changes in blending time
- Manufacturing site
  - Addition/change of manufacturing site
- Formulation
- May contain more than one change

Determining the Necessity and Type of BE Bridging Studies

- Depends on the specific changes

  Case studies

Case Study #1:
A nasal spray suspension product with changes in device

FDA BE Recommendations for Nasal Spray Suspension Product A at the Time of ANDA Assessment

Equivalent In Vitro Performance

1. Single actuation content (SAC)
2. Droplet size distribution by laser diffraction (DSD)
3. Drug in small particles/droplet size distribution by cascade impactor (CI)
4. Spray pattern
5. Plume geometry
6. Priming and repriming

Equivalent Systemic Exposure

Pharmacokinetic (PK) study

Equivalent Local Delivery

Comparative clinical endpoint study

Formulation and Device Design Similarity

Case Study #1: A Nasal Spray Suspension Product with Changes in Device

- For nasal spray product A, the applicant proposed changes in
  - Bottle dimension
  - Actuator skirt length
  - Dip tube length
  - Pump material (resin)
- Recommended conducting in vitro BE studies (SAC, DSD, and spray pattern) comparing the post-change test product with the RLD/RS product.

Case Study #2:
A metered dose inhaler (MDI) product with incorporation of a dose counter

FDA BE Recommendations for MDI Product B at the Time of ANDA Assessment

Equivalent In Vitro Performance

1. Single actuation content (SAC)
2. Aerodynamic particle size distribution (APSD)
3. Spray pattern
4. Plume geometry
5. Priming and repriming

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

Pharmacodynamic (PD) study

Formulation and Device Design Similarity

Case Study #2: An MDI Product with Incorporation of a Dose Counter

- For MDI product B, the applicant proposed to incorporate a dose counter after all of the BE studies were conducted using the test product without dose counter.
- Recommended conducting, at minimum, in vitro BE studies (SAC, APSD, spray pattern, plume geometry, and priming and repriming) comparing the post-change test product with a dose counter to the RLD/RS product with a dose counter.
- Upon review of the bridging data with dose counter, additional studies may be requested.

Case Study #3:
A dry powder inhaler (DPI) product with manufacturing process change

FDA BE Recommendations for DPI Product C at the Time of ANDA Assessment

Equivalent In Vitro Performance

1. Single actuation content (SAC)
2. Aerodynamic particle size distribution (APSD)

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

Comparative clinical endpoint study

Formulation and Device Design Similarity

Case Study #3: A DPI Product with Manufacturing Process Change

- For DPI product C, the applicant proposed a manufacturing process change (change in filling equipment).
- Recommended SAC and APSD studies comparing the post-change test product to the RLD/RS product for each strength using a single flow rate.

Case Study #4:
A MDI product with manufacturing site change

FDA BE Recommendations for MDI Product D at the Time of ANDA Assessment

Equivalent In Vitro Performance

1. Single actuation content (SAC)
2. Aerodynamic particle size distribution (APSD)
3. Spray pattern
4. Plume geometry
5. Priming and repriming

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

Pharmacodynamic (PD) study

Formulation and Device Design Similarity

Case Study #4: An MDI Product with Manufacturing Site Change

- For MDI product D, the applicant proposed a post-approval drug product manufacturing site change.
- Provided in vitro BE studies (SAC, APSD, spray pattern, plume geometry, and priming and repriming) comparing the post-change test product to the RLD/RS product for each strength.

Determining the Necessity and Type of BE Bridging Studies

- Depends on the specific changes

  Case studies
- The Agency can provide specific recommendations
  - If changes are planned prior to abbreviated new drug application (ANDA) submission, you may discuss with the Agency in controlled correspondence or a pre-ANDA meeting request
  - If changes are planned (or have questions on what to do) after an ANDA is submitted, you may contact the Regulatory Project Manager, or submit a post-complete response (CR) scientific meeting request or controlled correspondence as appropriate.

Considerations When Conducting BE Bridging Studies

- Typically, in vitro BE bridging studies are recommended.
  - Additional BE bridging studies (e.g., in vivo) may be needed depending on the type and number of changes and the BE bridging data already submitted within the ANDA.
- Recommend using batches that include all changes (e.g., device, formulation and/or manufacturing) in the BE bridging studies.
- Refer to the Product-Specific Guidance for details regarding the BE studies, unless the Agency provides specific recommendations for your situation.
- For in vitro BE bridging studies, use at least 3 batches of post-change product vs. at least 3 batches of unexpired RLD product, with no fewer than 10 units from each batch.

Tips for Submitting BE Bridging Studies

- Specify changes
  - Between the test product used in each in vitro and in vivo BE study and the to-be-marketed product
  - Specify the details of the changes, irrespective of the degree of the changes
- Provide justifications for why the BE bridging studies conducted could support the changes
  - Reference previous communication with the Agency, if any
- Provide relevant documents just as those for pivotal BE studies, for example:
  - Summary tables (in both .doc and .pdf formats)
  - Study protocols and reports
  - Standard operating procedure(s) (SOPs)
  - Certificate of analysis (s) (COAs) for test and RLD/RS product batches used
  - Study datasets (in SAS .xpt format)
- If no BE bridging studies are needed, provide justification explaining why

Conclusions

- For in vitro, PK, PD, and comparative clinical endpoint BE studies, prefer to use test batches that represent the proposed to-be-marketed/ commercial product.
- If there are changes such as in device, formulation, and manufacturing, BE bridging studies may be needed.
- The Agency can provide specific recommendations regarding if and what specific BE bridging studies are needed.
- Refer to the Product-Specific Guidance for details regarding the BE studies, unless the Agency provides specific recommendations for your situation.

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