Bioequivalence Considerations for Conducting Bridging Studies with Orally Inhaled and Nasal Drug Products

Tian Ma, Ph.D.
Office of Bioequivalence
Office of Generic Drugs

September 26, 2019

Disclaimer: This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Outline

- Overview of Agency's bioequivalence (BE) recommendations for orally inhaled and nasal drug products (OINDPs), e.g.,
  - Nasal spray suspensions
  - Metered dose inhalers (MDIs)
  - Dry powder inhalers (DPIs)
- Considerations for conducting BE bridging studies
- Conclusion

FDA BE Recommendations for Nasal Spray Suspension: Weight-of-Evidence Approach

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 (for nasal suspensions)

Equivalent Local Delivery

Comparative clinical endpoint study (for nasal suspensions)

Formulation and Device Design

FDA BE Recommendations for MDI: Weight-of-Evidence Approach

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
or
Comparative clinical endpoint study

Formulation and Device Design

FDA BE Recommendations for DPI: Weight-of-Evidence Approach

Equivalent In Vitro Performance

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

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

PD study
or
Comparative clinical endpoint study

Formulation and Device Design

When and Why Bridging Studies May Be Needed

- 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.
- However, changes in the drug product (e.g., in device, formulation and manufacturing) may occur after BE studies are completed.
- 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 recommended BE studies between the post-change test product and the RLD
  - Conducting in vitro or in vivo bridging studies between the post-change test product and the RLD 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 Bridging Studies

- Depends on the specific changes

  Case studies

Case Study #1: A Nasal Spray 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 reference product.

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 reference product with a dose counter.
- Upon review of the bridging data with dose counter, additional studies may be requested.

Case Study #3: A DPI Product with Manufacturing 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 reference product for each strength using a single flow rate.

Determining the Necessity and Type of Bridging Studies

- Depends on the specific changes

  Case studies
- The Agency can provide specific recommendations
  - If changes are made 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 made (or have questions on what to do) after an ANDA is submitted, you may contact regulatory project manager

Considerations When Conducting 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 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 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 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 reference product batches used
  - Study datasets (in SAS .xpt format)
- If no 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, bridging studies may be needed.
- The Agency can provide specific recommendations
  - Prior to ANDA submission: controlled correspondence or a pre-ANDA meeting request
  - After ANDA submission: contact regulatory project manager


FDA
U.S. FOOD & DRUG
ADMINISTRATION