Approaches for studies interrupted due to COVID-19 for Nasal and Inhalation Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 2, Session 2: (Nasal and Inhalation Products)

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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)
- Common questions due to COVID-19 for OINDPs
- How to submit questions related to interrupted BE studies during the COVID-19 pandemic
- 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)

In vitro method as a surrogate for comparative clinical endpoint study
E.g., Mometasone Furoate Nasal Spray

Formulation and Device Design

Slide taken from SBIA Complex Generic Workshop, 2019

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

Equivalent In Vitro Performance

1. 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

Slide taken from SBIA Complex Generic Workshop, 2019

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

Equivalent In Vitro Performance

1. SAC
2. APSD

Equivalent Systemic Exposure

PK study

Equivalent Local Delivery

PD study
or
Comparative clinical endpoint study

Formulation and Device Design

Slide taken from SBIA Complex Generic Workshop, 2019

Challenges in Development of OINDPs

- Drug-device combinations which include a formulation integrated with a device
- Lengthy development time
- Use of multiple batches to establish BE

Common questions due to COVID-19 for nasal and inhalation drug products

- Use of an expired reference listed drug (RLD) product
- Use of an authorized generic drug product
- Use of additional Test and RLD batches in comparative clinical end-point BE study
- Test product substitution in *in-vitro* BE studies

Case Study #1: An MDI Product with the use of Authorized Generic

- For an MDI product A, the applicant proposed to use a combination of lots from either or both the authorized generic (AG) and RLD to conduct *in vivo* and *in vitro* BE studies.
- Recommendation: The proposal to use a combination of lots from either or both the AG and RLD, within the *in vivo* and *in vitro* BE studies appears reasonable.

Case Study #1: An MDI Product with the use of Authorized Generic

Additional information to be considered:

- The applicant may contact the Office of Generic Drugs via controlled correspondence before conducting studies to inquire further and to discuss the necessary documentation.
- Complete lot information (lot number, expiration date, certificate of analysis) for each batch of AG product should be submitted to the Agency for confirmation of its acceptability for use as the reference product before conducting the BE studies.
- The final acceptability of the specific approach with respect to combination of lots across the BE studies will be determined upon the scientific assessment of the full abbreviated new drug application (ANDA) submission.

Case Study #2: An MDI Product with the use of Additional Test and RLD Lots

- For an MDI product B, the applicant proposed to use a fourth batch of Test (T4) and new lots of RLD (R4) and (R5) in their comparative clinical endpoint BE study that will not be used in the PK study and the *in vitro* BE studies. The applicant did not intend to use any previous batches of Test product and RLD lots used in the PK BE study and *in vitro* BE studies.
- Recommendation:
  - The proposal to use one batch of Test (T4) and two batches of RLD (R4 and R5) for the comparative clinical endpoint BE study is reasonable.
  - The applicant's proposal to not perform *in vitro* BE studies on the new Test batch (T4) and RLD (R4 and R5) batches is **not acceptable**.

Case Study #2: An MDI Product with the use of Additional Test and RLD Lots

Additional information to be considered:

- Test product batch used for the pivotal comparative clinical endpoint BE study be one of the batches used in the pivotal *in vitro* BE studies, whenever feasible.
- There should be no differences in the formulation.
- There should be no differences in any aspects with respect to the proposed commercial/to-be-marketed drug-device combination product and complete characterization.

Case Study #3: An MDI Product with Substitution of Test Lots

- For an MDI product C, the applicant mentioned the Test product lot will expire and must manufacture additional Test product lot to continue the comparative clinical end-point BE study. They proposed to utilize the existing *in vitro* BE dataset and "exchange" one of the previous Test product lot data with data generated on the new Test product lot and reprocess BE analysis.
- Recommendation: Substitution of Test lots is not recommended. However, it is reasonable to manufacture an additional Test product lot to continue the comparative clinical end-point BE study.

Case Study #3: Case Study #3: An MDI Product with Substitution of Test Lots

Additional information to be considered:

- The new test batch should be manufactured using the same equipment under the same manufacturing conditions.
- The batch size of the proposed new test batch should be based on the batch size recommendations provided in the guidance for industry ANDAs: Stability Testing of Drug Substances and Products – Questions and Answers (May 2014).
- The instrument and testing conditions are recommended to be the same as those used for the *in vitro* BE studies already conducted with the previous three test and RLD batches.

Submitting Questions on Interrupted Studies During the COVID-19 Pandemic

- For ANDAs that have been already submitted to FDA, ANDA applicants should direct questions to the Regulatory Project Manager for their ANDA.
- Prospective applicants may use OGD's genericdrugs@fda.hhs.gov mailbox to submit questions related to the impact of COVID-19 on BE studies or to notify FDA of BE studies that have been interrupted.
- For ANDAs that have not yet been submitted to FDA, prospective applicants should submit specific questions related to their impacted BE studies via the controlled correspondence process (https://edm.fda.gov), or if applicable, the pre-ANDA meeting request pathway (https://edm.fda.gov).

Conclusion

- Use of an expired RLD is generally not acceptable.
- Use of additional Test and RLD lots in comparative clinical end-point BE study is acceptable, provided pivotal *in vitro* studies have been conducted on the new lots.
- Use of authorized generic is acceptable.
- The Agency can provide specific recommendations
  - Prior to ANDA submission: controlled correspondence or a pre-ANDA meeting request if applicable
  - After ANDA submission: contact regulatory project manager

Challenge Question #1

What are some potential challenges in the development of OINDPs?

A. Drug-device combinations which include a formulation integrated with a device

B. Use of multiple batches to establish BE

C. Lengthy development time

D. All of the above

Challenge Question #2

Which of the following statements is NOT true?

A. Use of expired RLD is acceptable

B. Use of additional Test and RLD lots in comparative clinical endpoint BE study is acceptable, provided pivotal *in vitro* studies have been conducted on the new lots

C. Additional Test lots used should be manufactured using the same equipment under the same manufacturing conditions

D. Use of authorized generic is acceptable


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