Generic MDI LGWP Propellant Transition: OGD Framework and Data Submission Considerations

FDA-CRCG Workshop on Navigating the Transition to Low Global Warming Potential Propellants

Day 2 – Session 1: Generic LGWP MDI Development and Generic Industry Experience

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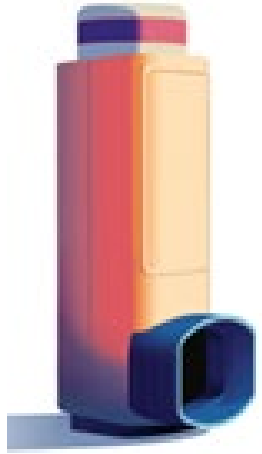
Outline

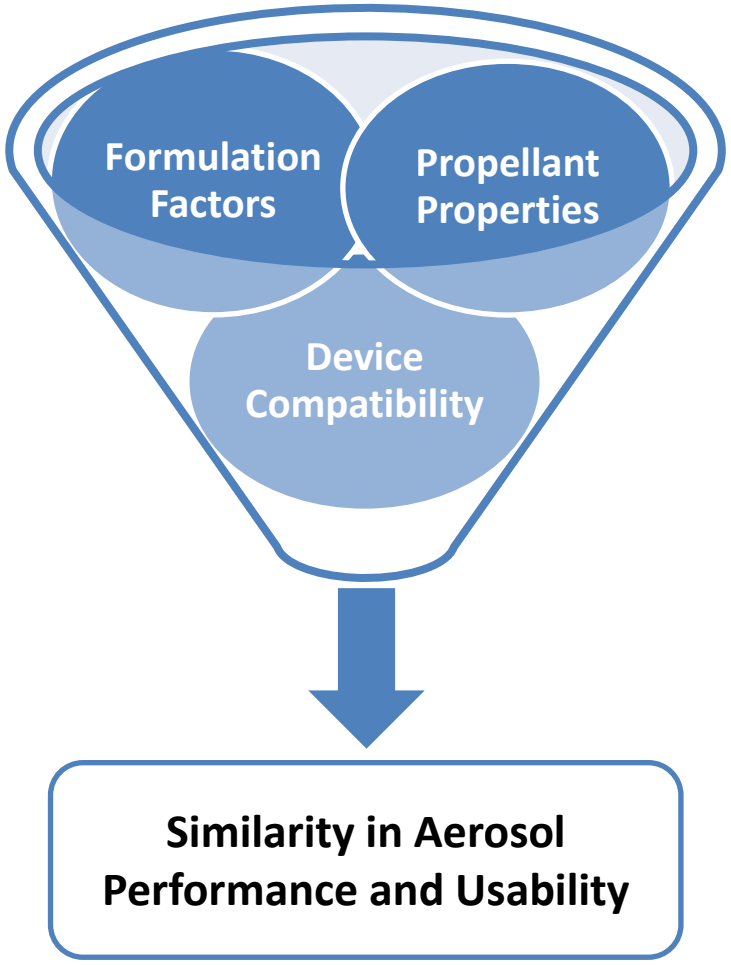
- Generic Low Global Warming Potential (LGWP) Propellent Metered Dose Inhaler (MDI) Drug Products:
  - Abbreviated New Drug Application (ANDA) Data Submission Considerations
  - Challenges and Research Opportunities
  - Conclusion

Generic LGWP MDI: ANDA Data Submission Considerations

Generic MDI LGWP Propellant Transition



Generic HFA MDI to LGWP MDI Transition



- **For approved ANDAs to transition their generic HFA MDI product to a LGWP propellant (post-submission change within the same application):**
  - **Multiple changes** are anticipated (***e.g., formulation, valve, actuator design, etc.***) to transition the HFA MDI to the LGWP MDI product.
  - These changes are considered ***major changes*** that could have the substantial potential for adverse effects on the identity, strength, quality, purity, or potency (e.g., biological activity, **bioavailability [BA], bioequivalence [BE]**) of a drug product as these factors may relate to the safety or effectiveness of the drug product.
    - ***Major Changes → Prior approval supplement (PAS)***
  - Within this context, **BE will need to be established** between the LGWP MDI product and the RLD/RS (e.g., ***BE studies and comparative analyses***) to support the PAS to an approved ANDA.

Data Submission: Quality and BE

- **Quality**
  - Expectations on quality assessment for generic LGWP MDI product are the ***same*** as those expected for an NDA.
  - These aspects were covered by Craig Bertha on Day 1 and prior presentations.*
- **Bioequivalence (BE)**
  - For **PAS to an approved ANDA** or **new ANDA**, ***BE*** will need to be established between the generic ***LGWP MDI product*** and the ***RLD/RS***.
  - Refer to the most recent ***product-specific guidance (PSG)*** on the MDI product of interest.**

*Bertha, C. Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective. *IPAC-RS Workshop on the Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers.* October 11, 2023. https://www.ipacrs.org/ipac-rsworkshoptransitiontolgwp.

** FDA PSG webpage is available at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

Data Submission to Demonstrate BE

Option 1^

Formulation Sameness
- The test (T) product should contain no difference in inactive ingredients or other aspects of the formulation relative to the RS that may significantly affect local or systemic availability of the active ingredient (e.g., Q1/Q2 sameness to RS)

Q1: qualitative; Q2: quantitative; RS: reference standard

In Vitro Studies
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming, rAPSD, Dissolution*

SAC: Single Actuation Content; APSD: aerodynamic particle size distribution; rAPSD: realistic APSD

**When BA of API is dissolution limited*

Comparative Characterization Studies
- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies
- PK BE Study, PK BE Study With Charcoal Block***

****When GI absorption of API affects systemic BA*

PK: Pharmacokinetic

Additional Information
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

Option 2 ^

Formulation Sameness
- None (e.g., Q1/Q2 or non-Q1/Q2 the same to the RS)

In Vitro Studies
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming

Comparative Characterization Studies
- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies
- PK BE Study, PD/CCEP BE Study

PD: pharmacodynamic; CCEP: Comparative Clinical Endpoint

Additional Information
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

^ Refer to the PSG on the MDI drug product of interest for the specific recommended BE studies.

BE recommendations are applicable to PAS and new ANDA submissions.

Data Submission to Demonstrate BE

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Formulation Sameness

- The test (T) product should contain no difference in inactive ingredients or other aspects of the formulation relative to the RS that may significantly affect local or systemic availability of the active ingredient (e.g., Q1/Q2 sameness to RS)

In Vitro Studies

- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming, rAPSD, Dissolution*

**When BA of API is dissolution limited*

Comparative Characterization Studies

- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies

- PK BE Study, PK BE Study With Charcoal Block***

****When GI absorption of API affects systemic BA*

Additional Information

- Optional Computational Modeling Study(ies)
- Device Similarity (i.e., design and user interface) to the RLD

Formulation Sameness

- *Demonstrate Q1/Q2 sameness to RS*
- *When non-Q1/Q2 the same, demonstrate formulation change will not affect local or systemic BA of API*
  - *Provide justification, which may include, but not limited to formulation characterization data, product development data, comparative characterization studies, and/or scientific literature.*

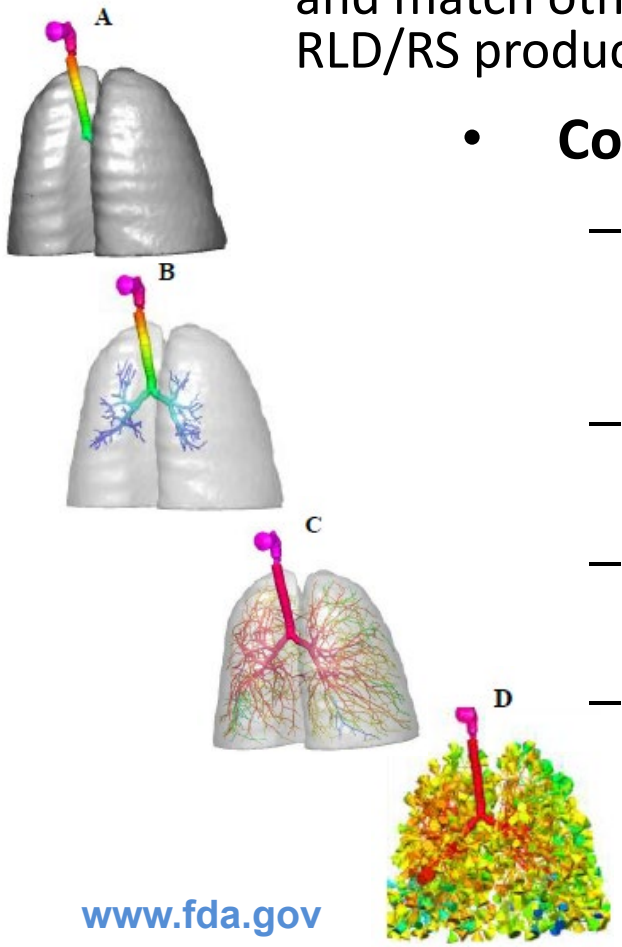
- *Goal: understand the formulation design space of critical excipients, their ranges, and their potential impact(s) on API BA.*
- *Information, data, and/or studies warranted will depend on the formulation changes being proposed.*

Q1: qualitative; Q2: quantitative; RS: reference standard; RLD: reference listed drug; SAC: Single Actuation Content; APSD: aerodynamic particle size distribution

rAPSD: realistic APSD; PK: Pharmacokinetic; BE: Bioequivalence

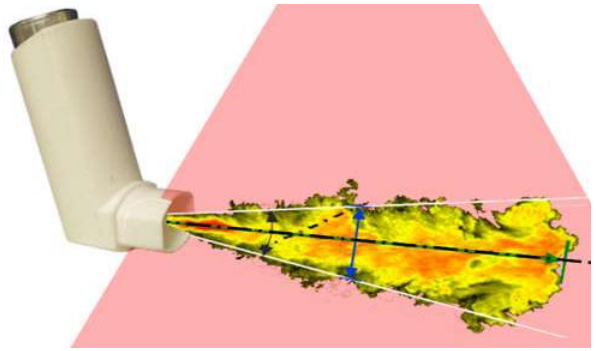
Data Submission to Demonstrate BE

- **Difficulty in meeting all expectations in establishing BE?**
  - **Example**: spray characterization expected to change and may not be able to meet BE criteria and match other performance metrics (e.g., SAC, APSD) between LGWP test product and RLD/RS product.



- **Consider optional computational modeling study(ies):**
  - Differentiate the impact of different products (i.e., device and formulation) on regional drug delivery, such that the results may be used to ***establish biorelevant limits*** for BE comparison.
  - Assess the BE in terms of ***regional lung deposition*** by conducting virtual BE simulations.
  - The ***specific purpose(s)*** of the model should be **clearly stated** in detail within the ANDA submission.
  - Refer to the most recent version of the FDA PSG on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered* (Recommended Jun 2015; Revised Nov 2023) (NDA 208294) for additional information.

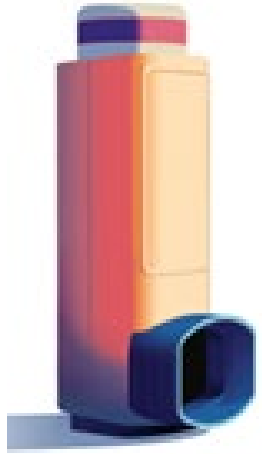
ANDA Data Submission: LGWP Propellant Safety



- **Reference of Safety Data on the LGWP Propellant**
  - **Excipient levels** in generic drug products can be justified by referring to the applicable **Inactive Ingredient Database (IID) listings** with **similar context of use** (i.e., ***dose, route of administration, duration of use, and patient population***).
  - If the **proposed level of the selected LGWP propellant cannot be justified based on IID**, a ***safety justification is warranted*** to address potential genotoxicity, local toxicity, and systemic toxicity to support its use in the proposed generic LGWP MDI drug product
  - A **controlled correspondence** may be submitted to the Agency to seek advice regarding the ***comparability*** of the proposed level of LGWP propellant in your LGWP product to levels in FDA-approved drug products with similar context of use.

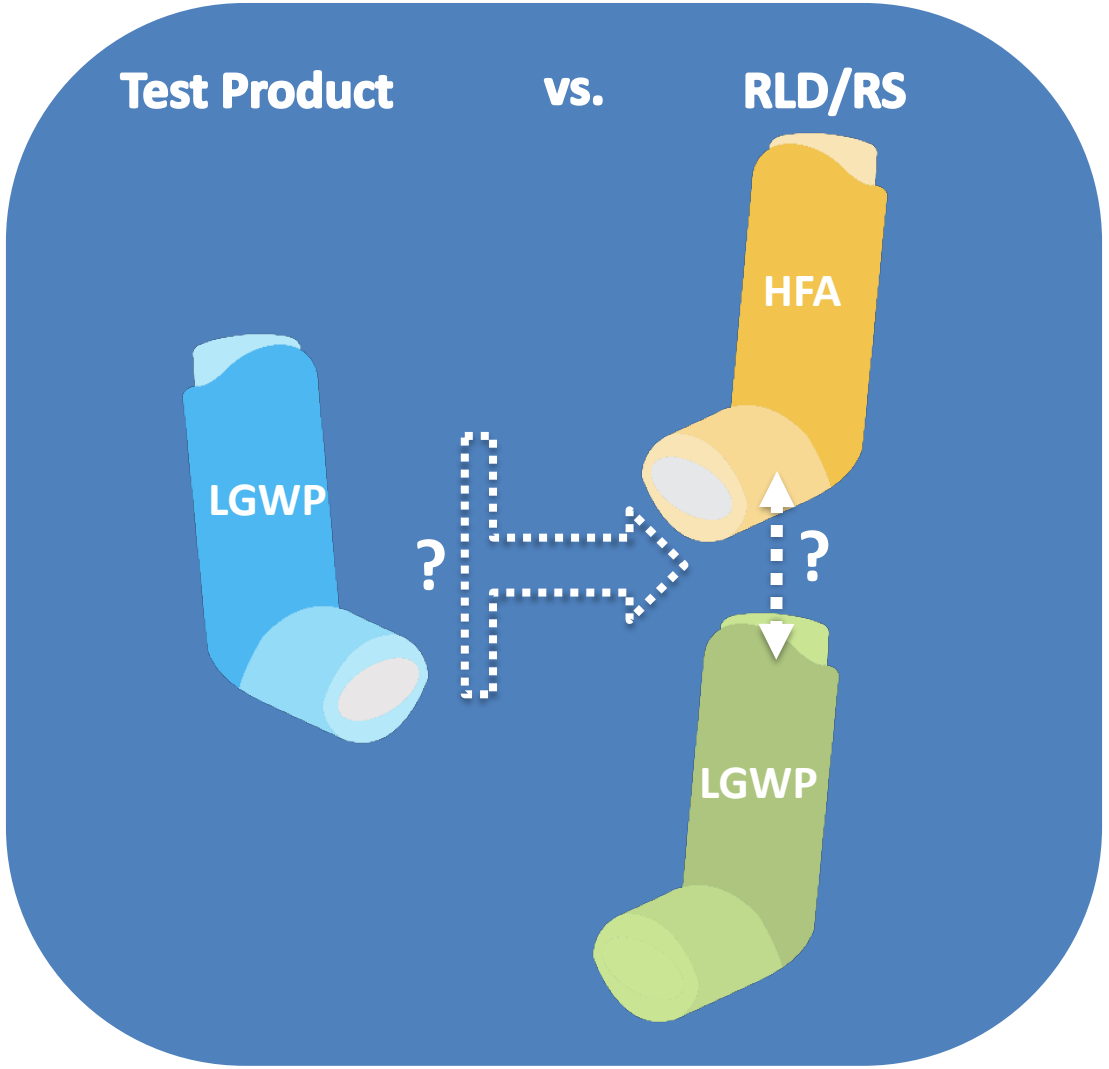
Generic LGWP MDI Development: Challenges and Research Opportunities

Generic MDI LGWP Propellant Transition



Challenges to Generic MDI Development

- **Uncertainty of RLD/RS transitioning:**
  - HFA MDI RLD/RS ***may*** or ***may not*** transition.
  - ***If/when*** HFA MDI RLD/RS will phase out.
  - Will transition of **HFA MDI RLD/RS** to **LGWP MDI version** be considered a ***same RLD/RS or new RLD/RS***?
- **Timing** of HFA to LGWP transitions of RLD/RS will be critical to consider.
- Ultimately, the generic LGWP MDI test product will need to compare to the RLD/RS product that is **available on the market**.



Challenges to Meeting BE

- **Landscape for the HFA MDIs transitioning to LGWP propellant versions is in the early stages.**
  - The RLD/RS LGWP propellant is an ***evolving landscape*** with some uncertainties still in play.
- **Communicate <u>early</u> and <u>often.</u>**
  - Prospective applicants are encouraged to discuss their development plans with the Agency to gain feedback.*
    - Challenges in ANDA development for complex drug product, alternative BE approaches, etc.
- **Agency's thinking on establishing BE may evolve as scientific understanding and experience is gained.**
  - Refer to most ***recent PSGs on MDI products*** which are updated periodically.

*FDA Final Guidance for Industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

Ongoing FDA Research Efforts on LGWP Propellants

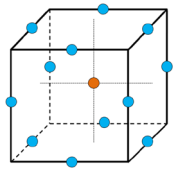
Research Contract 75F40123C00186, Aptar Pharma, September 2023-Current

- Aimed to **evaluate the challenges/ considerations** with developing a LGWP propellant MDI with ***equivalent performance*** to HFA propellant MDIs

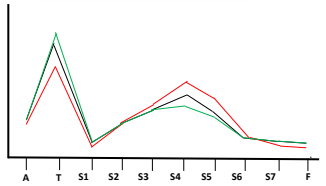
- **Improved understanding** of ***formulation/device design space*** for LGWP propellant MDI development
- **Identification** of ***sensitive analytical methods*** for evaluating equivalent performance between HFA and LGWP Propellant MDIs

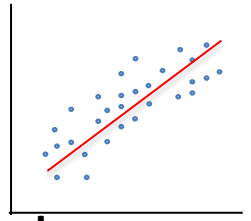
RLD Solution and Suspension MDI Characterization

Model Solution and Suspension MDI Manufacturing



Manufactured Solution and Suspension MDI Characterization

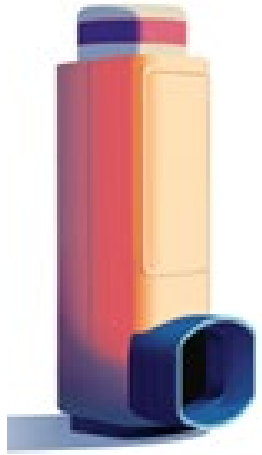




Data Analysis and Formulation/Device CQA Identification

Conclusions & Acknowledgements

Generic MDI LGWP Propellant Transition



Conclusions

- **Challenges yet remain** to understand the ***evolving landscape*** of the RLD/RS products transitioning to the LGWP that will ultimately impact generic drug development.
- In certain cases, BE may be difficult to establish. Thus, FDA continues scientific research to:
  - **Improve understanding** of ***formulation/device design space*** for LGWP propellant MDI development, and
  - **Identify** of ***sensitive analytical methods*** for evaluating equivalent performance between HFA and LGWP Propellant MDIs.
- **Continued ongoing discussions** with the Agency are encouraged to address ***scientific regulatory challenges*** for development of generic LGWP MDIs.

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