FDA Perspective on MDI Propellant Transitions – from Generic Drug Perspective

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Outline

- Brief Discussion on the CFC to HFA Propellant Transition
- Overview of the Recent FDA-CRCG Workshop
- Updates on FDA Research on Next Generation Propellants (NGPs)
- Considerations for ANDAs for NGP MDIs
- Conclusions

The Previous Propellant Transition: Phase Out of CFCs in MDIs

- Removal of CFC propellant MDIs from the market was a complex multi-year process that had a variable timeline based on the specific API
- To remove CFCs, each MDI required reformulation to either use new propellants or develop another platform for delivery
- HFAs, which include HFCs, became new propellants
  - Due to the different chemical properties between CFCs and HFAs, redesign of the MDI device was sometimes necessary in addition to the reformulation
- Every reformulated MDI submitted as an NDA required full clinical efficacy and safety studies for approval
  - Patents and exclusivity for new HFA propellant MDIs were granted
- Removal of CFC generics and the new patents/exclusivities for HFA MDIs led to long delays to generic access and increased patient costs[1,2]

CFC: Chlorofluorocarbon HFA: Hydrofluoroalkane HFC: Hydrofluorocarbon

FDA-CRCG Public Workshop

- **FDA-CRCG Workshop: Navigating the Transition to Low Global Warming Potential Propellants**
  - December 4-5, 2024
  - University of Shady Grove, Rockville MD
- **Objectives:**
  - Cover scientific and regulatory considerations regarding the data requirements to support an MDI transition program for brand name and generic drug products.
  - Engage subject matter experts from academia, industry, and health and regulatory agencies to discuss the current scientific understanding and challenges for NGP MDI transition development programs.

- **Day 1**
  - Session 1: Propellant Transition of New Drug MDIs
  - Session 2: Current Industry Experience on MDI Development for Propellant Transitions
  - Session 3: Small Group Working Sessions
- **Day 2**
  - Session 1: Generic MDI Development for Propellant Transitions and the Generic Industry Experience
  - Session 2: The Global Propellant Transition
  - Session 3: Lessons Learn/Closing Remarks

CRCG Website Link: https://www.complexgenerics.org/education-training/navigating-the-transition-to-low-global-warming-potential-propellants/

FDA-CRCG Public Workshop – Industry Feedback

General Expectations

- Physicochemical differences are not as large as with previous transition from CFCs to HFAs
- May require additional formulation or device changes (e.g., metering valve)
- Manufacturing processes will likely require changes
- Propellant flammability requires consideration and possible facility changes

Experienced / Anticipated Challenges

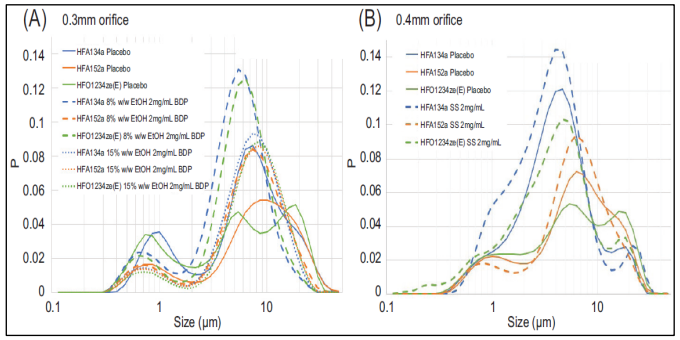
- Understanding the design space for NGP MDIs can impact investment decisions
- Differences in data requirements between regulatory agencies creates uncertainty
- Regulatory considerations (e.g., submission strategy, relevant reference and its availability) can impact developmental timelines and investment decisions

Studies for Development and Performance Testing

- HFA MDI knowledge informs NGP development
- SAC/APSD in vitro studies relevant but lack consensus for others (e.g., spray characterization, dissolution)
- PK studies more informative than PD/CCEP studies given their sensitivity to performance differences
- Charcoal-block PK studies may be useful in some instances along with other potential alternatives (e.g., partial AUCs)
- In silico methods can be supportive but require adequate validation/expertise

CRCG Website Link: https://www.complexgenerics.org/education-training/navigating-the-transition-to-low-global-warming-potential-propellants/

Understanding the NGP MDI Design Space



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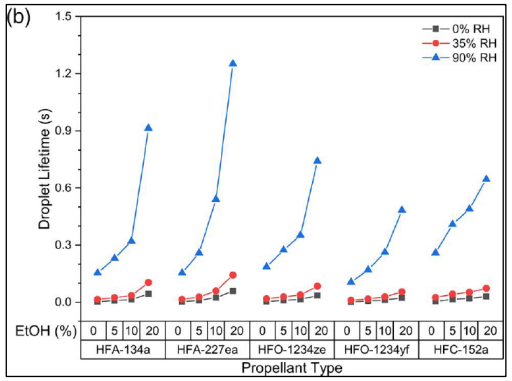

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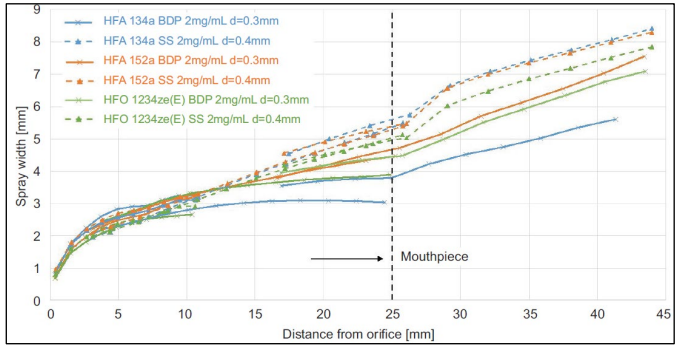

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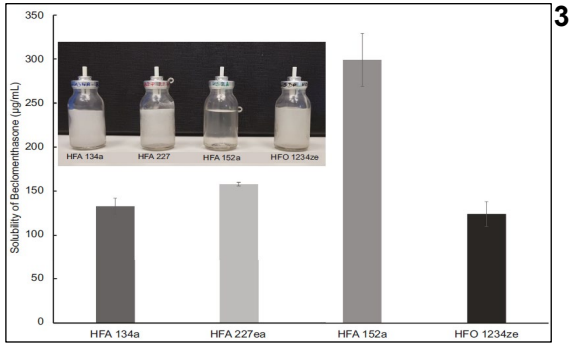

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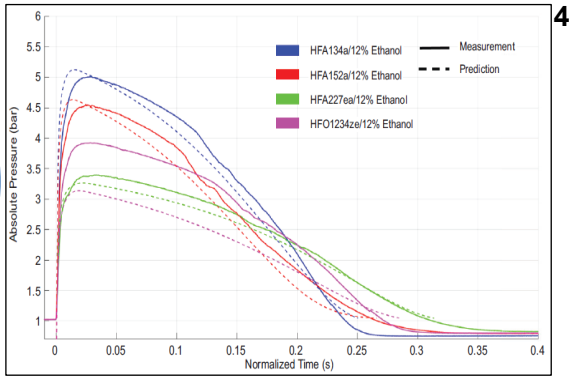

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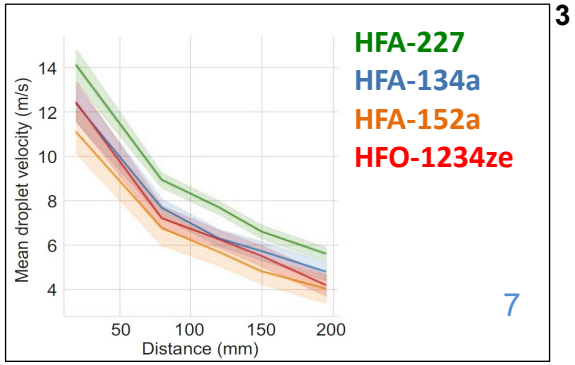

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Aerosol Droplet Size

Propellant Density on Drug Solubility

Pressures & Forces within the Actuator & Plume

Plume Velocity

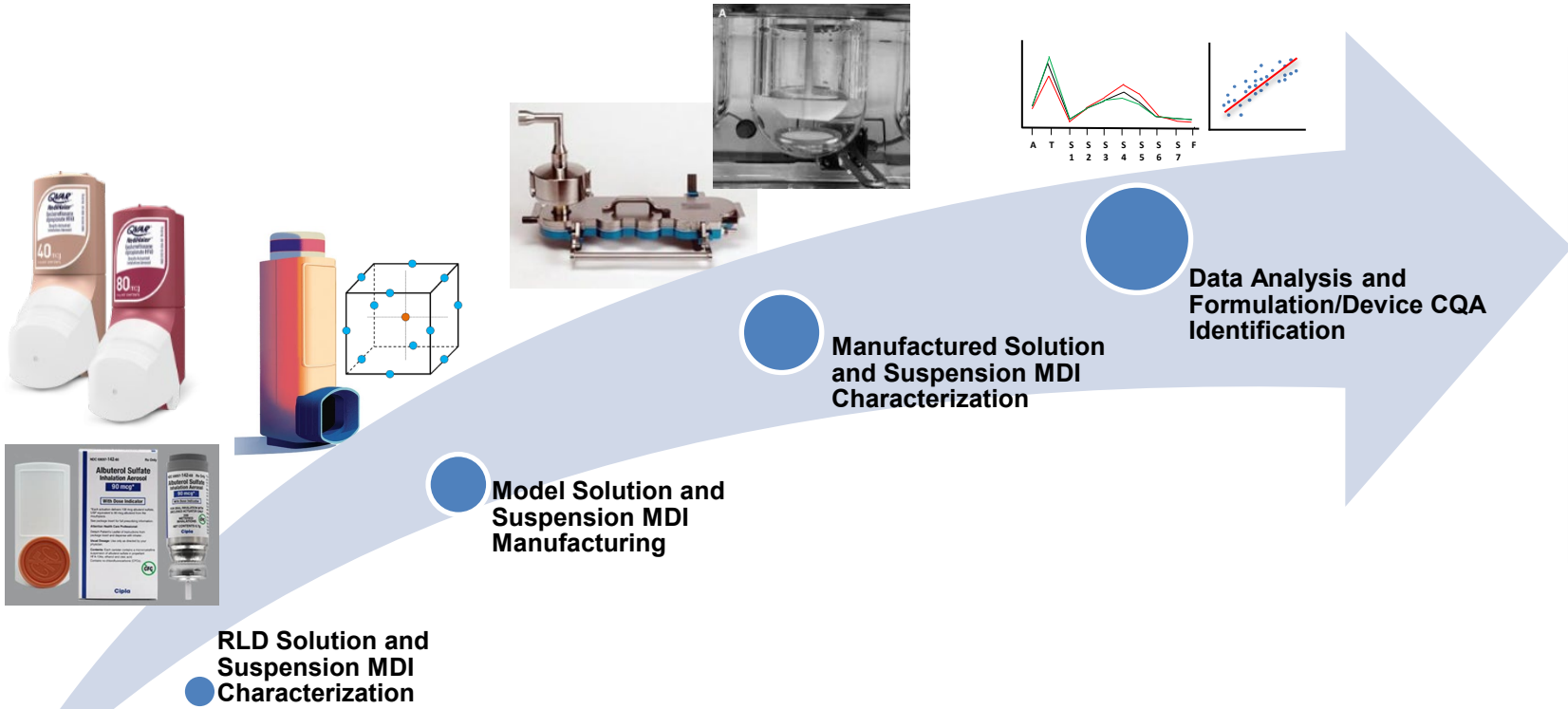
Plume Width

Droplet Evaporation & Lifetime

NGP Effects During Dose Delivery

Ongoing GDUFA Funded Research Efforts on NGPs

- **Research contract 75F40123C00186 was awarded to Aptar Pharma in September 2023**
- **Aimed to evaluate the challenges / considerations with developing a NGP MDI with equivalent performance to HFA propellant MDIs**



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

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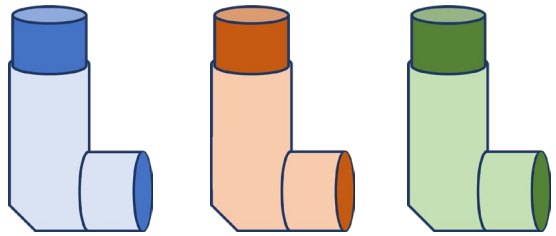
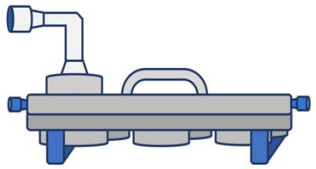
Ongoing GDUFA Funded Research Efforts on NGPs

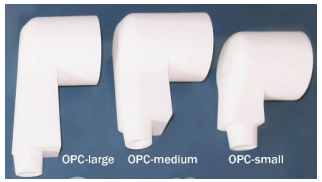
Exploring Differences in MDI CQAs

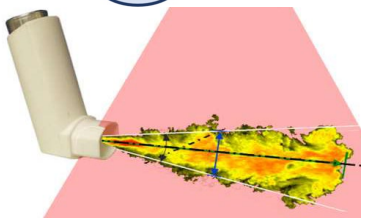


- **Suspension-based formulations of albuterol sulfate and solution-based formulations of beclomethasone dipropionate were developed based on deformulation of their respective RLDs**
  - Propellants used: HFA-134a, HFA-152a, HFO-1234ze
  - Other excipients varied: Ethanol, Oleic Acid
  - Device changes: Metering valve

In Vitro and Other Performance Testing



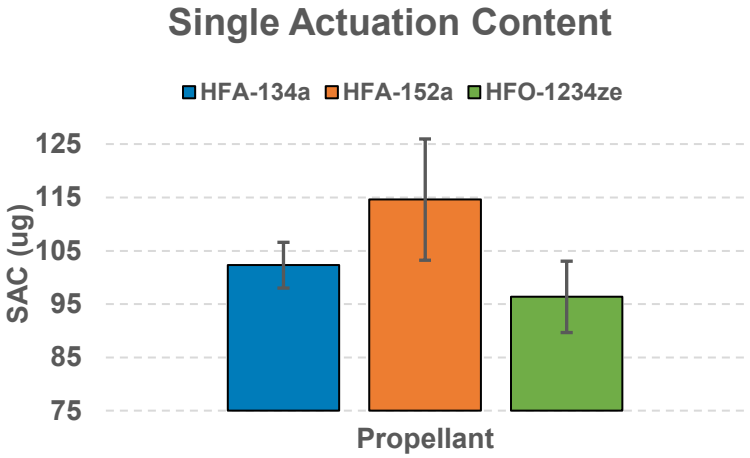


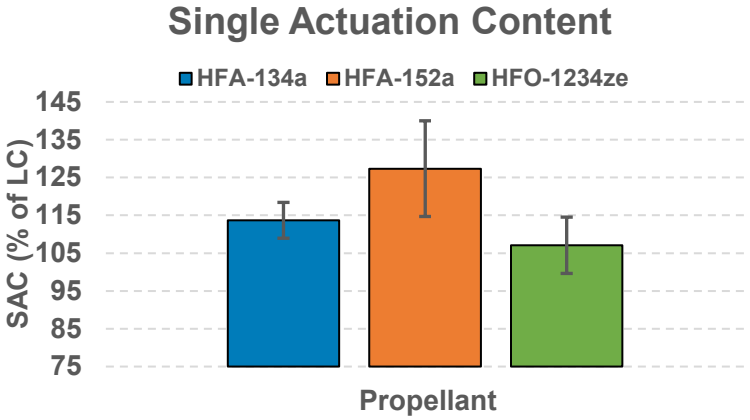


- **An assortment of in vitro and in silico methods will be used to evaluate performance differences across the different test MDIs**
  - SAC
  - APSD
  - Spray Pattern
  - Plume Geometry
  - Realistic APSD
  - Dissolution
  - Scanning Electron Microscopy w/ EDX
  - Electrodynamic Balance
  - Stroboscopic Droplet Analysis
  - In silico modeling

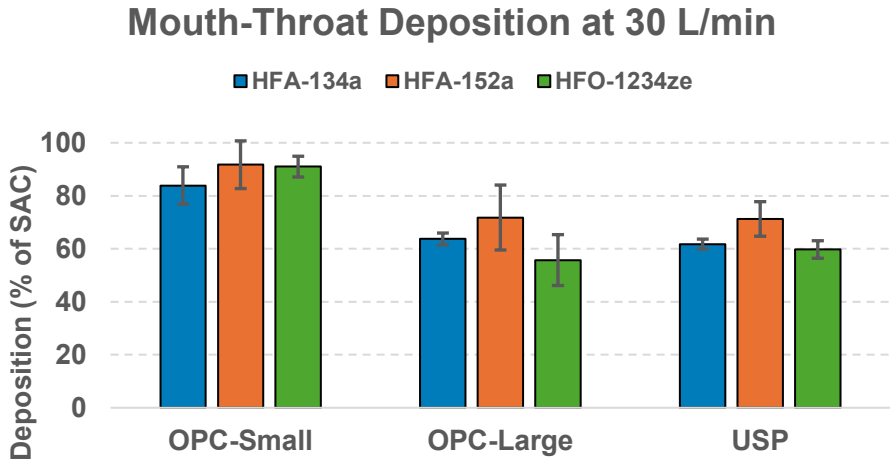
Ongoing GDUFA Funded Research Efforts on NGPs: Albuterol Sulfate MDIs

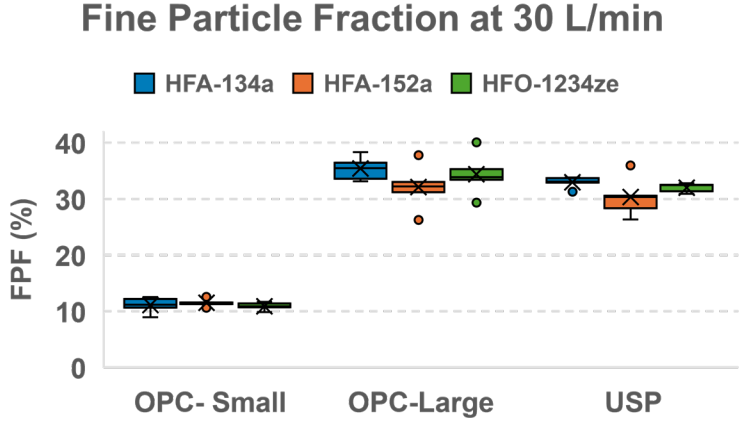
SAC

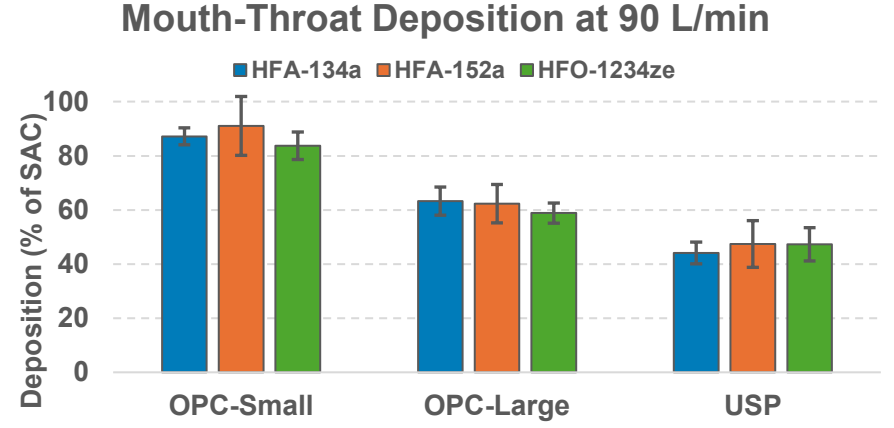


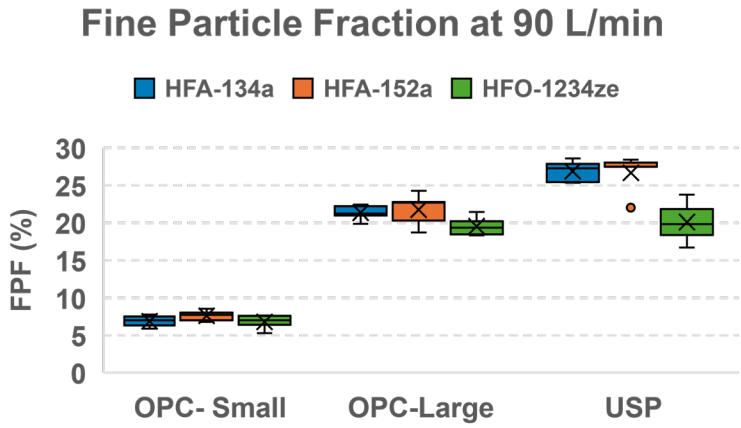


Realistic APSD



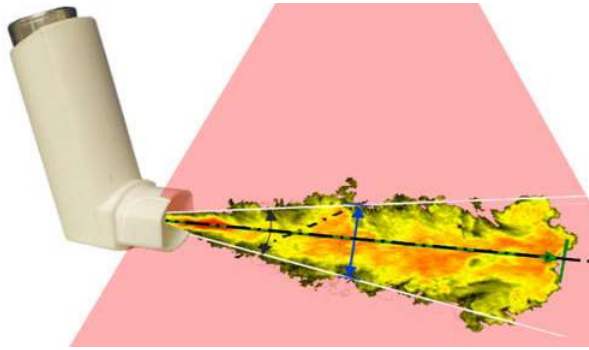






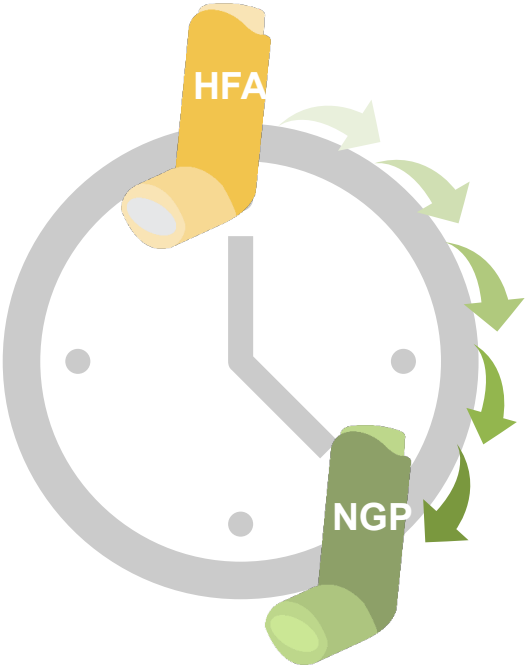
Considerations for ANDA Submissions

NGP Safety Considerations for a Generic HFA to NGP MDI Transition



- **ANDA submission is precluded if new clinical studies are necessary to establish the safety / effectiveness of the proposed drug product**
  - At least **one** NGP-containing MDI NDA approval is needed before an NGP generic can reference its safety data to support an ANDA submission.
- **Reference of Safety Data on the NGP**
  - **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 NGP 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 NGP MDI drug product
  - A **controlled correspondence** may be submitted to seek advice regarding the ***comparability*** of the proposed level of NGP in the NGP product to levels in FDA-approved drug products with similar context of use.

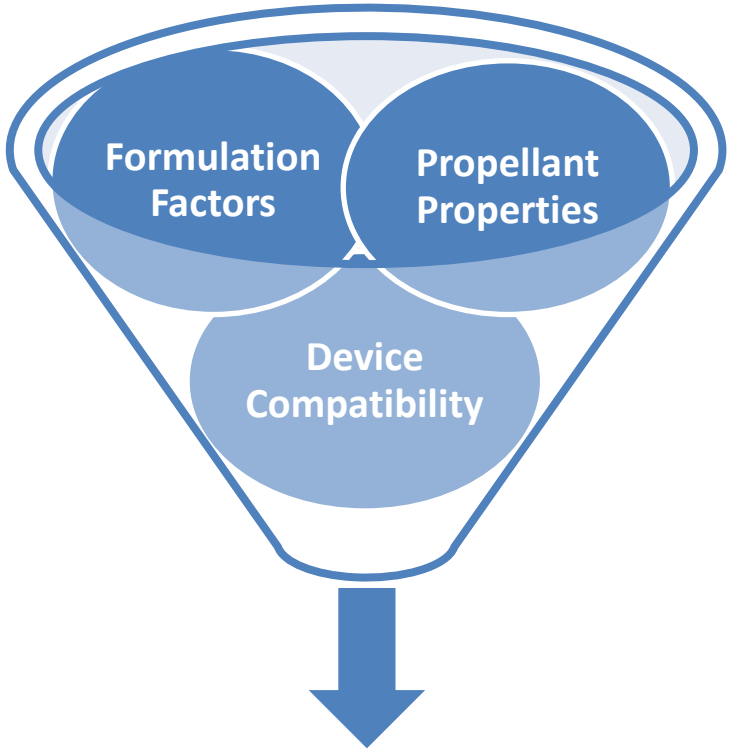
General Considerations for Generic NGP MDI Submissions



- **To transition an approved HFA MDI ANDA to a NGP MDI (post-approval change within the same application):**
  - **Multiple changes** could be needed (***e.g., formulation, valve, actuator design, etc.***) to transition the HFA MDI to the NGP 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 NGP MDI product and the RLD/RS (e.g., ***BE studies and comparative analyses***) to support the PAS to an approved ANDA.
  - The appropriate submission pathway for ANDAs is still an **ongoing discussion**
    - Meeting with FDA to discuss a proposed submission strategy and the accompanying study methods for establishing BE is ***highly encouraged***.
- **Timing** of HFA to NGP transitions of RLD/RS will be critical to consider.
  - HFA MDI RLD/RS ***may*** or ***may not*** transition.
  - ***If/when*** HFA MDI RLD/RS will phase out can affect conducting BE studies.
  - Ultimately, the generic NGP MDI test product will need to compare to the RLD/RS product that is **available on the market**.

Product Quality Considerations for an HFA to NGP MDI Transition

Impacting Factors



- **Match strength**
  - ***Amount (mg)*** per inhalation (i.e., actuation)
- **Minimize changes to the device and user interface**
  - Consider ***use***, ***storage***, ***cleaning***, ***priming***, and ***repriming***
- **Product quality similarity is the foundational first step, should be comprehensive, and data driven.**
- **Robust comparison of critical quality attributes between HFA and NGP products.**
  - **Product-specific guidances (PSGs)** can be consulted.
  - **BE** should be evaluated.
  - Comparative in vitro characterization is desired.
  - **Justification** for any **observed differences**.
- **Major differences in in vitro performance may require additional data/justifications.**

Utilizing Option-based BE Approaches for an HFA to NGP MDI Transition

Option 1^

Formulation Sameness
- No difference in inactive ingredients or other aspects of the formulation relative to the RS that may significantly affect local or systemic availability of API (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*

*When BA of API is dissolution limited

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

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.*

Utilizing Option-based BE Approaches for an HFA to NGP MDI Transition

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)

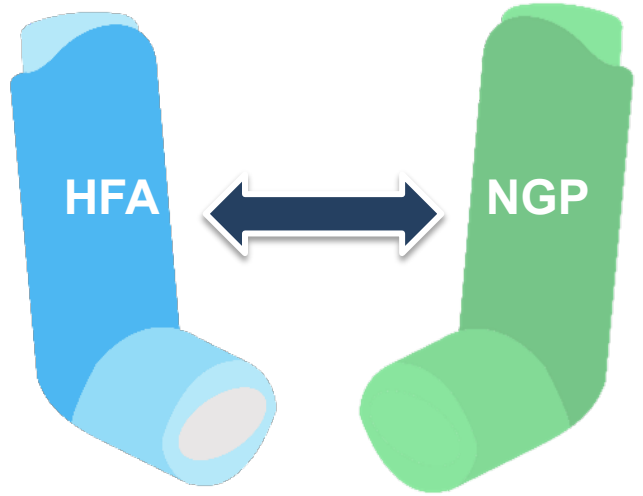
Formulation Sameness

- *NGP MDI will not be Q1/Q2 the same to HFA MDI*
- *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.*
- *Ensure formulation difference(s) do not impact desired outcomes in product performance, safety, and efficacy*

Ongoing Challenges and Future Directions

- **NGP MDI development could require multiple changes to the product properties to achieve BE**
  - Leverage existing knowledge on HFA MDI and scientific literature.
  - Allow for differences in inputs (formulation/device) that do ***not*** impact **in vitro and in vivo performance**, **safety**, and **efficacy**.



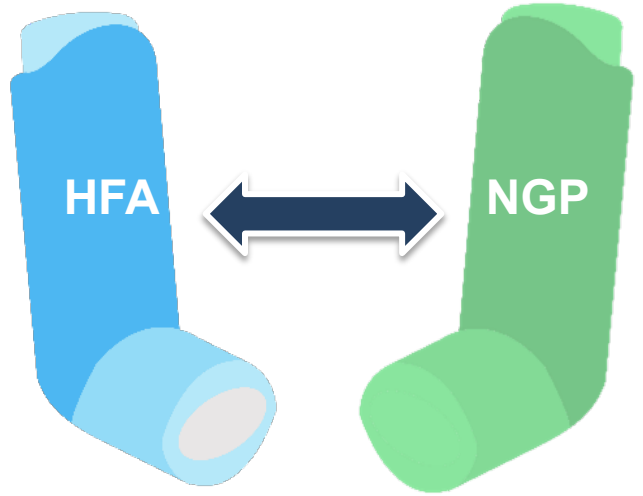
- **Establishing BE across all performance studies may be challenging for an HFA and NGP MDI**
  - Focus on matching **key characteristics first**
    - In Vitro: **SAC/DDU** and **APSD/rAPSD**
    - In Vivo: **PK study without charcoal**
  - For other performance tests (e.g., spray characterization), consider other study methods to support your application
    - In silico methods could help provide justification*
    - Understanding the ***in vitro-in vivo relationship(s) is critical***

*PSG on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered* (Recommended Jun 2015; Revised Nov 2023) (NDA 208294)

SAC: Single Actuation Content
DDU: Delivered Dose Uniformity
APSD: Aerodynamic Particle Size Distribution
rAPSD: realistic APSD

Ongoing Challenges and Future Directions

- **Standardization for certain methods is needed**
  - rAPSD
  - Dissolution
  - PK studies with a charcoal-block
    - **Charcoal dose** and **timing of administration(s)**
    - Applicants considering ***alternatives*** to conducting charcoal-block PK studies (e.g., partial area under the curve (pAUC), in silico methods) for assessment of systemic BA from the lung dose, are ***strongly encouraged*** to discuss with FDA.



- **Global harmonization**
  - While regulations may differ in each country, an attempt to harmonize data requirements, study designs, and statistical evaluation is possible
  - **Areas for consideration:**
    - Find ways to **minimize the need for clinical data** via sharing gained experience.
    - Amount and types of **NGP safety data.**
    - Applicability of **propellent only studies** for local tolerance (ciliary function and airway sensitivity).
    - Identify and agree upon **key in vitro studies** needed to demonstrate comparability/BE.
    - Clarify the appropriate design for **charcoal block PK studies,** when they are needed, and when other approaches may be applicable.

Communication is Key

- The NGP transition presents ***challenging*** and ***complex issues***
- Agency's thinking on establishing BE ***may evolve*** as scientific understanding and experience is gained.
- We strongly encourage ***direct and frequent interactions*** with the Agency
  - Prospective applicants can ***now*** submit product development pre-ANDA meeting requests to discuss BE approaches, study designs and related scientific questions for an NGP generic MDI program
  - For more information on submitting pre-ANDA meeting requests, refer to the FDA guidance *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022).*

* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry

Conclusions

- The December 2024 FDA-CRCG Workshop was held to facilitate conversations with all stakeholders on **where additional scientific and regulatory clarity is needed** to ensure an efficient and successful NGP transition of HFA MDIs.
- GDUFA funded research on the NGP design space is evaluating the impacts of potential formulation/device changes on MDI performance as well as examining the sensitivity of study methods to detect these differences.
- Multiple considerations can impact submission of an ANDA for an NGP MDI, including the NGP's safety information and availability for reference, the type and timing of the submission, along with the data requirements for product quality and establishing BE.
- Current option-based BE approaches detailed in PSGs are applicable for establishing BE between a proposed generic NGP MDI and its RLD/RS, which may require additional justification depending on whether formulation sameness is met.
- Given the product changes expected with an NGP transition, prospective applicants should consider matching performance on critical studies first; other alternative study methods may be suitable for providing additional justification to address potential performance differences where meeting BE could be challenging.
- BE method standardization for certain approaches and harmonization with other regulatory agencies is an ongoing process.
- If considering an NGP transition for a potential generic MDI, we strongly encourage frequent meetings with FDA to receive the Agency's current recommendations that may evolve as experience and scientific understanding change.
  - Refer to the FDA guidance *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) for more information.*

* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry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