Day 2 Overview

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

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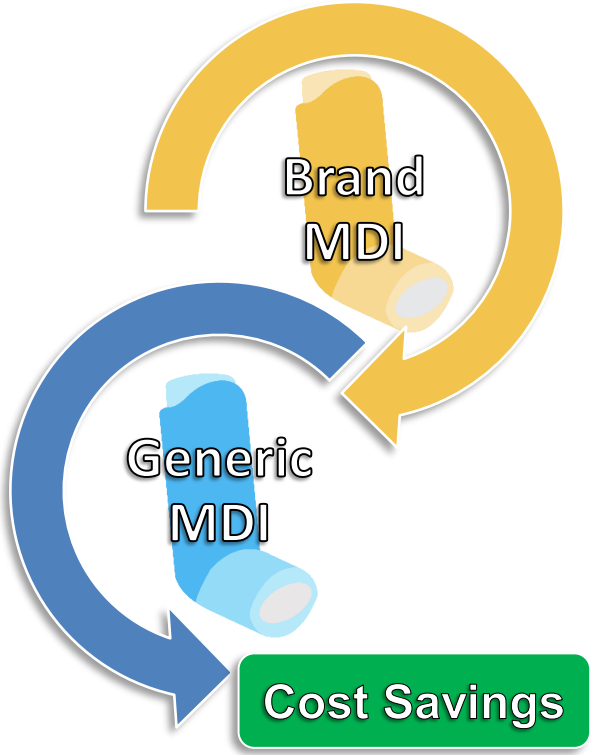
Office of Generic Drugs| CDER | U.S. FDA
December 5, 2024

Day 1 Recap

MDI: Metered dose inhaler
LGWP: Low Global Warming Potential

HFC: Hydrofluorocarbon
HFA: Hydrofluoroalkane

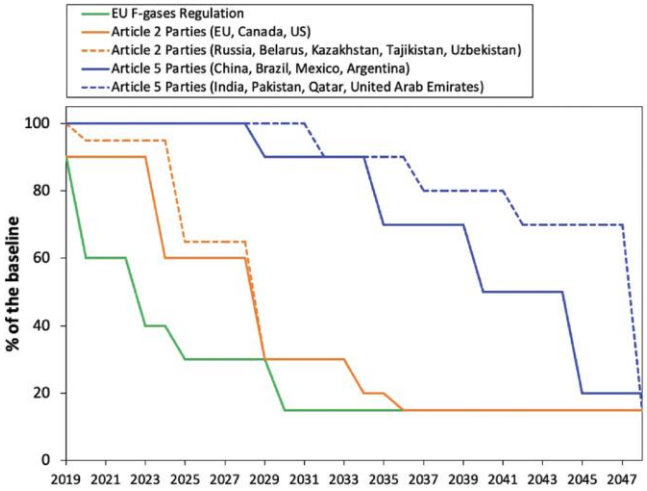
What to Expect During Day 2



SESSION 1: GENERIC LGWP MDI DEVELOPMENT AND THE GENERIC INDUSTRY EXPERIENCE

- Summary of Small Group Working Sessions on Day 1 *(Bryan Newman)*
- Policy Considerations for Generic MDIs Transitioning to an LGWP Propellant *(Rachael Dippold)*
- Generic MDI LGWP Propellant Transition: OGD Framework and Data Submission Recommendations *(Elizabeth Bielski)*
- Alternative In Vitro Bioequivalence Approaches for the Low GWP Propellant Transition *(Lucas Silva)*
- No Time to Lose: Adopting a Science-Based Approach to Ensure Continued Access to Generic pMDI Products *(Rupi Pannu)*
- Perspective on Generic LGWP MDI Development *(Siva Vaithiyalingam)*
- Q & A Session with Panel

What to Expect During Day 2



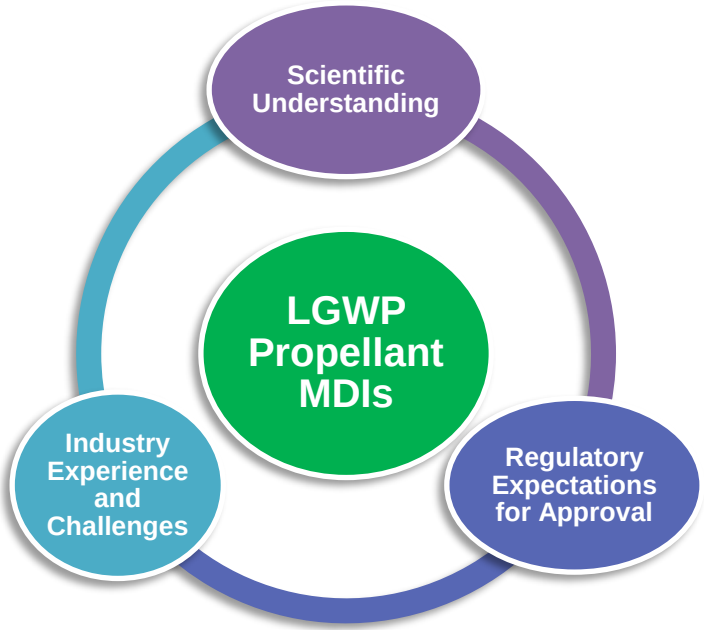
Phase down for different parties following Kigali amendment and EU F-gas regulation indicated as reduction % of the baseline.

SESSION 2: THE GLOBAL LGWP PROPELLANT TRANSITION

- Considerations from the Global Propellant Transition *(Karolina Törneke)*
- Current MHRA Approach on Data Requirements for the Transition to Low GWP Propellants in pMDIs *(Nithyanandan Nagercoil, Orla Ní Ógáin)*
- Navigating the Regulatory Landscape: Sustaining Patient Care with Next-Gen LGWP MDI Propellants *(Mark Boelens)*
- Key Considerations in the Business Decision to Reformulate a HFA-based pMDI with LGWP *(Geraldine Venthoye)*
- Considerations and Challenges Facing Generic Manufacturers Transitioning to LGWPs *(Giuseppe Randazzo)*
- Q & A Session with Panel

Buttini, R., et al. Metered Dose Inhalers in the Transition to Low GWP Propellants: What We Know and What is Missing to Make it Happen. Expert Opinion on Drug Delivery. 2023. 20:8, 1131-1143.

What to Expect During Day 2



SESSION 3: HOLISTIC PANEL DISCUSSION

- Session Moderator
  - *Darby Kozak*
- Panelists
  - *Stephen Stein*
  - *Richard (Rik) Lostritto*
  - *Lucas Silva*
  - *Mark Boelens*
  - *Markus Laubscher*
  - *Poonam Gulati*
  - *Uwe Niesner*
  - *Siva Vaithiyalingam*

NAVIGATING THE TRANSITION TO LOW GLOBAL WARMING POTENTIAL PROPELLANTS

DAY 2 SESSION 1: Generic LGWP MDI Development and the Generic Industry Experience

Introductions:	**Bryan Newman, PhD**	Lead Pharmacologist, DTP I, ORS, OGD, FDA
Presenters:	**Bryan Newman, PhD**	Lead Pharmacologist, DTP I, ORS, OGD, FDA
	Rachael Dippold, PhD, JD	Regulatory Counsel, DPD, OGDP, OGD, FDA
	Elizabeth Bielski, MS, PhD	Senior Pharmacologist, DTP I, ORS, OGD, FDA
	Lucas W. S. Silva, BSc	Senior Specialist, Analytical Development, Nanopharm, An Aptar Pharma Co.
	Rupi Pannu, PhD	Senior Director, Respiratory R&D Project Leader, Respiratory R&D, Viatris
	Siva Vaithiyalingam, PhD	Senior Vice President/Head of US Regulatory Affairs, Cipla, LTD
Moderator:	**Bryan Newman, PhD**	Lead Pharmacologist, DTP I, ORS, OGD, FDA
Panelists:	**Pradeep Bhadauria, MPharm**	President and Chief Scientific Officer, Cipla LTD
	Andrew Clerman, MD, PhD	Acting Lead Physician, DTP I, ORS, OGD, FDA
	William Feldman, MD, DPhil, MPH	Assoc. Physician, Pulmonary & Critical Care Med, Faculty, Regulation Program Therapeutics & Law, Pharmacoepidemiology & Pharmacoeconomics, Assoc. Dir., Ethics Service, Brigham & Women's Hosp., Asst. Prof, Harvard Med School
	Dhaval Gaglani, MS	Supervisor, OPQA I, OPQ, FDA
	Bing Li, PhD	Associate Director for Science, OB, OGD, FDA
	Rupi Pannu, PhD	Senior Director, Respiratory R&D Project Leader, Respiratory R&D, Viatris
	Lucas W. S. Silva, BSc	Senior Specialist, Analytical Development, Nanopharm, An Aptar Pharma Co.
	Siva Vaithiyalingam, PhD	Senior Vice President/Head of US Regulatory Affairs, Cipla, LTD
	Ross Walenga, PhD	Senior Chemical Engineer, DQMM, ORS, OGD, FDA

Summary of Small Group Working Sessions on Day 1

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

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NAVIGATING THE TRANSITION TO LOW GLOBAL WARMING POTENTIAL PROPELLANTS

Day 1 - Session 3: Small Group Working Session

Moderators:	**Rik Lostritto, PhD**	Science Advisor, IPAC-RS
	Christy Gilbert	Associate Director, CMC Regulatory Affairs, AstraZeneca
	Shyamala Ivatury	Senior Director, Inhalation Product Development, AstraZeneca
	Uwe Niesner, PhD	Head of Respiratory & Biologics Regulatory Strategy, Viatris
	Bryan Newman, PhD	Lead Pharmacologist, DTP-I, ORS, OGD, FDA
	Ross Walenga, PhD	Senior Chemical Engineer, DQMM, ORS, OGD, FDA
	Anubhav Kaviratna, PhD	Biomedical Engineer, DTP-I, ORS, OGD, FDA
	Hailing Zhang, PhD	Division Director, DPQA-XII, OPQA-II, OPQ, CDER, FDA
	Ann Purrington, BS	Regulatory Affairs Director, Kindeva Drug Delivery
Scribes:	**Lana Lyapustina, PhD**	Principal, Faegre Drinker - IPAC-RS Secretariat
	Lee Nagao, PhD	Principal, Faegre Drinker - IPAC-RS Secretariat
	Jennifer Edeline, MRes, PharmD	Senior Regulatory Affairs Manager, Aptar
	Sue Holmes, MS	CMC Regulatory Consultant, Sue Holmes CMC Consulting LLC
	Liangfeng Han, MD, PhD	Clinical Analyst, DTP-I, ORS, OGD, FDA
	Elizabeth Bielski, MS, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
	Sneha Dhapare, PhD	Senior Staff Fellow, DIIP, OCP, OTS, CDER, FDA
	Susan Boc, PhD	Pharmacokineticist, DTP-I, ORS, OGD, FDA
	David McChesney, PharmD	ORISE Fellow, DTP-I, ORS, OGD, FDA

Small Group Working Session Goals

- **Discuss the potential product development strategies and data requirements both new and generic drug developers may encounter during a LGWP propellant transition program**

- **Better understand how different development strategies and data requirements may impact a drug developer's decision making**

- **Identify critical areas of uncertainty where additional guidance can be beneficial for drug developer transition programs**

Discussion Focus

Possible Data to Establish Comparability:

In Vitro Data

- Single Actuation Content(SAC)/Delivered Dose Uniformity (DDU)
- Aerodynamic Particle Size Distribution (APSD)
- Spray Pattern
- Plume Geometry
- Priming/Repriming
- Realistic APSD (rAPSD)
- Dissolution
- Comparative Particle Morphology of Emitted Dose

In Vivo Data

- Pharmacokinetic (PK) Study w/o Charcoal Block
- PK Study with Charcoal Block
- Pharmacodynamic (PD) Study
- Clinical Endpoint (CCEP) Study

In Silico Models

- Computational fluid dynamics (CFD)
- Semi-empirical methods
- Physiologically based pharmacokinetics (PBPK) modeling

Other Studies?

Figure 1

Discussion Questions

The small group working session discussed a wide range of questions, including:

- Other than the propellant, what other types of changes are expected?
- Are certain changes considered high-risk in terms of potential impact on product performance (including bioavailability, bioequivalence, safety, or efficacy), and why?
- Across the studies proposed to evaluate performance between an HFA MDI and an LGWP MDI, which would be considered critical and why?
- If differences between products can be minimized, are certain studies not relevant or seen as redundant for evaluating performance and why?
- What situations would in silico models be useful to support the comparisons and why?
- What are the most relevant metrics and/or statistical approaches to compare the data?

Types of Product Changes Expected and Associated Risk

- Formulation Related:
  - Changes in density and excipients – novel excipients having higher risk
  - Changes in state of the API can be higher risk
  - Changes in the impurities and extractables/leachables can be higher risk
- Device/Container Closure Related:
  - Changes in actuator characteristics (e.g., orifice diameter, jet length, valve volume)
  - Changes to patient interface and actuation force could be present
- Manufacturing Related:
  - Process can change but even considering flammability, this may not present a high risk
- Overall, evaluating risk is challenging since more than one change may be present, and anything beyond a very minimum change can be risky
- Revisiting MDI design offers opportunity to utilize advancements in product design understanding but clarity on the real boundaries for design of new and generic LGWP propellant MDIs is needed since these can impact investment decisions

Critical Performance Tests and Potential Areas of Redundancy

- Generally, attendee comments noted the following when determining relevant in vitro and/or in vivo testing to support a LGWP propellant transition
  - Consideration for API usage and characterization history
  - Indication and population can inform on study criticality
- In Vitro Studies:
  - General consensus on the importance of DDU/SAC, APSD and rAPSD given relevance to characterize parameters impacting dose delivery and deposition
  - Time/cost of conducting rAPSD and availability of labs with sufficient technical expertise to perform the study should be considered
  - Spray characterization studies (spray pattern, plume geometry) may be more important for product development and informing computational models over need for matching performance in new and generic LGWP propellant MDIs
  - Importance of dissolution was uncertain as some questioned its need when in vivo PK studies are included while others noted the PK data can be convoluted as compared to dissolution; generally believed that more research and method standardization is needed
  - Uncertainty with use of particle morphology since it may serve as an orthogonal method to other in vitro studies and provided limited information for simple formulations as compared to those employing particle engineering

Critical Performance Tests and Potential Areas of Redundancy

- In Vivo Studies:
  - In vivo PK studies viewed as more informative over PD/CCEP studies given their greater sensitivity to performance differences
  - Uncertainty with need for PK for every strength, as this may depend on location on dose-response curve
  - Charcoal block PK can support determining the lung dose for certain products
  - In general, PD and CCEP studies still seen as a significant challenge with limited sensitivity as compared to PK studies
  - At least in terms of efficacy, some attendees believed there should be consideration for whether PD or CCEP studies are really needed if in vitro studies and in vivo PK studies (with and without charcoal) are found acceptable, particularly for APIs with many years of usage
  - Since alternative approach studies included in PSGs, some believed these could be applicable for supporting NDAs in lieu of the PD or CCEP study.
- In Silico Studies:
  - Can be supportive but validation is critical as well as having the technical expertise to develop the model

Methods and Metrics for Comparing and Analyzing Performance

- Some attendees commented that with the number of batches tested over the years, this could be used to develop an acceptable performance window for the LGWP propellant MDI
- For in vitro testing, meeting product specifications was suggested, however more robust testing could be needed for DDU and APSD studies
- The use of partial AUCs with in vivo PK studies was suggested to be further explored for understanding in vivo performance of LGWP propellant MDIs over the use of PD or CCEP studies

Conclusions

- Industry feedback noted a high likelihood for multiple types changes for an LGWP propellant MDI compared to the HFA version that complicates the assessment of risk, but ultimately product-specific
- Clarity on the design space drug developers may consider for their LGWP propellant MDI could help with determining whether to move forward with product development
- There was general consensus by industry attendees on the relevance of DDU/SAC, APSD and rAPSD in vitro studies for evaluating LGWP propellant MDIs, with less consensus around the use of spray characterization, dissolution, and particle morphology studies
- In vivo PK studies (with and without charcoal) were generally seen as more relevant for evaluating performance by industry as compared to PD or CCEP studies
- Experience with the HFA MDI and its product specifications may be informative for the acceptable performance for an LGWP propellant MDI


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