IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

SUMMARY OF IPAC-RS WORKSHOP ON THE TRANSITION TO LOW GLOBAL WARMING POTENTIAL (LGWP) PROPELLANTS FOR METERED DOSE INHALERS

Held on October 11th, 2023 in Washington, DC and Virtually

1. INTRODUCTION

1.1. Background

Since 1956, metered dose inhalers (MDIs) have been used to deliver life-saving medicines to the respiratory system. For decades, MDIs have delivered safe and effective therapies to those living with asthma, chronic obstructive pulmonary disease (COPD), or other respiratory illnesses. The first generation of MDIs, however, relied on chlorofluorocarbons (CFCs) to propel medication out of the canister. In the 1970s, however, it was discovered that CFCs were detrimental to the Earth's ozone layer, and subsequently they were also found to have a high global warming potential (GWP).

In the late 1980s, the world responded to the environmental harms posed by CFCs by enacting the Montreal Protocol.[1,2] The Montreal Protocol initiated a phasedown of CFCs, which culminated in an international ban on the production and consumption of these molecules in 2010. The transition away from CFCs under the Montreal Protocol has been heralded as a success of international law.

Throughout the 1990s, to comply with the Montreal Protocol, the MDI industry researched and re-developed their CFC products and transitioned to hydrofluoroalkane (HFA) propellants, HFA-134a and HFA-227ea. These propellants lack the ozone-depleting behavior of the predecessor CFCs, however they possess a relatively high GWP.[3] Recognizing the climate impact posed by these molecules and other HFAs (sometimes also called hydrofluorocarbons, or HFCs), parties to the Montreal Protocol developed the Kigali Amendment in 2016, which by now has been ratified by 155 participants, including the United States (US) and European Union (EU).[4]

As the signatories of the Kigali Amendment have instituted HFA-phasedowns in their national law, today the MDI industry is being called upon once again to transition to new, more sustainable propellants. Two new molecules, HFA-152a and HFO-1234ze(E) (collectively, "next-generation propellants"), represent promising alternatives to the currently used medical propellants. Although some research is still ongoing and more data are needed, publicly available information suggests that these new propellants offer viable alternatives to HFA-134a and HFA-227ea, with only a fraction of those propellants' GWP.

---

[1] United Nations Environment Programme. The Montreal Protocol https://www.unep.org/ozonaction/who-we-are/about-montreal-protocol

[2] U.S. Department of State. The Montreal Protocol on Substances That Deplete the Ozone Layer. https://www.state.gov/key-topics-office-of-environmental-quality-and-transboundary-issues/the-montreal-protocol-on-substances-that-deplete-the-ozone-layer/

[3] According to the US Environmental Protection Agency (EPA), HFA-134a has GWP of 1430; and HFA-227ea has GWP of 3220. - See transitioning_to_low-gwp_alternatives_in_aerosols.pdf (epa.gov), December 2016

[4] "Amendment to the Montreal Protocol on Substances that Deplete the Ozone Layer". Kigali, 15 October 2016. Available at UNTC

Before MDIs with next-generation propellants can be commercialized, however, they must be approved by relevant health authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Although the MDI industry has been working diligently to implement a transition to the new propellants, there is still uncertainty regarding the regulatory pathway for approval in the US and Europe. As of Fall 2023, FDA has not yet published any guidelines on this topic, while EMA has published a "Questions and Answers" document[5] on data requirements when replacing HFA propellants. More regulatory clarity is urgently needed in order to ensure a safe and effective transition to the next-generation propellants.

1.2. About the Workshop

On October 11th, 2023, IPAC-RS[6] hosted a free, public, hybrid (in-person and virtual) Workshop on the transition to low global warming potential (LGWP) propellants for metered dose inhalers. The goal of the Workshop was to convene stakeholders in industry and government in order to discuss regulatory and technical aspects of the transition to the new LGWP propellants. In this way, the Workshop served as both a forum for information sharing as well as a signal to regulators that more clarity is needed with respect to the approval process for next-generation propellants.

The Workshop took place in a hybrid format; IPAC-RS Secretariat hosted speakers in its office in Washington, D.C., USA, while viewers joined the live stream online. The Workshop was open to the public, free of charge, and featured speakers from industry, FDA and EMA. Over 200 attendees from more than 68 different companies and organizations attended the Workshop. A free recording, slide deck, summary of questions discussed during the Workshop and other materials are available on the IPAC-RS website.

This document offers a summary of the presentations from the Workshop. It is written from the perspective of each presenter, as identified in respective sections below. Additionally, please be aware that the viewpoints of the speakers are their own; they are not the opinions of IPAC-RS, its members, or regulatory agencies, unless otherwise specified.

1.3. About IPAC-RS

IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation & Science) is an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDPs) by collecting and analyzing data, and conducting joint research and development projects. Representing the OINDP industry since 2000, IPAC-RS aims to build consensus and contribute to effective

[5] EMA/477469/202323. At the time of this Workshop, the document was only available in draft form. On October 30, 2023, it was finalized. Final version is available at Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers - Scientific guideline | European Medicines Agency (europa.eu) 2023

[6] International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS, https://www.ipacrs.org/). Current IPAC-RS members are listed at www.ipacrs.org/about.

regulations and standards by sharing the results of its research through conferences, technical journals, webinars, and discussions with regulatory bodies. Contact the IPAC-RS Secretariat if you are interested in learning more.

2. INDUSTRY PERSPECTIVES

2.1. Rik Lostritto, *MDI Propellant Switch in the 2020s Compared and Contrasted to the Previous Propellant Switch of the 1990s: Don't Panic*!

In the first presentation of the Workshop, Dr. Lostritto offered perspectives on the MDI industry's current transition away from the currently used HFAs (134a and 227ea) to the next-generation LGWP propellants; HFA-152a or HFO-1234ze(E) and the lessons learned during the previous transition in the 1990s from CFCs to the HFA propellants.

Mark Twain once observed that "history doesn't repeat itself, but it often rhymes." Perhaps nowhere is this sentiment better reflected than in the MDI industry's latest transition from current HFAs to the next-generation, low global warming potential (LGWP) propellants.

In making this transition, regulators and industry should think carefully about possible steps forward. One critical lesson from the 1990s transition away from CFCs is that the MDI industry must act quickly – doing nothing can only lead to negative outcomes:

- Relying on allowances/derogations for the currently used HFA propellants is risky and ultimately unsustainable. Any allowances/derogations would not be long-term and would eventually run out via lost availability or deadline for use.
- Stockpiling current propellants is not a feasible solution either – due to quality concerns in storage, supply limitations imposed by mandated allocations, possible drug shortages, and possible deadlines for use.

In the US, MDI product types seeking a propellant switch may include the following:

1. brand-name MDIs (i.e., those approved via new drug applications, or NDAs),
2. NDAs in development,
3. generic MDIs (i.e., those approved via an abbreviated NDA, or ANDAs), and
4. ANDAs in development.

For generic MDIs, a critical issue is what will serve as the reference-listed drug (RLD) for approved ANDAs and ANDAs in development.

Manufacturers should consider the claims that they make in labelling. If the label contains safety or efficacy claims directly related to the propellant, the propellant would then be considered to be an active ingredient in a "fixed dose combination drug product" rather than an inactive ingredient. This should be avoided.

The 1990s transition from CFCs to HFAs required a total rethinking of MDIs in terms of formulation, materials selection and quality, manufacturing methods, testing methods, and specifications for components, ingredients, and final product. At the most basic level, the chemical properties of CFCs differ markedly from HFAs. HFAs have multiple C-H bonds,

which the CFCs lack. This fundamental difference dramatically impacts solubility and other key behaviors essential to MDI design, manufacture, quality, and function.

As a result of the chemical differences between CFCs and the currently used HFAs (plus other factors such as general modernization and heighted concern over leachables), the MDI industry had to undergo a major transformation, rather than a mere switch. First, a complete reformulation effort was required. The lost solubility of the then-used excipients precluded their use with HFAs, and new solubilizing excipients (e.g., ethanol) posed new problems of their own. Due to the difference in pressure between CFCs and HFAs, essentially all materials of construction that were compatible with CFCs became obsolete. This required multiple related industries to re-design valves (plastics, metals, and other materials), canister alloys and coating, and actuators. MDI manufacturers also had to re-design manufacturing methods.

Finally, the transition from CFCs in the 1990s grappled with problems of testing and performance. The then-existing quality control methods and corresponding MDI product quality requirements were already aged, and almost every *in vitro* performance test method and specification had to be re-designed and validated to the-then contemporary standards; some of which (e.g., leachables controls) were co-evolving.

Fortunately, the transition from current HFA propellants to their chemically similar next-generation propellants today appears much less dramatic from the chemical, physical, compatibility, manufacturing, testing, and performance perspectives. Chemically and physically, the next-generation propellants are more similar to the currently used HFAs than those HFAs were to CFCs. Although more data and studies are needed, this greater basic similarity is expected to translate into similar drug solubility, closer material compatibility properties (swelling, extraction, etc.), similar working pressures, and similar MDI manufacturing considerations.

Additionally, all aspects of MDI technology have evolved since the 1990s in a way that makes them better suited to facilitate the current propellant transition, due to:

- Cleaner, well understood, and better controlled materials of construction;
- Well-established and well controlled routine HFA MDI manufacturing;
- Continuous improvement in quality testing methods and metrics that better correlate with safety, efficacy, and bioequivalence;
- Better understood and controlled leachable and extractables.

At the same time, today, arguably more so than in the 1990s, there are, generally speaking, increasing issues and problems associated with supply chain vulnerability and drug shortages across most of the prescription drug space.

Despite the aforementioned advantages, a lot of work remains to be done, and a number of practical questions remain. First, there must be a robust data package supporting the switch to a next-generation propellant. Further, industry needs to know what type(s) of (abbreviated) human studies (if any) are needed to support a propellant switch to the next-generation propellants if adequate (and to-be-determined) *in vitro* comparability (bioequivalence, or "quality equivalence") exist. If key performance features, such as aerodynamic particle size distribution (APSD), delivered dose uniformity (DDU), and spray pattern are adequately aligned, what would testing in human subjects be expected to achieve?

Importantly, FDA's 2004 Guidance on Submitting Separate Marketing Applications provides that:

> "A change to an approved product based on chemistry, manufacturing, or controls data and bioequivalence, or other studies (e.g., safety and immunogenicity), that changes (1) the strength or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation (e.g., different excipients) can be submitted as a supplement to an approved application. Such a change would not ordinarily warrant a new original application unless it changes the dosage form or route of administration."

A reasonable interpretation of this guidance suggests that human data to support a propellant change for approved MDIs may be submitted as a Prior Approval Supplement (PAS) to an approved NDA (e.g., as "bioequivalence" data); and by reasonable extension to an approved ANDA in the same situation. The impact on a propellant switch program has unique (and in some instances overlapping) implications for NDAs and ANDAs that are approved or in development. Regulatory requirements need to consider NDAs and ANDAs holistically and together. To neglect either is to neglect both.

2.2. Sue Holmes, *Readout from the IPAC-RS/IPAC Surveys on Alternative Propellants*

The next Workshop presenter, Sue Holmes of GSK, provided an overview of the regulatory history of propellants in MDIs. Holmes focused on the "drivers for change" in the previous propellant transitions. She also presented findings from the IPAC-RS/IPAC survey on alternative propellants. A summary of this survey is available on the IPAC-RS website and is therefore not reproduced here.

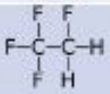
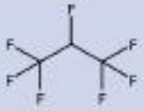
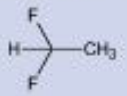
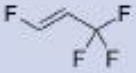
2.3. Dan Dohmeier, *Materials Aspects of the Transition to Alternative Propellants – an IPAC-RS Working Group Perspective*

In the final industry presentation of the Workshop, Dan Dohmeier of Kindeva, presenting on behalf of the IPAC-RS Materials and Propellants Working Group, addressed materials compatibility aspects of the transition. Amongst the Working Group members, there is "clear consensus" that the MDI industry is much more prepared to make the transition to new LGWP propellants today than it was in the 1990s. One reason for this is the similarity of the second- and third-generation propellants in key characteristics, as summarized in the table below:

Safety information for HFA-152a and HFO-1234ze(E) is being developed. Early data is promising, and more studies are ongoing. See the slides from the workshop[7] for further details, such as:

- See slide 96 for safety information.
- See slides 102-105 for studies conducted on materials compatibility

[7] IPAC-RS Workshop slides are available here.

	Current Propellants		Lower GWP Propellants	
Propellant	HFA 134a	HFA 227ea	HFA 152a	HFO 1234ze(E)
Formula	$C_2F_4H_2$	C_3F_7H	$C_2H_4F_2$	$C_3H_2F_4$
Chemical Structure				
GWP	1430[a]	3220[a]	124[b]	<1[c]
Molecular Weight (g/mol)	102.0[a]	170.0[a]	66.1[b]	114.0[c]
Density (liquid) at 20°C (g/mL)	1.23[a]	1.41[a]	0.91[b]	1.17[c]
Boiling Point (°C)	-26.3[a]	-16.5[a]	-24.0[b]	-19.0[c]
Vapor Pressure at 20°C (bar)	5.72[a]	3.90[a]	4.12[b]	4.28[c]
Water Solubility (ppm)	2200[a]	610[a]	2200[b]	225[c]
Dipole Moment (debye)	2.06[a]	0.93[a]	3.69[b]	1.44[c]
Log P (octanol/water)	1.1[a]	2.1[a]	0.75[d]	1.6[d]

3. REGULATORY PERSPECTIVES

3.1. Craig M. Bertha, *Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective*

Dr. Bertha's presentation focused on the robust Chemistry, Manufacturing and Controls (CMC) package that must support any submission – regardless of whether it is a new application or a supplement.

Dr. Bertha's presentation began with an overview of the physico-chemical properties of the second- and third-generation propellants.[8] Generally, HFA-152a possesses a similar boiling point, viscosity, polarity, and water solubility in comparison with HFA-134a. However, HFA-152a is flammable, which impacts manufacturing. HFO-1234ze(E) mirrors HFA-227ea in many of the same properties. Both new molecules contain a GWP that is a fraction of their predecessors'.

The drug solubility in the propellant impacts the design of formulation. Ultimately, propellant's physicochemical properties, composition of the formulation, and device configuration determine the MDI performance and usability.

The Agency's CMC reviewers pay close attention to delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) as the two most important quality attributes. Both metrics can be used to assess consistent quality within and between MDI canisters

[8] The second- and third- generation propellants include: HFA-134a and HFA-227ea; and HFA-152a and HFO-1234ze, respectively.

(intra-unit and inter-unit) as well as between-batch, over time (stability), and for product characterization.

The FDA 2018 Draft Quality Guidance[9] defines "significant change" in DDU and APSD as:

- DDU: a change in the mass of the mean dose of 10 percent or more (determined separately on samples taken from the beginning and end of product life;
- APSD: a change in the total mass of fine particles (e.g., particles less than five micrometers) more than 10 percent.

The assumption underlying both metrics is that the more comparable the *in vitro* DDU/APSD data, the more likely it would be that the *in vivo* lung deposition would be similar.

Quality Data to Support New LGWP MDI Products

- Drug Substance (Section S of Module 3)[10]:
  - Applicants may rely on previously submitted drug substance information if used for similar approved products.
  - If the new product is suspension-based and approved products had solution formulations, additional quality information may be needed.
- Drug Product (Section P of Module 3):
  - Similar to any drug product section.
- Must provide robust stability data (like any MDI application would contain).

Conclusions

- Drugs will likely have different solubility characteristics in the new LGWP propellants, which may require formulation change.
- Differences in densities of new propellants and drugs may impact physical stability of suspension formulations.
- As compared to device components used with second generation propellants, LGWP propellants may require changes.
- From the quality perspective, submissions for products formulated with LGWP propellants should include all data and information that would be applicable for a new product (per ICH M4Q - CTD modules 2 and 3); reference can also be made to pertinent previously submitted information.
- Due to the new propellant, usage instructions and storage instructions may need to be changed.

---

[9] FDA CDER (2018) Draft Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products--Quality Considerations | FDA

[10] Section and module refer to the Common Technical Document (CTD) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). For details, see FDA Guidance for Industry "M4Q: The CTD — Quality" (2001) available at https://www.fda.gov/media/71581/download.

3.2. Karolina Törneke, *Data Requirements when Switching to LGWP Propellants – the EU Perspective*

Dr. Törneke's presentation focused on the data requirements in the transition to new propellants as agreed within EU. This transition may be accomplished irrespective of legal grounds for the approval, e.g. as a variation application to any existing marketing authorization, not necessarily with an originator product being first. The key question is whether the new excipient is novel (i.e. used for the first time in a product for inhalation) or established. Any novel excipient should be supported by a data set showing safe use of the propellant as such (irrespective of active substances), including human in vivo data on airway hyperreactivity and ciliary function. In addition at least one three-month safety study is to be provided. Unless there are unexpected findings, this data package will only be required once for each novel propellant and may be a shared mission between companies.

Besides the need for data supporting any novel excipient, a data set should be provided supporting the transition in each approved product. This data set should include the same elements as those normally included for variations to marketing authorizations for approved products for inhalation. The changes made to the inhaler should be adequately characterized and therapeutic equivalence should be demonstrated according to practice for variations/extensions and abridged applications. The established step wise approach with set acceptance criteria for similarity in vitro and by means of pharmacokinetics will be applied.

These data requirements are outlined in the document Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers - Scientific guideline | European Medicines Agency (europa.eu)

4. CONCLUSION

All stakeholders are working towards the goal of a safe and efficient transition from the current medical propellants, HFA-134a and HFA-227ea, to the lower-GWP propellants, HFA-152a and HFO-1234ze(E). The new propellants possess similar physicochemical properties, but with a GWP that is a small fraction of current propellants. Environmental Agencies in the EU and US have initiated a process of phasing out the current propellants. Industry is investing and diligently preparing for this transition, drawing on lessons learned from the transition away from CFCs in the 1990s. Research and studies have demonstrated the general suitability of the molecules HFA-152a and HFO-1234ze(E) as replacement medical propellants, and further detailed data are being gathered. Despite the promise of the new propellants and the readiness of industry to utilize them, however, there is limited guidance from regulators. As environmentally-dictated phasedown deadlines approach globally, it is critical that regulators provide more clarity to the industry on the approval process and regulatory requirements for bringing MDIs with the new propellants to market.

5. SOURCE REFERENCES

Workshop Presentations on October 11, 2023 (a recording is available at the IPAC-RS LGWP Workshop Website):

Ann Purrington (Kindeva), Welcome & Introduction,

Rik Lostritto (Lostritto Consulting LLC), MDI Propellant Switch in the 2020s Compared and Contrasted to the Previous Propellant Switch of the 1990s: Don't Panic!

Sue Holmes (GSK), Readout from the IPAC-RS/IPAC Surveys on Alternative Propellants

Craig Bertha (FDA), Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective

Karolina Törneke (EMA), Data Requirements When Switching to LGWP Propellants – the EU perspective

Dan Dohmeier (Kindeva), Materials Aspects of the Transition to Alternative Propellants – an IPAC-RS Working Group Perspective

IPAC-RS, Questions Discussed During the Alternative Propellants Workshop on October 11, 2023 (A summary is available at the IPAC-RS LGWP Workshop Website)