IPAC-RS SURVEY ON STAKEHOLDER PERSPECTIVES ON SWITCHING CURRENT PRESSURIZED METERED DOSE INHALERS TO NEW PROPELLANTS

1. INTRODUCTION

1.1. Background

Pressurized metered dose inhalers (pMDIs) are currently the mainstay treatment of asthma and chronic obstructive pulmonary disease (COPD) in the US, Europe, and globally. Other delivery systems exist (e.g., dry powder inhalers and nebulizers) but may not be suitable for all patients and are not available for all therapeutic molecules. Currently, hydrofluoroalkanes HFA-134a and HFA-227 are used as "propellants" to expel medical formulation from pMDI canisters and to create a "puff" for patient to inhale. Due to environmental concerns, these propellants will most likely be phased out in the near future and become unavailable for medical use. Two potential replacements have been identified, HFA-152a and hydrofluoroolefin HFO-1234ze(E). Neither of these have yet been used in an approved pMDI, and HFO-1234ze(E) could moreover be banned under the recent proposal from the European Chemicals Agency (ECHA) restricting manufacture and use of per- and polyfluoroalkyl substances (PFAS). Nevertheless, pharmaceutical companies are exploring ways to reformulate current pMDIs away from HFA-134a and HFA-227, as they may soon become unavailable due to statutory prohibition or economics. Regulatory guidance on the requirements for the switch are currently lacking. It is therefore necessary to clarify regulatory requirements for implementing the change from the current to next-generation propellants, in order to enable an uninterrupted supply of life-saving medicines to patients.

In the 1990's, chlorofluorocarbons (CFCs) were replaced with HFA 134a and HFA-227 for (then) environmental concerns. To implement the switch, product manufacturers had to develop New Drug Applications (NDAs) in the US, or similar dossiers in Europe. To meet regulatory requirements, industry sponsors had to conduct costly and time-consuming clinical studies as well as develop completely new chemistry-manufacturing-controls (CMC) programs.

The contemporary replacement propellants are thought to be more physicochemically similar to HFA-134a and HFA-227 than these HFAs were to CFC. It seems reasonable, therefore, that a more facile switch (e.g., via a supplemental NDA in the US or a similar pathway in Europe) would be suitable for approved pMDIs currently on the market. This approach would balance the need to avoid disruptions in the supply of life-saving medicines to patients, while documenting the safety, efficacy and quality of pMDIs based on new propellants. To clarify specific requirements and thus enable the development and approval of such pMDIs, a dialogue among industry, regulators, and other stakeholders is urgently needed.

1.2. Survey Details

The survey was conducted from April 18 to June 13, 2023, with responders primarily from IPAC and IPAC-RS member companies.

IPAC (International Pharmaceutical Aerosol Consortium) was formed in 1989 in response to the mandates of the Montreal Protocol and fully supported a timely and effective transition away from chlorofluorocarbons (CFCs) under the Montreal Protocol that balanced patient health and environmental concerns. IPAC's mission is to ensure that environmental policies relevant to inhaled therapies are patient-centric and appropriately balance both patient care and sustainability objectives. HFC pressurized metered dose inhalers (MDIs) played a critical role to the transition as one of the key ozone-friendly alternatives developed to replace CFC MDIs. IPAC's members: AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Kindeva, Organon, and Teva. Further information available at www.ipacinhaler.org.

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 (OINDP) 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 regulations and standards by sharing the results of its research through conferences, technical journals, webinars, and discussions with regulatory bodies. IPAC-RS members are listed at www.ipacrs.org/about.

2. SURVEY OUTPUT

2.1. Demographics

The survey was completed by 26 participants, with half representing the opinions of their organization. Participants represented a cross-section of the pMDI business including formulation development, device development, manufacturing, testing and regulatory affairs. There was interest in branded and generic products both approved and in-development, globally. While a majority of the interest is in orally inhaled pMDIs, there were a number of respondents interested in nasal application of pMDIs.

The survey indicated that companies are at different stages in this journey, with some yet to commence internal discussions and others who have already received regulatory feedback.

2.2. Priorities

The overall rank of highest to lowest company priorities for the propellant switch was:

Item	Overall Rank	Rank Distribution	Score
Minimize the requirement for non-clinical and clinical studies relying on comparability of in vitro pharmaceutical performance and acceptable PK results	1		70
Ensure the switch is as rapid as possible	2		66
Minimize changes between current and proposed product, including the formulation and device component parts	3		63
Ensure comparable in vitro pharmaceutical product performance characteristics including ex-actuator delivered dose, aerodynamic particle size distribution (APSD) profile, and fine particle mass (FPM), even if this means making significant changes to the device and/or formulation	4		55
Use the opportunity to enhance the product performance	5		24

Priority 1 was a clear priority. Priorities 2-3 may be somewhat intermingled as a more rapid switch can potentially only be achieved by minimizing the changes between the current and proposed products. Priority 5 was very clearly the lowest ranking, and likely attributed to the thought that "to match existing products and enhancing product performance will require additional clinical work."

2.3. Challenges/Concerns

The overall rank of highest to lowest company concerns and challenges for the propellant switch was:

Item	Overall Rank	Rank Distribution	Score
Timings for phase down/ban(s) of PFAS propellant	1		144
Lack of health authority guidance	2		144
Uncertainty of requirements for in vivo data	3		109
Differing global expectations	4		104
Cost of industrial adjustments to handle flammable propellants	5		102
Acceptability of additional changes (eg formulation, device) as a consequence of the propellant change	6		100
Moving legislative target (i.e. will this happen again in the future?)	7		86
Cost of switch, with no expectation to change the pricing	8		79
Formulation challenges	9		78
Incomplete toxicological assessment of alternative propellants	10		68

Organizations challenges/concerns fell into 4 groupings, with 2 overall key challenges. With the growing awareness of the PFAS regulations/Kigali HFC discussions and suppliers announcing imminent changes to processes and materials to adhere to the timelines, pharmaceutical companies are unsurprisingly concerned, knowing the length of time it takes to make these kinds of changes in the supply chain. The lack of health authority (HA) guidance means companies must engage with the HA to ensure they have a robust development plan, all of which takes additional time.

The next grouping of concerns (3 to 6) encompassed uncertainty of requirements for in vivo data, differing global expectations, and acceptability of additional changes, all linked to the key concern of lack of health authority guidance; along with the cost of industrial adjustments to handle the different properties (such as flammability) of the new propellants. The cost, and time, to refurbish existing facilities or build from scratch, must all be factored into companies development plans.

The third grouping (7 to 9) included moving legislative target, in that industry is concerned about making this change for the propellant, knowing that other environmental challenges may also be coming, such as a ban on the can coating (currently proposed to be under a 12 year derogation enacted 18 months after implementation of the joint REACH Annex XV

restriction proposal, which is currently under consultation). The overall cost of the switch, with the expectation that the pricing will remain about the same was also in the grouping, as was, surprisingly, formulation challenges. This is potentially as companies have not yet started working on this aspect, and are still focusing on the general uncertainties encompassed in concerns 1 to 8 with an expectation that they can work out the formulation when needed.

The lowest ranked concern was regarding the incomplete toxicological assessment, as the expectation is that the propellant suppliers are doing the majority of the work in this space (presentations from the propellant suppliers at RDD and DDL conferences have highlighted some aspects of what they have undertaken[1]), and the pharmaceutical companies would only need to perform standard safety studies.

It was also noted that there is a concern in the lack of options of propellant suppliers and manufacturers, which can lead to monopolization of the market.

2.4. Additional Changes

The change in propellant is going to drive some additional consequential changes, such as valve seal materials which will need to have the appropriate properties to ensure chemical compatibility. 67% of responders agreed that additional changes would likely be required, while 5% did not and 29% were unsure. It may be that the 5% who did not think any additional changes would be required have either not started working on this transition or are not in the MDI field.

Labeling changes may also be required (above the basic changes to the propellant name for example), if there are any different patient instructions, safety data, or formulation aspects such as flammability information. 30% of responders agreed that labeling changes would likely be required, while 25% did not and 45% were unsure.

It was noted that guidance on what changes would be considered acceptable/consequential and what would be considered significant would be welcome.

2.5. Regulatory Pathway and Data Requirements

When considering the propellant change for an approved product, over 70% of responders expect to register the change as a variation (either CMC alone [25%] or as a line extension with some clinical aspects [46%]) and 13% expected the change to require a new marketing application. The remainder considered this to be decided on the product and business case.

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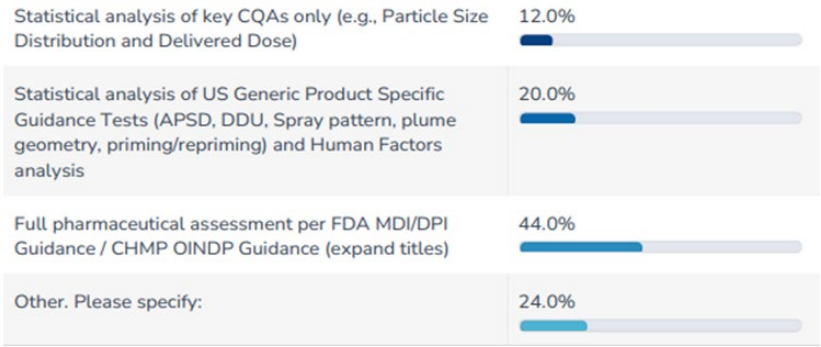
[1] HFO-1234ze(E): Propelling Towards Carbon Neutrality: Erik Boldt, et al Drug Delivery to the Lungs, volume 33, 2022
Corr, S: *HFA-152a as a Sustainable pMDI Propellant*. In: R N Dalby, P R Byron, J Peart et al (eds): *Respiratory Drug Delivery 2022* Virginia Commonwealth University, VA; pp361-364, 2022.
Kuehl PJ, Corr S, Leach CL: *Safety, tolerance and pharmacokinetics of HFA-152a in healthy volunteers*. In: R N Dalby, P R Byron, J Peart et al (eds): *Respiratory Drug Delivery 2022* Virginia Commonwealth University, VA; pp87-95, 2022
Hulse R, Boldt E, Decaire B, Smith G: *A journey to net zero using Solstice® Air*. In: R N Dalby, P R Byron, J Peart et al (eds): *Respiratory Drug Delivery 2022* Virginia Commonwealth University, VA; pp97-102, 2022.

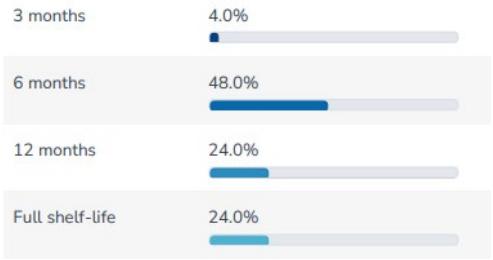
These expectations may be reflective of the EMA guidance that was issued at around the same time as this survey launched[2] and in the absence of any current FDA guidance.

In regard to the in vitro data requirements, there were a range of opinions, with an overriding comment that it will depend on the region and final product configuration/changes incorporated. Overall, a majority expected a full pharmaceutical assessment per FDA MDI/DPI guidance/CHMP OINDP guidance to be required. In retrospect, this question could have been interpreted in two ways, i.e., regarding the requirements for in-vitro data that demonstrates similarity or the in-vitro data to characterize the product. It is agreed by all that appropriate data are required to demonstrate the product is safe and effective and performs as expected.



Similarly responses regarding the clinical or "bio" requirements, was an equal split of responses, with 39% expecting a full BE analysis would be required (per current requirements in a given country) as is done for generics , with the new-vs-old propellant treated as Test-vs-Reference products, 35% expecting in vitro only should be enough and 26% expecting something else; such as the EU step-wise approach, or something similar with in vitro, PK and a small PD study. Again, this was potentially influenced by the EMA guidance and the lack of FDA guidance on this topic.

The question on the amount of expected stability data for a new propellant product with a proposed 24-month shelf-life, was also considered to be region dependent with the majority expecting 6 months to be sufficient for the submission. This is likely to reflect the earlier majority opinion that this would be a variation application rather than a new application. For a new application, ICH clearly lays out that 12 months data would be required to support a 24 month shelf-life.



[2] EMA/CHMP/83033/2023: Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers; 30 March 2023.

2.6. Future Discussions

There was a clear call for future discussions on the impact of the propellant switch scenarios not only on brand products but on approved generic products or on generics in development, as although there are guidances to inform industry on the process for developing a generic product, it is unclear how the generic product manufacturers can be making this change in parallel with, or ahead of, the branded product.

As outlined above there was a range of responses in the data requirements, and unsurprisingly responders requested a deeper discussion into what exactly the bridging requirements are (for brand and generics) that are currently in development using the current propellants that now need to transition also. This again, highlights industries uncertainty on approaches due to lack of guidance.

Regarding the ECHA proposals for the PFAS phase down/down, a majority of responders were aware, and are either concerned, or have not yet looked at this in detail. Primary concerns were around the timings and the limitations this puts on the propellant options and ultimately the impact this will have on patient access to pMDIs. This is considered to be a key topic for discussion going forward.

2.7. Regulatory Agency Questions

There were several questions targeted specifically at Regulatory Agencies, regarding progress within their agency, whether any acceleration of reviews, flexibility etc., was being considered, and their overall awareness of the F-gas/PFAS proposals. Unfortunately, no Regulatory Agencies participated in the survey.

3. NEXT STEPS

The information from this survey has been used to help guide the IPAC-RS Working Group to ensure key topics of interest and concern are discussed; for example at the Oct 11, 2023 Workshop (IPAC-RS Workshop: Transition to LGWP Propellants for MDIs (ipacrs.org)). The desire is that Regulatory Agencies will engage with industry to address some of these concerns and consider options for expedited pathways to ease the transition, all of which will benefit industry, regulatory agencies and most importantly the patients.