ECHA consultation submission on per- and polyfluoroalkyl substances (PFAS)

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Asthma + Lung UK is Britain's leading respiratory health charity and a champion of patients' voices on lung health. ECHA's proposal to restrict PFAS (herein referred to as 'the proposal') is well intentioned but fails to consider the full impact that such a restriction would have on patients, the medicines industry, and health services.

Asthma + Lung UK supports ECHA's efforts to reduce dangerous emissions, particularly in the pursuit of cleaner air. We have found that, when surveyed, 60% of pMDI users would consider switching to a greener inhaler for environmental reasons, and 85% think that asthma patients should be encouraged to switch.[1] However, the proposal's broad-brush approach to PFAS risks pressurised metered-dose inhalers (pMDIs) becoming unfeasible due to the lack of a viable propellant, removing vital medicines used by millions of people with lung conditions before they have had a chance to move to a suitable alternative. Were the proposal to restrict pMDIs and force a rapid or unplanned switching programme, however, this may be unsafe.

It is essential that ECHA make key amendments to the proposal in order to protect millions of patients' access to life-saving medicines, whilst also transitioning to cleaner models of inhaler, and that adequate time is allowed for suitable alternative medicines to be developed, without which patients and healthcare systems will face severe challenges.

Summary of recommendations:

1. That medical propellants currently used in pMDIs – namely HFC-134a and HFC-227ea – be afforded an appropriate derogation until at least 2030 to allow adequate time for suitable replacements to be developed and proven safe by the required statutory health organisations and ensuring continued access to vital medicines.

2. That HFO-1234ze be granted a permanent exemption as a medical propellant for pMDIs. HFO-1234ze is an important alternative to HFC-134a and HFC-227ea and presents a long-term option for the continued viability of pMDIs.

3. That ECHA include patient voice through direct consultation with patients and organisations that provide patient voice within its ongoing consultation on the proposal.

Evidence

In the UK, more than 60 million inhalers are prescribed annually to patients with lung conditions including asthma and chronic obstructive pulmonary disease (COPD).[2] pMDIs account for approximately 86% of the UK's inhaler usage,[3] with over 51 million pMDIs prescribed in the UK each year. This mirrors trends in most European nations, with pMDIs making up over 73% of inhaler prescriptions in Europe,[4] although there are countries which use a higher proportion of DPIs demonstrating that they can be safe and effective.[5]

PFAS are not an active pharmaceutical ingredient (API) within pMDIs; they are utilised as a propellant and as a protective layer within the cannister's construction. Despite this, PFAS are as vital to pMDIs as the medicines being propelled and should be protected, in this context, as if they were an API.

> **PFAS are as vital to pMDIs as the medicines being propelled**

The scale of pMDI prescribing hints at the unfeasibility of safe transition from PFAS at the rate described within the proposal[6] without the inclusion of the maximum derogation period of twelve years for HFC-134a and HFC-227ea (the PFAS currently used within pMDIs). We understand from discussions with pharmaceutical manufacturers that a prolonged derogation is essential to ensure safe supply of the PFAS currently in use – and thus a safe supply of pMDIs – which is necessary as replacement propellants (namely HFO-1234ze) are subject to stringent and lengthy approval processes by medical authorities.

The European Medicines Agency (EMA)'s approval process, for example, can take up to 25 months (including prior consultation), excluding the development of the product being tested.[7] Approvals for pMDIs run consecutive to the approvals of their respective propellants, further extending the approvals time for an approved pMDI.

Prolonging use of current generation propellants

Without an appropriate phasedown timeline, supply of approved PFAS propellants will be restricted – potentially by as early as 2029 through option RO1[8] – leaving clinicians and patients with limited choices of inhalers, and forcing clinicians to prescribe potentially unsuitable alternative medicines to patients. This poses three key risks:

- Rapid restriction of approved PFAS propellants (understood by this submission as any restriction of HFC-134a and HFC-227ea without the maximum possible derogation) risks removing all pMDIs from the global market as no suitable replacements have yet been approved by the relevant medicines agencies. (While HFC-152a is not covered within the proposed restrictions of PFAS, it, like HFO-1234ze, has not yet been approved for medical use, and would be unlikely to be usable within the initial 18 months of the proposed restriction period (by 2029).)

  The impact of such a significant change in the availability of critical medicines would be severe, both for individual patients and for healthcare systems.

  Asthma + Lung UK supports patients switching to lower-carbon inhalers as part of a shared decision making process with their healthcare professional, and where it is clinically appropriate for their condition, as it is for many patients. Were the proposal to restrict pMDIs and force a rapid or unplanned switching programme, however, this may be unsafe. It is vital for patient safety and good management of respiratory conditions that patients are confident in using their inhalers on both a daily basis and in an emergency.

  While many patients find DPIs easier to use,[9] there may be concerns for the youngest and oldest patients, and those suffering from significant breathing impairment, whether this impairment is a prolonged symptom of their condition, or resultant of an exacerbation.[10]

- Patients transitioning from pMDIs to alternative medicines (dry-powder inhalers (DPIs) or soft mist inhalers (SMIs)) without high quality support risk their conditions deteriorating, heightening the risk of exacerbations and increasing emergency admissions and mortality rates.[11] A 2020 study into forced, non-medical switching following the removal of budesonide/formoterol pMDIs from Medicare Part D in the United States found that up to 62% of patients reported “high/very high impact on their lives” during the switch, and up to 70% of patients required reliever (emergency) medication most days.[12]

- Transitioning patients to alternative medicines en masse, would likely be unfeasible and would pose an increased burden on healthcare systems, particularly primary care. Inhaler switching without an appointment with a clinician cannot be seen as a suitable option and falls far short of best practice; switching without an appointment increases the risk of incorrect inhaler technique, alienates the patient from their treatment and risks worsening their condition.[13]

Of the 5.4 million asthma patients in the UK, approximately 4.6 million use a pMDI inhaler.[14] Pre-Covid data shows that just over 70% of asthma patients were receiving annual asthma reviews, and that under 60% of the reviews conducted included an inhaler technique check, meaning that approximately 2.65 million pMDI users are going without an inhaler technique check each year. In the event of a mass inhaler switch, providing inhaler switch appointments for this number of people would account for around 30% of UK annual GP working hours when performed in person,[15] excluding follow-up appointments and associated administrative load. Though it is near-certain that these appointments would be performed incrementally over the period prior to PFAS restriction, this would pose a significant challenge to primary care capacity.

Protecting use of next generation propellants

As outlined above, many pharmaceutical companies working in this area view HFO-1234ze as an important future option for pMDIs, though it will be subject to necessary delay due to the need for approval by relevant medicines agencies, and subsequent approval of any device using HFO-1234ze as a propellant.[16]

HFO-1234ze's global warming potential (GWP) is significantly lower than current generation propellants'; over 200 times lower than HFC-134a; 460 times lower than HFC-227ea.[17] A 2022 report published by the Department for Environment, Food and Rural Affairs asserted that HFO-1234ze's GWP was so low as to be comparable with alternative DPIs and SMIs, both of which require more plastic than pMDIs and thus contribute to increased upstream emissions;[18] exempting next generation propellants would still allow for an 85% reduction of total greenhouse gas emissions associated with pMDIs.[19]

Were HFC-152a be left as the sole medical propellant, pMDIs would be in a position of unprecedented vulnerability as at least two options have always been available.[20] As such, we support the view that HFO-1234ze be granted a permanent exemption as a medical propellant for pMDIs. HFO-1234ze is an important alternative to HFC-134a and HFC-227ea and presents a long-term option central to the continued viability of pMDIs.

Recommendations

1. We recommend that medical propellants currently used in pMDIs – namely HFC-134a and HFC-227ea – be afforded an appropriate derogation until at least 2030 to allow adequate time for suitable replacements to be developed and proven safe by the required statutory health organisations and ensuring continued access to vital medicines.

   As outlined in the evidence given above, allowing the longest possible derogation of twelve years would allow sufficient time for next generation propellants to be developed and tested properly. This would ensure that pMDIs remain available for the millions of patients that rely on them as vital medication, including the significant portion of patients for whom there is no viable alternative. At the same time, it is vital that all relevant agencies work with the pharmaceutical industry to expediate the delivery of alternative propellants.

2. We recommend that HFO-1234ze be granted a permanent exemption as a medical propellant for pMDIs. HFO-1234ze is an important alternative to HFC-134a and HFC-227ea and presents a long-term option for the continued viability of pMDIs.

   HFO-1234ze is a vitally important potential next generation propellant for pMDIs, and has the lowest GWP of any prospective options. Transition to HFO-1234ze within pMDIs secures their manufacture and prescription for the long term, ensuring that patients have reliable, regular medicine supply and that clinicians can prescribe to meet patient need above all other considerations.

3. We recommend that ECHA include patient voice through direct consultation with patients and organisations that provide patient voice within its ongoing consultation on the proposal.

   Direct consultation with patients and patient organisations is vital if ECHA is to fully understand the proposal's potential impact on patients. Without directly involving patients, well intentioned efforts risk causing harm to patient health.

References

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[3] Bell, J. P., (2023) et al. *An Assessment of Pressurized Metered-Dose Inhaler Use in Countries in Europe and the Rest of the World*
[4] *ibid*
[5] *ibid*
[6] European Chemicals Agency (2023) *ANNEX XV RESTRICTION REPORT PROPOSAL FOR A RESTRICTION* p. 3
[7] European Medicines Agency (2015) *Applying for EU marketing authorisation for medicinal products for human use*
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[12] *ibid*
[13] Patient experience of inhaler switching without an appointment and associated technique check risks mirroring critical error rates similar to those outlined here: Makhinova, T., et al (2020) *Checking Inhaler Technique in the Community Pharmacy: Predictors of Critical Errors* [Accessed online 11 September 2023]
[14] Based upon pMDIs accounting for 86.5% of UK inhaler use. Bell, J. P., (2023) et al. *An Assessment of Pressurized Metered-Dose Inhaler Use in Countries in Europe and the Rest of the World*
[15] Approximate hours calculated (((5.4m x 0.86) x 0.70) x 0.60). Based upon an average appointment length of 10 minutes, totalling approximately 441667 hours across 35,897 full-time equivalent GPs; further reading here: Fraser, C. *The Health Foundation* (2023) *General practice tracker* [Accessed online 7 September 2023]
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