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EUROPEAN UNION

1. **Developments of metered-dose inhaler products using lower-global-warming-potential propellants**

There is ongoing work preparing for the transition to propellants with low global warming potential (LGWP) within EU and globally.

The **considered alternative propellants for pressurized MDIs** (pMDIs) for use in humans include both R152a with a GWP of 124 and R1234ze with a GWP of slightly more than 1 (but considered a PFAS under the OECD definition). This would allow for a reduction of at least magnitude in GWP compared to the currently used R134a (GWP=1430) and R227ea (GWP=3220).

A **new production facility of R152a** was opened in the UK in March 2022 ([1]). In December 2024 it was announced that construction of a larger scale medical propellant purification plant is advanced. Once operational, the plant will significantly expand production capacity for R152a. This facility will meet high-volume needs, supporting the transition of widely used medications. R1234ze is produced by another chemical company, also for use as a refrigerant. ([2])

Pharmaceutical companies have advanced initiatives towards replacing the existing propellants with LGWP propellants. Already in 2019 there were public announcements of the intention of bringing LGWP pMDI inhalers to the market. ([3]) Some further action, publicly announced, by some of these companies include:

- (IPA long-term phase II clinical safety trial has been announced in April 2024 by one manufacturer. ([4]) This follows the completion of two short term clinical trials assessing the safety of the new propellant (R152a), plus three clinical pharmacology studies on the new carbon minimal fixed combination of an inhaled corticosteroid (ICS), and a long-acting bronchodilator (LABA). These studies collectively provided reassuring evidence of a similar performance and tolerability of the new formulation, when compared to the current one, for patients with asthma and COPD. This milestone follows successful completion of similar studies in July 2022 with a fixed triple combination. A new manufacturing site in Italy focusing on LGWP inhalers and dry powder inhalers (DPIs) was announced on 26 March 2025. ([5]) The company is on track for the completion of the main clinical development by 2025. Subsequent introduction in the UK & Europe is planned, pending regulatory approvals (source: IPAC).

(1) Koura opens world's first HFA 152a medical propellant production facility - Koura

(2) Honeywell Teams With AstraZeneca To Develop Next-Generation Respiratory Inhalers That Use Near-Zero Global Warming Potential Propellant

(3) chiesi.com/en/chiesi-outlines-350-million-investment-and-announces-first-carbon-minimal-pressurised-metered-dose-inhaler-pmdi-for-asthma-and-copd/

(4) Carbon Minimal Inhalers | Chiesi Farmaceutici S.p.A.

(5) A new facility for the production of therapeutic solutions

- A second manufacturer has committed to converting the whole portfolio as quickly as possible and has announced (March 2025) to be on track to complete this by 2030. In February 2022 the success of a recently completed Phase I clinical trial of the propellant HFO-1234ze in a pMDI containing budesonide, glycopyrronium, formoterol fumarate in healthy adults was positive. Following this, the manufacturer has said to advance a commercial partnership with the gas producer to develop their triple-combination therapy. This manufacturer has more recently announced the submission of regulatory filings in the EU, the UK, and China, with other territories to follow soon. ([6]) In September 2024 the completion of the studies that support the first regulatory filings was announced. Regulatory submissions have been accepted in Europe, the UK and China (source: IPAC).

- A third manufacturer announced pre-clinical assessments to reduce GHG emissions from inhalers by 90%, by using a new propellant (i.e. R-152a;). In November 2023 phase III trials were started on the drug salbutamol. ([7])If successful, regulatory submissions will begin in 2025. (source: IPAC)

- A fourth manufacturer announced the completion of registration batches in 2024 and full commercial-scale operations in 2025. A co-development cooperation with a producer of R152a was announced in 2023. In May 2024 an investment in a second manufacturing line for the production of LGWP propellants in the UK was announced (a first production line will be completed in 2024). ([8])

EMA and national medical agencies are taking an active role in the ongoing dialogue with concerned companies, both nationally and at EU level, as well as exchanging with counterparts in third countries. A recent workshop on the topic was held involving the participation of European regulators. ([9])

The EU F-gas Regulation (Regulation (2024/573)), which applies since March 2024, includes HFCs intended for use in MDIs in the EU-wide quota system from 1 January 2025 to incentivise the use of LGWP propellants in pMDIs (previously such gases benefitted from an exemption).

At European level, the European Medical Agency (EMA) is responsible for approving medicinal products that are centrally authorised. For metered-dose inhalers this is the case for six products. The European Commission and EMA have exchanged frequently on the matter of LGWP inhalers during the review of the F-gas Regulation and the start of its implementation. The agency, together with stakeholders, national agencies and in consultation with the European Commission, has produced a public Questions & Answer document “Questions and answers on data requirements when transitioning to low global warming potential (LGWP)

(6) Transitioning our pMDIs with reduced climate impact | AstraZeneca

(7) GSK announces major step towards sustainability ambitions with advancement of low carbon Ventolin programme to Phase III trials | GSK

(8) Kindeva Drug Delivery invests in second manufacturing line for greener inhalers at UK manufacturing site - Kindeva

(9) Navigating the Transition to Low Global Warming Potential Propellants - The Center for Research on Complex Generics (CRCG)

propellants in oral pressurised metered dose inhalers" ([10]) in October 2023 that aims to inform pharmaceutical companies when seeking authorisations for their new inhaler products. This document summarises the data requirements that must be fulfilled by any company applying for products with one of the LGWP propellants, applicable to both new products and changes to existing ones. For some of these six products there are currently on-going approval processes which are expected to conclude in the second half of 2025. The exact nature and progress of these approval processes remains still confidential and will be known once authorization has been given.

There are also metered-dose inhalers that require authorisation at national level in the EU Member States.

In addition, a first approval to the use of R1234ze propellant in a COPD inhaler was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. This new version will be available in the UK from the second half of 2025. In the meantime, the current version will continue to be available to patients. The MHRA's approval is supported by clinical evidence showing that the new propellant, HFO-1234ze(E), delivers the same dose and therapeutic effect as the original formulation. The assessment included evidence on product quality, device performance and stability. ([11])

The Italian Medicines Agency (AIFA), in collaboration with the Ministry of the Environment, has informed stakeholders about the new labelling requirements for metered-dose inhalers (MDIs) containing fluorinated greenhouse gases, as set out in Regulation (EU) 2024/573 and Implementing Regulation (EU) 2024/2174. AIFA has urged marketing authorisation holders of such products to initiate the necessary procedures to ensure compliance.

The European Union and its Member States will provide relevant information on various topics as soon as further details become available. This includes the current status of European and national authorization procedures, as well as activities of the competent national authorities and coordination between environmental and health authorities.

(10) QAs when replacing HFC propellants - labelling updated

(11) MHRA approves world's first low-carbon version of COPD inhaler Trixeo Aerosphere - GOV.UK

2. Availability of other alternatives

Besides introducing low GWP propellants in pMDIs, other good alternative technologies have been available to patients for decades, are now widely available and avoid the use of a propellant, thus reducing their climate impact considerably.

The use of **Dry Powder Inhalers** (DPIs) is common in many countries and for most patients can fully replace pMDI applications. They require a more active inhaling as no additional propellant is used. On the other hand, they may result in more effective uptake of the medicinal agent compared to pMDIs where good coordination is needed to press the canister and breathe in fully at the same time. The first DPI was introduced to the market in Finland in 1993 ([12]).

Other options include **Soft Mist Inhalers** where a mist (aerosols) is created from a liquid medicinal agent that can be inhaled. In the same way, **Nebulisers** produce aerosols which are breathed in with a face mask or a mouthpiece. Nebulisers are more effective than normal inhalers and are used in hospitals to treat severe attacks.

The use of inhalers other than pMDIs (i.e. mostly DPIs) in Europe is about 50% of the inhalers prescribed ([13]), with large differences between single countries and Sweden attaining 87% ([14]) and Finland 57%. DPIs account for the largest share of usage in Finland at 53%, and the manufacturer anticipates continued strong growth in this market ([15]). Differing health policies, costs, health insurance issues, pharmaceutical/commercial aspects and prescribers' and patients' preferences may explain this variation. ([16])

On the 9th of April the '*Cross-cutting guideline for a climate-conscious prescribing of inhalation medication*' has been formally published in the Netherlands (17). It offers concrete guidance to prescribe medication in a more sustainable manner, without concessions to the quality of healthcare. The guideline will be updated once new pMDI products with low GWP have been formally approved/ registered and entered the Dutch market. The guideline was developed by several national medical organizations as part of a national Green Deal for a more sustainable healthcare.

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(12) Orion Oyj, https://www.orionpharma.com/products/medicines-and-self-care-products/

(13) Trends in low global warming potential inhaler prescribing: A UK-wide cohort comparison from 2018–2024 | npj Primary Care Respiratory Medicine

(14) Carbon footprint impact of the choice of inhalers for asthma and COPD | Thorax

(15) Orion Oyj

(16) Retail sales of inhalation devices in European countries: So much for a global policy - ScienceDirect

(17) https://www.zorginstituutnederland.nl/publicaties/publicatie/2025/04/09/transmurale-leidraad-klimaatbewust-voorschrijven-van-inhalatiemedicatie

3. **Implementation of lessons learned during previous MDI propellant transitions**

When CFCs were replaced with HFCs, their greenhouse gas potential and adverse impact on the environment was already known. Applicants in the EU for authorization of HFC-propellants were encouraged at the time (1993) ([18]) to develop and promote formulations which take into account both the therapeutic needs of the patient and **environmental considerations as part of their long-term strategy.** Similar considerations should be made today by pharmaceutical companies producing pMDIs and feasible alternative low carbon and propellant-free options.

The contemporary replacement propellants are thought to be more physicochemically similar to R-134a and R-227 than these HFAs were to CFCs. This greater similarity is expected to show in terms of solubility, swelling properties, working pressures, and MDI manufacturing considerations. It seems reasonable, therefore, that a more facile switch could be suitable for approved pMDIs currently on the market. ([19]) There is also a better grasp today of fundamental MDI function, materials, etc..and more meaningful in vitro regulatory expectations. ([20])

(18) 3BR2a

(19) LGWP Propellants | IPAC-RS

(20) Board Meeting