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IPAC & IPAC-RS SUBMISSION TO:

Substances Management Information Line
Chemicals Management Plan
Environment and Climate Change Canada
Gatineau, Quebec K1A 0H3
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JOINT COMMENTS TO ENVIRONMENT AND CLIMATE CHANGE CANADA AND HEALTH CANADA ON THE DRAFT STATE OF PFAS REPORT[1] AND RISK MANAGEMENT SCOPE FOR PFAS[2]

The undersigned organizations appreciate the opportunity to share information relevant to the Draft Report's and Risk Management Scope's recommendations to treat PFAS as a class under Section 64 of CEPA[3] and considerations regarding the impact on hydrofluorocarbons (HFCs) used in pressurized metered dose inhalers (MDIs). IPAC and IPAC-RS are also gathering data and information with regard to the availability of alternatives and potential impacts to patients. IPAC and IPAC-RS can share that additional information at a later date during any subsequent public comment periods regarding the Environment and Climate Change Canada and Health Canada's PFAS considerations. A thoughtful approach is needed to avoid abrupt changes in the availability of MDIs which would put patients' care at risk. We recognize that the current Draft Report and Risk Management Scope do not propose bans and/or limits. We share below our initial comments and resources to inform decision making, and outline the key considerations relevant to MDIs as the Canadian government moves forward in its deliberations.

[1] Draft state of per- and polyfluoroalkyl substances (PFAS) report - Canada.ca May 2023.
[2] Risk management scope for per- and polyfluoroalkyl substances (PFAS) - Canada.ca May 2023.
[3] The Canadian Environmental Protection Act, 1999.

Summary of Considerations:

- Two medical propellants currently used in MDIs - HFC-134a and HFC-227ea - are considered PFAS under the OECD[4] definition. Rapid removal of these propellants from the supply chain and the market is not technically or economically feasible and would risk the health of patients in Canada and around the world. For example, prematurely banning these essential products could lead to drug shortages of essential, life-saving medicines. Adequate time must be provided to allow replacement products to be developed, tested, and approved by medicines regulators, and for patients to be safely and seamlessly transitioned. As noted in the Draft Report (Section 8.1.7, page 108), companies are developing next-generation, more sustainable propellants to mitigate climate impact. One of these propellants, HFC-152a, is not classified as a PFAS.

  However, the other sustainable propellant for MDIs, HFO-1234ze, is classified as a PFAS. As outlined below, HFO-1234ze represents an important alternative option to accomplish the phase down of the existing medical propellants and will have a long-term future role as a potential option for transitioning MDIs away from the existing medical propellants, HFC-134a and HFC-227ea.

- Any proposals to ban essential medications must take a patient-centric approach, and we urge Canada to proactively consult closely with patients, clinicians, and relevant government authorities ***before*** removing products from the market. Advance planning and full understanding of implications is critical. The past experience with the phase out of CFC[5] MDIs under the Montreal Protocol[6] is informative and lessons learned from that process should be understood and adopted.

Overview of Key Considerations:

- Asthma and chronic obstructive pulmonary disease (COPD) are serious, potentially life-threatening illnesses. Inhaled therapy products, including MDIs, Dry Powder Inhalers (DPIs) and Soft Mist Inhalers (SMIs), are the standard of care to treat asthma and COPD. Asthma and COPD impact millions of patients in Canada and worldwide.

- To propel medication from an MDI canister and generate a "puff" inhalable by a patient, hydrofluorocarbons (HFCs) are currently used, and to date only two types have been approved by pertinent regulatory authorities such as Health Canada – namely HFC-134a and HFC-227ea. MDIs remain an essential treatment for an important subset of asthma and COPD patients. All human exposure to substances in marketed MDIs has been tested and approved in accordance with pharmaceutical regulations. The industry is working to develop next generation propellants for MDIs that will have a significantly lower carbon footprint than HFC-134a and HFC-227ea. Replacements will have to be cleared by relevant regulatory authorities in each

[4] The Organisation for Economic Co-operation and Development.
[5] Chlorofluorocarbon.
[6] About Montreal Protocol (unep.org)

country on a product-by-product basis. There are currently two next-generation propellants under development: HFC-152a and HFO-1234ze. HFC-152a is not within the scope of PFAS considerations.

- It is not possible to simply "drop in" an alternative medical propellant to MDIs. Propellants for medical uses must be non-toxic and must have specific physico-chemical properties to enable appropriate performance, meeting high standards of safety and efficacy; they cannot be replaced easily. Ensuring that a new propellant is safe for patients, compatible with the device components and formulation, and supports required particle size distributions and delivered dose uniformity, is an extensive, resource-intensive process. The change in propellants also impacts many elements of the supply chain, including elastomers, valves, and any other device components in the drug delivery pathway. Many of these materials and components must be tested and/or redesigned with each new propellant for compatibility, and final product tested for leachables (chemical substances that leach from the device components into formulation upon storage). New manufacturing equipment must be developed and built to adapt to the characteristics of any new medical propellants (e.g., flammability). These changes involve regulatory assessment, and depend on regulatory approval by, e.g., Health Canada.

- Given the challenges to identify alternative propellants, it is important to maintain propellant options for next generation MDIs, including HFO-1234ze. It should also be noted that if this option is eliminated as a medical propellant, it would leave only a single potential propellant available in the long-term (i.e., HFC-152a). There have always been at least two options (three for CFCs) and this is important for compatibility with medicines and to mitigate supply chain risks.

- As noted in the Draft Report (Section 8.1.7, page 108), the existing Ozone-depleting Substances and Halocarbon Alternatives Regulations (ODSHAR) already regulates HFCs in a comprehensive manner, mandating reduction in domestic HFC consumption by 2036. That regulation is robust and will ensure that HFC-134a and HFC-227ea are phased down consistent with the Kigali Amendment to the Montreal Protocol. It is important that any PFAS restrictions are coherent with this existing regulation.

- Non-fluorinated hydrocarbon propellant gases are not suitable alternatives for MDIs as they are very flammable and thus pose an inherent safety risk, and they do not have clinical studies establishing safety in humans. MDI propellants are required to be toxicologically safe, minimally flammable, and chemically inert with appropriate boiling points and densities. Several hydrocarbon propellants have been explored and rejected, namely propane, n-butane, isobutane, n-pentane, isopentane, neopentane, and dimethylether.

- Transitioning patients to next generation MDIs – **when available** – and to DPIs or SMIs must be managed cautiously with a focus on effectively managing an individual patient's disease. There may also be cost considerations for patients and health care systems.

- Care should be used to ensure a robust understanding of impacts to supply of MDIs for patients in Canada.

Information Resources and References:

1. In order to assess the risks and socio-economic impact, the burden and impacts of respiratory illnesses should be considered. Asthma is a life-threatening condition affecting patients of all ages, from the very young to the very old. (See, for example, The Global Asthma Report 2022). Similarly, COPD was responsible for 3.3 million deaths in 2019 (see Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019 | The BMJ). MDIs remain the product of choice for managing those conditions (see for example, 2022 GINA Main Report - Global Initiative for Asthma - GINA (ginasthma.org) and 2023 GOLD Report - Global Initiative for Chronic Obstructive Lung Disease - GOLD (goldcopd.org)). In Canada, 3.8 million people over the age of one are living with asthma, and 2.0 million are living with chronic obstructive pulmonary disease (COPD), per the Report from the Canadian Chronic Disease Surveillance System: Asthma and COPD in Canada, 2018. The Canadian government has identified asthma and COPD as "significant public health concerns."

2. The European Medicines Agency (EMA) recently launched a public consultation on the *Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers (EMA/CHMP/83033/2023).* The EMA document notes that "[P]ropellant replacement constitutes a major change to the finished product formulation with potential impact also on the construction of the inhaler; therefore, data confirming maintenance of adequate finished product performance need to be provided for each modified product. In addition, data addressing possible toxicity and local tolerance of novel propellants need to be provided." The EMA Q&A document may be a useful basis for Health Canada, US Food and Drug Administration (FDA), and other regulatory authorities. The vast majority of MDIs marketed in Canada are manufactured in the United States, UK, and European Union.

3. IPAC has prepared a set of slides summarizing the key elements of the research and development process for MDIs. Please see attached.

4. The Intergovernmental Panel on Climate Change (IPCC) and Technology and Economic Assessment Panel (TEAP) published a comprehensive Special Report on Safeguarding the Ozone Layer and the Global Climate System (2005). Chapter 8 (Medical Aerosols) of the IPPC/TEAP Special Report details the technical performance characteristics for MDIs. The Report notes that an MDI "is a complex system designed to provide a fine mist of medicament for inhalation directly to the airways as treatment for respiratory diseases." The Report also describes the "exhaustive search" for an appropriate alternative medical propellant. "An inhalation propellant must be safe for human use and meet several additional strict criteria relating to safety and efficacy: (i) liquified gas, (ii) low toxicity, (iii) non-flammable, (iv) chemically stable, (v) acceptable to patients, (vi) appropriate solvency characteristics, and (vii) appropriate density." (p. 355). "It was extremely difficult to identify compounds fulfilling all of these criteria." (p. 355). The IPCC/TEAP reviewed cost issues (pp. 356-357) and concluded that with a hypothetical switch for one of the widely used medicines (salbutamol) from HFC MDIs to DPI, the "projected recurring annual costs would be on the order of US$ 1.7 billion with an effective mitigation cost of between 150-300 US$ tCO2-equivalent."

5. See also, *The CFC to HFA Transition and Its Impact on Pulmonary Drug Development*, Leach C. (Respiratory Care, Sept. 2005, Vol 50. No. 9) outlining the extensive toxicological testing on HFC-134a and HFC-227ea undertaken by two testing consortia: IPACT-I and IPACT-II. Table 1 of the paper summarizes clinical and other studies. The paper also provides insights on the technical issues encountered in reformulating MDIs to a new propellant (pp. 1204 to 1206).

6. In connection with the phase-out of CFC MDIs under the Montreal Protocol, Canada developed a thorough and thoughtful strategy in consultation with a range of stakeholders, including clinicians, patients, industry, and regulatory authorities. See: *Canadian Initial Transition Strategy For the Phase-Out of Chlorofluorocarbon (CFC) Use in Metered Dose Inhalers (MDIs)* (for ease of reference submitted as attachment).

The Canadian Transition Strategy set forth the following principles:

1. The health of patients and their access to supplies of medicine will be safeguarded.
2. All those involved must work towards a smooth and efficient transition towards CFC-free treatments of asthma and COPD.
3. The transition strategy will be developed and implemented in consultation with stakeholders, in a transparent and consistent manner.
4. Health care professional and patient education and voluntary acceptance of CFC-free treatments will form the basis of the strategy.

The Strategy illustrates the complex, multifaceted undertaking to transition to new propellants and the myriad of considerations to ensure patient care.

7. The Parties to the Montreal Protocol convened an expert group to serve as technical resource on MDIs – the Medical and Chemical Technical Options Committee (MCTOC). The MCTOC recently published its Quadrennial Assessment Report and it is an excellent resource on the current use of HFC-134a and HFC-227ea in MDIs, as well as current and prospective alternatives. The MCTOC Report notes:

- "Inhaled therapy remains the mainstay of treatment for established asthma and COPD. Inhalers offer effective symptomatic benefit and control of disease, by delivering drugs directly to the airways, whilst minimising systemic side effects." (p. 235). Oral drugs are only used in limited circumstances given risks of side effects and limited efficacy. (p. 236)

- "Complex considerations are necessary when patients and healthcare professionals make an informed choice about a patient's inhaled therapy, taking into account therapeutic options, patient history, patient preference, ability (e.g., dexterity, inspiratory flow, vision) and adherence, patient-borne costs, as well as environmental implications, with the overall goal of ensuring patient health." (p. 238)

- The process of reformulating CFC MDIs to use HFC-134a and HFC-227ea took decades and was a complex and resource-intensive process. "Each new pMDI underwent extensive

regulatory assessment of safety, efficacy, and quality, much the same as for the development of any new drug product." (p. 239)

- The MCTOC recommends that countries consider "how to ensure that adequate bulk HFC-134 and HFC-227-ea pMDIs are available in markets to "avoid risks to the continuous supply of pMDIs." (p. 256).

- "mDPI [multi-dose DPI] and SMI manufacturing capacity may not be able to pivot rapidly to increase global production to replace the demand for pMDIs. Ramping up DPI and SMI production would take time." (p. 258).

About Organizations

IPAC 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. IPAC's members: AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Kindeva, Organon, and Teva. Further information available at www.ipacinhaler.org.

IPAC-RS 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 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.