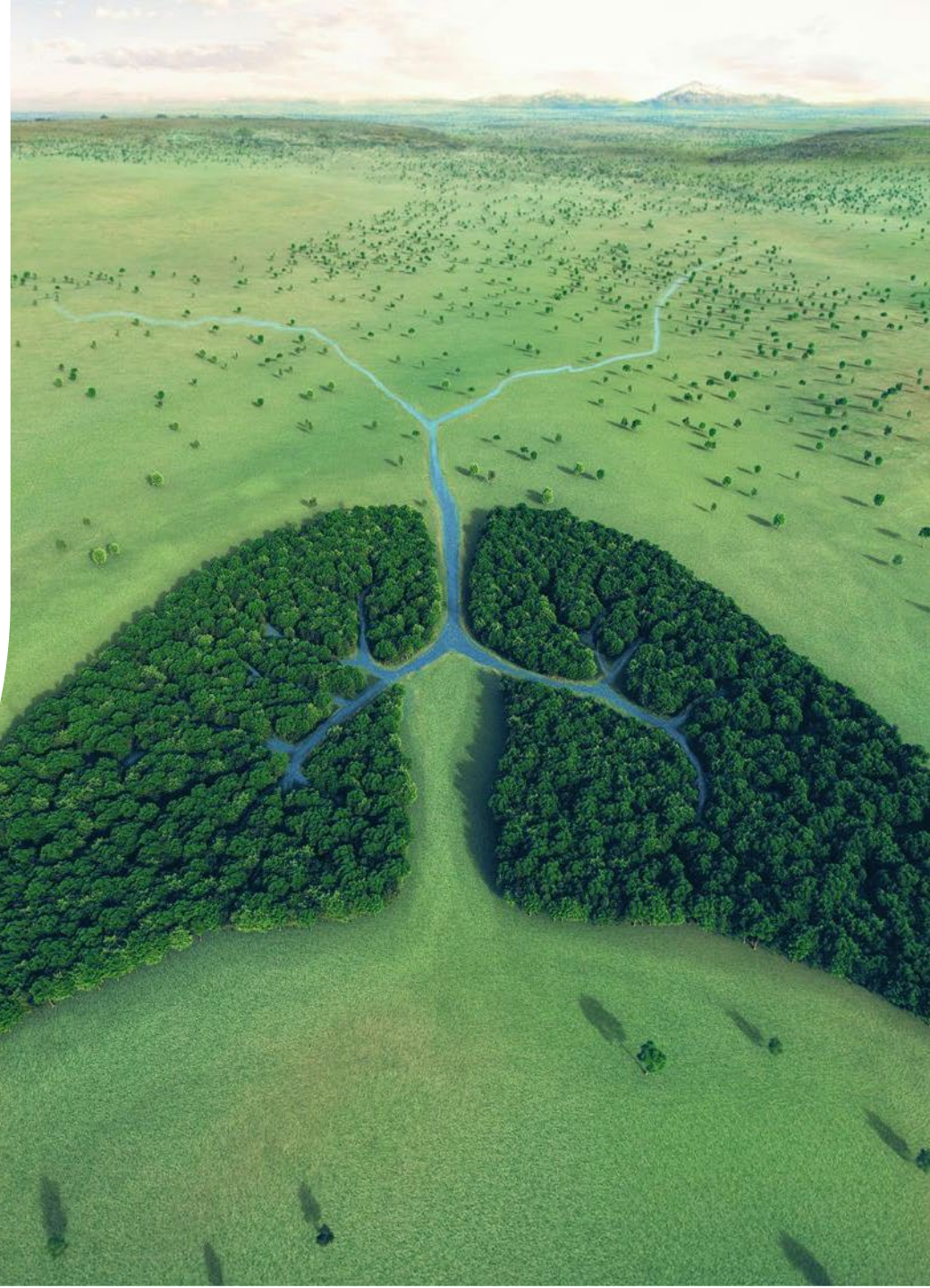
IPAC

International Pharmaceutical Aerosol Consortium

Sustainable Respiratory Care: The role of the Montreal Protocol in ensuring effective patient care while reducing the environmental impact of inhaled respiratory treatments

10 July 2024

Side Event at OEWG-46 in Montreal, Canada



MDIs and the Montreal Protocol: Reflections on the Journey and Lessons Learned

IPAC Secretariat: Maureen Hardwick

IPAC

IPAC: Background

- 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) that balanced patient health and environmental concerns.
  - IPAC engages in Montreal Protocol process and serves as a resource for MCTOC
- 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 pMDIs played a critical role to the transition as one of the key ozone-friendly alternatives developed to replace CFC pMDIs.
  - IPAC companies produce a range of therapies: Dry Powder Inhalers (DPIs), Metered Dose Inhalers (MDIs) and Soft Mist Inhalers (SMIs)
- IPAC members: AstraZeneca, Bespak, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kindeva, Organon, and Teva

Perspectives on the Success of the Montreal Protocol and Prospects for the Future

- In 2016, the global phase out of CFCs in MDIs was accomplished
  - Important achievement
- How do we build on this success and go into the future?
- MDI sector is complex sector with a myriad of unique facets; thus intergovernmental dialogue and coordination, and multistakeholder approach is essential to success
- Centering patient care is a core priority
- MCTOC is a valuable resource for Parties
  - Important to leverage their experience and expertise
  - Mindful of history and lessons learned
  - MCTOC Quadrennial Assessment (2022)
- Parties can share experiences and strategies

Journey to Sustainability: Snapshot on MDIs

CFC MDIs
CFC 11, CFC12, CFC 114

Montreal Protocol – phase OUT
MCTOC – Advisory Resource
National implementing regulations

HFA MDIs
HFA-134a & HFA-227ea

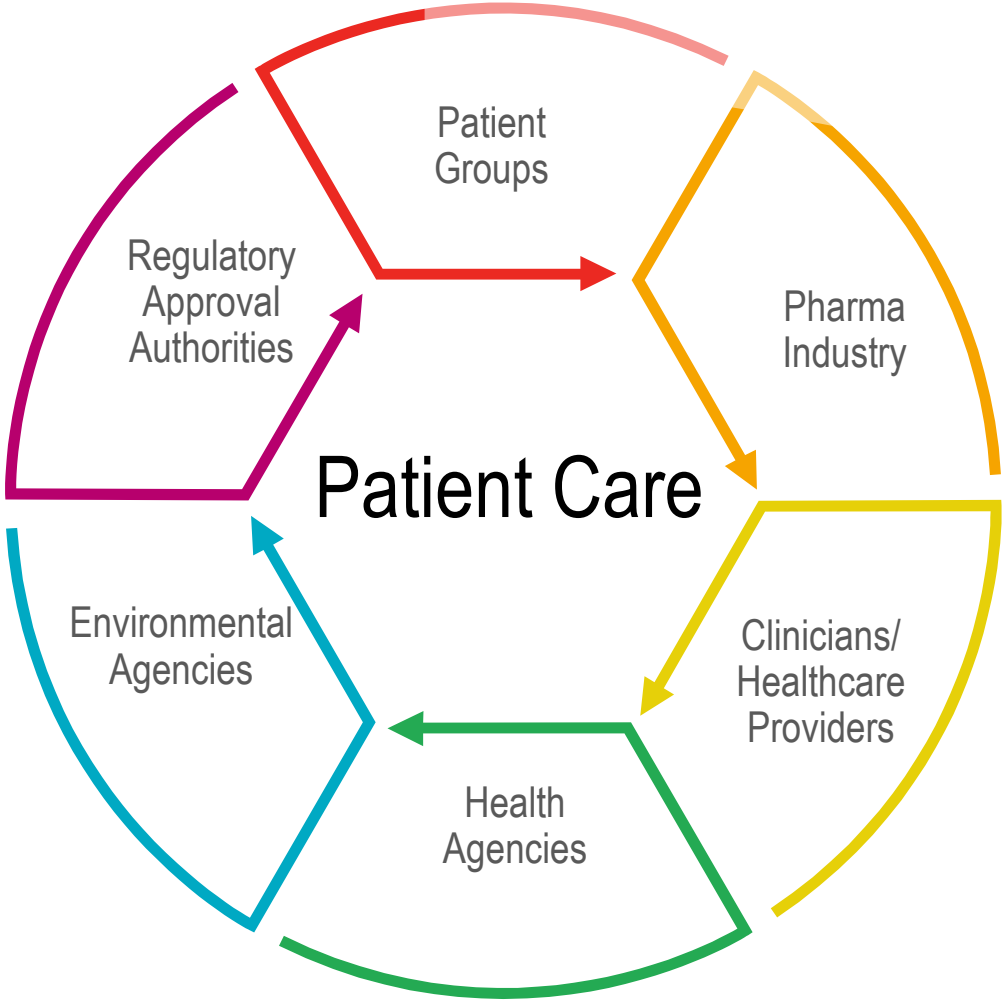
Kigali Amendment to Montreal Protocol (2016)
phase DOWN
MCTOC – Advisory Resource
National regulations underway
Health regulatory agencies key

LOW GWP MDIs
HFA-152a & HFO-1234ze

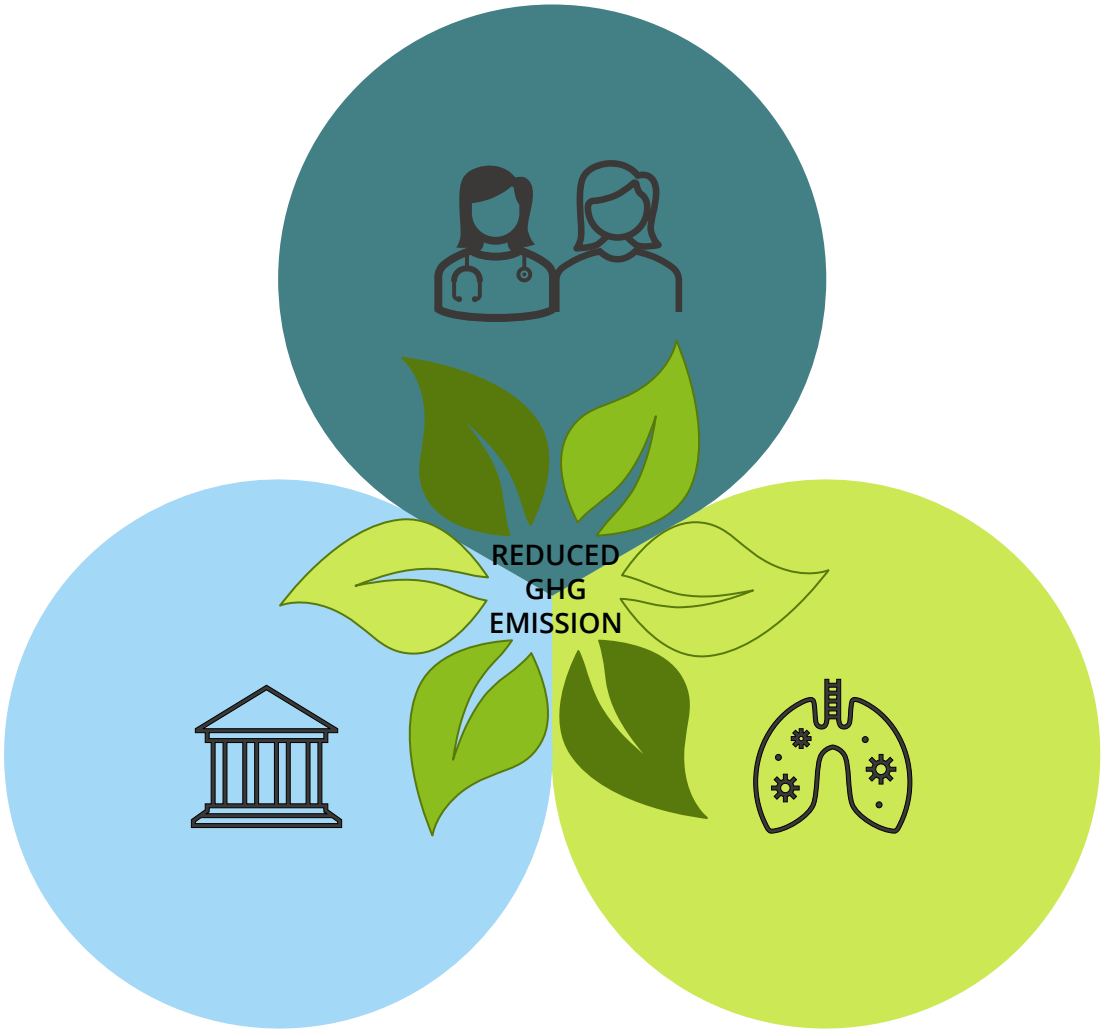
Progress toward next generation is underway
MCTOC continues to be a valuable resource
Proactive engagement of health authorities is key

Two options for propellants are absolutely necessary
Strict technical and performance requirements

Core Factor for Success: Centering Patients



Multi-stakeholder approach is essential for success



Holistic patient care approach. The well controlled patient is the greenest.

Patients & Health Care Professionals

- Achieve & maintain symptom control
- Right inhaler allied to right technique

Industry

- Continue to develop low GWP inhalers
- Deploy low GWP MDI propellant

Legislators and Policymakers

- Climate change targets
- Montreal Protocol Compliance

International Pharmaceutical Aerosol Consortium

MCTOC Resources

MCTOC Assessment Report – Insights and Current Context

- *Approximately 800–825 million HFC MDIs (assuming a global weighted average fill weight: 14.61 g/HFC-134a MDI and 11.38 g/HFC-227ea MDI) are currently manufactured annually worldwide, using approximately 10,700 tonnes HFC-134a and HFC-227ea in 2021.*
- *Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the respiratory tract. Inhalation therapy is the mainstay of treatment for asthma and COPD. Inhalers offer effective symptomatic benefit and control of disease, by delivering drugs directly to the airways, whilst minimising systemic side effects. Oral drugs are also prescribed for asthma and COPD; some of these can have serious side effects.*

MCTOC Assessment Report – Insights and Current Context (II)

- *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. Patient choice may be enhanced with an increase in publicly available information about the environmental impact of different inhaler products. Healthcare professionals and their patients may benefit from this information to take environmental impact into account in their choice of inhaler.*
- *MCTOC has identified potential challenges for MDIs, including continuity in, and stability of pharmaceutical-grade HFCs, globally and outlined stockpiling considerations in their 2023 Progress Report*
  - *These challenges and realities reinforce the need for a well planned transition to ensure patients do not face critical shortages or price increases that make pMDIs unaffordable.*

MCTOC Assessment Report – Insights and Recommendations (II)

- *Parties may wish to consider the range of technical and economic issues associated with the transition from high GWP HFC pMDIs to ensure adequate supplies of pMDIs and other inhalers during HFC phase-down.*
- *Parties may wish to consider the need for global and national coordination in the HFC phase-down and its impact on the transition away from high GWP HFC pMDIs to ensure patient safety.*
- *Parties may wish to consider how to ensure that adequate bulk HFC-134a and/or pMDIs are available in their own markets, and in their export markets, to avoid risks to the continuous supply of pMDIs. This necessity may persist for up to 10 years, until full ranges of affordable low GWP pMDIs are available worldwide.*
- *Parties may wish to consider measures that facilitate efficient, timely development while assuring the safety and effectiveness of the new pMDIs.*
- *The transition of high GWP HFC pMDIs to lower GWP pMDIs within the global HFC phase-down is a complex manufacturing and marketing transition that requires careful forward planning of the supply chain to avoid patient harm. Market authorisation of the new lower GWP pMDIs by health authorities is another critical factor in a successful transition and could benefit from a coordinated approach.*

Thank you!

- We welcome your feedback and collaboration
- Contact:
  - Maureen Hardwick at info@ipacinhaler.org
  - www.ipacinhaler.org
  - +13019807837

Change the inhaler and save the world!!
Really?

Alan Kaplan MD CCFP(EM) FCFP CPC(HC)

Does 

=  ?

Introductions and Disclosures

FAMILY PHYSICIAN airways group

Alan Kaplan MD CCFP(EM) FCFP, CPC(HC)

- •Chairperson, Family Physician Airways Group of Canada
- •Vice President , Respiratory Effectiveness Group
- •Honorary Professor of Primary Care Respiratory Research, OPRI
- •Senate member, International Primary Care Respiratory Group
- •Scientific committee GINA

Relationships with commercial interests

- Speaking Engagements/Honoraria/Consulting fees: Astra Zeneca, Boehringer Ingelheim, Cipla, Covis, Eisai, GSK, Idorsia, Pfizer, NovoNordisk, Sanofi, Teva, Trudell, Valeo
- Educational companies: MD Briefcase, PeerView, Respiplus
- Other:
- Co-chair, Health Quality Ontario (HQO) COPD Community Standards
- Member of HQO Asthma Quality Based Standards
- Medical Director LHIN Pulmonary Rehabilitation Unit

Learning Objectives

- Learn the different kind of inhalers
- Review pMDIs and their place in greenhouse gas emissions
- Review what we can (and should) do to make a difference in a patient-centric approach

Top Ten Global Threats per World Health Organization

World Health Organization

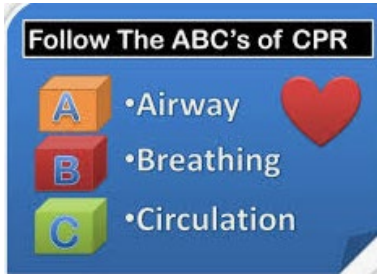
WHO's Ten Threats to Global Health in 2019

1. Air pollution and climate change.
2. Noncommunicable diseases. Noncommunicable diseases, such as diabetes, cancer and heart disease, are collectively responsible for more than 70% of all deaths worldwide, or 41 million people.
3. Global influenza pandemic. The world will face another influenza pandemic; the only thing unknown is when it will hit and how severe it will be.
4. Fragile and vulnerable settings. More than 1.6 billion people (22% of the global population) live in places where protracted crises (through a combination of challenges such as drought, famine, conflict and population displacement) and weak health services leave them without access to basic care.
5. Antimicrobial resistance. Antimicrobial resistance — the ability of bacteria, parasites, viruses and fungi to resist these medicines — threatens to send medicine back to a time when infections such as pneumonia, tuberculosis, gonorrhea and salmonellosis were not easily treatable.
6. Ebola and other high-threat pathogens.
7. Weak primary health care.
8. Vaccine hesitancy. Vaccine hesitancy — the reluctance or refusal to vaccinate despite the availability of vaccines — threatens to reverse progress made in tackling vaccine-preventable diseases.
9. Dengue. Dengue, a mosquito-borne disease that causes flu-like symptoms and can kill up to 20% of those with severe dengue, has been a growing threat for decades. An estimated 40% of the world is at risk of dengue fever, and there are around 390 million infections a year.
10. HIV. Despite progress against HIV, nearly a million people die every year from HIV/AIDS.

Source: WHO

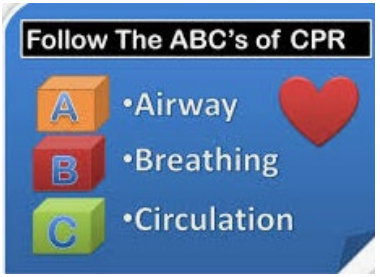
Epidemiology of Asthma and COPD

- **3.8 million** people over the age of one are living with asthma
- **2.0 million** are living with chronic obstructive pulmonary disease (COPD)



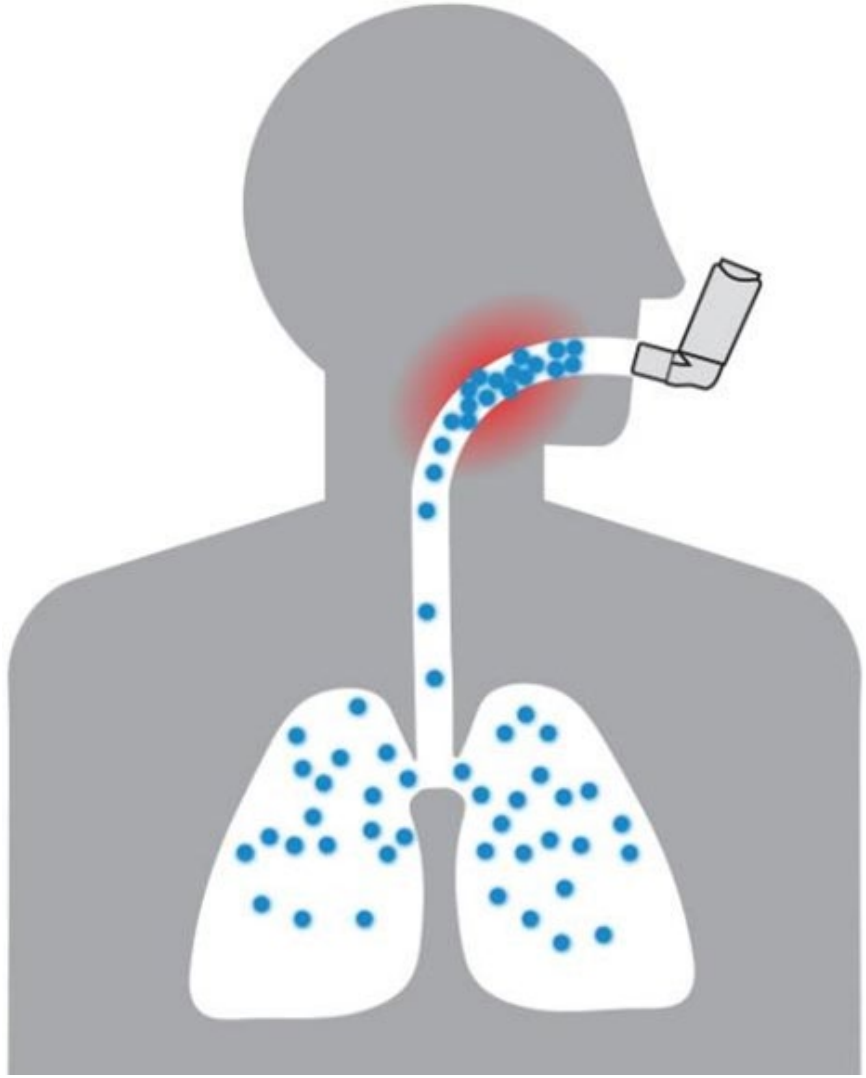
Epidemiology of Asthma and COPD - Globally

- Asthma affects around **339 million** people worldwide[1]
- **384 million** people suffer from COPD[2]

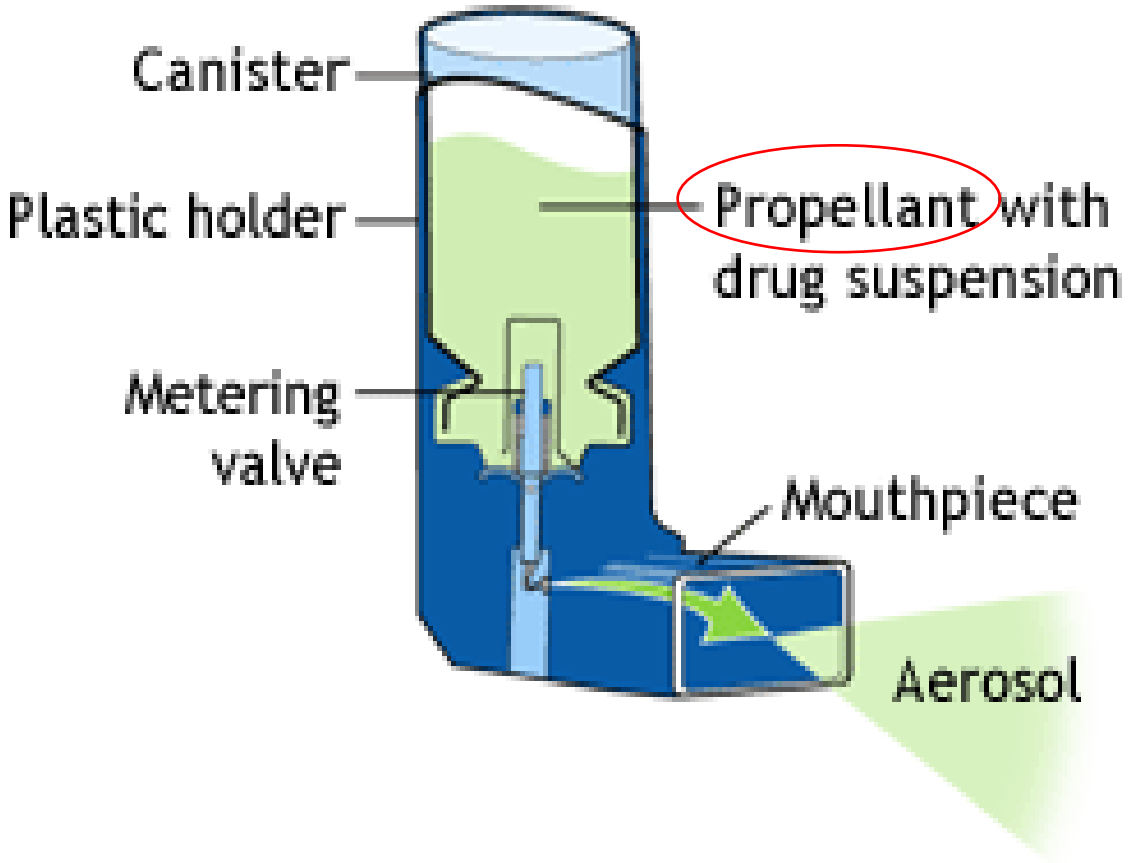


1 Global Asthma Report 2018. http://globalasthmareport.org/index.html 2 Global Initiative for Chronic Obstructive Lung Disease. (GOLD). https://goldcopd.org/world-lung-day-2019-respiratory-groups-unite-to-call-for-healthy-lungs-for-all/

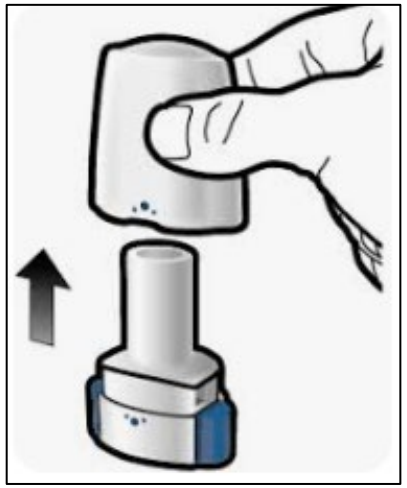
Medications have to get into the lung to be absorbed there!

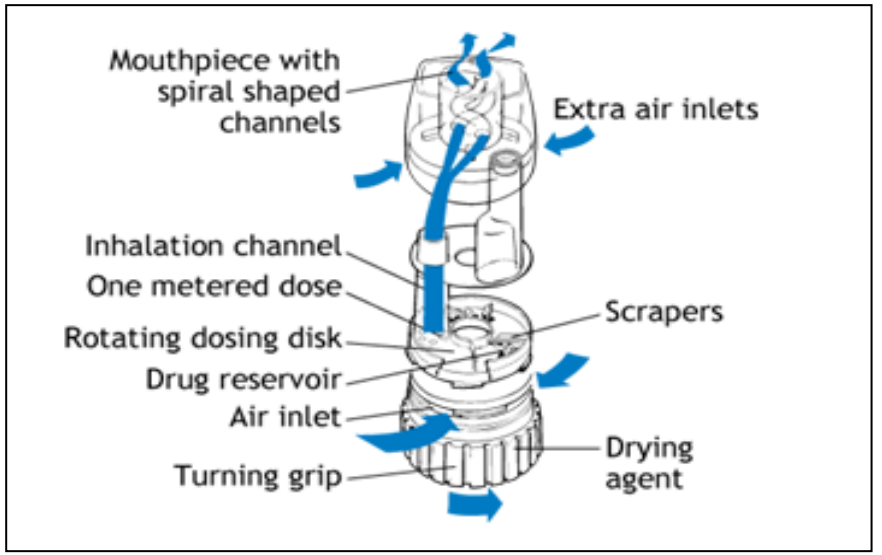


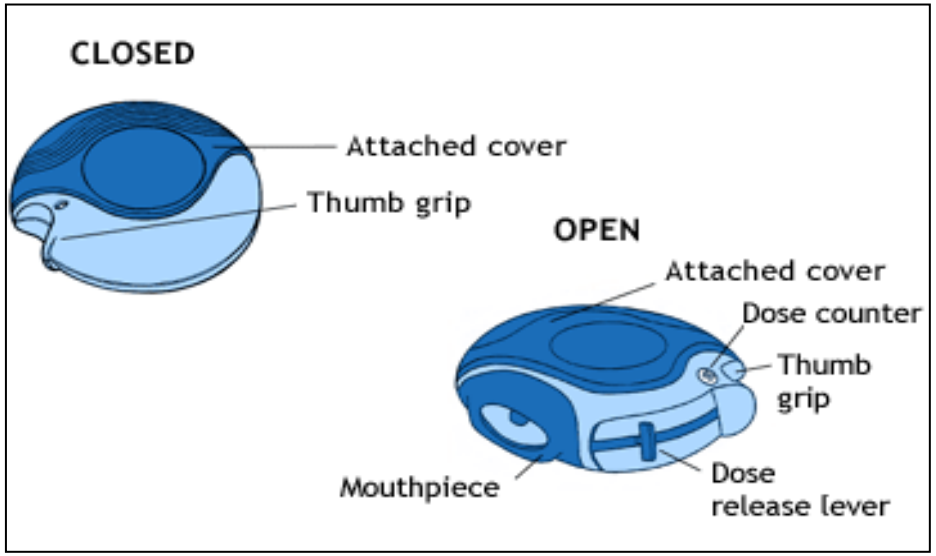
Pressurized Metered Dose Inhaler (pMDI)

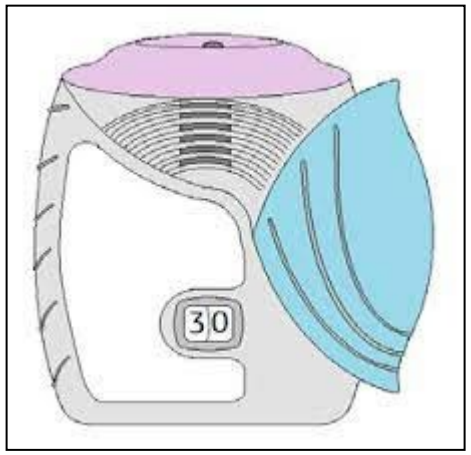


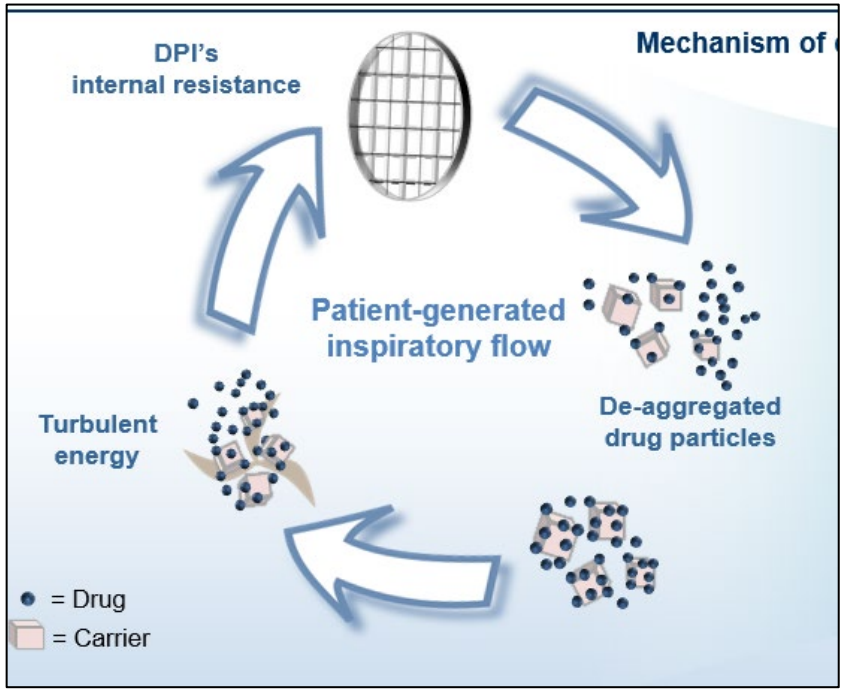
Dry Powder Inhalers





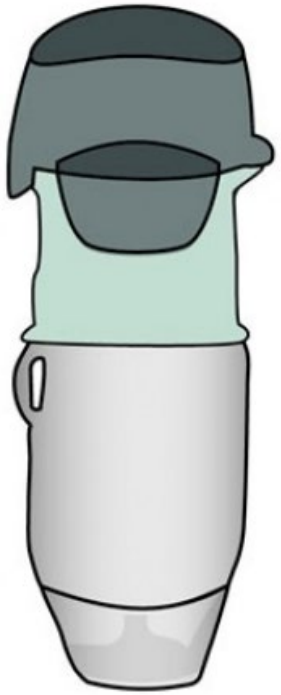






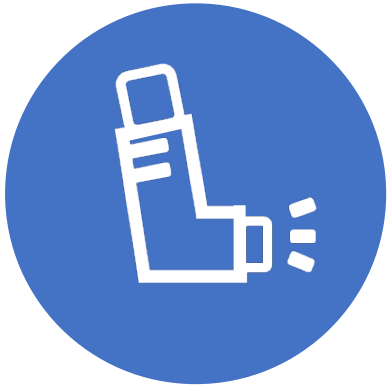
Slow Mist Inhaler

- Slow/Soft mist
- Much slower than MDI
- No propellant
- Two streams hit each other and cause dispersal of droplets



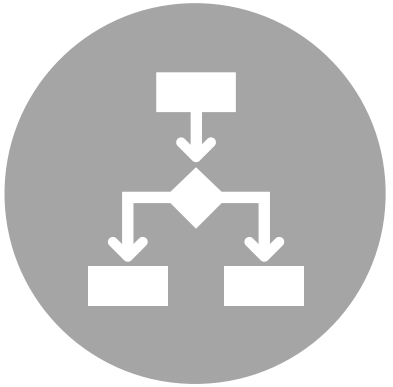
Inhaler regimens are the mainstay of respiratory disease management[1]

A **personalised inhaler regimen** can improve treatment adherence and patient outcomes[2]



Inhaler regimens are **not readily interchangeable**

Inhaler regimen switching can have **variable clinical consequences**[3,4]



There are **multiple reasons** which may **prompt an inhaler regimen switch**

A **framework** is required for appropriate and safe inhaler regimen switching

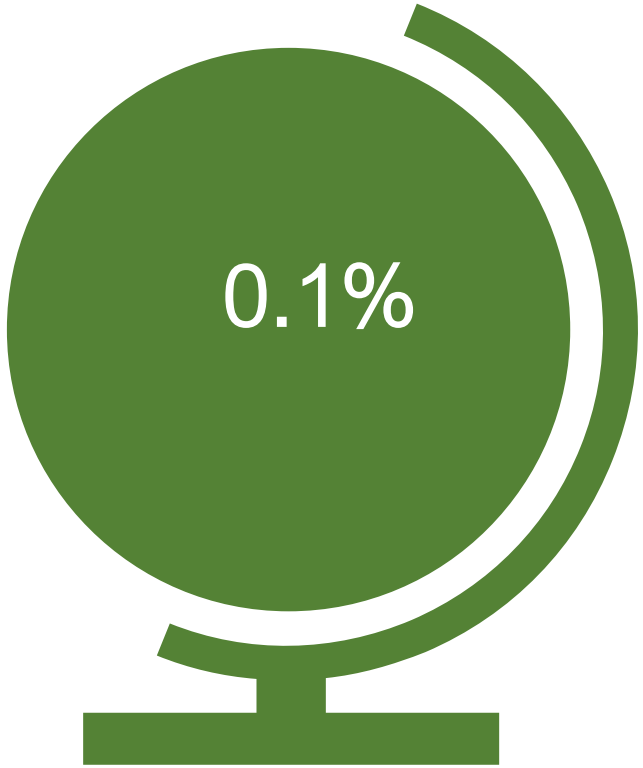
References: 1. Björnsdóttir et al. International Journal of clinical practice 2013; 67(9):904-10; 2. Usmani et al. *Ther Clin Risk Manag* 2019;15:461–72; 3. 3. Usmani et al. *JACI: In Practice* 2021;9:3033–40; 4. Usmani et al. *JACI: In Practice* 2022;10:2624–37;

But remember….

- Not all drug classes are available in all devices
- There are differences between drugs even of the same classes, leading to clinician decision to preferentially want a particular medication

So, not easily interchangeable!!

Let's look at the BIG PICTURE!



Currently, medical use of F-gases accounts for approximately **0.1%** of global greenhouse gas (GHG) emissions.

Pernigotti D, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. BMJ open respiratory research. 2021;8(1):e001071

BIGGER pictures

China

'coal to generate **56.2%** of it's electricity last year[1]'

China leans on coal amid energy security push

By **Andrew Hayley**

March 6, 2023 3:51 AM EST · Updated 3 months ago

India

Coal generates **55%** of the electricity[2]

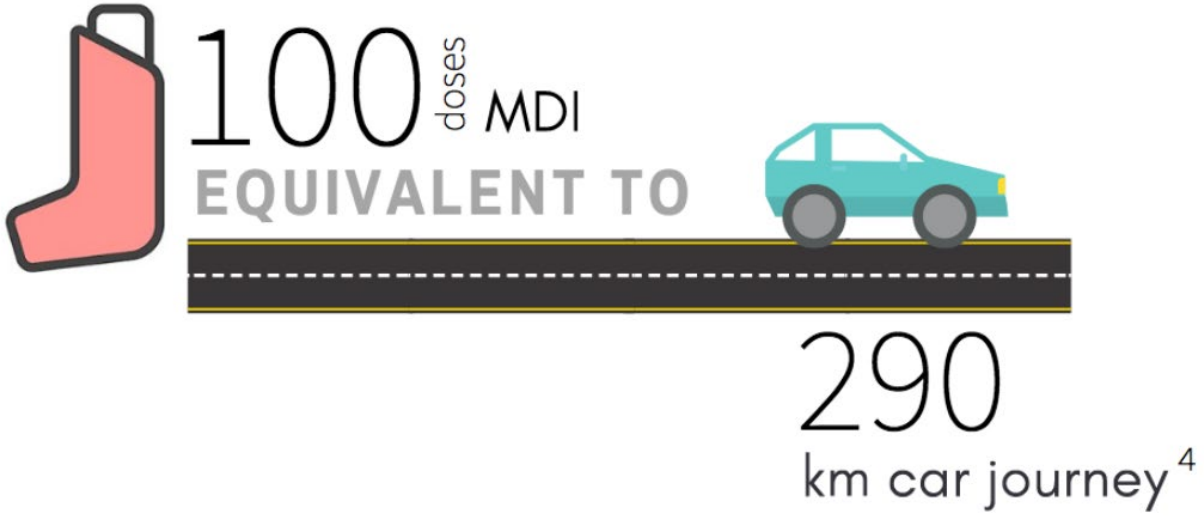
Germany

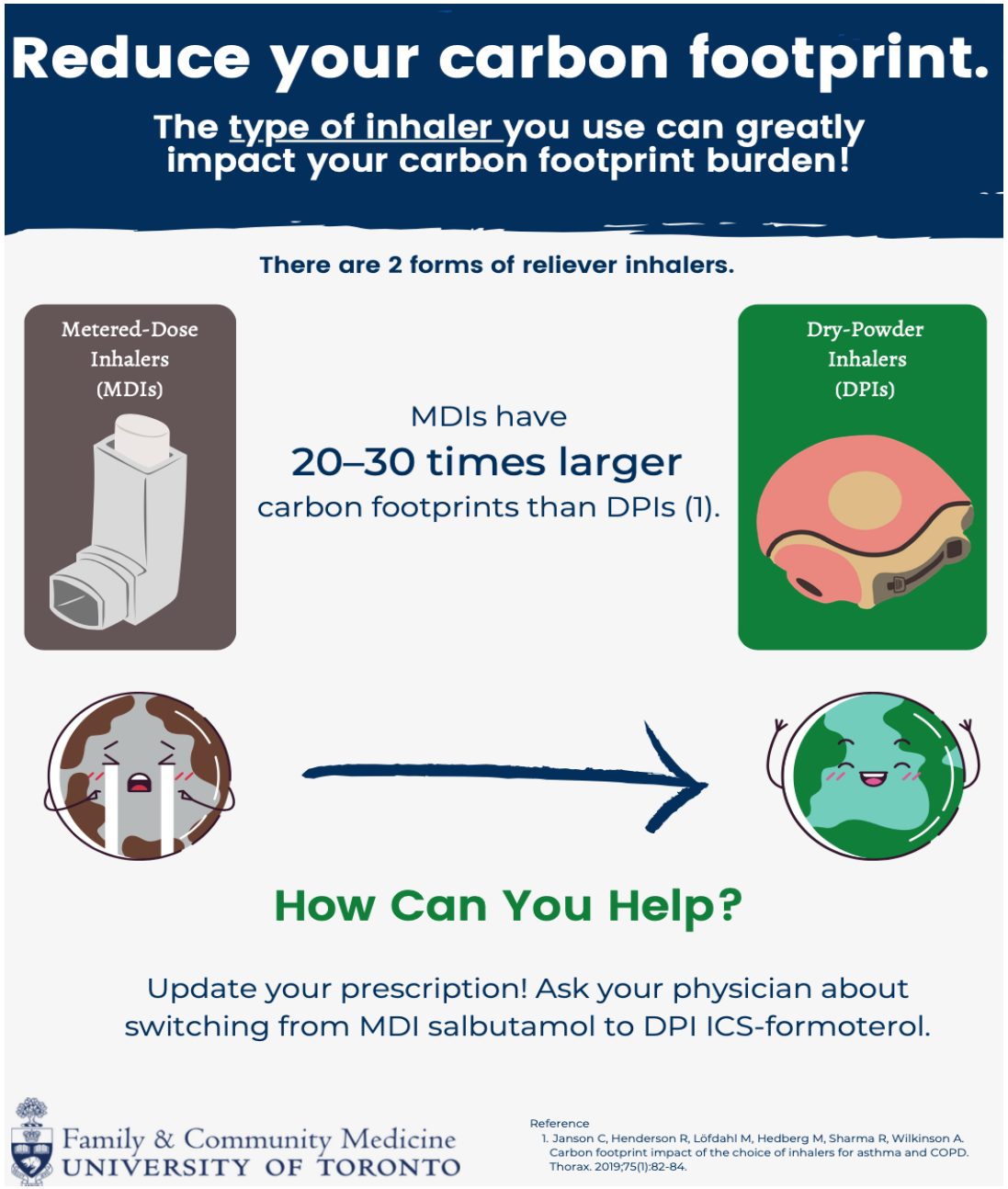
In 2022 coal generated **36.2%** of the electricity[3]

1. https://www.reuters.com/business/energy/china-underlines-key-role-coal-amid-energy-security-drive-2023-03-05/
2. https://coal.nic.in/en/major-statistics/coal-indian-energy-choice
3. https://www.reuters.com/markets/commodities/energy-crisis-fuels-coal-comeback-germany-2022-12-16/

You have likely seen initiatives like this CASCADES program

- Inhaler propellants are potent greenhouse gases
- Significant contributor to carbon footprint of healthcare sector





Developed Grace Huang, Medical Student,
St. Michael's Hospital Academic FHT.

Respiratory Organizations have responded!

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

5 May, 2021

European Respiratory Society position statement on asthma and the environment

"For the generation of my children, Europe is a unique aspiration. It is an aspiration of living in a natural and healthy continent.

"I am convinced that the old growth model based on fossil fuels and pollution is out of date and out of touch with our planet."

- Ursula von der Leyen, President of the European Commission (European Commission, 2019)

Section 1: Introduction

Aim

This statement outlines how climate change and air pollution currently affect patients with asthma and how the ambitious European Union Green Deal can provide solutions. It also considers the complex interplay between asthma inhalers, the respiratory patient and climate change, highlighting the example of the review of F-gases legislation in the EU. In addition, it presents how the European Respiratory Society addresses the topic of asthma and the environment, and while the primary emphasis to tackle climate change and air pollution must always be on regulatory action and legislative change, we introduce the concept of the "green asthma patient", which we define as a patient who is facilitated in making conscious choices to reduce their carbon footprint without compromising health outcomes.

Who we are

The European Respiratory Society (ERS) is an international organisation that brings together physicians, healthcare professionals, epidemiologists, patient representatives, scientists and other experts working in respiratory medicine. We are one of the leading medical organisations in the respiratory field, with a growing membership representing over 160 countries. Our mission is to promote lung health and alleviate suffering from disease, and drive standards for respiratory medicine globally. Science, education and advocacy are at the core of everything we do. This position statement has been developed and led by the

"As clinicians, our duty of care is to the **patient first. Patient safety, efficacy** and **choice** must remain the **primary drivers** in deciding the most suitable medical device for respiratory patients."

CTS Position Statement - Climate change and choice of inhalers for patients with respiratory disease

KEY MESSAGES

- Inhalers contribute to climate change, with metered dose inhalers (MDIs) currently accounting for the greatest greenhouse gas emissions among all inhalers.
- Shared decision making with patients, incorporating inhaler indication, effectiveness, technique, patient preference, patient capability, cost and side-effects, as well as the environmental impact of different inhaler delivery systems is the preferred approach when choosing an inhaler with a patient.
- A multi-layered approach involving clinicians, patients, health system organizations, regulators and manufacturers is needed to reduce the impact of inhalers on the environment.

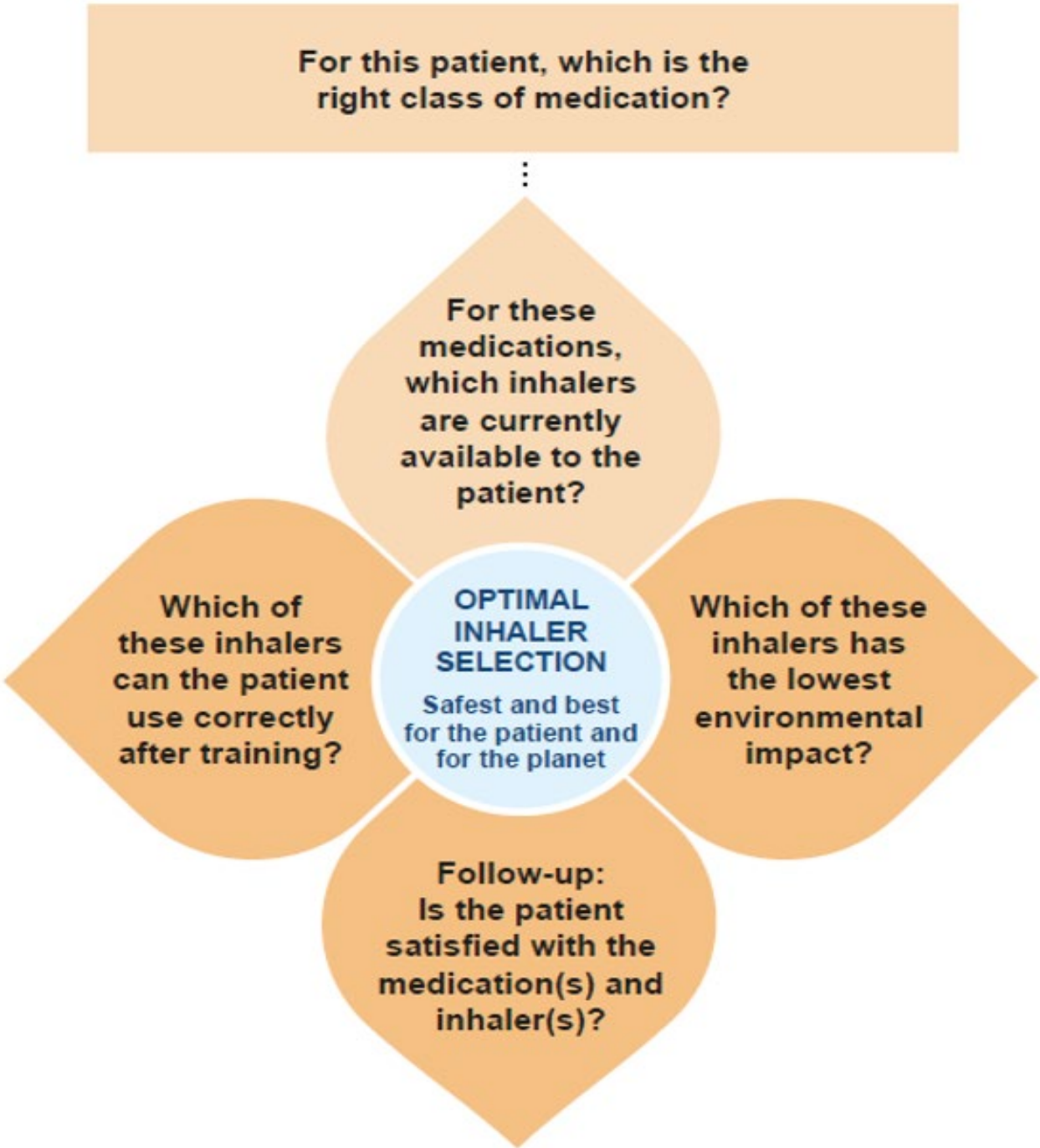
Box 1. Practical considerations when selecting an inhaler device.

- Patient preference
- Impact of inhaler device on adherence
- Inhalation technique (patient ability)
- Inspiratory flow rate/pressure required for adequate medication delivery (patient ability)
- Patient age
- Cost for patient and/or public healthcare system
- Side effect profile
- Environmental footprint

Gupta S et al. Canadian Thoracic Society Position Statement on Climate Change and Choice of Inhalers for Patients with Respiratory Disease. Canadian Journal of respiratory, CritiCal Care, and sleep Medicine. https://www.tandfonline.com/doi/full/10.1080/24745332.2023.2254283

Respiratory Effectiveness Group

- Every patient has a right to the device that best meets **their** needs
- The greenest inhaler is the one the patient **can use and will use**
- DPIs lead to immense **plastic** burden and damage marine ecology
- That industry will have **new inhalers** with much lower GWP emissions than current propellants where the environmental lifecycle analysis of pMDIs will be equivalent to current DPIs in a year away (by **2025**)
- We need to embed **inhaler education** in all respiratory specialist (doctors, physios, nursing, pharmacist) UG and PG training programmes in order to better educate our patients in inhaler use so they get the best possible outcomes from 'correct inhaler technique'
- We need to **diagnose better** so patients are not on unnecessary inhalers
- **Control disease better** and reduce SABA reliver burden


For this patient, which is the right class of medication?
For these medications, which inhalers are currently available to the patient?
Which of these inhalers can the patient use correctly after training?
OPTIMAL INHALER SELECTION
Safest and best for the patient and for the planet
Which of these inhalers has the lowest environmental impact?
Follow-up: Is the patient satisfied with the medication(s) and inhaler(s)?

So, if no pMDIs..what to do ?

Change everyone to Dry powders (will we have enough?)

Can we get new pMDIs with less GWG potential?

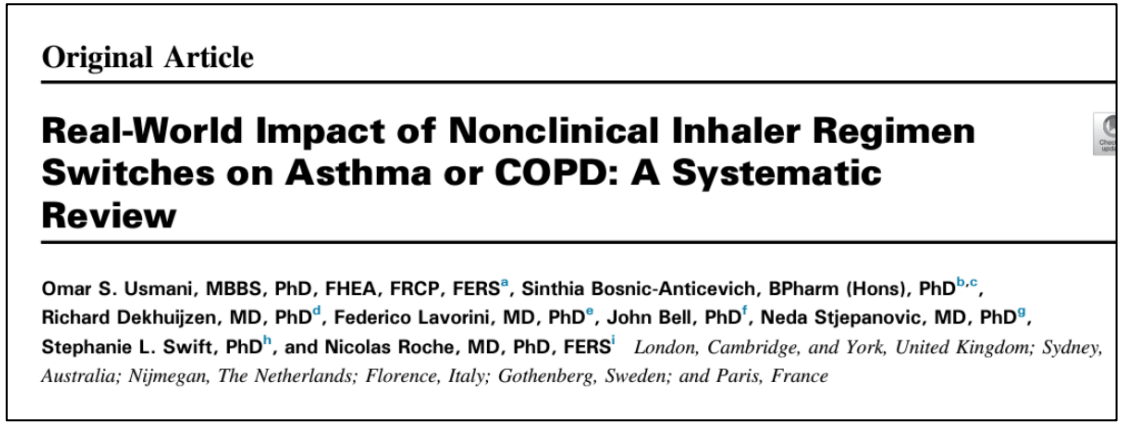
FIRST: Do a better job treating obstructive airways disease!!!
-make the correct diagnosis
-stop overuse of short acting relievers
-prevent exacerbations/admission

So, just use DPIs instead?

- Inhalers are not interchangeable[1].
- Asthma and COPD are complex and difficult to treat diseases[2,3,4].
- Non-consensual inhaler device switching has been shown to be associated with lower therapeutic adherence and reduced disease control[1].
- A systematic review of the real-world consequences of switching inhaler regimens for non-clinical reasons reported that switching inhaler regimens is a complex issue that can have variable clinical consequences and **can harm the patient-doctor relationship** and **worsen respiratory disease**[1].

1. Usmani OS, Bosnic-Anticevich S, Dekhuijzen R, et al. Real-World Impact of Nonclinical Inhaler Regimen Switches on Asthma or COPD: A Systematic Review. J Allergy Clin Immunol Pract. 2022;10(10):2624-2637.
2. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed: May 2023.
3. The Global Asthma Report 2022. Available at: http://globalasthmareport.org/. Accessed: May 2023.
4. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Section 2, Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma. Available at: https://www.ncbi.nlm.nih.gov/books/NBK7223/. Accessed May 2023.

Conclusions:



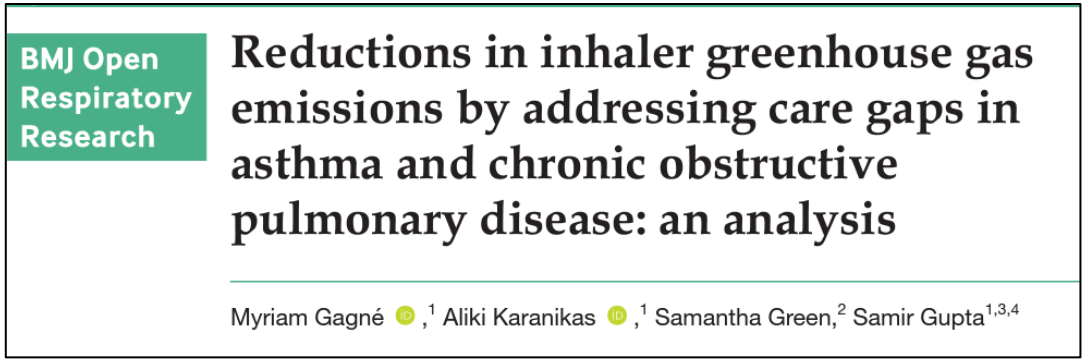
Original Article

Real-World Impact of Nonclinical Inhaler Regimen Switches on Asthma or COPD: A Systematic Review

Omar S. Usmani, MBBS, PhD, FHEA, FRCP, FERS[a], Sinthia Bosnic-Anticevich, BPharm (Hons), PhD[b,c], Richard Dekhuijzen, MD, PhD[d], Federico Lavorini, MD, PhD[e], John Bell, PhD[f], Neda Stjepanovic, MD, PhD[g], Stephanie L. Swift, PhD[h], and Nicolas Roche, MD, PhD, FERS[i] *London, Cambridge, and York, United Kingdom; Sydney, Australia; Nijmegan, The Netherlands; Florence, Italy; Gothenberg, Sweden; and Paris, France*

- Need to:
  - Engage patients in the switching process
  - Obtain patient consent prior to the switch
  - Develop new strategies to ensure patients do not feel that nonclinical reasons for switching outweigh their health and well-being in order to maintain positive patient-HCP relationships
  - Provide mandatory formal training to patients both before and after switching.

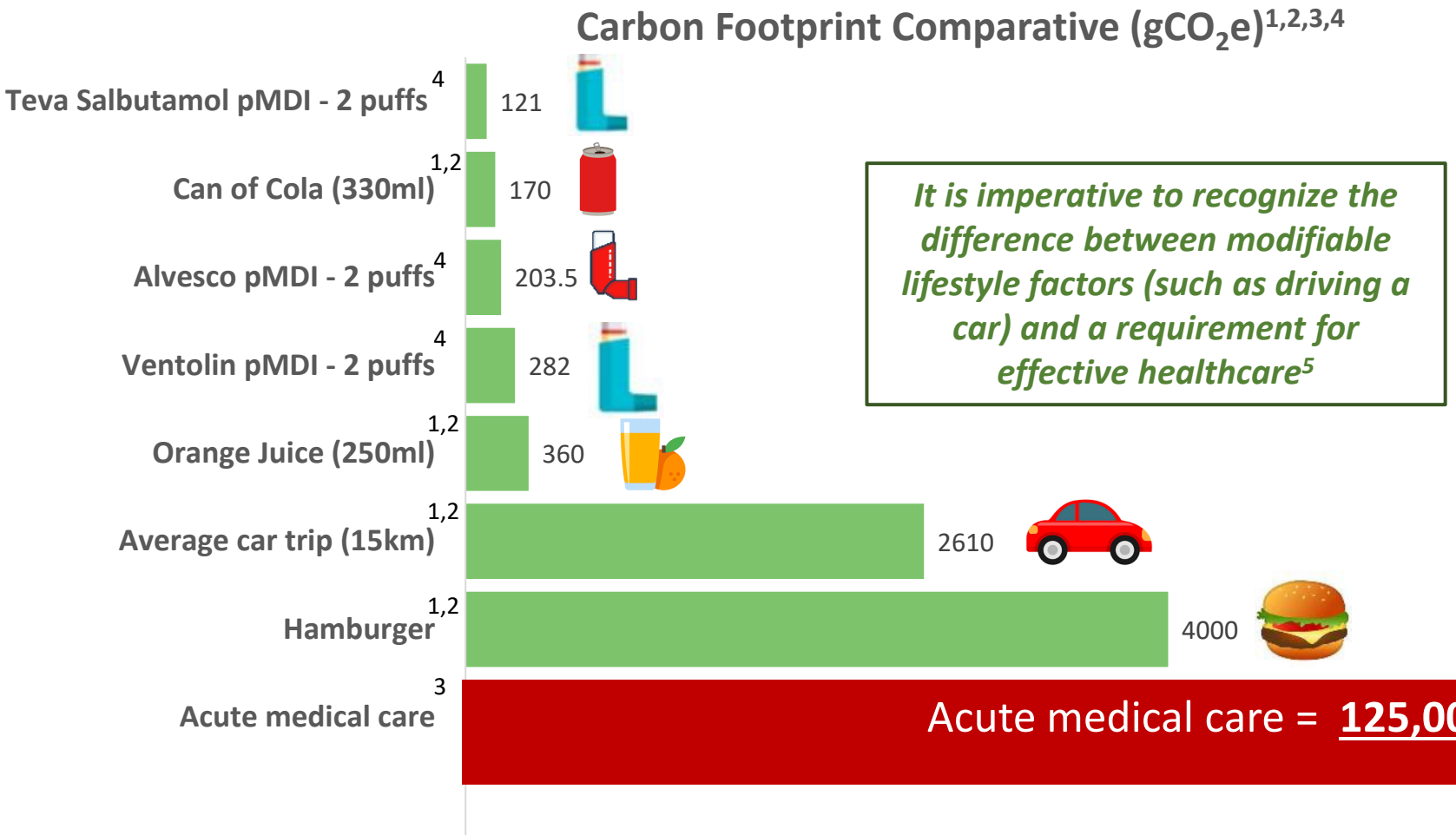
Usmani OS, Bosnic-Anticevich S, Dekhuijzen R, et al. Real-World Impact of Nonclinical Inhaler Regimen Switches on Asthma or COPD: A Systematic Review. J Allergy Clin Immunol Pract. 2022;10(10):2624-2637.



- Measured GWG potential from
  - Asthma and COPD misdiagnosis
  - Overuse of rescue inhalers due to suboptimally controlled symptoms
  - Switching 25% of patients with existing asthma and COPD to an otherwise comparable therapeutic option with a lower GHG footprint.
- **The carbon savings from addressing misdiagnosis and suboptimal disease control are comparable to those achievable by switching one in four patients to lower GHG-emitting therapeutic strategies!**

Gagné M, Karanikas A, Green S, et alReductions in inhaler greenhouse gas emissions by addressing care gaps in asthma and chronic obstructive pulmonary disease: an analysis. BMJ Open Respiratory Research 2023;10:e001716. doi: 10.1136/bmjresp-2023-001716

Again, perspective…



It is imperative to recognize the difference between modifiable lifestyle factors (such as driving a car) and a requirement for effective healthcare[5]

CF data for specific MDI products, compared with standard data reported for commonly used products. Adapted from references listed below.[1,2,3] Data for inhaled products are reported per dose, equal to two actuations.

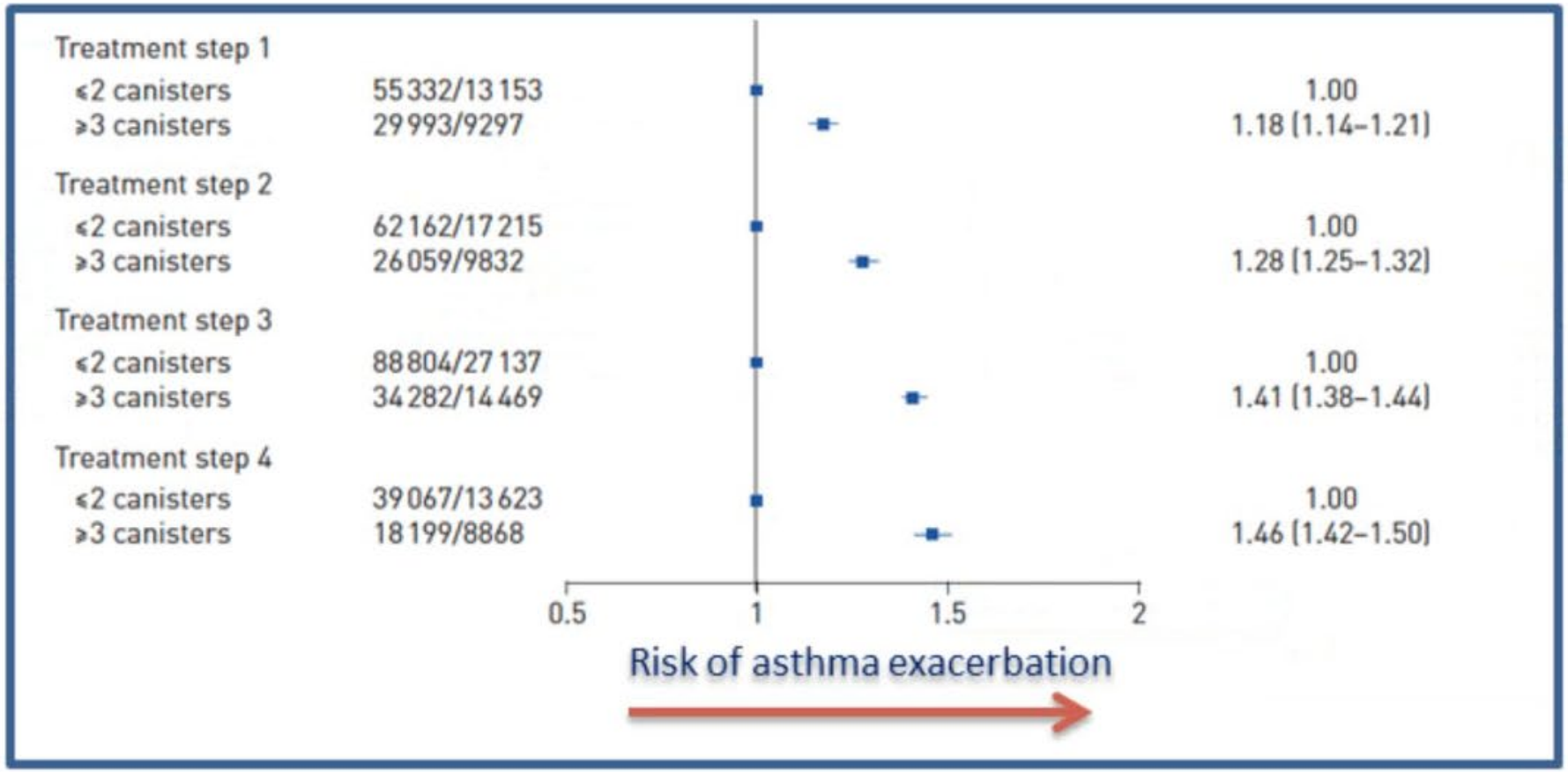
1 United Nations. Montreal protocol on substances that deplete the ozone layer. 2018 report of the medical and chemical technical options Committee (MCTOC), 2018. Available: https://ozone.unep.org/sites/default/files/2019-04/MCTOC-Assessment-Report-2018.pdf [Accessed 21 Nov 2019]. 2. Panigone S, Sandri F, Ferri R, *et al*. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. *BMJ Open Resp Res* 2020;**7**:e000571. doi:10.1136/ bmjresp-2020-000571. 3. Tennison et al. Health care's response to climate change: a carbon footprint assessment of the NHS in England. *Lancet Planet Health* 2021; 5: e84–92. 4. PrescQIPP Inhaler Carbon Footprint Data. Oct 2021. 5 Usmani O, Levy M. Effective respiratory management of asthma and COPD and the environmental impacts of inhalers. Npj Primary Care Respiratory Medicine (2023) 33:24; https:/doi.org/10.1038/s41533-023-00346-7

Most of the pMDIs used are for…

- Rescue!
- And they are overused, with ++ consequences!

SABA use (canisters/year) and asthma exacerbations at all treatment steps

381 741 patients in Sweden with ≥2 SABAs prescriptions within 12 months (2006-2014) assessed over mean 85.4 months



SABA ≥ 3 canister/year in all steps -> Exacerbations

Nwaru BI, *et al.*, *Eur Respir J* 2020; 55: 1901872.

Get better control!

- Most of the pMDI use is in rescue SABA inhalers (Salbutamol)
- Ensure adequate technique so what is used works!
- Use of controller medications regularly lead to
- A) less exacerbations
- B) less use of rescue puffs

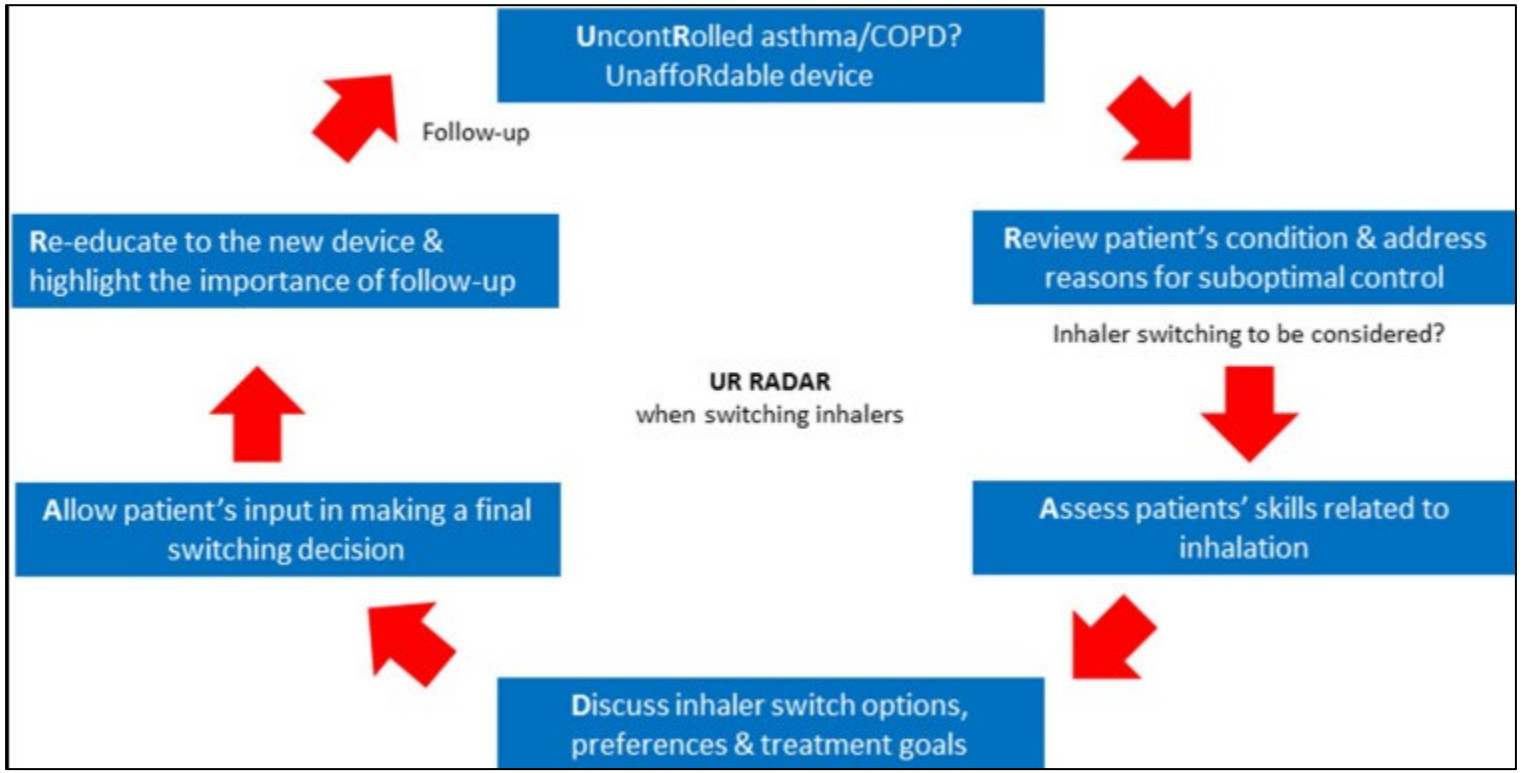
Switching is not simple, even when planned

Pulm Ther (2020) 6:381–392
https://doi.org/10.1007/s41030-020-00133-6

PRACTICAL APPROACH

Switching Inhalers: A Practical Approach to Keep on UR RADAR

Alan Kaplan · Job F. M. van Boven



Kaplan, A., van Boven, J.F.M. Switching Inhalers: A Practical Approach to Keep on UR RADAR. Pulm Ther 6, 381–392 (2020). https://doi.org/10.1007/s41030-020-00133-6

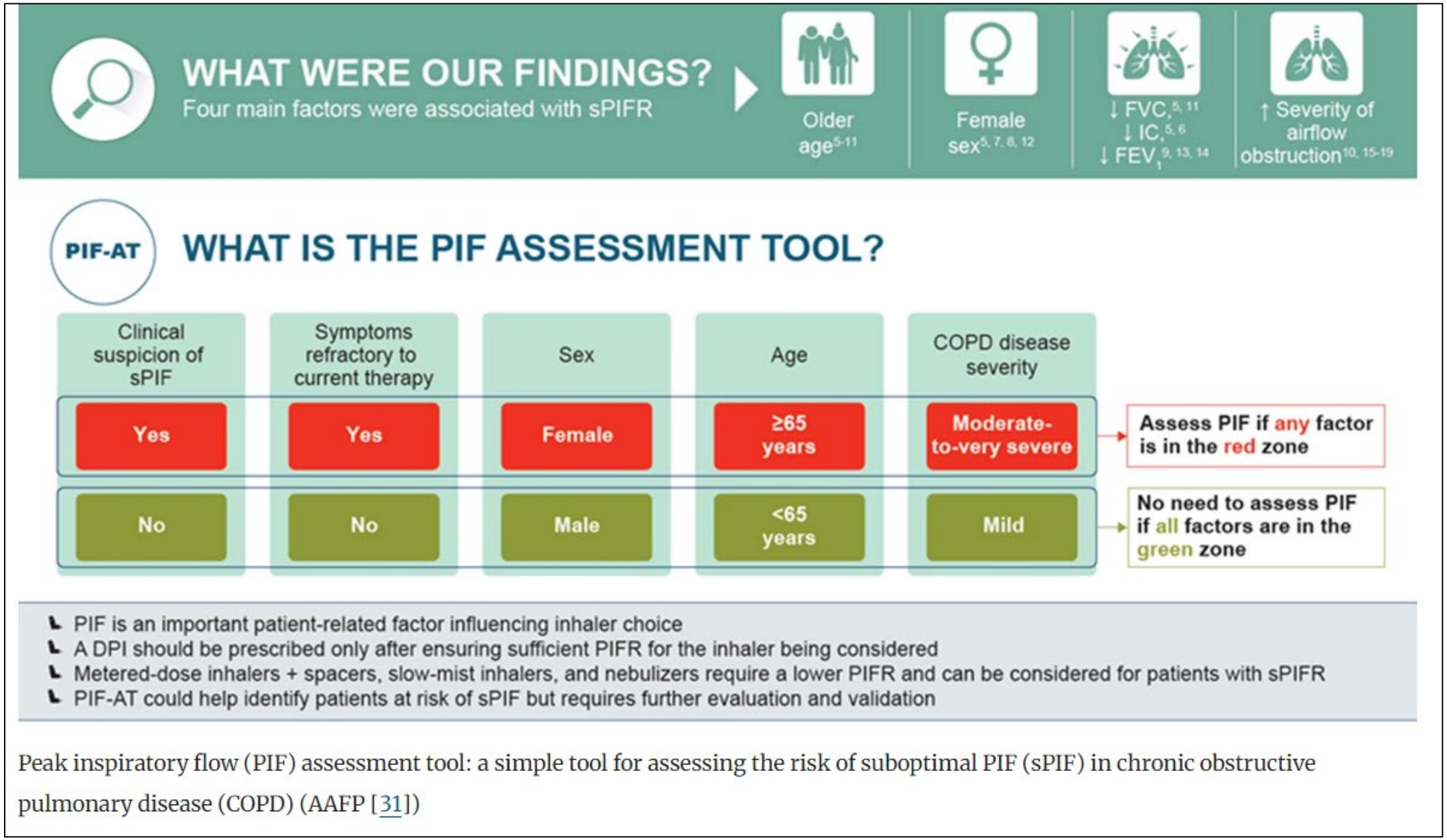
But can all of our patients use a DPI?

- Very young
- Very old
- Suboptimal PIFR

So, what happens to these patients when their lifesaving medications are removed?

UNINTENDED CONSEQUENCES!!

- Answer: Some, but NOT all!!



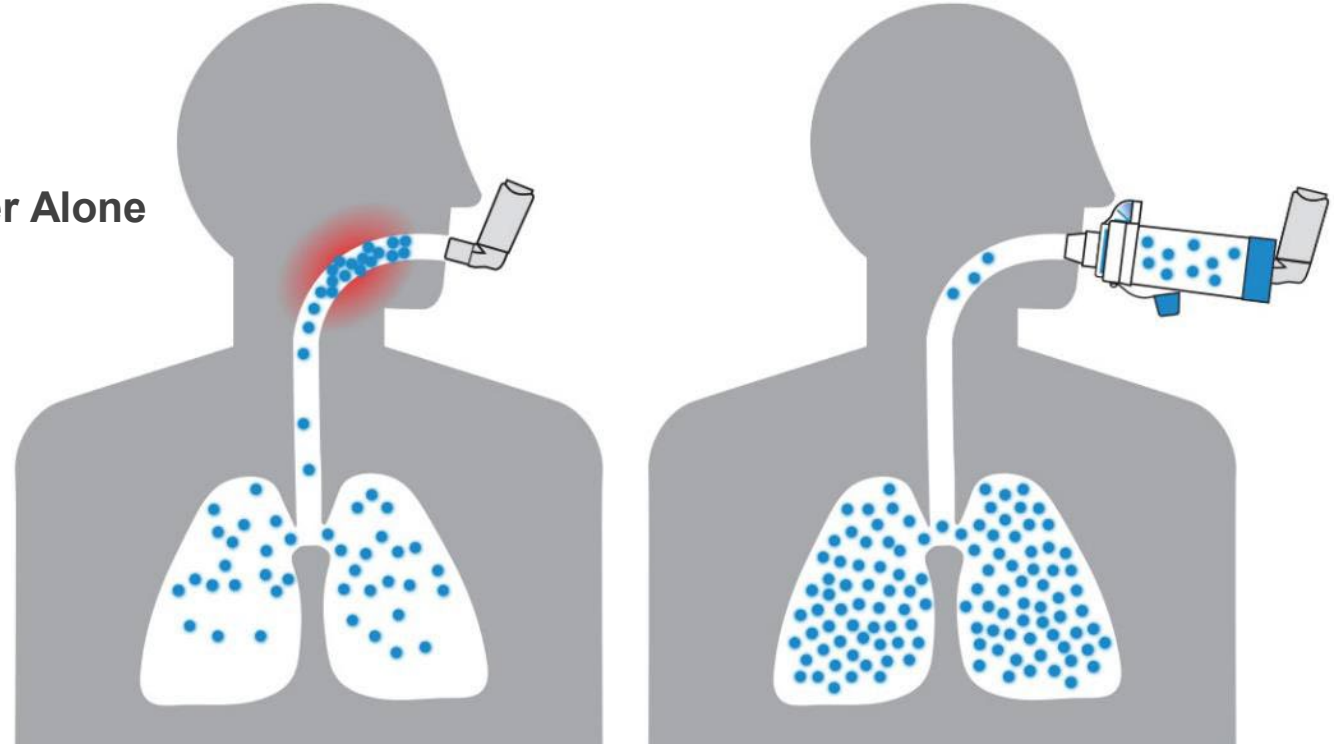
Peak inspiratory flow (PIF) assessment tool: a simple tool for assessing the risk of suboptimal PIF (sPIF) in chronic obstructive pulmonary disease (COPD) (AAFP [31])

Kaplan, A., van Boven, J.F.M. Switching Inhalers: A Practical Approach to Keep on UR RADAR. Pulm Ther 6, 381–392 (2020). https://doi.org/10.1007/s41030-020-00133-6

Spacers optimise pMDI medication delivery[1]

Make every puff count

Inhaler Alone



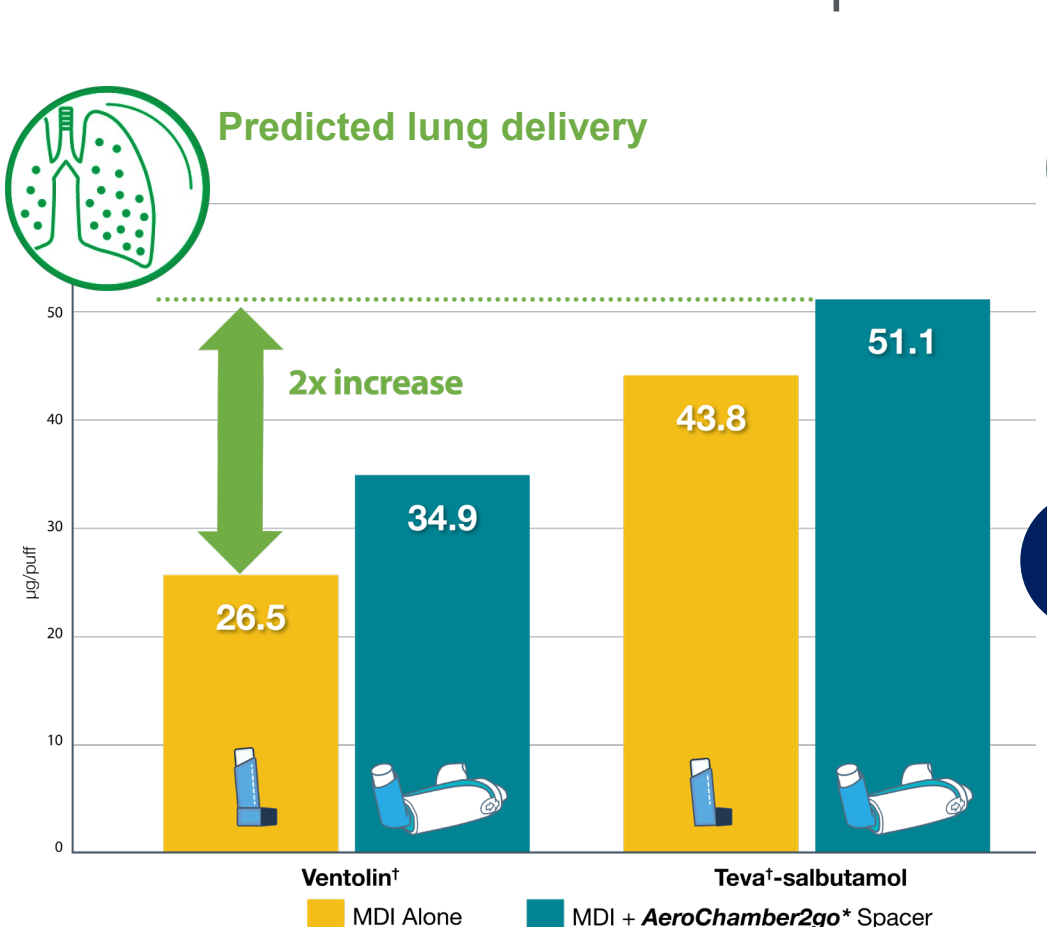
- Patient inhales with own timing
- Improves medication delivery to the lungs
- Reduces medication depositing in the throat by up to 90%[4]
  - Less side effects
- People who use a spacer with their inhaler have been shown to have **better asthma control**.[5]
  - Less reliever inhaler use!

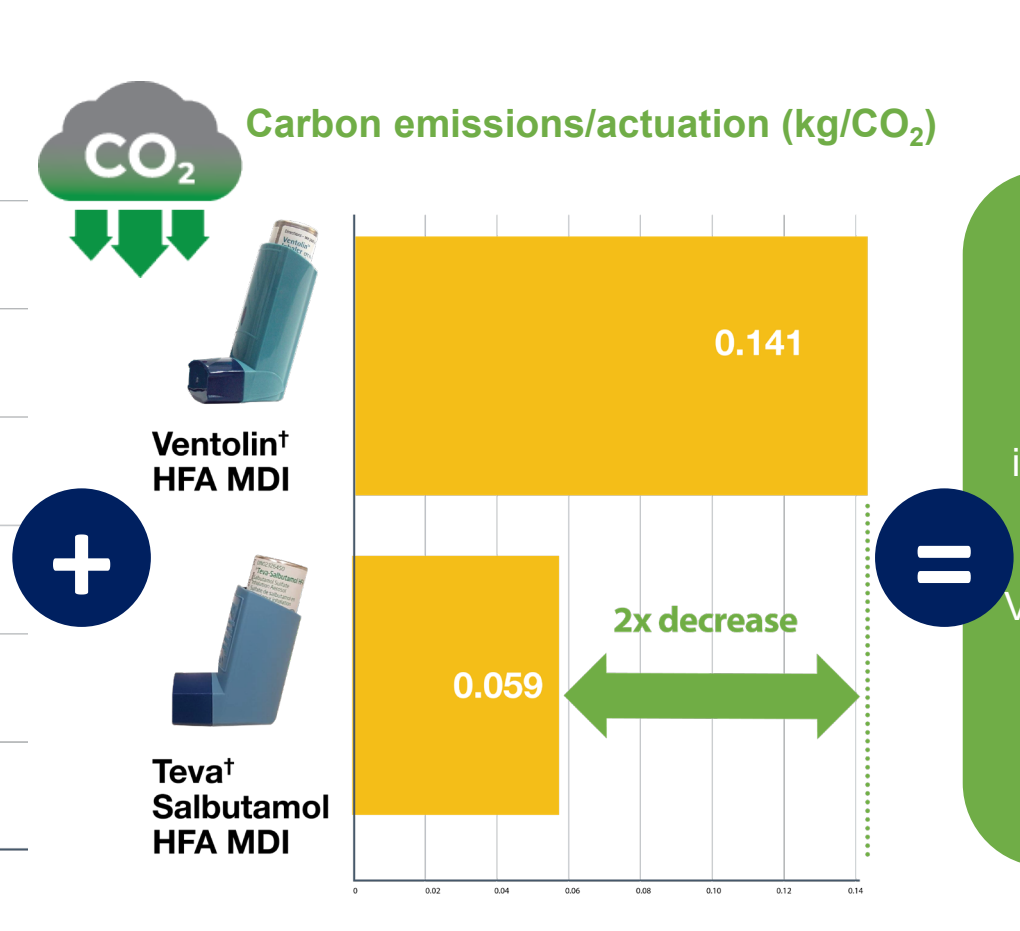
Chambers are designed to improve medication delivery, reduce side effects and help patients overcome difficulties in taking their medication[2,3]

[1] Dorinsky P, DePetrillo P, DeAngelis K, Trivedi R, Darken P, Gillen M. Relative Bioavailability of Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Administered With and Without a Spacer: Results of a Phase I, Randomized, Crossover Trial in Healthy Adults. Clin Ther. 42 (2020), 634-648. https://doi.org/10.1016/j.clinthera.2020.02.012 . [2] Lavorini F, Fontana GA. Targeting drugs to the airways: the role of spacer devices. Expert Opin Drug Deliv 2009;6(1):91-102. [3]GINA Global Strategy for Asthma Management and Prevention, 2021. [4] Suggett J et al. Assessment of potential mouth/ throat deposition and lung delivery of suspension-and solution-formulated inhaled corticosteroid formulations delivered by pressurized metered dose inhaler without and with valved holding chamber using an anatomic adult upper airway. Drug Delivery to the Lungs 28, Dec 2017. [5] Levy ML, Hardwell A, McKnight E, Holmes J. Asthma patients' inability to use a pressurized metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the Global Initiative for Asthma (GINA) strategy: a retrospective analysis. Prim Care Respir J. 2013; Dec;22(4):406-11.

Results CHEST poster 2022

- More efficient delivery of inhaler medication leads to less use of medication and therefore less carbon footprint.





Make every puff count

Up to 4x reduction

in the carbon emissions when using an ***AeroChamber2go**** VHC in combination with Teva†-Salbutamol

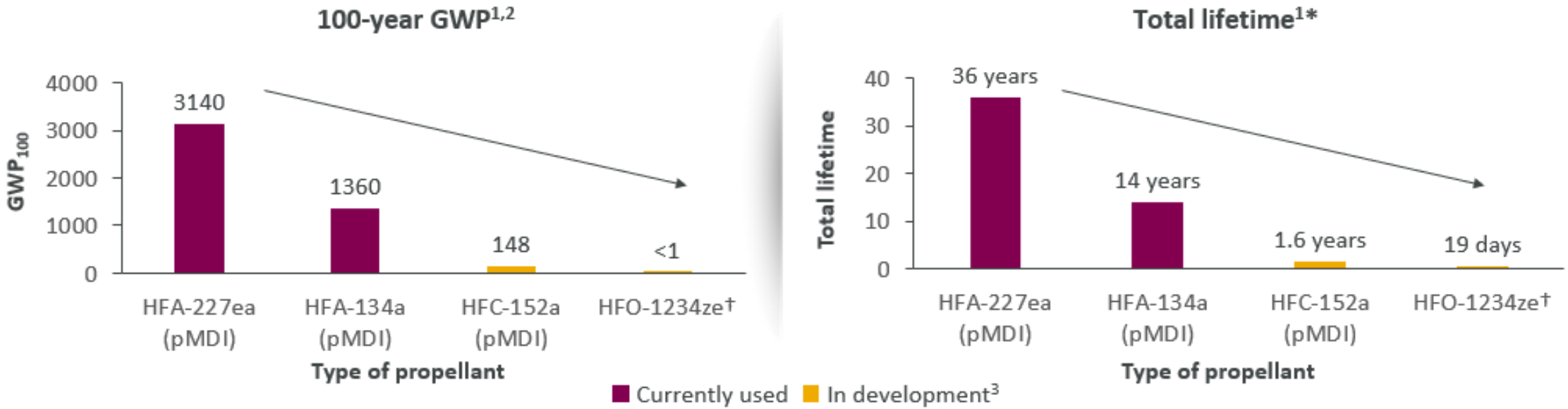
*Note: a conservative assumption was made that no savings are achieved through the spacer retaining any carbon emissions

Kaplan A. Suggett J. (4222) How might choice of salbutamol metered-dose inhaler (MDI) type and use of a spacer impact drug delivery and emissions: best options for patients and the environment. CHEST, Nashville, Oct 2022

Could not use a dry powder in this case!

And there are new climate friendly propellants!

Next-generation propellants that would have near zero greenhouse gas emissions are in development and will be launched from 2025



Up to 98%

"For the pMDIs, the main hotspot is the emission of propellants to the atmosphere during the use stage, **contributing 98% to the GWP of the HFC-134a inhaler** and **90% for the impact of the HFC-152a and HFC-227ea inhalers**"[2]

The 2018 WMO/UNEP assessment contains the most up-to-date understanding of ozone depletion, reflecting the thinking of hundreds of international scientific experts who contribute to its preparation and review
**Total lifetime, tHFC, reported in the 2018 assessment; †in development for use as medical propellant
GWP, global warming potential; HFA, hydrofluoroalkane; HFC, hydrofluorocarbon; HFO, hydrofluoroolefin; pMDI, pressurised meter-dose inhaler
1. World Meteorological Organization. Global Ozone Research and Monitoring Project – Report No. 58. 2018. Available from: https://ozone.unep.org/sites/default/files/2019-05/SAP-2018-Assessment-report.pdf; Last accessed July 2023.
2. Jeswani HK et al. J Clean Prod. 2019;237:117733; 3. Hargreaves C, Budgen N, Whiting A, et alS60 A new medical propellant HFO-1234ze(E): reducing the environmental impact of inhaled medicinesThorax 2022;77:A38-A39

There are other issues than GHGs.. Everything we use has a cost!!

Note: MDI and DPI data from: 1 Jeswani HK, Azapagi A. Life cycle environmental impacts of inhalers. Journal of Cleaner Production. Vol 237, 10, Nov 2019; 117733.


AH, POGO, THE BEAUTY OF THE FOREST PRIMEVAL GETS ME IN THE HEART.
IT GETS ME IN THE FEET, PORKYPINE.
EARTH DAY 1971
PUBLISHERS-HALL SYNDICATE, INC.


IT IS HARD WALKIN' ON THIS STUFF.
YEP, SON, WE HAVE MET THE ENEMY AND HE IS US.
© 1971 WALT KELLY

Don’t Just Throw Used Inhalers Away!!!

- Main reasons you shouldn’t just throw used or expired inhalers away.
  - One, there may be medication left in it. (one study showed 29% had meds left in them!)
  - Two, the can will explode when compacted or heated too much (like sitting in a garbage truck for a few hours).
  - Also, some inhalers, when broken open, will release greenhouse gasses. Inhaler related greenhouse gasses are responsible for about 5 million tons of CO2 emissions across the world.
  - If these inhalers go into a landfill, the medication will leak out and contaminate our local water supplies.

https://www.medprodisposal.com/what-do-with-old-inhalers/

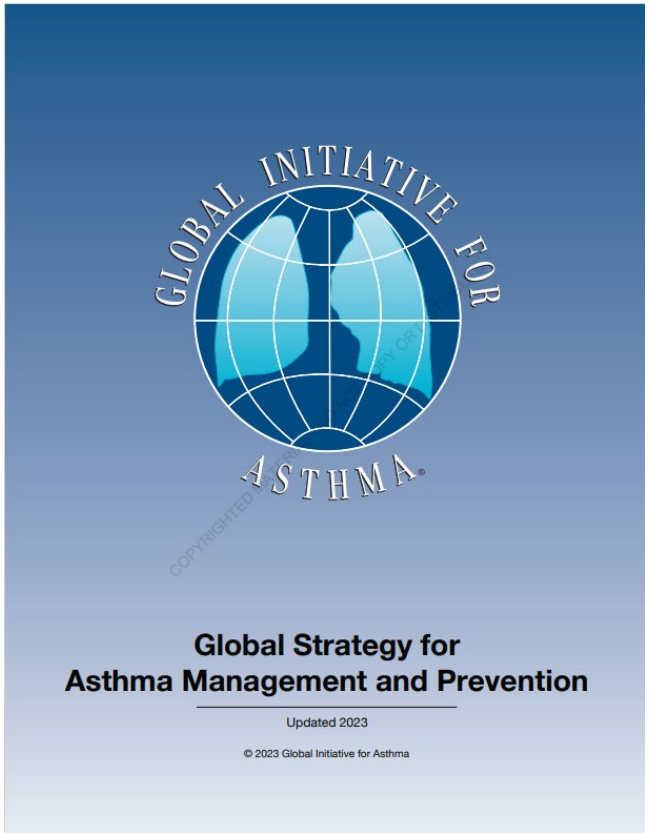
- They estimate that if 30% of their patients changed their behaviour and disposed inhalers at their local pharmacy, 11 tonnes of CO2e would be saved annually.
- Assuming that each patient uses 4 inhalers per year, this saving would be 44 tonnes CO2e.

Roome C, Bush O, Steinbach I, et al562 Reducing the environmental impact of inhaler use and disposal within paediatrics and the local communityArchives of Disease in Childhood 2021;106:A41-A42.

Clinicians need to be aware of the potential to place an additional burden on patients of so called *“green guilt”*

“Clinicians need to be aware of the potential to place an additional burden on patients of so called **“green guilt”**, which **could impact negatively on adherence and increase the risk of exacerbations**.”

“For all age-groups, **selecting the right inhaler for the individual patient is crucial** to asthma care, not only to reduce patients’ symptom burden, but also to reduce the need for emergency healthcare and hospitalization, **which have even greater environmental impacts than use of pMDIs.”**



SOURCE: Global strategy for asthma management and prevention 2023. GINA.

People must not be shamed for using pMDIs[1,2]

1 Keeley D et al. Minimising the environmental impact of inhaled therapies: problems with policy on low carbon inhalers. Eur Respir J. 2020;55(2):2000048. 2 Pritchard J, Usmani O. The Greenest Inhaler: A Patient-centric Approach. EMJ Respir. 2022;10[Suppl 2]:2-7.

Environmental sustainability: Conclusions and future implications

1. GHG emissions in medicine comes from multiple different sources
2. GHG emissions are correlated to respiratory disease that is not well controlled

    -**An 8-fold larger excess carbon footprint due to suboptimal asthma control**

3. SABA use is the largest contributor to GHG emissions associated with asthma care

-SABAs represent ~2/3 of GHG emissions from inhalers

-Get control and reduce medication use and HCRU (adequate controllers for both Asthma and COPD!)

-Use Spacers when appropriate when using pMDIs/ensure adequate technique

4. Reduce the carbon impact associated with disease care at a population and personal level

-DPI use in those who can and will use them

-Identify and approve (FAST TRACK THEM!) new propellants that have been proven to be safer

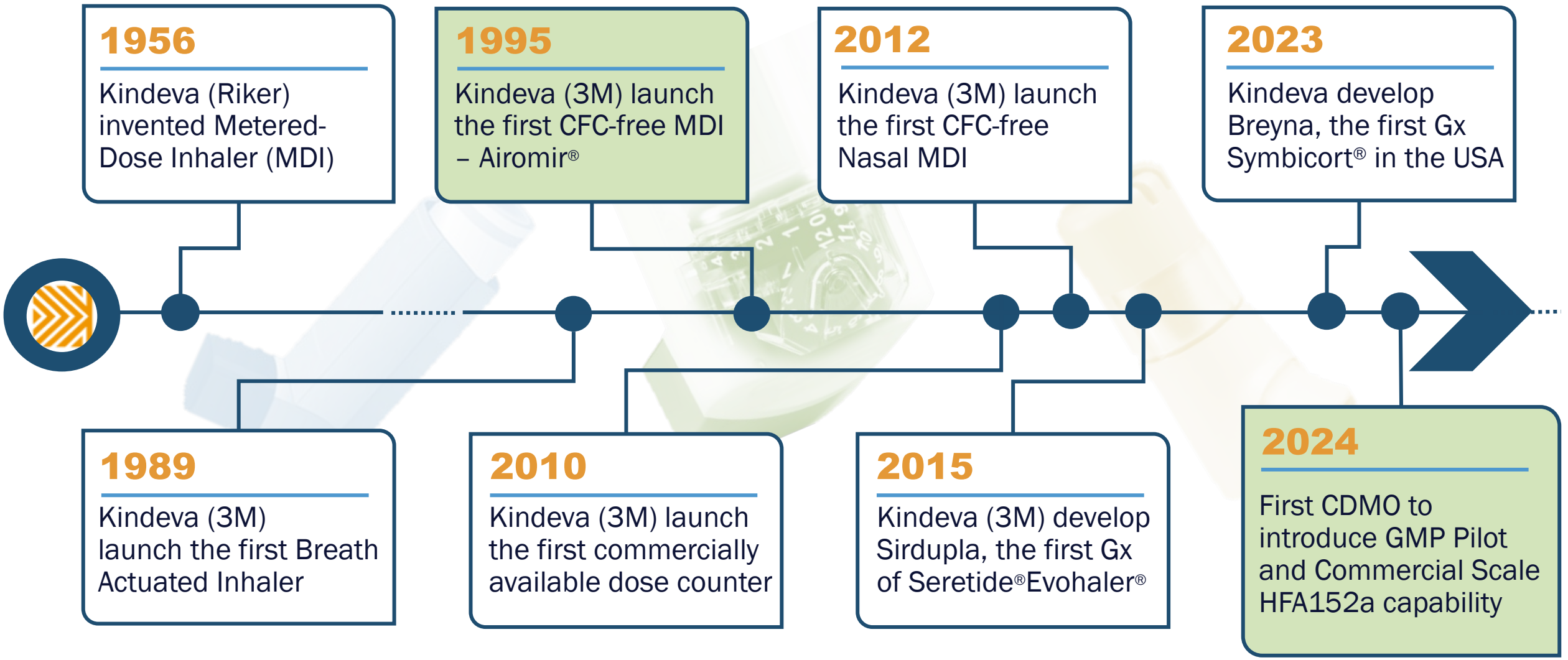
-Ensure proper disposal of all inhaler devices

US Regulatory Considerations for Transition to LGWP Propellant pMDI

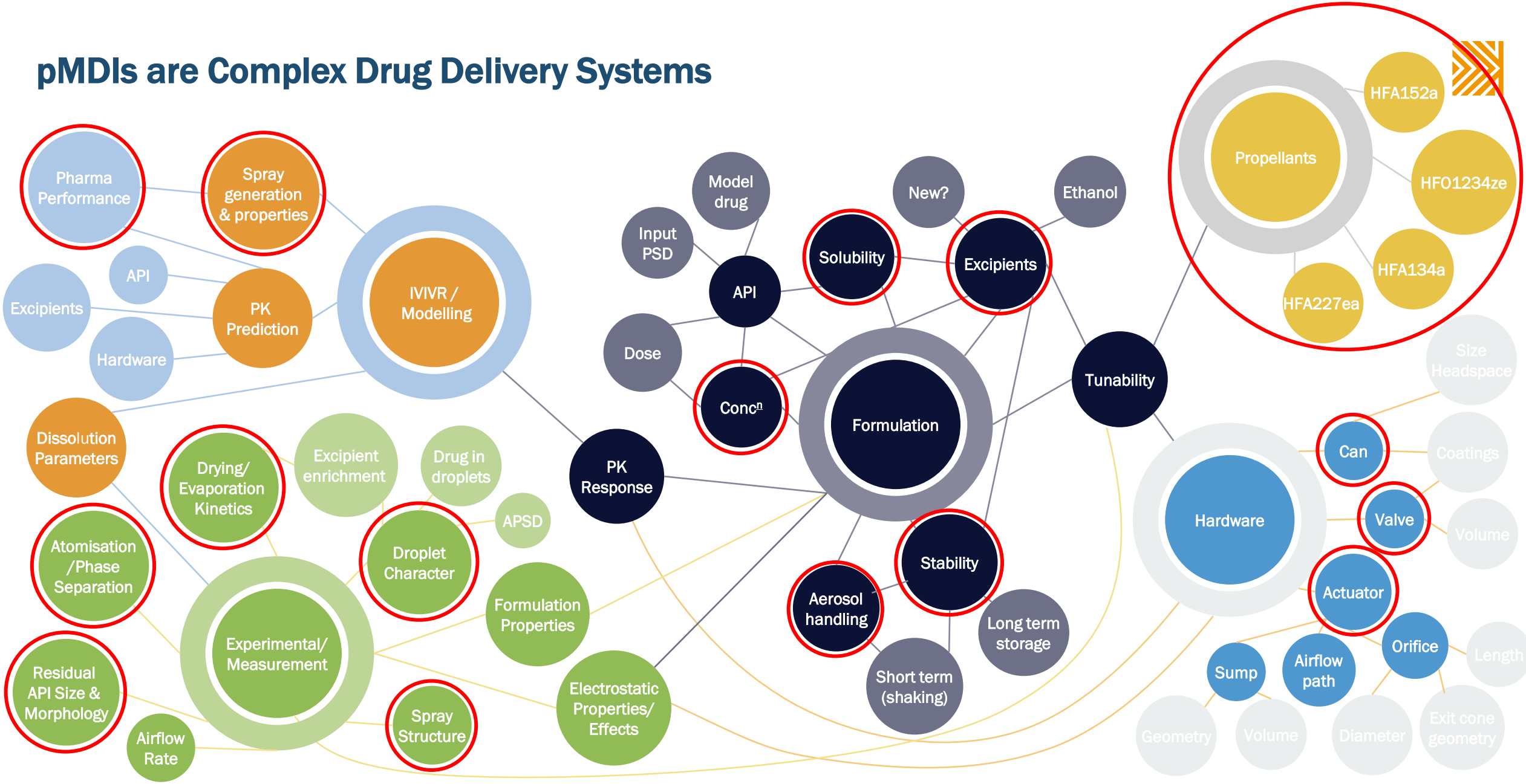
Ann Purrington, R.Ph. RAC
Regulatory Affairs Director, Kindeva Drug Delivery
IPAC-RS Board Member, IPAC US Subteam Lead

Navigating the Transition

Kindeva's track-record in managing transitions – A history of firsts



pMDIs are Complex Drug Delivery Systems



Low-GWP MDI Program at a Glance

Main stages

Feasibility Stage

Well-Established Approach via Incorporation of the Wide Range of Componentry to Maximise Success

- Define a suitable formulation
- Appropriate CCS selection (Valve, Can, Actuator, etc.)
- L-GWP (HFA-152a & HFO-1234ze(E) propellants evaluation

Full Development Stage

Development Activities for the Intended Market/Regulatory Authority, Enabling a Successful Submission

- Undertake the stability package, one-time studies
- Consider toxicological package/clinical requirements for the market and undertake
- Scale-up the manufacturing process to commercial production
- **Compile the submission package, submit and obtain regulatory approval**

Commercialization

Filling and Packaging L-GWP MDI Products at Scale, Including Stock Build

- Allocation of capacity on manufacturing lines, based on the incoming demand
- Filling, assembling, and packaging products
- Outbound logistics including shipment and transportation

What Regulatory Pathways Exist for Registration of Products With LGWP Propellants?

FDA Regulatory Pathways to Maintain Availability of Products

- New Drug Application (NDA)
  - 505(b)1: Application contains full reports of safety and effectiveness (S&E)
  - 505(b)2:[1,2] Application where some of S&E information is not conducted by or for the applicant
- Abbreviated New Drug Application (ANDA)
  - 505(j):[2] Application where product is same with respect to active ingredient, dosage form, strength, route of administration, conditions of use and labelling. Bioequivalence to RLD and ensuring product's identity, strength, quality and purity are also required. Relies on FDA's finding of S&E of the RLD.
- Prior approval supplement (PAS) to existing NDA or ANDA
  - Mechanism to provide changes to an approved application, allowed under Food and Drug Administration Modernization Act (FDAMA, Nov 1997)
  - Category is defined by a change that has substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product and its relationship to safety and effectiveness of the drug product.
  - Similar to a variation procedure in Europe.
  - Proposed pathway [3]

[1] *United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 'Determining Whether to Submit an ANDA or 505(b)(2) Application', final guidance, May 2019.*

[2] *United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 'Applications Covered by Section 505(b)(2)', draft guidance, October 1999.*

[3] *International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) Workshop on the Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers, 'Readout from the IPAC-RS/IPAC Surveys on Alternate Propellants', Sue Holmes GSK; and 'MDI Propellant Switch in the 2020s Compared and Contrasted to the Previous Propellant Switch of the 1990s: Don't Panic!', Dr. Richard Lostritto Independent Consultant. Workshop held 11Oct2023.*

Considerations for a Regulatory Submission

Categories of Information to be Submitted to FDA

- PreClinical (Animal) Data
- Safety and Effectiveness Data
- Chemistry, Manufacturing and Controls Data
- Pharmacokinetic (PK), Bioavailability (BA) and Bioequivalence (BE) Data
- Labeling

- Extent of information for these categories will depend on the regulatory pathway (NDA, ANDA, PAS)
  - In general, all categories need to be fulfilled for NDA, All but the first two are to be addressed in ANDA, and the primary emphasis will be Chemistry, Manufacturing and Controls Data for a prior approval supplement.
  - There are cases where PK will also be required for PAS.
- Other factors in considering submission type
  - Review timing – There are cases where review timing will be shorter for PAS, potentially enabling faster access to the updated product for patients
  - Filing fees – PAS does not have filing fees, NDA and ANDA do have filing fees.

- Largest Consideration
  - Amount of data required will impact amount of time needed to prepare the complete data package, and submission. Extent of data could impact timing for availability of updated product for patients.
  - Continued availability of existing products, in relation to phase down and supply of existing propellants, is of consideration.

Considerations to Maintain Therapy for Patients

Patients' Impact

- Lower price to patients vs. other dosage forms
- Patients' preference
- Reliever (SABA)

Health Authority Regulatory Strategy

- New NDA vs. PAS
- In-vitro route with comparative PK?
- Safety data from suppliers for LGWP propellant

Economics

- Product pricing
- Propellant cost increase
- Generics and payor price pressure
- Development and clinical costs

Legislative Framework

- Kigali Amendment
- EPA via AIM Act
- US state legislation

Now is an important time to engage and discuss regulatory requirements, to enable continued access for patients

Why Does Regulatory Path Matter?

Need to balance availability of existing propellants against time to approval for LGWP products

Is supply of existing propellants becoming an issue?

- The supply of p227ea is already at a critical point
  - There is virtually no industrial use of p227ea due to its high GWP (historically used in fire-suppression systems)
  - Medical grade propellant price continues to rise significantly
  - Raw materials for production are becoming difficult to procure

- The supply of p134a is becoming more difficult
  - Industrial use (e.g., air-conditioning and refrigeration) is declining quickly due to adoption of similar lower GWP alternatives at lower prices (e.g., p152a) and impact of Kigali-related legislation
  - One manufacturer of p134a (Koura) has also invested heavily in p152a capabilities so is driving the transition
  - Major MDI manufacturers using medical grade p134a have publicly stated timelines for transition to lower GWP alternatives in the 2025-2027 time frame

Current Thinking and Next Steps

FDA Information on Regulatory Paths and Options

FDA has previously shared insights on CMC requirements for NDA LGWP products [1]

- Respiratory Drug Delivery Conference, May 2024 – Five FDA scientists presented
  - Design and Implementation of In Vitro and In Vivo Alternative Bioequivalence Approaches[2]; also In Silico Studies,[3]
  - US Regulatory Considerations for Low Global Warming Potential Propellant Transition for Brand and Generic MDIs, [4]

- FDA is conducting research, and presenting recommendations on current thinking for
  - Bioequivalence approaches for generic MDIs, which may potentially be used for brand MDIs
  - Regulatory paths for transition to LGWP propellant products
    - Early days – and positions are in discussion at conferences

- **Upcoming key meeting to hear current thinking from FDA**
- FDA – CRCG Workshop, Navigating the Transition to Low Global Warming Potential Propellants, Dec 2024
  - *No guidance issued by FDA, as has been issued by EMA*
  - Coordination ongoing with stakeholders, including IPAC-RS

[1] *IPAC-RS Workshop held 11Oct2023. 'Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective', Dr. Craig Bertha, Chemist, CMC reviewer, Office of Pharmaceutical Quality, Office of New Drug Products.*

2 Bielski and Boc, Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, CDER, FDA; Walenga, Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, CDER, FDA

[3] Neman and Luke, Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, CDER, FDA

Next Steps

Consortia Available as a Resource to Answer Questions of the Parties Regarding Transition

- IPAC (International Pharmaceutical Aerosol Consortium)
  - Consortia of industry
  - Focused on environmental policy and initiatives
  - Aim to maintain MDIs as an available therapy for patients
- IPAC-RS (International Pharmaceutical Aerosol Consortium for Regulation and Science)
  - Consortia of industry, suppliers, and research providers
  - Advancement of science of orally inhaled and nasal drug products
  - Build consensus and contribute to effective guidance and standards by sharing results of research
  - Conferences, technical journals, webinars, discussions with regulatory bodies.
  - Established in 2000

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11 July 2024

COMBINE FORCES

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OUR EXPERTISE BRINGS IT INTO THE WORLD.

Application Content	505(b)1 NDA	505(b)2 NDA	505(j) ANDA	Prior Approval Supplement
Preclinical (Animal) Data	√	√ - case by case, depends on differences to RLD, and data needs for propellant.	No, S&E 'inherited' from RLD	No, PAS used to address chemistry, manufacturing and control (CMC) changes
Safety and Effectiveness Data	√	√ - case by case, depends on differences to RLD.		
Chemistry, Manufacturing and Controls Data	√	√	√	√
Pharmacokinetic (PK), Bioavailability (BA) and Bioequivalence (BE) Data	√ PK and BA	√ PK and comparative BA	√ BE	√ Case by case – BE, depends on support needed for the CMC change
Labeling	√	√ - focus on those items that differ from RLD	√ - same as RLD, certain exceptions	√ - same as approved product, certain exceptions
Review Timing	PDUFA = Review and act on in 10 months (non-NME)	PDUFA = Review and act on in 10 months (non-NME)	PDUFA = Review and act on in 10 months	PDUFA = Review and act on in 4 months GDUFA -= Review and act on in 6/10 months
Filing Fee	$4,048,695 – clin	$4,048,695 – clin	$252,453	None

Data requirements, review timing and filing fees are favorable for PAS pathway – and LGWP product is proposed as a Chemistry, Manufacturing and Controls Change