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The Transition to More Climate-Friendly Medical Inhalers in the EU – EMA's role

European Medicines Agency (EMA) perspective

46th meeting of the Open-ended Working Group of the Parties to the Montreal Protocol

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Contents

How to deliver a medicine to the lungs

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Particles should generally be within the 1-5 micrometer range to reach the lower respiratory tract. This can be achieved using the following pharmaceutical forms:

- Pressurised Metered Dose Inhalers (pMDIs) ~ 70% of marketed products
  - They use propellants to deliver the active substance(s)

- Dry Powder Inhalers (DPIs) ~ 17%
  - They use a powder as a carrier

- Soft Mist Inhalers (SMIs) ~ 7%
  - Active substance in solution, they do not use propellants, they rely on mechanical energy to create the aerosol mist (e.g. spring)

- Nebulisers ~ 6%
  - They use ultrasonic systems or thermal energy to deliver active substance(s) in aqueous solutions.

Propellant in pressurised metered dose inhalers (p)MDIs

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They are volatile compounds that are used to create pressure within a container, enabling the release of the product as an aerosol spray.

The propellant dissolves or disperses the active substance(s) in a homogenous system.

It is the main component of the MDI formulation with impact on the stability and delivery of the active substance(s), hence on the therapeutic effect.

Key role in MDIs

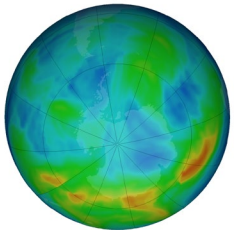
Change of propellant is complex: different solubilities, compatibilities (also with device parts), stability, safety and efficacy.
New device components may be needed
→ *extensive data needed*

Drivers for change of propellant

Montreal Protocol on Substances that Deplete the Ozone Layer regulates the production and consumption of ozone depleting substances (since 1987) & HFCs (since 2016)

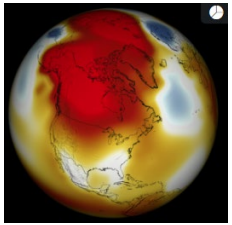
1st generation

CFCs deplete the ozone layer



2nd generation

High GWP
Used in all current approved MDIs



3rd generation

Low GWP
Not yet approved

EMA's role

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Informal interaction with stakeholders	Scientific advices	Guidance	What's next: Submissions
First queries received from Pharma in 2019 Interactions with European Commission (EC)	More than 10 SAs with pharma and propellant manufacturers	Q&A on change in propellant (October 2023)	Companies will apply for product with 3rd generation propellants (low GWP) 1st expected 4Q 2024

The Q&A

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30 October 2023
EMA/477469/202323
Committee for Medicinal Products for Human Use (CHMP)

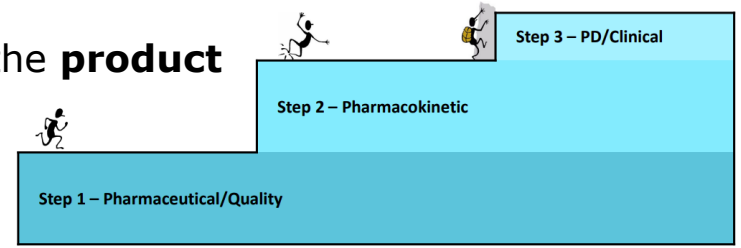
Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers

Agreed by Methodology Working Party, Non Clinical Working Party, Scientific Advice Working Party, Paediatric Committee/Formulation Working Group, Rheumatology and Immunology Working Party	February 2023
Adopted by CHMP for release for consultation	30 Mar 2023
Start of public consultation	April 2023
End of consultation (deadline for comments)	31 May 2023
Agreed by Rheumatology and Immunology Working Party	September 2023
Adopted by CHMP	30 October 2023

Keywords	question and answer, oral pressurised metered dose inhalers, hydrofluorocarbon replacement and propellant

Change of excipient - requirements

- For the **excipient (i.e. propellant)**: Is it novel or established?
- For the **product**



  - "It is generally **not** recommended to aim at demonstrating therapeutic equivalence using pharmacodynamic (PD) or clinical endpoints (= step 3) as these are deemed insensitive."
- Data in children may be waived
- Usability studies may be needed

Collaboration between companies would avoid repetition of studies (e.g. safety)

Regulatory procedures in the EU

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Data requirement

Type II variations – variation to an existing marketing authorisation application (MAA) with potential impact on quality, safety, efficacy (e.g. change in excipient)

Active days: 60 days + 30 days + … - Total procedural times: 9 months – 1 year +

- 1st expected 4Q2024

Line extension variation – different strength (if linked to the change in propellant)

Active days: Up to 210 days - Total procedural times: 1 – 1.5 year +

'Generic' hybrid applications – to a marketed product

Active days: Up to 210 days - Total procedural times: 1.5 year +

Initial MAA - stand-alone MAA with full data package

Active days: Up to 210 days - Total procedural times: 1.5 year +

How can EMA help?

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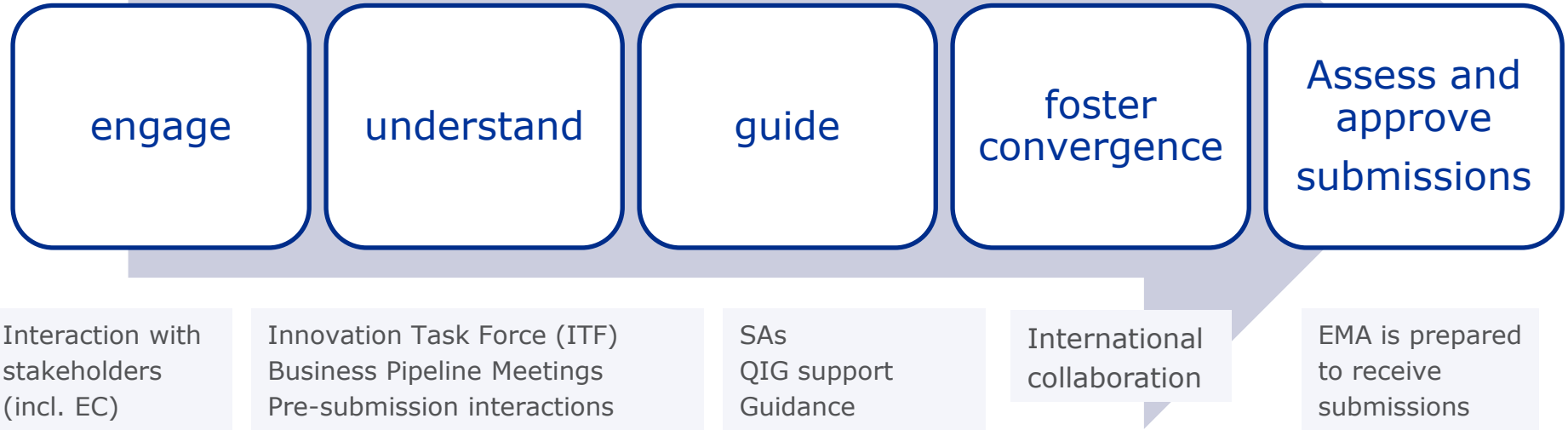

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Any questions?

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