Metered Dose Inhaler Propellants
The driving force behind inhaled medications for 60 years

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Acknowledgements

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The MDI
MDI Propellants past and present

Generic requirements:
- Non-toxic
- Stable. No chemical reactivity with drug
- Non flammable

Suitable physical properties:

<table>
<thead>
<tr>
<th>FC No.</th>
<th>Formula</th>
<th>B.Pt (°C)</th>
<th>S.G. (g/cc, 20°C)</th>
<th>ODP+</th>
<th>++GWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC 11</td>
<td>CFCl₃</td>
<td>23.7</td>
<td>1.49</td>
<td>1</td>
<td>4660</td>
</tr>
<tr>
<td>CFC 12</td>
<td>CF₂Cl₂</td>
<td>-29.8</td>
<td>1.33</td>
<td>1</td>
<td>10800</td>
</tr>
<tr>
<td>HFA 134a</td>
<td>CF₃-CFH₂</td>
<td>-26.2</td>
<td>1.23</td>
<td>0</td>
<td>1300</td>
</tr>
<tr>
<td>HFA 227ea</td>
<td>CF₃-CFH-CF₃</td>
<td>-16.5</td>
<td>1.41</td>
<td>0</td>
<td>3350</td>
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+ Ozone depletion potential
++ Greenhouse warming potential, time horizon 100y, IPCC AP5
MDI history - The impact of environmental regulation

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**Early MDIs**
- No environmental regulation
- Medihaler (1956)
- Ventolin (1969)
- CFC 11+12

**1980’s**
- Technology development
  - Two stage filling
  - CFC11 slurry to open can
  - Crimp up
  - Gas with CFC 12
  - Substantial growth
  - B-agonists, corticosteroids and antichologenics
  - Ozone hole discovered

**Transition to HFAs 1990-2015**
  - HFAs 134a or 227ea replace CFC 12
  - Airomir (SS 1995)
  - Ventolin Evohaler (SS1997)
  - Seretide (FP, SX 2000)
  - Clenil (BDP 2006)
  - Symbicort (FF, BUD 2006)
  - China last out of CFCs (2015)
  - Strong platform technology
  - Growing focus on global warming

**2015→**
- 2016 ~ 750m units w/w*
- GWP Regulation

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* Source: Mexichem estimate
Environmental regulation of Fluorine-containing Gases

1. Montreal Protocol
   - 1989-2015. Phase *out* of CFC gases
     - Annually reviewed essential use allowances for MDI
     - Last authorised use in 2015 (China)

2. F-Gas regulation of refrigerants
   - EU: F-Gas regulations 2015-30. Phase *down*
     - 21% of current use by 2030 – carbon equivalent based
     - MDI application partially exempted

3. Montreal Protocol Mk II
   - Protocol amended to cover HFC gases 2018-2036
     - Global
     - Phase-*down* to ~ 15% of baseline. Carbon equivalent based
     - Supersedes existing local regulations
     - No automatic MDI exemption, **but review mechanism**
Current and future regulation

North America MP Proposal
summary of phase-down schedule for Art.5 and non-Art.5 countries and EU

% of CO2e baseline vs. years

- Non-Art.5
- Art.5
- EU
Respiratory Industry Commitment to Environmental Improvement

Steady movement towards lowering carbon footprint of respiratory dosage forms:
• MDIs:
  • Less HFA per shot
  • Recycle schemes
  • Alternative dosage forms

How can a propellant supplier contribute?
• Good stewardship (customer advice, eliminate losses)

• A new low carbon medical propellant? It would need:
  – Correct safety profile, *sufficiently* inert
  – Acceptable physical characteristics (Bpt, liquid density)
  – Cost, availability, future sustainability
  plus
  – Significant performance gains

We have been looking…..
New MDI propellant development
1,1-difluoroethane (HFA 152a)

A colourless, odourless, low-toxicity low boiling liquid. In large scale industrial use, as:

- Polymer precursor
- Consumer aerosol propellant
- Foam blowing agent
- Made at scale (~80-100 ktpa)
HFA 152a: Basic Physical Properties compared

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<tr>
<td>HFA</td>
<td>CF₂H-CH₃</td>
<td>-24.7</td>
<td>0.91</td>
<td>0</td>
<td>138</td>
</tr>
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• HFA 152a is flammable - but less so than hydrocarbons
• Not categorised as a Volatile Organic Compound in the US
  • Good environmental balance
Dosage form carbon footprints compared

**Whole device carbon footprint**

- Comparable footprint to DPI
- Majority of MDI footprint due to propellant
  - 99% HFA134a
  - 89% HFA152a

Based on IPAC estimate of 1.5-6.0kgCO2 for 200-dose DPIs
HFA 152a – Mexichem’s Safety Studies

- Inhalation safety
  - GLP exposure safety studies ongoing

- Patient flammability risk assessment
  - No increase in risk over current formulations

- MDI manufacturing safety
  - Ongoing risk assessment of MDI filling options
Does it work?

Aerodynamic performance and chemical stability of salbutamol sulphate suspensions in HFA 134a and HFA 152a
Salbutamol Sulphate: Emitted Dose & APSD Performance

Bench filled aerosols
Suspension Stability Using Turbiscan

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<th>System</th>
<th>Floc size (µm)</th>
<th>Time to Sediment (mins)</th>
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<tr>
<td>Salbutamol Sulphate + 134a</td>
<td>3.77</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Salbutamol Sulphate + Ethanol + 134a</td>
<td>3.62</td>
<td>1.5</td>
</tr>
<tr>
<td>Salbutamol Sulphate + Oleic acid + Ethanol + 134a</td>
<td>3.55</td>
<td>3.0</td>
</tr>
<tr>
<td>Salbutamol Sulphate + 152a</td>
<td>3.97</td>
<td>2.0</td>
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Enhanced suspension stability of Salbutamol Sulphate in HFA152a
In Conclusion

• HFAs 134a & 227ea will remain available for MDI applications
• Based on industry experience of CFC/HFA transition, HFA 152a to date shows promise
  • Environmental sustainability
  • MDI formulation benefits include
    – Good suspension behaviour compared to existing HFAs
    – Enhancement of the chemical stability of labile active ingredients
    – Ease of solution formulation

• Mexichem will continue investigation into the utility of HFA 152a in this area
  • Mexichem’s GLP safety studies are in progress
  • Supply chain
  • Further formulation studies
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