Mexichem
Medical Propellants

Metered Dose Inhaler Propellants

The driving force behind inhaled medications for 60 years

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Acknowledgements

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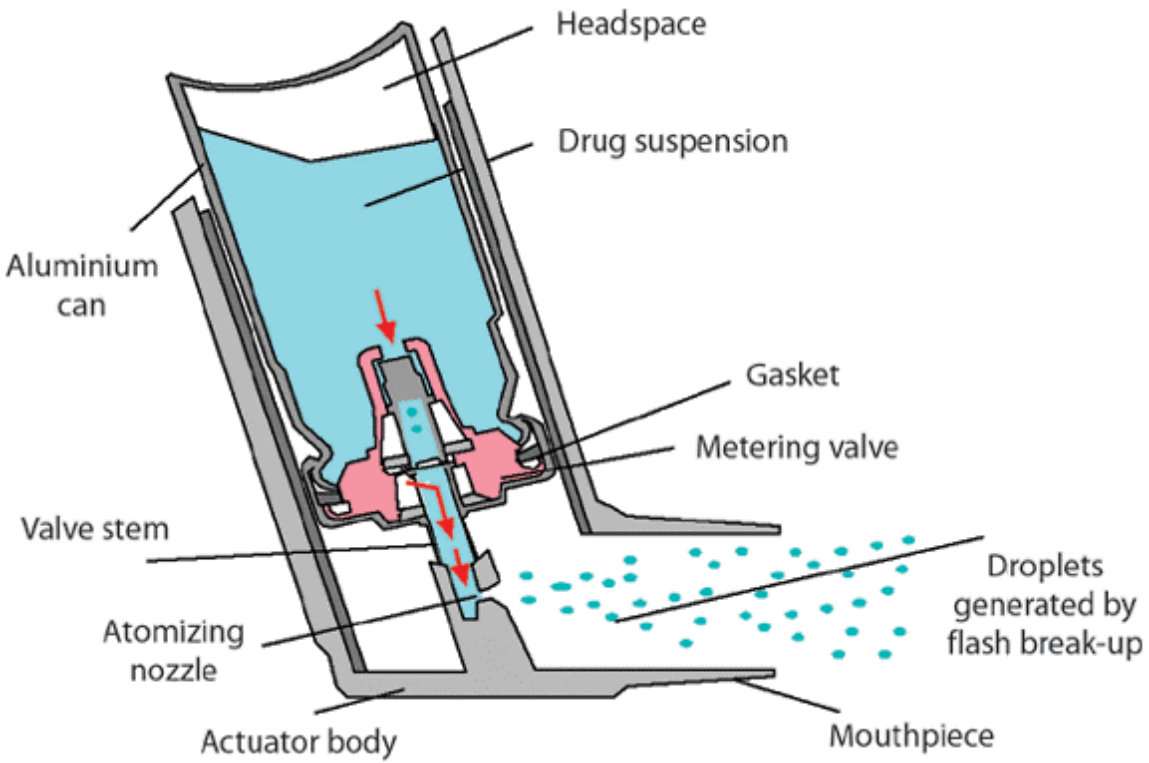
The MDI



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MDI Propellants past and present

Generic requirements:

-Non – toxic

-Stable. No chemical reactivity with drug

-Non flammable

Suitable physical properties:

	FC No.	Formula	B.Pt (°C)	S.G. (g/cc, 20°C)	ODP[+]	[++]GWP
CFC	11	$CFCl_3$	23.7	1.49	1	4660
CFC	12	CF_2Cl_2	-29.8	1.33	1	10800
HFA	134a	CF_3-CFH_2	-26.2	1.23	0	1300
HFA	227ea	CF_3-CFH-CF_3	-16.5	1.41	0	3350

[+] Ozone deletion potential

[++] Greenhouse warming potential, time horizon 100y, IPCC AP5

MDI history - The impact of environmental regulation

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 anticholegenics
- Ozone hole discovered

Transition to HFAs 1990-2015

- **Montreal Protocol** (1988)
- 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**

* **Source: Mexichem estimate**

Environmental regulation of Fluorine-containing Gases

Montreal Protocol

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

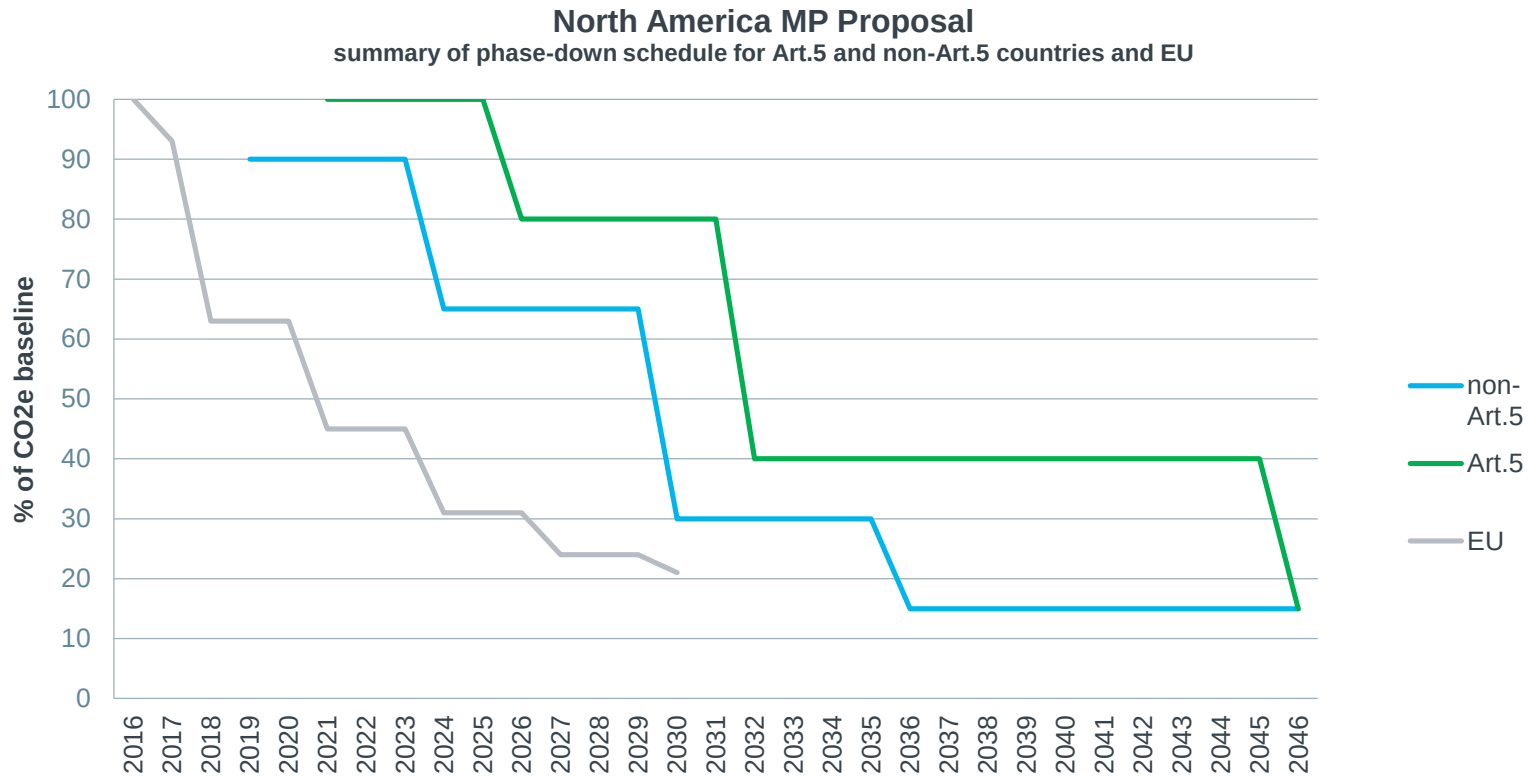
F-Gas regulation of refrigerants

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

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



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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)

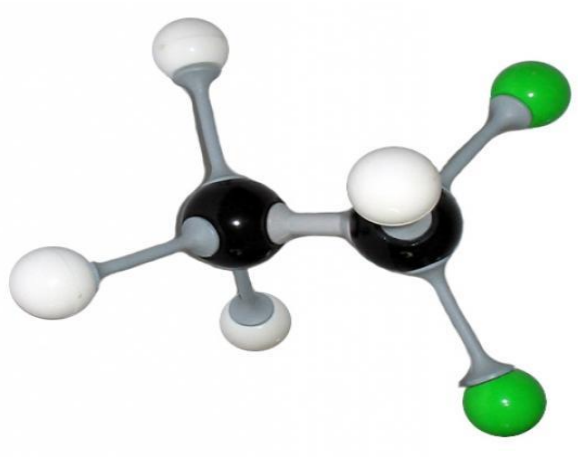
A colourless, odourless, low-toxicity low boiling liquid. In large scale industrial use, as:

Polymer precursor

Consumer aerosol propellant

Foam blowing agent

Made at scale (~80-100 ktpa)



HFA 152a: Basic Physical Properties compared

	FC No.	Formula	B.Pt (°C)	S.G. (g/cc, 20°C)	ODP[+]	[++]GWP
CFC	11	$CFCl_3$	23.7	1.49	1	4660
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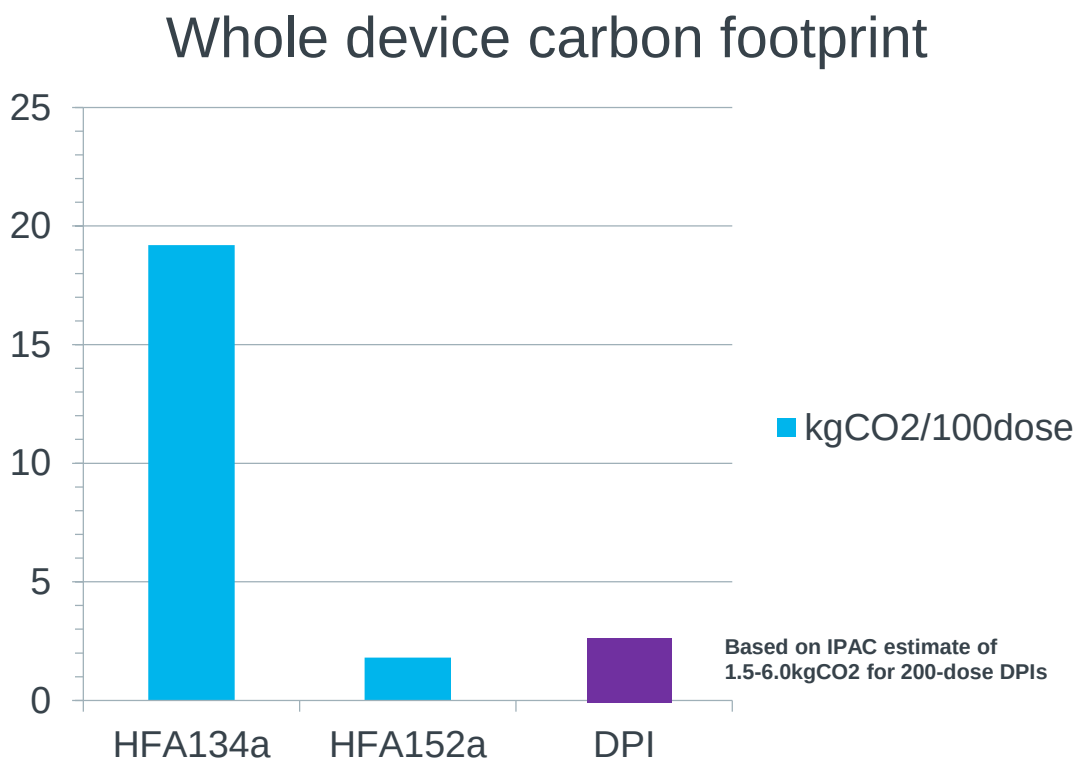
HFA	227ea	CF_3-CFH-CF_3	-16.5	1.41	0	3350
HFA	152a	CF_2H-CH_3	-24.7	0.91	0	138

- 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



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

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HFA 152a – Mexichem's Safety Studies

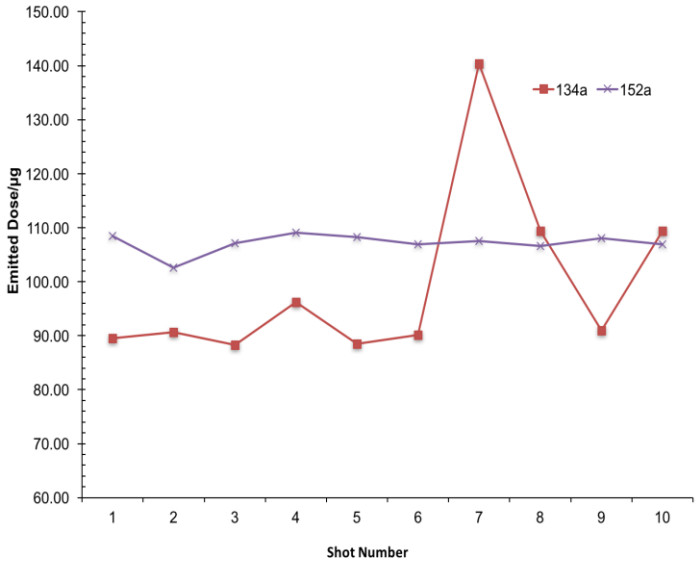
- Inhalation safety
  - GLP exposure safety studies ongoing
- Patient flammability risk assessment
  - No increase in risk over current formulations
- MDI manufacturing safety
  - Ongoing risk assessment of MDI filling options

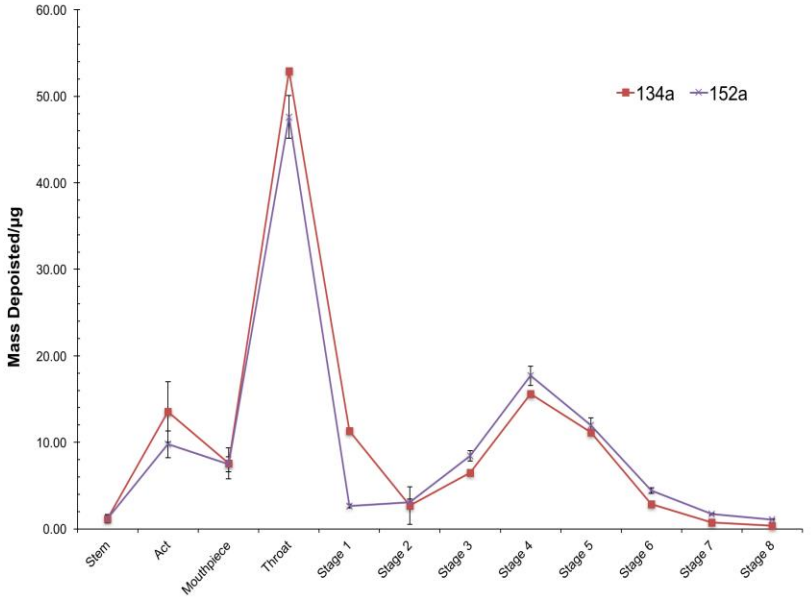
Does it work?

Aerodynamic performance and chemical stability of salbutamol sulphate suspensions in HFA 134a and HFA 152a

Salbutamol Sulphate: Emitted Dose & APSD Performance

Bench filled aerosols





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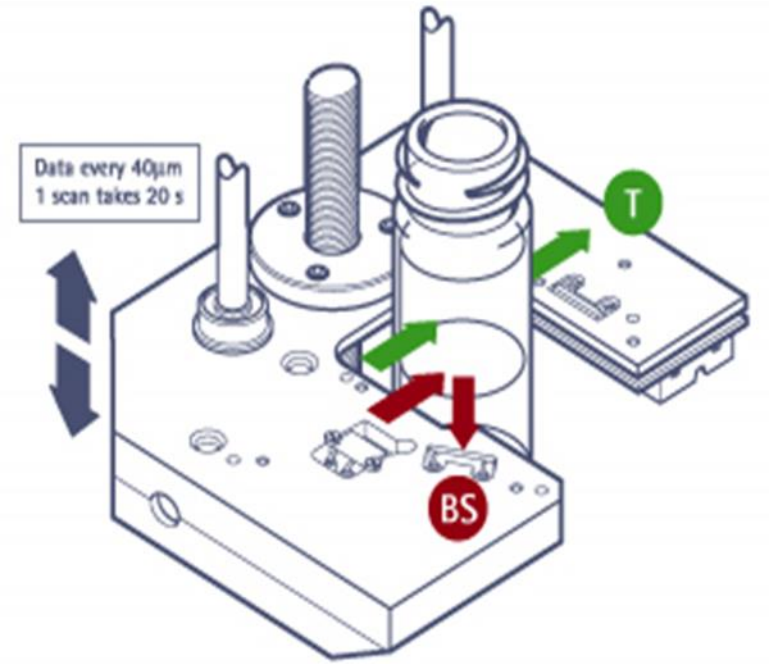
Suspension Stability Using Turbiscan



System	Floc size (µm)	Time to Sediment (mins)
Salbutamol Sulphate + 134a	3.77	<0.5
Salbutamol Sulphate + Ethanol + 134a	3.62	1.5
Salbutamol Sulphate + Oleic acid + Ethanol + 134a	3.55	3.0
Salbutamol Sulphate + 152a	3.97	2.0

Enhanced suspension stability of Salbutamol Sulphate in HFA152a

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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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