


## The Transition to CFC-Free MDIs: Status Update and Looking to the Future

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## CFC Phase out: It has taken a long time!



CFCs (chlorofluorocarbons) are being phased out to protect the ozone layer. Du Pont will stop selling CFCs as soon as possible, but no later than year-end 1995 in the U.S. and other developed countries. We've already reduced our total production by 50 percent when compared to 1986.

We now offer a broader range of substitutes than anyone else. We've invested \$350 million and have three commercial facilities. We also have programs for our customers to reclaim CFCs and reduce emissions. And we're converting our internal refrigeration and air conditioning equipment to use substitutes.

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## The Montreal Protocol and MDIs

- Ø As of January 1st, 1996, Montreal Protocol banned all use of CFCs in developed countries; 2010 deadline for developing countries
- Ø International decision under Protocol allowed CFCs to be produced for “essential uses”
  - § Criteria established to ensure that CFCs only produced where necessary for public health – i.e. adequate alternatives (technically & economically) unavailable
  - § MDIs for asthma and COPD emerged as the primary essential use
- Ø Allocation of CFCs to MDI manufacturers strictly controlled by Protocol process
  - § Requests reviewed annually by technical experts (MTOC) and environmental/health regulators in US, EU, and other Protocol Parties
- Ø Reformulation effort required substantial resource investment (\$billions!) and took much longer than expected - some factors:
  - § MDIs are complex devices and change in propellant required redesign of many aspects
  - § Health agencies did not always prioritize MDI transition

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## The Reformulation Effort

- Ø Industry wide effort (450 million plus MDIs; ca 20 companies)
- Ø The MDI is a complex device
- Ø It was not possible to “drop in” a new propellant to replace the CFC propellants
- Ø Nearly all physical components and elements were redesigned or reconfigured; changes to drug salt form
- Ø Manufacturing processes were redesigned and validated
- Ø New formulation approaches were developed (solutions)
- Ø Different replacement strategies have been adopted;

DPIs; Like for like MDIs; Enhanced MDIs

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## MDI Transition: Where are we today?

- Ø The transition from CFC to HFA MDIs and other CFC-free products is well underway
- Ø Country and company approaches have been diverse and dictated by local circumstances
- Ø EU, Canada, Australia, Japan have completed transition or are close to end
- Ø US transition has presented challenges and is somewhat behind other countries
- Ø Biggest challenge is Article 5 countries; expect a long "tail" unless CFC supply becomes limited

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## CFC MDI Transition in the United States

- Ø Major product: albuterol (salbutamol) CFC MDI
  - § 45 million units per year (roughly half of the US market; 10% global units)
  - § Special challenges for regulators and patients: significant price difference between CFC MDI (generic) vs new HFC MDIs
  - § FDA has established phase-out deadline of **31 December 2008**
- Ø Other CFC MDIs remaining on US Market
  - § FDA has proposed regulations (not yet final) on all CFC products; one rulemaking for 7 prescription products (flunisolide, metaproterenol, pirbuterol, cromolyn, triamcinolone, nedocromil, and albuterol & ipratropium (in combination)) and one for OTC product (epinephrine)
  - § End 2009 proposed deadline for 7 prescription products; end 2010 for epinephrine
  - § Unclear when FDA will issue final rules; phase-out deadlines may be extended
- Ø Some patients have been reluctant to make the switch
  - § Patient and physician stakeholders have engaged in process; generally support transition
  - § Several news articles published on the challenges of the MDI transition

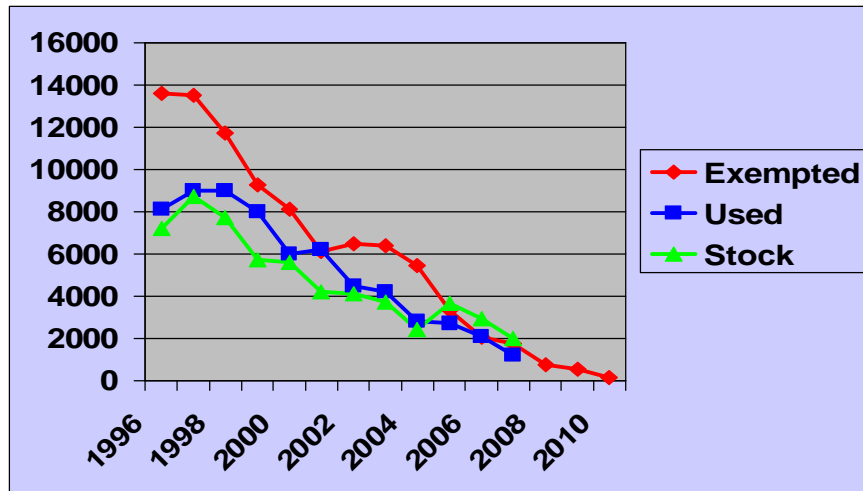
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## Trends in Global CFC Essential Uses



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## MDI Transition: What Does the Future Hold?

- Ø CFC MDIs will be (mostly?) gone by 2010-2011
- Ø New HFA MDIs will continue to be developed but it is not easy!
- Ø More DPIs will be developed (both unit and multi-dose systems)
- Ø Climate change policies and regulations may impact HFAs

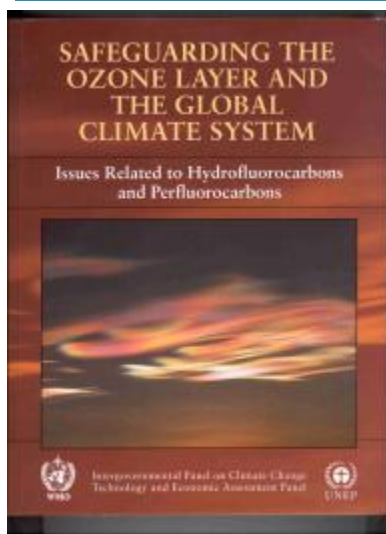
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## Climate Change: Challenges



- ◊ Political vs. Scientific agenda
- ◊ Will Governments take more action. (EU by 2010)?
- ◊ Regulatory challenges with HFA products
- ◊ A rapid phase out of CFC's has best impact on climate (Kyoto assumed MP would be fully enacted)
- ◊ Switch to DPIs possible with minimal cost except for salbutamol (\$ 1.7 billion)

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## Climate Change and HFA MDIs (I)

- ◊ HFAs 134a and 227ea are not ozone depleting substances so represented the environmental solution under the Montreal Protocol; however they are "potent" global warming gases
- ◊ HFAs included in international climate treaty (Kyoto Protocol) and many adopted/pending/proposed climate policy initiatives globally
  - § E.g. EU Framework Regulation on F-Gases and California climate regulations
  - § Policies, to date, have focused on larger "commercial" sectors (e.g., air-conditioning/refrigeration)
- ◊ Most existing policies are aimed at minimizing emissions, rather than phase-out of HFAs; however science and policy are evolving and pressure will likely increase for bans
- ◊ Europe has enacted legislation to ban HFAs in mobile air-conditioning within next 5 years
- ◊ Potential alternatives with lower global warming potential are under development for all HFA sectors, including HFA MDIs

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## Climate Change and HFA MDIs (II)

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- Ø Policy context is evolving; many “moving pieces”
- Ø Future international climate treaty is under negotiation
- Ø Politics in US will be impacted by presidential election
  - § Both candidates support action on climate change
- Ø Important for MDI manufacturers to engage in policy debate
  - § International Pharmaceutical Aerosol Consortium (IPAC – [www.ipacmdi.com](http://www.ipacmdi.com)) has closely monitored developments and worked to educate policymakers on unique patient health implications associated with MDIs
  - § IPAC has recently convened working group to evaluate safety and other performance characteristics of novel medical propellants

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