The Montreal Protocol and the Phase-out of CFC-based Metered Dose Inhalers

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The Montreal Protocol

- Binding international agreement for the preservation and recovery of the ozone layer
- The Protocol establishes commitments for the Parties to phase-out ozone depleting substances (ODS)
- Among international environmental agreements only the Montreal Protocol has achieved universal ratification
- First international agreement that applied the precautionary principle
- The first agreement where financial cooperation between developed and developing countries has been demonstrated successful (common but differentiated responsibilities)
- Several amendments and adjustments to reflect scientific progress and to add further commitments
The Montreal Protocol

- **Objective:** protecting the ozone layer by phasing out the production and consumption of Ozone Depleting Substances.
  - Production of ODS
  - Refrigerants
  - Foam-blowing agents
  - Aerosols
  - Solvents
  - Fumigants

- **Funding**
  - Multilateral Fund
  - Bilateral Funding (Italy, Japan, Spain, Canada, Sweden)

- **Implementing Agencies**
  - UNIDO
  - UNEP
  - UNDP
  - World Bank
  - Bilateral Agencies: GTZ (Germany), Environment Canada, Agence Française de Developpement, METI (Japan), US Environmental Protection Agency, Swedish Environmental Protection Agency.
Chemicals listed in the Montreal Protocol

- Chlorofluorocarbons (CFCs)
- Halons
- Carbontetrachloride
- 1,1,1-Trichloroethane
- Methyl bromide
- Hydrobromofluorocarbons (HBFC)
- Hydrochlorofluorocarbons (HCFC)
Reduction and phase-out plans

- CFCs, carbontetrachloride and halons – complete phase-out of production and consumption by 2010
  - Exemptions (essential uses, i.e. metered dose inhalers and laboratory uses) have to be approved by the Meeting of the Parties to the Montreal Protocol
- Methyl bromide and trichloroethane – complete phase-out by 2015
- Phase-out schedule for HCFCs:
  - 2009-2010 – Baseline
  - 2013 – Freeze
  - 2015 – 10% reduction
  - 2020 – 35% reduction
  - 2025 – 67.5% reduction
  - 2030 – 97.5% reduction
  - 2040 – Total Phase-out
Typical Phase-down scenario during the past decade (example CFCs)
Essential use exemptions:

**Estimated CFC usage for MDI manufacture by nominating Parties, 2010-2014**

<table>
<thead>
<tr>
<th>Country</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>11</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>19.0</td>
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<tr>
<td>Argentina</td>
<td>178</td>
<td>107</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>288.2</td>
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<tr>
<td>Bangladesh</td>
<td>156.7</td>
<td>57</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>240.7</td>
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<tr>
<td>China</td>
<td>652.0</td>
<td>741.2</td>
<td>650</td>
<td>400</td>
<td>345</td>
<td>2,788.2</td>
</tr>
<tr>
<td>Egypt</td>
<td>227.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>227.4</td>
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<tr>
<td>India</td>
<td>344</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>343.6</td>
</tr>
<tr>
<td>Iran</td>
<td>2.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.2</td>
</tr>
<tr>
<td>Mexico</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.0</td>
</tr>
<tr>
<td>Pakistan</td>
<td>35</td>
<td>39.6</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>84.5</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>212</td>
<td>212</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>454.0</td>
</tr>
<tr>
<td>Syria</td>
<td>44.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>44.7</td>
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<tr>
<td>United States</td>
<td>92.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>92.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1,954.6</td>
<td>1,165.0</td>
<td>720.0</td>
<td>400.0</td>
<td>345.0</td>
<td>4,584.5</td>
</tr>
</tbody>
</table>
Replacement of CFCs in metered dose inhalers (MDIs)

• Purpose of MDIs
  – Treatment of asthma and chronic obstructive pulmonary disease

• Alternative technologies
  – Hydrofluorocarbons (HFCs)
  – Dry powder inhalers
  – Nebulisers and soft mist inhalers

All alternatives are “ozone friendly”, the ozone depleting potential (ODP) is zero!
# Evaluation of alternative technologies

<table>
<thead>
<tr>
<th>Type of inhaler</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metered dose inhalers (MDI)</strong></td>
<td>- Simple actuation system</td>
<td>- Dosage accuracy may be dependant on the formulation</td>
</tr>
<tr>
<td></td>
<td>- Reliable accurate dose</td>
<td>- Coordination between actuation and breathing required (except breath-actuated systems)</td>
</tr>
<tr>
<td></td>
<td>- Compact and portable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Easy to use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Economically viable solution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Good resistance to moisture</td>
<td></td>
</tr>
<tr>
<td><strong>Dry Power Inhalers (DPI)</strong></td>
<td>- No propellant used</td>
<td>- Drug release depends on the breathing capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Inhaled fraction is reduced if patient breathes into the system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Relatively expensive</td>
</tr>
<tr>
<td><strong>Nebulizers</strong></td>
<td>- No special breathing coordination required</td>
<td>- Not portable</td>
</tr>
<tr>
<td></td>
<td>- Useful for new or rarely used drugs</td>
<td>- Power supply necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Operation takes a long time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Requires preservatives to reduce risk of bacterial contamination</td>
</tr>
</tbody>
</table>

**Selected technology**
Other environmental considerations, in particular climate impact

Carbon footprints of respiratory devices and treatment methods

<table>
<thead>
<tr>
<th>Respiratory devices and treatment methods</th>
<th>Carbon footprint Per 200 doses (Kilograms CO$_2$eq.)</th>
<th>Carbon footprint Per 2 puffs (Grams CO$_2$eq.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC MDI</td>
<td>150-200</td>
<td>1,500-2,000</td>
</tr>
<tr>
<td>HFC-134a MDI</td>
<td>20-30</td>
<td>200-300</td>
</tr>
<tr>
<td>HFC-227 MDI</td>
<td>60-80</td>
<td>600-800</td>
</tr>
<tr>
<td>Dry Powder Inhaler</td>
<td>1.5-6.0</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Tablets</td>
<td>1.5-5.0</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

Source: MTOC assessment report 2010
Estimated relative carbon dioxide emissions of everyday items compared with asthma inhalers

Source: MTOC assessment report 2010
General objectives of the project

- Phase-out of chlorofluorocarbons (CFCs) in the manufacture of metered dose inhalers (MDIs)
- Conversion of production facilities to CFC-free technology
- Technology transfer
- Introduction of more advanced pharmaceutical products
MDI market in Mexico

- **National Companies**
  - Eligible to receive funding from the Multilateral Fund (MLF)
  - Laboratorios Salus

- **Multi-national Companies**
  - Not eligible for MLF support
  - Glaxo-Smithkline
  - Ivax
  - Astra – Zeneca
  - Boehringer Ingelheim
Outline of the strategy - principles

• Patients' health has highest priority in the transition period. The patient is at the core of the transition.
• All parties involved should actively manage the transition to ensure the patient's access to needed treatments is not interrupted.
• Transparency and efficacy in the authorization and follow-up of new products in the market is required.
• Awareness activities with the active participation of all stakeholders, health professionals, Ministries, pharmaceutical companies, and the community.
Criteria to consider for the selection of alternatives (1)

• Specific needs of the patients
• Relatively high incidence of asthma, allergic respiratory diseases, and chronic obstructive pulmonary disease (COPD) in all ages of the Mexican population
• Familiarity of patients with the existing MDI design as a device for delivery of the required medication
• Patient acceptance of CFC-free MDIs
• Resistance of the market to accept a significant increase in the cost of treating patients
Criteria to consider for the selection of alternatives (2)

- The maturity and established commercialization of alternative MDI technology
- Price of an alternative propellant, product availability, and cost-effectiveness of the new MDI formulation
- Properties CFC-MDI products manufactured by Laboratorios Salus
- Existing experience and skills of the personnel
Products converted (by active ingredient)

- Salbutamol registered 1st April 2011
- Beclamethasone registration submitted
Thank you!