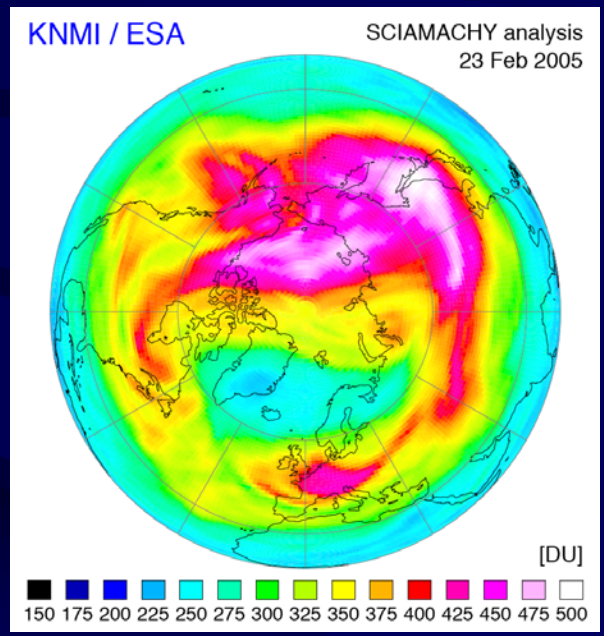
FDA's NPRM on Removing the Essential-use Designations of 7 Marketed "Moieties"



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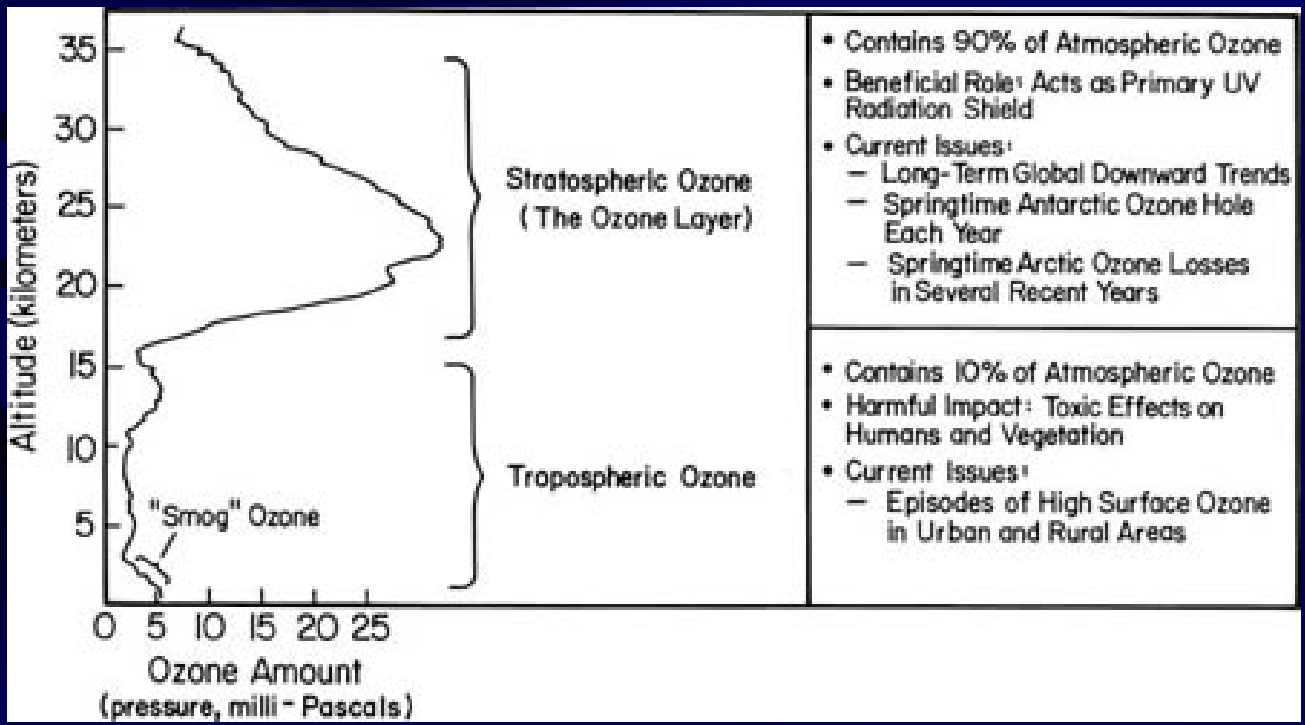
Overview

- General background on the issue of ozone depletion
- Introduction to relevant decisions of the Montreal Protocol, U.S. Laws, and FDA and EPA regulations
- Overview of the “7 moiety” proposed rule

General Background on Ozone

The earth's ozone layer is a region of relatively higher ozone concentrations in the stratosphere



General Background on Ozone

- This “layer” reduces the amount of ultraviolet radiation (UV-B) reaching the surface from sunlight
- As a result of ozone loss, UV-B has increased at the earth’s surface, leading to increases in skin cancers (melanoma and non-melanoma), cataracts, and impairing immunity
- Other deleterious effects on the environment, as well as accelerated effects of sun exposure on man-made substances (like plastics)

Legal, Regulatory History

- Development of U.S. Statutory law, FDA and EPA regulations, and the Montreal Protocol have proceeded in overlapping timeframes, so these topics will overlap in this part of the presentation

History of the Montreal Protocol and 21 CFR 2.125

- 1974- Work by Molina and Rowland published tying ozone depletion to stratospheric chlorine from degraded CFCs[1]
- At that time, use of CFCs was widespread in the US
  - Refrigerators, A/C, foams, and many consumer and medical aerosol products, including MDIs

1 – Nature, 1974; vol 249:810-812

History of the Montreal Protocol and 21 CFR 2.125

- 1978 – In response to growing evidence of CFCs harming the ozone layer, CFCs were generally banned in aerosols in U.S. by EPA *(e.g. spray paint)*
- FDA published 21 CFR 2.125 banning use of CFCs in FDA regulated products (*e.g. hairspray)* with essential exemptions

History of the Montreal Protocol and 21 CFR 2.125

- 1987 - 27 nations (including U.S.) initiate a global ozone treaty in Montreal, known as the "Montreal Protocol on Substances that Deplete the Ozone Layer"
    - hereafter referred to as the "MP"
- The MP now has over 190 signatory Parties (countries) and is regarded as the model for successful, global environmental treaties

History of the Montreal Protocol and 21 CFR 2.125

- Original phase-out of CFCs slated for 2000 (*London - 1990*)
- Phase-out of CFCs is moved up to end of 1995 (*Copenhagen - 1992*) due to evidence of increasing ozone depletion, especially over the Antarctic (ozone "hole")
- While depletion is most prominent over southern hemisphere, the depletion is global
- MP controls *many* ozone depleting substances (ODS): CFCs, but also Halons, HCFCs, methyl bromide, carbon tetrachloride,…

History of the Montreal Protocol and 21 CFR 2.125

- As of January 1st, 1996, all use of new CFCs banned in industrial countries; rest of the world in 2010
- MDIs for asthma and COPD temporarily exempted under essential use process
- Nominations for essential uses reviewed annually (e.g., in New Delhi in 2006, the Parties reviewed 2008 nominations)

History of the Montreal Protocol and 21 CFR 2.125

MP has stipulated the following:

- **Decision IV/25** - All essential uses of CFCs based on products necessary for public health without adequate alternatives (technically & economically) - 'macroscopic' determination of essentiality (i.e., general use of CFCs in MDIs for asthma and COPD)

History of the Montreal Protocol and 21 CFR 2.125

MP has stipulated the following:

- **Decision XII/2** - Any product approved after Dec. 2000 must individually meet IV/25
  - Product-centered determination of essentiality that essentially precluded new CFC generic MDIs or other new CFC products unless the new product individually met or exceeded the stringent requirement of IV/25

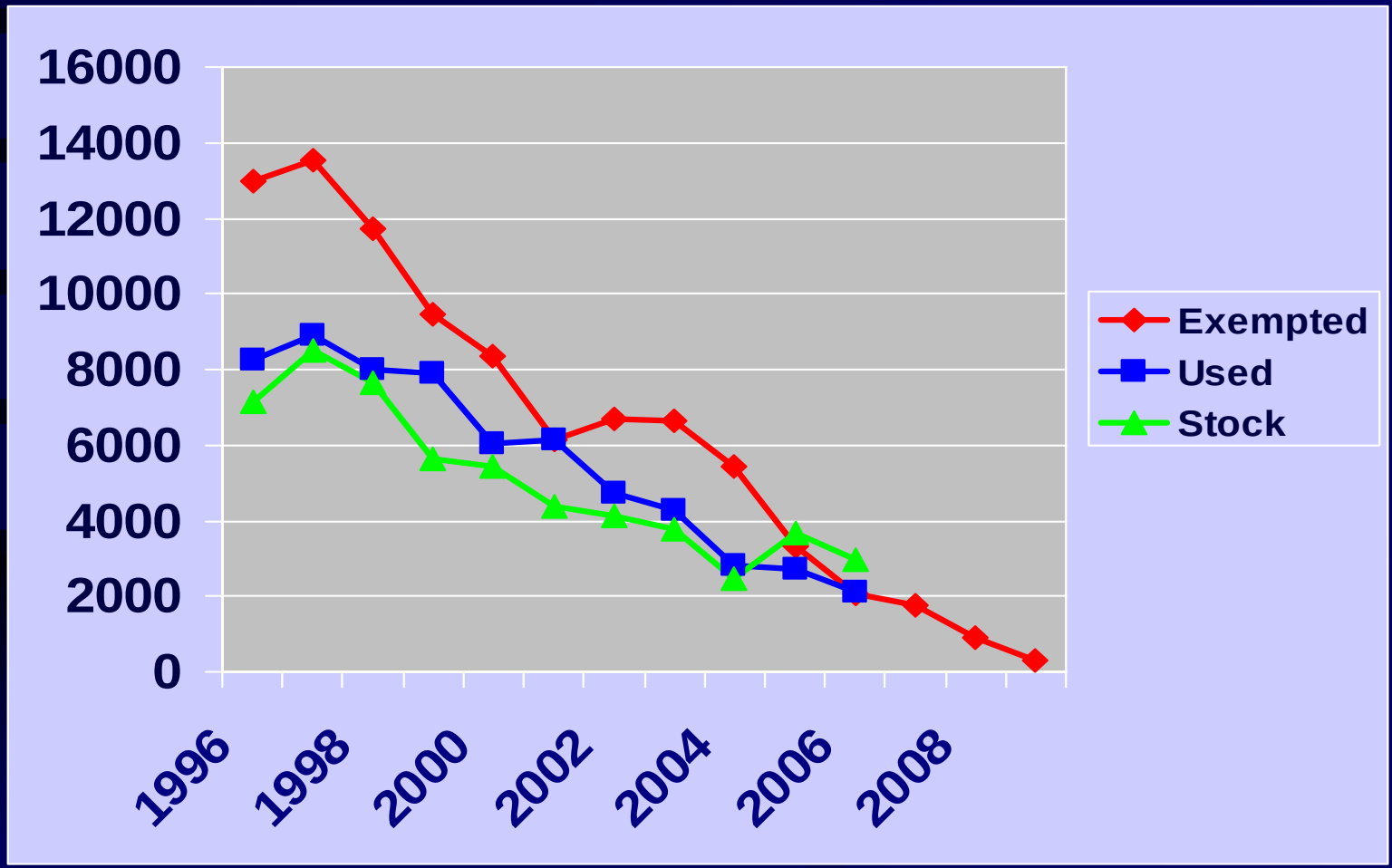
History of the Montreal Protocol and 21 CFR 2.125

MP has stipulated the following:

- **Decision XVII/5** - that Parties [that are developed countries] submit a date to the Ozone Secretariat prior to the 18th Meeting of the Parties by which time a regulation or regulations to determine the non-essentiality of the vast majority of CFCs for MDIs where the active ingredient is not solely albuterol will have been proposed.

Trends in Global CFC essential uses:

(Tonnes of CFCs) TEAP Update Report 2007



History of the Montreal Protocol and 21 CFR 2.125

- Clean Air Act amendments of 1990 harmonized U.S. law with the MP
- Implementing EPA regulations refer to FDA ‘s regulations at 21 CFR 2.125 for definition of medical essentiality

History of the Montreal Protocol and 21 CFR 2.125

- In 1978 § 2.125 was published stating that regulated products containing CFCs were misbranded/adulterated unless deemed essential
- "Essential" based on:
  - No technically feasible alternatives
  - Provides substantial (health, public, or environmental) benefit
  - Release of CFC small, or justified given benefit

History of the Montreal Protocol and 21 CFR 2.125

- 1978 FDA rule had no mechanism to determine when uses are no longer essential and to delist them (only mechanisms to add new classes/drugs to the list)
- Many important drugs not listed separately, but in broad classes
  - e.g., "Adrenergic bronchodilators for human use…."
- Final Rule amending § 2.125 published on July 24, 2002, and went into effect January 20, 2003

History of the Montreal Protocol and 21 CFR 2.125

2002 revisions to § 2.125:

- Listed individual moieties as essential uses of ozone depleting substances (ODS) in § 2.125(e) rather than classes (e.g., albuterol is listed, rather than all adrenergic bronchodilators)
- Added a higher hurdle for IND use of ODSs and to raise the bar for new listings of essential uses
- Lists criteria for determining individual uses are no longer essential

History of the Montreal Protocol and 21 CFR 2.125

- Since a moiety-by-moiety approach does not effectively address drugs not being reformulated, the 2002 final rule stated that:

  [FDA] has therefore revised § 2.125(g)(2) to permit the agency to undertake an evaluation of all ODS products after January 1, 2005, not just those products without a non-ODS replacement.

Moieties currently listed as essential with no marketed direct alternative product:

1. β -agonists*
   - Epinephrine
   - metaproterenol (Alupent)
   - pirbuterol (Maxair)
2. Inhaled Corticosteroids
   - flunisolide (Aerobid),
   - triamcinolone (Azmacort)
3. Cromones
   - cromolyn (Intal)
   - nedocromil (Tilade)
4. β agonist /Anticholinergic combination
   - albuterol/ipratropium (Combivent)

Teal denotes those products addressed by the proposed rule

History of the Montreal Protocol and 21 CFR 2.125

- Beginning in 2005, FDA may convene public meetings (i.e., PADAC meetings or NDAC/PADAC in the case of epinephrine) to discuss those products still listed as essential to determine if changes in the medical practice and availability of alternatives render these products as no longer essential

Procedure for Removal

- On July 14th, 2005, the PADAC met to discuss all remaining uses of CFCs in MDIs (with the exception of epinephrine)
- Considerations and results from PADAC discussed below by class of agents

Procedure for Removal

Found in 21 CFR §2.125(g)(2)

- ✓Consult Advisory Committee
- ✓Propose Rule
- ✓Open Public Meeting
- ❑Final Rule (responsive to public comments)

Intro: Criteria for Removal

Found in § 2.125(g)(2)

(which cross refers to §2.125(f))

For Moieties Where There are No Direct Alternatives:

- ✓ No technical barriers to reformulation
- ✓ No otherwise unavailable important public health benefit
- ✓ Release of ODSs is cumulatively significant and not warranted by public health benefit

Meeting *any* one criterion is sufficient to remove essential use

Technical Barriers

Numerous moieties in various therapeutic classes have been formulated as HFA MDIS or dry powder inhalers (DPIs)

- ✓No over-riding technical barriers to reformulating any of the CFC MDIs in the NPRM

Release of ODSs

CFCs for MDIs are the last CFCs made in developed countries and the US and other countries have committed to full cessation of CFC use

- ✓All MDIs in NPRM release “cumulatively significant amount” of ODSs
- ✓Release not justified by public health benefit for the 7 marketed moieties

Proposed Effective Dates

- Current draft has 12/31/09 as date
- Proposed effective date is 1 year after effective date of finalized albuterol rule
- Date would allow time for ramp up of alternative production (including albuterol) & sale of remaining supply of affected products
  - Albuterol HFA demand could rise 33%
- NPRM mentions possibility of different dates for different drugs

“Moieties” subject to the relevant proposed rulemaking

1. Flunisolide
2. Triamcinolone
3. Metaproterenol
4. Pirbuterol
5. Cromolyn
6. Nedocromil
7. Albuterol and Ipratropium in combination (Combivent)

Flunisolide & Triamcinolone

Aerobid and Azmacort

- Two of several largely interchangeable corticosteroids

Potential non-CFC Therapeutic Alternatives:

- Beclomethasone dipropionate MDI (QVAR),
- Budesonide DPI (Pulmicort Turbuhaler),
- Fluticasone propionate MDI (Flovent HFA)
- Mometasone furoate DPI (Asmanex Twisthaler)

Flunisolide & Triamcinolone

Aerobid and Azmacort

- FDA has approved a Flunisolde HFA MDI, but it is not yet marketed.
- Summary of PADAC discussion:
  - No significant debate and general agreement that the standard of "*No otherwise unavailable important public health benefit*" was not met

Metaproterenol & Pirbuterol

Alupent and Maxair

Older and less often prescribed short-acting beta–agonists for bronchospasm

Maxair is only “autohaler” MDI in U.S.

Metaproterenol & Pirbuterol

Proposed Therapeutic Alternatives:

- Albuterol sulfate HFA MDIs
  - Proair HFA
  - Proventil HFA
  - Ventolin HFA
- Levalbuterol tartrate HFA MDI
  - Xoponex HFA

Metaproterenol & Pirbuterol

Conclusion at PADAC Meeting

- Each was discussed separately
- No significant debate and general agreement that both are non-essential

Cromolyn & Nedocromil

Intal and Tilade, respectively

- *Very similar, long acting control drugs*

Proposed alternatives for most users:

- *Corticosteroid inhaled products*
- *Oral agents*

Proposed alternative for “niche” populations (if these populations exists):

- *Albuterol HFA MDIs for E.I.B.*
- *Cromolyn in portable nebulizer*

Cromolyn & Nedocromil

PADAC Meeting

- Agreement that corticosteroids are generally better alternatives (*e.g., CAMP study*)
- Debate on need for Cromolyn for “niche” population (not well characterized)
- No support for Nedocromil as essential

Albuterol & Ipratropium in combination

Combivent

- Combination of two different bronchodilators with differing mechanisms:
  - *Albuterol and ipratropium*
- Indication is limited to COPD (not asthma)
- Largely older / geriatric patients

Albuterol & Ipratropium in combination

Alternatives:

- Ipratropium HFA MDI (Atrovent) used with an Albuterol HFA MDI

Albuterol & Ipratropium in combination

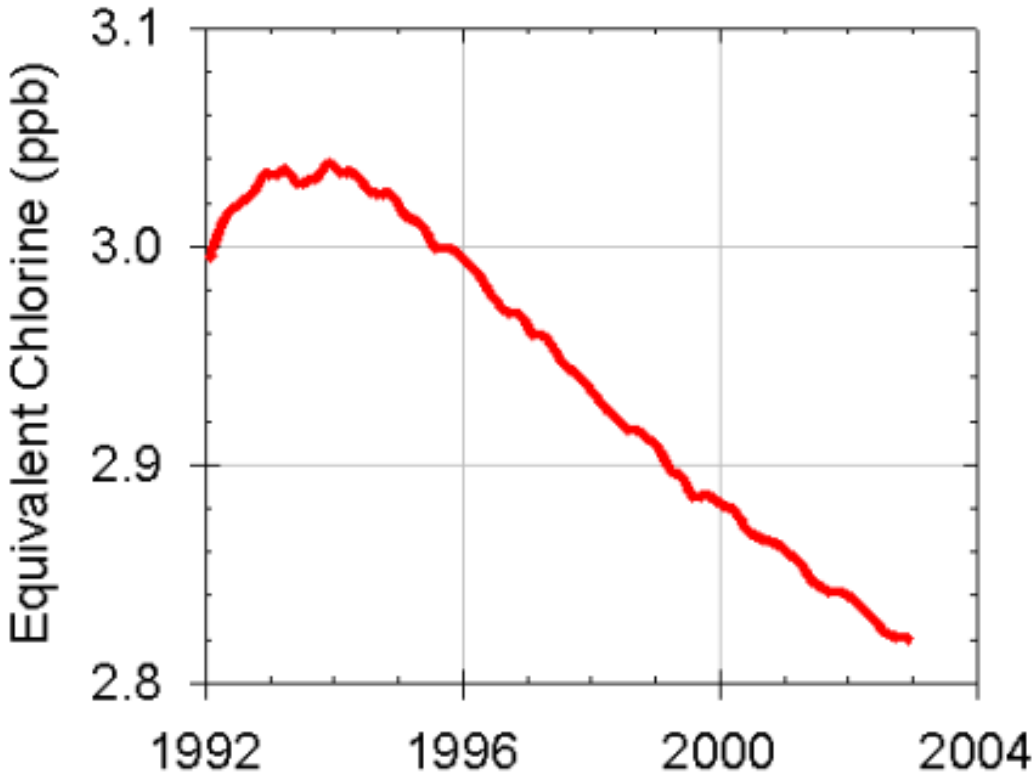
Issues:

- *As a combination product, reportedly may increase compliance*
- *That raises the question: Is there a medical benefit from increased compliance for a symptom-relieving drug?*
- *Reformulation has been attempted and is on-going*
- *To date, reformulation has proven technically challenging (perhaps related to 2 active ingredients)*

Albuterol & Ipratropium in combination

Opinion at the PADAC meeting was evenly divided on whether Combivent provided an "*otherwise unavailable important public health benefit*"

Ozone-Destroying CFCs are Declining
Ozone Layer Recovery expected by 2050



Source: NOAA

Comment Period

Graceway Pharmaceuticals has submitted a request for a 90-day extension of the comment period on the 7-moiety NPRM.

FDA has determined that a 30-day extension is appropriate.

The comment period will close on September 10, 2007

Please check http://www.accessdata.fda.gov/scripts/oc/ohrms/advdisplay.cfm for confirmation

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