

August 13, 2004

**Re: FDA Docket Number 2003P-0029  
Citizen Petition Requesting FDA Initiate a Rulemaking to Consider Whether CFC  
Albuterol MDIs are an Essential Use of Ozone-Depleting Substances**

Dear Sir or Madam,

INEOS Fluor is a company that since 1988 has taken a leading role in the development and production of the hydrofluoroalkane (HFA) replacements for the chlorofluorocarbons (CFCs), and is a supplier of both CFC and HFA propellants to the metered dose inhaler (MDI) industry. It is currently supplying HFA 134a as the propellant for an HFA containing albuterol MDI which has been approved for use in the United States. INEOS Fluor is also the largest supplier of HFA 134a to the global MDI industry.

As a supplier to the pharmaceutical industry of both the historically used CFC propellants, and the replacement HFA propellants, INEOS Fluor is filing comments to contribute to and assist in the current deliberations on the proposed rule to amend the *Use of Ozone Depleting Substances; Removal of Essential Use Designations* regulation.

## **1 History of INEOS Fluor Propellant Supply**

INEOS Fluor was originally part of Imperial Chemical Industries (ICI) and operated as ICI Klea. Following acquisition by the INEOS Group in 2001, ICI Klea became INEOS Fluor. In 1990 ICI operated the largest CFC 11/12 production facilities in Europe, supplying a range of applications with these products, including medical aerosols. In addition ICI owned and operated plants producing carbon tetrachloride (CTC), the feedstock for the CFC 11/12 production plant. In our experience access to high quality CTC was critical to the quality of the CFC products since the impurities in the CTC had a direct impact on the impurity profile of the end CFC product. Carbon tetrachloride quality was therefore critical to meeting the required specifications for CFCs in pharmaceutical, specifically MDI, use.

INEOS Fluor/ICI closed its own CFC assets over ten years ago, but has continued to obtain, and qualify for pharmaceutical use, CFCs from two other European producers. This continued involvement in the supply of CFC propellants was part of our



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commitment to support a smooth transition to HFA containing products and gives INEOS Fluor a current perspective on the pharmaceutical CFC supply situation.

In 1990 ICI commissioned the world's first commercial scale HFA 134a production facility (located in the United Kingdom) and subsequently invested in major HFA 134a production facilities in the United States (1992) and in Japan (1993). INEOS Fluor is now the world's leading industrial grade HFA 134a manufacturer.

In 1995 ICI commissioned a dedicated, validated purification facility designed to purify industrial grade HFA 134a under cGMP controls to a pharmaceutical grade of material. This plant was built to meet the requirements of the developing HFA MDI market. This market has steadily grown with the phase out of CFCs in MDIs in many countries, including European Union Member States, Japan and Australia. INEOS Fluor is one of the largest global suppliers of HFA 134a to the MDI market and has invested in facilities and infrastructure to support the MDI manufacturers as they convert to the use of HFA propellants.

It should be noted that this purification plant approach has been adopted by other manufacturers of medical grade HFAs. A tightly controlled, purpose designed, dedicated purification asset gives a degree of assurance and control that is hard to achieve by other means. In contrast, CFCs for pharmaceutical use tend to be produced from a normal industrial grade CFC plant, albeit with additional controls in place.

## **2 Security of Future CFC and HFA Propellant Supply**

In order to maintain propellant supplies to the MDI industry INEOS Fluor has worked with other fluorochemical producers to source CFC 11 and CFC 12, and to ensure that they are manufactured and controlled to the requirements of the pharmaceutical industry. Within both Europe and the United States the Montreal Protocol has had the result of reducing the CFC 11/12 plant network from around ten plants in 1990 to two in 2004. Both remaining plants are located in Europe one of which, due to close by the end of 2005, currently supplies the US with CFCs for MDI manufacture.

Decreased sales volumes have resulted in the manufacture of small volumes of CFCs in campaign operations, or on swing (multi-product) plants. This mode of production carries risks not seen in dedicated facilities operated for steady production rates. The risks arise from the potential to contaminate the product with a previously manufactured different product, or its impurities.

The commercial risks of reduced operational loading of any asset is that the fixed cost base remains and this must be distributed over the reducing volume of product. The fixed cost base, coupled with the need to maintain required standards, act as a significant upward cost pressure on regulated products as they near end of life.

In contrast to CFCs there has been an increasing demand for industrial and pharmaceutical grades of HFA 134a. This demand has created significant investment in new and dedicated facilities that only manufacture single products and are operated in a steady and consistent operating mode. This minimizes the potential quality risks that may be associated with swing or campaign operation. Moreover, the required maintenance and support costs to keep the plant in a good 'state of the art' operating condition can be commercially justified.

Investment in HFA 134a technology has been made by several companies resulting in there being multiple industrial grade HFA 134a plants, that have many years of operation ahead. In addition, there are currently three manufacturers that have commissioned pharmaceutical grade HFA 134a purification plants; to date two of these companies (INEOS Fluor and one other) have their HFA 134a in albuterol MDIs that have been approved for use in the United States. In terms of installed capacity there is significant over-capacity. INEOS Fluor has sufficient industrial and pharmaceutical production to meet the forecast global MDI manufacturing needs. In brief the pharmaceutical grade HFA 134a manufacturing network can be considered as secure, established and modern.

### **3 Security of Feedstock Supply**

HFA 134a is produced by the reaction of trichloroethene with hydrogen fluoride, or by the reaction of perchloroethene with hydrogen fluoride with subsequent hydrogenation. Neither trichloroethene nor perchloroethene is controlled by the Montreal Protocol; they have many industrial uses and are widely available. In common with most of the other HFA manufacturing companies, INEOS has its own internal source of these materials. In contrast, the key raw material from which CFCs are made, carbon tetrachloride (CTC), is a substance which is regulated under the Montreal Protocol. Historically, CTC was used in a range of industrial applications as a solvent, and as a feedstock for CFC 11/12 manufacture. The Montreal Protocol has banned the use of CTC as a solvent and is eliminating its use as a feedstock for the manufacture of CFCs. This raises the prospect that regardless of any approval to operate limited CFC production in the future, there may be increasing difficulty in obtaining CTC of a suitable quality for use in the manufacture of pharmaceutical grade CFCs.

### **4 Summary**

HFA 134a production technology is fully supported by several major companies across the world. The ready availability of HFA 134a and its use in albuterol MDIs has enabled many developed countries to phase out the use of CFCs in albuterol products. The level of investment in HFA 134a production assets has created a global infrastructure for the supply of both industrial and pharmaceutical grades of product. In contrast CFCs are carrying increasing supply risk due to the reduced number of production plants and regulation of key feed materials.

INEOS Fluor, as a leading pharmaceutical grade HFA 134a supplier has successfully supplied European based MDI manufacturing facilities since 1997, and US based MDI manufacturing facilities since 2001. From a viewpoint of ensuring that albuterol MDIs continue to be available to the US population, it seems clear that the proposed rule to amend the *Use of Ozone Depleting Substances; Removal of Essential Use Designations* regulation can only be beneficial, in that it will ensure that the key propellant gases are provided from an established and secure supply base.

Regards,

A handwritten signature in black ink, appearing to read "Peter M. Geosits". The signature is written in a cursive, somewhat stylized font.

Peter M. Geosits  
Americas Commercial Director  
INEOS Fluor Americas