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Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Docket No. 2003P-0029
Use of Ozone-Depleting Substances;
Removal of Essential-Use Designation**

Dear Sir/Madam:

IVAX Research hereby submits the enclosed comments to Docket Number 2003P-0029 on the Use of Ozone-Depleting Substances; Removal of Essential-Use Designation.

As stated in our presentation during the June 10, CDER Pulmonary-Allergy Drugs Advisory Committee Meeting, IVAX supports the Food and Drug Administration ("FDA") issuance of a final rule that removes albuterol MDIs from its list of essential uses no later than December 31, 2005.

IVAX Research is pleased to say that our Albuterol Sulfate HFA Metered Dose Inhaler (MDI) was approved on October 29, 2004 and is currently being marketed. This is the third Albuterol Sulfate HFA MDI to reach the US market.

The purpose of this docket entry is to clarify IVAX commitments to production capacity, cost and access programs for patients for our Albuterol Sulfate HFA MDI. These commitments are described below.

IVAX Corporation

IVAX Research is a wholly-owned subsidiary of IVAX Corporation ("IVAX"), IVAX is a multinational company engaged in the research, development, manufacturing and marketing of branded and generic pharmaceuticals and veterinary products in the U.S. and internationally. IVAX has two primary missions: to provide high-quality pharmaceuticals that improve the health of its customers, and to operate as an ethical and honorable corporate citizen. Toward that end, IVAX was one of the first pharmaceutical companies to voluntarily market CFC-free products. IVAX is committed to ensuring that pharmaceutical products do not unnecessarily compromise environmental quality or needlessly deplete the ozone layer.

IVAX develops and markets respiratory products, particularly those that treat asthma. In the United States, IVAX recently filed new drug applications (NDAs) for a CFC-free formulation of albuterol in a standard metered-dose inhaler (“MDI”) and the same CFC-free formulation of albuterol in its Easi-Breathe breath-activated inhaler. As stated above, our HFA albuterol in an MDI was approved on October 29, 2004 and is currently being marketed. IVAX strives to advance the treatment of asthma through its dedication to improving the delivery of rescue medications that are essential to those suffering with the disease.

Background

Asthma

Asthma is a chronic disease that affects the breathing passages of the lungs, obstructing exhaled air. Its cause is unknown. Asthma attacks come on suddenly or may occur slowly over several days or hours. Because it causes obstruction, or resistance, asthma is considered a chronic obstructive pulmonary disease (“COPD”). Although asthma cannot be cured, it can be controlled with proper medication, prevention of attack triggers, and patient cooperation.

More than 17 million people are affected by asthma in the United States, over a third of whom are children. Asthma affects people of all ages and races, and is the most common chronic disease in children. Asthma costs the U.S. economy nearly \$13 billion per year, is one of the most common reason for emergency department visits and hospitalization, and is responsible for 5000 deaths per year in this country alone.

When an asthma attack occurs, a “rescue medication” should be administered. Rescue medications are for short-term control of attacks. The most commonly used rescue medications are short-acting beta-antagonists, of which albuterol (Proventil, Ventolin) is the most frequently used. Rescue medicines are administered through MDIs that utilize an inactive ingredient which serves as a propellant to move the beta-antagonist far into the breathing passages of the patient. Propellants may be chlorofluorocarbons (“CFCs”) or hydrofluroalkanes (“HFAs”) which contain no CFCs.

Availability of Pharmaceutical Products for the Treatment of Asthma

Albuterol MDIs were first approved for use in 1981 when the NDAs for Ventolin and Proventil were approved. In 1995, IVAX became the first company to get a generic Albuterol MDI approved. The CFCs used historically and today in MDIs are CFC-11 and CFC-12. The entire supply of CFC-11 and CFC-12 for use in MDIs prescribed in the United States is manufactured in one plant in Weert, the Netherlands. MDIs using non-ozone depleting substances were approved for use in 1996 and 2001. Proventil HFA and Ventolin HFA were introduced into the U.S. market in 1996 and 2002, respectively.

Production Capacity

IVAX, as well as its two leading competitors Schering-Plough and GlaxoSmithKline, believes that the industry is more than capable of meeting United States demand by December 2005

Certain Availability of Sufficient Supply of CFC-Free Albuterol MDIs by December 2005

The current annual United States demand for albuterol MDIs is 47 million units.¹ Schering-Plough, which manufactures Proventil HFA, a CFC-free albuterol MDI, predicted at the June 10, 2004 stakeholders meeting that it could produce 30 million units for the United States market within 12-18 months of the announcement of the final rule. It urged the agency to issue a final rule quickly so that it might begin ramping up to meet patient needs by December 2005. Similarly, GlaxoSmithKline (“GSK”) stated at the June 10th stakeholders meeting that it currently had capacity to produce 15 million units of Ventolin HFA, its CFC-free albuterol MDI, and we understand that it informed FDA in a recent letter that it could supply 30 million units by December 2005. These two manufacturers of currently-approved CFC-free albuterol MDIs predict sufficient capacity for United States consumption by December 2005. IVAX believes that it will have the capacity to supply 50-60 million units by the end of 2005, nearly doubling the availability (and likely causing downward pressure on the price) of CFC-free albuterol MDIs.²

FDA concluded that “capacity to produce adequate supplies of non-[ozone depleting substance] albuterol MDIs could be in place no sooner than 12 months after publication in the Federal Register of any final rule based on this proposed rule.” 69 Fed. Reg. 33606. With two producers of non-CFC albuterol MDIs, this conclusion is accurate. With the recent addition of IVAX’ CFC-free albuterol MDI, twelve months would be the outside, rather than the soonest, date for meeting the needs of asthma patients in the United States.

Questionable Availability of CFCs for Continued Production of Ozone-Depleting MDIs

By contrast, there is a reasonable question as to whether stable and secure supplies of CFC propellants will continue to be available. In its August 13, 2004, comments to this docket, INEOS Flour, which is a worldwide supplier of both CFC and

¹ Comments submitted on August 13, 2004, to this docket by National Economics Research Associates.

² We are also aware that other companies with products either in the market place or pending approval will contribute toward the market need.

non-CFC albuterol MDI propellants, stated that it anticipates a sharp decrease in the availability of CFC in the upcoming years.

The main producer of pharmaceutical grade CFCs used in ozone-depleting MDIs in the United States is Honeywell. Currently, the production occurs entirely in the Netherlands at a plant in Weert. The government of the Netherlands notified Honeywell that no further production may occur after 2005. Absent the ability to secure another production site, the availability of CFCs for use in MDIs after December 2005 is in doubt.

According to Honeywell, production of CFCs will move to the United States and occur in its Baton Rouge, Louisiana, plant. In its comments to this docket, Honeywell asserted its belief that, under applicable law, it may “recommence” production of pharmaceutical grade CFC-11 and CFC-12 because it has been issued production allowances by the Administrator of the Environmental Protection Agency (“EPA”) under the “essential use” exceptions to the Montreal Protocol. These allowances, however, are only effective while the United States has been granted an “essential use” exception to produce and use ozone depleting substances. At this time, CFC volumes have been issued for 2005 based on this “essential use” exemption. Although extension of the “essential use” exemption into 2006 is possible, CFC allocations already approved for 2006 are still subject to review by ATOC in April 2005 and are therefore not assured.

Additional concerns have been raised by the Stakeholders Group about the Honeywell Baton Rouge plant. Specifically, the Stakeholders note that questions have been raised about the facility and, in particular, whether CFC-11 has ever been produced at the site. The Parties to the Montreal Protocol will not approve any new capacity to produce CFCs and, if the Parties interpret CFC-11 production at the Baton Rouge plant to be new capacity, Honeywell may be barred from its production causing a significant drop in the availability of CFCs for albuterol MDIs. The Stakeholders Group also noted concerns regarding several serious safety violations that have occurred at the plant in the past eighteen months, including a fatality which caused a temporary closure of the plant. The ability to maintain an uninterrupted supply of medications to asthma patients may be thwarted if physicians and patients rely on Honeywell’s Baton Rouge plant as the sole source of pharmaceutical-grade CFCs.

FDA itself also noted concern that “there may be a disruption in supply of pharmaceutical-grade CFCs.” The uncertainty of the availability of an essential component in the CFC-containing albuterol MDIs provides further support for an earlier issuance of the final rule so that production of non-CFC albuterol MDIs will increase and any disruption in care for asthmatic patients can be avoided. There is no “wait and see” option to determine whether Honeywell will actually meet its production promises. If the final rule is not implemented in the near-term, triggering manufacturers to ramp up production of non-CFC albuterol MDIs, a severe shortage of rescue medication inhalers, similar to what we are now experiencing with respect to the flu vaccine, may occur. However, the ramifications may be far worse.

Cost

IVAX has set the price of our Albuterol Sulfate HFA MDI at a price below both that of Proventil HFA and Ventolin HFA. Our price is 20% below that of Proventil HFA, the market leader.

Elimination of Ozone-Depleting Inhalers Will Likely Cause a Reduction in the Price of MDIs

The adequate supply of CFC-free albuterol MDIs will not only ensure that no patient's health is jeopardized by the decision to ban ozone-depleting albuterol products by the end of 2005, but it will also ensure vibrant price competition in this highly competitive market. A number of stakeholders have raised concerns that prompt implementation of FDA's proposed ban on CFC-containing albuterol MDIs would pose economic hardships for patients. We do not believe this will be the case. The economic data suggest that, as production of CFC-free inhalers supplants their CFC counterparts, the same sorts of economies of scale and inter-product competition should force prices down approaching the current prices for generic CFC products. Moreover, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, dramatically restricts pricing of albuterol in the Medicare market and these constraints are likely to be adopted by private third-party payors as well.

As noted above, IVAX introduced its CFC-free albuterol MDI product into the market at a reduction to the then current market prices for the other two non-CFC products. It should also be expected that as volume of the HFA products increase, once the CFC products are removed from the market, greater demand and greater manufacturing efficiencies will result in further savings to the patient. IVAX has a long history of pricing drugs to reach those patient populations most in need of them. For example, QVAR, another of IVAX' respiratory products, is priced at a fraction of the competitive product prices. By encouraging price competition and through its own pricing policies, IVAX intends that CFC-free albuterol MDIs will be part of its tradition of successfully reaching patients with effective and affordable medications

Access Programs for Patients

IVAX will institute three types of access programs for patients through IVAX Laboratories. These three programs are described below:

Patient Assistance Program (PAP) – Coverage/Income Based

Through a recognized third party vendor, IVAX Laboratories will implement a patient assistance program on February 1, 2005. The goal of this program is to provide an easy to use patient assistance program which will deliver free medications to any resident (including non-citizens) of the United States, Puerto Rico and the U.S. Virgin Islands who is not covered by any prescription drug benefit and/or whose income level is not

sufficient to pay for prescription drugs. The HIPPA compliant program is designed in such a way that a patient can enroll via a 1-800 number, postal mail or fax. IVAX Laboratories has designed the program to ensure that the eligibility criterion is medium-to-low incomes households, thus expanding the reach to more patients. The patient's household income must be at or below 200% of the Federal Poverty level. However, initially, no proof of income will be required on behalf of the patient, making the enrollment process easier for patients in need of medication.

The hours of operation for this program will be from 9 a.m. to 6 p.m. EST Monday-Friday to ensure patient accessibility for both enrollment and customer service. Customers will be able to speak to a customer service representative. Medications will be distributed through all major retail pharmacies nationwide. The 1-800 number will service all patients and healthcare professionals, including physicians, nurses, physician assistants and pharmacists, should they have questions regarding any aspect of the program.

The following measures will be taken to ensure both patient eligibility and accessibility. The program will be promoted to every physician visited by the IVAX sales force including, Allergists, Pediatricians, Pulmonologists, ENTs and Primary Care physicians, many of whom are located in lower-income areas. Physicians will be given materials outlining the program and steps for enrollment. They will be encouraged to assist patients in enrolling in the IVAX PAP program through the designated 1-800 number. The IVAX Laboratories sales force will be informed about and trained on the details of this program during the month of February 2005.

As a final step to increase awareness, all participating pharmacies will receive a fax notification of this program during the last week of January 2005, further raising awareness of its availability.

As described above, IVAX Laboratories is taking all necessary measures to adequately promote the program and its elements to IVAX customer service employees, physicians and pharmacists to ensure all needy patients have adequate access to the IVAX PAP program.

Voucher/Sample Program

IVAX Laboratories is initiating a voucher/sample program to provide aid for covering the patients' cost of Albuterol Sulfate HFA MDIs. The program will be open to any resident (including non-citizens) of the United States who may not qualify for the IVAX PAP program outlined above. Through the IVAX Laboratories field sales force, vouchers will be distributed to healthcare professionals throughout the year. Healthcare professionals will in turn distribute these to their patients interested in switching to the HFA product. Vouchers will be valid for one free inhaler of Albuterol HFA, redeemable at all major pharmacy networks nationwide.

IVAX Laboratories intends to distribute between half a million and one million vouchers per year until the transition date, after which up to two million vouchers per year will be distributed. IVAX Laboratories will track and analyze utilization of this voucher program.

This program will begin February 2005 and extend through at least December 31, 2007. However, should the FDA choose an effective date for the removal of the essential-use designation significantly later than December 31, 2005, IVAX may re-evaluate the timing and scope of this program based on market conditions.

Chronic Disease Fund

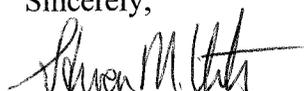
In addition to the two programs described above, IVAX Laboratories has made a donation to the Chronic Disease Fund (CDF) to provide co-pay assistance based on need for the under-insured. If a patient's income level is such that they do not qualify for the PAP and is in need of co-pay assistance the CDF will work with the patients to ensure access to Albuterol HFA. The Chronic Disease Fund is a non-profit organization providing financial assistance to the underinsured that are diagnosed with a chronic or life altering disease.

Conclusion

Canada and Australia have made plans to and will eliminate CFC-containing MDIs by the end of December 2005. The United Kingdom is doing the same. The United States will also be ready in December 2005 with capacity and access to reasonably priced products; it should follow the timeframes implemented by its co-Parties to the Montreal Protocol.

IVAX believes that the commitments made here regarding production capacity, cost and access programs for patients demonstrate our support for a smooth transition from CFC- to HFA-based albuterol MDI products to occur as soon as December 31, 2005. For the foregoing reasons, we urge FDA to prohibit the sale of ozone-depleting albuterol MDIs by the end of 2005. Further delay is not warranted by either supply constraints, of which there will be none, or pricing concerns, which will be mitigated due to the intense competition, excess supply, and federal regulation of Medicare pricing.

Sincerely,



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IVAX Research, Inc.