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June 3, 2003

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: COMMENTS REGARDING CITIZEN PETITION SUBMITTED BY U.S. STAKEHOLDERS GROUP ON MDI TRANSITION
Docket #03P-0029

INTRODUCTION

We respectfully submit these comments in response to the petition of the "U.S. Stakeholders Group on MDI Transition" ("petitioners"), which requests that the Commissioner of the Food and Drug Administration ("FDA") initiate rulemaking by July 28, 2003 to remove oral pressurized metered-dose inhalers ("MDIs") containing albuterol from the list of products deemed to be an "essential use" under the Clean Air Act.[1] As discussed below, the significant costs to patients, governments, and private payers of removing albuterol from the "essential-use" list would far outweigh the negligible (if any) benefits of such action. Moreover, the petition falls well short of satisfying the legal and regulatory standard that must be met before the agency may initiate the notice and comment process. That standard requires petitioners to provide

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[1] 21 C.F.R. § 2.125; Use of Ozone-Depleting Substances; Essential-Use Determinations, Final Rule, 67 Fed. Reg. 48, 370 (2002)..

"compelling evidence" establishing that specified criteria are met.[2] The petitioners fail to provide such evidence, and their request therefore should be denied.

It is important that FDA recognize not only the lack of legal justification for beginning the rulemaking process, but also the potentially grave consequence of initiating that process prematurely. Even prior to promulgation of a final regulation, publication of a proposed regulation could unduly disrupt the marketplace and negatively impact the millions of asthma patients who have relied upon CFC-containing albuterol MDIs for several decades. Moreover, merely beginning the rulemaking process could send a message to CFC suppliers that could lead them to suddenly terminate the production of CFCs, and leave millions of asthmatics no choice but to switch to the only other available medication at enormous economic cost to individuals, federal, state, and private payers.

Currently, there are only two FDA approved non-CFC containing albuterol products – Ventolin® HFA and Proventil® HFA. Both have patents that likely will protect them from generic competition for several years.[3] If CFC-containing albuterol products (which include generics) are unable to compete in this market, the price of these asthma medications can be expected to increase considerably.[4] As the Federal Trade Commission ("FTC") recognizes, the

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[2] 21 C.F.R. § 2.125(g).
[3] See e.g., patent number 5,766,573 (expiring on June 16, 2015); Ventolin HFA, patent number 6,251,368 (expiring on December 4, 2012).
[4] That corporations who profit from sales of the HFA products would benefit considerably from the grant of this petition makes us wonder who the true parties in interest are.

reduction of competition from even three to two entities will likely result in higher prices and fewer product choices for consumers of prescription drug products.[5] If the agency removes a multisource drug from the market whose pricing is competitive due to generic competition, and converts that market into one with single source products, the economic consequences would be potentially devastating. This would have especially tragic consequences, given the prevalence of asthma in low-income communities and the negligible impact that CFCs emitted from MDIs actually have on the environment.

Thus, granting petitioners' request would have particularly significant consequences to individuals of varying income levels who do not have insurance covering prescription drugs, to state governments that cover the costs of prescription drugs under Medicaid for low income citizens, and to private payers. It would also be inconsistent with the agency's stated priority of carrying out its mandate under the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments")[6] to promote the affordability of prescription drugs by increasing the availability of generic drugs.[7]

Pursuant to the final regulation promulgated on July 24, 2002, FDA cannot grant this request to initiate rulemaking unless the petitioners present "compelling evidence" that several

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[5] See FTC, "Pfizer, Pharmacia Will Divest Assets to Settle FTC Charges" (April 14, 2003) (announcing the required divestiture of Pfizer Inc.'s combination hormone replacement therapy product, femhrt, to Galen Holdings plc, as part of its merger with Pharmacia Corporation).
[6] Public Law 98-417 (1994).
[7] See Mark B. McClellan, M.D., Ph.D., Commissioner FDA, speech before Food and Drug Law Institute (April 1, 2003)

specified criteria have been met.[8] Failure to meet any one of these criteria compels denial of the petition.[9] The petitioners have failed with respect to several of these elements. In some instances, they present no data at all, and instead merely set forth bald, conclusory assertions. Conspicuously absent is any hard data regarding adverse events, and any objective evidence that would support the contention that an adequate supply of non-CFC containing products could be ensured. Perhaps most significantly, the petitioners fail to address how patients will be served, given that: (1) the price of available medications may increase drastically (and in no event will decrease); and (2) a large percentage of the affected population is poor, and either pays for the product out of pocket or relies upon Medicaid. As Dr. McClellan recently made abundantly clear, controlling health care costs is matched in importance only by the agency's counterterrorism responsibilities. Cost must be a serious consideration in all of FDA's decisions.[10] Failure to consider the costs to the public in a decision of this type is a failure to consider all the relevant factors and thus a legally flawed decision. Here, the interest in controlling the cost of medications critical to treating a disease with a disproportionate impact in poor, minority communities clearly is not overridden by the minimal benefit that reducing CFC emissions from MDIs would have on the environment.

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[8] 21 C.F.R. § 2.125(g).
[9] Id.
[10] See, McClellan speech to FDLI, supra., n. 7.

Initiating rulemaking would cause significant injury to the growing asthma patient population by increasing the price of their medications and decreasing their choices, without providing much (if any) benefit to the environment. Moreover, the petitioners have failed to provide compelling evidence, as mandated by the FDA regulation, that the large (and rapidly growing) asthma population will be adequately served by safe, effective and affordable alternatives to CFC-containing albuterol products. For these reasons, we request that FDA deny the petitioners' request and refrain from initiating rulemaking.

I. The Costs to Individuals, State Governments and Private Payers Associated with Eliminating CFC-Containing Albuterol MDIs from the Market Far Outweigh the Benefits of Such Action.

1. Decreasing the amount of available albuterol MDIs will increase their price and availability to the detriment of both patients and state governments.

Asthmatic patients presently enjoy the benefits of a vibrant, competitive market that keeps the price of albuterol MDIs reasonable. According to the FDA's latest version of "Approved Drug Products with Therapeutic Equivalence Evaluations" ("The Orange Book"), eight albuterol MDIs are marketed under approved New Drug Applications ("NDAs") or Abbreviated New Drug Applications ("ANDAs"). Four of the products are generic drugs marketed pursuant to ANDAs, and four others are branded products that are marketed under NDAs. All but two of these MDI products utilize CFCs as propellants, which are deemed

"ozone depleting substances" ("ODSs") under the Montreal Protocol and the Clean Air Act.[11] Both Proventil® HFA (manufactured by 3M and marketed by Schering-Plough) and Ventolin® HFA (manufactured and marketed by GlaxoSmithKline) utilize HFA-134a (1,1,1,2-tetrafluroethane) as the propellant, which is not deemed to be an ODS.[12]

If albuterol were to lose its "essential-use" designation, only Proventil® HFA and Ventolin® HFA could be marketed in the United States. Both are branded products with patent protection that will last into the next decade. Six patents remain effective for Proventil® HFA, the last of which does not expire until June 2015[13]. A patent for Ventolin® HFA does not expire until December 4, 2012.[14] Hence, promulgation of rulemaking would substantially decrease competition and create a virtual monopoly for these companies that could likely last for many years.

The almost certain result of this monopoly would be a substantial increase in the price of these critical medications as the Federal Trade Commission has noted. This would have significant reverberations. According to the National Institute of Allergy and Infectious Diseases ("NAIAD"), an estimated 17 million Americans had asthma in 1998.[15] In 1995, it caused over

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[11] See 42 C.F.R. § 7671a(a).
[12] Id.
[13] See patent number 5,766,573, supra, n. 3.
[14] See patent number 6,251,368, supra, n. 3.
[15] NIAID, NIH, "Focus on Asthma," available at <http://www.niaid.nih.gov/newsroom/focuson/asthma01/basics.htm> (last visited April 15, 2003).

1.8 million emergency department visits.[16] Accordingly, it ranks among the most common chronic conditions in the United States. Asthma also is currently one of the fastest growing diseases in the U.S. Its prevalence has been increasing since the early 1980s for all age, sex and racial groups.[17] From 1980 to 1994, the overall age-adjusted prevalence of asthma increased 75 percent from 30.7 per 1,000 persons in 1980 to a 2-year average of 53.8 per 1,000 persons in 1993-1994.[18] The prevalence among children ages 5 to 14 increased 74 percent over this time, reaching 74.4 per 1,000 persons in 1993-1994.[19] Thus, keeping the price of albuterol products reasonable is an issue of significant social consequence.

That the disease has taken a disproportionate toll in poor, urban and minority communities, due in part to living conditions and the absence of adequate medical care, exacerbates this. According to the (NIAID), African-American children with asthma experience more severe disability and have more frequent hospitalizations than do Caucasian children.[20] In 1993, African Americans were 3 to 4 times more likely than whites to be hospitalized for asthma.[21] In 1996 African Americans were 4 to 6 times more likely than whites to die from asthma. The Centers for Disease Control and Prevention ("CDC") has found that African

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[16] Id.
[17] National Heart, Lung, and Blood Institute, NIH, U.S. Department of Health and Human Services, "Data Fact Sheet: Asthma Statistics" (January 1999) ("NHLBI Data Fact Sheet").
[18] Id.
[19] Id.
[20] NIAID Fact Sheet, Asthma and Allergy Statistics, July 1999 ("NIAID Fact Sheet").
[21] Centers for Disease Control and Prevention, "Asthma Mortality and Hospitalization among Children and Young Adults, 1980-1993, *MMWR*, 45(17), 350-353,May 3, 1996. NIAID, "Focus on Asthma," supra., n. 15.

American children with asthma experience more severe disability. In 1995, the hospitalization rate among African-Americans was 3-1/2 times that among Caucasians.[22] The age-adjusted mortality rate among African-Americans was dramatically higher than that among Caucasians (3.8 versus 1.3 per 100,000 persons). In 1993, African Americans ages 5-24 were 4 to 6 times more likely to die from asthma than Caucasians.[23] As the NIAID has acknowledged:

> [a]sthma morbidity and mortality have been increasing in the United States for the past 15 years, and asthma morbidity and mortality are particularly high among poor, African American and Hispanic/Latino inner-city residents.[24]

Albuterol consists of almost 50% of the asthma treatment market, which translates into approximately 7.5 million asthmatics who rely on albuterol products. Thus, although the affordability of safe and effective medications is always important, it is absolutely critical that affordable versions of albuterol remain available.

2. *MDIs emit only negligible amounts of CFCs and have only a minimal impact on ozone layer*

To justify an action that has such detrimental consequences, there must be some great countervailing social or other benefit; however, no such benefit from granting this petition

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[22] Id.
[23] Id.
[24] NIAID, "Allergy, Immunology and Transplantation" available at: <http://web.fie.com/htdoc/fed/nih/ali/any/text/mti/nihtni13.html> (visited April 21, 1997). http://web.fie.com/htdoc/fed/nih/ali/any/text/mti/nihtni13.html>. See also David M. Lang & Marcia Polansky, "Patterns of Asthma Mortality in Philadelphia from 1969 to 1991," 331 NEJM 542 (1994) ("According to multivariate analysis, the rates of death from asthma from 1985 to 1991 were significantly higher in census tracts with higher percentages of blacks (P = 0.032), Hispanics (P= 0.013), female residents (P<0.001), and people with incomes in the poverty range (P<0.001).

awaits. In fact, the evidence suggests that there is almost no such benefit from taking these products away from the millions of people who have relied upon them since 1956.

The level of CFCs that MDIs emit into the atmosphere is negligible and will have minimal to no effect upon the ozone layer. In 1986, total worldwide CFC usage was approximately 1,100,000 tons. MDI usage of CFCs was only 3,000 to 4,000 tons – accounting for only 0.3 to 0.4 percent of the worldwide total. MDI usage in the United States was only 1,800 tons, accounting for only 0.16 percent of total worldwide usage. CFC emissions from MDIs contribute *less than 1%* of all CFCs released into the atmosphere. The marginal potential benefit to the ozone layer fails to justify shrinking the supply and potentially threatening the availability of CFC-containing MDIs that are currently relied upon by millions of asthmatics in the United States alone.

Given the minimal impact that the use of CFCs in MDIs has on the environment, the reliance upon MDIs by millions of asthma sufferers, and the prevalence of the disease in poor urban communities, granting this petition would be medically and socially unjustified.

3. *The FDA Commissioner's Recently Stated Commitment to Ensuring the Affordability of Drugs by Increasing the Availability of Generic Drug Products.*

Dr. McClellan highlighted the importance of promoting the availability of generic drug products in recent remarks presented at a conference of the Food and Drug Law Institute ("FDLI"). Indeed, he cited controlling health care costs, including the rising costs of

prescription drugs, as one of only two "areas of heightened concern" that his administration must address – the other being counterterrorism. The importance of economic considerations to FDA's decisions pervades Dr. McClellan's speech, and his statements acknowledging the significance of generic drugs reflect it. As he noted:

> [g]eneric drug manufacturers produce medications that are just as safe and effective as their brand counterparts – in fact, part of the FDA's mission is to make sure that's the case. Yet the prices of generics are much lower: a generic version of a $72 average brand-name prescription costs about $17. And thanks to more brand-name medications coming off patent – over 200 of them in the next few years – as well as to the ever-improving scientific knowledge and public awareness about the benefits of generic drugs, the health and economic benefits of using generic drugs are growing. Encouraging rapid and fair access to generic medications after the expiration of appropriate patent protection is, therefore, a key part of providing lower-cost, safe and effective treatment options for patients.[25]

The Commissioner recognized that FDA has significant authority to control health care costs by enhancing the availability of generic drugs. The agency has ambitious plans to wield this authority, including reforming the manner in which it implements the Drug Price Competition and Patent Term Restoration Act.[26] These plans have great potential. Granting this petition and thereby removing generic drugs from the market, however, is a step in the wrong direction.

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[25] Speech before FDLI, April 1, 2003, supra., n. 7.

[26] See Applications for FDA Approval to Market a New Drug. Patent listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying that a Patent Claim of a Drug is Invalid or Will Not be Infringed, Proposed Rule, 67 Fed. Reg. 65,447 (2002).

II. The Petitioners have Failed to Present "Compelling Evidence" that the Criteria for Removing an "Essential-Use" Designation Have been Met.

A petitioner requesting removal of an active moiety from the "essential-use" list set forth in 21 C.F.R. § 2.125 must submit "compelling evidence" that each of several criteria, designed to ensure that alternatives will adequately serve the relevant patient population, is met. The petitioners carry the burden of demonstrating that the evidence is compelling enough to satisfy each element. Here, the petitioners have failed to carry this burden with respect to several criteria. In many instances, rather than present hard evidence as is required by the rule, the petitioners provide mere assertions and speculation.

This is not enough to justify granting the petition, especially since even the initiation of rulemaking could have considerable consequences. As the petitioners note, the CFC market is becoming increasingly uncertain. The initiation of rulemaking is likely to send a message to CFC suppliers that their markets may evaporate. This could lead them to exit the market prematurely, leaving patients who have been relying upon CFC-containing MDIs in the lurch. FDA lacks the factual predicate to initiate a rulemaking proceeding. Accordingly, the agency should not initiate rulemaking with this deficiency and wait to consider whether compelling evidence is provided by the time the comment period closes. Instead, the agency must comply

with the Administrative Procedure Act and, without an adequate factual basis for compelling evidence, should deny this petition due to the absence thereof.[27]

1. Failure to Ensure Adequate Supply and Production Capacity

The petitioners fail to present any evidence, no less evidence that might be compelling (as required by the agency's regulation), to support the contention that adequate supplies of the non-CFC alternatives could be ensured. With medication indicated for the prevention and treatment of such a serious and pervasive disease as asthma, this element is critical. Yet the petitioners state only that such information is proprietary and therefore not publicly available. Whether such information might be confidential does not create an exemption from satisfying this element. The petitioners request that FDA should gather this information during the notice and comment process. As noted earlier, however, compelling evidence is required *at the outset.* This petition cannot be granted in the absence of compelling evidence. Thus, failure to produce evidence that there is an adequate supply of, and production capacity for, the non-CFC containing MDIs requires the denial of this petition.

The nascence of both non-CFC products magnifies the need for this data before any petition could be granted. Proventil® has only been on the market for just over six years. Ventolin® has barely been on the market for a year. The potential for production and quality problems is not overly speculative, as shown by the problems that Schering-Plough has faced in

[27] See 21 C.F.R. § 2.125(g)(3).

the past. The agency should consider this before initiating action that could severely impact the lives of millions of asthmatics to their detriment.

2. Absence of Adequate Postmarketing Data

The age of these products also precludes the petitioners from presenting enough postmarketing data to be compelling. In fact, they fail to produce any postmarketing data at all. Without an examination of such data, neither the agency nor the public is in a fair position to comment on the adequacy of the non-CFC containing MDIs. There have been several instances where significant adverse events have come to light several years after a product's initial introduction. Baycol represents one of the more recent, and infamous, examples. CFC-containing albuterol MDIs have been in existence for approximately forty-seven (47) years. It would be unwise to take these products off of the market before absolutely ensuring that the alternatives are as safe and as effective.

4. Failure to Ensure Patients are Adequately Served

With this element, FDA addresses the issue of cost. As the petitioners correctly note, FDA has always contemplated that cost should be a factor in determining whether adequate alternatives exist. This consideration is now more important than ever, as highlighted by the Commissioner's remarks at FDLI. As stated in the rule (and quoted by petitioners):

> [t]he agency recognizes that generic albuterol CFC-MDIs are currently marketed and that these products cost less than currently marketed albuterol sulfate MDIs that use hydrofluoroalkane (HFA) as a propellant. At the appropriate time, FDA will evaluate the

> essential-use status of albuterol under criteria established by this rule. In determining whether non-ODS products containing albuterol as the active moiety adequately serve patients, FDA will consider the cost of potential alternatives, such as the albuterol sulfate HFA-MDIs.[28]

Cost undoubtedly must be a significant consideration in deciding whether to grant this petition and initiate rulemaking. Petitioners argue that prices will be controlled, because there will be two alternatives available. The presence of two pioneer products, however, cannot have the same impact on the market as several generic drugs. This same situation existed in the CFC-MTA market prior to generic products. Prices for the sole source products were high and they were dramatically reduced under generic products came into the marketplace. Thus, with no generic competition history shows there is no pressure to reduce prices.

CONCLUSION

The petition to initiate rulemaking should be denied, because the significant costs to patients and state governments of removing albuterol from the "essential-use" list would far outweigh the negligible benefits of such action. Moreover, the petitioners fail to present "compelling evidence" that several of the criteria described in 21 C.F.R. § 2.125 have been met. Beginning the notice and comment process therefore is not legally justified and could, even prior to a final resolution, negatively impact the millions of asthma patients whose lives have depended upon the availability of CFC-containing albuterol MDIs for almost fifty (50) years.

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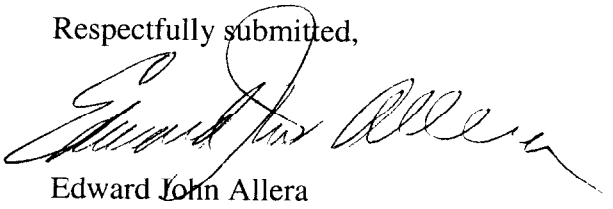
[28] 67 Fed. Reg., at 48,383.

Merely initiating rulemaking could send a message to CFC suppliers that could lead them to prematurely exit the market and force millions of asthma patients to, with almost no notice at all, terminate the production of CFCs.

The Commissioner has made it known how pivotal promoting the availability of generic drug products is to controlling health care costs. Indeed, he has made it a top priority for the agency. Granting this petition would mean sacrificing this "top priority" for a benefit that is negligible at best. Such action is not medically, legally or otherwise supportable. The petition therefore should be denied.

Respectfully submitted,



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