

October 5, 2006

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

Re: Citizen Petition on Combivent® (ipratropium bromide and albuterol sulfate)  
Inhalation Aerosol

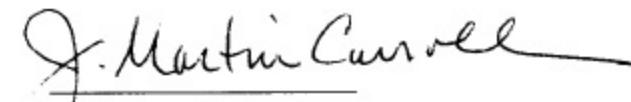
Dear Sir or Madam:

On behalf of Boehringer Ingelheim Pharmaceuticals, Inc. (BI), and pursuant to 21 CFR §§10.20 and 10.30, I am enclosing for filing an original and four (4) copies of a Citizen Petition.

The petition requests the Commissioner of the Food and Drug Administration to refrain temporarily from taking action to remove the chlorofluorocarbon (CFC) containing metered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use (COMBIVENT) from the list of essential uses of CFCs. As fully explained in the petition, *over two million patients* with chronic airway diseases rely on COMBIVENT to manage their symptoms and control their disease. BI has been working diligently to develop a CFC-free replacement for COMBIVENT, and is well advanced in that effort. Premature removal of the essential use status of COMBIVENT before a CFC-free version is available will create a gap in the product's availability, and thereby impose unnecessary disruption for patients. This disruption will include increased health risks and costs for a primarily elderly and especially vulnerable patient population. These risks and costs far outweigh any environmental benefits that might result from prematurely phasing out CFC-containing COMBIVENT before a CFC-free version is available.

BI and its affiliates are strongly committed to the recovery of the stratospheric ozone layer, and have clearly demonstrated this commitment by, among other things, aggressively transitioning their CFC-based products across the globe. The relief requested by this petition is wholly consistent with BI's commitment to the environment and, more importantly, with protecting the interests of patients.

Respectfully submitted,

  
J. Martin Carroll  
President & CEO  
Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road  
Ridgefield, CT 06877

2006 P-0428

CP 1

**CITIZEN PETITION**

Maintenance of Essential Use Status of CFC  
Metered-Dose Ipratropium Bromide and Albuterol Sulfate, in  
Combination, Administered by Oral Inhalation for Human Use

October 23, 2006

Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road  
Ridgefield, CT 06877

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submits this petition pursuant to 21 CFR §§ 10.20 and 10.30 requesting the Commissioner of the Food and Drug Administration (FDA) to *refrain* from taking any action to remove metered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use (trade name COMBIVENT) from the list of products<sup>1</sup> considered an essential use of chlorofluorocarbon (CFC) propellant *until* a CFC-free version of COMBIVENT is available.

As more-fully explained herein, FDA's premature removal of COMBIVENT from the essential use list will:

- Thwart the Montreal Protocol's policy of encouraging companies to diligently pursue CFC-free research and development by pre-empting BI's active, advanced, good faith, and substantial efforts to develop a CFC-free alternative for COMBIVENT;
- Create a gap in the availability of COMBIVENT and thereby unnecessarily disrupt patient care and increase health risks and treatment costs for *over two million U.S. patients*<sup>2</sup> suffering from chronic airway diseases including chronic obstructive pulmonary disease (COPD); and
- Not significantly decrease the cumulative release of CFCs into the atmosphere, nor have any discernible beneficial effect on the recovery of the stratospheric ozone layer. Any such effect would not outweigh the associated treatment disruption, health risks, and costs to COPD patients.

As FDA considers this petition, BI urges it to remain mindful of the longstanding and deep commitment BI has shown to the global transition away from CFC metered dose inhalers (MDIs). We believe our commitment has been, and continues to be, exemplary. Indeed, this petition is being submitted solely as a means to properly effect a CFC product transition, not prevent one.

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<sup>1</sup> See 21 CFR § 2.125(e).

<sup>2</sup> Verispan Total Patient Tracker (TPT). Verispan, L.L.C. provides patient longitudinal data which includes 2 billion prescription claims and 475 million medical claims per year, representing over 150 million de-identified unique patients. Prescription data samples nearly 59,000 pharmacies (a near-census of retail stores) in the US. TPT recorded 1.9MM patients from January-December 2005, and does not capture patients from hospital, long term care facilities, mail order, or Veterans Health Administration. BI internally estimates these channels that Verispan does not capture to account for well in excess of 100,000 additional patients.

## A. CONTEXT OF REQUEST

For the benefit of the uninitiated, this petition relates to restrictions on CFCs originally imposed by FDA in 1978 after scientific studies demonstrated that CFCs contribute to the depletion of the stratospheric ozone layer. Those original restrictions made exception for "essential uses" of CFCs. Broader, international restrictions followed nearly a decade later with the coming into force of an international treaty known as the Montreal Protocol.<sup>3</sup> As a party to the Montreal Protocol, the United States implemented its treaty obligations in 1990 by amending the Clean Air Act (CAA).<sup>4</sup> The Environmental Protection Agency (EPA) administers these provisions, but defers to FDA's judgment on MDI-related essential use designations. The Montreal Protocol provides that a use shall be considered "essential" if:

- "(i) *It is necessary for the health, safety or is critical to the functioning of society (encompassing cultural and intellectual aspects); and*
- (ii) There are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.*"<sup>5</sup>

In order to implement its obligations under the CAA, and ensure consistency between its essential use criteria and those of the Montreal Protocol, FDA amended its essential use regulations in 2002.<sup>6</sup> Since then, FDA has removed essential-use designations for moieties no longer marketed and for which CFC-free alternatives have been introduced, including most recently albuterol.<sup>7</sup> The albuterol ban (which expressly distinguished and excepted the combination of ipratropium bromide and albuterol sulfate) takes effect December 31, 2008.

## B. IMPETUS FOR REQUEST

This request is motivated by BI's concern that FDA may remove the essential use status of COMBIVENT before a CFC-free alternative is available to patients. This

<sup>3</sup> The treaty's full title is the *Montreal Protocol on Substances that Deplete the Stratospheric Ozone Layer*. It is administered under the auspices of the United Nations Environment Programme (UNEP), headquartered in Nairobi, Kenya. The full text of the treaty, as amended, can be accessed via UNEP's ozone website: <http://hq.unep.org/ozone/>.

<sup>4</sup> See CAA Title VI ("Stratospheric Ozone Protection"), 42 U.S.C. § 7671 *et seq.*

<sup>5</sup> Decision of the Parties IV/25.

<sup>6</sup> "Use of Ozone-Depleting Substances; Essential-Use Determinations", Final Rule (67 Fed. Reg. 48384, July 24, 2002). This rule also removed essential use designations for steroid MDIs for nasal inhalation and certain products no longer marketed.

<sup>7</sup> 70 Fed. Reg. 17168 (April 4, 2005). The rule provides that albuterol CFC MDIs cannot be marketed after December 31, 2008.

concern stems primarily from a meeting of FDA's Pulmonary and Allergy Drugs Advisory Committee (PADAC) convened in the summer of last year.<sup>8</sup>

The meeting's avowed purpose was to gather advice on whether non-reformulated CFC MDIs remaining on the market continue to be essential.<sup>9</sup> Specifically, the PADAC was asked to focus on moieties (1) that are not being reformulated into a CFC-free form, or (2) for which reformulation efforts are not progressing adequately. These moieties were distinguished from those for which CFC-free alternative delivery modes have been developed and placed on the market, e.g., albuterol. A list of seven products was presented for consideration, including COMBIVENT. After only a brief and general discussion, there was an impromptu, informal, non-binding straw poll requested by FDA on whether each product provided *an otherwise unavailable important public health benefit.*<sup>10</sup> Those PADAC members present and not abstaining concluded that five of the products do not provide such a benefit, while one does (cromolyn). In the case of COMBIVENT, the PADAC was evenly split.

During the PADAC meeting, FDA variously signaled its readiness to initiate a rulemaking process for phasing out remaining CFC products. It is the possibility of COMBIVENT being included in this action, and the health risks and disruption it would create, which prompt this petition. BI is at an advanced, critical stage in its pursuit of a CFC-free version of COMBIVENT (initial data expected to be submitted to FDA in 2008). This effort is challenging from a technical and clinical standpoint. Furthermore, the mere news of an FDA proposal risks giving rise to confusion and uncertainties for patients, prescribers, and payors, creating the potential for the sort of

<sup>8</sup> The meeting was held July 14, 2005. Materials on the meeting, including a transcript, can be viewed at: <http://www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy>.

<sup>9</sup> See "Office Director's Background Memorandum" dated July 5, 2005, from Robert J. Meyer, MD, Director, Office of Drug Evaluation II, to the PADAC.

<sup>10</sup> The background memorandum made it clear that the PADAC's task was to address only one of the three criteria by which these products are to be judged:

FDA will base a decision on whether the listed products remaining on the market containing CFCs remain essential based on whether or not they continue to meet the regulatory criteria on which they were designated an essential use (21 CFR 2.125(g)(2)). This includes the use of relevant advisory committee input. The criteria listed for this consideration are as follows (see 21 CFR 2.125(f), where they define the conditions of essentiality for a new use of CFCs):

- Substantial technical barriers exist to reformulating the product without [ozone depleting substances];
- The product provides *an otherwise unavailable important public health benefit*; and
- Use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the *unavailable important public health benefit*.

Your expert advice is particularly valuable in applying the second criterion to the relevant products cited in List A below and therefore, the July 14<sup>th</sup> meeting will focus on this second criterion. FDA will consider, as appropriate, other information and seek other expertise pertaining to the first and third criterion.

*Id.* at p. 2 (emphasis added).

market distortions and inordinate patient confusion being experienced in the ongoing albuterol transition.

We urge FDA to recognize that COMBIVENT, as evidenced by the PADAC discussion, is distinguishable from other CFC MDIs remaining on the market. Among other important differences, it is the only combination product. And though FDA may see it as expedient to include COMBIVENT with others in a rulemaking, it would, in fact, be premature to do so. Further, this approach risks tainting COMBIVENT by associating it with those MDIs that truly no longer satisfy the essential-use criteria. This petition therefore strongly urges FDA to refrain from including COMBIVENT in any upcoming rulemaking proposal, and instead postpone any action on COMBIVENT *at least until* the outcome of BI's ongoing clinical development programs for its leading CFC-free COMBIVENT replacement. At that point, a phase-out proposal would be timely and appropriate, and could be pursued in a separate rulemaking.

C. **BOEHRINGER INGELHEIM'S STRONG COMMITMENT TO THE RECOVERY OF THE STRATOSPHERIC OZONE LAYER**

It is important to reaffirm at the outset BI's commitment to the protection of the stratospheric ozone layer, and make clear its understanding that essential use exemptions were not intended to be permanent.

There are few MDI manufacturers in the world as committed to the CFC transition as BI. When the Montreal Protocol was ratified in 1989, BI co-founded the International Pharmaceutical Aerosol Consortium (IPAC), and has played a leadership role in its affairs over the years. IPAC has helped develop and implement policies to educate patients on the CFC phase-out, and to seamlessly transition patients to CFC-free therapies. In 1990, BI co-founded the IPACT-I and II toxicology testing consortia whose efforts have generated extensive bodies of safety data on HFA-134a and HFA-227 respectively. A key aim of these efforts was to expedite the transition away from CFCs by accelerating the testing necessary to demonstrate the safety, and thus availability, of HFAs for use in MDIs. BI also has maintained a representative on the United Nations Environment Programme technical committee responsible for monitoring and reporting on the MDI industry's progress in transitioning away from CFCs.

As part of its commitment, BI ceased launching CFC products in 1999. Moreover, BI has transitioned, is transitioning, or has phased out *over 24 CFC MDIs* throughout the world. Excluding time committed by its own personnel and substantial related expenses, the cost to BI of these efforts to date is approximately \$500 million, *excluding capital investment in plants and machinery.*

With respect to COMBIVENT specifically, BI embarked on developing a CFC-free version a full *two years before* FDA's 1996 approval of COMBIVENT CFC. Indeed,

BI has been developing not just one, but two possible CFC-free replacements: a hydrofluoroalkane (HFA) version and a propellant-free, "soft mist" version (trade name "Respimat®"). And although the development issues for each have proven to be complex, tremendous progress has been made toward realizing a CFC-free successor.

Because its ingredients are in both suspension and solution, COMBIVENT has been extremely challenging to reformulate to HFA form. These physio-chemical characteristics have greatly frustrated and lengthened the HFA development program. Nevertheless, robust development efforts continue and BI is confident that it will successfully complete the HFA development program. Although the RESPIMAT formulation does not pose the same challenge, as a new device it is being developed to clinical standards that differ from MDIs transitioning from CFC to HFA form. The RESPIMAT program has, as a result, also been prolonged. BI is embarking on a second phase 3 development program for RESPIMAT that is on track to commence in the fourth quarter of 2006.

In short, BI has not only honored the Montreal Protocol's mandate, it has actively promoted it. COMBIVENT is the last BI CFC MDI remaining to be reformulated.<sup>11</sup> And, as demonstrated below, there are compelling patient safety, policy, and economic reasons for FDA to refrain from removing the essential-use status of COMBIVENT prior to the availability of a CFC-free successor.

#### D. STATEMENT OF GROUNDS

The foundation of this petition is straightforward. COMBIVENT plays a unique and important therapeutic role in the treatment of COPD. Moreover, as a result of over a decade of intense research and development efforts, and the investment of many millions of dollars, we have every expectation that a CFC-free replacement for COMBIVENT will be available as early as 2010 or 2011. Hence, given a reasonable amount of time, COMBIVENT patients can enjoy a seamless transition of their therapy. This course is not only fair and prudent, but is the one envisioned by the Montreal Protocol. The premature removal of the essential-use status of COMBIVENT, on the other hand, is fraught with unnecessary risk and disruption to patients, with no justifiable, let alone discernable, offsetting environmental benefit. Put simply, the circumstances compel the FDA to adopt a cautious approach over more precipitous action, thereby enabling BI to continue its CFC-free COMBIVENT development efforts.

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<sup>11</sup> As announced by BI during the July 14, 2005 PADAC hearing, Alupent® MDI (metaproterenol sulfate) is not being reformulated and will be phased-out in the same timeframe as albuterol CFC MDIs are being phased out.

### **(1) COMBIVENT Serves an Especially Vulnerable Patient Population**

COPD is a large and growing health problem in the United States. An estimated 12 million American adults have been diagnosed with it, and 12 million more are believed to have airflow obstruction which could be COPD, but have not been diagnosed<sup>12</sup>. COPD was the country's *fourth-leading cause of death* in 2002, claiming the lives of 120,000 patients.<sup>13</sup> Severe COPD is often characterized by chronic breathlessness (even at rest), an inability to perform simple, common daily activities, and persistent coughing with mucus. Due to its high prevalence, enormous cost to the healthcare system, and consequent burdens on society, COPD is one of the more important chronic respiratory conditions facing patients.

COMBIVENT is a leading therapeutic treatment for COPD patients. With two distinct and complementary bronchodilators, ipratropium bromide (short-acting anti-cholinergic agent) and albuterol sulfate (short-acting beta-agonist), COMBIVENT treats bronchospasm associated with reversible obstructive airways diseases in patients requiring more than one bronchodilator. This serves the important benefit of simultaneously blocking the bronchoconstriction by two distinct mechanisms, relaxing the bronchial muscle of the large airways as well as the smaller, more peripheral airways. COMBIVENT is the only MDI on the market that combines two bronchodilators in one delivery system.

Though launched only a decade ago, COMBIVENT is now relied upon by over three million COPD patients worldwide, including over two million patients in the United States. Many of these patients have greatly compromised health due to COPD as well as co-morbid conditions, and most are elderly.<sup>14</sup> Nearly 50% are 65 or older, and 15% are 75 or older.<sup>15</sup> The vast majority of COMBIVENT patients (84%) have multiple diseases (one-third of whom have three or more diseases), and require a complex treatment regimen to stabilize their health.<sup>16</sup> In addition to suffering from COPD, COMBIVENT patients tend to have other significant health conditions (including

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<sup>12</sup> Lethbridge-Cejky M, Schiller JS, Bernadel L. Summary health statistics for U.S Adults: National Health Interview Survey, 2002. National Center for Health Statistics. Vital Health Stat. 10(222). 2004

<sup>13</sup> *Id.*

<sup>14</sup> In a survey profiling over 400 COMBIVENT users and 1,200 COPD patients, it was shown that over 50% of the COMBIVENT patient population are older than 65 years of age, and suffer from up to six co-morbidities alongside their respiratory problems. *Primary market research completed 1/06 by G&S, requested by Boehringer Ingelheim.* Data on file.

<sup>15</sup> Verispan.

<sup>16</sup> *Id.*

hypertension, hyperlipidemia, type II diabetes, shortness of breath) and, as a result, the typical COMBIVENT patient is on an average of eight (8) medications.<sup>17</sup>

Patients continuously depend on COMBIVENT to manage their COPD symptoms (continuing patients represent approximately 80% of COMBIVENT patients<sup>18</sup>), and over 225,000 healthcare professionals prescribed COMBIVENT in the US in 2005.<sup>19</sup> These numbers are even more compelling recognizing (i) the significant attrition rate for COPD patients<sup>20</sup>, and (ii) BI's cessation of COMBIVENT CFC marketing activities more than two years ago.

## (2) COMBIVENT Remains Essential

It was only ten years ago that FDA added COMBIVENT to its list of essential uses of CFCs.<sup>21</sup> In doing so, FDA found the use of COMBIVENT provides "*a special benefit that would be unavailable without the use of CFCs*" for some COPD patients, and "*does not involve a significant release of CFCs into the atmosphere.*"<sup>22</sup> The fundamental predicates upon which this determination was made have not changed.

Under FDA's relevant essential use provision, a non-essentiality finding must be compelled by (i) a change in the practice of medicine demonstrating that COMBIVENT no longer provides an otherwise unavailable public health benefit, or (ii) an available CFC-free alternative.<sup>23</sup> Neither prerequisite exists here.

First, there is no evidence that, in the absence of a CFC-free analog for COMBIVENT, physicians have retreated from using COMBIVENT CFC. To the contrary, COMBIVENT use among prescribers and patients has remained steady. Second, and more importantly, no CFC-free alternative exists. Hence, the critical trigger for an essentiality review is plainly absent. Although CFC-free versions of the individual component active ingredients in COMBIVENT are now on the US market, they are available only in separate inhalers (and as FDA is well aware, CFC-free albuterol has yet to meaningfully penetrate the market). As demonstrated below,

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<sup>17</sup> Harris Interactive primary market research completed June 2006 with 75 physicians from academic hospitals and 88 from community hospitals. Data on file.

<sup>18</sup> Verispan.

<sup>19</sup> IMS Xponent (sub national or doctor level prescription data) is a measure of dispensed retail prescriptions taken from approximately 6000 pharmacies on a weekly basis. IMS Health processes approximately 4.5 million prescriptions each week.

<sup>20</sup> Verispan.

<sup>21</sup> See 61 Fed. Reg. 15699 (April 9, 1996). FDA's action listing COMBIVENT as an essential use of CFCs was in response to a citizen petition filed by BI.

<sup>22</sup> *Id.* at 15700.

<sup>23</sup> 21 CFR §2.125(g)(2).

forcing doctors and patients to make a one-to-two inhaler switch would be a retrograde treatment step, risky to patients, of questionable environmental benefit, and costly.

(3) **The Premature Removal of COMBIVENT Will Impose Health Risks and Costs on Patients that Outweigh Any Resulting Environmental Benefit**

(a.) *Non-Compliance is a Significant Problem in COPD Patients*

Non-compliance is a significant barrier to improving outcomes for COPD patients. The successful management of COPD requires continual patient monitoring and repeated reinforcement of the need for effective therapy compliance. Ramsay refers to the extremely poor compliance with inhaled bronchodilator therapy found in the US Lung Health Study.<sup>24</sup> As part of the Lung Health Study, sub-study monitoring of ipratropium bromide compliance was performed over four months. Ninety-five participants were monitored for compliance by self-reporting their medication use, and 70 were monitored for compliance by canister weight change. This was compared to medication use in 251 participants whose inhalers were fitted with a nebulizer chronolog (NC), an electronic device that recorded the date and time of each inhaler activation. In the self-reporting group, 73% of the participants reported using their inhaler an average of three times daily, as prescribed. However, the NC data showed that *none* actually used their inhaler that frequently. In fact, the most compliant group (comprising 15% of the participants) used their inhaler an average of only 2.5 times per day.<sup>25</sup>

A number of factors contribute to the likelihood that compliance in the COPD patient population is even lower than the study showed. This sub-study was performed in relatively healthy patients on few medications, and under clinical trial conditions where compliance is assumed to be higher. The age range of participants in the Lung Health Study (35-60) was lower than that of the average COMBIVENT patient. Therefore, in the general COPD population of elderly patients, who likely have several illnesses, all requiring one or more drugs, compliance is likely to be much worse.

<sup>24</sup> The US Lung Health Study was a randomized clinical trial, sponsored by the National Heart, Lung and Blood Institute, and carried out in ten clinical centers in the US over a five-year period. It involved 5887 male and female smokers aged 35-60 years with mild or moderate COPD. The study's purpose was to determine whether a smoking intervention program, combined with regular use of an inhaled anticholinergic bronchodilator (ipratropium bromide), could slow the rate of decline in FEV1. A secondary objective was to assess whether intervention could affect compliance with inhaler therapy. Buist AS, The US Lung Health Study, *Respirology* 1997, 2:303-307.

<sup>25</sup> Rand CS, Wise RA, Nides M et al, *Metered-dose Inhaler Adherence in a Clinical Trial, Am Rev Respir Dis* 1992, 146: 1559-1564.

Compliance may vary among patients for a number of reasons.<sup>26</sup> Erratic compliance occurs in those who know when and how to take their medication but still fail to do so. This is more common with complex regimens, which interrupt daily activities. Simplifying the regimen or providing the patients with reminders to take their medication may overcome the problem to some extent. Unwitting non-compliance occurs when patients are unaware they are not complying due to misinterpreting instructions, not understanding the regimen, poor device technique, or language or intellectual barriers. This may often be missed at clinic visits. For example, in one study, upon consultation, 50% of patients could not recall what they were supposed to do, or at least could not recall it accurately.<sup>27</sup>

Social isolation and hearing, visual, and cognitive impairment are also common problems in the COPD patient population. Patients may also be reliant on a spouse of similar age and infirmity for assistance with taking their medication. All of these factors make compliance with a complex regimen more challenging. Therefore, increasing the manageability and simplicity of the treatment regimen for these patients represents a significant therapeutic benefit.

Another factor contributing to non-compliance is the patient's perception of benefit (or lack of immediate perception of benefit) from the medication. The rapid onset of benefit perceived by patients taking short-acting beta<sub>2</sub>-agonists tends to encourage compliance, whereas those bronchodilators with a longer onset of action, such as ipratropium bromide, have a perceived delayed or reduced benefit. This perception of delayed benefit, plus poor inhaler technique, increases the perception of a lack of clinical effect and will frequently lead to the administration of an additional dose<sup>28</sup> or to the omission of the second inhaler. Treatment of asthma patients with a combination of corticosteroids and beta<sub>2</sub>-agonists presents an analogous situation. Non-compliance with a prescribed regimen of inhaled corticosteroid (monotherapy) has been identified as one of the main reasons for a lack of improvement in asthmatics.<sup>29</sup> It is suspected that patient non-compliance is a result of the lack of perception of benefit from the steroid. Therefore, in the analogous situation, transitioning patients using a combination of a short-acting anticholinergic (ipratropium bromide) and a beta<sub>2</sub>-agonist (albuterol sulfate) in one inhaler to two separate inhalers containing these individual components poses a risk that patients will perceive a lack of efficacy with the anticholinergic and either overuse it or, worse, not use it at all.

<sup>26</sup> Rand CS. Patient and regimen-related factors that influence compliance with asthma therapy. Eur Resp Rev 1998; 8 (56): 270-274.

<sup>27</sup> Roter DL, Hall JA. Physicians' interviewing styles and medical information obtained from patients. J Gen Intern Med 1987; 2: 325-329.

<sup>28</sup> Chapman KR, Effect of the Inhaled Route of Administrations on Compliance in Asthma, Eur Resp Rev 1998, 8 (56), 275-279.

<sup>29</sup> Campbell LM, Once-daily inhaled corticosteroids in mild to moderate asthma: improving acceptance of treatment. Drugs, 1999; 58 (Supp. 4): 25-33; discussion 52.

*(b.) Use of a Combination Product with Similar Dosing Improves Compliance*

Clinical guidelines acknowledge the value of beta<sub>2</sub>-agonist/anticholinergic combination therapy based on the convenience of having both agents in a single MDI.<sup>30</sup> The British Thoracic Society Guidelines specifically mention that "combination bronchodilation therapy has the potential advantage of convenience and improved patient compliance."<sup>31</sup> Similarly the 1998 Canadian Guidelines recommend "combination therapy (ipratropium bromide 20 $\mu$ g and albuterol sulfate 100 $\mu$ g inhalation) two to four inhalations tid to qid as indicated in the regularly symptomatic COPD (patient)," and explain that "the combination preparation may be considered in order to simplify treatment."<sup>32</sup>

Tashkin reviewed the impact on compliance of multiple dose regimens and concluded that products combining individual agents commonly prescribed together in fixed doses for maintenance therapy represent pharmaceutical advances and are likely to enhance compliance by reducing the complexity and increasing the convenience of multi-drug treatment regimens.<sup>33</sup> Zablotskaia *et al* reported on the means of increasing compliance in COPD patients in a 616-patient observational study involving ipratropium bromide, fenoterol, albuterol, theophylline, and corticosteroids all as single agents or in combination.<sup>34</sup> A direct correlation between compliance and the volume of daily therapy was found. Patients were less compliant when they had to take more drugs separately. The authors recommended improving compliance and effectiveness through minimizing the volume of daily drugs by using combined forms. Petty concluded that combination therapy is additive but causes no increase in side effects,<sup>35</sup> and that the use of combination inhalers promised to be more convenient and less costly over time and may improve patient compliance.

<sup>30</sup> See American Thoracic Society Standards for the Diagnosis and Care of Patients with COPD, and British Thoracic Society Guidelines.

<sup>31</sup> BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS. *Thorax* 1997; 52:S1-28.

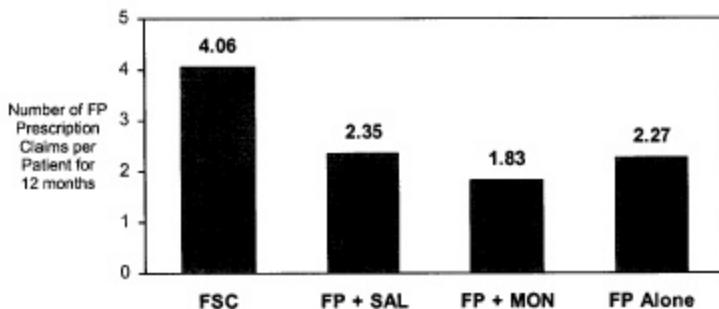
<sup>32</sup> Canadian Thoracic Society Guidelines for the Assessment and Management of COPD.

<sup>33</sup> Tashkin, D.P., Multiple Dose Regimens : Impact on Compliance, *Chest* Vol.117, 5 May 1995 Suppl.

<sup>34</sup> Zablotskaia, N., Ignatiev, V. *et al*, Means of Increasing Compliance in COPD Patients, *Eur Respir J* 14, Suppl 30.

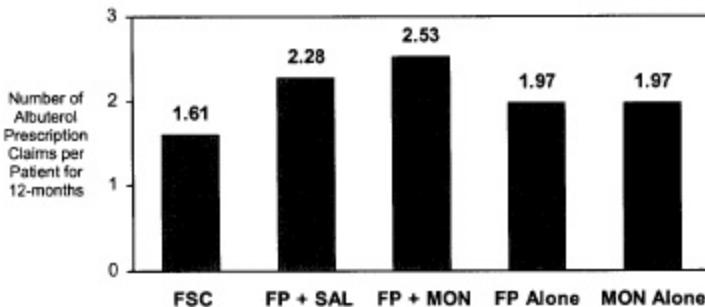
<sup>35</sup> Petty, T. L., Can "Old" Lungs be Restored? Strategies for Preserving Lung Health and Preventing and Treating COPD. *Postgraduate Medicine*, Vol. 104 No. 4, October 1995.

Retrospective studies of medical and pharmacy claims data confirm that patients prescribed combination inhalers with similar dosing are more compliant than those prescribed two separate inhalers. For example, in a study assessing compliance among asthma patients taking fluticasone and salmeterol, refill rates (a proxy for compliance) for the combination inhaler group were significantly higher than the rate for the group using two inhalers (Fig 1). In addition, the combination inhaler group was the only one where claims for rescue medication actually decreased (Fig 2).\*



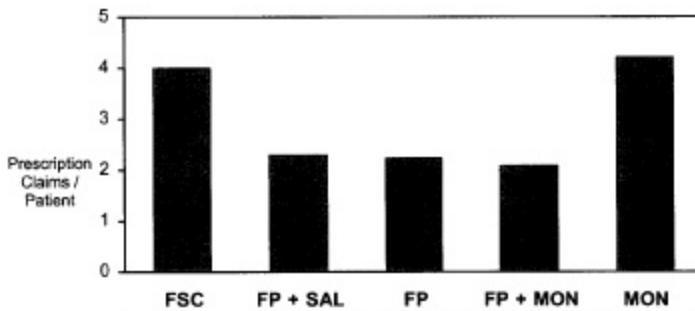
**Fig. 1.** Mean number of ICS prescription claims dispensed within the 12-month postindex period. Number of ICS claims refers to the number of FP prescriptions dispensed as a separate inhaler or in combination with other drugs. SAL, Salmeterol; MON, montelukast.  $p < .05$  compared with the number of ICS prescription claims dispensed in the other cohorts.

\* Stoloff, S.W., Stempel, M.A., Meyer, J., Stanford, R.H., Carranza Rosenzweig, J.R. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004; 113:245-51.



**Fig. 2.** Mean number of SABA prescription claims dispensed within the 12-month postindex period. SAL, Salmeterol; MON, montelukast.  $p < .05$ , FSC compared with combination cohorts. The FSC cohort had a significantly lower mean number of SABA claims dispensed in the 12-month postindex period compared with that in the FP plus salmeterol and FP plus montelukast cohorts.

In a similar study, claims from three commercial health plans and one Medicaid plan were evaluated to assess adherence to the combination inhaler versus individual inhalers.<sup>37</sup> The study covered nearly 9.6 million patients. Refill rates during the 12 month post-index period were compared and are shown below in Figure 3. Short-acting beta<sub>2</sub>-agonist rescue claims were also reduced in this study. Refill persistence was also significantly greater with the combination inhaler.



**Fig. 3.** Mean number of FP prescription claims dispensed in the 12-month post-index period.  $p < 0.05$  for FSC compared to FP+SAL, FP, FP+MON,  $P = 0.06$  for FSC compared to MON.

FSC = fluticasone + salmeterol single inhaler, FP + SAL = fluticasone and salmeterol individual inhalers, FP + MON = fluticasone and montelukast, FP = fluticasone alone, MON = montelukast alone

<sup>37</sup> Stempel DA, Stanford RH, Murphy T. Fluticasone propionate/salmeterol in a single inhaler improves refill persistence compared to fluticasone propionate and salmeterol in different inhalers [poster]. Presented at the American Thoracic Society 99<sup>th</sup> International Conference, May 16-21, 2003; Seattle, WA (pCS Data).

In another study examining refills, the number of prescription claims in the pre-period (two inhaler regimen) showed 4.44 claims for fluticasone and 4.68 claims for salmeterol in the previous 12-month period. In the same patients, the post-period use of the combination inhaler showed 6.93 claims for 12 months, indicating greater refill persistence. In all studies of fluticasone/salmeterol adherence in asthma, there was significantly better refill persistence with the combination inhaler. This study was a retrospective observational study conducted to evaluate refill persistence of combination inhaler fluticasone/salmeterol in patients who previously took this regimen through two separate inhalers.<sup>3</sup>

In COPD, this proposition is supported by a retrospective study comparing an ipratropium bromide/albuterol sulfate combination inhaler to its individual components.<sup>4</sup> The results showed combination inhaler users had a significantly lower risk of emergency department use or hospitalizations (relative risk = 0.58, 95% confidence interval = 0.36, 0.94), lower mean monthly healthcare charges ( $p=0.015$ ), shorter hospital stays (2.05 vs 4.61 days,  $p=0.04$ ), and greater likelihood of compliance (odds ratio = 1.77, 95% confidence interval = 1.46, 2.14) as compared to separate inhaler therapy users. This study concluded that a single inhaler containing both ipratropium and albuterol can increase compliance and decrease respiratory morbidity and healthcare expenditures over and above the effects achieved with separate inhalers for these two agents.

Cardiovascular literature also supports the correlation between combination therapy and better compliance. Subjects receiving a once-daily, single-capsule, fixed-dose combination of amlodipine/benzapril HCl demonstrated significantly better medication adherence and required fewer medical resources than did subjects receiving an angiotensin-converting enzyme inhibitor and a dihydropyridine calcium channel blocker as separate components.<sup>5</sup>

In summary, many COPD patients suffer from multiple, chronic co-morbidities, requiring multiple medications. The differing routes of administration and dosing regimens of these medications contribute to sub-optimal adherence. By simplifying a patient's daily dosing regimens, combination inhalers can increase compliance and adherence.

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\* *Id.*

<sup>4</sup> Chrischilles E., Gilden D., Kubisiak J., Rubenstein L., Shah H., Delivery of ipratropium and albuterol combination therapy for chronic obstructive pulmonary disease: Effectiveness of a two-in-one inhaler versus separate inhalers, 2002 *American Journal of Managed Care*, 8 (10), pp. 902-911.

<sup>5</sup> Taylor, A.A., Shoheiber, O., Adherence to antihypertensive therapy with fixed-dose amlodipine besylate/benazepril HCl versus comparable component-based therapy, 2003, *Congestive Heart Failure* (Greenwich, Conn.) 9 (6), pp. 324-332.

*(c.) A Switch from COMBIVENT to Two Component MDIs Containing the Individual Components (ipratropium bromide and albuterol sulfate) Will Decrease Compliance*

Given the added benefits of combination therapy, it is intuitive that switching from COMBIVENT CFC to its two individual components (ipratropium bromide and albuterol sulfate) is likely to decrease drug compliance and adherence for current COMBIVENT users. Compliance refers to the ability to properly administer medication according to prescription instructions, while adherence has been defined as the extent to which a patient's behavior (e.g., taking medication, following a diet, and/or executing lifestyle changes) corresponds with recommendations from a health care provider.

Because COMBIVENT patients are characterized by advanced age and multiple co-morbidities (often times including depression)<sup>41</sup>, compliance and adherence will be especially challenging. All of these factors have been demonstrated to be directly associated with decreased compliance and adherence.

Further, one cannot ignore the impact loyalty has on compliance. Data indicate that the majority of US COMBIVENT patients are continuing users and have been on therapy for an extended period of time.<sup>42</sup> This suggests COMBIVENT users are very satisfied with the product, and possibly have an emotional reliance on it.

Melani AS *et al* noted in a multi-center observational study that there is great confusion among asthma and COPD patients over how to correctly administer their MDI medications.<sup>43</sup> This study concluded that 24% of patients did not correctly administer their medication. Incorrect administration can compromise the amount of medication delivered in each puff. Forcing COMBIVENT patients to two separate individual component inhalers (ipratropium bromide and albuterol sulfate) only risks compounding this misuse.<sup>44</sup>

While the ultimate effects of moving COMBIVENT patients to two separate individual component inhalers (ipratropium bromide and albuterol sulfate) cannot be certain, the research described above suggests significant negative outcomes for patients are likely. For example, while COMBIVENT represents an important maintenance therapeutic treatment for COPD patients, it is also often utilized for rescue

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<sup>41</sup> Verispan.

<sup>42</sup> In November 2005, 81% of COMBIVENT patients were continuing patients, and only 19% of patients were new to COMBIVENT (switches or add-on users). Verispan.

<sup>43</sup> Melani AS, et al. Inhalation technique and variables associated with misuse of conventional metered dose inhalers and newer dry powder inhalers in experienced adults. Ann Allergy Asthma Immunol. 2004 Nov;(93):439-46.

<sup>44</sup> *Id.*

use. In patients with severe airflow limitation, the end of the dosing interval and accompanying trough of forced expiratory volume in one second (FEV<sub>1</sub>) could lead to increased symptoms that require prompt relief, periodically qualifying as rescue. The combination of ipratropium and albuterol in a single inhaler decreases the risk of drug confusion during a breathing "attack." It also ensures administration of accurate dosages of the two drugs.

Medical consequences are associated with not having available appropriate COPD treatment. In anticipating the onset of breathing problems (something most COPD patients work to avoid and something that drives maintenance use), a patient may experience treatment delays due to confusion over which MDI to use. This risk will be introduced if two separate individual component MDI inhalers (ipratropium bromide and albuterol sulfate) replace COMBIVENT in their treatment regimen. A patient inappropriately using the maintenance MDI thinking it will provide prompt relief could experience a delay in the relief of bronchospasm, with a resulting associated delay in symptom relief and in a full-blown breathing attack. In such a situation, the patient may also feel that the MDI is malfunctioning and continue taking the medication. While there is a favorable safety profile associated with ipratropium bromide, the likelihood of unwanted anticholinergic effects increase with increased dosing. Lastly, a patient using these two component MDIs may not be gaining the full benefit of combination therapy if visual, arthritic, or cognitive problems interfere with the sequential administration of two separate devices requiring two actuations each.

In a recent market research study,<sup>6</sup> non-compliance was found to be one of the leading factors behind patients visiting emergency rooms with COPD exacerbations. This is more likely to occur in COMBIVENT users due to their advanced age, multiple co-morbidities, and severe or very severe COPD, as compared to the average individual. This is compounded by potential language barriers and reliance on multiple medications.

*(d.) Current Mono Component Alternatives (ipratropium bromide and albuterol sulfate) are Inadequate*

The premature removal of the essential use status of COMBIVENT will pose unique and difficult issues when it comes to identifying adequate alternatives. All other CFC MDIs being reformulated will undergo a switch from a single inhaler to another. Though this is clearly in the best interest of patients, and obviously BI's goal for COMBIVENT, premature action will force a switch from one to two separate individual component inhalers (ipratropium bromide and albuterol sulfate).

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<sup>6</sup> A survey profiling 163 hospital based physicians (both Community- and Academic- based). Primary market research completed 10/05 by TNS Healthcare, requested by Boehringer Ingelheim. Data on file.

This switch to two separate individual component inhalers (ipratropium bromide and albuterol sulfate) would be challenging and risky enough if we were in a "business as usual" environment. As FDA is well aware, however, we are not; rather, we are steeped in an unprecedented transition of both patients and products that is presenting challenges on many fronts. To cite one challenge, the elongated and choppy albuterol transition must regain its equilibrium and be managed to a successful conclusion. This is a minimum hurdle to begin even considering whether one of the active moieties of COMBIVENT is available to patients. The other active moiety of COMBIVENT (ipratropium bromide, an anticholinergic), or an equally effective alternative, must also be available and selected by physicians for over two million patients in the US. Because these alternatives are not a direct replacement for COMBIVENT, this will no doubt take a considerable amount of educating, assessing, and monitoring, and, unfortunately, too many exercises in trial-and-error. Further, patient management issues aside, manufacturers of potential alternatives (e.g., albuterol and Atrovent® [ipratropium bromide HFA] Inhalation Aerosol)<sup>6</sup> must be in a position to meet the added demand of over two million US patients on a consistent basis.

The ipratropium bromide and albuterol sulfate component alternatives may also be inadequate from an economic standpoint. Increased drug costs can prevent some patients from effective access to their medication. For example, the current combined cost of two mono-therapy alternatives is more than the cost of COMBIVENT CFC. Requiring patients to switch to the more expensive separate individual component inhalers (ipratropium bromide and albuterol sulfate) would also increase health care costs for both private and governmental payors, and increase patients' out-of-pocket costs, as they would be faced with two co-payments instead of one. While most COMBIVENT patients have public or private coverage, many (approximately 25%) under private coverage do not have comprehensive healthcare packages. This could effectively deny them access to necessary treatments.

*(e.) A Switch from COMBIVENT to the Two Mono Component Inhalers (ipratropium bromide and albuterol sulfate) May Reduce Compliance and Increase Exacerbations, Thus Raising Costs to the Healthcare System*

As outlined above, there are several disruptive and risk posing consequences that are likely to result from a gap in the availability of COMBIVENT. Lower adherence and compliance levels, increased chance of drug confusion during rescue attacks, lack of drug availability, and potential lack of access due to higher drug prices, are all potential impacts on COMBIVENT patients. These impacts pose real medical risks. The irregular administration of necessary medication can lead to worsened disease states, increased

<sup>6</sup> BI's motivations here are not driven by its share of the market. This is corroborated by the fact that, in the event of a loss of COMBIVENT, at least two of its products—Atrovent® HFA and Spiriva®—would likely be leading replacement candidates (as a complement to albuterol).

occurrences of medical emergencies, additional co-morbidities, and an increased strain on the healthcare system.

Patient adherence to inhaled combination medications has been best studied in asthma. Improved adherence to inhaled corticosteroids has been associated with decreased asthma-associated morbidity and mortality, whereas under use of prescribed therapy, which includes poor adherence, significantly contributes to poor control of asthma. The consequences of poor adherence in asthma include increased morbidity and sometimes mortality and increased health care expenditures.<sup>47</sup>

A recent UK study showed that frequent exacerbations caused by patient non-compliance with the ipratropium treatment regimen resulted in increased hospitalizations and healthcare costs. The number of hospital admissions for COPD in the UK in 1994 was 203,193, with an average stay of 9.9 days.<sup>48</sup> In a study conducted in UK, the total annual direct costs of treatment for COPD were estimated to be £817.5 million, with 65% of the costs arising from the community managed setting, and 35% from hospitalizations.<sup>49</sup> In the US, it has been estimated that more than 70% of the total medical expenditure for COPD in 1987 was attributable to the hospitalization of patients.<sup>50</sup>

Non-compliance is a significant barrier to improving patient health. The rapid onset of the benefit perceived by patients when taking short acting beta<sub>2</sub>-agonists tends to encourage compliance, whereas ipratropium bromide with its longer onset of action, may have a perceived delayed or reduced benefit. Thus, ipratropium compliance is ensured when the two therapies are administered in a combined product.

Another study shows that a combined formulation therapy consisting of ipratropium and an inhaled beta<sub>2</sub>-agonist (2-in-1 therapy) leads to lower respiratory-related healthcare use and charges due to improved compliance, compared with treatment with separate ipratropium and beta<sub>2</sub>-agonist inhalers (separate inhaler therapy).<sup>51</sup> The study was designed as a retrospective inception cohort study, during which healthcare use, charges, and treatment compliance were examined. It reviewed health claims data on adults age 38+ who initiated ipratropium therapy on or after July 1997. The patients were enrollees from five health plans during the period July 1997

<sup>47</sup> Stoloff, S.W., Stempel, M.A., Meyer, J., Stanford, R.H., Carranza Rosenzweig, J.R. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004; 113:245-51.

<sup>48</sup> Sullivan SD, Ramsey S, Lee TA, The Economic Burden of COPD. *Chest* 2000; 117: 5-9.

<sup>49</sup> Guest J, Dis. Manage. Health Outcomes 1999, 5: 93-100.

<sup>50</sup> Strassels S et al, Eur Respir J 1996, 9 (suppl 23) 421S.

<sup>51</sup> Chrischilles E., Gilden D., Kubisiak J., Rubenstein L., Shah H. Delivery of ipratropium and albuterol combination therapy for chronic obstructive pulmonary disease: Effectiveness of a two-in-one inhaler versus separate inhalers. 2002 *American Journal of Managed Care*, 8 (10), pp. 902-911.

through December 1998. A total of 428 patients received 2-in-1 therapy, and 658 patients received separate inhaler therapy. After adjusting for baseline covariates, 2-in-1 therapy users had a significantly lower risk of emergency department use or hospitalization, lower mean monthly healthcare charges (an adjusted mean difference of \$46 per person per month), lower mean charges for respiratory medications (an adjusted mean difference of \$13.97 per month per person), and shorter hospital stays (2.05 vs. 4.61 days).<sup>32</sup>

An additional market research study in 2006 suggested that improved compliance was one of the primary results of switching patients from a dual component therapy regimen of ATROVENT and albuterol to combination therapy of COMBIVENT.<sup>33</sup>

**(4.) Sound Public Policy Dictates that FDA Maintain the Essential Use Designation for COMBIVENT**

To its great credit, FDA recognized early the need to give special consideration to CFCs used for essential MDIs. The Montreal Protocol parties later also did the right thing by following suit. The common objective behind these decisions was compelling and straightforward: *to ensure that the health and safety of the many millions of patients relying on CFC-based MDIs for their health and well-being are not compromised and continue to have access to adequate treatment options.* Inherent in this is the judgment that any environmental benefit that might result from denying CFCs for MDI production is outweighed by patient interests.

This exception, appropriately, was neither permanent nor without a *quid pro quo*. MDI manufacturers seeking CFC exemptions, in return, have been required to demonstrate diligent and meaningful research and development efforts into CFC-free replacements. As detailed earlier in this petition, BI has not only abided by this requirement, but its CFC-free efforts have yielded many successes. Indeed, COMBIVENT is the last of a long line of CFC products to be transitioned. As with any drug development effort, there is of course no guarantee of success. However, these efforts are very mature and promising. And it is our expectation that by as early as 2008, available clinical results will provide a sufficient basis for FDA to pass a definitive judgment on the viability of one program, the CFC-free RESPIMAT successor. The removal of the essential use status of COMBIVENT before that time would potentially needlessly disrupt and put at risk millions of patients (in ways that a one-to-one transition would not).

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<sup>32</sup> *Id.*

<sup>33</sup> In a survey profiling 150 COMBIVENT prescribers, it was shown that both pulmonologists and primary care physicians noted an improvement in patient compliance 4.3 (5 point scale) as a result of switching patients from a dual therapy regimen of Atrovent® and Albuterol to COMBIVENT. Primary market research completed 7/06 by G&S, requested by Boehringer Ingelheim. Data on file.

Sound public policy therefore dictates refraining from taking action on the essential use status of COMBIVENT at least until BI's ongoing development programs produce at least one CFC-free COMBIVENT replacement for patients.

#### E. ENVIRONMENTAL IMPACT STATEMENT

As part of its obligations under the National Environmental Policy Act<sup>54</sup> (NEPA), FDA's regulations require petitioners to prepare an environmental assessment unless the action falls within a so-called "categorical exclusion." Although the action (or inaction) sought herein is not subject to a categorical exclusion, it is otherwise exempted. Specifically, this petition requests FDA to refrain from taking action under the Clean Air Act (CAA).<sup>55</sup> Federal agency actions taken under the CAA are exempt from NEPA's requirements.<sup>56</sup>

Nevertheless, the action requested by this petition will not have a significant effect on the quality of the environment. Global annual emissions of CFCs attributable to COMBIVENT are no more than 500 metric tons. As FDA concluded when it approved the use of CFCs in COMBIVENT in 1996, this "...does not involve a significant release of CFC's into the atmosphere."<sup>57</sup> In fact, its potential effect in delaying full recovery of the ozone layer must be infinitesimal, and the relief sought by this petition would not result in ongoing emissions, but would cease after, at most, only a few years. Even if FDA could demonstrate a measurable environmental benefit, it would not trump the likely human and economic costs this petition seeks to avert. Unlike the albuterol context, a balancing of these costs is a key criterion<sup>58</sup> with which FDA must contend in assessing the ongoing essentiality of COMBIVENT.

From a policy standpoint, granting this petition will not send the wrong signal to other Montreal Protocol parties, or otherwise pose any political risks. The COMBIVENT case is distinguishable, supported by the merits, and involves only fleeting relief.

#### F. ECONOMIC IMPACT STATEMENT

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<sup>54</sup> 42 USC §4321 *et seq.*

<sup>55</sup> Id at 7401 *et seq.*

<sup>56</sup> See Energy Supply and Environmental Coordination Act of 1974 (15 U.S.C. 793(c)(1)).

<sup>57</sup> See note 21, *supra*.

<sup>58</sup> Specifically, the essentiality regulation invoked at the July 14, 2005, PADAC hearing requires consideration of whether "use of the [CFC] product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit." See 21 CFR §2.125(f) and (g)(2) and note 10, *infra*.

In accordance with 21 CFR §10.30, information under this section is to be submitted only when requested by the Commissioner following review of the petition.

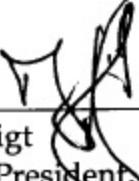
**G. CERTIFICATION**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and it includes representative data and information known to petitioners that are unfavorable to the petition.

**H. CONCLUSION**

For the foregoing reasons, BI respectfully requests FDA to grant this petition and refrain temporarily from taking action to remove COMBIVENT from the list of essential uses of CFCs. Specifically, we urge FDA to postpone action addressing the ongoing essentiality of COMBIVENT at least until BI's ongoing development programs produce at least one CFC-free COMBIVENT replacement for patients. At that point a phase out proposal may be timely and appropriate, and could be pursued in a separate rulemaking.

Respectfully Submitted,  
**BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**

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