

References

References

Those references noted with a "*" are appended to this petition. Copies of all other references are either readily available in the public domain or, as explicitly noted in the footnotes of the petition, available upon request from Boehringer Ingelheim.

¹ See 21 CFR § 2.125(e).

² 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.

³ 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/>.

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

⁵ Decision of the Parties IV/25.

⁶ "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.

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

⁸ 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>.

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

¹⁰ 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:

¹¹ 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.

¹² 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

¹³ Id

¹⁴ 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.*

¹⁵ Verispan

¹⁶ Id

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

- 18 Verispan
- 19 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.
- 20 Verispan
- 21 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.
- 22 Id. at 15700.
- 23 21 CFR §2.125(g)(2).
- 24 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.
- *25 Rand CS, Wise RA, Nides M et al, Metered-dose Inhaler Adherence in a Clinical Trial, *Am Rev Respir Dis* 1992, 146: 1559-1564.
- *26 Rand CS. Patient and regimen-related factors that influence compliance with asthma therapy. *Eur Resp Rev* 1998; 8 (56): 270-274.
- *27 Roter DL, Hall JA. Physicians' interviewing styles and medical information obtained from patients. *J Gen Intern Med* 1987; 2: 325-329.
- *28 Chapman KR, Effect of the Inhaled Route of Administrations on Compliance in Asthma, *Eur Resp Rev* 1998, 8 (56), 275-279.
- *29 Campbell LM, Once-daily inhaled corticosteroids in mild to moderate asthma: improving acceptance of treatment. *Drugs*, 1999; 58 (Suppl. 4): 25-33; discussion 52.
- *30 See American Thoracic Society Standards for the Diagnosis and Care of Patients with COPD, and British Thoracic Society Guidelines.
- *31 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.
- *32 Canadian Thoracic Society Guidelines for the Assessment and Management of COPD.
- *33 Tashkin, D.P., Multiple Dose Regimens : Impact on Compliance, *Chest* Vol.117, 5 May 1995 Suppl.
- *34 Zablotskaia, N., Ignatiev, V. et al, Means of Increasing Compliance in COPD Patients, *Eur Respir J* 14, Suppl 30.
- *35 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.
- *36 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.
- *37 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 99th International Conference, May 16-21, 2003; Seattle, W A (pCS Data).

- *38 Id
- *39 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.
- *40 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.
- 41 Verispan
- 42 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]
- *43 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.
- *44 Id
- 45 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.
- 46 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).
- *47 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.
- *48 Sullivan SD, Ramsey S, Lee TA, The Economic Burden of COPD. *Chest* 2000, 117: 5-9
- *49 Guest J, *Dis. Manage. Health Outcomes* 1999, 5: 93-100.
- *50 Strassels S et al, *Eur Respir J* 1996, 9 (suppl 23) 421S
- *51 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.
- *52 Id
- 53 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.
- 54 42 USC §4321 *et seq.*
- 55 42 USC 7401 *et seq.*
- 56 See Energy Supply and Environmental Coordination Act of 1974 (15 U.S.C. 793(c)(1)).
- 57 See note 13, *supra*.

⁵⁸ 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 9, *infra*.