



November 24, 2008

Kristine T. Khuc, PharmD, RPh
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

RE: Docket No. FDA-2008-N-0038

Dear Dr Khuc and Committee Members:

The American Academy of Pediatrics (AAP) is an organization of 60,000 pediatricians committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults. The AAP, at the request of the Section on Allergy and Immunology and the Section on Pediatric Pulmonology, urges the FDA to carefully reconsider any proposal to remove long-acting beta-agonist bronchodilators from the market, and act to keep these medications available for children with asthma.

This request is based on a careful consideration of the data available in the pediatric age group on the efficacy and safety of this class of medication when used in concert with inhaled corticosteroids. Multiple publications have shown that the addition of long acting beta agonists to inhaled corticosteroids is a highly efficacious and effective approach to treating asthma that is not adequately controlled with inhaled corticosteroids alone. Long acting beta agonist bronchodilators, when studied in thousands of patients who were on concomitant inhaled steroids, have not been associated with increased exacerbations or increase of severity of exacerbations of asthma. This has been demonstrated already to the FDA when one of the drugs, Salmeterol, received approval in children as young as 4 years of age. The only study that may indicate a tendency to increased risk of severe exacerbations and death was the SMART study, which enrolled a limited number of adolescents and no children, and most of the subjects in that study were not on concomitant inhaled steroids. Furthermore, since these medications are currently available in fixed dose combinations, the use of the long-acting beta-agonist with concomitant inhaled steroids can be assured.

The National Asthma Education and Prevention Program's Expert Panel considered these issues when writing the 2007 *EPR-3: Guidelines for the Diagnosis and Management of Asthma*, and included inhaled corticosteroids plus long-acting bronchodilators as preferred therapy for persistent asthma (Step 3 in children from 5-11 years of age and children 12 years of age and over, Step 4 therapy in children 0-4 years of age). Using this important evidence-based reference, as well as other data, the AAP's updated eQIPP (Education in Quality Improvement for Pediatric Practice) module on asthma, also consistently recommends the same treatment.

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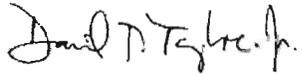
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To remove these products from the armamentarium of asthma therapies for children would both deprive children of a valuable medication, and also undo years of education provided to pediatricians by experts in the AAP with little data to support the action.

We strongly encourage the FDA to keep long acting beta agonist medications available for the management of asthma.

Respectfully submitted,

A handwritten signature in black ink that reads "David T. Tayloe, Jr." in a cursive style.

David T. Tayloe, Jr., MD, FAAP
President

DTT/dlb

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AAW/AX
25th November 2008

**Statement for the FDA
Joint Advisory Committee Meeting on LABAs**

Dear Sirs,

I am writing to you from the United Kingdom, to express my extreme concern about the threat to my asthma patients posed by any threat to supply of long acting beta two agonist (LABA) drugs.

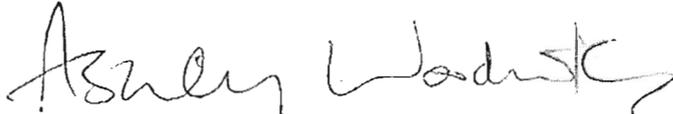
Asthma patients using inhaled steroids (ICS) alone can have good asthma control; but they usually still need to use a rescue inhaler frequently - they never escape their disease. It is not surprising that compliance is notoriously poor for this preventive treatment when used alone. And data from Canada shows that asthma mortality is directly related to poor compliance.

LABAs must always be used with ICS. I am sufficiently experienced (old!) to remember the initial introduction of salmeterol and the first patients coming back to my clinic with mild and moderate asthma. For the first time in their memory, they were effectively "cured" - by this I mean that they had absolutely no symptoms by day or night, and didn't need to use rescue salbutamol (albuterol). This initial favourable impression was borne out, by both clinical experience, and large-scale clinical trials. When LABAs are used with inhaled steroids in combination therapy, they improve patient compliance (compared to inhaled steroids alone), provide optimal asthma control, and reduce exacerbations substantially. The introduction of combination LABA/ICS inhalers in many countries and especially the United States has been contemporaneous with falls in asthma mortality.

I welcome a careful assessment of safety. However, publications on safety using meta-analyses without the full clinical context distort the risk-benefit analysis. Authors of these articles and the attendant publicity carry heavy responsibility. They create great uncertainty for our patients, loss of treatment compliance, and a breakdown in patient confidence with their physicians. Patients have stopped treatments inappropriately, had exacerbations, and most probably some have died.

The clinical benefits for patients must not be underestimated. We are not talking here is that about a statin with potential benefits in a decade, or a Cox2 inhibitor for which there are alternatives. Combination inhalers really have revolutionised the care of asthma patients worldwide, and alternative treatments are clinically inferior. I predict that the unwarranted withdrawal of LABAs would destabilise asthma treatment and increase asthma mortality not only in the US, but worldwide.

Yours sincerely,



Ashley Woodcock OBE MD BSc MB ChB FRCP FMedSci
Professor Respiratory Medicine

Co-chair, Medical Technical Options Committee of the Technology
Environmental Assessment Panel under the Montreal Protocol

Head of School of Translational Medicine University of Manchester

Consultant Respiratory Physician – University of South Manchester Hospital
Foundation Trust

Prof Woodcock has acted as Consultant/Study Principal Investigator for
AstraZeneca, Chiesi, GlaxoSmith Kline, and Schering Plough.



Asthma and Allergy
Foundation of America

Delivered via email: Kristine.Khuc@fda.hhs.gov

November 25, 2008

The Pulmonary-Allergy Drugs Advisory Committee
The Drug Safety and Risk Management Advisory Committee
The Pediatric Advisory Committee
Food and Drug Administration
c/o Kristine T. Khuc, Pharm.D, R.Ph.
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Joint meeting to discuss the benefit risk assessment of long acting beta-2 adrenergic agonists for the treatment of asthma in adults and children

Dear Committee Members:

I am writing on behalf 20 million Americans with asthma. Since 1953, the Asthma and Allergy Foundation of America (AAFA) has been dedicated to improving the quality of life for people with asthma and allergies. Patients, their families, and their caregivers turn to our organization for education, research, and advocacy.

AAFA appreciates your taking time to diligently review and discuss the benefit risk assessment of long acting beta-2 adrenergic agonists (LABAs) for the treatment of asthma in adults and children. AAFA appreciates heightened vigilance at the FDA regarding drug safety and thanks the members of the three FDA committees who are meeting jointly to discuss potential safety concerns with this class of drugs. Asthma, of course, is a treatment-intense condition for many patients and your advice to the Agency today will affect millions of individuals who depend on these products as part of their regimen for asthma control.

One such patient is Chris Ward, who is the Immediate Past Chair of our national Board of Directors. In 2005, when the Pulmonary-Allergy Drugs Advisory Committee (PADAC) met regarding safety of LABAs, Mr. Ward stated, "...as we understand it, there are no concerns with the efficacy of this class of drugs and their important role in asthma control, which is reflected in both the national and international guidelines for asthma clinical care ... When we weigh this evidence of effectiveness against the evidence of potential risk, which is at best still undefined, we believe it would be difficult for asthma patients to understand why these products would not continue to be available to them."

Unless there is compelling new evidence of potential risk beyond our current understanding, we reiterate Mr. Ward's point that withholding this class of medications will be difficult to understand for the asthma patients who rely on them.

We have heard concerns about the safety of these drugs. Indeed, this Agency warned that

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that these medications can cause a "small but significant risk in asthma-related deaths" and issued a black-box safety label for them. In 2006, GlaxoSmithKline, the sponsor of Salmeterol Multicenter Asthma Research Trial (SMART), a 28-week randomized clinical study, terminated the study early reportedly due to preliminary findings in its African-American study participants and difficulties in enrollment. The study's authors speculated about what might have led to these findings but drew no firm conclusions. They suggested additional research to identify factors that contributed to the outcomes in that population. A 2006 meta-analysis by Bateman et.al. of random efficacy studies by GlaxoSmithKline found no clinically significant effect of Salmeterol on asthma-related hospitalizations, but offered no useful guidance on the apparently higher mortality rates in African-Americans noted in SMART.

We hope that findings from scientific experts based on reliable, demonstrable clinical evidence are presented for full review and discussion by you in your committee meeting. Patients have to look to the scientific-clinical community for expertise and guidance. We hope you will approach this issue with a strong appreciation that patients rely on this medication and are using it successfully in their treatment plans. We urge you to approach risk assessment for this class of medications with integrity, objectivity and compassion.

At this point, we find the advice offered by Kevin B. Weiss, MD in an editorial published in the July 1, 2008 edition of the *Annals of Internal Medicine* to be compelling.

Because we cannot expect any more new data, how should physicians and patients use combination therapy? Perhaps the best advice is to consider using combination therapy only for indications that accord with nationally accepted clinical guidelines (*2007 NHLBI Asthma Guidelines*). Specifically, long-acting β -agonists with or without inhaled corticosteroids should not be used as first-line treatment and especially not for persons with mild asthma. In addition, the prudent course would be to use this treatment only when the physician is confident that the patient will adhere to close monitoring and instructions to seek care when asthma is out of control. Moreover, physicians should consider alternative therapy for patients at high risk for severe exacerbations, including those who have difficulty accessing health care in an emergency (because of lack of health insurance or other sociobehaviorial factors that may affect ability to adhere to treatment recommendations).

- Kevin Weiss, MD, *Annals of Internal Medicine*, July 1, 2008

We do not dismiss concerns raised in the 2006 SMART study. To the contrary, we urge further investigation, particularly into the apparent disparate outcomes associated with its African-American subjects. Other studies have well documented the higher prevalence of asthma among Americans of African descent. This group is also associated with significant under treatment of asthma especially among children (a 2000 study by Rand, et. al. published in the *Journal of Allergy and Clinical Immunology* 2000 found that only 12% of Black children had used long-term control medications for their asthma in the past six months). We hope that your discussions will acknowledge the needs of African-Americans who suffer from asthma, but caution that restricting

medications for non-African-American patients like Chris Ward will also diminish treatment opportunities for others with asthma like the daughter of the President-Elect. We also note the continued need to address access to care so that all who have asthma may benefit from the best treatment options available for them, but that issue is not before you.

To Dr. Weiss' advice, we caution physicians to avoid the pitfall of stereotyping patients as less likely to be medication adherent based on obvious sociobehavioral factors like ethnicity or lack of health insurance alone. We prefer a commonsense approach involving direct communication with patients about factors that promote adherence, notwithstanding ethnicity or other sociobehavioral factors.

We hope that as you examine and discuss evidence that LABAs may be associated with higher risks for some asthma patients that you fully consider the benefits of this class of medications for patients like Mr. Ward who successfully relies on them as part of his asthma management. We look forward to reviewing and communicating the Committee's discussion to asthma patients. We hope that your recommendations are not difficult for asthma patients to understand, and that your decision-making process is calculated to guide physicians and patients without unduly alarming them.

Sincerely,

A handwritten signature in cursive script, appearing to read "William M. McLin".

William McLin, M.Ed.
President

Statement to the Pulmonary and Allergy Disease Advisory
Committee Hearing at FDA, Dec 10-11, 2008 on Safety of Long-
Acting Beta-Agonists.

Nicholas J Gross MD PhD FCCP
Professor, Departments of Medicine & Molecular Biochemistry
Stritch-Loyola School of Medicine, Maywood IL
Volunteer Attending Physician, Hines VA, IL

I wish to address the issue of the safety of long-acting beta-agonists (LABAs), specifically in COPD. I have a career-long interest in COPD as well as asthma. I have performed numerous clinical studies with many investigational drugs including LABAs, written extensively on the basic and therapeutic issues surrounding these diseases and treatments, and for many years have conducted a COPD clinic where I have seen and treated many patients with COPD and used LABAs extensively.

Although the subject of this hearing is the safety of LABAs in relation to their use in asthma, the safety concern has not been limited to that condition. The box warnings attached to all LABAs have even been applied to LABAs that do not have an asthma indication. Thus both recently approved nebulizer solutions of formoterol, Performist® and Brovana®, although only indicated for the treatment of COPD, have box warnings that draw attention to an “.. increased risk of asthma-related deaths..”. I am concerned that the safety warning should state that the risk, if any, is limited specifically to the use of LABAs in asthma and that their use in COPD has not been associated with a similar risk. As it stands, the box warning has given rise to alarm amongst COPD patients, some of whom have been reluctant to use LABAs despite their clinical need for them and the well-established place of LABAs in COPD Guidelines (1, 2).

The safety of long-term use of LABAs for COPD, both as monotherapy and in combination with inhaled corticosteroids, has recently been extensively reviewed (e.g. 3, 4). They do not indicate a risk of increased mortality or serious adverse events in COPD patients. In addition, the 3-year prospective randomized, controlled trial of a salmeterol-fluticasone combination and each of its components in approximately 6,000 COPD patients (5) showed that serious adverse events tended to be less frequent and survival tended to be better in the salmeterol containing arms. Recent studies of the long-term use of formoterol in COPD patients similarly reveal no safety concerns (e.g. 6). The evidence, therefore, strongly suggests

that the long-term use of both the currently available LABAs is not associated with any increase in all-cause or respiratory specific mortality, and that other important patient-centered outcomes such as the frequency of acute exacerbations are improved.

I share the interest of the FDA and its PADAC in reviewing the safety of LABA use in asthma; my comments are not directed to that use. My concern is solely that warnings about the potential risks of LABA use in asthma not be extended to drugs that only have a COPD indication and that any safety statement that the FDA requires for these agents not be made in a manner that might give the impression that there is a similar concern about the use of these important drugs in patients with COPD.

1. The Global Strategy for Diagnosis, Management and Prevention of COPD (2007). www.goldcopd.org
2. Celli BR, MacNee W, and committee. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932-46.
3. Rodrigo GJ, Nannini LJ, Rodriguez-Roisin R. Safety of Long-Acting beta-agonists in stable COPD. *CHEST* 2008;133:1079-87.
4. Jara M, Lanes SF, Wentworth C, et al. Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. *Drug Safety* 2007;30:1151-60.
5. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;365:775-89
6. Donohue JF, Hanania NA, Fogarty C, et al. Long-term safety of nebulized formoterol: results of a twelve-month open-label clinical trial. *Ther Avd Respir Dis* 2008;2:199-208.

FDA Statement for December 10, 2008

FDA Advisory Panel for review of long-acting β -adrenergic agonists

– prepared by Stanley J. Szeffler, MD on behalf of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology on November 22, 2008

Thank you for allowing me to make a statement on behalf of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. My name is Dr. Stanley Szeffler and I am an asthma specialist trained in pediatrics, allergy and immunology and clinical pharmacology. Currently, I am the Director of the Pediatrics Section of the Weinberg Clinical Research Unit at National Jewish Health and Professor of Pediatrics and Pharmacology at the University of Colorado Denver School of Medicine. I am also a member of the Expert Panel-3 responsible for the recently revised NIH asthma guidelines. I am also a member of four NIH asthma networks currently conducting asthma management research in children and adults including a network focused on the inner city.

My purpose today is to remind you of the advances in current therapy that have been provided by the asthma guidelines and the introduction of several new medications including long-acting β -adrenergic agonists or LABAs. Both directions have revolutionized asthma care. We have now successfully replaced a system of symptom-reaction based treatment that applied short acting β -agonists and systemic steroids for symptom relief to a system focused on asthma control or symptom prevention with a well organized algorithmic approach to treatment based on appropriate use of long-term controllers, primarily inhaled corticosteroids.

Not long ago, maintenance therapy consisted of the use of theophylline, a drug well known for its adverse effects and requirement for careful dose titration with blood level monitoring. This treatment often required supplementary oral steroids and their consequent adverse effects when this therapy was inadequate. The transition period included the use of low potency inhaled corticosteroids that required high doses and frequent administration to manage moderate to severe asthma in children.

The recognition of inflammation as a core to persistent asthma redirected treatment to ICS as the preferred long-term controller therapy for asthma management including children of all ages. This led to the development of higher potency inhaled corticosteroids to manage moderate to severe asthma and also allowed improved asthma control with twice daily administration. However, it is well known that long-term use of high dose inhaled corticosteroids carries a risk of adverse effects, such as growth and adrenal suppression.

The introduction of long-acting β -agonists not only replaced the need for theophylline but also reduced the need for high-dose ICS therapy. Consequently, theophylline is rarely used and the need for high-dose ICS is also limited. By combining LABA with low to medium dose ICS, we have observed several major changes in asthma outcomes. The last seven years shows a pattern for reduced asthma mortality and at least a plateau in hospitalizations due to asthma. There also appears to be a marked reduction in the number of severe asthmatics requiring maintenance oral steroid therapy and therefore a reduction in severe steroid-related adverse effects.

The benefits of combined ICS and LABA have been well described in studies conducted in adults, but admittedly less information is available in children less than 12 years of age. The asthma guidelines clearly addressed this issue and called for additional studies. Meanwhile, the asthma guidelines did recognize the benefits of LABA as an optional choice for Step 3 therapy in those inadequately controlled on low-dose ICS.

Based on the asthma guidelines, a physician faced with a patient inadequately controlled on low dose ICS can choose from increasing to medium dose ICS or adding LABA, leukotriene blockers or theophylline to low dose ICS. A preferred supplementary choice can not be recommended due to lack of comparative studies in children. However, it is well known that the clinical experience with theophylline is now limited and younger physicians are not familiar with the drug interactions associated with theophylline. Furthermore, the need for blood level monitoring is not a desirable option for asthma management in children. Although leukotriene blockers are another alternative, studies to date have pointed to their limited efficacy as a supplementary therapy in adults with moderate to severe asthma. Evidence is much clearer for the benefits of LABA as a supplementary therapy.

There is no doubt that LABA should not be used as monotherapy for asthma management in either children or adults and this is supported by current asthma guidelines. However, based on concern regarding adverse effects and limited comparative data, a step to reduce the availability of LABA as a supplementary therapy for asthma management in children and adults would limit therapeutic options to those with less efficacy or more significant adverse effects. In effect, this would move asthma care back to a state of management we witnessed over 20 years ago that was fraught with serious neurological adverse effects related to theophylline and the requirement for blood level monitoring. In addition, the lack of efficacy of other alternatives, such as cromolyn and leukotriene blockers, in this level of severity would lead to more exacerbations and thus prompt dependence on rescue oral steroid therapy also associated with severe adverse effects related to growth, osteoporosis, skin atrophy, and adrenal suppression, as well as increased risk for cataracts.

Furthermore, answers to questions related to the comparative effect of increasing ICS to medium dose or adding a LABA or leukotriene blockers to low dose ICS await the completion of an NIH Childhood Asthma Research and

Education (CARE) Network study that should be presented in early 2010. That study promises to show the best treatment for Step 3 therapy in children older than 5 years of age and also the associated features of patients responding to each medication option.

Until the results of this CARE Network study are available, the principles of the asthma guidelines should be supported regarding the careful assessment of the need for LABA as supplementary therapy for ICS rather than the consideration for prohibiting its use. LABA is particularly helpful in improving pulmonary function in those children and adults with low pulmonary function and serves as a bronchoprotective agent in those patients with exercise-induced asthma and a tendency for nocturnal exacerbations. When combined with ICS therapy, LABA helps provide immediate relief of symptoms while the inflammatory component of asthma is addressed with continued ICS therapy. Certainly attempts to step down therapy should be prompted when control is established.

There is also no doubt that evidence is lacking for the role of LABA in children less than 5 years of age. Although the guidelines list LABA as supplementary therapy in this age group for asthma inadequately controlled by medium dose ICS, there is admittedly no information to base this recommendation on other than projected efficacy from studies conducted in adults. Therefore, one cannot argue against a recommendation to avoid use of LABA in young children unless the diagnosis is confirmed and other options such as medium dose ICS and a trial of leukotriene blockers have failed.

Therefore as a spokesman for the AAAAI and ACAAI, I ask you to carefully analyze the available data on LABA in children and adults. Physicians are already aware and should continue to be reminded of potential adverse effects of LABA. Efforts to prohibit its use in children and adults would push us back to alternatives with demonstrated greater risks and more limited effectiveness, especially for children 5 to 11 years of age. Such studies in this age group are already in progress and must be evaluated before directions in therapy are made. In addition, carefully conducted studies on the benefits and adverse effects of LABA therapy in young children should be conducted if there is demonstrated need for this treatment as determined by a noticeable increase in the use of this medication for respiratory symptom management in this specific age group. However, based on many studies and patient outcomes, there is no question that LABA is a most beneficial treatment option for asthma patients of all ages. The risk to benefit ratio clearly favors their use. It is for these reasons the expert panel prominently recommended their use in the new asthma guidelines. I urge you to trust that the expert panel has done due diligence in reviewing all treatment options and continue to support the availability of these valuable agents to better manage our patients with asthma.