DIVISION DIRECTOR MEMORANDUM

Date: June 15, 2005

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug Products, CDER, FDA

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials prepared for the meeting to discuss the implications of the available data related to the safety of long-acting beta-agonist bronchodilators

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on July 13, 2005. As members of the PADAC, you provide important expert scientific advice and recommendations to the U.S. Food and Drug Administration (the Agency) on various regulatory decision making processes, including those related to the continued assessment of safety and efficacy of drugs marketed in the United States. The objective of the upcoming meeting is to discuss the implications of available data related to the safety of long-acting beta-agonist bronchodilators. There are two long-acting beta-agonist bronchodilators marketed in the United States that will be discussed in the meeting. These are salmeterol xinafoate, marketed as a single ingredient product under the trade name Serevent and as a combination product with fluticasone propionate, marketed under the trade name Advair, and formoterol fumarate, marketed as a single ingredient product under the trade name Foradil. Products containing salmeterol available in the United States are from GlaxoSmithKline (GSK), and products containing formoterol in the United States are from Novartis.

Products containing salmeterol and formoterol are indicated for use as bronchodilators in patients with asthma and chronic obstructive pulmonary disease (COPD) as maintenance treatment. Salmeterol and formoterol are effective bronchodilators with extended durations of action and they also improve various aspects of the patients' diseases. These drugs form an important component of the treatment options available for asthma and COPD. Salmeterol and formoterol have adverse effects that are typical of beta-adrenergic agonists. Additionally, an important adverse effect that has been observed in association with these drugs in patients with asthma is the occurrence of severe asthma exacerbations, reported in a small number of patients. These occurrences were seen in a large post-marketing study conducted by GSK with salmeterol, called the Salmeterol Multicenter Asthma Research Trial (SMART), and in the phase-3 clinical studies conducted by Novartis with formoterol to support registration of formoterol in the United States. The intent of this PADAC meeting is to discuss and deliberate on this specific finding of severe asthma exacerbations. Since the available data pertains only to asthma patients, the focus of the discussion is intended to be on asthma and not COPD.

The safety of the short-acting bronchodilators, such as albuterol, is not the subject of this PADAC meeting. Although albuterol has indications similar to long-acting beta-agonists, various asthma treatment guidelines recommend that albuterol be used as needed as a reliever medication in the treatment of asthma. Long-acting beta-agonists, on the other hand, are recommended to be used continuously as controller medications in the treatment of asthma, consistent with their pharmacology. Also, the scientific literature suggests that scheduled use of albuterol may be associated with worsening control of asthma in some patients.[1,2]

Background materials, relevant to this meeting, are attached to this memorandum. These background materials include several documents which were prepared by the Agency, some published articles, as well as the labels for formoterol and salmeterol-containing products. The documents prepared by the Agency include summaries of post-marketing studies conducted by GSK for salmeterol (SMART study) and by Novartis for formoterol, including findings and opinions based on the clinical reviews of the applicants' submissions.

Subsequent sections of this memorandum summarize some relevant findings from the salmeterol and formoterol clinical development programs and the post-marketing studies, and the key issues and questions for discussion at the PADAC meeting.

Salmeterol

There are three salmeterol containing products that have been approved for marketing in the United States. These are Serevent (salmeterol xinafoate) Inhalation Aerosol, Serevent Diskus (salmeterol xinafoate inhalation powder), and Advair Diskus (fluticasone propionate and salmeterol). GSK has chosen to discontinue the marketing of the Serevent Inhalation Aerosol in the United States, consistent with the phase-out of inhalation aerosols containing chlorofluorocarbons, which deplete the ozone layer of the earth's atmosphere.

The clinical development program conducted by GSK to support an asthma indication in adult and adolescent patients for salmeterol was typical of a drug of this class. The Serevent Inhalation Aerosol phase 3 program included two placebo- and active-controlled (albuterol inhalation aerosol) 12-week studies in patients 12 years of age and older with mild-to-moderate asthma (n=556). The Serevent Diskus phase 3 program included two placebo- and active-controlled (albuterol inhalation aerosol) 12-week studies in patients 12 years of age and older with mild-to-moderate asthma (n=451). GSK subsequently conducted four studies in patients with asthma on concomitant inhaled corticosteroids to assess the effect of adding salmeterol to inhaled corticosteroids (n=1,922). These latter studies utilized the inhalation aerosol formulation of salmeterol for a treatment period of 6 months. The Advair Diskus clinical development program included three 12-week studies in patients 12 years of age and older with asthma where Advair Diskus was compared to its individual components fluticasone and salmeterol (n=1,208). These studies supported the efficacy and safety of

---

[1] Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. NEJM 1996; 335:841-7.

[2] Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the β_2-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med 2000; 162: 75-80.

salmeterol both as a single ingredient product and as a combination product with fluticasone in patients with asthma. These studies did not show a signal of severe asthma exacerbations.

The first salmeterol containing product approved for marketing in the United States for use in patients with asthma was Serevent Inhalation Aerosol. The product was approved in 1994. At that time there were concerns that chronic use of beta-agonists in patients with asthma may worsen asthma control in some patients. Although the clinical program conducted to support registration of Serevent in the United States did not show any signal of acute exacerbation and worsening of asthma, there were literature reports suggesting that chronic use of salmeterol may worsen asthma. A study published in the British Medical Journal in 1993 (the Serevent Nationwide Surveillance Study, the SNS study[3]) that involved approximately 25,000 patients with asthma (16,787 on salmeterol and 8,393 on albuterol) showed that chronic use (16 weeks) of salmeterol was associated with a small and statistically non-significant excess of asthma related death compared to chronic use of albuterol (0.07% compared to 0.02%, a relative risk of 3). Early post-marketing adverse reports suggested that Serevent use may lead to severe adverse asthma outcomes, including deaths. However, spontaneous adverse event reporting cannot, in such cases, establish causality, especially when the adverse event of interest is a manifestation of the disease being treated. Due to accumulating concerns regarding the safety of chronic, regular use of beta-agonists in general and salmeterol specifically, FDA worked with GSK to have them conduct a large, controlled prospective safety study to address this issue. As a result, GSK initiated the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996.

The SMART was a randomized, double-blind study that enrolled patients with asthma not currently using long-acting beta-agonists patients with asthma (average age 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (Serevent Inhalation Aerosol, 42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The study consisted of one clinic visit during which baseline demographic information, medical history, asthma history, concomitant medication use, vital signs, and peak expiratory flow measurements were obtained. To be enrolled, patients were required to have a diagnosis of asthma and be taking prescription asthma medication other than long-acting beta-agonist, and be free of significant systemic diseases. Patients were dispensed with study medication at the clinic visit, and they were contacted by phone approximately on weeks 4, 8, 12, 16, 20, 24, and 28. Due to practical issues of the power of such a study for detecting important differences in a very rare event, the primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation), though the clear interest of the Agency was to look specifically at issues of mortality. Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. The study initially was intended to enroll 30,000 patients, 15,000 patients per treatment arm, to detect a relative-risk difference of 1.4 between salmeterol and placebo. After a total of approximately a total of 15,000 patients had been enrolled, the Data Safety Monitoring Board noted that the observed occurrence of the primary endpoint overall was approximately half of what was expected. The sample size was then revised to enroll 60,000 patients, 30,000 patients per

[3] Castel W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993; 306:1034-7.

treatment arm. GSK halted the study prematurely in January 2003, after a total of approximately a total of 30,000 patients had been enrolled. The study was halted because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including death, particularly in African Americans, but difficulty in enrolling patients would have precluded completing the study within an acceptable time frame.

GSK submitted the preliminary summary results of the SMART to the Agency once they were available. Subsequent to discussion with the Agency, GSK incorporated the preliminary results of the study in all salmeterol-containing product labels, including the addition of a boxed warning cautioning the use of salmeterol in patients with asthma. The labeling changes were performed expeditiously, before a full Agency review of the SMART data, due to the seriousness and importance of the findings. Subsequently, there were some additional minor changes in the labeling language and the data results in the label as complete study results were made available to the Agency by GSK and following a comprehensive review of the data by FDA.

There are two important points in GSK's analysis of the SMART data that are worth noting. First, GSK decided to include the spontaneously reported post-study adverse events for 6 months beyond the 28 weeks of the study, and second, they decided to include data from a National Death Index (NDI) search to capture as many of the outcome events as possible. The protocol did not specify inclusion of the NDI data or the 6 month post-study adverse events data in the analyses data set. The Agency disagreed with GSK's position of including events beyond the protocol specified 28-week study period in the analyses because this post-study period was not controlled and it was possible that patients could take approved treatments for asthma, including salmeterol, once they had completed the 28 weeks of protocol specified treatment. The Agency agreed that capturing events from the NDI search would be reasonable. Table 1 shows the results of the primary endpoint and selected secondary endpoints. The analysis shown in the table does not include events that occurred beyond the 28 week treatment period, but includes events identified in the NDI search.

Table 1. Overall incidence of primary and selected secondary outcomes

	Serevent MDI (n=13,176)	**Placebo (n=13,179)**	**Relative Risk (95% CI)**
Primary Endpoint: Respiratory-related deaths or life-threatening experiences			
Total	50 (<1%)	36 (<1%)	1.40 (0.91, 2.14)
Caucasians	29 (<1%)	28 (<1%)	1.05 (0.62, 1.76)
African Americans	20 (<1%)	5 (<1%)	4.10 (1.54, 10.90)
Secondary Endpoint: Asthma-related deaths or life-threatening experiences			
Total	37 (<1%)	22 (<1%)	1.71 (1.01, 2.89)
Caucasians	17 (<1%)	16 (<1%)	1.08 (0.55, 2.14)
African Americans	19 (<1%)	4 (<1%)	4.92 (1.68, 14.45)
Secondary Endpoint: Respiratory-related death			
Total	24 (<1%)	11(<1%)	2.16 (1.06, 4.41)
Caucasians	16 (<1%)	7 (<1%)	2.29 (0.94, 5.56)
African Americans	8 (<1%)	2 (<1%)	3.88 (0.83, 18.26)
Secondary Endpoint: Asthma-related death			
Total	13 (<1%)	3 (<1%)	4.37 (1.25, 15.34)

	Serevent MDI (n=13,176)	Placebo (n=13,179)	Relative Risk (95% CI)
Caucasians	6 (<1%)	1 (<1%)	5.82 (0.70, 48.37)
African Americans	7 (<1%)	1 (<1%)	7.26 (0.89, 58.94)

While there is interest in assessing the influence of concomitant use of inhaled corticosteroids on the effect of salmeterol, the SMART study was not adequately designed to assess this. For instance, use of inhaled corticosteroids was not randomly assigned, and the best data for inhaled corticosteroids use was collected only at baseline and not during the treatment period. Nevertheless, the data were analyzed based on baseline inhaled corticosteroids use (Table 2). The numbers of events in the subgroups are too small for the basis of any firm conclusion. However, it should be noted that reported use of inhaled corticosteroids at baseline did not have any notable "protective" effect in the African American racial group in whom the signal of concern was most noticeable. Because of significant uncertainties arising from these post-hoc analyses, the labeling changes based on the SMART data, including the boxed warning, were applied to all salmeterol containing products, including the Advair Diskus (fluticasone propionate and salmeterol) label.

Table 2. Primary and selected secondary outcomes by baseline Inhaled Corticosteroid use

	Inhaled Corticosteroids at baseline			No Inhaled Corticosteroids at baseline		
	Serevent	**Placebo**	**Relative Risk**	**Serevent**	**Placebo**	**Relative Risk**
Number of patients						
Total	6127	6138		7049	7041	
Caucasians	4586	4637		4695	4724	
African Americans	906	875		1460	1444	
Primary Endpoint: Respiratory-related deaths or life-threatening experiences						
Total	23	19	1.21 (0.66, 2.23)	27	17	1.60 (0.87, 2.93)
Caucasians	13	15	0.88 (0.42, 1.84)	16	13	1.25 (0.60, 2.60)
African Americans	9	3	3.02 (0.82, 11.11)	11	2	5.61 (1.25, 25.26)
Secondary Endpoint: Asthma-related deaths or life-threatening experiences						
Total	16	13	1.24 (0.60, 2.58)	21	9	2.39 (1.10, 5.22)
Caucasians	6	9	0.68 (0.24, 1.90)	11	7	1.62 (0.63, 4.17)
African Americans	9	3	3.02 (0.82, 11.11)	10	1	10.46 (1.34, 81.58)
Secondary Endpoint: Respiratory-related death						
Total	10	5	2.01 (0.69, 5.86)	14	6	2.28 (0.88, 5.94)
Caucasians	7	3	2.31 (0.60, 8.93)	9	4	2.29 (0.71, 7.42)
African Americans	3	1	3.12 (0.33, 29.92)	5	1	4.43 (0.52, 37.89)
Secondary Endpoint: Asthma-related death						
Total	4	3	1.35 (0.30, 6.04)	9	0	
Caucasians	1	1	0.96 (0.06, 15.35)	5	0	
African Americans	3	1	3.12 (0.33, 29.92)	4	0	

Formoterol

There is only one formoterol containing product approved for marketing in the United States, Foradil Aerolizer (formoterol fumarate inhalation powder). The product was approved for use in asthma in 2001. The product is marketed in one dose strength containing 12 mcg of formoterol, and the recommended dose is 12 mcg every 12 hours.

The clinical development program conducted by Novartis to support the asthma indication was typical for a drug of this class. The Foradil Aerolizer phase 3 program included three pivotal studies: two placebo- and active-controlled (albuterol inhalation aerosol) 12-week studies in patients 12 years of age and older with mild-to-moderate asthma (n=1,095), and one placebo-controlled 1-year study in patients 5-12 years of age with asthma (n=518). In each of the three studies two different doses of formoterol were used, 12 mcg every 12 hours and 24 mcg every 12 hours. The three studies supported the efficacy of formoterol, however there was no remarkable added benefit from formoterol 24 mg every 12 hours over formoterol 12 mcg every 12 hours. In the safety assessment, it was noted that formoterol 24 mcg every 12 hours tended to be associated with more episodes of serious asthma exacerbations as compared to formoterol 12 mcg every 12 hours (Table 3)[4]. A serious asthma exacerbation was defined as an asthma exacerbation that resulted in a life-threatening experience, inpatient hospitalization or prolongation of hospitalization, persistent disability or incapacity, or death. Because of the safety concerns with asthma exacerbations seen consistently across the pivotal phase 3 studies with formoterol 24 mcg, and due to the absence of clear benefits of 24 mcg over the 12 mcg dose, the only dose of formoterol approved for marketing in the United States was 12 mcg every 12 hours.

Table 3. Occurrence of serious asthma exacerbations in three asthma studies with formoterol, results expressed as number of patients with serious asthma exacerbation/total patients in the study (%)

	Placebo	Albuterol 180 mcg BID	Formoterol 12 mcg BID	Formoterol 24 mcg BID
12-wk study in adults and adolescents (study 040)	0/136 (0%)	2/134 (1.5%)	0/136 (0%)	4/135 (3%)
12-wk study in adults and adolescents (study 041)	2/141 (1.4%)	0/138 (0%)	1/139 (0.7%)	5/136 (3.7%)
1-yr study in 5-12 year old children (study 049)	0/176 (0%)	NA	8/171 (4.7%)	11/171 (6.4%)

As a result of concerns arising from the possibility of acute exacerbation and worsening of asthma with the use of the long-acting beta-agonist, salmeterol, and the findings of the formoterol phase 3 studies, the Agency asked Novartis to perform a phase 4 clinical study to further investigate the relative safety of the two different doses of formoterol.

The formoterol phase 4 study was a randomized, blinded, placebo controlled study of 16 weeks duration in 2,307 patients 12 years of age and older with mild-to-moderate persistent asthma (average age 38 years, 79% Caucasian, 13% African American). The study consisted of one baseline visit and visits on weeks 1, 4, 8, 12, 16, during which vital signs, physical examination, pre-and 2-hour post-dose spirometry, and concomitant medication use were recorded, and determination and solicitation of adverse events were made. This study allowed liberal use of anti-inflammatory medication. More patients enrolled in this study received inhaled corticosteroids during the study than those in the phase 3 studies (58% vs. 47%). Patients were randomized approximately equally to receive Foradil Aerolizer 12 mcg BID, Foradil Aerolizer 24 mcg BID, Foradil 12 mcg BID with up to two additional on-demand 12 mcg doses per day, and placebo. The Foradil fixed-dose groups and placebo

[4] Mann M, Chowdhury BA, Sullivan EJ, et al. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. Chest 2003; 124:70-4.

group were treated in double-blind fashion, and the Foradil on-demand group was open-label. There were no deaths in this study. Key safety findings of interest are shown in Table 4. The patients who had serious asthma-related adverse events satisfied the criteria by virtue of requiring hospitalizations. The information about serious asthma exacerbations was generated by the Agency following the criteria that were used in the phase 3 program. Two patients had serious asthma exacerbations that required intubation, one in Foradil 12 mcg BID group and one in Foradil 24 mcg BID group. The overall rates of events of interest in this relatively small study were too small to draw any firm conclusion, although the trends were in the direction of the phase 3 study finding. The lower age bound of this phase 4 study was 12 years, whereas in the phase 3 clinical program a numerically stronger signal was seen in the pediatric study that enrolled children 5 to 12 years of age (Table 3).

Table 4. Occurrence of asthma exacerbations, results expressed as number of patients with event (%)

	Formoterol 24 mcg BID (n=527)	Formoterol 12 mcg BID (n=527)	Placebo (n=514)	Formoterol Open-label (n=517)
Serious asthma-related adverse events	5 (0.9%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
Serious asthma exacerbations	3 (0.6%)	2 (0.4%)	1 (0.2%)	1 (0.2%)

Key issues and questions

Salmeterol and formoterol are effective bronchodilators and form important components of the treatment options available for the patients with asthma. These products are included in common asthma treatment guidelines (such as the National Asthma Education and Prevention Program guidelines) as regular “controller” medications. These drugs are clearly effective in terms of improvements in FEV1, peak expiratory flow rate, rescue albuterol use, asthma symptom score, and nocturnal awakenings.

As discussed above, both of these products have been associated with severe asthma exacerbations in a small number of patients. This signal was observed for salmeterol in large post-marketing studies, including the recently conducted SMART study, and for formoterol in the phase 3 clinical program (which is comparatively small, relative to the SMART or SNS studies). The phase 4 study conducted by Novartis with formoterol did not show a clear signal with scheduled formoterol use, but again is a small study relative to the salmeterol studies.

The significant regulatory actions that the Agency has so far taken pertaining to these findings is the incorporation of the results of the SMART study in all salmeterol containing product labels, including the addition of a boxed warning cautioning the use of salmeterol in patients with asthma; and not approving Foradil 24 mcg twice daily dose for marketing in the United States. Confirmation of a potential role for concomitant inhaled corticosteroids in protecting patients against severe asthma exacerbations associated with the use of beta-agonists could not be answered with results from the SMART study. Rather, the data suggested that the concomitant use of inhaled corticosteroids was not protective. Therefore, results of the SMART study and the boxed warning were also included in the Advair Diskus (fluticasone propionate and salmeterol) label. The Foradil label does not currently have a

similar warning because of a lack of specific data related to the Foradil 12 mcg product. However, given that salmeterol and formoterol are both long-acting beta-agonists, and that severe asthma exacerbation was observed when using a higher dose of formoterol, one might conclude that the currently recommended dose of formoterol could have an effect similar to that of salmeterol. The data with formoterol to date do not either confirm or refute such a conclusion. On the other hand, there are some pharmacological differences between salmeterol and formoterol, which could lead them to behave differently.

It should be noted that the phase 3 clinical studies and post-marketing studies with salmeterol and formoterol did not include any evaluation to explore the possible underlying mechanisms, including pharmacogenomic analyses, which could explain the underlying operative cause of acute asthma exacerbation and worsening of asthma seen in some patients. Indeed, the pharmacogenomics of the beta-receptor and data suggesting a potential role of certain polymorphisms in explaining worsening of asthma related to beta-agonist use were not developed at the times these programs were conducted.

The purpose of the PADAC meeting is to discuss the implications of the available data, and also the relevant scientific literature relating to the safety of long-acting beta-agonist bronchodilators in patients with asthma. At the PADAC meeting, there will be a general presentation on the pharmacology and clinical use of long-acting beta-agonists, and presentations on salmeterol and formoterol data by the Agency and the pharmaceutical companies involved. There may also be presentations by other interested parties during the open public presentations.

Please keep in mind that the following questions that will be discussed and deliberated upon following the presentations and discussion.

1. The product labels of salmeterol containing products have been modified to include warnings related to the SMART study.
    a. Based on currently available information, what further actions, if any, do you recommend that the Agency take to communicate or otherwise manage the risks of acute asthma exacerbation and worsening of asthma seen in the SMART study?
    b. Based on the currently available information, do you agree that salmeterol should continue to be marketed in the United States?

2. The label of the formoterol containing product does not include warnings comparable to the warnings that are present in the salmeterol containing products.
    a. Based on the currently available information, should the label of formoterol containing products include warnings similar to those in the salmeterol label?
    b. Based on the currently available information, do you agree that formoterol should continue to be marketed in the United States?

3. What further investigation, if any, do you recommend to be performed by GSK that can improve the understanding of the nature and magnitude of the risk of salmeterol?

4. What further investigation, if any, do you recommend to be performed by Novartis that can improve the understanding of the nature and magnitude of the risk of formoterol?

The questions above are tentative and may be changed prior to the meeting. The final list of questions will be available at the meeting. It is our intention that questions 1 b, 2 a, and 2 b, above should generate a yes or no answer, and will be voted on by the voting members of the Committee.

We look forward to an informative and productive meeting and thank you in advance for your time and commitment to this important public health issue.