

Long-Acting Beta Agonists: Background and Regulatory History

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary and Allergy Products



Outline

- **Introduction**
- **Regulatory History of LABAs**
 - **Approval Dates**
 - **Basis of Approval**
 - **Safety Studies**
 - **Advisory Committees**
 - **Communications**
 - **Labeling History**
- **Current Labeling**
- **Summary**

Introduction

LABAs

Salmeterol xinafoate

- **Serevent Diskus**
- **Serevent Inhalation Aerosol**
 - no longer marketed
- **Advair Diskus**
 - salmeterol and fluticasone propionate
- **Advair HFA Inhalation Aerosol**
 - salmeterol and fluticasone propionate

Formoterol fumarate

- **Foradil Aerolizer**
- **Foradil Certihaler**
 - not currently marketed
- **Symbicort Inhalation Aerosol**
 - formoterol and budesonide
- **Perforomist Inhalation Solution**
 - COPD only
- **Brovana Inhalation Solution**
 - COPD only

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Regulatory History

LABA Approval Dates

Drug name	Asthma Adult/ Adolescents (≥12 yrs)	Asthma Pediatrics (<12 yrs)	EIB	COPD
Serevent Inhalation Aerosol	Feb 1994	X	Feb 1994	Feb 1998
Serevent Diskus	Sep 1997	Sep 1998	Sep 1998	Mar 2002
Advair Diskus	Aug 2000	Apr 2004	X	Nov 2003
Foradil Aerolizer	Feb 2001	Feb 2001	Feb 2001	Sep 2001
Advair HFA	Jun 2006	X	X	X
Symbicort Inhalation Aerosol	Jul 2006	X	X	X
Foradil Certihaler	Dec 2006	Dec 2006	X	X

Regulatory History

Basis of Approval – LABAs

Adults/Adolescents \geq 12 Years of Age

- Dose ranging
 - inform dose selection
 - PD effects on safety variables, e.g. glucose, K^+ , HR
- Safety and efficacy trials
 - minimum 2 clinical trials in asthma patients \geq 12 years
 - minimum 12 weeks duration
 - primary efficacy variable - FEV₁
 - supportive efficacy variables
 - PEF, rescue medication use, symptom scores, nocturnal awakenings
- Long-term (one year) safety trial
 - safety primary purpose
 - efficacy also evaluated

Regulatory History

Basis of Approval – LABAs

Pediatrics < 12 Years of Age

- **Prior to pediatric program, evaluate efficacy and safety in patients ≥ 12 years of age**
- **Pathophysiology of asthma and response to bronchodilators expected to be similar in patients < 12 years of age**
 - **pediatric program not as extensive**
- **Clinical program required in patients < 12 years of age**
 - **evaluate dosing, safety, and efficacy**
- **Dose ranging**
 - **inform dose selection**
- **Safety and efficacy trial(s) in asthma patients <12 years of age**
 - **number and duration of trials depends on novelty of drug substance/product**
 - **efficacy and safety assessed**

Regulatory History

Written Request for LABAs

- **Best Pharmaceuticals for Children Act**
- **Written Request (WR)**
 - request studies for additional pediatric data
 - input from pediatric group
- **WR for salmeterol issued May 1999**
 - clinical studies in children 24 to 47 months of age
 - clinical studies in children 6 to 23 months of age
- **WR for formoterol issued December 2001**
 - clinical studies in children 2 to < 5 years of age
 - clinical studies in children 6 months to < 2 years of age

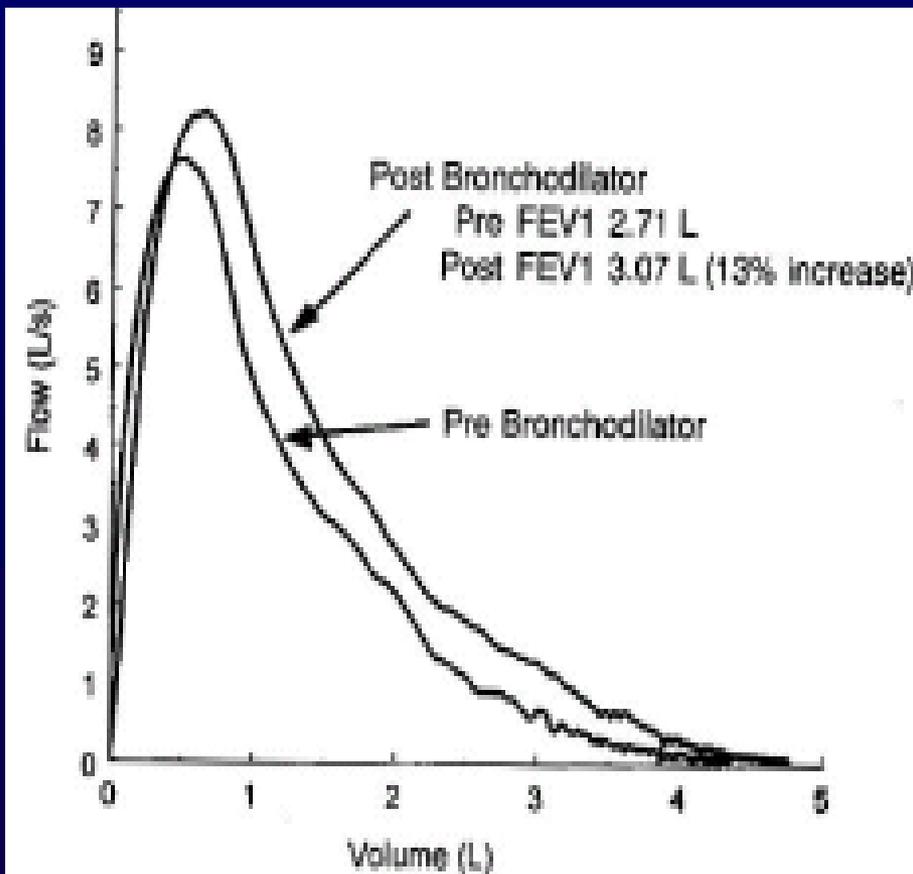
Regulatory History

Basis of Approval – LABAs

- **Combination products**
 - establish contribution of each component
 - product of convenience
- **LABAs are bronchodilators**
 - primary efficacy – FEV₁
 - supportive efficacy variables
- **Basis of approval of LABA products similar to other asthma medications**
- **Efficacy variables are also measures of asthma control as outlined in asthma guidelines, such as NAEPP**

Regulatory History

Basis of Approval –FEV₁



- FEV₁ - volume of air exhaled in first second of forced expiration
- Measurement of airflow – useful for obstructive airway disease, e.g. asthma or COPD
- Standards for measurement

Regulatory History

Basis of Approval –FEV₁

- **Percent predicted FEV₁ used to grade severity of impairment**
- **Component of asthma severity and control**
 - **symptoms, night-time awakenings, rescue medication use, interference with normal activity, exacerbations**

	FEV ₁ > 80% predicted	FEV ₁ 60- 80% predicted	FEV ₁ < 60% predicted
Asthma severity	Intermittent Mild persistent	Moderate persistent	Severe Persistent
Asthma control	Well controlled	Not well- controlled	Very poorly controlled

Regulatory History

Serevent Diskus Efficacy Data

Adults/Adolescents > 12 Years of Age

Change from baseline End of treatment period (Week 12)	Serevent Diskus 50mcg BID N=149	Placebo N=152	Change over placebo
% predicted FEV ₁ at 12 hours	+20.3	+3.3	+20
AM PEF (L/min)	+32	+2	+30
Rescue inhalations/day	-2.7	-0.9	-1.8
% of days with no asthma symptoms	+20	+6	+14
% of nights with no awakenings	+22	+3	+19
Asthma exacerbations	15%	14%	

Source: Serevent Diskus Product Label;
Medical Officer review Serevent Diskus
Combined data from Studies SLD311 & 312

Regulatory History

Foradil Aerolizer Efficacy Data

Adults/Adolescents > 12 Years of Age

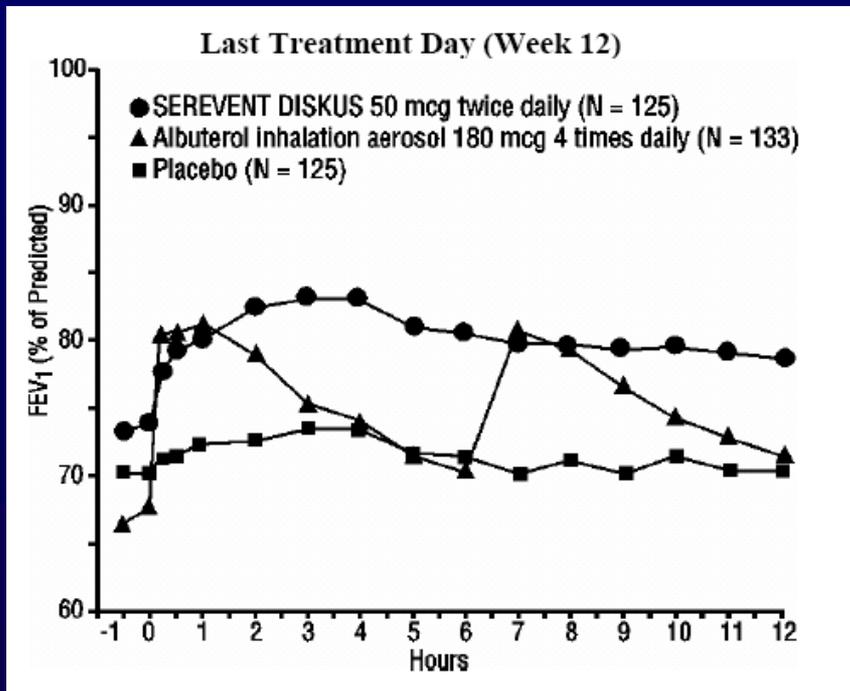
Change from baseline End of treatment period (Week 12)	Foradil Aerolizer 12mcg BID N=136	Placebo N=136	Change over Placebo
FEV ₁ at 12 hours (L)	0.4	0.1	0.3*
FEV ₁ at 3 hours – peak (L)	0.6	0.2	0.4*
AM PEF (L/min)			*
Rescue inhalations/day			*
Symptom scores (0-4) combined day and night (Wks 1-12)	-0.3	-0.1	-0.2*
% nights awakened (not Δ from baseline)	27.6	47.5	

* Statistically significant compared to placebo

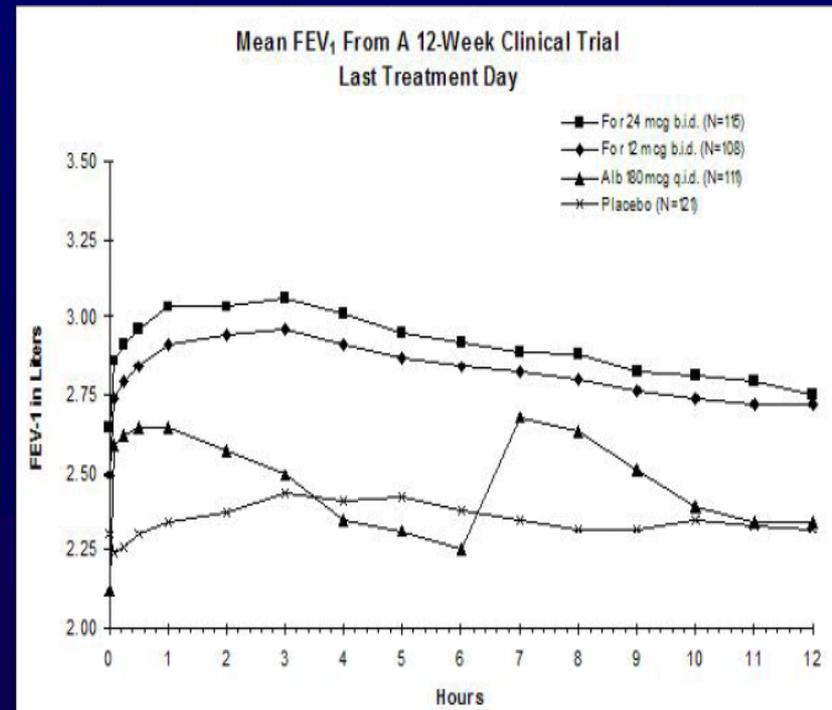
Regulatory History

Serevent Diskus and Foradil Aerolizer Efficacy Data

Adults/Adolescents > 12 Years of Age



Source: Serevent Diskus product label



Source: Foradil Aerolizer product label

Regulatory History

Serevent Diskus Efficacy Data

Pediatrics 4 to <12 Years of Age

Change from baseline End of treatment period (Week 12)	Serevent Diskus 50mcg BID N=102	Placebo N=105	Change over placebo
12 hour % Predicted FEV ₁	+7.8	+4.5	+3.3
12 hour % Predicted PEF _R	+17.6	+12.2	+5.4
Rescue inhalations/day	-0.8	-0.3	-0.5
% nights with no awakenings	9.1	4.1	+5
Symptom scores (0-5) mean maximum	-0.4	-0.1	-0.3

Regulatory History

Foradil Aerolizer Efficacy Data

Pediatrics 5 to < 12 Years of Age

Change from baseline (12 weeks)	Foradil Aerolizer 12mcg BID N=171	Placebo N=176	Change over placebo
FEV ₁ AUC ₁₋₁₂ (L)			+0.15
AM PEF (L/min)	+26	+13	+13
Rescue inhalations/day	-0.20	-0.12	-0.08
Rescue inhalations/night	-0.13	-0.04	-0.09
Symptom scores – Day (0-4)	-0.28	-0.21	-0.07
Symptom scores – Night (0-4)	-0.23	-0.14	-0.09

Regulatory History

Advair Diskus Efficacy Data

Adults/Adolescents > 12 Years of Age

Change from baseline	Advair Diskus 100/50 N=92	Salmeterol 50mcg N=92	Fluticasone 100mcg N=90	Placebo N=82
Pre-dose FEV ₁ (L)	+0.52	+0.16	+0.30	-0.06
AM PEF (L/min)	+54	-2.3	+18	-22
% rescue free days	+30.7%	+4.7%	+10.1%	-9.1%
% days without symptoms	+25%	+8%	+7%	-4%
% of awakening free nights	+4.7	-6.9%	+2.2%	-16.7%
Asthma Quality of Life Questionnaire (AQLQ)	+0.99	-0.3	+0.56	-0.33

Regulatory History

Advair Diskus Efficacy Data

Pediatrics < 12 Years of Age

Change from baseline	Advair Diskus 100/50 N=101	Fluticasone 100mcg N=102
Pre-dose FEV ₁ (L) 6 to 11 year olds	+0.16	+0.10
AM PEF _R (L/min)	+25	+17
Rescue inhalations/day	-0.5	-0.4
Symptom scores (0-5)	-0.6	-0.5
% days without symptoms	+24%	+21%

Regulatory History

Symbicort Inhalation Aerosol Efficacy Data

Adults/Adolescents > 12 Years of Age

Change from baseline	Symbicort 160/4.5 N=124	Budesonide + Formoterol N=115	Budesonide 160 N=109	Formoterol 4.5 N=123	Placebo N=125
Pre-dose FEV ₁ (L)	+0.17	+0.13	+0.05	-0.09	-0.20
Average FEV ₁ over 12-hrs(L) Wk 2	+0.32	+0.31	+0.13	+0.17	-0.05
AM PEF _R (L/min)	+35	+28	+8	+2	-13
Rescue inhalations/day	-1.0	-1.4	-0.6	-0.7	+0.7
% rescue free days	+29.6%	+34.7%	+10.6%	+17.2%	-2.8%
Average daily symptom scores	-0.28	-0.32	-0.13	-0.12	+0.07
% of awakening free nights	+12.6%	+13.8%	+15.6%	+10.8%	+8.6%
Predefined asthma exacerbations	29.8%	20.9%	44.0%	55.3%	67.2%
AQLQ (total)	+0.43	+0.53	+0.14	-0.17	-0.27

Regulatory History

Asthma Medications AQLQ Data

Adults/Adolescents > 12 Years of Age*

Δ from baseline Δ over placebo	Advair Diskus 100/50	Symbicort 160/4.5	Singularir 10mg QD	Xolair (dose based upon weight and IgE)
AQLQ	1.32	0.7	0.32	0.3

* Singularir – patients 15 years and older

Source: Medical Officer review – Advair Diskus, Study SFCA30002;
 Medical Officer review – Symbicort Inhalation Aerosol, Study 717;
 Medical Officer review – Singularir, Study 031
 Xolair – Study 008; Ann Allergy Asthma Immunol 2006; 96: 316-326

Regulatory History

LABAs - Asthma Indications

- **Maintenance treatment of asthma & prevention of bronchospasm in patients with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma**
- **Only prescribe for patients not adequately controlled on other asthma-controller medications (e.g. low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies**

Regulatory History

- **Serevent Inhalation Aerosol approved February 1994**
 - **PADAC on February 26, 1993 prior to approval**
 - **Serevent Nationwide Surveillance (SNS) Study (April 1993) considered during approval**

Serevent Nationwide Surveillance Study (SNS)

- Randomized, double-blind, active-controlled (salbutamol), parallel group, 16-week trial in UK
- N=25,180 (2:1 randomization) patients with asthma – 12 years of age and older
- Salmeterol 50mcg BID vs. salbutamol 200mcg QID

Outcome	Salmeterol n=16,787	Salbutamol n=8393	Relative Risk	Significance
Respiratory & asthma related death	12 (0.7%)	2 (0.2%)	3	p=0.105
Respiratory & asthma related hospitalizations	193 (1.2%)	102 (1.2%)	0.95	p=0.65
Other respiratory and asthma related serious events	198 (1.2%)	100 (1.2%)	0.99	p=0.94
Respiratory and asthma related withdrawals	488 (2.9%)	318 (3.8%)	0.77	p=0.0002

BMJ 1993; 306:1034-7

Regulatory History

February 26, 1993 PADAC

- **Serevent Inhalation Aerosol NDA**
 - Dose and dosing interval supported
 - Safety adequately demonstrated, but “a few caveats and concerns as would be expected with any drug in this particular class”
 - Pediatric data not sufficient and recommendation for additional studies
- **Unanimous recommendation to approve salmeterol for chronic asthma and EIB in patients 12 years and older**
- **Unanimous recommendation to not approve salmeterol for chronic asthma in patients < 12 years of age**

Regulatory History

- **Following approval of salmeterol in 1994, post-marketing reports of severe asthma exacerbations, including death**
- **Label revised in January 1995**
 - **New Warnings**
 - **serious acute respiratory events, including fatalities have been reported with salmeterol**
 - **salmeterol not for acute symptoms**
 - **salmeterol not a substitute for inhaled corticosteroids**
 - **salmeterol should not be initiated in worsening or acutely deteriorating asthma**
 - **patients should have a short acting beta agonist for acute symptoms**

Regulatory History

- **GSK developed large simple trial to assess the risk of asthma related death and serious asthma exacerbations**
- **Salmeterol Multicenter Asthma Research Trial (SMART)**
 - multi-center, randomized, double-blind, placebo-controlled, 28 week, parallel group study
 - 30,000 patients with asthma 12 years and older
 - treatment groups
 - salmeterol inhalation aerosol 50mcg BID
 - placebo BID (usual care)
 - 1° endpoint – respiratory related death or respiratory related life threatening experiences
 - initiated June 1996

Regulatory History

- **Advair Diskus approved 2000**
 - **November 23, 1999 PADAC**
- **Foradil Aerolizer approved 2001**
 - **24mcg dose not approved due to safety concerns**
 - **phase 4 commitment to further evaluate safety**
- **In 2002 DSMB for SMART**
 - **noted increase in asthma events with salmeterol, particularly in African Americans**
 - **noted enrollment was slow**
 - **recommended if the study could not be completed in a timely fashion, terminate the study and disseminate the findings**

Regulatory History

- SMART terminated January 23, 2003
- Summary of interim analysis for SMART submitted to FDA January 2003
- FDA released communication January 2003
- Boxed Warning added August 2003 based upon interim results of SMART
 - small but significant increase in asthma-related deaths
 - risk may be greater in African American patients compared to Caucasians
 - applied to both Serevent and Advair labels

Regulatory History

- **FDA released communication in August 2003**
- **Novartis submitted results of phase 4 commitment for Foradil Aerolizer in August 2004**
- **Boxed Warning and Warning revised September 28, 2004, for Serevent and Advair Diskus**
 - **response to GSK submission of updated SMART results**
 - **include results from appropriate datasets and statistical analyses**

Regulatory History

- **Pulmonary Allergy Drugs Advisory Committee meeting July 13, 2005**
 - discuss results of SMART and Phase 4 study with formoterol
- **Labeling at the time of the PADAC**
 - **Boxed Warning on Serevent products and Advair Diskus**
 - **no Medication Guides**
 - **no Boxed Warning on Foradil Aerolizer**

Regulatory History

July 2005 PADAC - SMART Results

Primary Endpoint – Combined Respiratory Related Deaths or Respiratory Related Life Threatening Experiences*

Life table analyses at 28 weeks	Salmeterol N=13,176	Placebo N=13,179	Relative Risk	95% Confidence Interval
All (N=26,355)	50	36	1.40	(0.91, 2.14)
Caucasian (N= 18,642)	29	28	1.05	(0.62, 1.76)
African American (N=4685)	20	5	4.10	(1.54, 10.90)

Key Secondary Endpoint Asthma Related Deaths

All (N=26,355)	13	3	4.37	(1.25, 15.34)
Caucasian (N= 18,642)	6	1	5.82	(0.70, 48.37)
African American (N=4685)	7	1	7.26	(0.89, 58.94)

*Intubation and mechanical ventilation

July 13, 2005, PADAC FDA Briefing Document

Regulatory History

July 2005 PADAC - Phase 4 Foradil Study

- **Randomized, blinded, placebo-controlled study of 16 weeks duration in 2,307 patients with asthma 12 years of age and older**

Phase 4 Study with Formoterol				
number of patients with event (%)	Formoterol 12 mcg BID (n=527)	Formoterol 24 mcg BID (n=527)	Placebo (n=514)	Formoterol Open Label (n=517)
Serious asthma related 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%)
* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death † 1 patient required intubation				

Regulatory History

July 2005 PADAC Questions

- Based on currently available information, do you agree that salmeterol should continue to be marketed in the US?
 - **Yes 13, No 0**
- Based on currently available information, do you agree that formoterol should continue to be marketed in the US?
 - **Yes 13, No 0**
- Based on currently available information, should the label of the formoterol containing product include warnings similar to those in the salmeterol label?
 - **Yes 12, No 0, Abstain 1**

Regulatory History

July 2005 PADAC -Recommendations

- **Modify Boxed Warning to discourage monotherapy and encourage co-administration with an ICS**
- **Provide Medication Guide and direct patient information**
- **Maintain Boxed Warning on all salmeterol containing products**

Regulatory History

- **Public Health Advisory November 2005**
 - FDA requested LABA manufacturers update product labels with new warnings for all LABA products
 - **LABAs should be used as additional therapy in patients who have not adequately responded to other asthma controller medications**
 - FDA requested Medication Guide for each LABA product
- **Healthcare Professional Sheets November 2005**
 - Serevent Diskus
 - Advair Diskus
 - Foradil Aerolizer

Medication Guide

21 CFR 208.1

- **Required patient labeling necessary for patients' safe and effective use of a drug.**
 - **Patient labeling could help prevent serious adverse events**
 - **Drug product has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product**
 - **Drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness**

Regulatory History

- **Updated product labels with new warning language and Medication Guide**
 - **Advair Diskus & Serevent Diskus March 2006**
 - **Foradil Aerolizer June 2006**
- **Symbicort Inhalation Aerosol approved in July 2006**
 - **product label included Boxed Warning and Medication Guide**
- **Pediatric Exclusivity granted March 2006 for salmeterol**

Regulatory History

- **Pediatric Advisory Committee November 27-28, 2007**
 - **salmeterol was one of many products discussed**
 - **expanded discussion of salmeterol due to its safety profile**
 - **concern raised regarding risk-benefit ratio in pediatric patients**
 - **FDA committed to discuss this issue at a future advisory committee meeting**

Regulatory History

November 2007 PAC Questions

The committee has been provided background information on safety issues related to salmeterol, including previous deliberations by the Pulmonary Advisory Committee of June 2005 in relationship to the class labeling box warning for asthma-related deaths and that salmeterol only be used as additional therapy for patients not adequately controlled on other asthma controller medications. Since this meeting, there has been additional safety information concerning the pediatric population, and the Office of Surveillance and Epidemiology, FDA, has provided an analysis of the available observational pharmacoepidemiology studies and a subgroup analysis of the pediatric populations in clinical trials.

In view of the evolving issue of risks for the pediatric population, the Agency thinks further assessment of the role of this product in the treatment of pediatric asthma is warranted and plans to bring this issue to a future advisory committee. In the interim, please address the following questions:

Regulatory History

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In view of the evolving issue of risks for the pediatric population, the Agency thinks further assessment of the role of this product in the treatment of pediatric asthma is warranted and plans to bring this issue to a future advisory committee. In the interim, please address the following questions:

Regulatory History

November 2007 PAC Questions

Pending completion of further analyses regarding the risks and benefits of salmeterol in pediatric patients, please discuss whether the **current labeling and MedGuide adequately communicate the potential risks in children**. Please include in your discussions whether the present warning on asthma deaths is adequate for the pediatric population. Also, please address the observed safety signal of **increased pediatric hospitalizations and whether the current labeling adequately addresses this issue**.

Please discuss whether the **current labeling and MedGuide are clear in the recommendation that salmeterol only be used as additional therapy for patients not adequately controlled on other asthma controller medications [e.g., low-to-medium dose inhaled corticosteroids (ICS)] or whose disease clearly warrants treatment with two maintenance therapies**. In particular, please comment on whether the **current labeling and MedGuide clearly communicate that there is no clear evidence that ICS mitigate the risk of asthma-related deaths in patients receiving salmeterol**.

Regulatory History

November 2007 PAC Responses

- **Discussion of possibility of removal of salmeterol from the market, but agreed more extensive discussion needed**
- **Requested report back after additional review of data**
 - **expressed sense of urgency from public health perspective**
- **Update labeling to identify pediatric risks, including hospitalizations**
- **PAC agreed with FDA recommendation to continue assessment of the risks of LABAs and seek advice from a future advisory committee**

Regulatory History

- **FDA requested manufactures of LABA products to provide data from controlled clinical trials to further evaluate the safety of LABAs when treating asthma in January 2008**
- **In March 2008, FDA updated website with plans for future AC**
- **PADAC/DSARM/PAC meeting December 10-11, 2008**
 - **Discuss the benefit risk assessment of long-acting beta agonists (LABAs) for the treatment of asthma in adults and pediatric patients**

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Labeling

LABA Risk Information

- **Boxed Warning**
 - asthma related death
- **Clinical Trials**
 - SMART
 - Foradil Aerolizer safety study
- **Indications and Usage**
- **Warnings and Precautions**
- **Adverse Reactions**
- **Dosage and Administration**
- **Medication Guide**

Labeling

Boxed Warning

- **Asthma related death**
 - applies to salmeterol and formoterol products
 - applies to all age groups
- **Appropriate use of LABA**
 - only use as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g. low- to medium-dose inhaled corticosteroids)
- **SMART data**
 - salmeterol product labels
 - description in formoterol product labels

Labeling

Boxed Warning – Serevent Diskus

WARNING

Long-acting beta2-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: *Asthma: Salmeterol Multi-center Asthma Research Trial*).

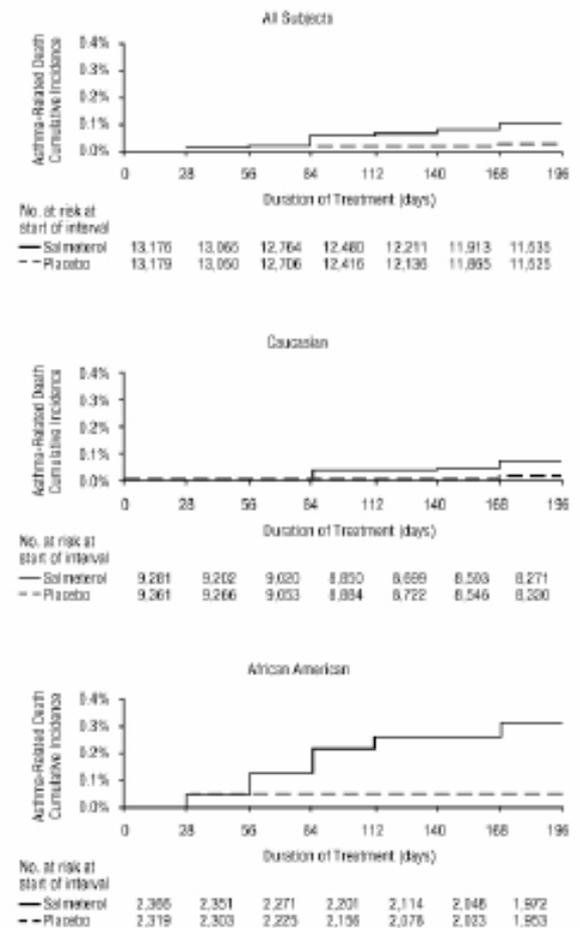
Labeling Salmeterol Product Labels

Discussion of SMART and results

Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (%)	Placebo n (%)	Relative Risk [†] (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients [‡] (95% Confidence Interval)
Total Population[‡] Salmeterol: N = 1,3176 Placebo: N = 1,3179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

Figure 2. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



Labeling

Boxed Warning – Foradil Aerolizer

WARNING:

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including FORADIL AEROLIZER. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta₂-adrenergic agonist), the active ingredient in FORADIL AEROLIZER (see WARNINGS).

Labeling

Adverse Reactions - Foradil Aerolizer

Discussion of safety findings regarding serious asthma exacerbations with formoterol

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 12 YEARS OF AGE AND OLDER FROM TWO 12-WEEK CONTROLLED CLINICAL TRIALS

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Albuterol 180 mcg four times daily	Placebo
	Trial #1			
Serious asthma exacerbations	0/136 (0)	4/135 (3.0%) ¹	2/134 (1.5%)	0/136 (0)
	Trial #2			
Serious asthma exacerbations	1/139 (0.7%)	5/136 (3.7%) ²	0/138 (0)	2/141 (1.4%)

¹ 1 patient required intubation

² 2 patients had respiratory arrest; 1 of the patients died

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 12 YEARS OF AGE AND OLDER FROM A 16-WEEK TRIAL

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Placebo
Serious asthma exacerbations	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 5-12 YEARS OF AGE FROM A 52-WEEK TRIAL

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Placebo
Serious asthma exacerbations	8/171 (4.7%)	11/171 (6.4%)	0/176 (0)

Labeling

LABA Risk Information

- **Boxed Warning**
 - asthma related death
- **Clinical Trials**
 - SMART
 - Foradil Aerolizer safety study
- **Indications and Usage**
- **Warnings and Precautions**
- **Adverse Reactions**
- **Dosage and Administration**
- **Medication Guide**

Labeling

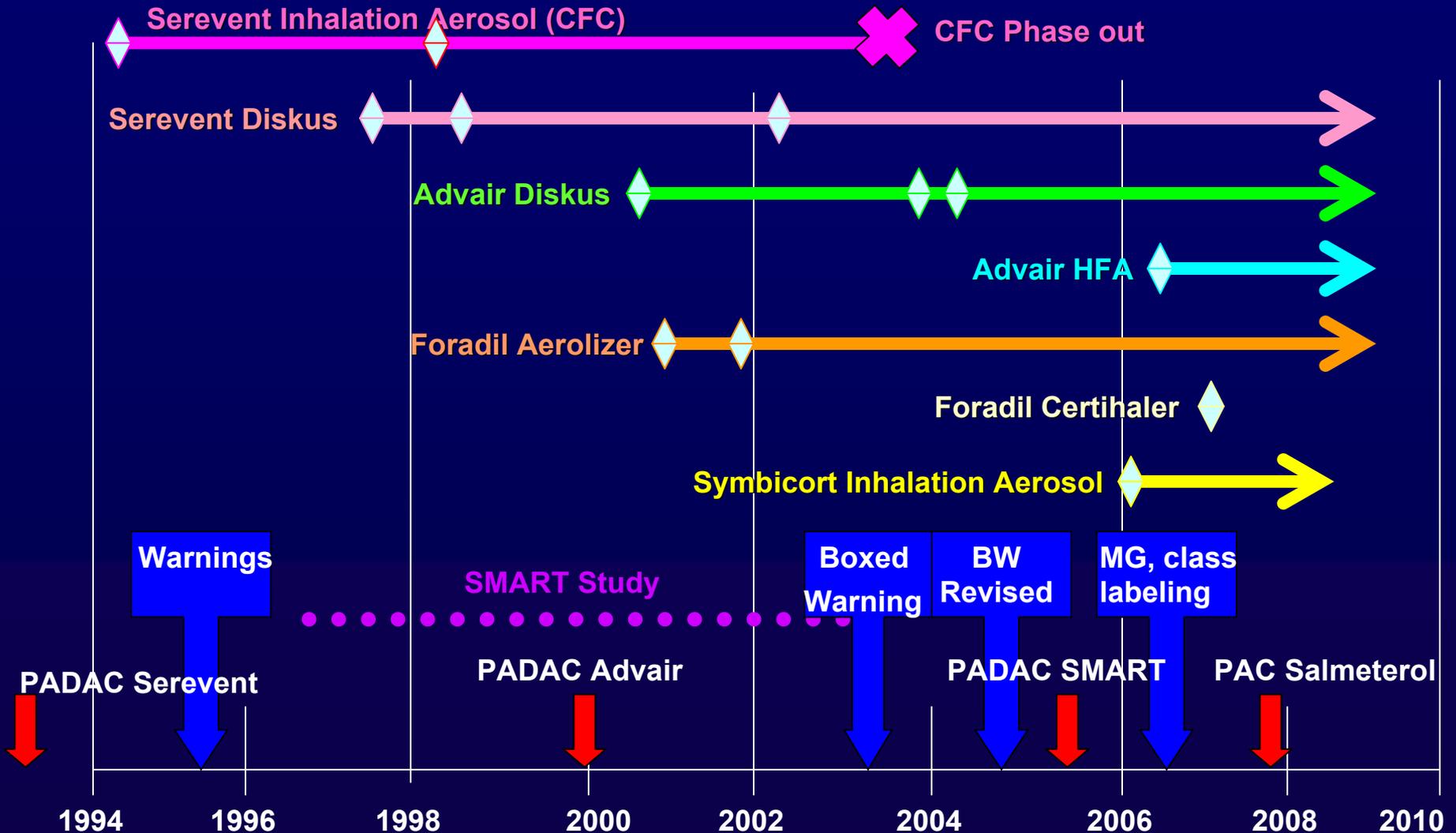
Combination Products

- **Boxed Warning**
 - asthma related death
 - only use for patients not adequately controlled on other asthma controller medications
- **Indications and Usage**
- **Warnings and Precautions**
 - SMART results
- **Adverse Reactions**
- **Dosage and Administration**
- **Medication Guide**

Outline

- **Introduction**
- **Regulatory History of LABAs**
 - **Approval Dates**
 - **Basis of Approval**
 - **Safety Studies**
 - **Advisory Committees**
 - **Communications**
 - **Labeling History**
- **Current Labeling**
- **Summary**

LABA Timeline Summary



Summary

- **Benefits of LABAs**
 - bronchodilators - FEV₁
 - supportive efficacy measures
 - rescue medication use, PEF, asthma symptoms, nocturnal awakenings
- **Risks of LABAs**
 - asthma related deaths and serious asthma exacerbations
 - **Boxed Warning** regarding asthma related death
 - applies to all ages
 - applies to salmeterol and formoterol containing products
 - LABAs should only be used as additional therapy in patients not adequately controlled on other asthma controller medications
- **Today's discussion is a continuation of the benefit risk assessment of LABA for the treatment of asthma**

Thank you