Update on the Safety of Long Acting Beta Agonists (LABA)

Robert Lim, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
US Food and Drug Administration

Outline

- Background
- LABA Safety Trials
- Results of Safety Trials and Meta-analysis
- Revised Labeling
- Summary

Background

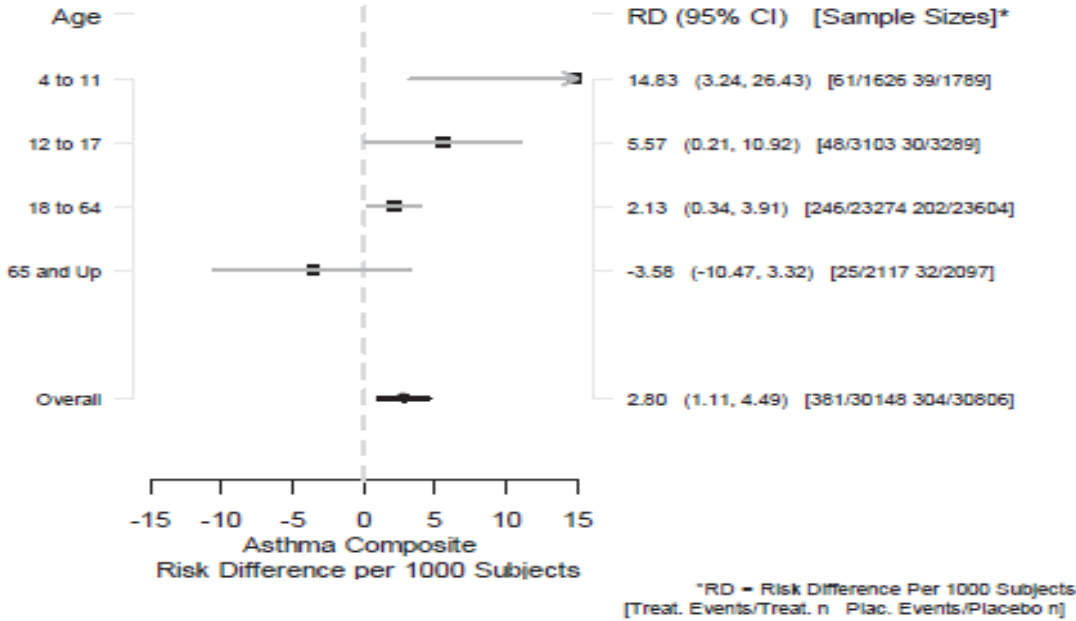
- Serious asthma outcomes – hospitalizations, intubation, death
  - Serevent Nationwide Surveillance Study (SNS)
  - Salmeterol Multicenter Asthma Research Trial (SMART)
    - potential increased risk in African American patients
  - FDA- meta-analysis
    - potential increased risk of hospitalizations in pediatric patients

- Extensive regulatory history
  - Boxed Warning, Advisory Committee meetings

- FDA required large safety trials (post-marketing requirements)
  - Evaluate risk of LABA when added to ICS
  - Now completed

LABAs and Hospitalizations in Pediatric Patients

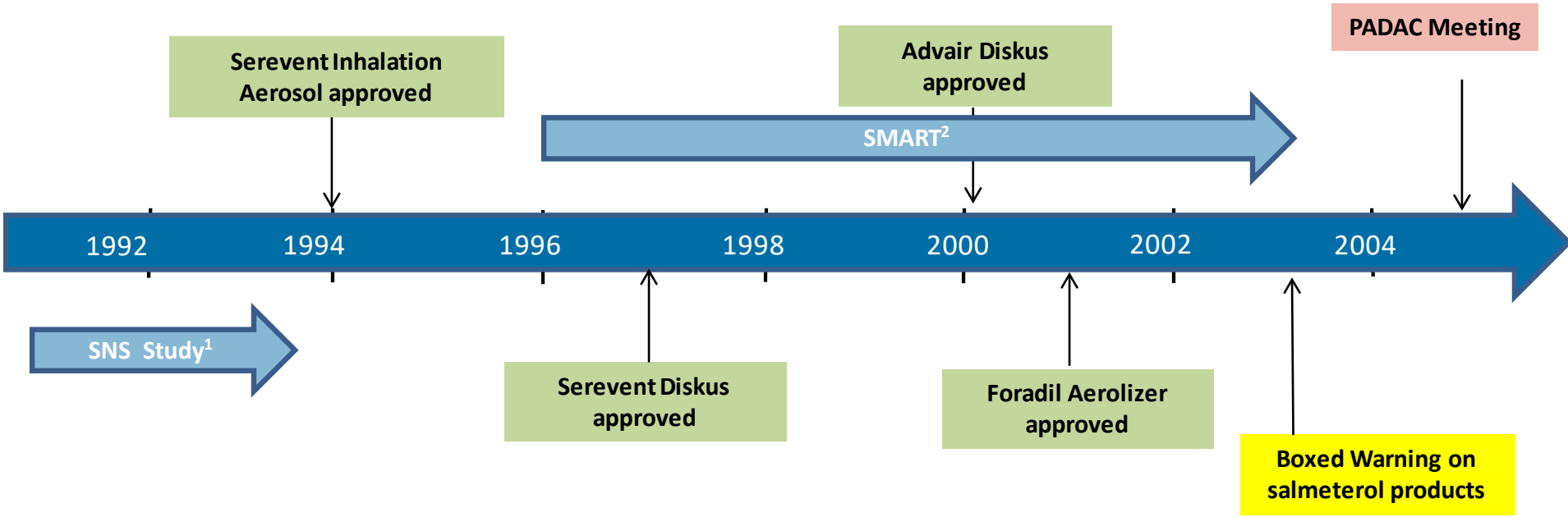
- Excess in serious asthma outcomes higher in children
- Risk Difference for asthma hospitalization, intubation, and death according to age LABA vs. no LABA
- For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs.



FDA Briefing Package December 10-11, 2008 http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf

Pediatrics 2011;128:e1147–e1154

Relevant LABA Regulatory History



[1] *BMJ 1993; 306:1034-7*
[2] *Chest* 2006; 129; 15-26

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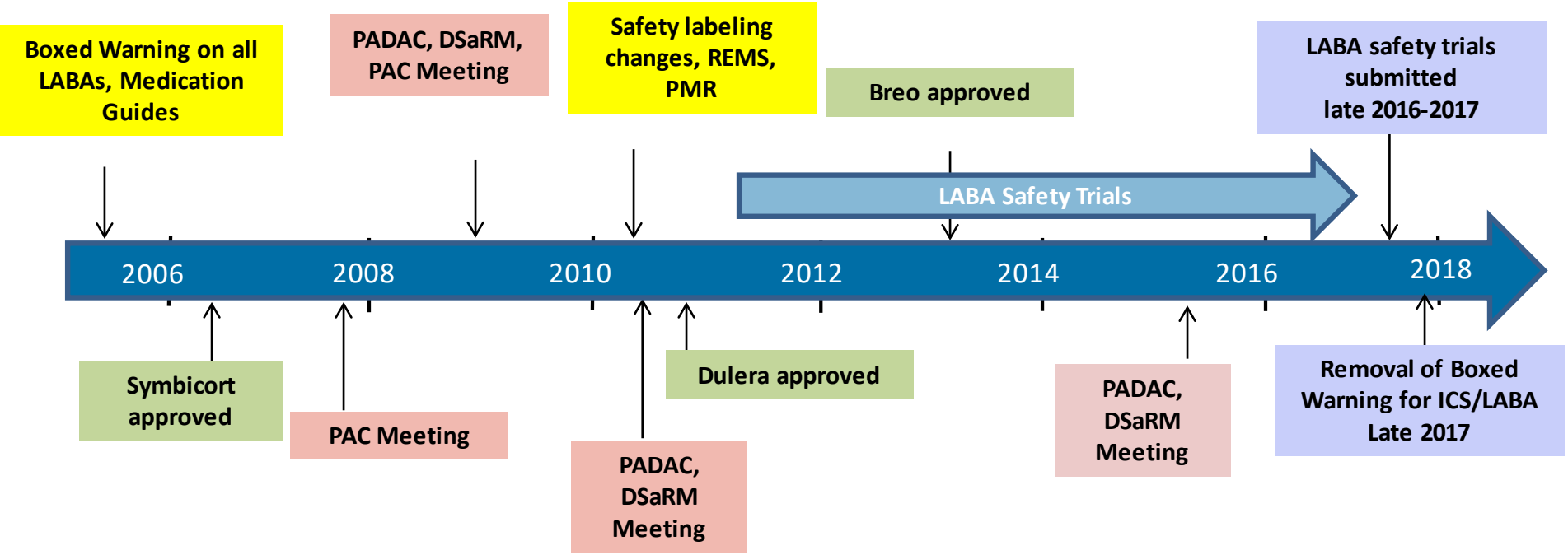

LABA Post-marketing Required Trials

- Trial required for each sponsor of LABA product approved for asthma
- Safety of LABA when added to ICS
- Serious asthma outcomes
  - hospitalizations, intubations, death
- Efficacy assessment - exacerbation
- Particular interest in pediatric population
- Individual trials, but similar design to potentially analyze results together for rare events, e.g. asthma related death
  - Joint Oversight Steering Committee
  - Joint Data Monitoring Committee
  - Shared Adjudication Committee

Adult and Adolescent Required Safety Trials

- Four randomized, double-blind, active-controlled, 26 week trials
  - Advair Diskus, Dulera, Foradil Aerolizer, Symbicort
- 11,700 patients 12 years and older with asthma per trial
  - 10% patients 12-17 years of age
- ICS/LABA vs. ICS
- Serious asthma outcomes
  - hospitalizations, intubation, death
- Non-inferiority design
  - 90% power to rule out 2 fold increase in event rate
- Required final report submission June 2017

[1] N Engl J Med 2011;364;2473-75

Pediatric Required Safety Trial

- One randomized, double-blind, 26 week trial
  - Advair Diskus
- 6200 patients 4 to 11 years with asthma
- ICS/LABA vs. ICS
- Serious asthma outcomes - hospitalizations, intubation, death
- Non-inferiority design
  - 90% power to rule out 2.7 fold increase in event rate
- Required final report submission June 2017

[1] N Engl J Med 2011;364;2473-75

Results of Safety Trials

- Trials completed in staggered fashion and submited to FDA
  - Advair Diskus (adult and adolescent) – January 2016
  - Advair Diskus (pediatric) – May 2016
  - Symbicort - May 2016
  - Dulera – September 2017

- Novartis withdrew formoterol fumarate (Foradil Aerolizer) from US market[1], so safety study terminated

- Each trial excluded the pre-specified NI margin
  - Very few intubations and deaths
    - 5 total across the trials

- Significant reduction in asthma exacerbations
  - majority of events were those requiring systemic corticosteroids

[1] FDA Drug Shortages [https://www.fda.gov/Drugs/drugsafety/DrugShortages/default.htm]

LABA and Serious Asthma Outcomes

	Advair (fluticasone/ salmeterol)		Advair (fluticasone/ salmeterol) Pediatric		Symbicort (budesonide/ formoterol)		Dulera (mometasone/ formoterol)	
	FP/SAL	FP	FP/SAL	FP	BUD/FOR	BUD	MOM/FOR	MOM
N	5834	5845	3107	3101	5486	5487	5868	5861
Serious asthma outcomes	34 (0.6)	33 (0.6)	27 (0.9)	21 (0.7)	43 (0.7)	40 (0.7)	39 (0.7)	32 (0.5)
Hazard Ratio (95% CI)	1.03 (0.6, 1.7)		1.29 (0.7, 2.3)		1.07 (0.7, 1.7)		1.22 (0.8, 1.9)	
Deaths	0	0	0	0	2 (<1%)	0	0	0
Intubation	0	2 (<1%)	0	0	1 (<1%)	0	0	0
Hospitalization	34 (0.6)	33 (0.6)	27 (0.9)	21 (0.7)	42 (0.7)	40 (0.7)	39 (0.7)	32 (0.5)

FP=fluticasone propionate, FP/SAL=FP/salmeterol xinafoate; BUD = budesonide, BUD/FOR = BUD/formoterol; MOM = mometasone, MOM/FOR = MOM/formoterol
Source: Approved labels for Advair Diskus, Symbicort, and Dulera

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Meta-Analysis of Serious Asthma-Related Events

	ICS/LABA N= 17,537[a]	ICS N= 17,552[a]	ICS/LABA vs. ICS Hazard Ratio (95% CI)
Serious Asthma-related event	116	105	
Asthma-related death	2	0	1.10 (0.85, 1.44)
Asthma-related intubation	1	2	
Asthma-related hospitalization	115	105	

[a] Includes data from the adult/adolescent safety trials with Advair Diskus, Dulera, and Symbicort

Source: Labels for approved ICS/LABA with an asthma indication

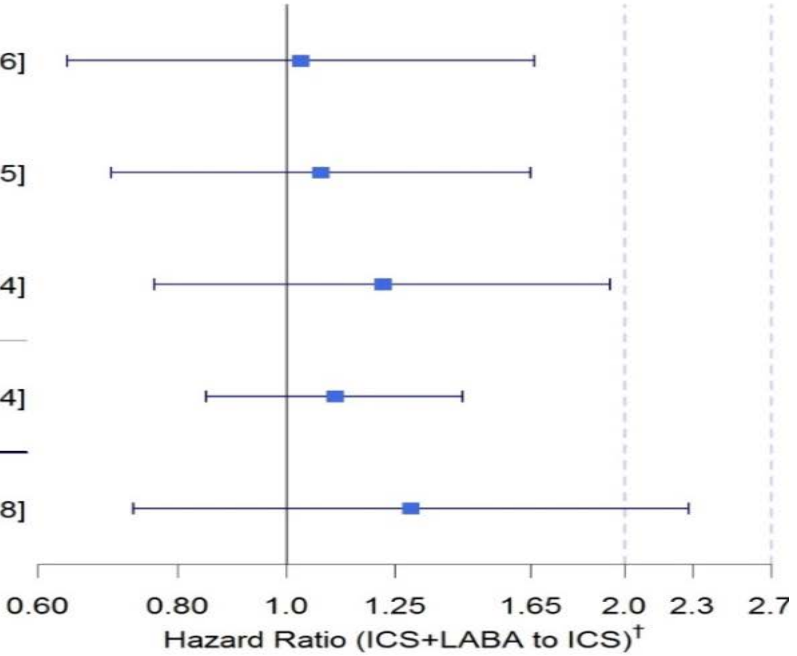
Meta-Analysis of Serious Asthma-Related Events Subgroup by Age

	ICS/LABA N= 17,537[a]	ICS N= 17,552[a]	ICS/LABA vs. ICS Hazard Ratio (95% CI)
Serious Asthma-related event	116	105	1.10 (0.85, 1.44)
Age 12-17 years	**n=1,735**	**n=1,796**	
Serious Asthma-related event	8	9	0.93 (0.36, 2.4)
Age 18-64 years	**n=13,720**	**n=13,690**	
Serious Asthma-related event	90	75	1.20 (0.88, 1.62)
Age >64 years	**n=2,080**	**n=2,065**	
Serious Asthma-related event	18	21	0.85 (0.45, 1.6)

[a] Includes data from the adult/adolescent safety trials with Advair Diskus, Dulera, and Symbicort

Serious Asthma-Related Events
Individual Trials and Meta-analysis

	ICS+LABA	ICS	HR [95% CI]
Advair (adults/adolescents)	34/5834	33/5845	1.03 [0.64, 1.66]
Symbicort	43/5838	40/5843	1.07 [0.70, 1.65]
Dulera	39/5865	32/5864	1.22 [0.76, 1.94]
Meta-analysis* (adults/adolescents)	116/17537	105/17552	1.10 [0.85, 1.44]
Advair (pediatrics)	27/3107	21/3101	1.29 [0.73, 2.28]



Note: Only randomized subjects who took at least one dose of treatment were included.
** Fitted by a Cox model stratified by trial using a single covariate of planned arm.*
† 2.0 and 2.7 are NI magins for individual adult/adolescent and pediatric trials, respectively.

Efficacy – Asthma Exacerbations

	Advair (fluticasone/ salmeterol)		Advair (fluticasone/ salmeterol) Pediatric		Symbicort (budesonide/ formoterol)		Dulera (mometasone/ formoterol)	
	FP/SAL	**FP**	**FP/SAL**	**FP**	**BUD/FOR**	**BUD**	**MOM/FOR**	**MOM**
N	5834	5845	3107	3101	5486	5487	5868	5861
Patients with EXB (%)	480 (8)	597 (10)	265 (9)	309 (10)	539 (9)	633 (11)	708 (12)	779 (13)
Hazard Ratio (95% CI)	0.79 (0.70, 0.89)		0.86 (0.73, 1.01)		0.84 (0.75, 0.94)		0.89 (0.80, 0.98)	

Exacerbation defined as deterioration in asthma requiring use of systemic corticosteroids (≥3-days), inpatient hospitalization, or emergency department visit requiring systemic corticosteroids

Source: Approved labels for Advair Diskus, Symbicort, and Dulera

Labeling

- Removed Boxed Warning from ICS/LABA products

- Warning revised
  - Emphasize risk of LABA monotherapy (without ICS)
  - Describe results of available trials and meta-analysis

- Medication Guide changed to Patient Information Leaflet

ICS/ LABA Products for Asthma

Product/Dosage Strength	Sponsor	Approval Date for Asthma	Approved Age Range
Advair Diskus (FP/SAL Inhalation powder) 100/50, 250/50, 500/50	GSK	August 2000	≥ 4 years
Advair HFA (FP/SAL Inhalation Aerosol) 45/21, 115/21, 230/21	GSK	June 2006	≥ 12 years
AirDuo (FP/SAL Dry powder) 55/14, 113/14, 232/14	Teva	January 2017	≥ 12 years
Breo Ellipta (FF/VIL Inhalation Aerosol) 100/25, 200/25	GSK	May 2013	≥ 18 years
Dulera (MOM/FOR Inhalation Aerosol) 100/4.5, 200/4.5	Merck	June 2010	≥ 12 years
Symbicort (BUD/FOR Inhalation Aerosol) 80/4.5, 160/4.5	Astra-Zeneca	July 2006	≥ 12 years

FP=fluticasone propionate, SAL=salmeterol, FF=fluticasone furoate, VIL=vilanterol, MOM=mometasone, FOR=formoterol

Single Ingredient LABA Products for Asthma

Product/Dosage Strength	Sponsor	Approval Date for Asthma	Approved Age Range
Serevent Diskus (salmeterol xinafoate inhalation powder)	GSK	August 2000	≥ 4 years
Foradil Aersolizer (formoterol fumarate inhalation powder)	GSK	June 2006	≥ 5 years

Summary

- Completed studies excluded pre-specified NI margin
  - Few intubations and deaths
- FDA conducted combined analysis
  - Subgroup analysis consistent with overall analysis
- Decrease in asthma exacerbations (glucocorticoid use) with ICS/LABA compared to ICS
- Boxed Warning removed from ICS/LABA products

Thank you