Summary Minutes of the
Joint Pulmonary-Allergy Drugs Advisory Committee (PADAC), Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC)
December 10-11, 2008
Location: Hilton Washington DC North/Rockville, The Ballrooms, 1750 Rockville Pike, Rockville, Maryland.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the December 10-11, 2008 meeting of the Joint Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee of the Food and Drug Administration were approved on January 26, 2009.

I certify that I attended the December 10-11, 2008 meeting of Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kristine Khuc, Pharm.D.
Designated Federal Official, PADAC

_____/s/_____
Erik Swenson, M.D.
Acting Committee Chair, PADAC

_____ /s/_____
Marsha Rappley, M.D.
Committee Co-Chair, PAC

The Pulmonary-Allergy Drugs Advisory Committee (PADAC), Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC) met on December 10-11, 2008 at the Hilton Washington DC/Rockville, Plaza Ballrooms, 1750 Rockville Pike, Rockville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Erik Swenson, M.D., (Acting Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Official). There were approximately 350 persons in attendance. There were six speakers for the Open Public Hearing session.

Attendance:
Pulmonary-Allergy Drugs Advisory Committee Member Present (Voting):
Daren L. Knoell, Pharm.D.

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Sean Hennessy, Pharm.D., Ph.D., Judith Kramer, M.D., Sydney Wolfe, M.D.

Drug Safety and Risk Management Advisory Committee Member Present (Non- Voting):
D. Bruce Burlington, M.D. (Industry Representative)

Pediatric Advisory Committee Members Present (Voting):
Marsha Rappley, M.D. (Co-Chair), Amy Celento, Avital Cnaan, Ph.D., M.S., Carl D'Angio, M.D., Melissa Hudson, M.D., Keith Kocis, M.D., Daniel Notterman, M.D., Geoffrey Rosenthal, M.D., Ph.D., Elaine Vining

Pediatric Advisory Committee Member Present (Non-Voting):
Brahm Goldstein, M.D. (Industry Representative)

Special Government Employee Consultants Present (Temporary Voting Members):
Mark Brantly, M.D., Fernando Martinez, M.D., Andrea Holka, Lee Newman, M.D., Jesse Joad, M.D., John Hoidal, M.D., David Schoenfeld, Ph.D., Sebastian Schneeweiss, M.D., Deborah Shatin, Ph.D., Julie Zito, Ph.D., David Margolis, M.D., Ph.D.,
Edward Krenzelock, Pharm.D., Jacqueline Gardner, Ph.D.

Regular Government Employee Present (Temporary Voting Member):
Erik Swenson, M.D. (Acting Chair)

Guest Speaker: (Non-voting):
Robert Lemanske, Jr., M.D., University of Wisconsin School of Medicine and Public Health

FDA Participants Present (Non-Voting):
M. Dianne Murphy, M.D., Robert Nelson, M.D., Ph.D., John Jenkins, M.D.,
Curtis Rosebraugh M.D., Badrul Chowdhury, M.D., Ph.D., Sally Seymour, M.D.,
Ann McMahon, M.D., Henry Francis, M.D., David Graham, M.D., Andrew Mosholder, M.D.,
Mark Levenson, M.D.

Open Public Hearing Speakers:
Stanley Szefler, M.D., American Academy of Allergy, Asthma, and Immunology, Alfred Munzer, M.D., American Thoracic Society, Carolyn Britton, M.D., National Medical Association, Shelley Salpeter, M.D., Stanford University School of Medicine, Nancy Sander, Allergy and Asthma Network Mothers of Asthmatics, Anne Dorsey/Julian Dorsey (co-speakers)

Designated Federal Official:
Kristine Khuc, Pharm.D.

Issue: To discuss the benefit and risk assessment of long acting beta-2 adrenergic agonists for the treatment of asthma in adults and children.

The Agenda was as follows:

December 10, 2008

Call to Order Introduction of Committees	Erik Swenson, M.D. Acting Chair, PADAC
	Marsha Rappley, M.D. Co-Chair, PAC
Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, PADAC
Opening Remarks	Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary Allergy Products, Center for Drug Evaluation and Research (CDER), FDA
	Henry Francis, M.D. Deputy Director, Office of Surveillance and Epidemiology (OSE), CDER, FDA
Recent Advances in Asthma Treatment	Robert Lemanske, Jr., M.D. Professor of Pediatric Medicine, University of Wisconsin
FDA Presentations	
Background and Regulatory Approval History of Long Acting Beta2 Agonists	Sally Seymour, M.D. Deputy Director for Safety, Division of Pulmonary and Allergy Products, CDER, FDA
Background on Long Acting Beta2 Agonists Safety Issues	Andrew Mosholder, M.D. Medical Officer, Division of Epidemiology, OSE, CDER, FDA
Meta-analysis of Data Summarizing the Risks of Long Acting Beta2 Agonists	Mark Levenson, Ph.D. Statistical Safety Reviewer Quantitative Safety and Pharmacoepidemiology, Office of Biostatistics, CDER, FDA

Benefits in the Context of Risks of Long Acting Beta2 Agonists	Ann McMahon, M.D. Acting Director, Division of Pharmacovigilance II OSE, CDER, FDA
Public Health Considerations of Benefits and Risks with LABAs	David Graham, M.D. Associate Director for Science and Medicine, OSE, CDER, FDA
Benefits in the Context of Risks of Long Acting Beta2 Agonists- Division of Pulmonary and Allergy Products Perspective	Badrul Chowdhury, M.D., Ph.D. Director, Division of Pulmonary and Allergy Products, CDER, FDA

Sponsors Presentations

Overview of Asthma and Guidelines for the Diagnosis and Management of Asthma	Stuart Stoloff, M.D. Clinical Professor of Family and Community Medicine, University of Nevada
Benefit Risk Assessment of Salmeterol for the Treatment of Asthma in Adults and Children	C. Elaine Jones, Ph.D. Vice President, Respiratory Regulatory Affairs, GlaxoSmithKline Katherine Knobil, M.D. Vice President, Respiratory Medicines Development Center, GlaxoSmithKline
Introduction and Regulatory History of Foradil	Mathias Hukkelhoven, Ph.D., Senior Vice President, Global Head of Drug Regulatory Affairs, Novartis
Efficacy and Safety of Foradil	Linda Armstrong, M.D., Executive Medical Director, Clinical Development and Medical Affairs, Novartis
Benefits and Risks of AstraZeneca Formoterol-containing Products	Catherine Bonuccelli, M.D. Vice President, Development Projects, Symbicort, AstraZeneca Tomas Andersson, M.D., Ph.D. Medical Science Director, Symbicort, AstraZeneca Kevin Carroll, MSc Vice President, Statistics and Chief Statistician, AstraZeneca

Adjourned at 5:55 p.m. for December 10, to resume at 8:30 a.m. on December 11

December 11, 2008

Call to Order Introduction of Committees	Erik Swenson, M.D. Acting Chair, PADAC
	Marsha Rappley, M.D. Co-Chair, PAC
Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, PADAC
Opening Remarks	Ann McMahon, M.D. Acting Director, Division of Pharmacovigilance II OSE, CDER, FDA
The Path to this Meeting	M. Dianne Murphy, M.D. Director, Office of Pediatric Therapeutics, Office of the Commissioner, FDA
Open Public Hearing	
Clarification/Questions to FDA and Sponsors	
FDA Division of Pulmonary- Allergy Drug Products Summary Remarks	Badrul Chowdhury, M.D., Ph.D. Director, Division of Pulmonary and Allergy Products, CDER, FDA
FDA Office of Surveillance and Epidemiology Summary Remarks and Questions to Committees	Ann McMahon, M.D. Acting Director, Division of Pharmacovigilance II, OSE, CDER, FDA
Committees Discussion/Vote	
Adjourned at 4 p.m.	

Questions to the Committee:

Question 1:

Discuss the benefits of using salmeterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

- In adults [≥18 years of age]
- In adolescents [12-17 years of age]
- In children [4-11 years of age]

The Committees discussed and strongly stressed that the appropriate use of all LABAs, including salmeterol, i.e., following clinical guidelines, is necessary for the optimal control of asthma symptoms. The Committees discussed and emphasized that individual LABA agents should not be used as monotherapy for the asthma indication. Futher, they considered the possibility that the use of single product LABA agents may provide more flexibility in the choice of inhaled corticosteroids versus combination therapy consisting of a LABA and a corticosteroid. The Committees expressed that there are still not enough pediatric and subpopulation group studies to accurately assess the benefits of the product.

(Please see official transcript for details)

Question 2:

Discuss the benefits of using formoterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

- In adults [≥18 years of age]
- In adolescents [12-17 years of age]
- In children [5-11 years of age]

The Committees discussed that the appropriate use of the medication, following the clinical guidelines, is necessary for the optimal control of asthma symptoms. The Committees discussed and emphasized that individual agents should not be used as monotherapy for the asthma indication. They considered the use of single product LABA agents may provide more flexibility in the choice of inhaled corticosteroids versus combination therapy (LABA and a corticosteroid). The Committees expressed that there are still not enough pediatric and subpopulation group studies to assess the benefits.

(Please see official transcript for details)

Question 3:

Discuss the risks of using salmeterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

- In adults [≥18 years of age]
- In adolescents [12-17 years of age]
- In children [4-11 years of age]

The Committees discussed the negative consequences of inappropriate use for these drugs and that these risks are greater for the single agent medications than for the combination products (LABA and corticosteroid). The Committees discussed the need for more studies to include the African American subpopulation, and recommended that additional clinical safety data for the 4-11 age group be collected.

(Please see official transcript for details)

Question 4:

Discuss the risks of using formoterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

- In adults [≥18 years of age]
- In adolescents [12-17 years of age]
- In children [5-11 years of age] (Note that Symbicort is not indicated in this age group)

The Committees discussed the consequences of inappropriate use for these drugs and that the risks are stronger for the single agent medication. The Committees discussed the need for more studies to include the African American subpopulation. The Committees considered the need for more clinical trials and safety data for the 4-11 age group.

(Please see official transcript for details)

Question 5:

Do the benefits of Serevent (salmeterol xinafoate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

- In adults [≥18 years of age] (Voting question)
- In adolescents [12-17 years of age] (Voting question)
- In children [4-11 years of age] (Voting question)

In adults: YES= 10, NO= 17, Abstain= 0

The Committees discussed the advantages of strengthening the product labeling to indicate the appropriate use of combination therapy versus single agent monotherapy with salmeterol xinafoate for the above indication. The consensus was that stronger labeling and better patient education may provide an advantage in risk management.

In adolescents: YES= 6, NO= 21, Abstain= 0

The Committees suggested stronger labeling and better patient education may help to manage the risks. The Committees discussed the need for more studies with this age group.

In children: YES= 0, NO= 27, Abstain= 0

The Committees discussed that clinical trial safety data is lacking in this age group and that more safety studies are needed to address this issue.

(Please see official transcript for details)

Question 6:

Do the benefits of Foradil (formoterol fumarate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

- In adults [≥18 years of age] (Voting question)
- In adolescents [12-17 years of age] (Voting question)
- In children [5-11 years of age] (Voting question)

In adults: YES= 9, NO= 18, Abstain= 0

The Committees discussed the flexibility of use of this drug product in this age group and that the single drug product allowed for individualization of combination corticosteroid therapy. The Committees expressed concerns regarding the current lack of clinical safety data. The Committees considered the need for improved patient education regarding the risks of this class of drugs.

In adolescents: YES= 6, NO= 21, Abstain= 0

The Committees discussed the lack of safety data in this age group.

In children: YES= 0, NO= 27, Abstain= 0

The Committees discussed the lack of safety data in this age group.

(Please see official transcript for details)

Question 7:

Do the benefits of Advair (fluticasone propionate; salmeterol xinafoate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

- In adults [≥18 years of age] (Voting question)
- In adolescents [12-17 years of age] (Voting question)
- In children [4-11 years of age] (Voting question)

In adults: YES= 27, NO= 0, Abstain= 0

The concensus of the Committees was that sufficient evidence was available to support the efficacy and safety of the product. While the Committees considered the benefits associated with use of the product to outweigh its risks, they generally agreed that there was still lack of safety data from long-term clinical trials.

In adolescents: YES= 23, NO= 3, Abstain= 1

The Committees expressed that the available data, although not strong and limited, suggest safety and efficacy of the product in this age group. However, the Committees expressed their concerns that negative safety signals are still present and they expressed their interest in seeing large randomized studies be conducted to better identify the risks.

In children: YES= 13, NO= 11, Abstain= 3

The Committees were concerned with the identified risks of the product in this age group. They felt that there was a lack of safety data for this class of patients and suggested that additional, large clinical trials be conducted to better define the risks.

(Please see official transcript for details)

Question 8:

Do the benefits of Symbicort (budesonide and formoterol fumarate dihydrate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

- In adults [≥18 years of age] (Voting question)
- In adolescents [12-17 years of age] (Voting question)

In adults: YES= 26, NO= 0, Abstain= 1

The concensus of the Committees was that the available evidence supports the safety and efficacy of the product in this patient population.

In adolescents: YES= 20, NO= 5, Abstain= 2

Concerns were raised that the available safety data on the product was minimal. The majority of the committees' members felt that based on the limited amount of data, the product's safety and efficacy were supported. The concensus of the Committees was that additional clinical trial safety data be gathered.

(Please see official transcript for details)

Question 9:

Based on your discussion and votes above, are there further labeling changes or risk mitigation strategies for individual LABA products, or the class as a whole, that would be advisable?

The Committees discussed:

- *current labeling contents are inadequate and emphasized that labels and medication guides should reflect current clinical guidelines*

- *improved educational efforts to enhance adherence to guidelines and standards of care*

- *increased communication to the public regarding the recommendations of combination therapy (LABA and corticosteroid) versus single agent therapy (LABA)*

- *the need for more trials to be conducted on pediatric and subpopulation groups*

- *expedition of information and reporting from Sponsors to Agency to Committees*

- *establishment of a comprehensive registry of patient treatments and deaths*

(Please see official transcript for details)

Question 10:

What further studies, if any, would clarify important unanswered questions of safety and efficacy for individual LABA products or the class as a whole?

The Committees considered the following:

- *studies to address safety of the class as a whole and to conduct more studies in adolescents, children, and African Americans*

- *studies to look at the effectiveness of mitigation strategies for the risks of these drugs*

- *studies looking at differential mechanism between salmeterol and formoterol*

- *the need for more comprehensive measures in studies about functional improvements in asthma*

- *studies on etiology of drug-related, condition-related deaths in asthma*

- *studies on drug utilization and adherence to guidelines and standards of care*

- *the need to conduct studies to better understand and encourage compliance, particularly with subpopulations*

- *the need for a more comprehensive evaluation of data sets*

- *studies to link severity level to both benefits and risks seen in asthma outcomes*

(Please see official transcript for details)