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by Lynne Peterson

SUMMARY

Internally, the FDA has been split about what to do about long-acting beta agonists (LABAs). Three FDA advisory committees, meeting together, recommended that GlaxoSmithKline's Serevent and Novartis/Schering-Plough's Foradil lose their indication for the treatment of asthma, though both drugs could continue to be marketed for other conditions. If the FDA doesn't take away the asthma indication, the panel said the Serevent and Foradil labels should be changed to contraindicate use of either drug without an inhaled corticosteroid. Panel members also recommended that GlaxoSmithKline's Advair and AstraZeneca's Symbicort remain on the market, but they were undecided about continued use of Advair in children.

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FDA Panel Recommends Two Inhaled Drugs No Longer Be Used in Asthma

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Three FDA advisory committees met to discuss the safety of long-acting beta agonists (LABAs) for asthma. After two days of lectures and discussion, the panel sent the FDA a strong message: the two single-agent LABAs – GlaxoSmith-Kline's Serevent (salmeterol) and Novartis/Schering-Plough's Foradil (formoterol) – should no longer be approved for asthma treatment, though they can be left on the market for chronic obstructive pulmonary disease (COPD). The benefits outweigh the risk for GlaxoSmithKline's Advair (salmeterol + fluticasone) and AstraZeneca's Symbicort (formoterol + budesonide) in adults, the panel decided, but it was divided on whether Advair should be allowed for children without more safety data.

Final Advisory Committee Votes on LABA Risk:Benefit

Drug	Do the benefits outweigh the risks for		
	Adults ≥18 years of age	Adolescents 12-17 years of age	Children 4-11 years of age
Serevent	No 17, Yes 10	No 21, Yes 6	Unanimously No
Foradil	No 18, Yes 9	No 21, Yes 6	Unanimously No *
Advair	Unanimously Yes	Yes 23, No 3, Abstain 1	Yes 13, No 11, Abstain 3
Symbicort	Yes 26, No 0, Abstain 1	Yes 20, No 5, Abstain 2	---

* Age 5-11, not 4-11

At the request of the Pediatric Advisory Committee in November 2007, the FDA conducted a meta-analysis of the risk:benefit of LABAs, and the panel was persuaded by the data.

Two other LABAs currently have FDA approval for treatment of COPD: Sepracor's Brovana (arformoterol) and Dey's Perforomist (formoterol). These were not included in the meta-analysis, which was based on data from 110 trials and 60,954 patients, with 6% age 4-11, 11% age 12-17, and 77% age 18-64. Median treatment duration was 169 days. Overall, the study found LABAs were associated with an increased risk of asthma-related events vs. non-LABA treatment, with an increased risk of 180% (HR 2.80).

Before and during the advisory committee meeting, the split ***within*** the FDA over LABAs was clear over what to do about these data. The FDA's Office of Surveillance and Epidemiology (OSE) believes that the evidence of benefit from LABAs is slim and that the evidence for risk is so strong that the burden of proof

LABA Meta-Analysis

Company	Brand name	Generic name	Description	Number of patients analyzed	Hazard ratio	Deaths
GlaxoSmithKline	Advair	Salmeterol + fluticasone	Combination of LABA and inhaled corticosteroid (ICS)	13,212	Increased but Nss	0
GlaxoSmithKline	Serevent	Salmeterol	LABA	43,824 **	HR 3.36	16
AstraZeneca	Symbicort	Formoterol + budesonide	Combination of LABA and ICS	1,270	Increased but Nss	0
Novartis/Schering-Plough	Foradil	Formoterol	LABA	3,765	Nss	0
TOTAL	**---**	**---**	**---**	**60,954 ***	**---**	**16**

*** 1,117 had more than one LABA.** **** 26,355 were from the SMART trial.**

should shift – that it must be proved that LABAs are safe, and approval should be withdrawn until that proof is provided. On the other hand, the Division of Pulmonary and Allergy Products believes that the benefits that LABAs provide to many patients outweigh the serious risk – that LABAs should remain on the market, though the safety needs to be managed.

After the panel discussion and votes, FDA officials and one of the panel co-chairs spoke with reporters. Asked if OSE officials felt their concerns were adequately addressed by the committee's actions, Dr. Henry Francis, deputy director of OSE, said, "Yes. We have to balance the population kinds of things vs. a more patient-centric view. We looked at all the viewpoints…In this process I think we had a successful resolution and an idea where we need to go next." Dr. David Graham, associate director for science and medicine in the FDA's Office of Surveillance and Epidemiology – the most outspoken FDA critic of LABAs – did not speak with reporters after the meeting.

Dr. John Jenkins, director of the FDA's Office of New Drugs, Center for Drug Evaluation and Research (CDER), said the Agency has gotten the message that panel members are very concerned about LABA monotherapy, "They were much more comfortable with combination therapy with a LABA with an inhaled corticosteroid (ICS). Many of the members, as they voted on (against) single ingredients, expressed the view that their concern was that with single ingredient LABAs, you could not assure the patient would also receive an ICS, and with the combination you can be certain that any LABA patient also gets an ICS. They felt more comfortable the benefits (of a combination LABA) outweighed the risk…The main message to convey to patients is that they should not stop taking any of their asthma medications without consulting their physicians. The other main message is that the primary concern at this point is that LABAs not be used as a monotherapy maintenance treatment for asthma…Patients should not be moved to LABAs until they don't respond to appropriate doses of an ICS." Dr. Diane Murphy, director of the FDA's Office of Pediatric Therapeutics in the Office of the Commissioner, added, "It was pretty clear the committee also thought we need more information on safety in pediatrics and asked for that study."

While the OSE officials may believe that the panel recommendations will be followed and the asthma indications for Serevent and Foradil removed, the final decision lies with Dr. Jenkins and the Division of Pulmonary and Allergy Products, not OSE. At a minimum, all LABA monotherapy going forward is likely to be contraindicated in asthma, and pediatric use of LABAs is likely to be sharply curtailed if not eliminated entirely.

The more concerning issue is what this means for newer agents in development, and that answer is: It's going to be much tougher to get them approved, requiring more and different data. An ~500-patient trial, as was used for Advair's approval, is almost certainly not going to be sufficient for safety.

Asked how the panel's recommendations will affect the regulatory path for new asthma drugs in development, Dr. Jenkins said, "I'm not sure what other LABAs are under development. The concern is fairly unique for LABAs at this time. The main area of development in the whole beta agonist field for the last 10 years has been changing from CFC inhalers to non-CFC inhalers." Dr. Badrul Chowdhury, director of the FDA's Division of Pulmonary and Allergy Products, CDER, said, "The development of LABAs is ongoing, and, of course, there potentially are drugs being developed, including in the future even longer-acting LABAs. On the impact of what we heard today, we have to have time to think about it, and how it applies, but the general message is there is a concern about the use of LABAs alone without an ICS."

Dr. Jenkins said new LABAs are now in the same boat as new diabetes drugs, "This (LABAs) may be similar to discussions on diabetes drugs, where the advisory committee (last summer) discussed what level of certainty we have to have before approval before ruling out an unacceptable risk…And there they want more data than in the past that the new drugs to treat diabetes are not unnecessarily raising the cardiac risk. For new LABAs we have to consider how much certainty and data there are before approval to assure ourselves that they are not raising the risk of asthma exacerbation and death to an unacceptable level. It is a similar paradigm. Once you know the risk, how much data do you have to have to approve a subsequent member of the class?"

Asked whether the agency plans to take meaningful action to stop doctors and patients from using single-agent LABAs

without an ICS or to "continue to shout in the wind," Dr. Jenkins said, "The label (on LABAs) is not as careful in saying monotherapy is something that should never be done, and it isn't as forceful in emphasizing that an ICS should be added on top of a LABA. We did hear some members say if the labeling changed, their vote would have gone from no (the benefits don't outweigh the risk) to yes. We will have to work internally on whether we want to change the label and manage the risk – and even put some other REMS (risk management program) in place to try to do that – and is all that warranted to preserve what some committee members referred to as choice, so that doctors have a choice of which ICS to combine with LABAs. Those are things we need to take back and discuss… And there were data that 97%-98% of LABAs use is already the combination product, so there is a very small percent of prescribing that is currently single ingredient."

Dr. Jenkins added, "We heard many times that committee members want additional safety data for LABAs and the combinations with ICS, across all age groups, with particular focus on pediatrics. We now have the authority to require studies post-approval, and that is something we will go and think about. What type of studies would be useful to quantify the risk going forward?...But our authority is for safety studies, not efficacy studies…We heard some people saying a simple safety trial (like SMART) might be useful because the practice of medicine and the treatment of asthma has changed dramatically in the past 10 years…Now, the paradigm has shifted, and we have to consider if we want ICS combined with beta-agonist studies."

Panel co-chair Dr. Eric Swenson, a pulmonary and critical care specialist from the University of Washington, said, "Therapy for asthma will continue to evolve…Coming up are a number of potentially good anti-inflammatory therapies, so though corticosteroids remain the gold standard, maybe there are better options (coming) to control asthma…There was some sense of maintaining flexibility (not removing choices from physicians)."

Dr. Murphy chimed in that the FDA will be discussing internally how to better use the pediatric incentive program to encourage more trials. However, she noted that the Agency can only use the incentive program once for any particular drug.

Asked about the feasibility of a LABA registry which at least one panel member recommended, Dr. Jenkins said, "My initial reaction is that for this situation it would be very hard to interpret because there would be no control. You really need randomization to therapy to understand what you are seeing in a registry, keeping in mind that the events we are worried about are the same events that occur naturally in the disease." Dr. Gerald Dal Pan, director of the FDA's Office of Surveillance and Epidemiology, agreed, "A registry would be very difficult to gauge the significance of the risk because if an asthma exacerbation happens, how do you know it is the disease and not the drug?"

LABA Background

This was the fifth advisory committee the FDA has convened on the question of LABA safety. Prior panels were:

- February 26, 1993.
- November 23, 1999.
- July 13, 2005 – The panel recommended unanimously that both salmeterol- and formoterol-containing products continue to be marketed in the U.S. but that all these products should have similar boxed warnings.
- November 28, 2007 – The panel noted that "salmeterol may have an unfavorable risk:benefit ratio in the treatment of pediatric asthma" and discussed removing it from the market but determined the benefit was worth the risk.

The labels for LABAs currently contain a boxed warning about asthma-related deaths and specifies that they should only be used for patients not adequately controlled on other asthma-controller medications or whose severity clearly warrants initiation of treatment with two maintenance therapies.

In terms of the **efficacy** of LABAs, the FDA noted:

- The largest clinical differences between LABA and comparator were ~1.5 fewer puffs of rescue medicine per day or 15%-20% more symptom-free days with the LABA vs. comparator.
- Although the pediatric studies met the spirometric endpoints, there was little improvement over comparator in the secondary endpoints for children <12 years old.

The FDA Perspective

FDA meta-analysis results

These recommendations are based on the FDA's meta-analysis, which found:

- LABAs as a group were associated with an **increased risk of a composite of events** – asthma-related hospitalization, asthma-related intubation, and asthma-related death. The overall unadjusted risk per 1,000 subjects was estimated to be:
  - 0.4 for death.
  - 2.80 overall for the composite of asthma-related events.
  - Without an ICS, the composite risk was 4.3 vs. 0.4 with an ICS. There was no increased risk when the LABA was taken with an ICS.
- An increased risk was seen for Foradil, Serevent, and Symbicort – but not for Advair. **Only Serevent had a statistically significant increased risk**, and all the asthma-related deaths were in Serevent-treated patients.
  - **Advair.** There was no risk difference between Advair and fluticasone. "Advair had an estimated risk

difference of essentially zero. Although an argument could be made that this was due to the impact of ICS, the data from the FDA meta-analysis may not support that point of view."

- **Symbicort.** There was a 7.49 excess of asthma-related serious events per 1,000 subjects vs. non-LABA therapy, though this was not statistically significant.

Risk Difference with LABAs in the Meta-Analysis

Measurement	LABA vs. no LABA risk difference per 1,000 patients
Asthma-related risk by age	
4-11 (n=3,415 patients)	**+ 14.83, significant**
12-17	+ 5.75, significant
18-64	+ 2.13, significant
≥65	- 3.58, Nss
Asthma-related risk by race	
Black/African Americans (11%)	+ 8.13
Caucasians (72%)	+ 1.96
Asian (4%)	+ 0.94
Other (13%)	+ 3.00
Asthma-related risk by gender	
Males (43%)	+ 0.96
Females (57%)	+ 4.20
Asthma-related risk by geography	
U.S.	+ 3.23
Non-U.S.	+ 1.89

Events in the LABA Meta-Analysis

Measurement	Non-LABAs	LABAs	Risk difference per 1,000 patients
Asthma-related events – overall			
Number of patients	30,806	30,148	---
Asthma death	0.01% 4 patients	0.05% 16 patients (all Serevent)	+ 0.40
Asthma death/intubation	0.9%	0.15%	+ 0.57
Asthma hospitalization	0.97%	1.22%	+ 2.57
Primary endpoint: Composite of asthma-related hospitalization, asthma-related intubation, and asthma-related death	0.99%	1.26%	**+ 2.80**
All-cause death	0.13%	0.17%	---
Asthma-related events – LABA without ICS vs. no LABA			
Number of patients	24,474	22,286	---
Asthma death	0.02%	0.07%	---
Asthma death/intubation	0.11%	0.19%	---
Asthma hospitalization	1.12%	1.52%	---
Composite	1.14%	1.57%	**+3.63, significant**
All-cause death	0.15%	0.21%	---
Asthma-related events – LABA with ICS vs. ICS alone			
Number of patients	7,330	7,862	---
Asthma death	0	0.01%	---
Asthma death/intubation	0	0.01%	---
Asthma hospitalization	0.35%	0.39%	---
Composite	0.35%	0.39%	+0.25
All-cause death	0.05%	0.05%	---

- **Serevent.** The FDA could not exclude a **potential risk difference of 1 per 180 for Serevent**, 1 per 106 for Symbicort, and 1 per 61 for Foradil.
- **Formoterol.** The FDA estimated it has 4 more asthma-related serious events per 1,000 patients vs. a non-LABA, but this was not statistically significant.

➢ The results were **driven by asthma-related hospitalization and asthma-related deaths**.

➢ **Youths (age 4 – 11 years) were the age group at greatest risk**, except with Advair. In young children, driven by the data for Serevent and formoterol, the estimated risk difference increased to almost 15 more serious asthma events per 1,000 patients or an excess of 1.5 serious asthma events for every 100 patients treated with LABAs vs. non-LABA therapy. The age effect was not only marked in the youngest patients but also gradually decreased with each age bracket, suggesting this is a robust finding.

➢ **Blacks/African Americans had a higher risk** than other racial subgroups.

➢ **Females** had a higher risk than males.

➢ The Kaplan-Meier curves appear to diverge over one year, suggesting that the increased **hazard risk continues** out to at least one year.

➢ **The worst risk:** no ICS use, black, female, young (age <17), U.S. asthmatics.

The Serevent trial SMART accounted for a substantial portion (43%) of total subjects in the meta-analysis, but FDA analyses indicated that the results hold up with or without the SMART results.

FDA speakers

Dr. Robert Lemanske Jr., professor of pediatrics from the University of Wisconsin School of Medicine and Public Health, was asked by the FDA to provide a review of the history of asthma treatments. He said the primary goal of asthma therapy is to enable patients to achieve and maintain control over their asthma – to eliminate impairments, including symptoms, functional limitations, poor quality of life, and other manifestations of asthma; and to reduce the risk of exacerbations, emergency room use, and hospitalizations. Treatment goals are identical for all levels of asthma severity.

He speculated on possible reasons for the differences between results with short-acting beta agonists (SABAs) and not with LABAs:

- Higher doses of ICS blunt a genotype-specific effect of salmeterol.

- Genotype-specific differences occur only with SABAs, not with LABAs when LABAs are used with inhaled corticosteroids.
- Genotype-specific effects may be more prominent in subpopulations under-represented in the study.

He concluded:

- "I could not recommend LABA use as monotherapy."
- Are responses to therapy based on beta adrenergic receptor genotype different with SABAs than with LABAs? "This is a question we need to think about answering."
- Do children respond differently to LABAs (not adversely but therapeutically), and there are data to suggest that might not be the case – that they are not doing much more than monotherapy with ICS?

Benefits and Risks of LABAs

Benefits	Risks
Bronchodilators (FEV_1)	Asthma-related deaths and serious asthma exacerbations
Reduction in rescue medication use	Boxed warning on asthma-related death applies to all ages and to salmeterol- and formoterol-containing products
Improvement in peak expiratory flow (PEF)	LABAs should only be used as additional therapy in patients not adequately controlled on other asthma-controller medications
Improvement in asthma symptoms	
Fewer nocturnal awakenings	

Comparison of Efficacy of LABAs †

Measurement	Serevent	Foradil	Advair
Age >12 change vs. placebo			
FEV_1 at 12 hours	+ 20%	+ 0.3%	---
A.M. peak expiratory flow rate (PEFR)	+ 30 L/min	---	+ 76 L/min
Rescue inhalations/day	- 1.8	---	---
Days with no asthma symptoms	- 14%	---	+ 29%
Nights with no awakenings	- 19%	- 19.6%	+ 21.4%
Asthma exacerbations	- 19	---	---
Symptom score change	---	- 0.2	---
Age <12 change vs. placebo			
FEV_1 at 12 hours	+ 3.3%	+ 0.15%	+ 0.16% *
A.M. PEFR	+ 5.4 L/min	+ 13 L/min	+ 25 L/min *
Rescue inhalations/day	- 0.5	- 0.08	- 0.5 *
Days with no asthma symptoms	---	---	+ 24% *
Nights with no awakenings	+ 5 %	---	---
Asthma exacerbations	---	---	---
Symptom score change	- 0.3	- 0.08	- 0.6 *

* Change from baseline, not placebo.

† These were not head-to-head studies, so comparisons are not direct.

- Combination therapy significantly improves asthma control in both the current impairment and future risk domains.
- The concept of maintenance and relief with ICS + beta agonist needs further study. "Does it need to be a LABA, or can it be replaced with a SABA?"

Dr. Sally Seymour, deputy director for safety of the FDA's Division of Pulmonary and Allergy Products, CDER, provided a long review of the background and regulatory history of LABAs. She also offered the FDA view of the benefits, risks, and efficacy of LABAs.

PUBLIC WITNESSES

Anne Dorsey and her 13-year-old son Julian, who has life-threatening asthma. Ms. Dorsey said that due to "Advair and a combination of other drugs" her son "is still here." She urged the FDA to keep the LABAs available to asthma patients, "I ask you to keep allowing my son to keep taking these drugs. He needs them." Then, her son made his own plea, "I spend a lot of time in hospitals…and have a lot of IVs and blood gasses (taken), but when I took Advair, that almost cut in half the amount of time I spent in the hospital. Life got a lot easier, and without Advair, I don't know (what I would do)."

Dr. Stanley Szefler, a member of the asthma guidelines committee, speaking on behalf of both the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI). He told the panel that if LABAs were removed from the market, "It would be a disaster…I can speak on behalf of six million patients. If this drug (Advair) were removed, it would make a difference…I don't think you want a panel (that) took asthma back 20 years…I think our two societies…will try to educate physicians as much as possible to be careful with the use of these drugs if you make the decision to step up the education process."

Dr. Carolyn Britton, president of the National Medical Association. The prevalence and severity of asthma is worse in the African-American population, Dr. Britton said, adding, "Black box warnings for asthma medications is a potential deterrent for use…Use of black box warnings must be carefully considered and should be supported by solid evidence. There is long-standing concern about LABAs, especially in children…Current data show that, when used appropriately in accordance with an ICS, the efficacy of these medications is well established…We recommend that beta-2 agonists continue to be available in conjunction with an ICS…(But) the guidelines for use should be clear and unambiguous…We underscore the disproportionate impact of asthma mortality in the African-American community."

Dr. Shelly Salpeter, Stanford University School of Medicine. She said that in 2006 she and her colleagues did a meta-analysis on LABA hospitalizations, intubations, and deaths and found LABAs were associated with a 2-fold increase in serious, life-threatening and fatal asthma events, "Now in 2008, five more meta-analyses have been published – most of them sponsored by pharmaceutical companies – and each only looked at one part…I pooled all the available data from drug-sponsored and non-sponsored data on formoterol." She found, "LABAs significantly increase the risk of life-threatening or fatal asthma events with and without use of concomitant ICS. No protective effect of ICS was seen."

- For LABAs and variable ICS there is a 2-fold intubation increased risk (p=0.05), where the greatest weight came from the SMART study (of salmeterol). If that was removed, there was a 5-fold increase in asthma intubations or death (p=0.01).
- There is little or no heterogeneity between trials, with all trials reporting more events in the LABA group.
- If SMART is removed, all the events were in the LABA group and zero event in the control."
- There was no significant difference for any subgroup.

Stanford Pooled Analysis of LABA Safety

Drug	Odds ratio of death/intubation	
	Variable ICS use	Concomitant ICS use
Salmeterol	2.0	9.9
Formoterol	4.5	5.4

Nancy Sander, speaking on behalf of the non-profit Allergy and Asthma Network Mothers of Asthmatics. She urged the panel to leave LABAs on the market, noting, "Children do fear death and the isolation of asthma."

Dr. Alfred Munzer, speaking on behalf of the American Thoracic Society (ATS). He thanked the FDA for its commitment to patient safety and said, "There is conclusive research evidence, supported by years of clinical experience, that demonstrates that adjunctive use of LABAs is effective in controlling asthma symptoms…Recent evidence suggests that there is a small but significant increase in mortality. A meta-analysis also suggests that asthma-related events are increased by LABA use. The increase in all asthma adverse effects appears greatest in women, children, and those of African-American descent…An increase in hospitalizations and intubations does occur with LABAs, even in combination with ICS…While expert opinion is divided, the American Thoracic Society believes the following recommendations are supported by the existing data and are prudent risk:benefit management:

1. *LABAs in combination with ICS should remain on the market.* "Should the FDA remove LABAs from the market, patients will be denied the most effective therapy for uncontrolled asthma…There (also) is a mortality risk with poorly controlled asthma, and the addition of a LABA to ICS is the recommended therapy for asthma that is poorly controlled by ICS in adults and children <age 12."
2. *Single-agent LABAs should remain on the market.* "It is reasonable for the Advisory Committee to discuss the removal of a single-agent LABA, but we know that the Pediatric Advisory Committee considered taking this measure at previous meetings, but did not make that recommendation…We are concerned that removing a single-agent LABA would send a confusing signal to providers and patients about the step-wise approach to LABA use, increase the out-of-pocket expenses of patients forced to switch (agents)…and cause patients to deviate from their treatment plan…And the removal of education about asthma would not cause removal of the product from the market since it is being used for COPD. Thus, off-label use would often occur inappropriately."
3. *Any further change to the black box warnings for LABAs should be consistent with recommendations.* "The Advisory Committee may consider making…warnings clear about the potential risk:benefit. Additionally, if a LABA is considered appropriate ***only*** for asthma control …ATS welcomes any change that more effectively conveys this message."

The Industry Perspective

As expected, industry representatives defended the efficacy and safety of their products. However, their presentations came at the end of a long, tiring day, and there was nothing surprising in the talks. Panel members decided to adjourn without asking the speakers any questions.

Dr. Stuart Stoloff, clinical professor of family and community medicine from the University of Nevada, a member of the asthma guidelines committee, put a patient face on the LABA discussion on behalf of GlaxoSmithKline, Novartis, and Astra-Zeneca. He said he currently has >2,000 asthma patients in his practice and gave a detailed example of one young boy whose quality of life and activity level was rescued by a LABA. Dr. Stoloff also challenged estimates that 5,000 Americans die each year from asthma-related events, putting the number at 3,400-3,600 annually, though he later added, "We still have ~10 people a day dying from asthma." He made a fairly impassioned plea for the FDA to leave all the LABAs on the market, unrestricted, "My concern is what options will be available to patients if there is ***any*** restriction on access to LABAs."

GlaxoSmithKline's Serevent and Advair

C. Elaine Jones PhD, vice president/respiratory regulatory affairs at GlaxoSmithKline (GSK), reviewed the approval and labels for Serevent and Advair. She said the company conducted a meta-analysis of all 215 GSK-sponsored studies of 106,575 patients and found no significant safety concern.

However, she said the company is proposing a stepped-up risk management program, including:

- Revised indication to restrict use only as concomitant therapy with an ICS.
- A boxed warning about asthma-related hospitalizations.
- Strengthened Medication Guide, with an emphasis that patients must continue taking their LABA every day and that the ICS must be taken every day and not stopped or dose-reduced even if patients feel better.
- Healthcare practitioner initiatives about the labeling change, with targeted education (Dear Healthcare Provider letters and an education program for healthcare providers).
- Managed care/pharmacy initiatives to update formulary algorithms and pharmacy computer systems so that pharmacists would be alerted if Serevent is prescribed without an ICS.

Then, Dr. Katharine Knobil, vice president/respiratory development center at GlaxoSmithKline, defended both the efficacy and safety data on Serevent and Advair. Among her key comments were:

➢ **Salmeterol.** "All studies comparing salmeterol + ICS have consistently been better than ICS alone…Salmeterol is a very effective bronchodilator…And preventing exacerbations is so important (especially in children)…There is a 35% reduction in asthma exacerbations with salmeterol."

➢ **ICS.** "Higher doses of ICS may not provide better asthma control…Because of the risk of dose-related adverse effects with ICS, the guidelines recommend that after achieving control, ICS should be titrated to a lower dose...Advair allows better control at a lower ICS dose…In 1996 only one-third of Serevent was dispensed with ICS…Today, Serevent is dispensed with ICS >98% of the time…currently 98% of salmeterol use is in Advair."

➢ **Serevent.** "GSK acknowledges that there is a question whether Serevent should continue to be available, but we favor continued availability and proposed labeling showing that it is required that Serevent only be used concurrently with an ICS. We believe the benefits of Serevent, used concurrently with an ICS, outweigh the potential risk…the case for Serevent is more complex. We know it is inappropriate to use Serevent without an ICS. However, there is no increased risk when Serevent is used with an ICS…And the Serevent patients are a relatively small number of patients whose needs can't be met with Advair."

➢ **Advair.** "Asthma-related deaths and hospitalizations with Advair have been zero in more than 22,000 patients… There has been no increased risk of asthma-related hospitalization and no asthma-related intubations…In children, there have been no asthma-related deaths (with Advair) in >2,400 children, no increase in asthma-related hospitalizations, and no asthma-related intubations…GSK did a year-long study in African Americans…The results showed no difference in the exacerbation rate (0.45 with Advair vs. 0.53 with control) or hospitalizations (4 patients vs. 4 patients)."

She said that a meta-analysis of observational studies of Advair use, covering 59,000 Advair patients, found Advair was associated with a 16% decrease in asthma-related emergency room visits and a 15% decrease in asthma-related hospitalizations vs. ICS alone. Her conclusion: "The case for Advair is clear – substantial efficacy has been shown, and there is no evidence of untoward outcomes."

NOVARTIS/SCHERING-PLOUGH's Foradil

Mathias Hukkelhoven PhD, senior vice president/global head of drug regulatory affairs at Novartis, said, a review of "the totality of clinical data for formoterol and the postmarketing surveillance data indicated that Foradil continues to exhibit a favorable risk:benefit ratio." He outlined the risk mitigation strategies that Novartis has completed or is continuing since approval of Foradil, which includes:

- A planned epidemiological study of the Medicaid database from seven states. This would include 870,000 asthmatics (436,000 <age 12), looking at asthma-related mortality, emergency room visits, hospitalizations, and intubations." This report is expected to be available in 2009.
- A Medication Guide.
- Label change.
- Physician education.
- Patient education on the Foradil website.
- Global pharmacovigilance.

Dr. Linda Armstrong, executive medical director/clinical development and medical affairs at Novartis, reviewed selected clinical trials of Foradil and presented a pooled safety analysis. She said that the majority of patients with asthma use Foradil with an ICS – 77% overall and 84% of children age 5-12 – but only 20% of Foradil use is in patients with asthma. She added that no asthma-related Foradil serious adverse events have been reported in the FDA's Adverse Event Reporting System (AERS) database since the label change in 2006.

Novartis Pooled Analysis of Foradil Safety

Measurement	Foradil n=5,367	Albuterol n=976	Placebo n=2,026
Asthma-related deaths *	0.02%	0	0
Composite of asthma-related deaths, intubations, and hospitalizations (% and number per 100 patient-years)			
Overall	0.7% (2.7)	0.4% (1.4)	1.0% (4.5)
>age 18	0.4% (1.8)	0.3% (1.4)	0.7% (3.1)
Age 13-18	0.5% (1.8)	1.5% (6.1)	1.8% (8.4)
Age 5-12	2.4% (0.5)	0.3% (0.5)	3.1% (16.2)

*** No deaths or intubations among pediatric patients.**

Dr. Armstrong also noted that other add-on therapies that could be used in lieu of a LABA have their own problem such as seizures and arrhythmias for theophylline and liver toxicity for zilueton (Abbott's Zyflo). She concluded: "Foradil improves lung function, reduces rescue bronchodilator use, reduces symptoms in all populations. It remains an important treatment option as add-on therapy for patients not controlled on an ICS alone. It also provides physicians and patients the choice of adding Foradil, delivered in a dry powder inhaler, to a variety of ICS over the range of approved doses."

She admitted Foradil may be associated with an increased risk of asthma-related hospitalization but said this risk is reflected in the current label, and the pooled analysis showed more asthma-related hospitalization in patients 5-12 years of age, but this was primarily based on findings for a 1-year safety study in which more patients treated with placebo discontinued prematurely. She concluded, "There have been no reports of asthma-related pediatric deaths since U.S. approval in 2001."

AstraZeneca's Symbicort

Dr. Tomas Andersson, medical science director/Symbicort at AstraZeneca, said the benefits of Symbicort include prevention of asthma exacerbations and asthma worsening as well as current control of asthma symptoms, improvement in lung function (FEV_1 and morning PEF), and better asthma-related quality of life. For example, in studies, Symbicort:

- Reduced *severe* asthma exacerbations by 26% (p=0.01).
- Reduced mild exacerbations by 40% (p=0.01).
- Improved quality of life significantly ($p \leq 0.001$ in adults and children).

Kevin Carroll, vice president/statistics and chief statistician at AstraZeneca, said the company's own analysis of all 23,510 patients in the 42 trials of formoterol found no increase in the risk of death, asthma-related intubations, or asthma-related hospitalizations per 100 patient-years. These data were provided to the FDA, but the FDA meta-analysis only included 1,270 of these patients who met the FDA's specific criteria. Dr. Catherine Bonuccelli, vice president/development projects/Symbicort at AstraZeneca, contended that the AstraZeneca analysis is more comprehensive and more precise than the FDA analysis.

AstraZeneca Analysis of the Safety of Formoterol-Containing Products

Measurement	Formoterol-containing products n=13,542	Non-LABA-containing products n=9,968	Relative risk of formoterol
Asthma-related deaths	0	0	---
All-cause death	0.02%	0.04%	---
Death rate per 1,000 patients per year	0.53	0.82	0.64
Patients with ≥1 asthma-related hospitalization	0.58%	0.83%	---
Asthma-related hospitalizations per 1,000 patients per year	12.05	16.40	0.73

The bottom line, according to Dr. Bonuccelli:

- Symbicort is safe, effective, and important treatment for patients not well controlled with an ICS alone.
- Current labeling reflects appropriate use of LABAs – always with inhaled corticosteroids.
- Potential risks are adequately described in the current Symbicort label.
- Symbicort should remain a therapeutic option.

Panel Questions for FDA and Industry Speakers

Why are LABAs associated with serious adverse events? Dr. Seymour said, "We don't know."

What percent of pediatric patients get a LABA? Dr. Lemanske, the FDA expert, said that in his university-based practice, he prescribes them for 25%-50% of asthmatic children, "That said, I've shown data that show children respond very well to monotherapy with corticosteroids, and many, many children do not need combination (LABA) therapy…We, as clinicians, need to decide if we should push the steroid dose or try something else. We know as soon as we get to a dose >200/day, we get an adverse effect on growth in some children. That is the cut point where you have to start thinking about other options."

What would the burden be for patients if LABAs were taken off the market? Dr. Lemanske didn't like the idea of his choices being limited, saying, "It would be a burden for me because I would have to choose something else, like give more steroid… but maybe that is the best option...The thing about asthma is that it is so individualized. Each patient is unique. What works for Johnny won't work for Jane…And if we limit our options, the ability to (tailor treatment) gets more and more limited."

The FDA's Dr. Jenkins asked the panel, "Given the background of ICS, what is the added risk by adding a LABA? …That is fundamentally the question we face in managing the risk with these drugs. We can all agree patients should not be on a single-agent LABA alone except in very rare situations."

Asked about the FDA's AERS database, the FDA's Dr. Graham told the panel, "AERS is unreliable…so we never use AERS as a means of monitoring the effect of an intervention because it is so unpredictable...All AERS tells us is that there are asthma deaths with the product…not a trend…In observational studies, the single greatest problem we have is misclassification that drives the odds ratio toward the no effect level…So, our view on asthma and the question of the LABAs is that it can only be resolved by large, randomized clinical trials."

Asked about the efficacy of LABAs, Dr. Graham said, "There is not a whole lot of juice for the squeeze…One study had 90% power to show a (beneficial) effect, and it was not there...We didn't see a lot of translation for FEV_1 (improvement) to (clinical) benefit…With what we hear about patients taking these drugs off the market themselves (by stopping them, not complying with use), it is a tough argument to make that it will be catastrophic if they are taken off the market."

Asked how many deaths there have been with Symbicort, an AstraZeneca official said, "In a 23,510-patient dataset, we had no asthma-related deaths." Another AstraZeneca expert said, "Use of Symbicort is not only safe but increases the safety vs. on-LABA treatments. I have no wish to go back to how we treated asthma in the 1970s and 1980s, or even the early 1990s …The message is that patients are individuals, need to be assessed properly, need the appropriate treatment, and need to be followed."

Dr. Marsha Rappley, a pediatrician from Michigan State University, a member of the Pediatric Advisory Committee, and a co-chair of this joint panel meeting, summarized the sense of the panel at this point: "You are hearing some frustration that the overall time has not been enough on pediatric issues…What I have heard from OSE is that they believe the evidence of benefit is slim and that the evidence for risk with a LABA is so strong that the burden of proof should shift...so that it must be proved that LABAs are safe and approval should be withdrawn until that proof is provided…What we heard from the Division of Pulmonary Products is different – that the evidence is that most patients do derive benefit from LABAs and that the risk can be managed by informing prescribers, patients, and the public. From industry, we hear the benefits outweigh the risks. And from the public, five speakers were urging us to allow continued use, and one was further emphasizing the risk. The FDA meta-analysis shows an increased risk with young age groups, which is our particular concern. And in all of this, the risk of not treating patients was alluded to."

PANEL DISCUSSION AND VOTES ON FDA QUESTIONS

The panel combined questions 1-4 into one discussion, with no vote. The questions were:

QUESTION 1. Discuss the ***benefits of using salmeterol*** for the treatment of asthma in 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, in each of the following age groups:

a. in adults ≥18 years of age
b. in adolescents 12-17 years of age
c. in children 4 to 11 years of age

QUESTION 2. Discuss the ***benefits of using formoterol*** for the treatment of asthma in 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, in each of the following age groups:

a. in adults ≥18 years of age
b. in adolescents 12-17 years of age
c. in children 5 to 11 years of age

QUESTION 3. Discuss the ***risks of using salmeterol*** for the treatment of asthma in 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, in each of the following age groups:

a. in adults ≥18 years of age
b. in adolescents 12-17 years of age
c. in children 4 to 11 years of age

QUESTION 4. Discuss the ***risks of using formoterol*** for the treatment of asthma in 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, in each of the following age groups:

a. in adults ≥18 years of age
b. in adolescents 12-17 years of age
c. in children 5 to 11 years of age

Panel comments on Questions 1-4, considered collectively, included:

- *Dr. Sidney Wolfe, director of Health Research Group of Public Citizen:* "What is the evidence that once a patient is stabilized with ICS of getting added benefit with salmeterol or formoterol? A lot of people have jumped to (those products)…That is a major problem here because we don't have a great body of data on people who went through (the step approach to therapy before getting a LABA)…The benefits of ICS are more in (reducing) exacerbations and hospitalization, and the effect of LABAs is on FEV_1…We can't answer in terms of really important health benefits (for LABAs)…The most objective benefit measure is FEV_1 and fewer uses of rescue medications…There is no evidence of benefit with LABAs, and we have increased hospitalization and death …The seriousness of the benefit is less than the seriousness of the risk. That is my assessment."
- *Dr. Fernando Martinez, director of the Arizona Respiratory Center at the University of Arizona:* "There is one study…that was adequately done…Patients were first on ICS and then, if they were not controlled, either given control or a LABA….Those data could be re-analyzed looking at the comparison of adding a LABA or increasing the ICS dose…but other data show that you get better control by adding a LABA than increasing the ICS dose."

- *Daren Knoell, PharmD, Ohio State University College of Pharmacy:* "The concern I have is: Do we really have a good sense of the non-compliance issue? How many patients are vulnerable to a single agent, taking themselves off an ICS?...That is a study we may need in the future." Dr. Andrew Mosholder, a medical officer in the FDA's Division of Epidemiology, OSE, CDER, responded, "Most of the use is Advair which is automatically with an ICS…It's about 1% without ICS… But among patients on a single-entity inhaler, it is about 50/50."
- *Dr. Rappley, co-chair:* "(For) single agents, we need to consider the consequences of inappropriate use. If, in fact, we think the risk is stronger for a single agent, then that should drive that decision rather than evidence that applies to combination data."
- *Dr. Judith Kramer, an associate professor of medicine in the Division of General Internal Medicine at Duke University Medical Center:* "I think perhaps we have an unreliable risk signal in African Americans. That is my take-away…We talk of death, but patients talk about quality of life, subjective things. It concerns me for us to talk only about risk and life-threatening risk while the patient population is concerned about more subjective things."
- *Dr. Martinez:* "There is no doubt the advent of LABAs has improved the lives of the majority of patients with asthma. In my opinion, it would be irresponsible to withdraw this medication (all LABAs)."
- *An industry representative:* "I haven't heard the risk:benefit put in the context of other drugs and conditions…For every drug there are rare safety concerns but greater overall benefit…Could Dr. Graham, who is so vociferous about the risk, tell us where is the risk:benefit vs. other drugs?" Dr. Graham responded, "(With NSAIDs), we accept the risk of GI bleeding. There is a lot of NSAID use, but the actual…attributable death rate in the overall population is pretty low – much lower than is possible here with LABAs…What I've heard at this meeting is: (1) That the average duration of LABA use is ~3 months, so three out of 12 months, it is used…Is that continuous or a week here and there? (2) The risk if a drug is abruptly stopped might be worse than the drug itself…and if you have non-compliant use, you have people withdrawing themselves all the time, and (3) At least with single entities, the lion share of prescriptions was a single prescription…Anecdotally, in our LABA investigation team of 4 people, three of us had a family member prescribed Advair inappropriately. My daughter had bronchitis and was wheezing, and her doctor gave her Advair."
- *Dr. Jesse Joad, a pediatrician from the University of California, Davis:* "I don't consider the benefit (of LABAs) trivial at all…I don't think people look at black box warnings the way they should, and I think there is an alternative in the combined product. It is not that these people will be out with nothing…The argument of choice is a weak argument. I am told by my patients' insurance which corticosteroid to use. It isn't like a big menu I get to pick from…Also, the argument that all drugs have side effects doesn't go over well with me with the side effect of death and hospitalization…If you get a drug you know makes the disease you are treating worse, that is a big concern to me…I am convinced Advair is safe in children and adults, so I feel we can use this drug that has made a huge difference, and the company convinced me that Symbicort is safe in adults, but I don't think they had evidence in kids, which leaves me uncomfortable with adolescents…I think there may be a small growth suppression (with ICS), but it is small if at all."
- *FDA's Dr. Jenkins:* "Asthma in many patients is an episodic disease, so it is not surprising they don't use it 12 months a year. They may not be symptomatic all year… There are a lot of drugs for symptomatic conditions that carry risk – like chronic use for osteoarthritis (OA), where you treat pain but use an NSAID on a regular basis, and we are talking of potentially life-threatening GI bleeds. In patients with OA, the doctor and the patient judge the benefits of pain relief chronically vs. the potential for a GI bleed…And there are any number of those comparisons you could make. Basically, that is true of any of the pain drugs."
- *Dr. Lee Newman, an adult pulmonologist from the University of Colorado:* "I was on the advisory committee in 2005. I considered efficacy then, and my view hasn't changed…It has been very clear to me that there is a little trouble reconciling my qualitative experience (with LABAs) with the quantitative data that have been used to qualify the drugs for the FDA."

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 (e.g., low-to-medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, in each of the following age groups:

a. In adults ≥18 years of age
VOTE: NO=17, YES=10, Abstain=0

b. In adolescents 12-17 years of age
VOTE: NO=21, YES=6, Abstain=0

c. In children 4 to 11 years of age
VOTE: Unanimously NO

FDA's Dr. Jenkins clarified that the question was posed in this manner for individual products because this is the current labeling. He said the FDA also is asking the panel to elaborate on whether this labeling remains appropriate and would it be sufficient if monotherapy were okay.

General panel comments included:

- *Dr. Kramer:* "What are the operational implications, given that the drugs would still be on the market for COPD, and we would have…no asthma indication, and therefore no warnings, and there could be off-label use as great as current use?"
- *David Margolis, a dermatologist from the Hospital of the University of Pennsylvania:* "I feel if it were still available for COPD, it will be used for asthma."

Panel ***no*** vote comments included:

- *David Schoenfeld PhD, a biostatistician from Massachusetts General Hospital:* "No. The data are that single-agent use is dangerous…And the choice of ICS doesn't appear a crucial part of therapy…And compliance with two inhaler therapy appears too difficult."
- *Pharmacist Knoell:* "No. I'm not convinced a change in label will help."
- *Sean Hennessy, PharmD, PhD, an assistant professor of epidemiology from the University of Pennsylvania School of Medicine:* "I voted no because I think LABAs are dangerous, and there will be single-agent use without ICS if the drug is initiated for asthma as a solo agent."
- *Dr. Daniel Notterman, a molecular biologist from Princeton University:* "I voted no because I think the label is ambiguous and should be greatly strengthened and should indicate use of these agents as monotherapy is contraindicated."
- *Avital Cnaan PhD, director of the Multi-Center Studies Section at Children's National Medical Center:* "No…I have serious problems with the label and the data on inappropriate use support that even more."
- *Dr. Rappley, panel co-chair:* "No, I think the risks outweigh the benefits…I would like to consider label changes."
- *Dr. John Hoidal, chair of the department of internal medicine at the University of Utah:* "No. I think the labeling needs to be substantially strengthened…I'm not convinced by the flexibility argument."
- *Jacqueline Gardner PhD, an associate professor of pharmacy at the University of Washington:* "No. I think the labeling needs to target what we're trying to say…We focused on kids here…And if we are making significant changes in managing the risk of these drugs in adults…I would like a different conversation on how to manage risk in adults vs. kids...I think that's a different question."
- *Dr. Joad:* "No. I don't think changing the label would fix it."
- *Dr. Keith Kocis, a pediatrician from the University of North Carolina at Chapel Hill:* "No, and there should be a contraindication. I don't think labeling can affect it."
- *Dr. Wolfe:* "No. Safety should be managed through labeling…One is that this drug is no longer approved for asthma. That label would be more effective than what is there now. I am all for educating physicians, but it still (would be) prescribed as a single-entity drug…It looks as though…the only way to take care of this, given the way doctors practice medicine is to 'contraindicate' it – make it no longer approved for asthma. That is the safest way to change the label."
- *Julie Zito PhD from the University of Maryland School of Pharmacy:* "No. I'm not confident re-education will produce the desired effect."
- *Dr. Newman:* "No. I am not convinced the safety of LABAs can be managed through labeling...I hate to sound cynical, but having seen that label changes have not shown evidence of changing practice worries me…I don't think it is crucial to have monotherapy LABAs as an option."

Panel ***yes*** vote comments included:

- *Dr. Melissa Hudson, a hematologist/oncologist from St. Jude Children's Research Hospital:* "I voted yes to give physicians flexibility in prescribing."
- *Edward Krenzelock, PharmD, director of the Pittsburgh Poison Center at the University of Pittsburgh Medical Center:* "I voted yes…I'm sensitive to quality of life issues and giving physicians the opportunity to titrate."
- *Dr. Geoffrey Rosenthal, a pediatric cardiologist and epidemiologist from the Cleveland Clinic:* "Yes, but we need to strengthen the label."
- *Dr. Martinez:* "Yes…It would be contradictory to keep the combined (product on the market) and not the single agent."
- *Dr. Swenson, panel co-chair:* "Yes, with some hesitation …I feel the data just aren't overwhelming to rule out their benefits vs. risk...and we, as a profession and healthcare group, can do a better job of teaching to fill in the gap."
- *Andrea Holka of Attack on Asthma Nebraska, a patient representative:* "Yes. I do think it is important for physicians to have options…but there are many label changes that are needed."

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 (e.g., low-to-medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, in each of the following age groups:

a. In adults ≥18 years of age

VOTE: NO=18, YES=9, Abstain=0

b. In adolescents 12-17 years of age

VOTE: NO=21, YES=6, Abstain=0

c. In children 5 to 11 years of age

VOTE: Unanimously NO

Panel comments included:

- *Dr. Zito:* "It doesn't seem to change the case whether it is salmeterol or formoterol."
- *Dr. Wolfe:* "The only way to take care of this more serious problem of single ingredients is to disallow their use."
- *Dr. Schoenfeld:* "We don't have proof of a class risk… So, the safest thing is to assume it is a class effect."
- *Co-chair Dr. Swenson:* "I think the option should still be available."
- *Co-chair Dr. Rappley:* "I think it is a reasonable assumption that it is a class effect."
- *Knoell, a pharmacist:* "Formoterol and Serevent are not identical…In the future there might be more data to make more informed decisions."
- *Dr. Hudson:* "I think physicians should have flexibility."
- *Dr. Notterman:* "No, but with considerably less zeal than (with Serevent)…There are less data, less compelling data. And there are known chemical and PK differences, so while I consider it a class effect, I do want to encourage the FDA and the sponsor to develop more data for an indication for this drug in the future."
- *Dr. Margolis, a dermatologist:* "I would also encourage more study."
- *Dr. Kramer:* "Yes – assuming there would be a contraindication for monotherapy in the label. Guidelines and physician education should help to assure use with ICS… I'm concerned about giving a contraindication for a drug and then allowing it in combination…I think you need to think about whether you will have patients afraid to take a combination therapy."

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 (e.g., low-to-medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, in each of the following age groups:

a. In adults ≥18 years of age

VOTE: Unanimously YES

b. In adolescents 12-17 years of age

VOTE: YES=23, NO=3, Abstain=1

(The no votes were Dr. Wolfe, Dr. Zito, and Dr. Rosenthal. The abstention was Deborah Shatin PhD of Shatin Associates in Plymouth MN.)

c. In children 4 to 11 years of age

VOTE: YES=13, NO=11, Abstain=3

(NOTE: The FDA considers votes like this to be neutral votes, not a positive vote, so Advair very possibly could stay on the market for kids but get a significant label change.) The abstentions were Dr. Cnaan, Dr. Newman, and Dr. Notterman.)

Panel comments on the unanimous yes vote about ***adults***:

- *Dr. Kramer:* "Yes, and the sponsor should be congratulated for (a good study)."
- *Dr. Hennessy, an epidemiologist:* "Yes, but I would like to see a randomized safety trial evaluating serious asthma outcomes."
- *Dr. Notterman:* "I think there was clear and convincing evidence of safety."
- *Dr. Hudson:* "I think the evidence presented shows the benefits outweigh the risk."
- *Pharmacist Krenzelock:* "Yes, because I think it was shown to be safe and effective."
- *Pharmacist Knoell:* "I think the societal benefits far outweigh the risk…but I would like to see trials that would better determine the risk of these."
- *Dr. Cnaan:* "I would strongly urge an educational push for healthcare providers and the community."
- *Dr. Rosenthal:* "Yes, because I think this is a safer formulation than monotherapy."
- *Dr. Schoenfeld, a biostatistician:* "Despite no deaths on Advair, I still feel, given the other data we have from the whole picture, that we should presume there is a risk for the use of Advair, and I think we should be very careful that we retain the black box warning, continue to warn people of the risk, so individuals can decide whether or not to use it based on a good understanding of the risk."

- *Dr. Rappley:* "I think the risk can be managed through labeling and education."
- *Dr. Gardner:* "The risk:benefit ratio was more compelling."
- *Dr. Joad, a pediatrician:* "The 65 and up group may need more attention…It looked like there may be some safety issues with them, and the labeling should be changed that patients 'not adequately controlled on ICS' not (just) 'controllers.'"
- *Dr. Kocis:* "I think the risk:benefit favors use of the drug, but I don't want to say the risk is zero."
- *Dr. Wolfe:* "Yes, with enormous hesitation because in this age group we have a risk differential of 2.13…and I'm limiting my vote just to that age group."
- *Dr. Zito:* "Yes…with the plea that we develop substantial postmarketing information that relates to more comprehensive measures of functional improvement."

Comments on the vote on ***adolescents***:

- *Dr. Zito:* "No, because of uncertain benefit in that age group."
- *Dr. Wolfe:* "No, because I think this is a serious safety issue…I think this puts the safety folks at FDA first, where they need to be more often."
- *Dr. Schoenfeld:* "My benefit estimate for this and the previous question came from the experience of doctors on this panel."
- *Amy Celento, a patient-family representative:* "Yes, but my concern is that ICS is the first-line of defense, and that should be reinforced, and industry has a role there."

Comments on the mixed vote in ***kids***:

- *Dr. Notterman, a molecular biologist:* "There is a paucity of data to make a safety judgment on what we know today …I was unwilling to extrapolate data from teens and adults to children, particularly young children at the low end of this range. I strongly urge industry to do a safety study and the FDA to require these studies."
- *Co-chair Dr. Rappley:* "Yes. I would like to applaud the Agency (FDA) for taking a stand on both sides…I think the risk is significant and should be so acknowledged in labeling, but in the end my vote was not to deny these medications to children."
- *Co-chair Dr. Swenson:* "No, because of the lack of data in this age group and the trend to more problems with this age group."
- *Dr. Joad:* "This is a group I treat. I use this drug, and it appears to be working, but I definitely agree we need more research in this age group."
- *Dr. Wolfe:* "The risk difference is 14.8 events per 100 people in this age group."
- *Ms. Holka, a patient representative:* "Having two asthmatic sons, with one failing on ICS and put on a combination drug…And in three years, we have not been to the emergency room…When you have someone who needs it, they truly need it."
- *Dr. Kocis:* "Yes, but I'm troubled by my vote…I believe we need to continue to monitor this drug in this age group."
- *Dr. Newman:* "I was nearly a yes, but I am not at all sanguine about the safety signal here."

QUESTION 8. Do the benefits of Symbicort (budesonide and formoterol fumarate dehydrate) outweigh its risks for the maintenance treatment of asthma in 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, in each of the following age groups:

a. In adults ≥18 years of age

VOTE: YES=26, NO=0, Abstain=1

(Pharmacist Krenzelock said he abstained because of a conflict of interest with AstraZeneca.)

b. In adolescents 12-17 years of age

VOTE: YES=20, NO=5, Abstain=2

(The no votes were Dr. Rosenthal, Dr. Wolfe, Dr. Zito, Dr. Shatin, and Dr. Sebastian Schneeweiss, a pharmacoepidemiologist from Brigham & Women's Hospital. The abstentions were Dr. Joad and Pharmacist Krenzelock.)

- *Dr. Newman:* "I struggled a little more with this one but on the weight of evidence, we can support its use."
- *Dr. Wolfe:* "Yes, somewhat reluctantly."
- *Dr. Hennessy:* "The FDA should require a large clinical trial to look at LABA-related adverse events."
- *Dr. Carl D'Angio, a pediatrician from the University of Rochester:* "I would like to join the 'more data' camp."
- *Dr. Joad:* "I didn't know what to do with adolescents."
- *Dr. Kocis:* "A reluctant yes."

QUESTION 9. Based on your discussion and votes, are there further labeling changes or risk mitigation strategies for individual LABA products, or the class as a whole that would be advisable?

There was no vote on this, but comments included:

- *Dr. Mark Brantly, a pulmonary and critical care specialist from the University of Florida:* "I'm haunted by our (advisory panel) decision in 2005…Patients ask

me if this medication is going to kill them…Given that the data are not clear-cut as to the stratification of severity, I have concerns about having such a strong indication about African Americans and would like to have that message not necessarily softened but put into (better context)."

- *Ms. Holka, a patient representative:* "I have yet to read an entire patient insert…The language in the inserts is amazing…There are 15 different ways to say one thing…I think (there is a) disconnection between physician and patients, and that complicates and muddies the issues about these drugs."
- *Dr. Notterman:* "Physicians should understand they should ***never*** prescribe monotherapy in the absence of an ICS."
- *Dr. Wolfe:* "I mentioned contraindication in the context of…saying this drug is ***not*** approved for asthma."
- *Dr. Kocis:* "I used contraindication, and I meant it in the literal sense…I believe the risk is significant. We spent days trying to mitigate it, and I don't want to return to this committee in a few years and find out who did and who did not get steroids. In the event a practitioner wants to use any monotherapy, they do so with risk. Obviously, if there is a need, and there is room for individualization of an asthma plan to add an ICS with single therapy, but they do that, and patients know that and are aware that if they are not taking an ICS there is (harm)."
- *Dr. D'Angio:* "I'd use the word contraindication, but I think the sense I would convey is that these drugs – the only strategy that may mitigate the risk of these drugs – is the use of ICS. Is it possible another controller agent could be used? Maybe, but we have been dealing with little data on ICS and no data on that...To say you could use it with something else (other than ICS) would be over-reaching the data."
- *Dr. Zito, a professor of pharmacy:* "I said contra-indication because, based on patient experience, contraindication gets everyone's attention."

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 panel asked for further studies designed to answer questions about:

- LABAs in vulnerable populations – ages 4-11 and 12-17 – and in African Americans.
- The effect of the medication.
- New onset of use.
- The differential mechanism between salmeterol and formoterol and whether they can be considered a class effect.
- The etiology of conditions.
- Compliance.

Panel members also said there is a need for more comprehensive functional measures with credibility and validity. They also urged comprehensive evaluations of observational datasets from Medicare, large HMOs, etc.

There was a discussion about a possible asthma death registry, but FDA officials indicated that is probably not feasible. There also was talk about increasing the education effort for physicians and patients about the importance of drug compliance and for industry to institute some effort to encourage physician adherence to asthma practice guidelines.

Again there was no vote on this question. Panel member comments included:

- *Dr. Schoenfeld:* "If they (the trials) are too large, they will squash innovation in these diseases, and these are diseases where we want innovation…(But) we want to rule out risk...and we may get better information on risk …And we need to consider how to do such studies."
- *Dr. Wolfe:* "There are REMS (risk management plans) that work…You would expect that two-thirds of kids with asthma would be on ICS, and only about a third are…And you see lots of Advair ads and not too many Flovent (GlaxoSmithKline, fluticasone, an ICS) ads…I would like to see an experiment initiated by the FDA to find a way that the part of the label that says you should only use this with an adequate dose of ICS is more prominent against what appears to be an inappropriate number of children – and I'm sure adults – getting bumped up to combined drugs when they haven't been tried on adequate control with ICS."

INDUSTRY REACTION TO THE ADVISORY COMMITTEE VOTES

AstraZeneca issued a statement in which chief medical officer Dr. Howard Hutchinson said, "The safety and efficacy of Symbicort have been demonstrated in numerous clinical trials and from extensive postmarketing use around the world. We are pleased that the joint advisory committee's recommendation confirms our view on the positive risk:benefit profile of Symbicort."

GlaxoSmithKline also issued a statement in which chief medical officer Dr. Ellen Strahlman praised the panel's decision on Advair but urged the FDA not to follow the panel's recommendation on Serevent:

- "We welcome the committee's endorsement of Advair as a safe and effective treatment for asthma in adults and children. We believe this recommendation is consistent with national treatment guidelines – based on evidence and developed by experts – that support the combination of a LABA and ICS as a preferred treatment for children

and adults with persistent asthma. We will continue to work with physicians to encourage broader understanding of the national guidelines for appropriate use."

- "Serevent, when used with an ICS, is an important treatment option for some patients as outlined in national guidelines. We are confident that our proposed new labeling, medication guide, and risk management plan would help physicians safely manage the appropriate use of Serevent in conjunction with an ICS. We are concerned that – if the FDA adopts the panel's recommendation on Serevent – it is possible that Serevent would be severely restricted and deny patients needed treatment for optimal care of their asthma."

In a joint statement **Novartis and Schering-Plough** reacted sharply to the panel vote against Foradil, saying, "(We) strongly disagree with the Joint Advisory Committee's view that the benefits of Foradil do not outweigh its risk in patients using it according to current product labeling…We believe this opinion is inconsistent with clinical evidence supporting the risk:benefit profile of Foradil…Novartis and Schering-Plough remain confident in the safety and efficacy of Foradil …The companies will work closely with the FDA as the agency considers the Joint Advisory Committee recommendation to determine appropriate next steps."

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