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Public Meeting on FDA's Proposal to Remove Certain Designations for the Essential Use of Ozone Depleting Substances

Boehringer Ingelheim Comment on the Proposed Rule

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Agenda

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Background

Combivent® Public Health Benefits

Commitment to a CFC-Free Replacement

Conclusion

Q&A/Discussion

Criteria for Essential Use Designation

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1. Substantial technical barriers exist to formulating the product without ODSs; and

2. The product will provide an unavailable important public health benefit (i.e., no therapeutically equivalent CFC-free product is available); and

3. Use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit.

Question Posed by FDA

"*Does use of a single MDI containing albuterol and ipratropium in combination provide for better patient outcomes (e.g., fewer exacerbations, increased quality of life) compared to concomitant use of separate albuterol and ipratropium MDIs, and, if these improvements are shown to exist, should they be considered important public health benefits? "*

-FDA Meeting Notice
Use of Ozone-Depleting Substances; Removal of Essential-Use Designations
July 9, 2007

Combivent Provides an Important Public Health Benefit

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Removal of COMBIVENT will adversely affect a significant number of patients

No data exist supporting the adequacy of the free combination of the separate inhalers as therapeutically equivalent

Data exist demonstrating use of multiple inhalers leads to decreased compliance

- Decreased compliance negatively impacts health outcomes

We share the goal of avoiding these adverse impacts by providing patients with a seamless transition to a CFC-free COMBIVENT

Maintaining Bronchodilation Improves Patient Outcomes

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Maintenance treatment with bronchodilators provide meaningful benefits

Benefits can include:

- Reduced dyspnea
- Greater exercise tolerance
- Improved health-related quality of life
- Fewer exacerbations

Maximizing bronchodilation optimizes benefits

Mechanism is well-understood

Combining two mechanisms in one inhaler, COMBIVENT, facilitates improved bronchodilation

GOLD Guidelines 2006

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"Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. "

"Such drugs improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance."

"All categories of bronchodilators have been shown to increase exercise capacity in COPD… "

"Regular use of a long-acting 2-agonist or a short or long-acting anticholinergic improves health status. "

COPD is a Significant Public Health Burden

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Over 12 million patients diagnosed with COPD in the US

Over 120,000 COPD patients die each year

- Fourth leading cause of death

Second leading cause of disability

Significant co-morbidities

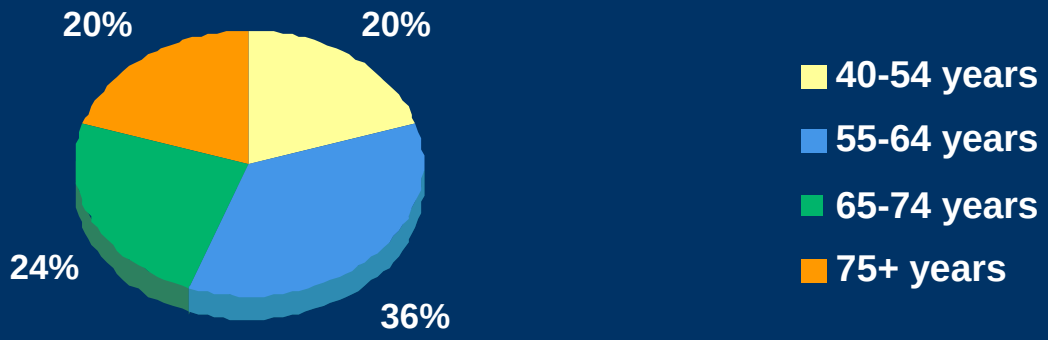
Multiple concomitant medications

Combivent Treats a Vulnerable Subpopulation

More than 2 million patients

- Prescribed by 225,000 physicians

Age distribution of COMBIVENT COPD population



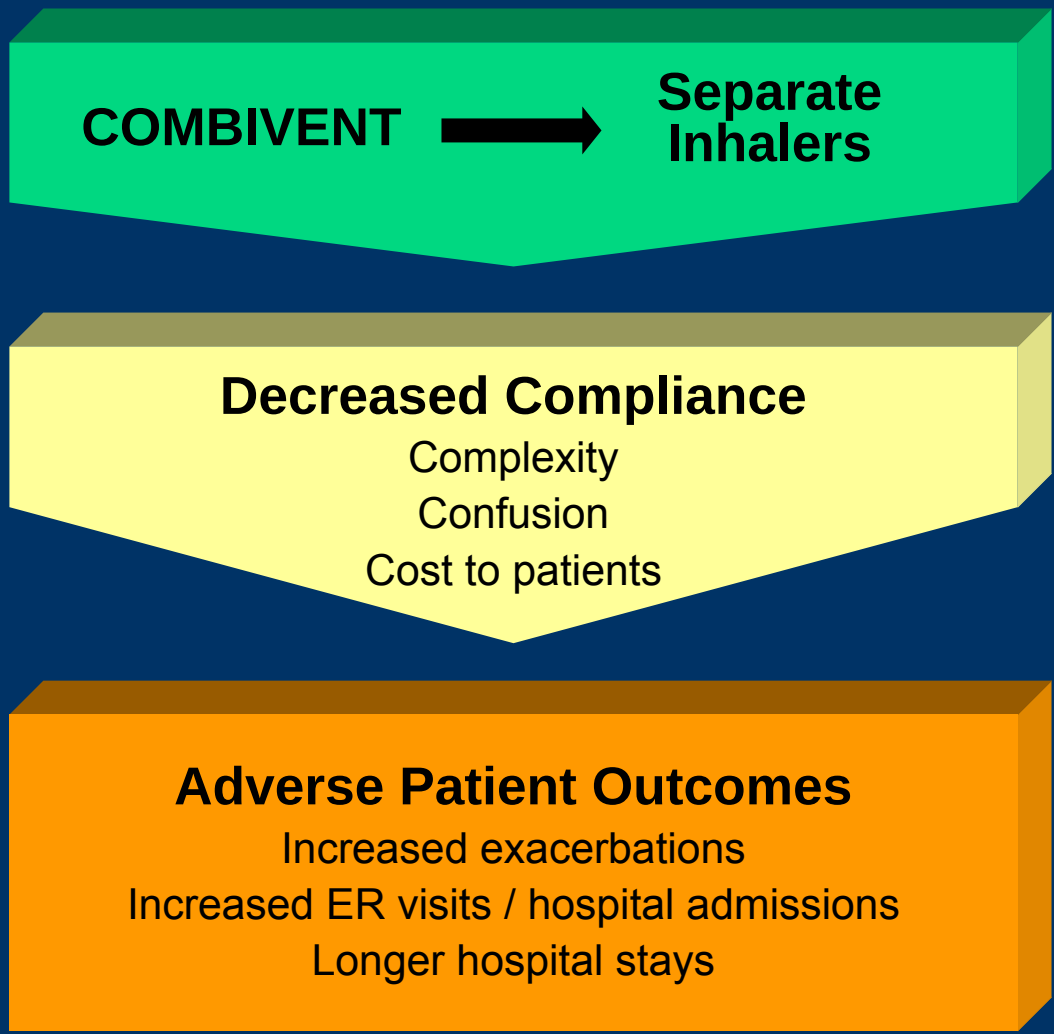
Significantly more severe COPD than non-COMBIVENT patients

- Severe (10.84% vs. 3.74%)
- Moderate (26.68% vs. 11.04%)
- Higher co-morbidity burden (Charlson Co-morbidity Index)

Complex drug regimens – average patient takes 6 other medications

Source: BI Market Research and Data on File

Switch from Combivent Will Adversely Impact Patient Outcomes



Combination Products Improve Compliance

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COPD – Chrischilles, E, et al. Am. J. Managed Care 2002; 8 (10): 902-911

Asthma – Stoloff, SW, et al. J. All. Clin. Immunol. 2004; 113: 245-251

Diabetes – Melikian, C, et al. Clin. Ther. 2002; 24: 460-467

HIV / AIDS – Eron, J, et al. AIDS 2000; 14: 671-681

Hypertension – Dezii, CM. Managed Care 2000; 9: 2-6

Taylor, A and O Shoheiber. CHF 2003; 9 (6): 324-332

Combination Products Improve Compliance in Asthma

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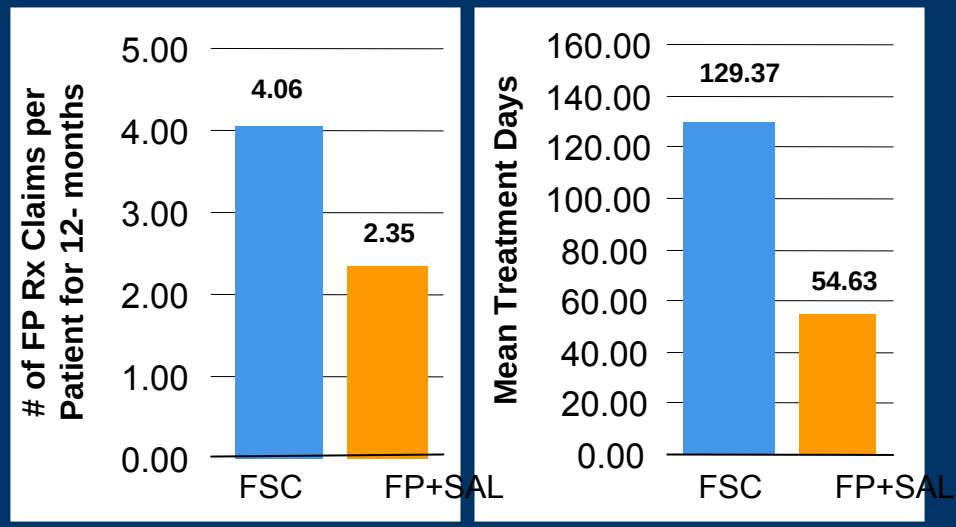
Design: Retrospective, observational
Medical and pharmacy claims database study

Population: 2,436 patients with asthma
(FSC: 563; FP+SAL: 224)

Results:



Conclusion: "…the use of FSC increases the refill persistence of ICSs over 12 months compared with using FP and salmeterol in separate inhalers…"

Source: Stoloff at al. *J Allergy Clin Immunol* 2004; 113:245-51

Separate Inhalers for COPD are Not Therapeutically Equivalent

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Design: Inception cohort design, United Healthcare enrollees

Population: 1,086 adults, ≥ 38 years

Patients on COMBIVENT (n=428); patients on separate inhalers (n=658)

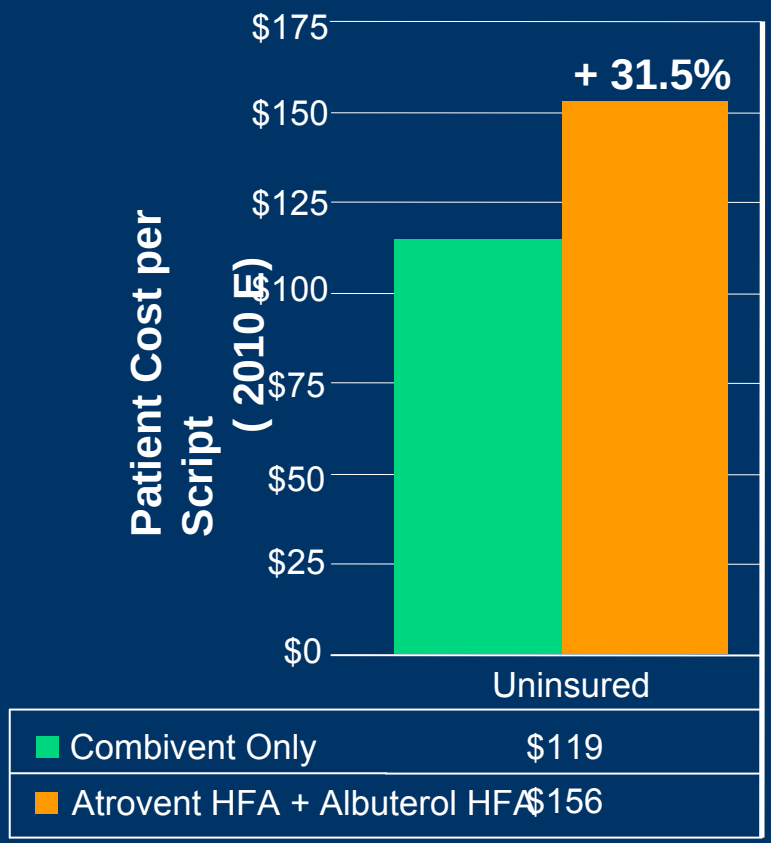
Results:

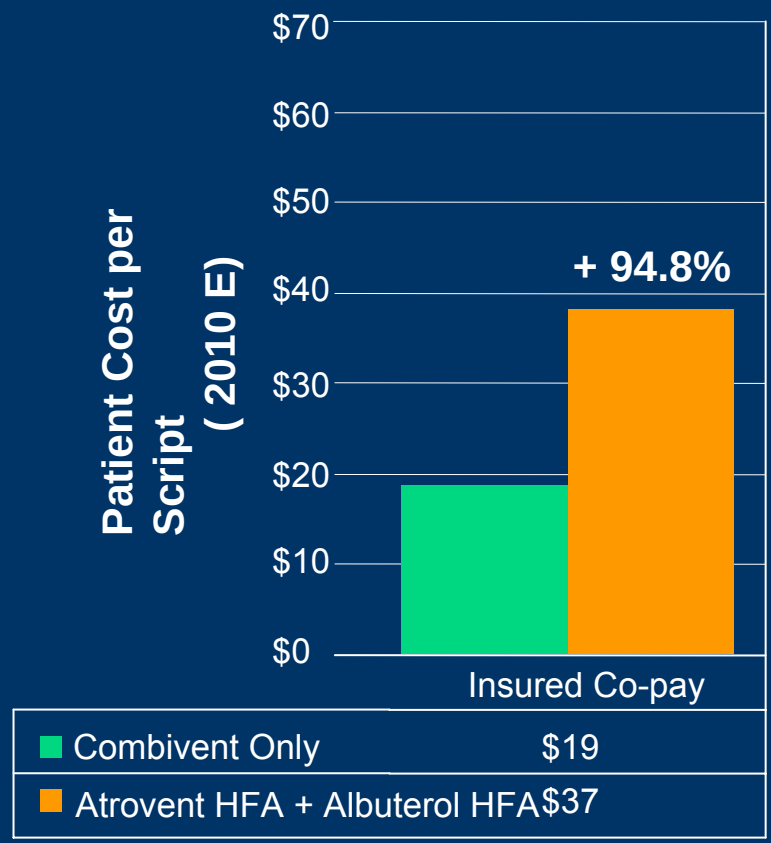
	Hazard Ratio	95% CI
Compliance	1.77	1.46, 2.14
ER Visits/Hospitalizations	0.58	0.36, 0.94
COMBIVENT patients had shorter hospital LOS (2.05 vs. 4.61 days)		

Conclusion: *"… initiation of combined ipratropium and albuterol therapy in a single inhaler was associated with a reduced risk of respiratory-related ED or hospital use and with reduction in hospital length of stay …compared with initiation of separate ipratropium and albuterol prescriptions…"*

Source: Chrischilles et al. *Amer. Journal of Managed Care,* 2005, 8(10); 903- 911

Cost Increases to Patients Lowers Compliance





Implication: "…for each 10% increase in cost sharing, overall prescription drug spending decreases by 2% to 6%..." (Goldman et al., *JAMA*, 2007; 298(1): 61-69)

Source: BI Internal Analysis

BI is Committed to CFC Elimination Worldwide

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BI is at the end-phase of fully transitioning or eliminating all 25 MDIs in its original, global CFC product portfolio

Since 1999, BI has been launching CFC-free products with appropriate patient transitions

These launches have included both a novel, propellant-free device (RESPIMAT) and several HFA formulations

The transition to a CFC-free COMBIVENT is planned for the near-term

CFC-Free Combivent Development: Substantial Technical Barriers

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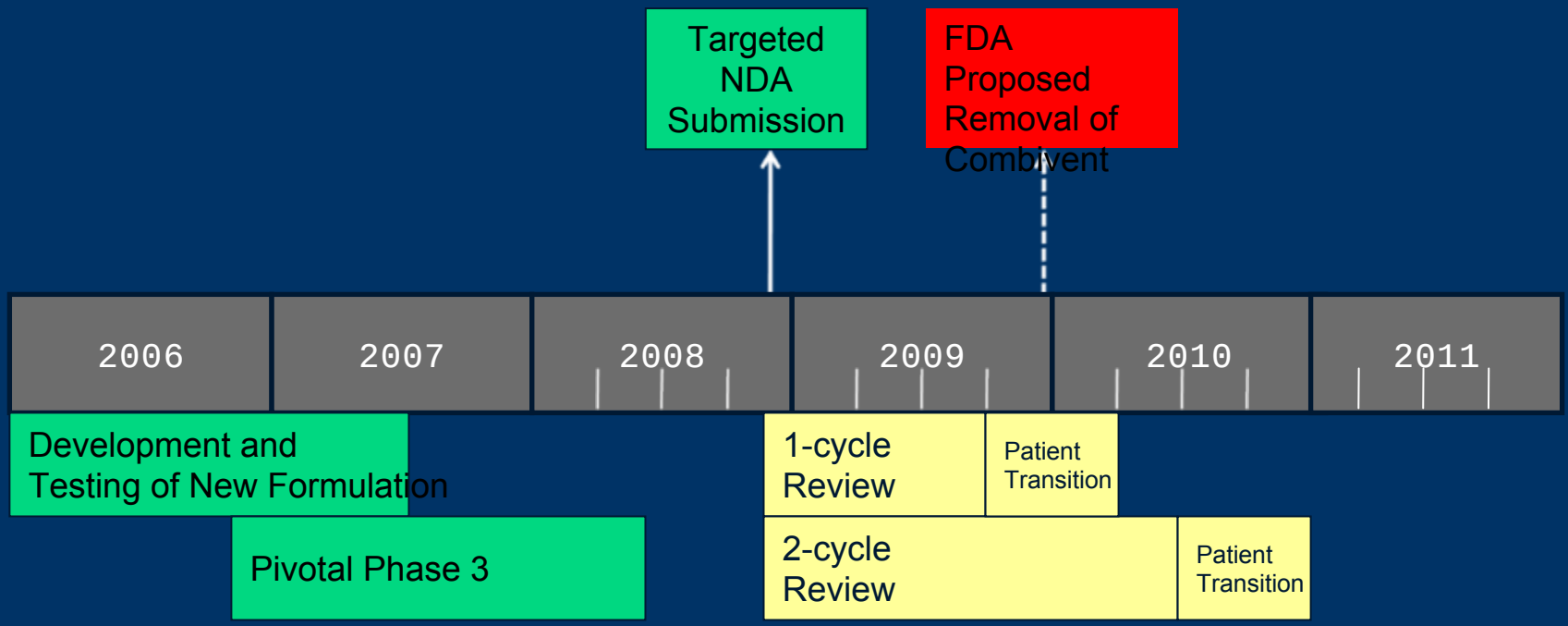
COMBIVENT HFA challenges

- Combination of two active ingredients presented unique formulation issues
- New MDI components needed to be developed
- Physico-chemical characteristics in HFA formulations
  - Excipients used for COMBIVENT CFC are not compatible
  - New excipients required additional toxicology studies
- Device-related failures in Phase 3

COMBIVENT RESPIMAT challenges

- Establishing “comparability” to the MDI is not sufficient
- Formulation and device differences result in varying lung / systemic exposures
  - Clinical data were different than predicted
  - Re-formulation work has been necessary

Combivent Respimat NDA Targeted for 4Q 2008



Allowing sufficient time for program completion:

- Results in no significant release of CFCs
- Requires no additional manufacturing of CFCs

Questions to Be Addressed

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"*Does use of a single MDI containing albuterol and ipratropium in combination provide for better patient outcomes (e.g., fewer exacerbations, increased quality of life) compared to concomitant use of separate albuterol and ipratropium MDIs, and, if these improvements are shown to exist, should they be considered important public health benefits? "*

Are there important adverse public health consequences when patients using a single MDI containing albuterol and ipratropium are switched to concomitant use of the separate inhalers?

Maintain Essential Use Designation for Combivent

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COMBIVENT provides an unavailable important public health benefit

- The proposed alternative use of separate albuterol and ipratropium inhalers together has *not* been demonstrated to be therapeutically equivalent to COMBIVENT

Significant technical barriers to the formulation of a CFC-free replacement exist

- Development of a suitable replacement is moving forward

COMBIVENT does *not* release significant amounts of CFCs into the atmosphere and the release is warranted in view of the public health benefit.

Combivent Should be Excluded From This Rulemaking

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Submission of COMBIVENT RESPIMAT NDA targeted for 4Q08

FDA review and approval of COMBIVENT RESPIMAT NDA, and an appropriate patient transition, is possible by the end of 2010

A separate rule specifically addressing COMBIVENT could be issued before December 31, 2009

Excluding COMBIVENT from this rulemaking avoids the adverse health outcomes associated with a switch to multiple inhalers and should allow for a seamless transition.