

Presentation to Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee



**EPINEPHRINE HFA MDI (E004):
A Proposed Reformulation to Replace
OTC Primatene[®] Mist CFC MDI**

*Armstrong Pharmaceuticals, Inc.
Amphastar Pharmaceuticals, Inc.*

February 25, 2014



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**Epinephrine HFA MDI: A Proposed Reformulation to Replace
OTC Primatene[®] Mist CFC MDI**

Introduction, Agenda & Presenters

Jason Shandell, J.D., M.B.A., Esq.
President of Amphastar

*Armstrong Pharmaceuticals, Inc.
Amphastar Pharmaceuticals, Inc.*

February 25, 2014



Epinephrine HFA MDI (E004) – A Replacement for OTC Primatene[®] Mist CFC MDI

- E004 and Primatene[®] Mist CFC Share the Same Key Elements
 - Same active moiety (ingredient): epinephrine;
 - Same administration route: oral inhalation; and
 - Same type of delivery device: pressurized MDI
- The FDA has proactively provided guidance and support for the development of E004, which we have implemented



Reformulation of Epinephrine HFA MDI (E004)

- Compared to Primatene® Mist CFC, the reformulation of E004:
 - Uses HFA-134a as propellant
 - Dose of epinephrine reduced by 43% with the same efficacy
 - pH changed from acidic (pH= 3.5 – 4.5) to neutral (E004, pH ~ 7)
 - Alcohol content reduced 34-fold to minimize problems such as irritation, unpleasant taste and false positive alcohol (breathalyzer) test
 - The aluminum canister is stronger and safer than the previous opaque glass bottle
 - Includes a dose indicator
- A detailed discussion of E004 benefits and risks follows



Agenda

Introduction, Agenda & Presenters		Jason Shandell, J.D., M.B.A., Esq. President of Amphastar Pharmaceuticals, Inc.
Part-A	Symptomatic Relief of Asthma: Treatment Options	Donald Tashkin, M.D., Emeritus Professor of Medicine University California at Los Angeles (UCLA)
Part-B	Clinical Pharmacology of Bronchodilators	Leslie Hendeles, Pharm.D., Professor College of Pharmacy and Professor of Pediatrics (Pulmonary), College of Medicine, University of Florida
Part-C	Efficacy and Safety	Edward Kerwin, M.D. Senior Director, Clinical Research Institute of Southern Oregon
Part-D	Consumer OTC Studies	David McCammon, M.S. CEO/Senior Consultant of PEGUS Research
Part-E	Conclusion	Jason Shandell, J.D., M.B.A., Esq. President of Amphastar Pharmaceuticals, Inc.



Responders and Participants

Consultants / Responders

1	Donald Bukstein, M.D.	Director of 3 "Free" Clinics in Milwaukee, Madison WI Over 30 years as a clinician, trialist, underserved patient care advocate
2	David Pearlman, M.D.	Director, Clinical Research Colorado Allergy + Asthma Centers, Denver, Colorado
3	Russ Bradford, M.D., MSPH	Vice President of Medical Affairs PEGUS Research
4	David Adams, J.D., Esq.	Venable Law Firm
5	Robert Dormer, J.D., Esq.	Hyman, Phelps & McNamara, PC

E004 Applicant

Amphastar / Armstrong Team	Responders and Supporting Staff
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**Epinephrine HFA MDI: A Proposed Reformulation to Replace
OTC Drug Primatene[®] Mist (CFC MDI)**

Part A: Symptomatic Relief of Asthma: Treatment Options

Donald P. Tashkin M.D.,

Emeritus Professor of Medicine

Division of Pulmonary and Critical Care Medicine

David Geffen School of Medicine at UCLA

Armstrong Pharmaceuticals, Inc.

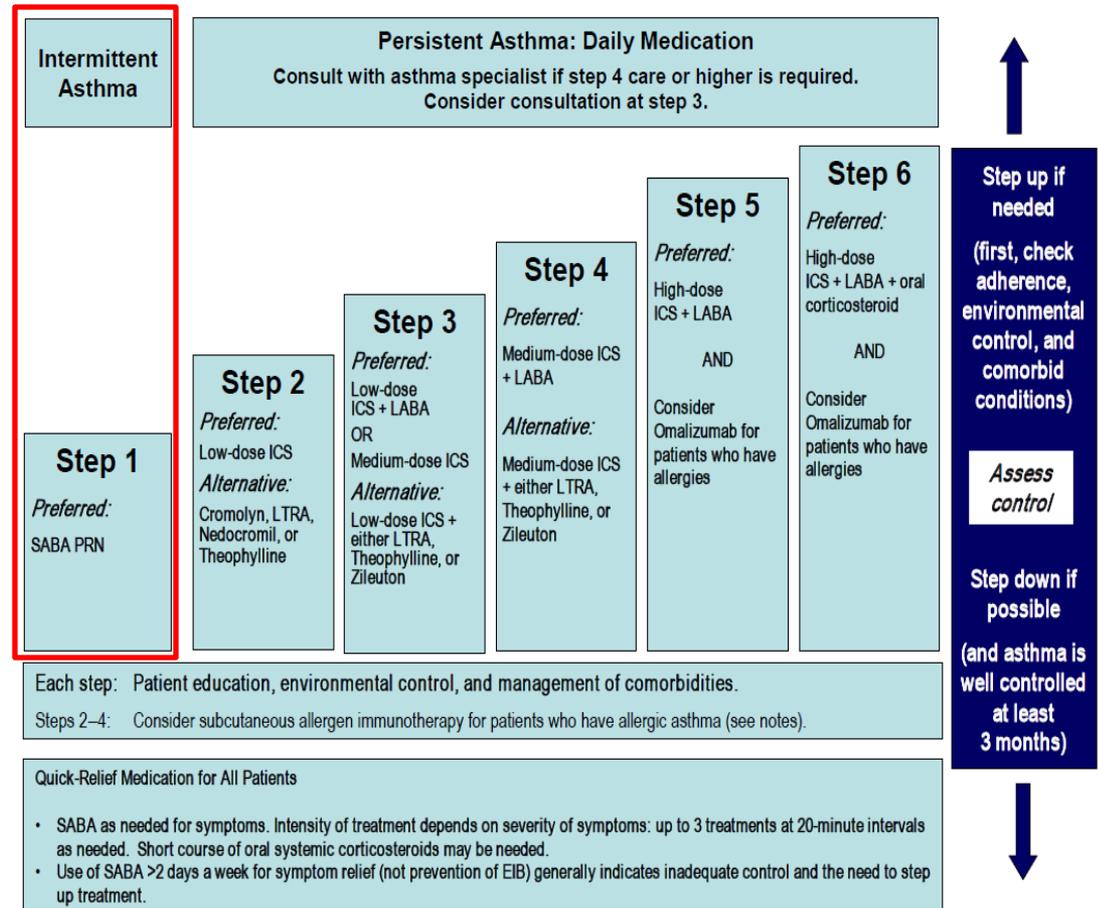
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The Four (4) Categories of Asthma Severity

- Intermittent
- Mild Persistent
- Moderate Persistent
- Severe Persistent



Intermittent Asthma

- Have symptoms 2 or fewer times per week
- Have nighttime awakenings 2 or fewer times per month
- Use a SABA for symptom control 2 or fewer days per week
- No interference of normal activities by asthma symptoms
- Normal baseline lung function
- Experience no more than 1 exacerbation per year¹

¹ NHLBI EPR-3, 2007



Epinephrine HFA MDI (E004)

- A short-acting adrenergic bronchodilator
- Indication: temporary relief of mild symptoms of intermittent asthma
 - Wheezing, tightness of chest, shortness of breath
 - 12 years or older



Epinephrine HFA MDI (E004) Profile

- E004 was developed to replace Primatene[®] Mist CFC
- Primatene[®] Mist CFC
 - Was an FDA approved NDA (1956)
 - Had over 50 years proven track record of safety and efficacy for OTC use
 - Sunset in 2011 was due to environmental concern, not safety/efficacy
- Improvements made from CFC to HFA reformulation
 - 43% reduction of Epinephrine
 - 34-fold reduction of alcohol to 1%
 - Use aluminum can
 - Includes a dose indicator



No Cardiac Safety Issues Found

- Broad concerns among health care professionals for many years
- No significant cardiac safety issues from the FDA long-term FAERS database, nor from Sponsor's pharmacovigilance program
- Consistent with the safety results revealed by Sponsor's clinical studies (46,000 vital and ECG data points)
- May be due to low amount of epinephrine entering into plasma (0.36%²), which is consistent with the findings of Hendeles et al. in 2005³

2 Sponsor's NDA data

3 L Hendeles et al, *Ann Allergy Asthma Immunol.* 2005;95:530-4



Comparison with Albuterol

- Albuterol is a selective β_2 agonist, and like inhaled epinephrine, has a quick onset, but with a relatively longer duration of bronchodilation
- Albuterol is indicated for general bronchodilation for persistent asthma and COPD
- After the sunset of Primatene[®] Mist CFC, patients with intermittent asthma were advised to use prescribed Albuterol, which is indicated for treatment of bronchospasm



Comparison with Albuterol (Cont.)

Based on the FDA AERS database, higher adverse event rates ^{4,**}

Assessment		Incidence Rate Ratio*: Albuterol / Primatene Mist CFC			p-value: Albuterol vs. Primatene Mist CFC		
		12-64	≥ 65	All ages	12-64	≥ 65	All ages
#	Type of Serious AEs						
1	Death	7.0	24	6.3	<.0001	<.0001	<.0001
2	Life-threatening	19	13	22	<.0001	<.0001	<.0001
3	Hospitalization (initial or prolonged)	13	19	18	<.0001	<.0001	<.0001
4	Disability or Permanent Damage	17	23	30	<.0001	<.0001	<.0001
5	Congenital Anomaly/Birth Defect	-	-	11	-	-	0.0035
6	Required Intervention to Prevent Permanent Impairment or Damage (Devices)	10	7.8	15	<.0001	0.0006	<.0001
7	Other Serious (Important Medical Events)	3.3	11	4.4	<.0001	<.0001	<.0001

* Ratio of serious AE incidence rate per million units sold.

- Noteworthy, **24 times** higher rate of death for aged population (≥ 65 years old) was found (Albuterol vs. Primatene[®] Mist CFC)



Unmet Need: Filling the Gap

- E004 was developed exclusively for intermittent asthma patients with mild symptoms (Category 1 – intermittent)
- E004 will fill the gap and address an unmet need
 - limited access to health care provider due to cost, lack of insurance, geography, forgetting to refill prescription for inhalers, leaving inhalers behind during travel, etc.



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Epinephrine HFA MDI: A Proposed Reformulation to Replace OTC Drug Primatene[®] Mist (CFC MDI)

Clinical Pharmacology of Bronchodilators

Leslie Hendeles, Pharm.D., Professor
College of Pharmacy and Pediatrics (Pulmonary)
University of Florida

*Armstrong Pharmaceuticals, Inc.
Amphastar Pharmaceuticals, Inc.*

February 25, 2014



Myths about Inhaled Epinephrine

- Weaker β_2 receptor agonist
- Less effective
- More cardiac effects
- Too short acting



Adrenergic Receptors

- α_1 – Vasoconstriction
- β_1 – Cardiovascular stimulation
- β_2 – Smooth Muscle Relaxation

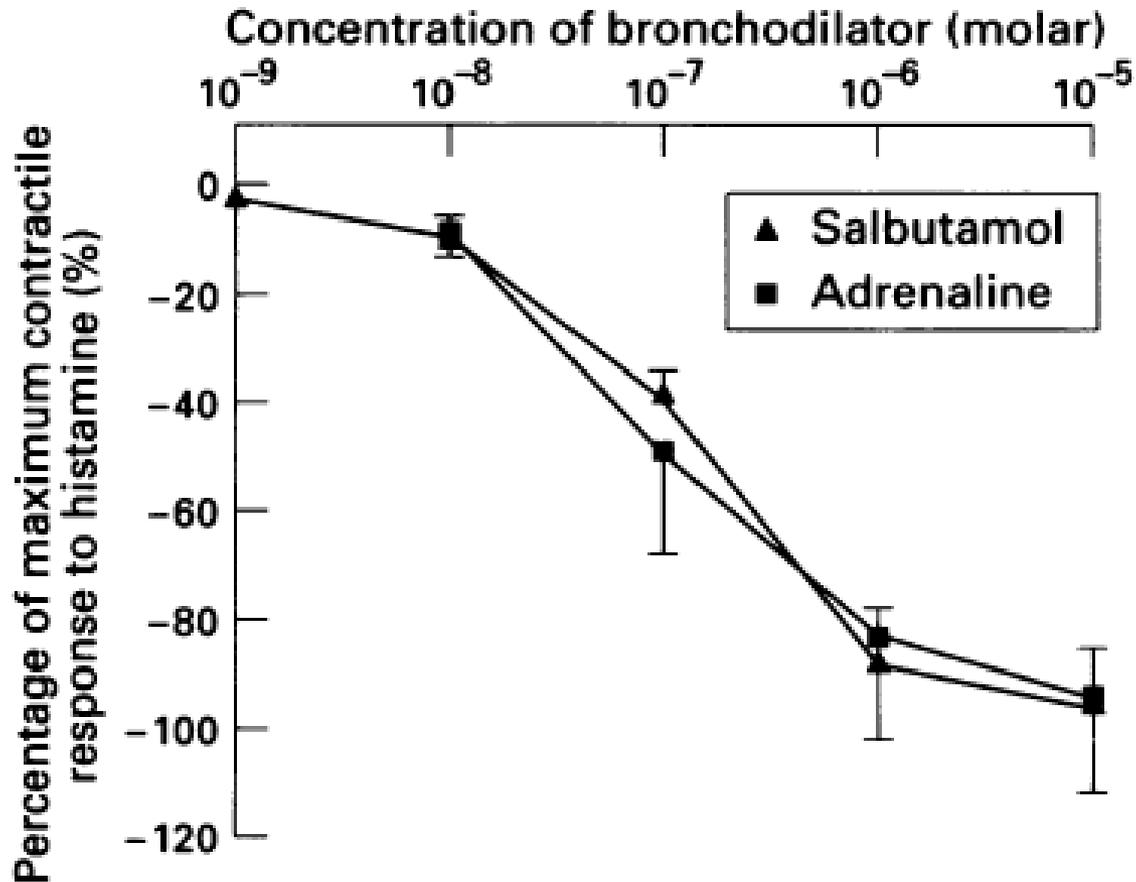


Adrenergic Receptor Agonists

- Epinephrine – α_1 , β_1 , and β_2
- Albuterol – relative β_2 selective



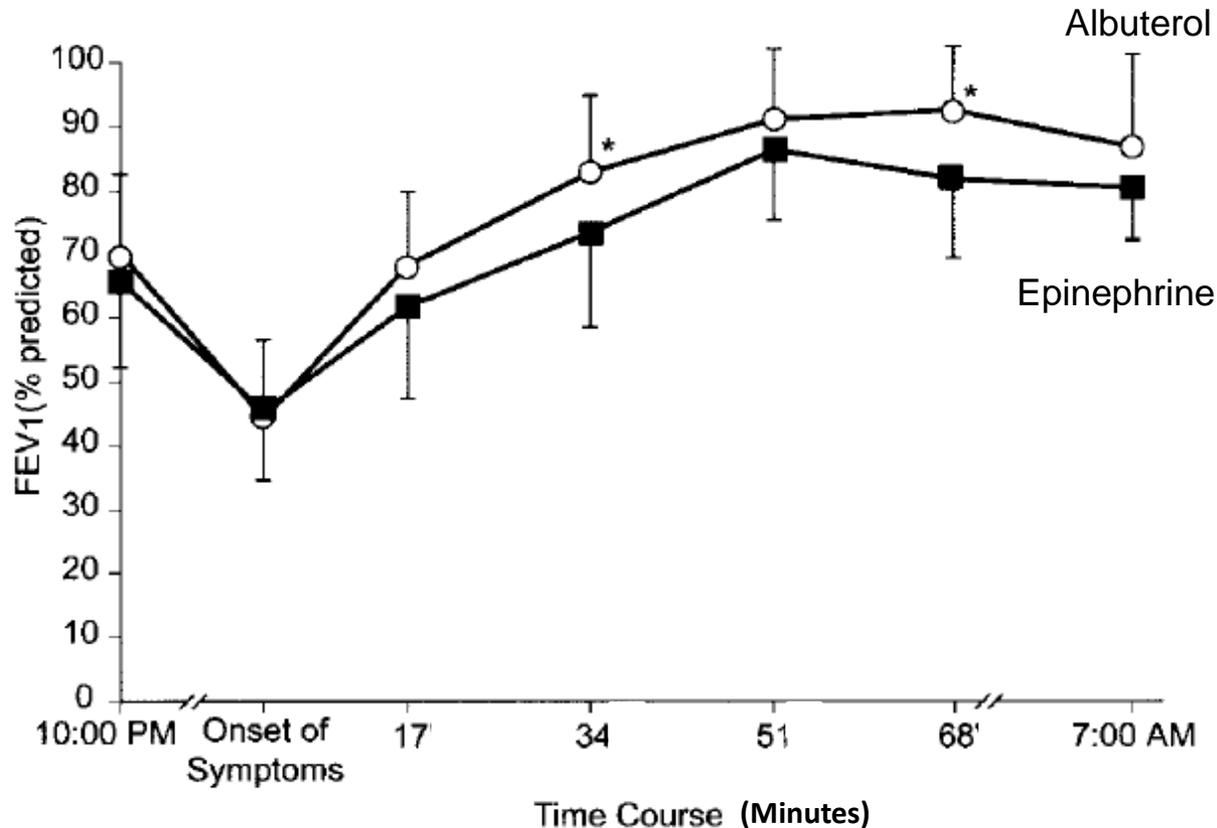
In vitro β_2 Stimulation: Epinephrine \sim Albuterol



⁵ D R Baldwin et al. *Thorax* 1994; 49:1103-1108



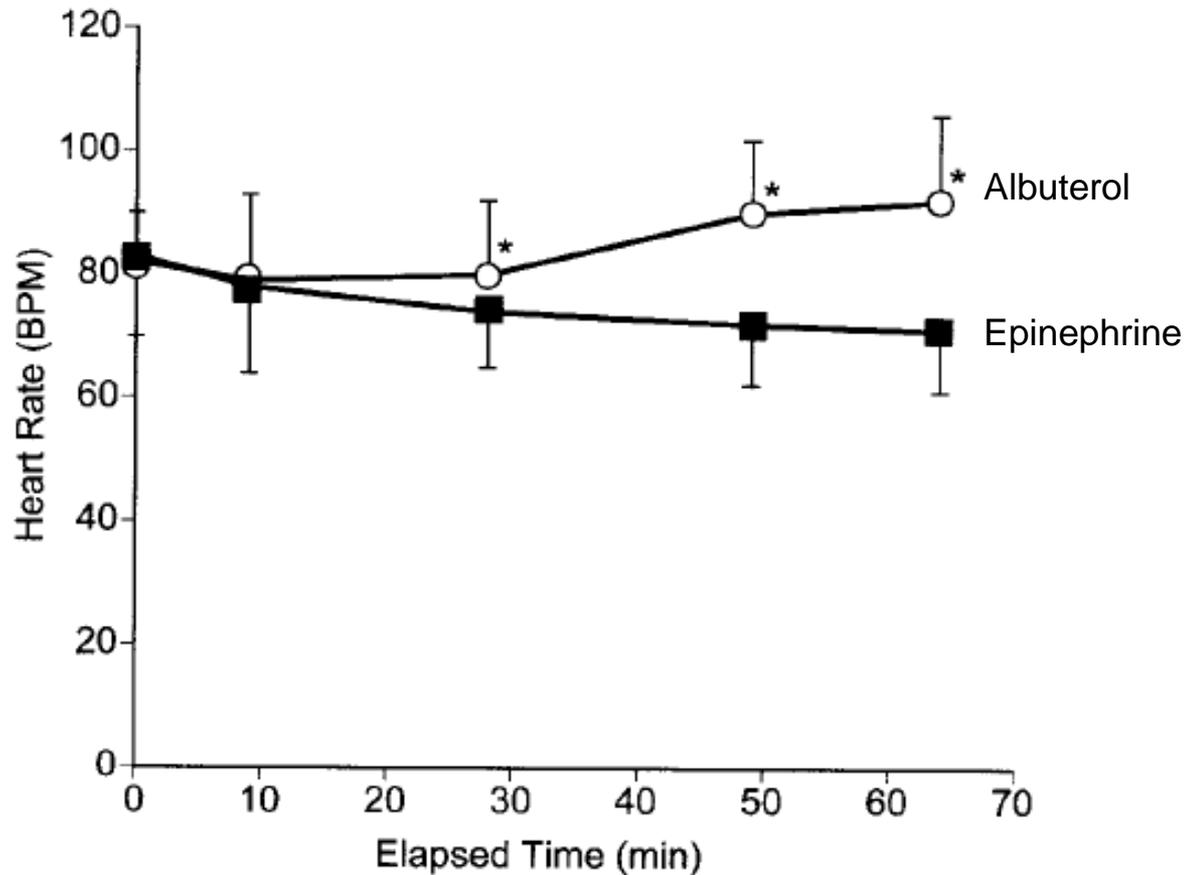
Bronchodilator Response During Nocturnal Bronchospasm



³ L Hendeles et al, *Ann Allergy Asthma Immunol.* 2005;95:530-4



Mean Heart Rate on Awakening and at Various Post-dose Points



³ L Hendeles et al, *Ann Allergy Asthma Immunol.* 2005;95:530-4



Poor Bioavailability of Inhaled Epinephrine

- COMT inactivates
- Alpha decreases absorption
- MAO rapidly metabolizes
- Inactivation of swallowed portion in gut



Take Home Messages

- β_2 agonist *in vitro* activity equivalent
- Nearly as effective relieving acute bronchospasm
- No cardiac effects because of poor bioavailability
- Short duration of action may be an advantage



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Epinephrine HFA MDI: A Proposed Reformulation to Replace
OTC Primatene[®] Mist CFC MDI

Part C: Efficacy and Safety

Edward Kerwin, M.D.

Senior Medical Director

Clinical Research Institute of Southern Oregon

Consultant for Amphastar Pharmaceuticals, Inc.

February 25, 2014



Proposed Asthma-Specific Indication of E004

- E004 is specifically indicated for “temporary relief of MILD symptoms of INTERMITTENT asthma”

Asthma-specific indication of E004

Intermittent Asthma	Mild Persistent Asthma	Moderate Persistent Asthma	Severe Persistent Asthma
COPD			

General bronchodilation Indication of Rx

Intermittent Asthma	Mild Persistent Asthma	Moderate Persistent Asthma	Severe Persistent Asthma
COPD			



Pharmacological Profile of E004

- High dosage was used for PK study – 10 x 125 mcg/inh*
- Normal maximum dose – 2 x 125 mcg/inh
- C_{max} for recommended dose: 0.18 ng/mL, about 4.5 times higher than that for Primatene[®] Mist CFC (0.046 ng/mL)
- This reflects improved delivery to airway via HFA vs. CFC
- $t_{1/2} = 2.6$ minutes (literature: 2 – 3.5 minutes^{6,7})
- Within 10 minutes after T_{max} , the plasma epinephrine level reduced to less than 1/10 of C_{max}
- The amount of epinephrine entering the blood is about 0.9 mcg or 0.36% of delivered total dose (250 mcg)
- E004 has an extremely low bioavailability

* Deuterium-labeled epinephrine was used

6,7 Sam Kacew, Drug Toxicity & Metabolism in Pediatrics, p57 (1989); 7 Imad Abboud et. al., Critical Care, 13:R120, 2009



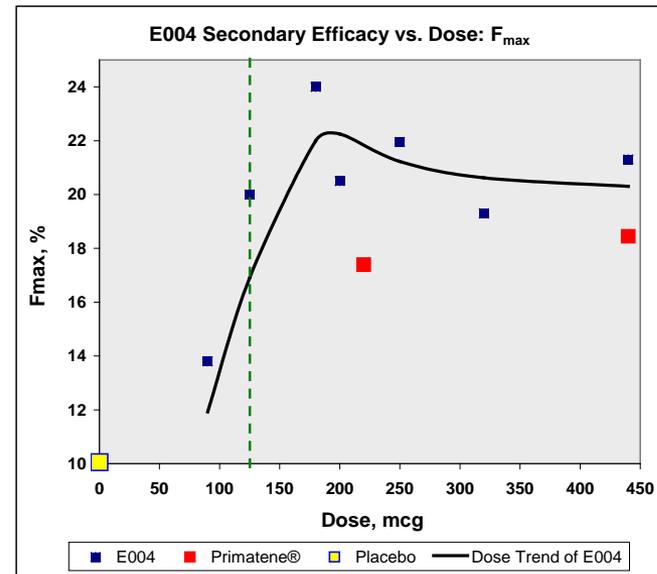
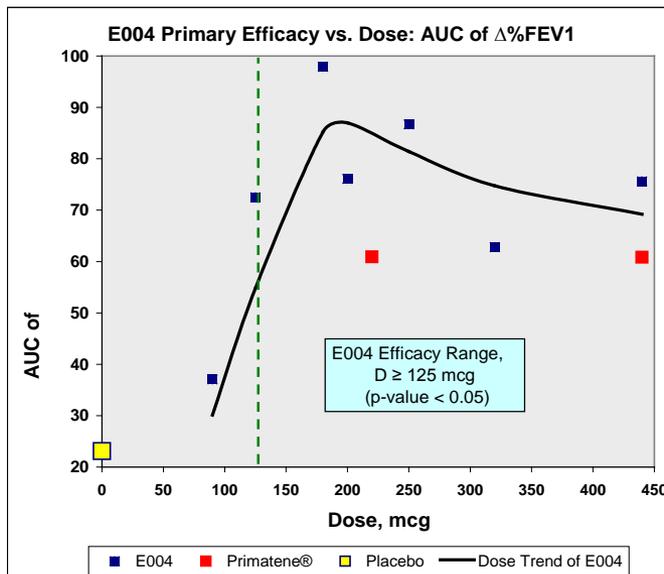
Clinical Impact of C_{\max}

- E004 provides an improved, low systemic bioavailability
 - ***Airway bronchodilation improves rapidly***, which may allow fewer puffs of medicine to be effective
 - ***Rapid clearance from serum*** reduces systemic side effects risks after a few minutes
 - These factors make it less likely consumers will inadvertently overdose
 - E004 used at maximum labeled dose did not have significant cardiovascular issues
- Any systemic AEs are likely to be brief and not sustained
- PK features of low BA indicate a favorable safety profile



Selection of Optimal Dose: 125 mcg/inhalation

- Single dose, dose ranging, crossover trials A, A2 (N = 26, 30)
- Primary endpoint is AUC_{0-6hrs} of $\Delta\%FEV1$
- $\Delta\%FEV1$ is defined as $[FEV1(t)-FEV1(0)]/FEV1(0) \times 100\%$
- 125 -250 mcg is the lowest dose range to show a stable efficacy
- 125 mcg/inhalation, 2 puffs, 4 times daily recommended for Phase III (FDA Communication, 5/10/2011)



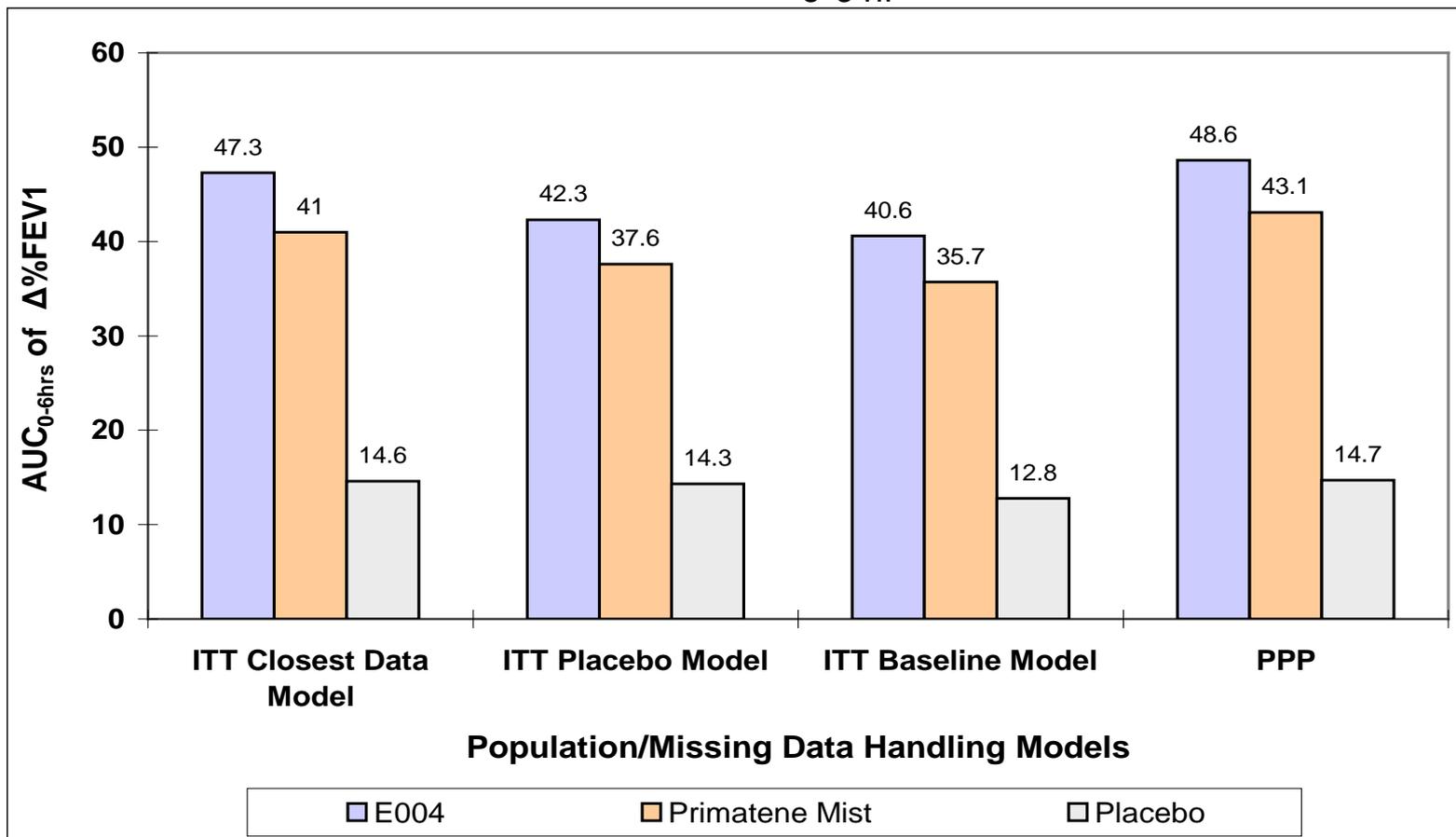
Primary Analysis of Efficacy

- Long-term randomized, DBPC parallel group Study C of maximum labeled dose: 125mcg, 2 puffs, 4 times daily asthmatics age 12 – 75 years, FEV1 50 – 90% predicted, 12% reversibility, treated up to 12 weeks
 - Mean treatment time per subject: 79 & 80 days (for E004 & Placebo)
 - Treatment doses per subject: 558 & 564 inhalations
 - Primary analysis: Intent-to-treat (ITT) population at week-12
 - 4:1:1 Randomization
 - ITT Population: N = 248, 61, and 64 for E004, Placebo, Primatene® Mist CFC, respectively
- Significant efficacy has been demonstrated in adult/adolescent asthma patients



Primary Analysis of Efficacy with Various Models

Percent change in FEV1 AUC_{0-6 hr} at Week 12 (Study C)



($P < 0.0007$ for all comparisons E004 vs. Placebo; $P < 0.014$ for all comparisons Primatene[®] Mist CFC vs. Placebo)



Improvement in FEV1 Reflects Asthma Symptom Relief

- Asthma symptoms are results of airway obstruction
- An improvement in FEV1 of greater than or equal to 12% in asthma patients with baseline airway obstruction is considered to be significant ¹
- The design of E004 efficacy studies was based on the proposed indication “the temporary relief of mild symptoms of intermittent asthma including wheezing, tightness of chest, and shortness of breath”
- The FDA standard requires a greater than 12% improvement of FEV1
- E004 efficacy studies demonstrated that the criteria for relief of asthma symptoms are adequately satisfied

¹ FDA Draft Guidance for Industry

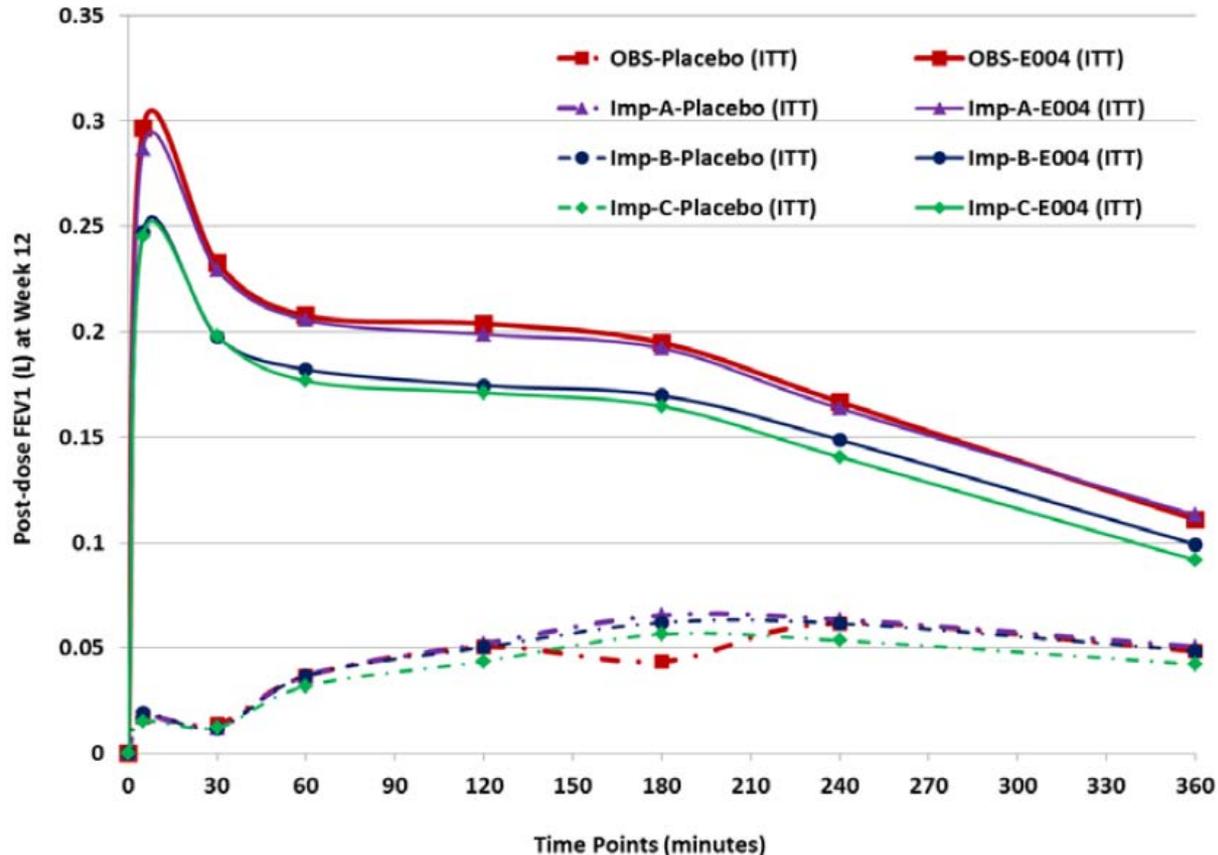


Tachyphylaxis Effect for Efficacy

- Both E004 and Primatene[®] Mist CFC consistently demonstrated a time trend of partial tachyphylaxis at the beta-2 receptor in Study C
 - the greatest efficacy was observed on Day 1
 - a 20% to 40% reduction of bronchodilatory effect, but still showed significant efficacy at Week 6
 - maintained at about the same level or even slightly higher levels of efficacy over the next 6 week period of time until the end of the study, i.e., Week 12
- No significant clinical concerns



Study C - Week 12, $AUC_{0-6\text{ hr}}$ of $\Delta FEV1$ Improved with All Statistical Models



- $\Delta FEV1$ showed rapid improvements of 200 mL and had peak improvement by 1 hour
- These changes were confirmed with all imputation models for MDH

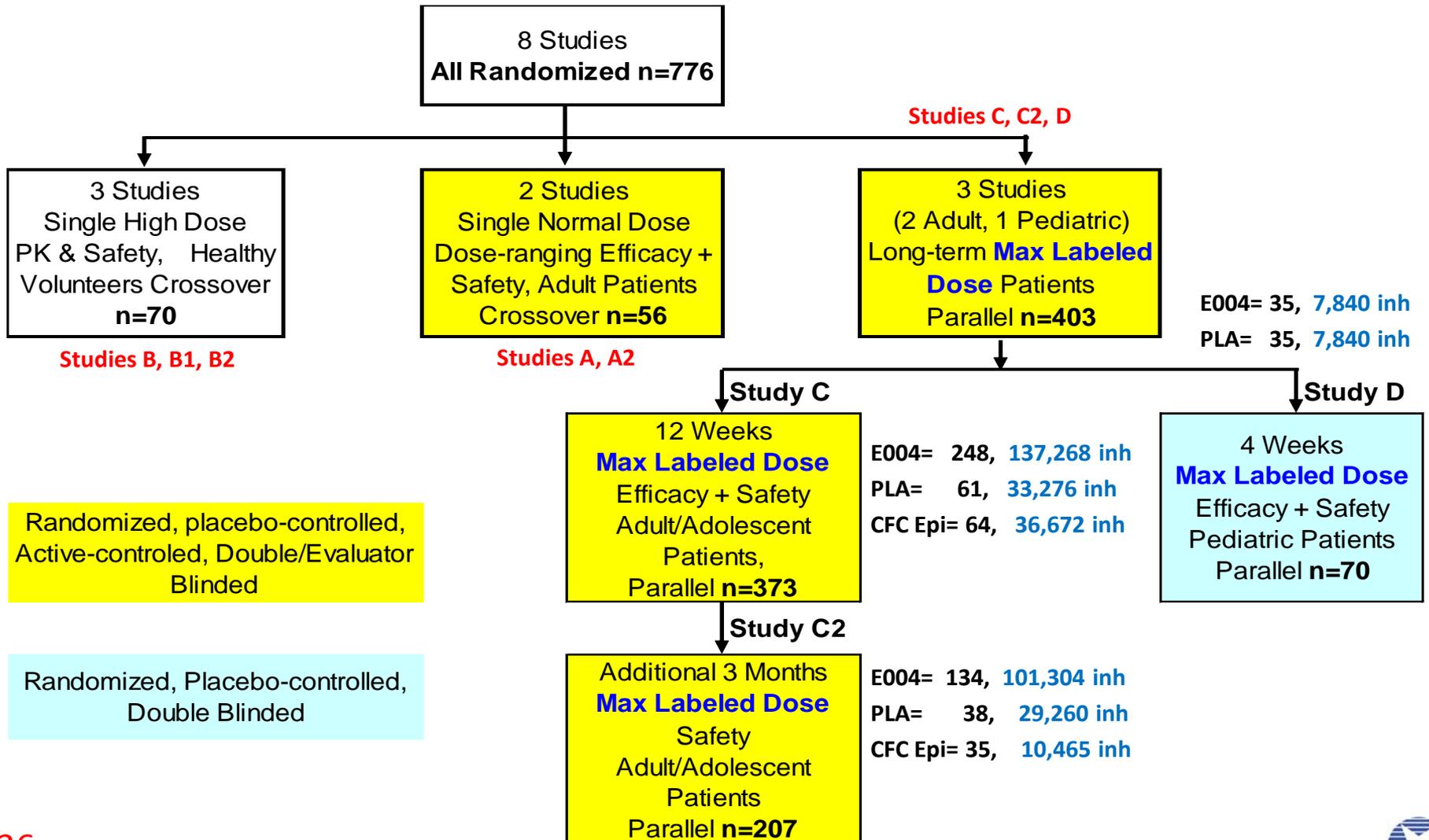


Efficacy Conclusions

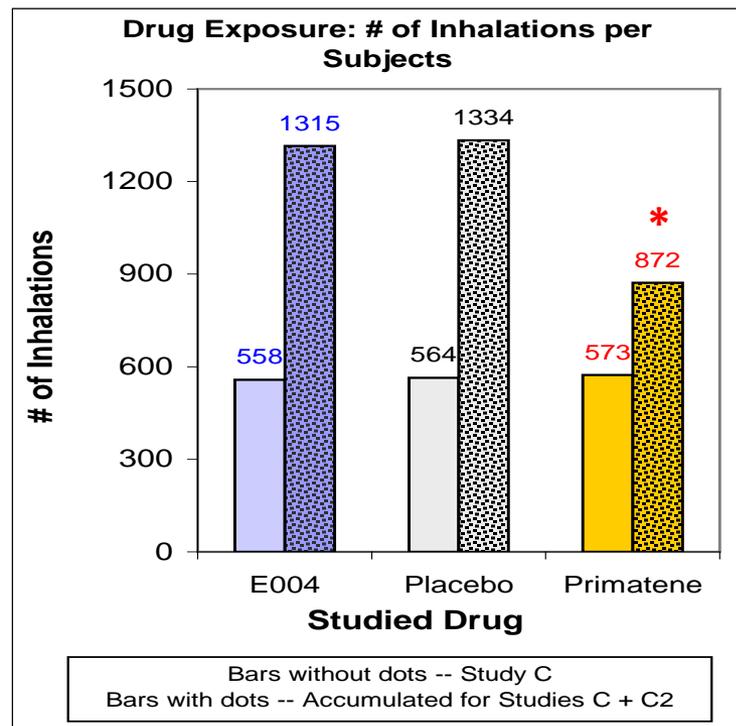
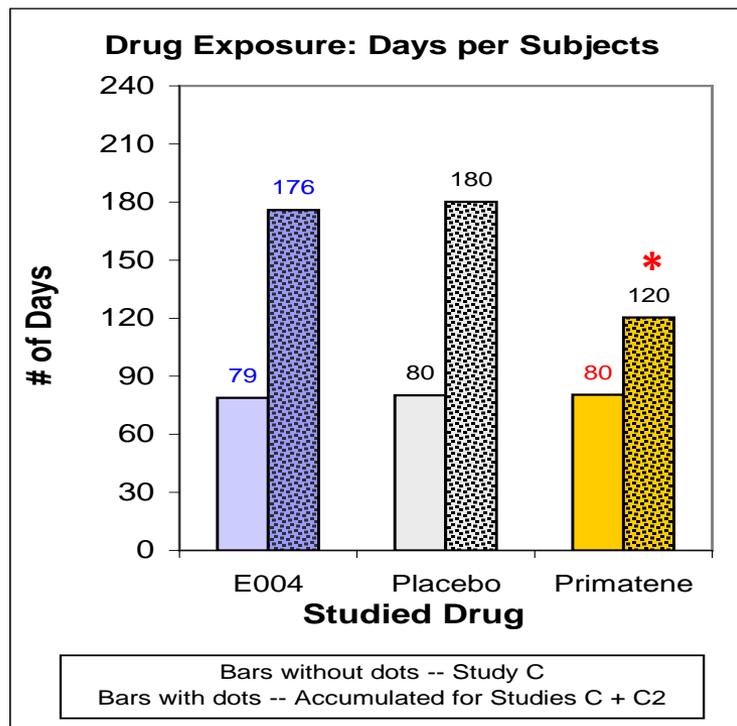
- E004 125 mcg, 1 or 2 puffs showed effectiveness in 0-6 hours post dose similar to Primatene[®] Mist CFC
- Statistically, E004 was significantly better than placebo for 15 of 16 secondary efficacy criteria (except Δ FEV1 at 360 minutes post-dosing)
- E004 showed rapid onset of effect ($> 12\%$ and > 200 mL improvement)
- One puff (125 mcg) may be effective in many patients
- Maximum recommended dose is 2 puffs up to 4 times daily, *AS NEEDED* (not to exceed 8 puffs in a day)



Safety Evaluation Profile



Drug Exposure Profile for Long-term (6-month) Studies



- Long-term safety studies were conducted at maximum labeled dose, QID for up to 6 months. The mean total drug exposure was 176 days or 1,315 inhalations per subject
- For Studies C and C2, respectively, N= E004 248, 134; Placebo 61, 38; and Primatene® Mist CFC 64, 35*



Serious AE (SAE)

From E004 Clinical Studies

- 2/248 (0.8%) of E004 subjects reported SAEs
 - One (1) breast cancer in a 59 yo female
 - One (1) pregnancy in a 33 yo female
- Both SAEs were considered “definitely not related” to the treatment by the investigators



Major Potentially Drug Related AEs Reported in E004 Clinical Studies

#	Type of ADEs	All ADEs Reported			All Severe ADEs Reported			All Serious ADEs Reported		
	Studied Products	E004 n = 248	Placebo n = 61	Primatene n = 64	E004 n = 248	Placebo n = 61	Primatene n = 64	E004 n = 248	Placebo n = 61	Primatene n = 64
1	Tremor	9.7%	1.6%	1.6%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%
2	Throat Irritation	5.2%	0.0%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
3	Cough	4.4%	0.0%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
4	Chest Discomfort	3.6%	1.6%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
5	Feeling Jittery	3.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

- Occurring in >3% and higher in E004 group than placebo
- Few subjects discontinued early for AEs (7%, 5% and 5% for E004, Placebo and Primatene[®] Mist CFC arm)
- All these reported severe AEs were resolved without any residual effects



Evaluation of Vital Signs and ECG

- The profile of vital signs and ECG data for E004 was comparable with those for placebo and Primatene[®] Mist CFC
- No significant cardiovascular issues occurred in terms of frequency, severity or seriousness
- The maximum upper limits of the 95% confidence interval for change (relative to the same day baseline) of vital sign, or ECG within 60 minutes after dosing (based on >35,000 data for Study C)
 - **Δ SBP** -- **1.7 mmHg** for E004, vs. 3.5 mmHg for Placebo
 - **Δ DBP** – **2.1 mmHg** for E004, vs. 3.3 mmHg for Placebo
 - **Δ HR** – **1.6 bpm** for E004, vs. 1.4 bpm for Placebo
 - **Δ QT** – **5.4 ms** for E004, vs. 11.3 ms for Placebo
 - **Δ QTc** – **4.0 ms** for E004 vs. 4.2 ms for Placebo



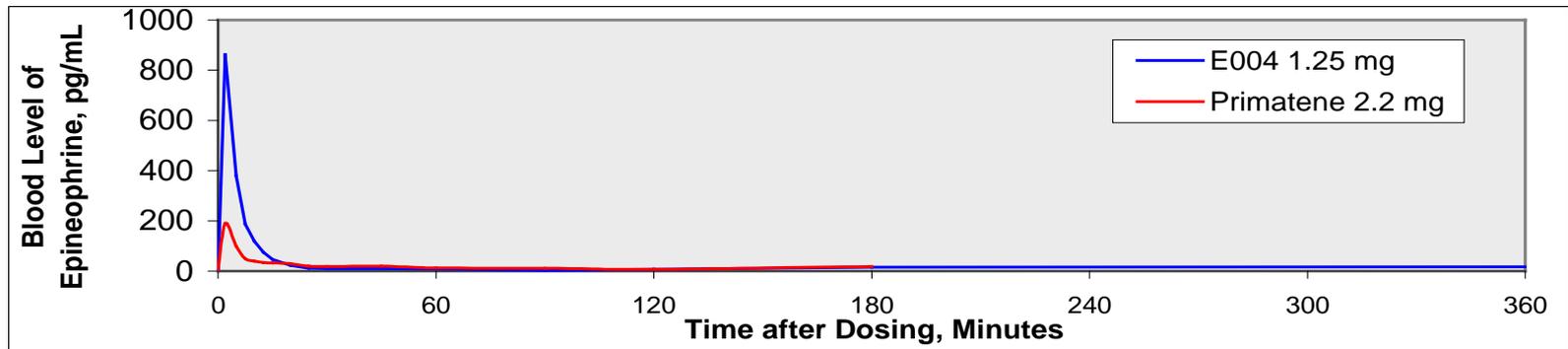
AE of Special Interest – Tremor

- Hand tremor was reported in the first 10 minutes after dose (even in PK studies with 5 times of the regular dose)
- High Dose Study B (10 puffs PK study) graded hand tremor
 - 0 – none 1 – mild 2 – moderate 3 – severe
- All patients who noted tremors on the high dose study scored it as mild (i.e., 1). There were no tremors graded as 2 or 3
- The highest mean tremor score was 0.2 (very mild) and fell off rapidly as drug level dropped 10 fold by 12.5 minutes post-dosing
- 24 Tremor AEs for E004 treatment were reported, with IR 9.7%, in long-term adult/adolescent Studies C and C2
 - None were considered to be a serious AE by the investigators
 - All were resolved without residual effects except one subject due to being lost to follow up



AE of Special Interest – Tremor (cont.)

- PK Study B: 10 puffs of E004 125mcg or Primatene[®] Mist CFC 220mcg
- Dose-response of Hand Tremor score to the blood level of epinephrine
- Tremor Scores were mild and reported only in first 10 minutes after dose.



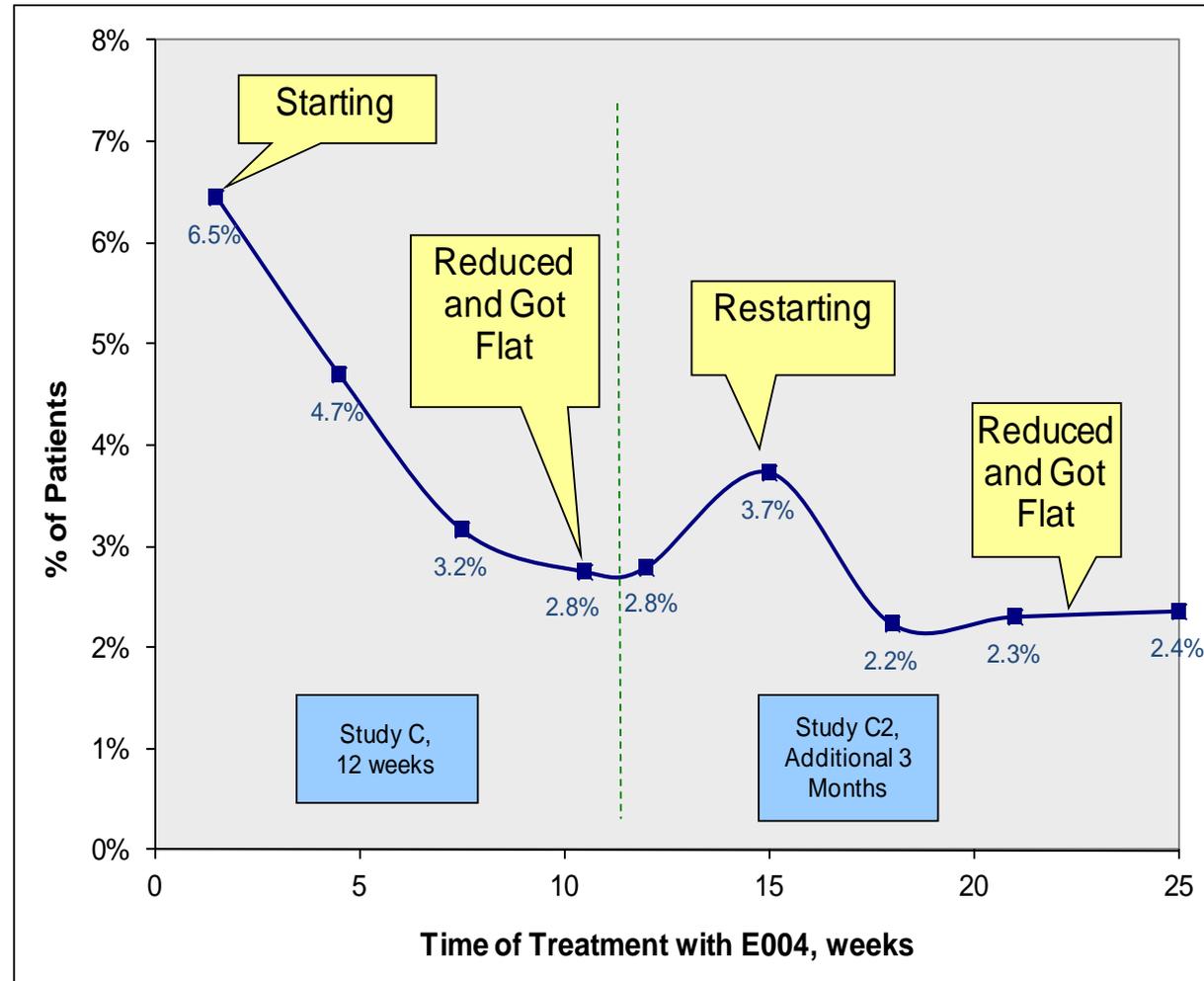
AE of Special Interest – Tremor (cont.)

- Tremor rates decreased with duration of participation in long-term trials. Tachyphylaxis may develop for the tremorigenic side effects of beta-agonists over time
- Noteworthy, long-term trials administered 8 puffs daily (125 mcg, 2 puffs, 4 times daily) for up to 6 months
- Actual OTC use is expected to be *AS NEEDED* 1 or 2 puffs, for intermittent asthma symptoms (usually 2 or fewer days per week)



AE of Special Interest – Tremor (cont.)

- Tachyphylaxis
Effect of Tremor
 - At beginning of use of E004 at the maximum labeled dose, the IR for Tremor was 6.5%
 - After use for 3 months, the IR for Tremor was reduced to 2.8%
 - After use for 4 months or longer, the IR for Tremor was reduced to 2.2% - 2.4%



Cardiovascular AEs

#	Category of Safety Data	ADE Incidence Rates in 6-month Clinical Studies (%)		
	Studied Products	E004 n=248	Placebo n=61	Primatene Mist n=64
1	Blood Pressure Increase	0.4%	0.0%	1.6%
2	Heart Rate Increase	0.4%	0.0%	0.0%
3	Hypertension	0.0%	1.6%	1.6%
4	Palpitations	1.2%	0.0%	1.6%
5	Tachycardia	0.4%	0.0%	0.0%
6	Myocardial Infarction	0.0%	0.0%	0.0%
7	Cardiac Arrest	0.0%	0.0%	0.0%
8	Hypotension	0.0%	0.0%	0.0%
Total		2.4%	1.6%	4.7%

- E004's cardiovascular AE profile
 - very similar to that of Primatene[®] Mist CFC or Placebo
 - consistent with FAERS Postmarketing AE data of Primatene[®] Mist CFC
- E004 had no significant cardiovascular issues in terms of frequency, severity or seriousness



Device Performance

- 3,754 units of E004 or Placebo used in long-term clinical studies (99.4% unit return rate) and lab testing was performed
- The previous report was solely based on patients' diary records
- A thorough investigation completed the following dose indicator (DI) deficiency rates **based on data generated prior to NDA filing**

	DI at risk Rate*	DI Undercounting Rate
E004 units (n=2,895)	0.14%	0.17%
Placebo Units (n=847)	1.1%	1.1%
E004 + Placebo (n=3,742)	0.35%	0.37%

* When the medication in the canister was at least 8 puffs more than the dose indicator reading, the unit was defined to be classified as “non-risk”. It was found that 99.83% of 2,895 E004 MDI units were classified as “non-risk”.



Device Performance (cont.)

- Malfunction unit evaluations
 - 251 **potential** malfunction units (PMFU) from 3,752 units were reported based on patients' diaries or subject comments: the PMFU were 100% tested (1,658 testing data points)
 - Eight (8) of the 251 PMFU were **confirmed** as **true** malfunctions

Items	E004 (n = 2,904)	Placebo (n=848)	E004 + Placebo (n = 3,752)
# of Malfunction Units	4	4	8
Malfunction Rate (%)	0.14%	0.47%	0.21%

- **Not 7%** (=251/3,752), which was an **overgeneralization** based on patients' diaries or comments
- For E004 clinical units, the **low DI at risk rate of 0.14%**, **DI undercounting rate of 0.17%**, and **malfunction rate of 0.14%** demonstrated the robustness of device performance



Efficacy and Safety Conclusion

- E004 shows robust efficacy similar to Primatene[®] Mist CFC for both 125 mcg, 1 puff and 2 puff doses
- The safety profile was reassuring and comparable with Primatene[®] Mist CFC
- The most common AEs that occurred more frequently with E004 and in over 3% of subjects were Tremor, Throat Irritation, Cough, Chest Discomfort and Feeling Jittery. These are expected for adrenergic agonists
- There were no drug-related serious AEs
- The safety and efficacy profile is comparable to that of Primatene[®] Mist CFC and Drug Facts Label (DFL) provides appropriate cautions



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Epinephrine HFA MDI: A Proposed Reformulation to Replace
OTC Primatene[®] Mist CFC MDI

Part D: OTC Consumer Studies

David McCammon, M.S.
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February 25, 2014



Basis of E004 OTC Labeling

- OTC Labeling for E004 is amended/updated based on the OTC labeling for Primatene[®] Mist (CFC MDI)
 - The OTC labeling for Primatene[®] Mist CFC was used for more than 50 years in the U.S. OTC market
- The labeling for E004 consists of two components:
 - Drug Facts Label (DFL); and
 - Insert (Consumer Information Leaflet)



E004 OTC Labeling Study Methods

- FDA instructed to test only the unique aspects of E004, comparing it to Primatene[®] Mist CFC
- FDA recommended testing methods:
 - Label comprehension – cognitive understanding
 - Human factors – behavioral demonstration
- Study results support consumer OTC use of E004



Considerations in Updating E004 Labeling

- Per Primatene[®] Mist CFC DFL
- Current FDA guidance
- Reformulation and strength
- Clinical results for doses, user age, efficacy, and safety
- Post-marketing safety data for Primatene[®] Mist CFC
- Inclusion of the required warning and improvement of E004



Main Changes for Instructions of Use

Item	Primatene® Mist CFC	E004
User age	4 years of age and over	12 years of age and over*
Daily maximum dose	12 inhalations**	8 inhalations
Minimum time between doses	3 hours	4 hours
Priming/Repriming	Not Required	4 times prior to 1 st use 1 time after 2 days of not using or if actuator is wet
Shaking	Not Required	Vigorous shaking before use/priming/repriming
Cleaning	After each use	After daily use
Monitoring remaining puffs	No Method	Dose indicator

* clinical studies for pediatric patients (4-11 years old) are in process

** Primatene® Mist CFC DFL indicated “see a doctor if you need 12 inhalations in any day”



Overview of E004 DFL

Primatene[®] Mist HFA

Epinephrine Inhalation Aerosol
Bronchodilator
0.125 mg per inhalation
Total contents:
160 inhalations

For temporary relief
of MILD symptoms
of INTERMITTENT asthma



CONTAINS MOUTHPIECE AND
CONTAINER WITH DOSE INDICATOR

Drug Facts (continued)

Directions For Dosing:

- do not use more than directed
- adults and children 12 years of age and over
 - 1 to 2 inhalations for each dose
- Start with one inhalation, wait at least 1 minute. If not relieved, use once more
- Wait at least 4 hours between doses
- Do not use more than 8 inhalations in 24 hours
- children under 12 years of age: ask a doctor

Inhaler storage and other information

- store at room temperature, between 15-25°C (59-77°F)
- contains no sulfites
- see insert for mouthpiece use and care instructions

Inactive ingredients

dehydrated alcohol (1%), hydrofluoroalkane (HFA 134a), polysorbate 80, thymol

Questions or comments?

call 1-8 Primatene or
1-877-462-8363
Mon.- Fri. 7 am - 5 pm PST

Manufactured by:

Armstrong Pharmaceuticals, Inc.
Canton, MA 02021
© 2014 Made in USA
See www.armstrong-pharma.com

IMPORTANT:
Shake product
before each use.

Drug Facts

Active Ingredient (in each inhalation)	Purpose
Epinephrine 0.125 mg.....	Bronchodilator

Uses

For temporary relief of mild symptoms of intermittent asthma

- wheezing
- tightness of chest
- shortness of breath

Warnings

- **Asthma alert: Because asthma may be life threatening, see a doctor if you**
 - are not better in 20 minutes
 - get worse
 - need more than 8 inhalations in 24 hours
 - have more than 2 asthma attacks in a week
- These may be signs that your asthma is getting worse
- For inhalation only

Do not use

- unless a doctor said you have asthma
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or a pharmacist before taking this product

Ask a doctor before use if you have

- ever been hospitalized for asthma
- heart disease
- high blood pressure
- diabetes
- trouble urinating due to an enlarged prostate gland
- thyroid disease
- seizures
- narrow angle glaucoma
- a psychiatric or emotional condition

Ask a doctor or pharmacist before use if you are

- taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions
- taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)

Open Here

Drug Facts (continued)

When using this product

- your blood pressure or heart rate may go up. This could increase your risk of heart attack or stroke, which may cause death
- your risk of heart attack or stroke increases if you
 - have a history of high blood pressure or heart disease
 - take this product more frequently or take more than the recommended dose
- avoid foods or beverages that contain caffeine
- avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect
- do not puncture or incinerate. Contents under pressure
- do not store near open flame or heat above 120°F (49°C). May cause bursting.

Intentional abuse of this product can be harmful or fatal.

If pregnant or breast-feeding, ask a health care professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Stop use and ask a doctor if

- your asthma is getting worse (see Asthma alert)
- you have difficulty sleeping
- you have a rapid heart beat
- you have tremors, nervousness, or seizures



Main Changes of the Updated E004 Insert

#	Item	Primatene® Mist CFC	E004
1	Take Inhalation	√	√ Updated for shaking
2	Priming, including shaking	No	New
3	Dose Indicator	No	New
4	Clean the Mouthpiece	√	√ Updated



Main Changes of the Updated E004 Insert (cont.)

Take Inhalation

Take Inhalation

The Primatene[®] Mist HFA mouthpiece, should be used for inhalation only with the Primatene[®] Mist HFA container.

1. Take cap off mouthpiece
(See Figure 1).



Figure 1

2. **SHAKE** the inhaler immediately
before each inhalation (See
Figure 2).



Figure 2

3. • Place thumb on bottom
of mouthpiece.
• Place finger on **center**
of dose indicator (See
Figure 3).

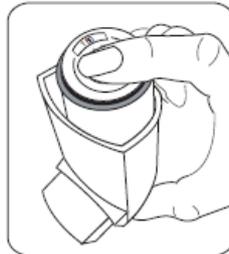


Figure 3

4. Empty the lungs as completely as possible
by **exhaling**.

5. Place mouthpiece in mouth.
 - Lips closed around opening
 - Inhale deeply while squeezing
mouthpiece and container
together (See Figure 4).
 - Continue the deep breath,
drawing medication
into the lungs.
 - Hold breath as long as
possible.



Figure 4

6. • Release and remove from
mouth.
• Exhale slowly keeping lips
nearly closed (See Figure 5).
• This helps distribute the
medication in the lungs.

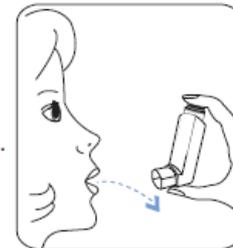


Figure 5

7. After the inhalations cover the mouthpiece
opening with plastic cap for storage.

Main Changes of the Updated E004 Insert (cont.)

Priming/ Repriming

Priming

When to prime

Before 1 ST use	4 times
Not used in more than 2 days	1 time
Still wet after cleaning	1 time
If dropped	1 time

How to prime

1. Remove cap.
2. Shake.
3. Hold with dose indicator up and away from your face or others.
4. Place forefinger on **center** of dose indicator.
5. Immediately spray.



Shake



Spray

Before first use, prime four (4) times

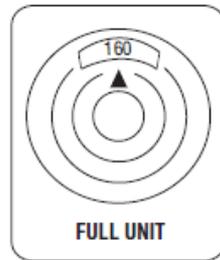
Main Changes of the Updated E004 Insert (cont.)

Dose Indicator

Dose Indicator- shows how many sprays you have left

A full container holds 160 sprays

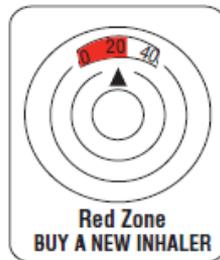
- The dose indicator **number** changes after you spray 20 times.
- The number **does not** change by one (1) each time you spray the inhaler.



**Starts at 160:
160 sprays remaining**

Red Zone

- Once the red zone appears and the display reads "20", buy a new Primatene[®]HFA inhaler soon.
- **The dose indicator will stop counting at "0" and the inhaler must not be used any longer.**
- When the dose indicator hits zero, the correct dose in each spray cannot be assured (even though there may be medication in the container).



**Red Zone
BUY A NEW INHALER**

**Red Zone:
Buy a new Inhaler**

CAUTION- Never try to change the numbers or take the dose indicator off the container.

The dose indicator cannot be reset, it should remain permanently attached to the container.

Daily Clean

Clean the Mouthpiece DAILY if used

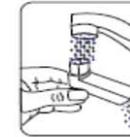
1. Remove Cap



2. Remove Container

3. Wash opening

- warm water
- 30 seconds



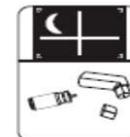
4. Wash top

- warm water
- 30 seconds

5. Shake off excess water



6. Air Dry overnight



7. Assemble

Remember:

- **DAILY** wash both ends, if used
- **Air dry** after washing
- If **wet**, prime one (1) time before use
- It is normal to see some discoloration in the mouthpiece due to residual drug left on it after use.



Label Comprehension Studies

- E004 Label Comprehension Study (LCS)
 - Conducted per the FDA Guidance document
 - Included 3 LCS, in total 1,345 participants at 23 study sites
- General sample of consumers
 - Low-literacy participants included
 - Different ethnic participations
 - Each study includes some Primatene[®] Mist CFC users (17% of 1,345)
 - Representative Demographics, e.g., gender, age etc.
- Asked primarily open-end questions:
 - Direct questions and/or hypothetical scenarios
 - No multiple choice questions
- Consumer responses scored as incorrect or correct / acceptable

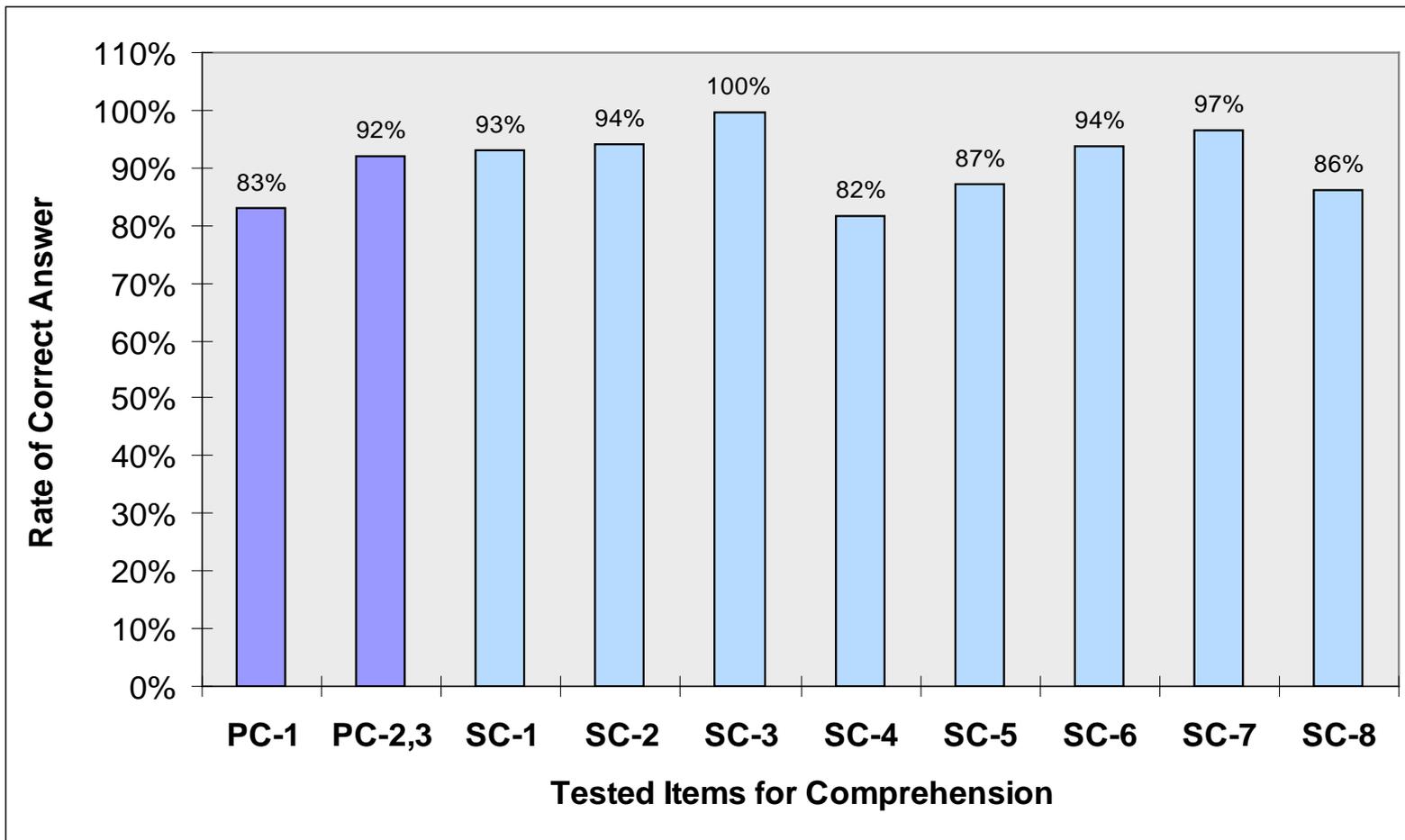


Label Comprehension Endpoints

- LCS assessment included 3 primary communications (PC) and 8 secondary communications (SC)
 - Primary endpoints regarding dose indicator use
 - Designated 85% target performance, based on the risk that consumers face if undercounting the number of doses occurs (a low potential safety risk that the amount of medicine remaining in the inhaler is overestimated)
 - Secondary endpoints: priming/re-priming, clean the mouthpiece, take inhalation, and dose indicator
- After 3 LCS and label improvement, the important elements of the E004 insert were demonstrated to be well understood.



Results of E004 LCS



PC – Primary Communication

SC – Secondary Communication



Developing the E004 Label Was an Iterative Process

- The consumer comprehension of the PC-1, for example, was improved after multiple LCS tests and label improvements
- The comprehension of participants with different literacy levels, ethnicity were elevated

Primary Communication-1: If the Inhaler is Dropped ...		
LCS-1		
Entire Sample 51.40%	Normal Literacy 55.6%	Low Literacy 39.10%

↓

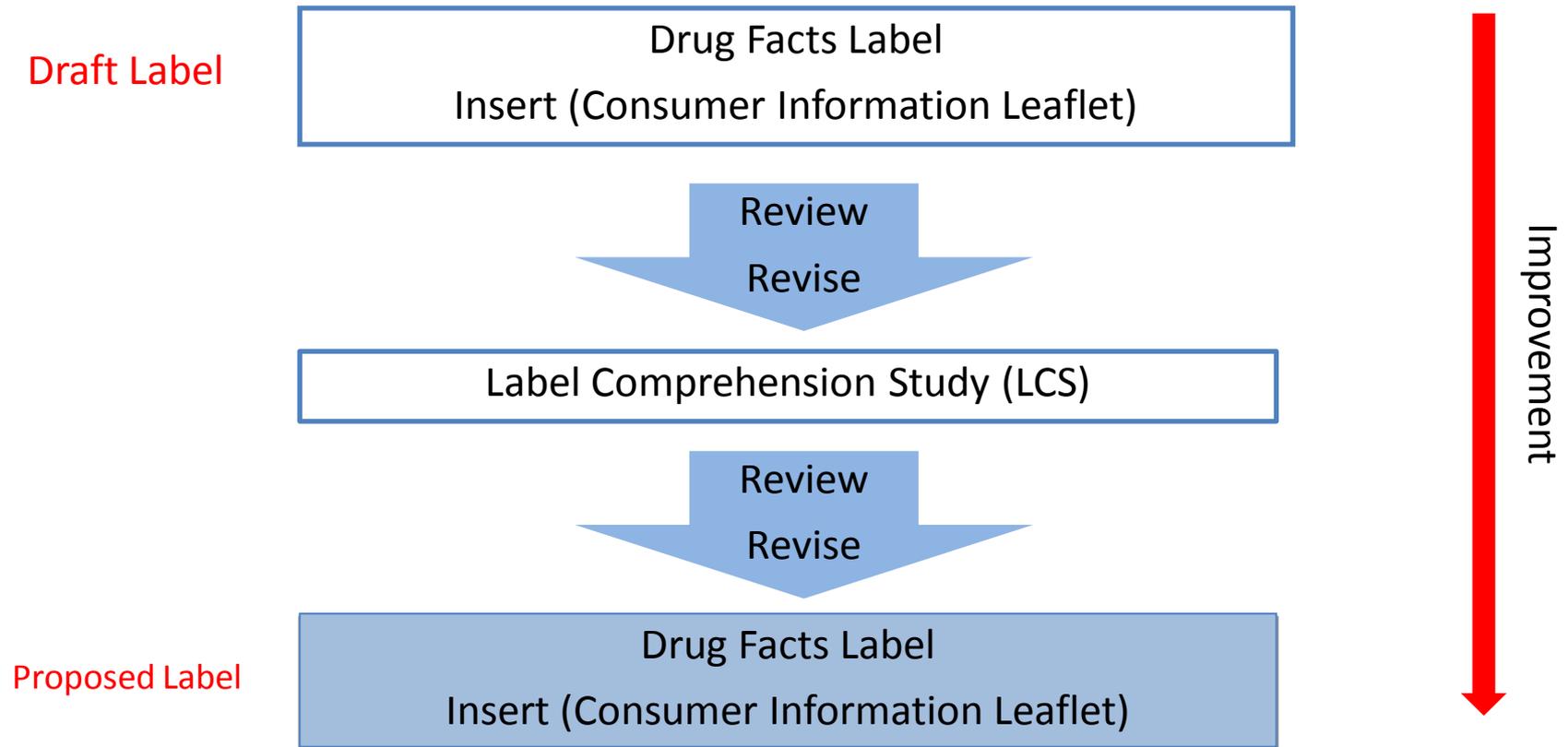
LCS-2		
Entire Sample 67.90%	Normal Literacy 72.6%	Low Literacy 56.0%

↓

LCS-3		
Entire Sample 83.0%	Normal Literacy 87.1%	Low Literacy 72.1%



Developing the E004 Label Was an Iterative Process



Analysis for the “Off Goal” items

- Undercounting could be caused by
 - the consumer not correctly understanding the instructions regarding how to interpret the dose counter readings, or
 - a malfunction of the inhaler (for example dropping the inhaler, or other improper uses) may cause an incorrect dosage use display
- For PC-1 “If you drop the inhaler, do not rely on the dose indicator. Keep track of the number of sprays you take” 83% vs. 85%, 2% difference
 - dropping is a rare circumstance
 - could be a potential but low probability of lack of response to therapy related to overestimation of the amount of medication remaining in the inhaler
 - DFL directs consumers what to do in the event they do not experience relief after use of the product
- The reported % was an overkill by considering a “NO” for those answers saying the dropped unit would be abandoned. Abandon a unit should not be considered a risk of DI.



Label Behavioral Study

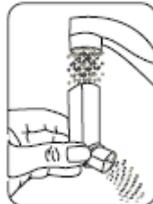
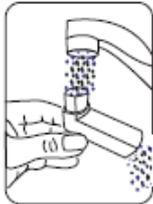
- E004 label behavior study focused on assessing the procedures needed by a consumer to use and maintain the product unit properly
- Behavioral Study included:
 - 61 participants at multiple study sites
 - low literacy participants
 - different ethnic groups
 - adolescents (12 – 17 years old)
 - prior users of Primatene[®] Mist CFC



Some Primary Label Steps Tested

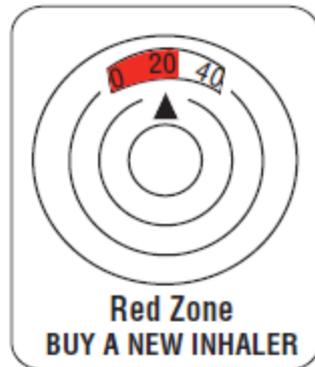
Wash opening

- warm water
- 30 seconds



Wash top

- warm water
- 30 seconds



**Red Zone:
Buy a new Inhaler**

- Place thumb on bottom of mouthpiece.
- Place finger on **center** of dose indicator (See Figure 3).



Figure 3

Place mouthpiece in mouth.

- Lips closed around opening
- Inhale deeply while squeezing mouthpiece and container together (See Figure 4).
- Continue the deep breath, drawing medication into the lungs.
- Hold breath as long as possible.

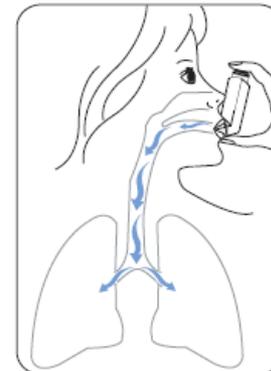


Figure 4

Summary of Scores for Label Behavioral Study

- 13 primary or significant (primary) steps among 32 label steps tested are in the following 4 categories
- Mean score for primary steps was 88% and for all items it was 91%

#	Tested Categories	# of Items Tested		Mean of Scores	
		Primary Items	All Items	Primary Items	All Items
1	Prime the Inhaler	3	4	87% ± 11%	86% ± 10%
2	Clean the Mouthpiece	5	9	85% ± 14%	85% ± 14%
3	Reassemble the Inhaler	0	2	- -	94% ± 8%
4	Actually delivering a dose	5	17	92% ± 10%	94% ± 9%
	Total	13	32	88% ± 12%	91% ± 11%



Summary of Scores for Label Behavioral Study (cont.)

- Participants performed remarkably well in steps of actually delivering the dose. Some steps include:
 - Holding with dose indicator up: 93.4%
 - Finger placement: 88.5%
 - Lips closed around mouthpiece: 98.4%
- Participants demonstrated a high understanding in the LCS:
 - 94% understood to clean product daily
 - 95% understood directions to prime before first use
 - 87% understood when to re-prime
- It is not uncommon to see high and low scores in all label studies, but good LCS outcomes indicates good label comprehension, in general



Analysis for Root Cause for the “Off Goal” Steps

- “Off goal” steps for use and care of E004 units
 - 64% correctly washing the mouthpiece through the top opening
 - 74% shaking the MDI prior to use
 - 74% of subjects shaking the MDI prior to priming
 - 82% priming prior to use
- Analysis of Study Results
 - Likely root cause: part of the former Primatene[®] Mist CFC users who were included in the study was too dependent on their prior experience of using Primatene[®] Mist CFC, and did not pay attention to the changed new instructions during the E004 behavioral study



The Proposed Corrective Action – Updating E004 Labeling

- Proposal to include instructions advising Primatene[®] Mist CFC consumers to pay special attention to the differences in use and care of E004
- Place on the top panel of E004 DFL Carton



Results E004 Label Behavior Study

- Participants in this behavior study demonstrated a very good ability to read and perform the steps of use and care of the E004 inhaler
- In particular, participants performed remarkably well in the steps of actually delivering a dose



Presentation to Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee



Epinephrine HFA MDI: A Proposed Reformulation to Replace
OTC Primatene[®] Mist CFC MDI

Part E: Conclusion

Jason Shandell, J.D., M.B.A., Esq.
President of Amphastar Pharmaceuticals, Inc.

*Armstrong Pharmaceuticals, Inc.
Amphastar Pharmaceuticals, Inc.*

February 25, 2014



Clear Need for an OTC Asthma MDI Medication

- Asthma substantially disrupts people's daily life at work, study, and sleep
- Asthma is a common and important public health issue and costs the United States \$56 billion each year⁸
- Current market available medications leave unmet needs and there is no OTC MDI asthma-specific medication available on the market
- OTC asthma MDI medication should be readily available for those without access to prescription



Risks of E004

- E004 Device performance was acceptable in clinical trials
 - The detailed analysis for E004 and placebo showed:
 - The rate that dose indicator reading at risk* is 0.35%
 - Dose indicator undercounting rate is 0.37%
 - Malfunction rate is 0.21%
- Risk that OTC consumers may use a higher dose than indicated
- The most common AE for E004 was tremor, which occurred in close to 10% of patients, compared to 2% in the placebo and active control groups



Benefits of E004

- E004 demonstrated statistically significant efficacy at Week 12. In general, efficacy results are comparable to those shown with Primatene[®] Mist CFC
- E004 did not demonstrate clinically significant increases in heart rate or blood pressure with the proposed dose. The 50 year post-marketing history of Primatene[®] Mist CFC does not demonstrate a significant cardiac signal either
- There are currently no approved asthma-specific MDI on the OTC market; E004 has the asthma-specific indication
- A quick relief OTC inhaler is needed by US consumers including low-income and uninsured individuals who might otherwise not have access to medical treatment



The Benefits Outweigh the Risks

- The potential safety risks of using E004 without a physician's oversight would not be different or greater than those for OTC Primatene[®] Mist CFC, which was OTC for more than 50 years
- The risks are manageable through the OTC labeling
 - Drug Facts Label and insert contain critical information necessary for the safe and effective use of the product and are understandable by the average consumer
- OTC E004 would address:
 - Safe, affordable, effective and broad access
 - Asthma-specific indication: temporary relief for mild symptoms of intermittent asthma



SEE SIDE PANEL AND INSERT FOR SPECIAL DIRECTIONS ON:
 Maximum Daily Dose
 Shaking Before Each Use
 Priming & Repriming
 Daily Cleaning
 Using Dose Indicator

Primatene[®] Mist HFA
 Epinephrine Inhalation Aerosol
 Bronchodilator
 0.125 mg per inhalation
 Total contents:
 160 inhalations

For temporary relief of MILD symptoms of INTERMITTENT asthma



CONTAINS MOUTHPIECE AND CONTAINER WITH DOSE INDICATOR

UPC-A BARCODE
 TO READ: 3 17270 55300 7

NON-VARNISH AREA

Drug Facts (continued)
Directions For Dosing:
 ■ do not use more than directed
 ■ adults and children 12 years of age and over
 ■ **1 to 2 inhalations** for each dose
 ■ Start with one inhalation, wait at least 1 minute. If not relieved, use once more
 ■ Wait at least **4 hours** between doses
 ■ Do not use more than **8 inhalations in 24 hours**
 ■ children under 12 years of age: ask a doctor

Inhaler storage and other information
 ■ store at room temperature, between 15-25°C (59-77°F)
 ■ contains no sulfites
 ■ see insert for mouthpiece use and care instructions

Inactive ingredients
 dehydrated alcohol (1%), hydrofluoroalkane (HFA 134a), polysorbate 80, thymol

Questions or comments?
 call 1-8 Primatene or 1-877-462-8363
 Mon.- Fri. 7 am - 5 pm PST

Manufactured by:
 Armstrong Pharmaceuticals, Inc.
 Canton, MA 02021
 © 2013 Made in USA
 See www.armstrong-pharma.com

IMPORTANT:
 Shake product before each use.

NON-VARNISH AREA

↓

BARCODE TYPE C128
 TO READ U5530B

U5530B

Drug Facts
Active Ingredient (in each inhalation) Purpose
 Epinephrine 0.125 mg.....Bronchodilator

Uses
 For temporary relief of mild symptoms of intermittent asthma
 ■ wheezing
 ■ tightness of chest
 ■ shortness of breath

Warnings
 ■ **Asthma alert: Because asthma may be life threatening, see a doctor if you**
 ■ are not better in 20 minutes
 ■ get worse
 ■ need more than 8 inhalations in 24 hours
 ■ have more than 2 asthma attacks in a week
 ■ These may be signs that your asthma is getting worse
 ■ For inhalation only

Do not use
 ■ unless a doctor said you have asthma
 ■ if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or a pharmacist before taking this product

Ask a doctor before use if you have
 ■ ever been hospitalized for asthma
 ■ heart disease
 ■ high blood pressure
 ■ diabetes
 ■ trouble urinating due to an enlarged prostate gland
 ■ thyroid disease
 ■ seizures
 ■ narrow angle glaucoma
 ■ a psychiatric or emotional condition

Ask a doctor or pharmacist before use if you are
 ■ taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions
 ■ taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)

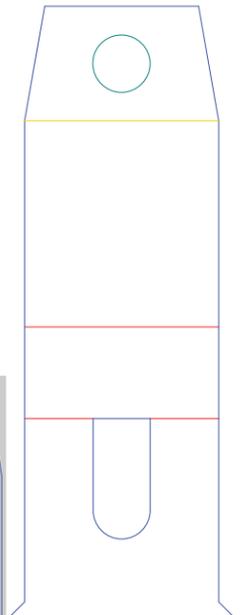
Open Here

U5530B

TO READ U5530B

BARCODE TYPE C128

↑
 NON-VARNISH AREA



Drug Facts (continued)
When using this product
 ■ **your blood pressure or heart rate may go up. This could increase your risk of heart attack or stroke, which may cause death**
 ■ **your risk of heart attack or stroke increases if you**
 ■ have a history of high blood pressure or heart disease
 ■ **take this product more frequently or take more than the recommended dose**
 ■ avoid foods or beverages that contain caffeine
 ■ avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect
 ■ do not puncture or incinerate. Contents under pressure
 ■ do not store near open flame or heat above 120°F (49°C). May cause bursting.
 Intentional abuse of this product can be harmful or fatal.

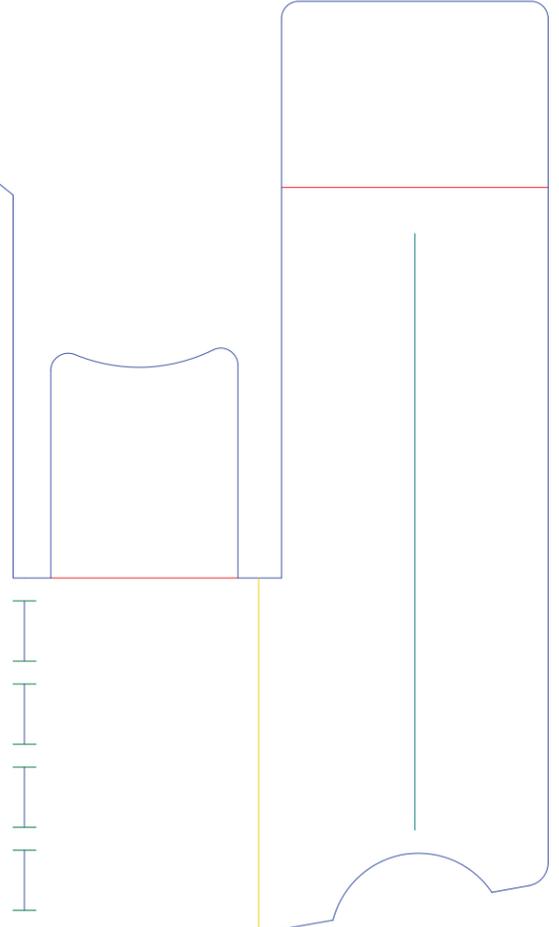
If pregnant or breast-feeding,
 ask a health care professional before use.

Keep out of reach of children.
 In case of overdose, get medical help or contact a Poison Control Center right away.

Stop use and ask a doctor if
 ■ your asthma is getting worse (see Asthma alert)
 ■ you have difficulty sleeping
 ■ you have a rapid heart beat
 ■ you have tremors, nervousness, or seizures

U5530B

DRUG FACTS FONT SPECS
 • DRUG FACTS HEADING FONT SIZE = HELVETICA 9 POINT
 • BODY OF DRUG FACTS TEXT = HELVETICA 7 POINT



DESCRIPTION: Primatene Mist HFA
 LABEL NO: U5530B
 SIZE: 1.9375 X 1.3125 X 5.125
 COLORS: PMS 4625, PMS 485, PMS 430, CMYK
 BARCODES: CODE 128 TO READ: U5530B
 UPC-A TO READ: 317270553007

Primatene[®] Mist HFA

Epinephrine Inhalation Aerosol
Bronchodilator

For temporary relief of **MILD** symptoms
of **INTERMITTENT** asthma

BENEFITS OF PRIMATENE[®] MIST HFA

This product is intended for use by individuals with **mild** symptoms of **intermittent** asthma.

When used according to directions, Primatene[®] Mist HFA provides an easy and effective way to obtain temporary relief of **mild** symptoms of **intermittent** asthma. Primatene[®] Mist HFA contains epinephrine, which is a dependable inhalation aerosol bronchodilator. It is packaged in an aluminum container fitted with a specially designed valve, for use with the Primatene[®] Mist HFA mouthpiece only. The special valve is designed to deliver the same amount of medication with each spray. Primatene[®] Mist HFA can be used at any time of the day or night. Use only as directed.

Take Inhalation

The Primatene[®] Mist HFA mouthpiece, should be used for inhalation only with the Primatene[®] Mist HFA container.

1. Take cap off mouthpiece
(See Figure 1).

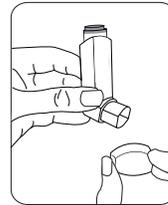


Figure 1

2. **SHAKE** the inhaler immediately before each inhalation (See Figure 2).



Figure 2

3. • Place thumb on bottom of mouthpiece.
• Place finger on **center** of dose indicator (See Figure 3).

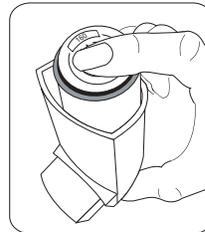


Figure 3

4. Empty the lungs as completely as possible by **exhaling**.

5. Place mouthpiece in mouth.
 - Lips closed around opening
 - Inhale deeply while squeezing mouthpiece and container together (See Figure 4).
 - Continue the deep breath, drawing medication into the lungs.
 - Hold breath as long as possible.



Figure 4

6. • Release and remove from mouth.
• Exhale slowly keeping lips nearly closed (See Figure 5).
• This helps distribute the medication in the lungs.

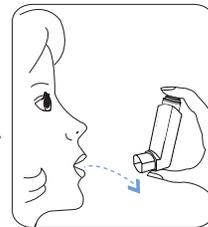


Figure 5

7. After the inhalations cover the mouthpiece opening with plastic cap for storage.

Manufactured by: Armstrong Pharmaceuticals, Inc., Canton, MA 02021 © 2014 Made in USA F5530C

CODE 128 BARCODE
TO READ F5530C

FRONT

Priming

When to prime

Before 1 st use	4 times
Not used in more than 2 days	1 time
Still wet after cleaning	1 time
If dropped	1 time

How to prime

1. Remove cap.
2. Shake.
3. Hold with dose indicator up and away from your face or others.
4. Place forefinger on **center** of dose indicator.
5. Immediately spray.



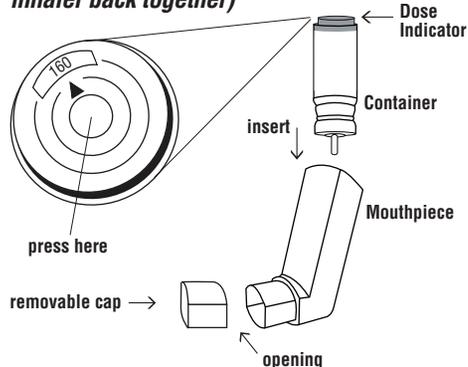
Shake



Spray

Before first use, prime four (4) times

How to Assemble the Inhaler (How to put inhaler back together)

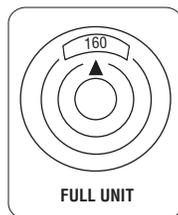


Dose Indicator- shows how many sprays you have left

A full container holds 160 sprays

- The dose indicator **number** changes after you spray 20 times.

- The number **does not** change by one (1) each time you spray the inhaler.



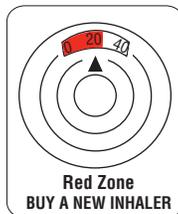
**Starts at 160:
160 sprays remaining**

Red Zone

- Once the red zone appears and the display reads "20", buy a new Primatene[®] HFA inhaler soon.

- **The dose indicator will stop counting at "0" and the inhaler must not be used any longer.**

- When the dose indicator hits zero, the correct dose in each spray cannot be assured (even though there may be medication in the container).



**Red Zone
BUY A NEW INHALER**
**Red Zone:
Buy a new Inhaler**

CAUTION- Never try to change the numbers or take the dose indicator off the container.

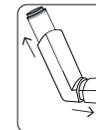
The dose indicator cannot be reset, it should remain permanently attached to the container.

If you **DROP** your inhaler:

- **DO NOT RELY ON DOSE INDICATOR**
- Keep track of the number of sprays you take
- Prime one (1) time

Clean the Mouthpiece DAILY if used

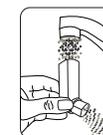
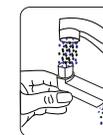
1. Remove Cap



2. Remove Container

3. Wash **opening**

- warm water
- 30 seconds



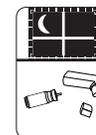
4. Wash **top**

- warm water
- 30 seconds

5. Shake off excess water



6. Air Dry overnight



7. Assemble

Remember:

- Clean **DAILY if used**

- If **wet**, prime one (1) time before use

- It is normal to see some discoloration in the mouthpiece due to residual drug left on it after use.

BACK

DESCRIPTION: Primatene Mist HFA

LABEL NO: F5530C

SIZE: 5 1/4" X 8.8"

COLORS: PMS 485, PMS 659, PMS 430, BLACK

BARCODE: CODE 128 to read F5530C

Primatene[®] MIST

Epinephrine Inhalation Aerosol
Bronchodilator

For the Temporary Relief of
BRONCHIAL ASTHMA

**Primatene[®] Mist (CFC) will not be available after December 31, 2011.
Talk to your doctor and/or pharmacist about other asthma medicines.**

BENEFITS OF PRIMATENE[®] MIST

When used according to directions, Primatene[®] Mist provides an easy and effective way to obtain temporary relief of bronchial asthma. Primatene[®] Mist has been used safely by millions. Primatene[®] Mist contains epinephrine, which is a dependable inhalation aerosol bronchodilator.

It is packaged in a plastic-coated safety-glass bottle, fitted with a specially designed valve, for use with the Primatene[®] Mist mouthpiece only. The special valve is designed to deliver the same amount of medication with each spray. Primatene[®] Mist can be used at any time of the day or night. Use as directed.

Manufactured by: Armstrong Pharmaceuticals, Inc., West Roxbury, MA 02132 ©2009 Made in USA F5030J

CODE 128 BARCODE
TO READ F5030J

FRONT

Drug Facts

Active ingredient (in each inhalation)

Epinephrine 0.22 mgBronchodilator

Purpose

Uses

- for temporary relief of occasional symptoms of mild asthma:
 - wheezing
 - tightness of chest
 - shortness of breath

Warnings

Asthma alert: Because asthma can be life threatening, see a doctor if you

- are not better in 20 minutes
- get worse
- need 12 inhalations in any day
- use more than 9 inhalations a day for more than 3 days a week
- have more than 2 asthma attacks in a week

For inhalation only

Do not use

- unless a doctor said you have asthma
- if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs taken for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- ever been hospitalized for asthma
- heart disease
- high blood pressure
- diabetes
- thyroid disease
- seizures
- narrow angle glaucoma
- a psychiatric or emotional condition
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are

- taking prescription drugs for asthma, obesity, weight control, depression, or psychiatric or emotional conditions
- taking any drug that contains phenylephrine, pseudoephedrine, ephedrine, or caffeine (such as for allergy, cough-cold, or pain)

Drug Facts (continued)

When using this product

- increased blood pressure or heart rate can occur, which could lead to more serious problems such as heart attack and stroke. Your risk may increase if you take more frequently or more than the recommended dose.
- nervousness, sleeplessness, rapid heart beat, tremor, and seizure may occur. If these symptoms persist or get worse, consult a doctor right away.
- avoid caffeine-containing foods or beverages.
- avoid dietary supplements containing ingredients reported or claimed to have a stimulant effect.
- do not puncture or throw into incinerator. Contents under pressure.
- do not use or store near open flame or heat above 120°F (49°C). May cause bursting.

Contains CFC 12, 114, substances which harm public health and environment by destroying ozone in the upper atmosphere.

If pregnant or breast-feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- do not exceed dosage
- supervise children using this product
- adults and children 4 years and over: start with one inhalation, then wait at least 1 minute. If not relieved, use once more. Do not use again for at least 3 hours.
- children under 4 years of age: ask a doctor

Other information

- store at room temperature, between 20-25°C (68-77°F)
- contains no sulfites
- see insert for mouthpiece use and care instructions

Inactive ingredients ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid, purified water

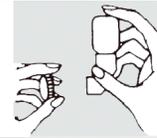
Questions or comments?

call 1-8 PRIMATENE or 1-877-462-8363

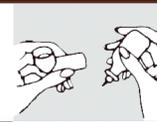
Intentional abuse of this product can be harmful or fatal.

DIRECTIONS FOR USE OF MOUTHPIECE The Primatene® Mist mouthpiece, which is enclosed in the Primatene® Mist 15 mL size (not the refill size), should be used for inhalation only with Primatene® Mist.

1. Take plastic cap off mouthpiece. (For refills, use mouthpiece from previous purchase.)



2. Take plastic mouthpiece off bottle.



3. Place short end of mouthpiece on bottle.



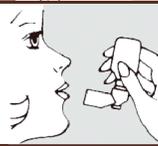
4. Turn bottle upside down. Place thumb on bottom of mouthpiece and forefinger on top of vial. Empty the lungs as completely as possible by exhaling.



5. Place mouthpiece in mouth with lips closed around opening. Inhale deeply while squeezing mouthpiece and bottle together. Release immediately and remove unit from mouth, then complete taking the deep breath, holding breath as long as comfortable.



6. Exhale slowly keeping lips nearly closed. This helps distribute the medication in the lungs.



7. For storage, place long end of mouthpiece back on bottle and cover with plastic cap.



CARE OF THE MOUTHPIECE The Primatene® Mist mouthpiece should be washed after each use with hot, soapy water, rinsed thoroughly, and dried with a clean, lint-free cloth.

If the unit becomes clogged and fails to spray, please write and send the clogged unit to: Armstrong Pharmaceuticals, Inc., 423 La Grange Street, West Roxbury, MA 02132

NO COPY

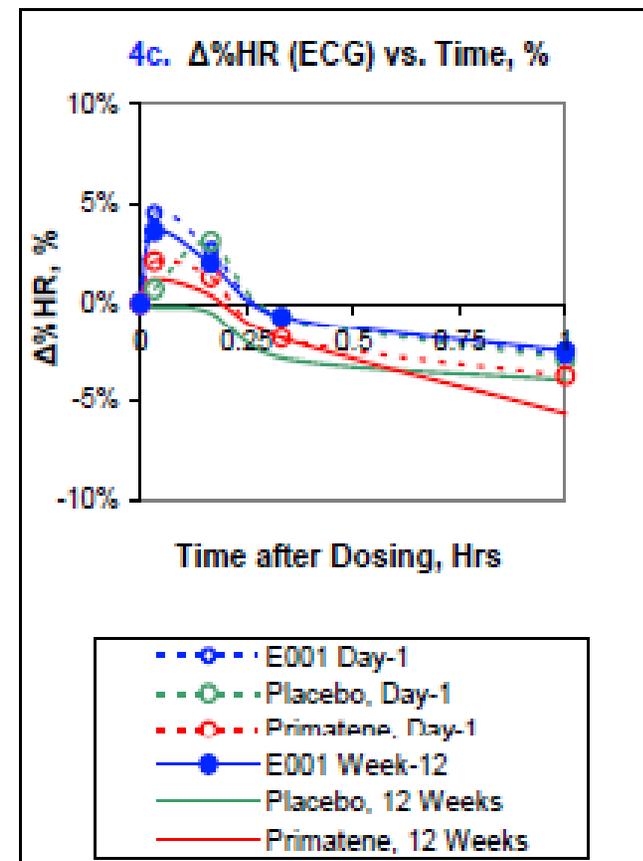
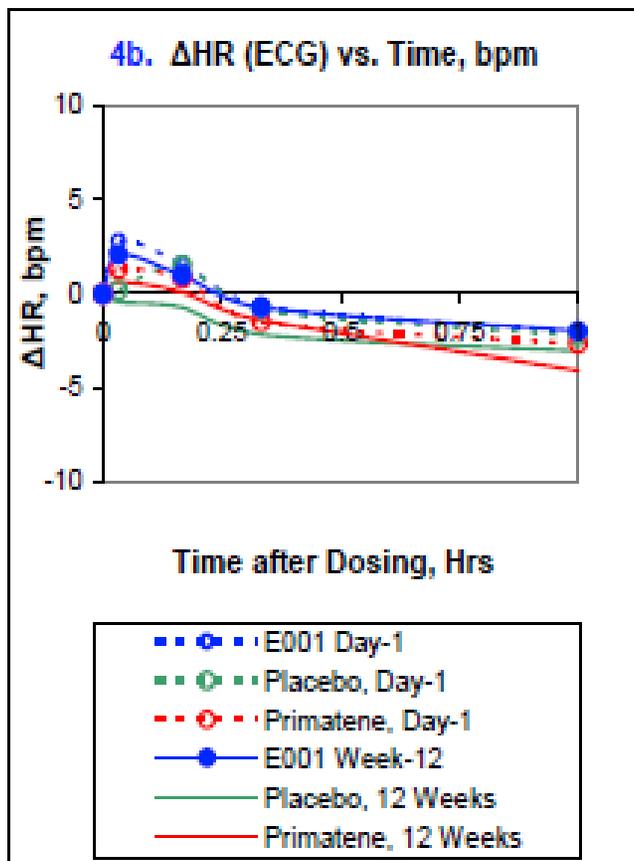
BACK

DESCRIPTION: Primatene Mist Insert
LABEL NO.: F5030J
SIZE: 9" x 4 3/4"
COLORS: PMS 4625, PMS 485
BARCODE: CODE 128 TO READ F5030J

DRUG FACTS TEXT DEFINED	TYPE SIZE
• DRUG FACTS TITLE	9 pt
• DRUG FACTS CONTINUED	8 pt
• HEADINGS	8 pt
• SUBHEADINGS/BODY TEXT	6 pt
• LEADING	6.5 pt
• # OF CHARACTERS PER INCH	<39
• BULLETS	5 pt
• SPACE BEFORE BULLET	2 ems
• BARLINES, HAIRLINES	1.5 pt, .5 pt
• SPACE BETWEEN HAIRLINES AND BOX END	2 spaces

Heart Rate, Change

- Changes for Baseline in HR in Study C of E004 125x2 puffs 4x daily vs PLA + Primatene Mist CFC



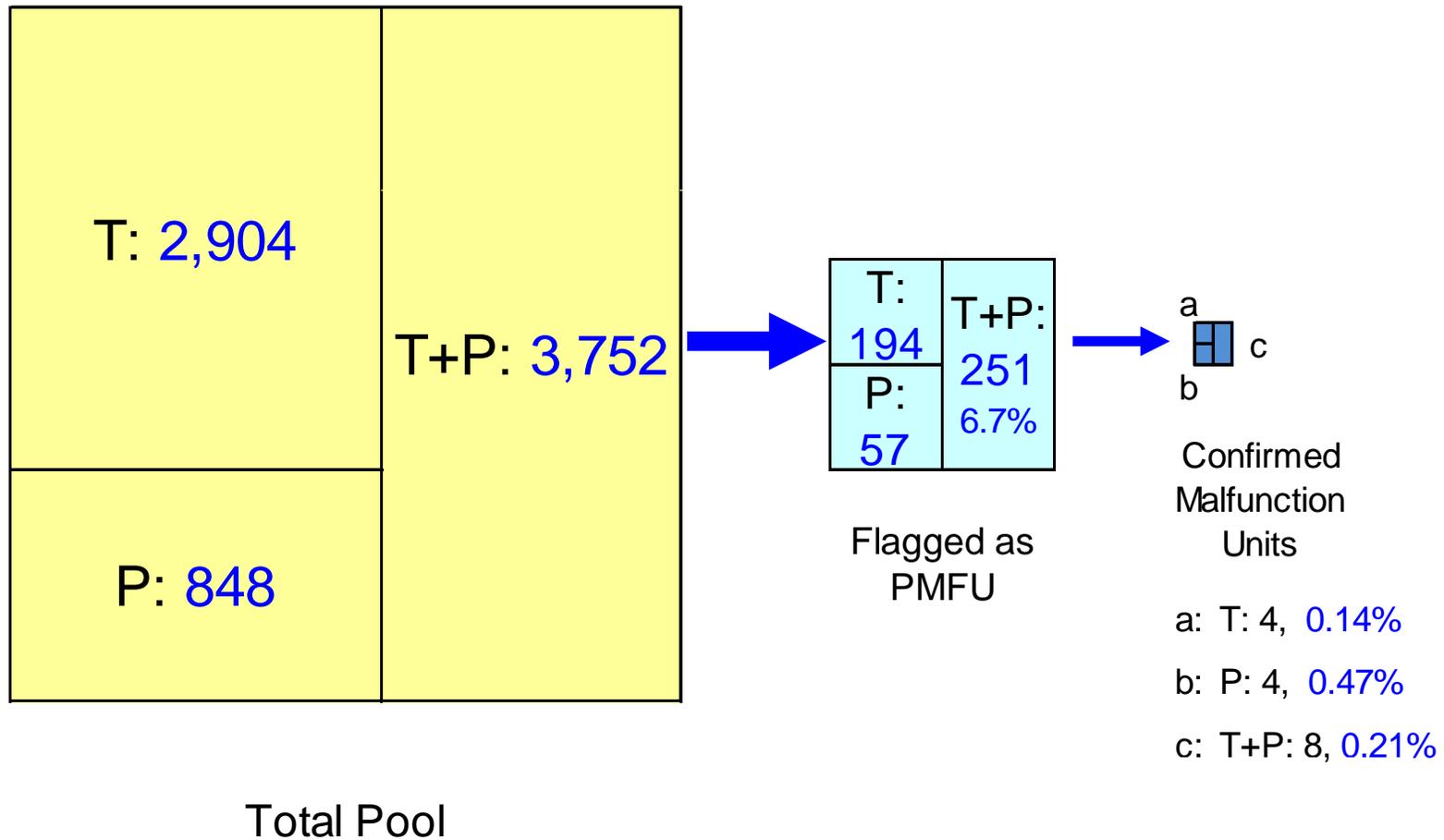
Study of “Potential Malfunction Units”

- Nightly subject diary question “Difficulties or malfunction with inhaler (yes/no)” This were asked ~43,000 times
- Subjects were interviewed ~2,500 times at the study sites
- When diary records or interview results were noted with a “Yes”, the associated clinical unit would be flagged as a PMFU
- Even if there was no “Yes” marked if interview statement shows possibility during document review, it would be flagged as a PMFU
- 251 PMFU were flagged



Profile of “Potential Malfunction Units”

General Profile: Returned Units → PMFU → Confirmed Malfunction



Categorization of “Potential Malfunction Units”

By carefully reviewing the flagged information, 18 types and 7 categories were classified for 251 PMFU

Seq. #	Categories		Key Word of Reporting		Number of PMFUs	
	No.	Code	Used in Appendix-5	Explanation	For the Category	For the Code
1	1	1	No detail	there is no any details	69	69
2	2	2a	Clog	Suspect clog	53	61
3		2b	Susp Clog		8	
4	3	3a	NDP	Not dispense properly	31	47
5		3b	Imp Spray	Improper Spray	16	
5	4	4a	DI Move??	DI moves incorrectly	38	45
6		4b	DI Issue		7	
7	5	5a	Imp Assem	Improper Assembling	1	8
8		5b	Pt use error		3	
9		5c	eDiary error		4	
10	6	6a	Dirty	Brown Residue	7	8
11		6b	Brown		1	
12	7	7a	DI Jump	Canister cannot be pushed down	3	13
13		7b	DI Over Count		1	
14		7c	DI stuck		1	
15		7d	Broken		2	
16		7e	Can not down		1	
17		7f	Malfunction?		2	
18		7g	Leak		3	
Total					251	251



DASS/NASS and PEF – Study C

Categories	Self-Monitored Results (PPP)*						p-values of Statistical Analysis		
	Arm-T		Arm-A		Arm-P		T vs. P	A vs. P	T vs. A
Study Arms	E004, n=205		Primatene, n=53		Placebo, n=53				
Studied Drugs									
Items	Mean ± SD	Δ%**	Mean ± SD	Δ%**	Mean ± SD				
Mean Daily Asthma Symptom Scores (DASS)	0.81 ± 0.57	-15%	0.91 ± 0.69	-4%	0.95 ± 0.64	0.161	0.767	0.344	
Mean Nighttime Awakening Scores (NAS)	0.15 ± 0.27	-35%	0.20 ± 0.44	-13%	0.23 ± 0.34	0.114	0.746	0.388	
Mean Daily Morning Pre-dose Peak Expiratory Flow Rate (PEF)	405 ± 114	7%	406 ± 130	7%	378 ± 101	0.095	0.228	0.982	

* See table 5.3.5.1.3-9-2218

** Δ% is relative to the mean for Placebo arm.



Thymol

- According to IIG database, Thymol up to 0.01% has been used in inhalation liquid:

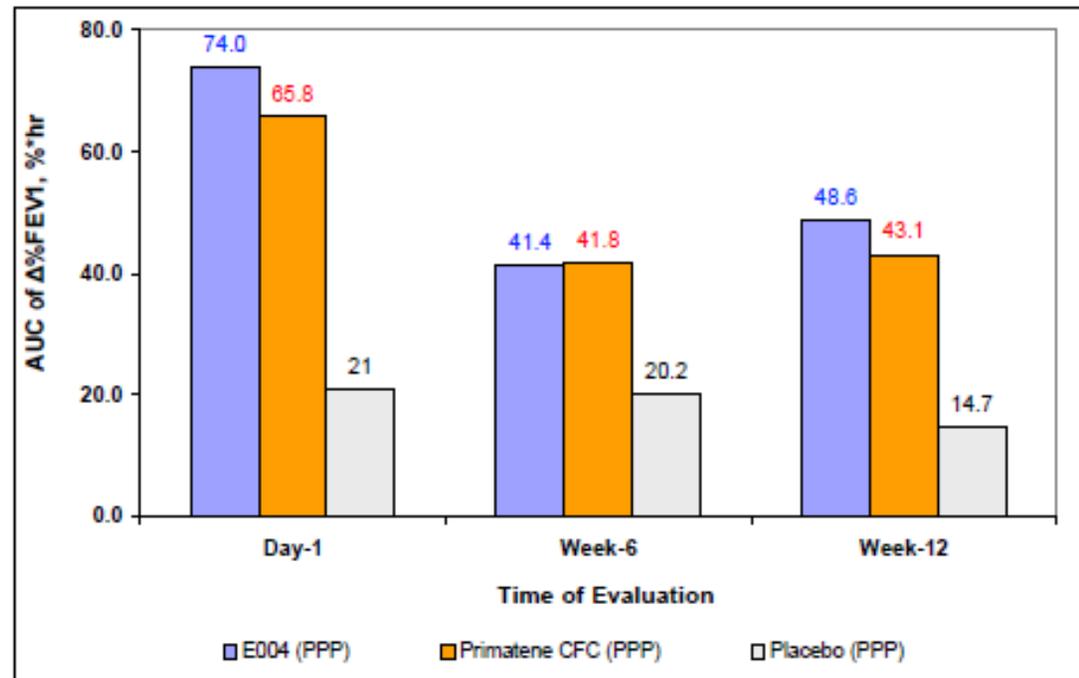
INACTIVE INGREDIENT ⁶	ROUTE; DOSAGE FORM ⁷	CAS NUMBER ⁸	UNII ⁹	MAXIMUM POTENCY ¹⁰
THYMOL	INHALATION; LIQUID	89838	3J50XA376E	0.01%
THYMOL	ORAL; POWDER, FOR SOLUTION	89838	3J50XA376E	

- E004 contains 0.01% of Thymol.
- Thymol is considered by the FDA as Generally Recognized as Safe (21 CFR 172.515, 182.10 and 182.20)⁴ for human consumption, as well as food additives.

⁴ EPA. R.E.D. FACTS: Thymol.



Primary Efficacy Analysis -



- E004, maximum recommended dose, 125 mcg x 2 puffs, 4x daily showed similar efficacy to Primatene[®] Mist CFC, 220 mcg x 2, 4 x daily
- Effectiveness shown on Day 1, week 6 and week 12
- AUC_{0-6h} of delta % FEV1 were slightly decreased by week 6 and week 12.

